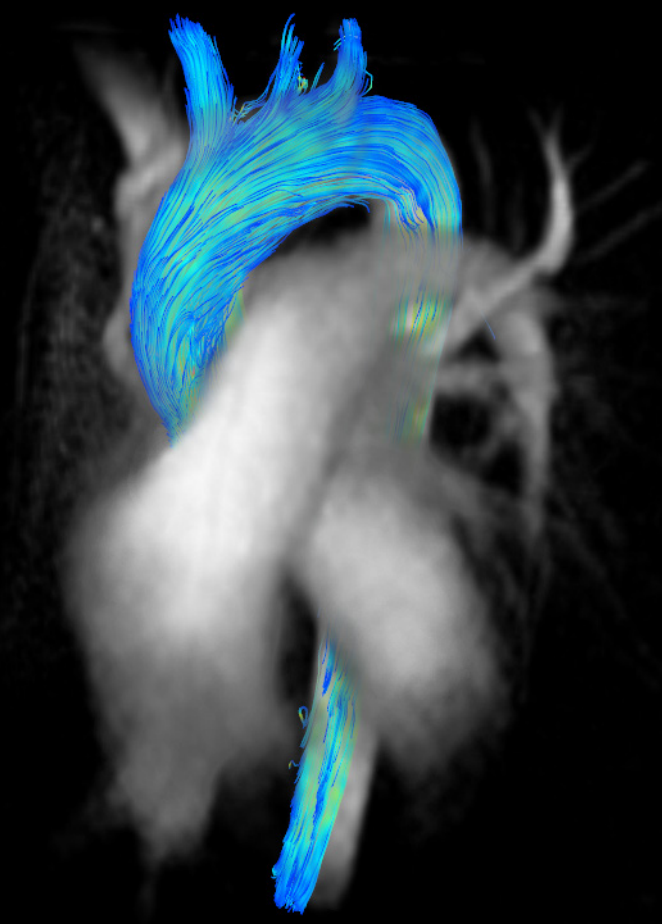
Thoracic Aortic Disease: Imaging and Clinical Aspects



Lidia R. Bons

Thoracic Aortic Disease: Imaging and Clinical Aspects

Aandoeningen van de thoracale aorta:
beeldvorming en klinische aspecten

Lidia Rianne Bons

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General introduction and thesis outline

Anatomy of the thoracic aorta

The aorta is the main artery of the body, which originates from the heart at the level of the aortic valve, and extends to the lower abdomen, where it continues as two smaller arteries. The portion located in the chest or thorax until the diaphragm is considered the thoracic aorta, whilst the lower part is named the abdominal aorta. The thoracic aorta can be divided in four segments as is shown in figure 1: the aortic root, ascending aorta, aortic arch and descending aorta.

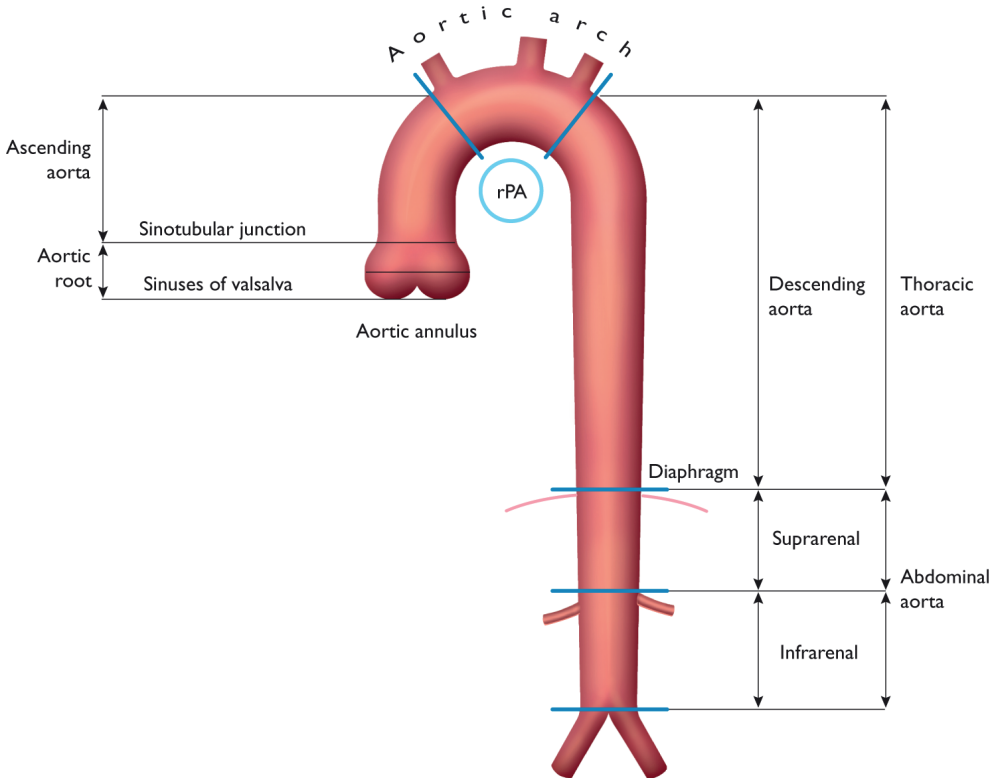


Figure 1. The aorta divided into different anatomical segments. Originally from Erbel at al. Eur Heart J 2014[1]. Permission was obtained from Oxford University Press.

Because the aorta collects all the blood that is pumped through the heart to the entire body, the aorta has a solid wall consisting of three layers named intima, tunica media, and tunica externa. The intimal layer is the thin and smooth inner lining of the vessel wall. A more prominent layer in the thoracic aortic wall is the tunica media, which contains smooth muscle cells and two important proteins named elastin and collagen. The tunica externa or adventitia is the outer layer of the vessel wall and consists of collagen, vasa vasorum, and lymphatics. Besides the conduit function of the thoracic aorta, the elasticity

allows the aorta to accept the pulsatile output of the left ventricle in systole. Additionally, this elasticity modulates continued forward flow during diastole facilitating diastolic perfusion of the coronary arteries[2, 3]. The wall of the thoracic aorta shows changes during lifetime with thinning and fracture of the elastin fibers, collagenous remodeling and progressive disorganization of the media with development of cystic media degeneration[4, 5]. These changes result in a longer [6] and stiffer [7] thoracic aorta with larger aortic diameters[8, 9] with increasing age. By looking at the differences in aortic diameters between younger and older people, the growth of the thoracic aortic diameter during lifetime is estimated to be around 1 mm per 10 years[10].

Epidemiology of thoracic aortic aneurysm and dissection

An **aortic aneurysm** has previously been defined as 'a permanent localized dilatation of an artery, having at least a 50% increase in diameter compared with the expected normal diameter of the artery in question'[11]. A value of 40mm has also been mentioned as a reference for thoracic aortic aneurysm[12, 13], however, this is derived from cohorts with relatively young individuals with ages ranging between 9 and 59 years[14, 15]. Since it is known that age, gender and anthropometric measurements (height and weight) are associated with the aortic diameter, these factors have been included in the presentation of new upper physiological limits of thoracic aortic dimensions for echocardiography[9], computed tomography[8] and magnetic resonance imaging[16]. These new upper physiological limits refer to a dimension that is greater than the 95th percentile based on a group of the same age, sex and body size. The various definitions mentioned above have resulted in multiple reported prevalence's or incidences for thoracic aortic aneurysm. Studies which defined ascending aortic aneurysm as a diameter above 50 mm, found a prevalence of 0.16-0.34% [17, 18], while reported incidences of 10 per 100.000 person-years are mainly based on the definition of an aortic diameter 1.5 times larger than normal [19, 20]. The majority of thoracic aortic aneurysms occur in the aortic root or ascending aorta, followed by the descending aorta and only a small amount is represented by the aortic arch[21, 22]. However, an aneurysm may involve multiple aortic segments. The epidemiology of thoracic aortic aneurysms is also challenging because it is typically a clinically silent disease. Most of the aneurysms are found during family screening, as a coincidental finding when a person receives an imaging test for other medical reasons, or when a complication occurs, such as aortic dissection or rupture.

A more clinically relevant definition of severe aortic aneurysm would be the dimension at which a person is at increased risk of these complications, particularly **aortic dissection**. In case of an aortic dissection, a tear in the intima layer of the vessel occurs which causes the blood to flow into the vessel wall. The intima layer separates from the media and/or adventitia layers, creating a true lumen and a false lumen. Aortic dissection can occur at different locations, well described by two classifications shown in figure 2, the Stanford[23] and De Bakey classification[24]. Stanford type A or DeBackey type 1 and 2, in which the

ascending aorta is dissected, accounts for 60% of all aortic dissections [25, 26] and has a high mortality rate. Within 30 days of the index event 67% of all Stanford type A patients died compared to 31% of all Stanford type B patients [26]. Therefore, immediate surgery for type A aortic dissection is necessary for patients who are eligible to undergo surgery [27]. Type B aortic dissection can be initially treated medically unless complicated by organ or limb malperfusion, progressive dissection, extra-aortic blood collection (impending rupture), intractable pain, uncontrolled hypertension, or early false lumen expansion.

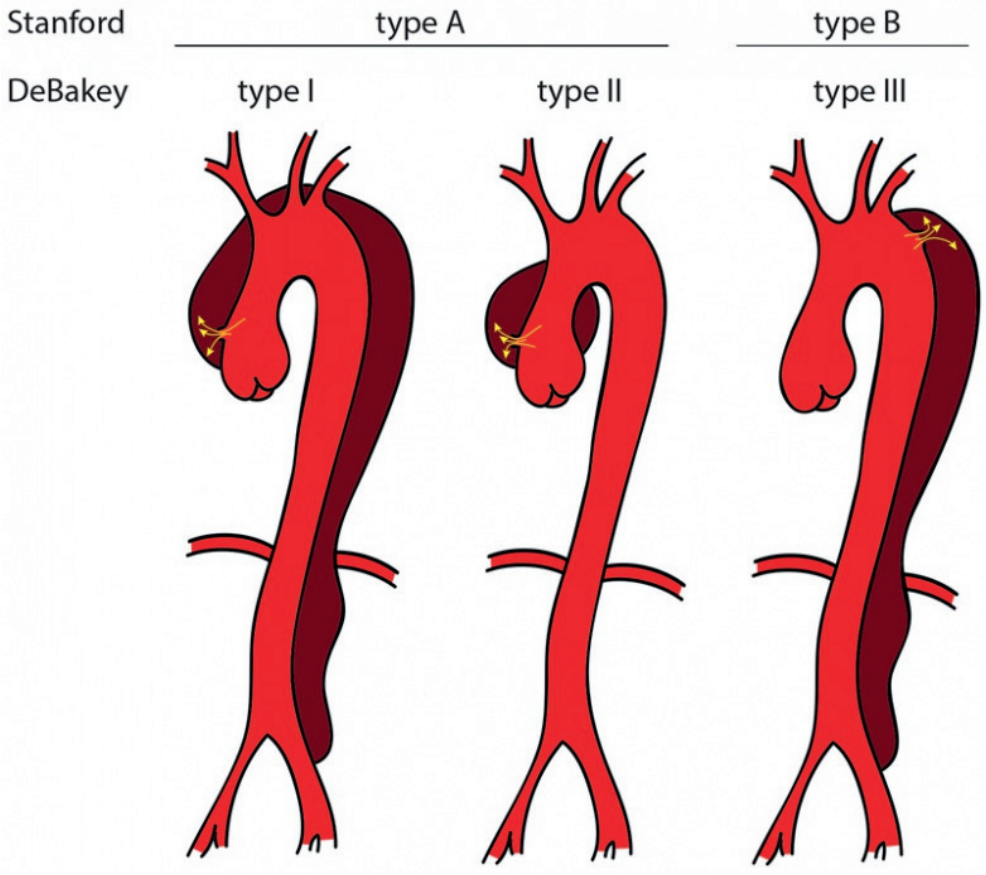


Figure 2. Classification of aortic dissection according to Stanford and DeBakey. True lumen is illustrated in red and false lumen in brown. In a Stanford type A or DeBackey type 1 and 2 aortic dissection, the ascending aorta is dissected. The intimal tear only occurs at the ascending aorta in DeBackey type 2, but expands to the aortic arch or descending aorta in DeBakey type 1. In case of Stanford type B or DeBackey type 2, the dissection is limited to the descending aorta. Originally from Gawenicka et al. Swiss Med Wkly. 2017. Permission was obtained from EMH Swiss Medical Publishers Ltd.

The underlying diagnosis, in combination with the diameter of the aorta, is most important for the risk of complications. An absolute aortic diameter exceeding 60 mm is associated with an increased risk of aortic dissection or death, with a yearly rate of at least 16% [28]. Therefore, guidelines have been developed which advise patients with a severe dilated thoracic aorta (≥55 mm) to undergo preventive aortic surgery [1, 11]. In some patients with genetically mediated disorders of the ascending aorta, such as Marfan or Loeys-Dietz syndrome, an elective operation is already advised at smaller aortic diameters due to a more vulnerable aortic wall. Since taller or heavier patients show larger aortic diameters[29], currently aortic diameters adjusted for body measurements are increasingly used. Especially for patients with Turner syndrome, adjustment for body measurements is preferred because of their small stature. The aortic size index (ASI) is the term used for the aortic diameter divided by the body surface area (DuBois & DuBois formula: body surface area = 0.20247 x height$^{0.725}$ x weight$^{0.425}$). In general, patients with an aortic size index above 27.5 mm/m^2 are at increased risk for aortic dissection or death with a yearly rate of 8%, while patients with a value of more than 42.5 mm/m^2 have a yearly risk of 20% [30]. In addition, the aortic diameter may also be divided by height only, named the aortic height index (AHI). Correcting solely for height could be a more precise and simpler risk assessment tool. Two individuals with an identical height and aortic diameter but a 5 kilogram difference in weight, will have the same risk of aortic dissection when using AHI. However, the heavier individual will have a lower risk of aortic dissection based on ASI because of his weight. A more recent study showed that correcting for height alone is at least as good as correcting for body surface area in predicting the risks of rupture, dissection, and death in patients with thoracic ascending aortic aneurysms[31]. Based on the results of this study, an AHI of >24.4 mm/m indicates moderate risk and >32.1 mm/m high risk. However, in the literature the use of uncorrected or corrected diameters is still an ongoing discussion. Risk prediction of patients who will develop an aortic aneurysm or dissection would obviously be of great value. In addition to the underlying diagnosis, age and diameter, possible new diagnostics might be helpful, among which blood[32] and imaging biomarkers[33] will probably gain more attention in the coming years.

Etiology of thoracic aortic disease

The formation of a thoracic aortic aneurysm can have various causes. Most often it is a **degenerative aortic aneurysm**, which is associated with older age and high blood pressure[16, 34]. Degenerative dilatation of the descending aorta is also associated with smoking and lipid profile [8, 16]. An infection of the aorta, called aortitis, can also be accompanied by an aortic aneurysm. Furthermore, a relatively rare cause of an aneurysm of the thoracic aorta is trauma. In contrast to abdominal aortic aneurysm, a large number of patients with thoracic aortic aneurysm have a genetic predisposition. This genetic predisposition may be present in the context of a syndromic connective tissue disease whereby the most well-known is **Marfan syndrome**. This syndrome is caused by a FBN-1

gene and the main features of this autosomal dominant disorder include disproportionate long bone overgrowth, ectopia lentis and aortic aneurysm[35]. Aneurysms in these patients are mainly located in the aortic root, the first part of the aorta after the aortic valve, but can be found at any level of the aorta. Cardiovascular disease (including aortic dissection at young age) is the number one cause of death in these patients [36, 37]. Other connective tissue diseases, which show also aneurysms of the aorta or other arteries, are (1) **Loeys-Dietz syndrome,** caused by a pathogenic variant in the genes encoding the TGF-β receptors (*TGFBR1* or *TGFBR2*) or proteins (*TGFB2* or *TGFB3)*[38], (2) **vascular Ehlers-Danlos syndrome**, resulting from a pathogenic variant in the COL3A1 gene[39] and (3) **aneurysm-osteoarthritis syndrome,** caused by a pathogenic variant in the SMAD3 gene[40]. These genes influence mechanosignaling in the cells of the aortic wall, making patients more susceptible to thoracic aortic disease. The aneurysm-osteoarthritis syndrome has been first described in the Erasmus Medical Center. It presents with early-onset osteoarthritis in multiple joints, skeletal and craniofacial abnormalities and affects major arteries leading to aneurysms and tortuosity[41]. The SMAD3 gene is active in the same TGF-ß signaling as the TGFBR1 and TGFBR2 responsible for Loeys-Dietz syndrome. Therefore, the aneurysm-osteoarthritis syndrome is also being called Loeys-Dietz syndrome type 3.

Of the patients with thoracic aortic aneurysm, 20% show one or more first-generation relatives with an aortic aneurysm[42]. Patients with thoracic aortic disease who have a family history of aneurysmal disease but do not meet the criteria for the aforementioned connective tissue syndromes are referred to as having **familial thoracic aortic aneurysm and dissection (FTAAD)**. The predominant mode of inheritance is autosomal dominant and screening of first degree relatives of patients with thoracic aortic aneurysm at young age is essential[13, 43]. Another non-syndromic disease, which has a genetic predisposition for aortic aneurysm is the most common congenital heart defect, found in 1-2% of the population, namely the **bicuspid aortic valve (BAV)**[44]. The abnormal development of the aortic valve results in a valve with two instead of three valve leaflets[45]. A bicuspid aortic valve can also primarily consist of three leaflets, but during development two of them are not well separated. This is demonstrated by a central raphe or ridge between the two connected leaflets and is called a 'functional' bicuspid aortic valve. At first, hemodynamic alterations caused by a bicuspid aortic valve were held responsible for the development of aortic aneurysm, most often seen at the ascending aorta. However, more recent literature has shown that family members of patients with BAV could have an aortic aneurysm in the absence of BAV, suggesting that the component features, BAV and thoracic aortic aneurysm, are independent manifestations of a single or multiple gene defects[46]. Additionally, formation of aortic aneurysm seems to continue after valve replacement of the bicuspid aortic valve[47, 48], making a genetic background more plausible. Probably the combination of genetic and flow factors have to be taken into account. A bicuspid aortic valve is often seen (14-34%) in patients with **Turner syndrome[49]**, which is caused by partial or complete absence of an X chromosome. Patients are known for their

typical short stature and webbed neck, but besides these phenotypical features, ovarian insufficiency and aortic aneurysm or dissection are important clinical features. Ascending aortic aneurysm is found in 24% of the patients[50]. Because these patients, probably due to their small height, can develop aortic dissection at smaller aortic diameters than the general population[51], the identification of Turner patients at risk for aortic dissection remains an important topic of research. An aortic aneurysm in an individual without a family history of thoracic aortic disease or without syndromic features is called a **sporadic aortic aneurysm**.

Diagnostics of the thoracic aortic aneurysm

Because the aortic diameter is the key measurement in the decision to treat a patient with invasive preventive surgery, it is very important that the aorta is measured in an accurate and standardized manner. There are three different modalities that can be used to measure the aorta, see figure 3 [2]. **Echocardiography** uses the physical properties of ultrasound waves to construct images of cardiac tissue and structures such as the aorta[52]. It is a relatively inexpensive and accessible modality, but can usually visualize only the first portion of the aorta, namely the aortic root and proximal ascending aorta. **Computed tomography (CT)** and **magnetic resonance imaging (MRI)** imaging can visualize the entire aorta but these modalities are more expensive and CT has the additional disadvantage of radiation use[53]. MRI uses a strong magnetic field and radiofrequency waves to create detailed images. Contraindications for MRI are mostly related to the presence of metallic implants and/or devices in a patient and claustrophobia.

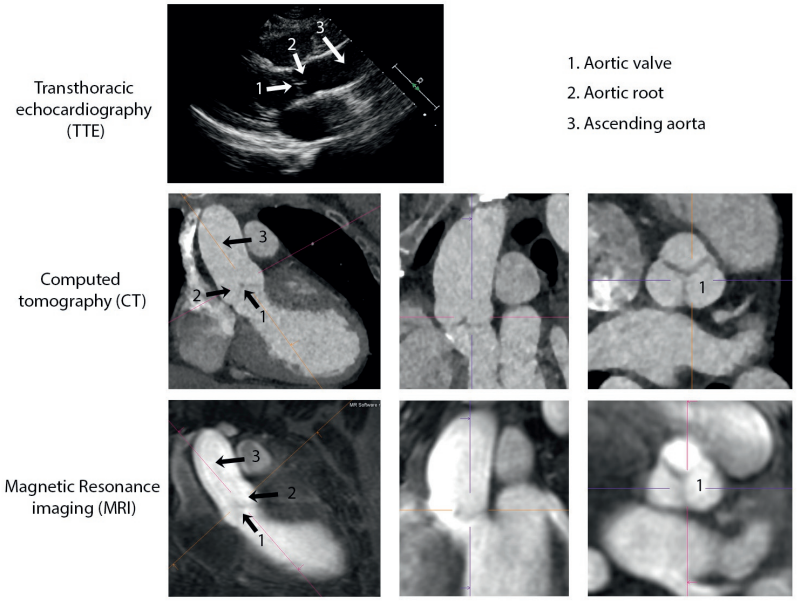


Figure 3. Imaging of the thoracic aorta by different modalities

In addition to the different modalities which can be used to image the thoracic aorta, various techniques are used to measure the aorta. Only the diameter of the aortic lumen can be measured, but the aortic wall can also be included in the diameter (figure 4). Additionally, there is no standardized approach for the time during the cardiac cycle at which the measurement is performed[54]. During ventricular contraction (systole), the aorta is slightly larger than during relaxation (diastole) due to the increase in blood flow through the aorta. Furthermore, since the aortic root is not circular, there is debate of whether to report cusp-to-commissure or cusp-to-cusp measurements for sinus of Valsalva measurements.

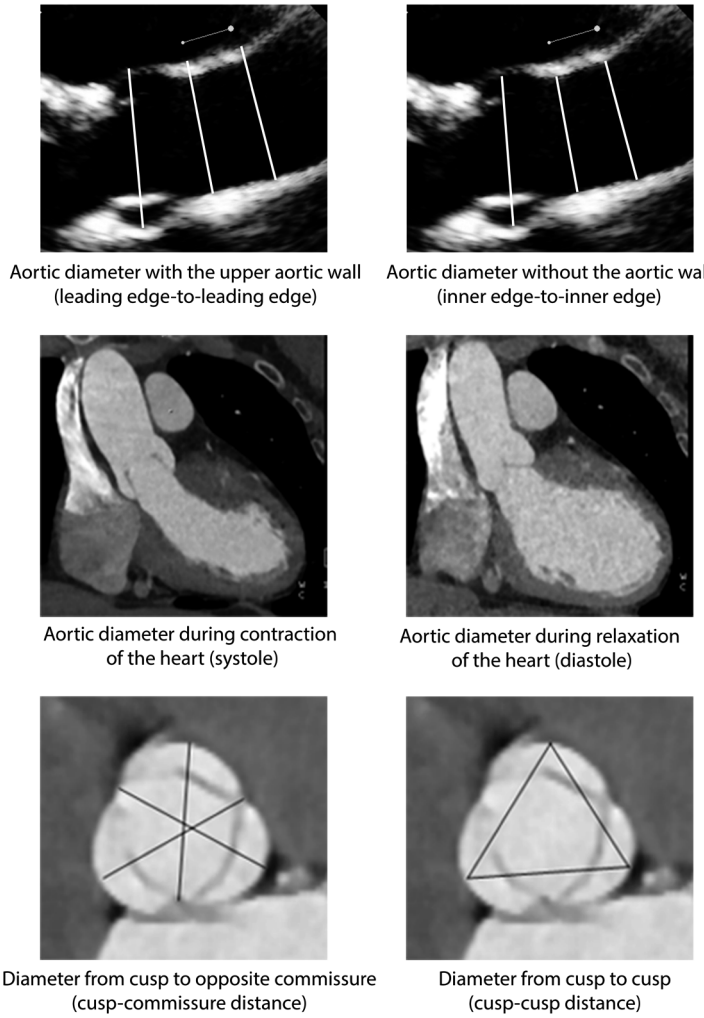


Figure 4. Different methods to measure the thoracic aorta

Recently, different guidelines specifically focusing on the thoracic aorta have been published[2, 11, 55, 56]. However, these guidelines, coming from different professional societies, are inconsistent in their advice [57, 58]. To accurately compare measurements within one patient or to compare patients with each other there should be one standard, used by cardiologists, radiologists and other professionals in which the same modality, same technique and same time point is advised.

Aim and outline of this thesis

The aim of this thesis is to investigate the epidemiology, optimal diagnostic method and outcome of thoracic aortic disease and study its impact on quality of life.

The following research questions are addressed:

- What are the different ways to image the thoracic aorta and what is the optimal method? **(Chapter 1-4, 8)**
- What is the distribution of the normal diameter and growth of the thoracic aorta? **(Chapter 5-7)**
- Which factors contribute to the risk of developing complications from aortic disease? **(Chapter 9 and 11)**
- What is the long-term outcome for patients with Turner syndrome or Aneurysm-osteoarthritis syndrome? **(Chapter 10 and 12)**
- What is the psychological burden of aortic pathology? **(Chapter 13)**
- What is the risk of pregnancy and of exercise in patients with thoracic aortic disease? **(Chapter 14 and 15)**

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Part I



Imaging of the thoracic aorta

CHAPTER 1



Intermodality variation of aortic dimensions: How, where and when to measure the ascending aorta

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Background

No established reference-standard technique is available for ascending aortic diameter measurements. The aim of this study was to determine agreement between modalities and techniques.

Methods

In patients with aortic pathology transthoracic echocardiography, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) were performed. Aortic diameters were measured at the sinus of Valsalva (SoV), sinotubular junction (STJ) and tubular ascending aorta (TAA) during mid-systole and end-diastole. In echocardiography both the inner edge-to-inner edge (I-I edge) and leading edge-to-leading edge (L-L edge) methods were applied, and the length of the aortic annulus to the most cranial visible part of the ascending aorta was measured. In CTA and MRA the I-I method was used.

Results

Fifty patients with bicuspid aortic valve (36 ± 13 years, 26% female) and 50 Turner patients (35 ± 13 years) were included. Comparison of all aortic measurements showed a mean difference of 5.4 ± 2.7 mm for the SoV, 5.1 ± 2.0 mm for the STJ and 4.8 ± 2.1 mm for the TAA. The maximum difference was 18 mm. The best agreement was found between echocardiography L-L edge and CTA during mid-systole. CTA and MRA showed good agreement. A mean difference of 1.5 ± 1.3 mm and 1.8 ± 1.5 mm was demonstrated at the level of the STJ and TAA comparing mid-systolic with end-diastolic diameters. The visible length of the aorta increased on average 5.3 ± 5.1 mm during mid-systole.

Conclusions

MRA and CTA showed best agreement with L-L edge method by echocardiography. In individual patients large differences in ascending aortic diameter were demonstrated, warranting measurement standardization. The use of CTA or MRA is advised at least once.

Abstract

Introduction

Progressive dilation of the ascending aorta is an important risk factor for aortic dissection and rupture[1], which is associated with significant morbidity and mortality. The estimated incidence of thoracic aortic enlargement (including ascending aortic aneurysm) is 10.4 cases per 100.000 person-years[2, 3]. This figure varies in part by non-standardized definitions of how the aorta should be measured or what constitutes an abnormal diameter. The more widespread application of multiple imaging modalities in a given patient adds to the variations seen in clinical practice. Three imaging modalities are currently in use for measuring the ascending aorta: transthoracic two-dimensional echocardiography (2DE), computed tomography (CT) and magnetic resonance imaging (MRI)[4]. Each modality has its strengths and weaknesses[5]. Recently, guidelines specifically focused on the ascending aorta have been published. The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines[6] recommend measuring the outer edge-to-outer edge (O-O) edge of the vessel wall for CT or MRI derived diameters, but the inner edge-to-inner edge (I-I) for 2DE. In contrast, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) guidelines for 2DE suggest that the leading edge-to-leading edge (L-L edge) convention at end-diastole should be used[7, 8]. Finally, the 2010 ASE pediatric guidelines[9] pose that by 2DE the I-I measurement, during systole is preferred. Just as guidelines are inconsistent[10, 11] so is clinical practice. By CT, the I-I method is most frequently used when contrast is given since the wall itself is hardly visible[12, 13], while the O-O method is used in non-contrast enhanced scans[14, 15]. In contrast, most physicians using 2DE prefer the L-L edge method[16, 17]. Also in the general population, age, gender and BSA have impact on aortic diameters as discussed by Vriz et al. [18]. Furthermore, since the aortic root is not circular, there is debate of whether to report cusp-to-commissure or cusp-to-cusp measurements for sinus of Valsalva measurements. Despite attempts at congruency, the ASE/EACVI concluded that there was insufficient data to favor one standard[7]. Some studies have compared reported measurements, though currently there are no studies comparing all three imaging modalities performed in the same patient on the same day. The aim of this study was to determine agreement between modalities and techniques and provide guidance on the optimal approach to measure the ascending aorta. The following measurements were compared: (1) ascending aortic measurements on echocardiography, CTA and MRA, (2) cusp-to-cusp and cusp-to-commissure diameter at the level of the sinus of Valsalva on CTA and (3) aortic measurement during diastole and systole.

Methods

Study population

The study population consisted of adult patients with a bicuspid aortic valve (BAV) and/or Turner syndrome who had been included in a prospective cohort study to elucidate the

etiologies and pathogenic mechanisms leading to BAV/aneurysm formation and unravel risk factors for disease progression[19]. For research purposes the patients were scheduled for 2DE, CTA and magnetic resonance angiography (MRA) on the same day. Therefore, the data of this cohort made it possible to directly compare 2DE, CTA and MRA measurements of the ascending aortic diameter. Patients visited our tertiary center between October 2014 and March 2016. The inclusion criteria for BAV patients were age ≥18 year and one of the following: (1) aortic stenosis (gradient >2.5 m/sec), (2) aortic regurgitation (at least moderate) or (3) ascending aortic dilation ≥40 mm and/or aortic size index >2.1 cm/m2. All three types of a bicuspid aortic valve according to the Sievers classification were included. This classification is based on the number of raphes, which is a fused area between two cusps. Bicuspid aortic valves with no raphe are called type 0, valves with one raphe type 1 and valves with two raphes type 2. Turner patients needed to have a genetically confirmed 45,X or 45,X/46,XX mosaic karyotype. Patients with contra-indication to CTA, MRA or contrast agents were excluded. Renal function was checked in all patients. Patients with no MRA due to claustrophobia or technical problems remained in the study, but patients who did not receive either 2DE or CTA were excluded. Patients without MRA were included, because some of our research questions do not require information about MRA measurements. Patients also underwent physical examination. Hypertension was defined as current use of antihypertensive medication. The study complied with the Declaration of Helsinki and was approved by the medical ethical committee of the Erasmus Medical Center (MEC14-225). Written informed consent was provided by all patients.

Transthoracic two-dimensional echocardiography (2DE)

Standard 2DE was performed by one of two experienced sonographers. All studies were acquired using harmonic imaging on an iE33 or EPIQ7 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with an x5–1 matrix-array transducer (composed of 3040 elements operating at 1-5 MHz). The aorta was measured from either the standard parasternal long axis view or from a more cranial intercostal window to improve visualization of the ascending aorta[6]. Aortic stenosis was defined based on peak aortic velocity and aortic regurgitation was evaluated according to the EAE/ASE guidelines[20].

Computed tomography angiography (CTA)

A retrospectively ECG-gated spiral CTA was performed using a dual-source CT system (Somatom Force or Somatom Definition Flash, Siemens Healthineers, Forchheim, Germany). In order to image the ventricles, aortic valve and aorta, the scan range was set from the aortic arch to the inferior border of the heart. Dose modulated ECG-pulsing was employed with nominal tube current during the 0 to 40% window of the R-R interval, and tube current reduced to 20% of the nominal output for the remainder to reduce the radiation dose. In total 20 different reconstructions with a 1.5-mm slice thickness and 1.0-

mm overlap were made in each patient at each 5% of the R-R interval. Reference tube current was set at 150 mAs per rotation. Automatic kV selection was used. The table speed was adapted to the heart rate. No beta blockers were administered prior to the scan. A 65 ml bolus of iodinated contrast material (Iodixanol 320, Visipaque, GE. Health Care, Cork, Ireland) was administered through an antecubital vein followed by a 40 ml 70/30% saline/ contrast medium bolus, both at 5 ml/s. Image acquisition was started using bolus tracking in the ascending aorta.

Magnetic resonance angiography (MRA)

Image acquisition was performed using a 1.5 T scanner (Discovery MR450, GE Medical Systems, Milwaukee, WI, USA) using a 32-channel phased-array cardiac surface coil. For aortic imaging an angiography sequence was used. First a test bolus of 1 ml gadobutrol (Gadovist, Bayer Schering Pharma, Leverkusen, Germany) followed by 20 ml of saline flush, was injected to identify the individual scan delay time to the maximum enhancement of contrast in the descending aorta. Second, non-ECG-gated MRA images were acquired in coronal orientation after injection of a double dose of 7 ml gadobutrol (0.05-0.18 mmol/ kg) followed by 20 ml of saline flush, both with an injection rate of 2.5 ml/s. Typical scan parameters were: FOV 460 mm (phase 90%), matrix size 320 x 192, slice thickness 2.0 mm, flip angle 17°, NEX 0.75, bandwidth 83.3 kHz, TR 3.1 ms, TE 1.09 ms.

Measurements of the ascending aorta

Analyses of the 2DE, CTA and MRA images were performed by experienced investigators blinded to the results of the other imaging modalities. Images were analyzed offline with the use of dedicated software: Xcelera (version R4.1, Philips Medical Systems, the Netherlands) for 2DE and Syngo.Via (Version VB10B, Siemens, Germany) for CTA and MRA. For CTA and MRA maximal aortic diameters were measured from reconstructed short-axis images generated with double-oblique multiplanar reformation[21]. To compare the diameter between the three modalities the aorta was measured at three predefined levels for all three imaging techniques: sinus of Valsalva (SoV), sinotubular junction (STJ) and tubular ascending aorta (TAA, 1 cm cranial of the sinotubular junction), as indicated in figure 1A. When referring to the widest diameter at any level of the ascending aorta, we used 'ascending aorta'. Both the L-L edge and I-I edge methods were applied in 2DE (figure 1B). For CTA and MRA only the I-I edge method was applied, because the vessel wall is difficult to distinguish on contrast-enhanced images in the absence of atherosclerotic disease. For this reason, measurements with the O-O edge method were not possible for CTA and MRA. Calcified plaques were included in the diameter measurement. Measurements were made at both end-diastole and mid-systole for 2DE and CTA according to the guidelines(7,8) (figure 1C). The MRA was acquired without ECG-synchronization. The measurements on MRA were compared with both the end-diastolic and mid-systolic measurement on CTA. End-diastole was defined as the moment before opening of the aortic valve and ranged

between 75% and 100% of the R-R interval on CTA. Mid-systole was defined as the phase exactly halfway between opening and successive closure of the aortic valve and ranged between 15% and 35% of the R-R interval on CTA. The maximal length of the aorta that was visualized with 2DE (defined as the length from the aortic annulus to the most cranial part of the ascending aorta which was visible) was measured during mid-systole and end-diastole (figure 1A). For CTA and MRA three cusp-to-commissure distances were measured at the level of the SoV (widest plane) when patients had a tricuspid aortic valve or bicuspid aortic valve type 1 or 2 according to the Sievers classification[22]. In CTA the diameter was also measured with the cusp-to-cusp method according to Goldstein et al.[7](figure 1D). For bicuspid aortic valves type 0 this was measured in two directions (maximum diameter and diameter perpendicular to the maximum diameter). At the level of the sinus of Valsalva the largest measurements on CTA and MRA was compared to echocardiography. Detailed information about separate analysis of the three cusp-to-cusp measurements (tricuspid or bicuspid type 1 or 2 valves) and measurements in two directions (bicuspid type 0 valves) can be found in the supplemental material. Using this protocol, the aorta was measured with seven different methods across all modalities at each of three levels (supplemental table 1). The absolute value of the maximum difference between these seven measurements at each level (maximum difference) was calculated for each patient. Inter- and intra-observer agreement was assessed by repeated analyses of a randomly selected sample of 25 subjects.

Statistical analysis

Categorical variables are presented as frequencies with percentages. Comparison of categorical variables was done using the Chi-square test and in case of an expected count <5 in one of the cells of the crosstable the Fisher's exact test was used. All continuous variables are presented as mean with standard deviation when normally distributed, and in case of non-normal distribution, medians with interquartile ranges are provided. Data distribution was checked using histograms. Comparison of normally distributed continuous variables was done using the Student's t-test or, in case of a skewed distribution, the Mann-Whitney test. Comparison of normally distributed continuous variables between two imaging modalities or techniques in one patient was done using the paired student's t-test or, in case of a skewed distribution, the Wilcoxon one-sample test. Pearson correlation coefficient and linear regression analysis was applied for associations. Mean differences between imaging modalities or techniques were determined by Bland-Altman plots, and the limits of agreement calculated using the mean and standard deviation of the difference. To assess intra- and inter observer variability the intraclass correlation coefficient (ICC) was calculated. The IBM SPSS® statistics 21.0 software was used for data analysis. Two-sided p values of <0.05 were considered statistically significant.

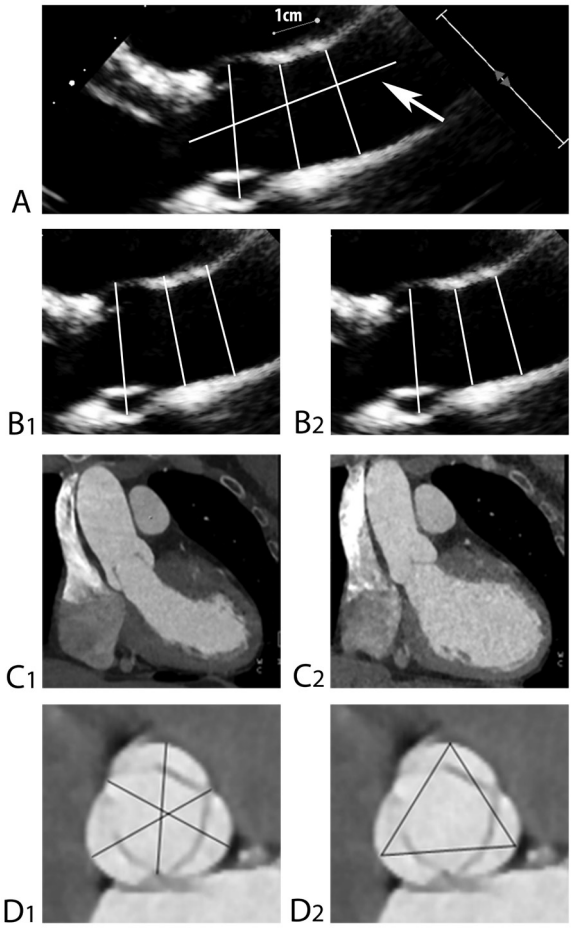


Figure 1. Measurements of the aortic root and ascending aorta.
Aortic diameters are measured at three predefined levels: the Sinus of Valsalva, the sinotubular junction and the ascending aorta (A), with use of the leading edge-to-leading edge (B1) and inner edge-to-inner edge (B2) methods in echocardiography and during mid-systole (C1) and end-diastole (C2) in both echocardiography and CTA. Also the length of the aorta (arrow in A) was measured by 2DE. At the level of the sinus of Valsalva both the cusp-to-commissure diameter (D1) and the cusp-to-cusp diameter (D2) were measured by CTA

Results

Study population

In total 100 subjects were included: 50 subjects with BAV (age 36±13 years; 26% female) and 50 subjects with Turner syndrome (age 35±13 years, 100% female, 24% BAV). Nineteen patients had BAV type 0, 36 patients BAV type 1 and 7 patients BAV type 2. Renal function

was normal in all. MRA was not performed in 12 subjects due to claustrophobia (n = 4), technical problems (n = 4), contra-indications (n = 2) and logistic reasons (n = 2). In 26 subjects (26%) the investigations were not performed on the same day. In these subjects the median time between investigations was 7 (IQR 6.5-22.8) days, mostly due to technical or practical issues. The mean total dose length product was 362.2 ± 196.4 mGy * cm. Table 1 shows the baseline patient characteristics of the total study population and separately for the three groups: BAV subjects, Turner subjects without BAV and Turner subjects with BAV.

Table 1. Baseline characteristics

	All (n=100)	Bicuspid aortic valve without Turner syndrome (n=50)	Turner syndrome (n=50)		p-value BAV and TS vs BAV without TS	p-value TS and BAV vs TS without BAV
			Tricuspid aortic valve (n=38)	Bicuspid aortic valve (n=12)		
Age (y)	35 ± 13	35 ± 13	35 ± 13	36 ± 13	0.882	0.892
Gender, female	63 (63%)	13 (26%)	38 (100%)	12 (100%)	<0.001†	-
Height (cm)	169 ± 16	181 ± 12	157 ± 9	154 ± 7	<0.001	0.330
Weight (kg)	72 ± 17	78 ± 15	69 ± 18	61 ± 11	<0.001	0.131
Systolic blood pressure (mmHg)	124 ± 16	124 ± 15	124 ± 18	126 ± 16	0.685	0.719
Diastolic blood pressure (mmHg)	80 ± 11	80 ± 10	80 ± 12	83 ± 14	0.319	0.449
Hypertension	16 (16%)	8 (16%)	7 (18%)	1 (8%)	0.675†	0.661†
Coarctation	13 (13%)	9 (18%)	0 (0%)	4 (33%)	0.256†	0.002†
Aortic dilatation (>40mm and/or ASI>2.1 cm/cm^2)	47 (47%)	33 (66%)	7 (18%)	7 (58%)	0.618	0.023†
Aortic stenosis (echo V_{max} >2.5 m/s)	29 (29%)	28 (56%)	0 (0%)	1 (8%)	0.003†	0.240†
Aortic regurgitation (moderate or severe)	17 (17%)	16 (32%)	0 (0%)	1 (8%)	0.153†	0.240†
Echocardiography	100 (100%)	50 (100%)	38 (100%)	12 (100%)	-	
Computed tomography angiography*	100 (100%)	50 (100%)	38 (100%)	12 (100%)	-	
Diameter sinus of Valsalva (mm)	35 ± 6	39 ± 6	31 ± 3	34 ± 5	0.005	0.140
Diameter sinotubular junction (mm)	31 ± 6	34 ± 6	27 ± 3	29 ± 6	0.016	0.233
Diameter ascending aorta (mm)	33 ± 7	37 ± 7	29 ± 4	31 ± 6	0.004	0.244
Magnetic resonance angiography	88 (88%)	44 (88%)	33 (87%)	11 (92%)	1.000†	1.000†

Data are expressed as mean ± SD or number (percentage). ASI=aortic size index (aortic diameter divided by BSA), TS = Turner syndrome, Vmax=maximum velocity. *Aortic measurements during systole and with the inner-to-inner edge method. † Fisher's exact test.

Comparison of aortic diameters among different imaging modalities

All absolute measurements of the aorta with 2DE, CTA and MRA are shown in supplemental table 2 and 3. Comparison between MRA and CTA showed a Pearson correlation coefficient of 0.84 -0.95 at the level of the SoV and >0.96 at the levels of the STJ and TAA (table 2 and supplemental table 4).

When comparing 2DE with CTA, the L-L edge method showed best agreement with CTA compared to the I-I edge method at the level of the STJ and TAA in both end-diastole and mid-systole (table 2 and supplemental figure 1). The smallest difference between 2DE and CTA was found at the STJ in mid-systole with the L-L edge method ($r = 0.96$, mean difference 0.1 ± 1.8 mm). At the level of the SoV the I-I edge method underestimated the diameter compared to the cusp-to-commissure method in CTA (supplemental figures 2 and 3 and supplemental table 5). In the majority of cases, lower Pearson correlation coefficients and higher mean differences were found at the level of the SoV.

Table 2. Agreement between echocardiography, CTA and MRA.

			Lower limit-upper limit of agreement (mm)						
Mean difference ± standard deviation (mm)			**Echo L-L Diastole**	**Echo L-L Systole**	**Echo I-I Diastole**	**Echo I-I Systole**	**CTA I-I Diastole**	**CTA I-I Systole**	**MRA I-I**
	Echo L-L Diastole	SoV		-3.4 - 1.4	1.1 - 4.2	-0.6 - 4.1	-6.6 - 5.9	-7.6 - 4.6	-7.1 - 5.3
		STJ		-4.5 - 1.8	1.1 - 4.7	-2.0 - 4.9	-3.2 - 3.8	-5.0 - 2.6	-5.3 - 3.5
		AA		-4.6 - 2.3	1.2 - 4.1	2.6 - 5.3	-3.1 - 4.8	-5.7 - 3.5	-4.9 - 4.9
	Echo L-L Systole	SoV	-1.0 ± 1.2		0.9 - 6.3	1.1 - 4.3	-5.8 - 7.0	-6.7 - 5.8	-6.2 - 6.4
		STJ	-1.3 ± 1.6		0.9 - 7.6	1.1 - 4.5	-2.1 - 5.3	-3.4 - 3.7	-3.9 - 4.6
		AA	-1.2 ± 1.8		0.1 - 7.5	1.2 - 3.9	-2.3 - 6.2	-3.8 - 4.0	-3.4 - 5.7
	Echo I-I Diastole	SoV	2.7 ± 0.8	3.6 ± 1.4		-3.3 - 1.4	-9.3 - 3.2	-10.4 - 2.1	-9.7 - 2.6
		STJ	2.9 ± 0.9	4.3 ± 1.7		-4.6 - 1.7	-6.3 - 1.2	-8.3 - 0.0	-8.4 - 7.0
		AA	2.7 ± 0.7	3.8 ± 1.9		-5.3 - 2.7	-5.8 - 2.2	-8.5 - 1.0	-7.9 - 2.5
	Echo I-I Systole	SoV	1.8 ± 1.2	2.7 ± 0.8	-0.9 ± 1.2		-8.4 - 4.1	-9.5 - 3.0	-8.9 - 3.5
		STJ	1.5 ± 1.8	2.8 ± 0.9	-1.4 ± 1.6		-5.1 - 2.7	-6.5 - 1.1	-7.0 - 2.1
		AA	1.4 ± 2.0	2.5 ± 0.7	-1.3 ± 2.0		-5.0 - 3.9	-6.6 - 1.7	-6.2 - 3.4
	CTA I-I Diastole	SoV	-0.3 ± 3.2	0.6 ± 3.2	-3.0 ± 3.2	-2.1 ± 3.2		-4.0 - 1.8	-4.2 - 3.0
		STJ	0.3 ± 1.8	1.6 ± 1.9	-2.6 ± 1.9	-1.2 ± 2.0		-4.0 - 1.1	-4.8 - 2.3
		AA	0.9 ± 2.0	2.0 ± 2.2	-1.8 ± 2.0	-0.6 ± 2.3		-4.6 - 1.1	-4.3 - 2.7
	CTA I-I Systole	SoV	-1.5 ± 3.1	-0.5 ± 3.2	-4.1 ± 3.2	-3.2 ± 3.2	-1.1 ± 1.5		-3.0 - 4.1
		STJ	-1.2 ± 2.0	0.1 ± 1.8	-4.1 ± 2.1	-2.7 ± 1.9	-1.5 ± 1.3		-3.0 - 3.7
		AA	-1.1 ± 2.3	0.1 ± 2.0	-3.8 ± 2.4	-2.4 ± 2.1	-1.8 ± 1.5		-2.2 - 4.4
	MRA I-I	SoV	-0.9 ± 3.2	0.8 ± 3.2	-3.6 ± 3.1	-2.7 ± 3.2	-0.6 ± 1.8	0.6 ± 1.8	
		STJ	-0.9 ± 2.3	0.3 ± 2.2	-3.8 ± 2.3	-2.5 ± 2.3	-1.3 ± 1.8	0.3 ± 1.7	
		AA	-0.0 ± 2.5	1.1 ± 2.3	-2.8 ± 2.7	-1.4 ± 2.4	-0.8 ± 1.8	1.1 ± 1.7	

Mean difference ± standard deviation (colored boxes) and lower limit-upper limit of agreement (non-colored boxes) for comparison between different measurements at the level of the sinus of Valsalva (SoV) sinotubular junction (STJ) and the ascending aorta (AA). Green: mean difference < 1.0 mm. Orange: mean difference 1.0 - 2.0 mm. Red: mean difference ≥ 2.0 mm.

Comparison between cusp-to-commissure and cusp-to-cusp diameter

Between the cusp-to-commissure and the cusp-to-cusp diameter measured on CTA no significant difference was found (mean difference 0.0 ± 1.5 mm, p = 1.00). The maximum difference between these two methods in one patient was 4 mm.

Comparison between end-diastole and mid-systole

Mid-systolic aortic diameters were significantly larger than end-diastolic diameters at nearly all levels (supplemental table 6). Comparison of mid-systolic and end-diastolic aortic diameters demonstrated mean differences from 0.7 ± 2.3 mm up to 1.8 ± 1.5 mm. The standard deviations of mid-systole and end-diastole did not differ significantly at all levels by both 2DE and CTA (Levene's test p>0.05). The aortic length by 2DE was significantly longer during mid-systole (51.1 ± 13.8 mm) compared to end-diastole (45.8 ± 13.2 mm) with a mean difference of 5.3 ± 5.1 mm (p<0.001).

Maximum single-subject difference between all aortic measurements

Distribution of differences by aortic level are displayed in figure 2. The maximum difference was 5.4 ± 2.7 mm for the SoV (maximum 18 mm), 5.1 ± 2.0 mm for the STJ (maximum 11 mm) and 4.8 ± 2.1 mm for the TAA (maximum 11 mm). The maximum difference is a result from both inter-modality differences as from differences between modalities, but was most often explained by the differences between measurements on 2DE (29%) or between 2DE and CTA (38%, supplemental figure 4). Maximum difference showed a moderate positive correlation with the absolute diameter at each level (supplemental figure 5), specifically SoV ($r = 0.42$, $p \leq 0.001$), STJ ($r = 0.41$, $p \leq 0.001$) and TAA ($r = 0.45$, $p \leq 0.001$). Patients with BAV showed a larger maximum difference (SoV $p = 0.001$, STJ $p < 0.001$, TAA $p < 0.001$). After adjustment for aortic diameter, this correlation remained significant for the STJ ($\beta = 0.87$, $p = 0.042$) and TAA ($\beta = 0.95$, $p = 0.027$). Patients in which investigations were performed on different days (n = 26), did not show a larger maximum difference compared to the patients who received all investigations on the same day.

Intra- and interobserver variability

Intra- and interobserver variability for 2DE, CTA and MRA are shown in supplemental tables 7 and 8. There was good agreement with most comparisons. Agreement was least optimal at the SoV.

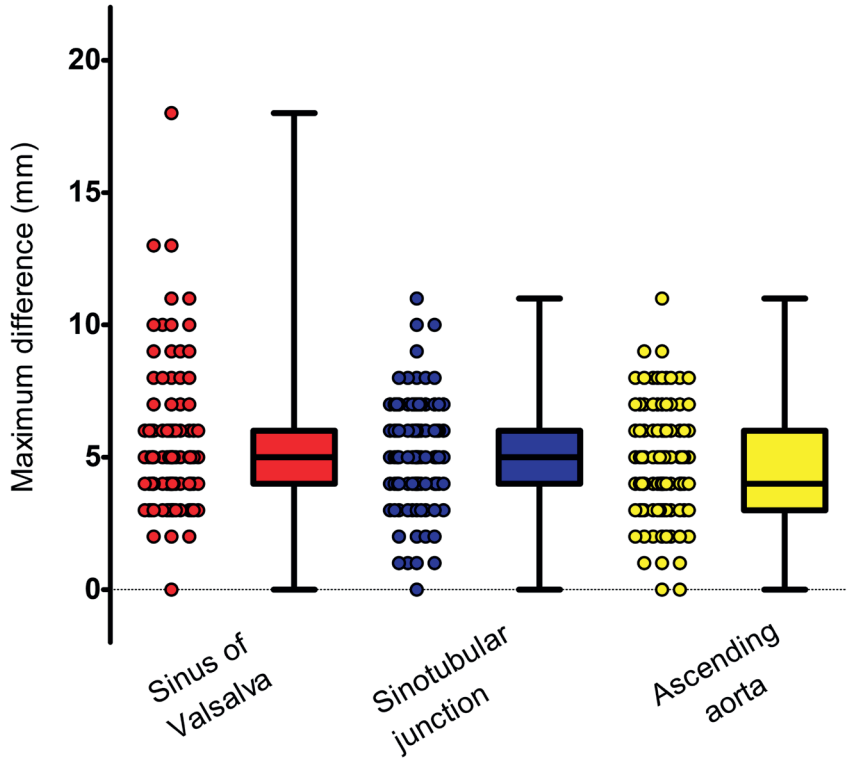


Figure 2. Distribution of maximum differences found between the seven measurements. The maximum difference are plotted for the three different levels: sinus of Valsalva, the sinotubular junction and the ascending aorta.

Discussion

Our study compared measurements of three aortic levels using three imaging modalities (CTA, MRA and 2DE), different edge detections and different cardiac phases. Our goals were to determine agreement and provide guidance on the optimal approach to measure the ascending aorta. We included two groups of patients giving a wide spectrum of aortic dimensions and leaflet configurations. The findings are important for all patients with confirmed or suspected aortic pathology.

Although overall agreement was very good, the maximum difference between two measurements in any given subject was high. Despite measurements performed by experienced investigators, we showed differences up to 18 mm at the SoV, 11 mm at the STJ and 11 mm at the TAA. Given the guideline thresholds for the definition of aortic dilation (>40 mm) and indications for preventive surgery (>55 mm)[6, 23], measured differences of this range are too large to be of use in clinical practice. Intra- and interobserver variability

were good to excellent, so these differences are probably related to the differences in technique and not to differences in individual measurements. Larger maximum differences were found in larger aortas, and most often between the different measurements on 2DE or between 2DE and CTA. Also patients with BAV show larger maximum differences. Since the root is generally well-imaged on all standard 2DE, one would assume that there would be better agreement at this level. Yet lower Pearson correlation coefficients and higher mean differences were observed at the SoV relative to higher up the aorta, suggesting that for patients with dilation at this level CTA or MRA may be preferable for accurate follow-up.

Our data also showed that the L-L edge method by 2DE corresponds best with the I-I edge method by CTA and MRA. Although it seems logical to use the same method for comparison between modalities, it appears that the L-L edge method is preferable for 2DE. This supports current clinical practice, since most physicians who use 2DE already apply the L-L edge method and current reference values are based on this method[16, 17].

An advantage of the current study is that in most subjects imaging with all three modalities was performed on the same day, meaning any variation due to loading conditions should be controlled. In addition, the twenty-six patients who received the investigations on different days, did not show larger maximum differences. Although our data does not contain information about physiological conditions, such as heart rate or blood pressure, we assume this will probably not have affected our results. However, we have to admit that our MRA protocol was not completely optimal. Despite this limited MRA sequences, we found excellent agreement between CTA and MRA, as others have similarly reported(24,29). Also intermodality comparisons between echocardiography and CTA/MRA are previously published using studies in varying aortic patient groups, with some findings that are congruent with our own. By 2DE for example, better agreement with CTA has been shown using L-L techniques rather than I-I [24-30]. Several studies show echo dimensions to be smaller than either MRI or CTA[31, 32] including our previous study[28]. Consistency with other publications adds credibility to the findings overall.

Based on these results, several recommendations can be made to maximize intermodality agreement. Our findings support the necessity of using the same imaging modality and technique in an individual patient to accurately compare serial measurements. CTA or MRA should be performed at least once in addition to 2DE for optimal imaging of the aorta. In patients with good agreement 2DE may be used for serial follow-up. We found no difference between the cusp-to-commissure and cusp-to-cusp methods in CTA. Although another study[26] found a slightly larger diameter of 1.3 mm when using the cusp-to-cusp method, there is currently not enough evidence for the use of one technique over another. Preferably the same technique should be used every time.

Our study is the first to assess the length of aorta visible during 2DE. Echocardiographic images showed on average a 5.3 mm longer segment of the aorta during mid-systole compared to end-diastole. This could be an additional reason to measure the aorta

during systole. Guidelines generally advise end-diastolic measures because of the greater reproducibility (blood pressure is most stable and distension is more plateaued), but this is not confirmed in our and other studies[25, 33]. In addition, physicians prefer to use the largest diameter of the aorta in their decision making. For this reason, the higher values found during mid-systole shown in our together with one other study[34], could be an additional reason to choose systole. Yet since natural history studies have largely been based on 2DE measurements in diastole, some have argued that changing conventions would adversely impact clinical management.

A limitation of our study was the inclusion of both bicuspid and tricuspid valve subjects. Because in some bicuspid aortic valves it was not possible to measure three cusp-to-commissure distances, we also analyzed this group separately at the level of the SoV. This resulted in a small number of subjects for analysis. We did not include healthy participant, which could have made the results even more generalizable. Because we used the protocols of a previous developed cohort study, the imaging modalities showed some limitations, such as the reduced tube current during the last 60% of the R-R interval. Also, the slice thickness of CTA was 1.5 mm, which is slightly thicker than recommended by guidelines[7]. Our MRA protocol was non-ECG-gated, which caused some blurring and limited comparisons to averaged diastole/systole measurements from CTA. Others have shown sharper edge detection and favorable variation for steady-state free precession imaging without contrast[35, 36] than the methods we were able to use here. Despite these potential limitations there was good agreement between CTA and MRA. Also the large maximum single-subject difference was not caused by the limited MRA sequences.

In conclusion, our study supports the L-L edge method by 2DE to provide the best agreement with the I-I edge method by CTA or MRA. This is also recommended by the ASE/EACVI guidelines[7, 8]. CTA or MRA should be performed at least once and follow-up measurements of the aorta should be done at the same level, during the same cardiac phase and using the same technique and modality.

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Supplemental material

Supplemental table 1. Seven different methods for aortic measurement used and compared

Echocardiography	Inner edge-to-inner edge during mid-systole(1)
	Inner edge-to-inner edge during end-diastole(2)
	Leading edge-to-leading edge during mid-systole(3)
	Leading edge-to-leading edge during end-diastole(4)
CTA*	Inner edge-to-inner edge during mid-systole(5)
	Inner edge-to-inner edge during end-diastole(6)
MRA*	Inner edge-to-inner edge(7)

*At the level of the sinus of Valsalva the highest value of the three cusp-to-commissure measurements was used

Supplemental table 2. Aortic measurements with 2DE

	End-diastole			Mid-systole		
	n	Inner edge-to-inner edge	Leading edge-to-leading edge	n	Inner edge-to-inner edge	Leading edge-to-leading edge
Sinus of Valsalva	99	31.3 ± 5.6	34.0 ± 5.8	99	32.3 ± 5.7	35.0 ± 6.0
Sinotubular junction	92	27.2 ± 5.6	30.1 ± 5.7	92	28.6 ± 5.5	31.4 ± 5.8
Ascending aorta	86	30.2 ± 6.7	32.9 ± 7.0	88	31.4 ± 6.8	33.9 ± 6.9

Data are expressed as mean ± SD (mm).

Supplemental table 3. Aortic measurements with computed tomography angiography and magnetic resonance angiography

	Computed tomography angiography				Magnetic resonance angiography	
	n	End-diastole	n	Mid-systole	n	
Sinus of Valsalva						
Tricuspid or BAV Sievers type 1						
RCC-commissure	78	30.0 ± 5.0	81	31.7 ± 4.7	68	31.1 ± 5.2
LCC-commissure	78	32.4 ± 5.2	81	34.0 ± 5.3	68	33.2 ± 5.2
NCC-commissure	78	32.7 ± 5.9	81	33.9 ± 6.1	68	33.8 ± 6.1
BAV valve Sievers type 0						
Maximum diameter	18	36.8 ± 6.6	19	37.7 ± 6.6	16	37.5 ± 6.9
Perpendicular diameter	18	30.2 ± 4.8	19	31.3 ± 5.3	16	30.1 ± 4.9
Sinotubular junction (STJ)	97	29.5 ± 6.2	100	31.0 ± 6.2	88	30.7 ± 6.4
Ascending aorta	97	31.7 ± 7.0	100	33.4 ± 6.8	88	32.5 ± 7.4

RCC-commissure = right coronary cusp to commissure, LCC-commissure= left coronary cusp to commissure, NCC-commissure = non-coronary cusp to commissure. Data are expressed as mean ± SD (mm).

Supplemental table 4. Magnetic resonance angiography vs computed tomography angiography

	n*	Max absolute difference (mm)	Mean difference ± SD (mm)	Pearson coefficient †	Lower limit/Upper limit (mm)	
CTA end-diastole vs MRA						
Sinus of Valsalva						
Tricuspid or BAV Sievers type 1						
RCC-commissure	65	8.0	-0.9 ± 2.3	0.90	-5.4	3.6
LCC-commissure	65	7.0	-0.3 ± 2.2	0.91	-4.6	4.0
NCC-commissure	65	7.0	-0.7 ± 2.0	0.95	-4.6	3.2
BAV Sievers type 0						
Maximum diameter	15	6.0	-0.9 ± 2.2	0.95	-5.2	3.4
Perpendicular diameter	15	8.0	0.0 ± 2.8	0.84	-5.5	5.5
Sinotubular junction	85	8.0	-1.3 ± 1.8	0.96	-4.8	2.2
Ascending aorta	85	7.0	-0.8 ± 1.8	0.97	-4.3	2.7
CTA mid-systole vs MRA						
Sinus of Valsalva						
Tricuspid or BAV Sievers type 1						
RCC-commissure	68	7.0	0.9 ± 2.3	0.90	-3.6	5.4
LCC-commissure	68	5.0	1.2 ± 1.9	0.93	-2.5	4.9
NCC-commissure	68	7.0	0.4 ± 2.0	0.95	-3.5	4.3
BAV Sievers type 0						
Maximum diameter	16	5.0	-0.1 ± 2.2	0.95	-4.4	4.2
Perpendicular diameter	16	7.0	1.2 ± 2.8	0.87	-4.3	6.7
Sinotubular junction	88	8.0	0.3 ± 1.7	0.96	-3.0	3.6
Ascending aorta	88	5.0	1.1 ± 1.7	0.97	-2.2	4.4

RCC-commissure = right coronary cusp to commissure, LCC-commissure= left coronary cusp to commissure, NCC-commissure = non-coronary cusp to commissure. * Not possible to measure the sinus of Valsalva with CTA during end-diastole in 1 subject (artefact) and with MRA in 4 subjects (bad quality). In 12 patients MRA was missing and in 3 patients the CT could not be performed during end-diastole. † All $p < 0.0001$

Supplemental table 5. Echocardiography versus computed tomography angiography in mid-systole

	n	Max difference (mm)	Mean difference ± SD (mm)	Pearson coefficient*	p-value	Lower limit/Upper limit (mm)
Echo leading edge-to-leading edge vs CTA						
Sinus of Valsalva						
Tricuspid or BAV Sievers type 1						
RCC-commissure	81	10	3.1±2.5	0.921	0.000	-1.8/8.0
LCC-commissure	81	10	0.8±3.1	0.861	0.000	-5.3/6.9
NCC-commissure	81	6	1.0±2.3	0.926	0.000	-3.5/5.5
BAV valve Sievers type 0						
Maximum diameter	18	13	-2.2±4.7	0.684	0.002	-11.4/7.0
Perpendicular diameter	18	10	3.8±4.1	0.754	0.000	-4.2/11.8
Sinotubular junction	92	8	0.1±1.8	0.959	0.000	-3.4/3.7
Ascending aorta	88	6	0.1±2.0	0.960	0.000	-3.8/4.0
Echo inner edge-to-inner edge vs CTA						
Sinus of Valsalva						
Tricuspid or BAV Sievers type 1						
RCC-commissure	81	6	0.4±2.2	0.930	0.000	-3.9/4.7
LCC-commissure	81	13	-1.8±3.0	0.857	0.000	-7.7/4.1
NCC-commissure	81	9	-1.7±2.4	0.918	0.000	-6.4/3.0
BAV valve Sievers type 0						
Maximum diameter	18	16	-5.2±4.6	0.691	0.002	-14.2/3.8
Perpendicular diameter	18	6	0.9±3.7	0.794	0.000	-6.4/8.2
Sinotubular junction	92	11	-2.7±1.9	0.954	0.000	-6.5/1.1
Ascending aorta	88	9	-2.4±2.1	0.953	0.000	-6.6/1.7

RCC-commissure=right coronary cusp to commissure, LCC-commissure=left coronary cusp to commissure, NCC-commissure=non-coronary cusp to commissure. *All p<0.001.

Supplemental table 6. Difference between end-diastole and mid-systole by echocardiography and CTA

	n	Max difference (mm)	Mean difference ± SD (mm)	p value paired T-test	Mid-systole ≥ end-diastole (%)	Pearson coefficient*	Limits of agreement (mm)	
							Lower limit	Upper limit
Echocardiography								
Leading edge-to-leading edge								
Sinus of Valsalva	99	5	1.0 ± 1.2	<0.001	90	0.98	-1.4	3.4
Sinotubular junction	92	5	1.3 ± 1.6	<0.001	88	0.96	-1.8	4.5
Ascending aorta	86	5	1.2 ± 1.8	<0.001	87	0.97	-2.3	4.6
Inner edge-to-inner edge								
Sinus of Valsalva	99	5	0.9 ± 1.2	<0.001	89	0.98	-1.4	3.3
Sinotubular junction	92	5	1.4 ± 1.6	<0.001	90	0.96	-1.7	4.6
Ascending aorta	86	6	1.3 ± 2.0	<0.001	86	0.95	-2.7	5.3
Computed tomography angiography								
Sinus of Valsalva								
Tricuspid or BAV Sievers type 1								
RCC-commissure	78	7	1.6 ± 1.7	<0.001	95	0.94	-1.7	4.9
LCC-commissure	78	5	1.5 ± 1.7	<0.001	92	0.95	-1.8	4.8
NCC-commissure	78	4	1.1 ± 1.6	<0.001	89	0.97	-2.0	4.2
BAV valve Sievers type 0								
Maximum diameter	18	7	0.7 ± 2.3	0.200	78	0.94	-3.8	5.2
Perpendicular diameter	18	10	1.1 ± 3.8	0.260	78	0.75	-6.3	8.5
Sinotubular junction	97	5	1.5 ± 1.3	<0.001	96	0.98	-1.1	4.0
Ascending aorta	97	6	1.8 ± 1.5	<0.001	96	0.98	-1.1	4.6

RCC-commissure = right coronary cusp to commissure, LCC-commissure= left coronary cusp to commissure, NCC-commissure = non-coronary cusp to commissure. * Number of measurements missing by the second observer during mid-systole due to insufficient quality of images: 4x Sinus of Valsalva, 2x sinotubular junction, 6x ascending aorta.

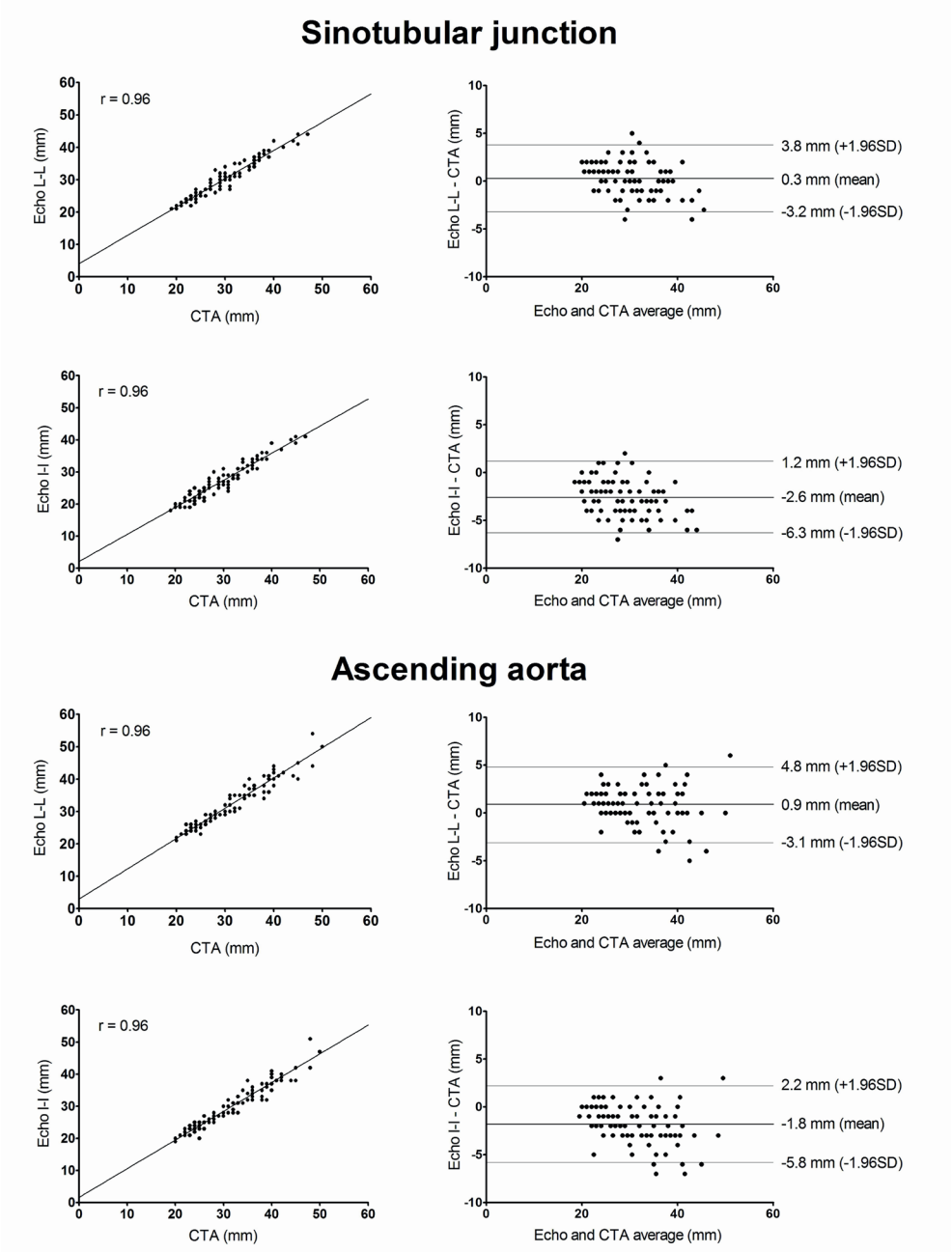
Supplemental table 7. Intra- and interobserver variability in echocardiography

		Inner edge-to-inner edge				Leading edge-to-leading edge			
		End-diastole		Mid-systole		End-diastole		Mid-systole	
	n*	Mean difference ± SD (mm)	ICC	Mean difference ± SD (mm)	ICC	Mean difference ± SD (mm)	ICC	Mean difference ± SD (mm)	ICC
Intraobserver variability									
Sinus of Valsalva	25	-0.3 ± 0.9	0.98	-0.3 ± 0.7	0.99	-0.6 ± 0.9	0.98	-0.5 ± 0.7	0.99
Sinotubular junction	25	0.1 ± 0.9	0.99	0.3 ± 1.0	0.98	-0.0 ± 0.9	0.99	0.1 ± 1.0	0.99
Ascending aorta	25	0.1 ± 1.1	0.99	0.7 ± 1.1	0.98	0.2 ± 0.9	0.99	0.3 ± 1.3	0.98
Interobserver variablity*									
Sinus of Valsalva	25	-0.3 ± 2.0	0.94	0.1 ± 1.4	0.97	-0.2 ± 1.8	0.95	0.3 ± 1.5	0.97
Sinotubular junction	25	-0.4 ± 1.6	0.97	0.6 ± 1.5	0.96	0.1 ± 1.7	0.96	1.1 ± 1.5	0.96
Ascending aorta	25	-0.5 ± 2.0	0.97	0.3 ± 1.5	0.98	0.3 ± 2.0	0.96	1.2 ± 1.7	0.97

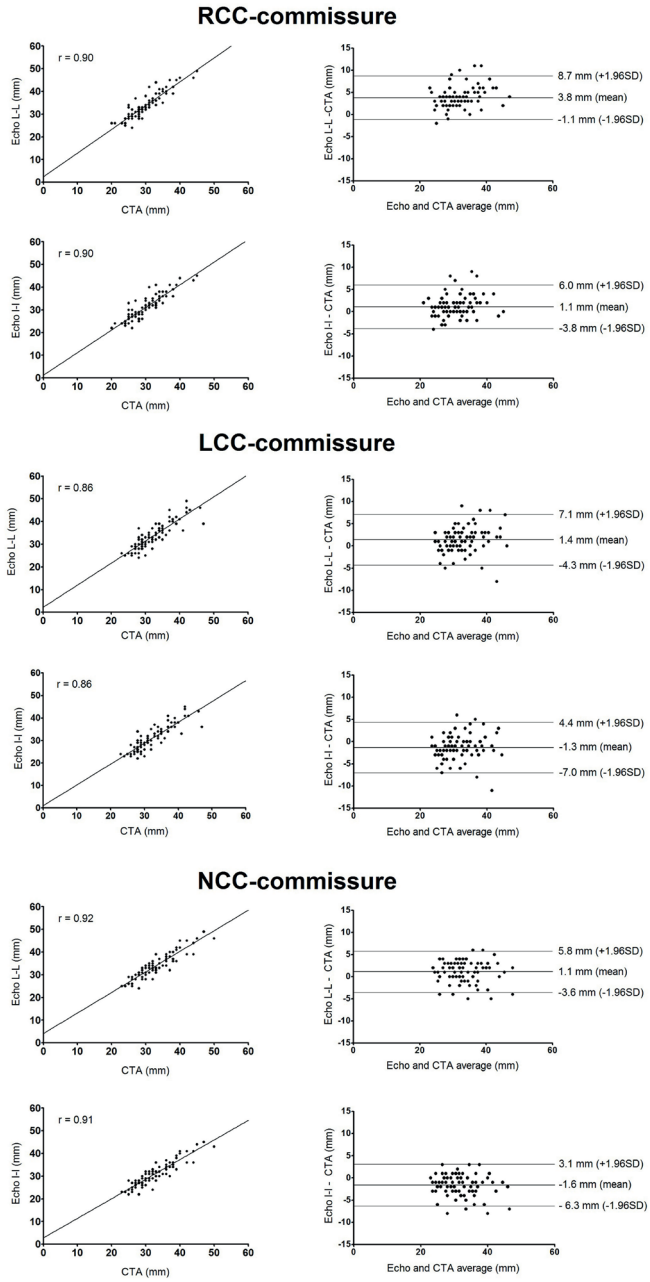
Supplemental table 8. Intra- and interobserver variability in computed tomography angiography and magnetic resonance angiography

		Computed tomograhpy angiography				Magnetic resonance angiography	
		End-diastole		Mid-systole			
	n	Mean difference ± SD (mm)	ICC	Mean difference ± SD (mm)	ICC	Mean difference ± SD (mm)	ICC
Intraobserver variability							
Sinus of Valsalva							
Tricuspid or BAV Sievers type 1							
RCC-commissure	20	-0.1 ± 0.8	0.99	-0.5 ± 0.9	0.98	0.4 ± 1.8	0.92
LCC-commissure	20	-0.1 ± 1.1	0.97	-0.3 ± 0.8	0.99	-0.1 ± 1.4	0.96
NCC-commissure	20	-0.2 ± 1.0	0.99	-0.2 ± 0.6	1.00	0.7 ± 1.6	0.96
BAV valve Sievers type 0							
Maximum diameter	5	0.0 ± 0.0	1.00	0.2 ± 1.1	0.98	0.6 ± 0.9	0.99
Perpendicular diameter	5	-0.6 ± 1.1	0.98	0.8 ± 0.8	0.99	0.8 ± 1.1	0.97
Sinotubular junction	25	0.0 ± 0.7	1.00	0.2 ± 0.8	0.99	0.4 ± 1.4	0.98
Ascending aorta	25	-0.1 ± 0.4	1.00	-0.2 ± 0.8	0.99	0.1 ± 1.2	0.99
Interobserver variability							
Sinus of Valsalva							
Tricuspid or BAV Sievers type 1							
RCC-commissure	20	0.6 ± 1.1	0.97	0.1 ± 1.1	0.97	0.2 ± 2.6	0.85
LCC-commissure	20	1.0 ± 1.3	0.94	0.5 ± 1.2	0.96	0.2 ± 1.7	0.93
NCC-commissure	20	0.5 ± 1.4	0.97	0.6 ± 1.0	0.98	0.6 ± 1.6	0.97
BAV valve Sievers type 0							
Maximum diameter	5	0.8 ± 0.8	0.98	0.8 ± 1.5	0.96	0.2 ± 1.6	0.97
Perpendicular diameter	5	1.2 ± 1.9	0.92	2.6 ± 2.4	0.85	4.0 ± 2.3	0.63
Sinotubular junction	25	0.4 ± 0.8	0.99	0.7 ± 1.0	0.99	0.6 ± 1.6	0.97
Ascending aorta	25	0.4 ± 0.9	0.99	0.2 ± 1.1	0.99	0.3 ± 1.4	0.98

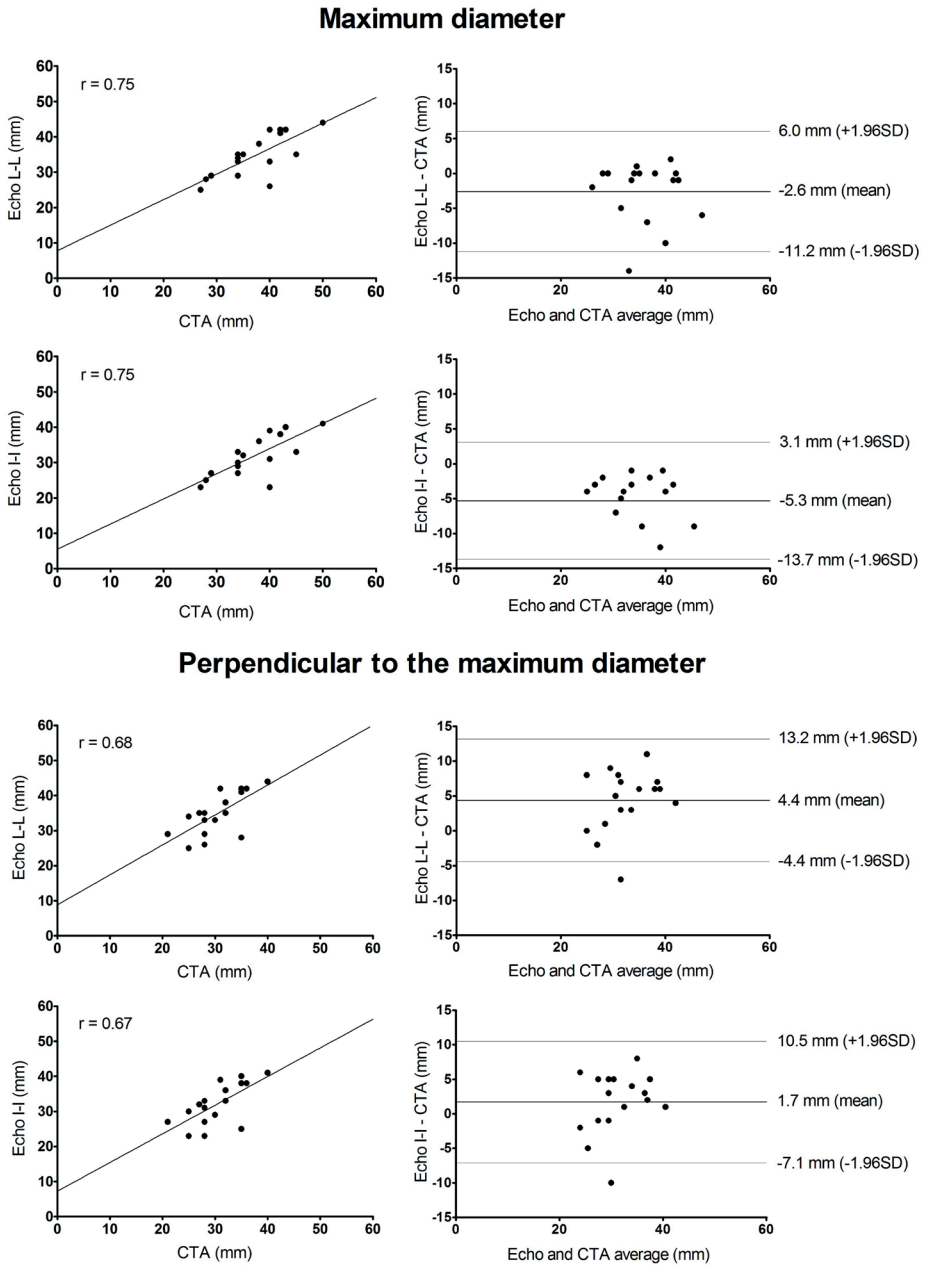
RCC-commissure = right coronary cusp to commissure, LCC-commissure= left coronary cusp to commissure, NCC-commissure = non-coronary cusp to commissure.



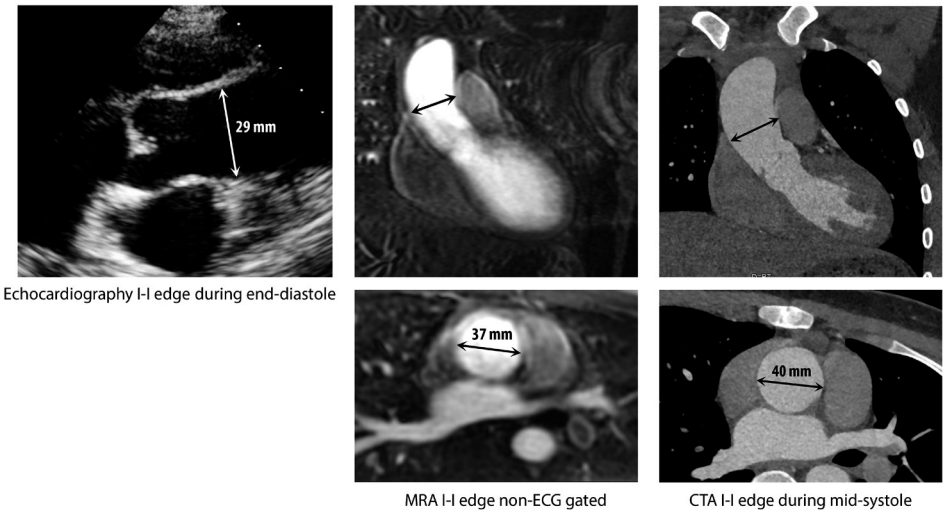
Supplemental figure 1. Agreement between echocardiography and CTA (STJ and ascending aorta). Linear regression lines and Bland-Altman plots for echocardiography and computed tomography angiography at the level of the sinotubular junction and the ascending aorta using the I-I edge method and L-L edge method during end-diastole.



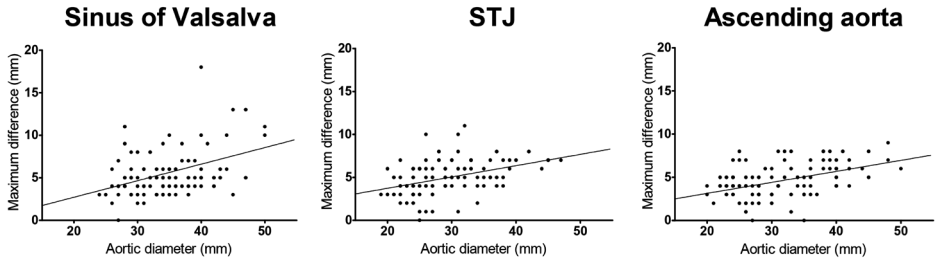
Supplemental figure 2. Agreement between echocardiography and CTA for tricuspid or bicuspid type 1 aortic valves (sinus of Valsalva). Linear regression and Bland-Altman plots for echocardiography and computed tomography angiography at the level the sinus of Valsalva for tricuspid or bicuspid type 1 aortic valves using the L-L edge method and I-I edge method during end-diastole. RCC-commissure = right coronary cusp to commissure, LCC-commissure= left coronary cusp to commissure, NCC-commissure = non-coronary cusp to commissure.



Supplemental figure 3. Agreement between echocardiography and CTA for bicuspid type 0 aortic valves (sinus of Valsalva). Linear regression and Bland-Altman plots for echocardiography and computed tomography angiography at the level of the sinus of Valsalva for bicuspid type 0 aortic valves using the I-I edge method and L-L edge method during end-diastole. One data point is outside the axis limits in the Bland-Altman figure of the perpendicular to the maximum diameter with use of the I-I edge (X = 31.50, Y = -17.00).

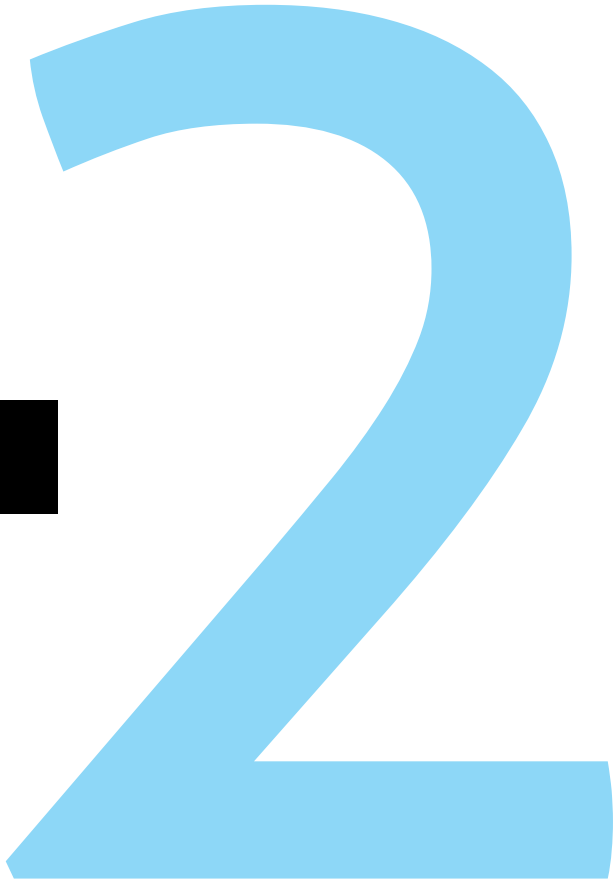


Supplemental figure 4. Maximum differences in the diameter of the ascending aorta (1cm above the STJ) in one patient (difference 11mm). Aortic diameter measured with CTA during mid-systole was 40mm and measured with MRA 37mm. The aortic diameter measured with echocardiography during end-diastole and with the inner edge-to-inner edge method was 29mm.



Supplemental figure 5. Scatter plot of maximum differences (found between the seven different measurements) and the absolute diameter measured with end-diastolic diameter of CTA. The regression line is plotted for the three different levels: sinus of Valsalva, the sinotubular junction and the ascending aorta.

CHAPTER 2



Screening for thoracic aortic pathology: Clinical practice in a single tertiary center

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Abstract

Objective

The aim is to present current clinical practice of thoracic aorta screening in a tertiary referral center. We identified how often imaging techniques were used for screening and established the value of transthoracic echocardiography (TTE) in comparison with computed tomography (CT) to detect aortic dilation. We also investigated which additional abnormalities of the heart, aorta or smaller arteries were discovered.

Design

All patients ≥15 years who visited our tertiary center in 2012-2016 for first thoracic aortic screening were retrospectively included. Diameters of the sinus of Valsalva (SoV) and maximum ascending aorta (AA) were compared between TTE and CT. The sensitivity and specificity of TTE to detect aortic dilation (≥40 mm) was assessed with CT as reference standard. Intracardiac abnormalities found with TTE and arterial abnormalities found with CT were identified.

Results

In total 349 patients (155 men, age 41 ± 15 years, 10% genetic mutation) were included. Screening was performed with TTE only in 35% and with TTE and CT in 65%. Patients who underwent TTE only were younger, had less often hypertension and less often a family history of aortic pathology. Although there was a good correlation between TTE and CT, the diameters measured with TTE were typically lower (SoV −1.0, 95%CI −6.6 to 4.7 and AA −0.4, 95%CI −6.5 to 5.8). Sensitivity of TTE for detecting aortic dilation was 61% (SoV) and 57% (AA) and specificity was 96% (SoV) and 100% (AA). Valve abnormalities, ventricular dilation or reduced ventricular function was found with TTE in 26 patients (7%). In 47 patients (13%) ascending aortic dilation was diagnosed and in 10 patients (4%) relevant peripheral arterial abnormalities were identified using CT.

Conclusions

Most often patients received both TTE and CT (65%). Since TTE showed a low sensitivity to detect aortic dilation, CT imaging is advised at least once in patients referred for thoracic aortic screening.

Introduction

Thoracic aortic aneurysm (TAA) is typically clinically silent. Very often the first presentation is an acute aortic dissection or rupture with high rates of mortality[1]. The estimated prevalence of a TAA in the general population is 0.3%[2], but there can be a genetic predisposition. Screening of patients at risk for thoracic aortic dilation (eg, family members, mutation carriers) is important to timely detect dilation and allow preventive intervention before dissection or rupture will occur. Persons who are referred for screening can undergo several possible imaging examinations to assess the thoracic aorta. Currently, transthoracic echocardiography (TTE), computed tomography (CT) and magnetic resonance imaging (MRI) are used for diagnostic imaging of the aorta. TTE excels in temporal resolution, is harmless, cheap and can be used in any clinical setting, but it will not show the entire thoracic aorta. Especially, the upper part of the ascending aorta and the arch may be hard to visualize. The primary strength of CT is the high spatial resolution, but the drawback is the radiation exposure and, for optimal visualization, need for the use of intravenous iodinated contrast. MRI falls between these extremes: it images the entire thoracic aorta, requires no radiation and can be performed without contrast administration. Current guidelines[3-5] advise to offer screening to first-degree relatives of patients with a TAA, especially in case of a bicuspid aortic valve or Marfan syndrome. However, no specific imaging modality is advised for screening of the thoracic aorta, in contrast to the existing clear guidelines for screening for abdominal aortic aneurysms which favor ultrasound[6, 7]. The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (AECI)[4] choose TTE as first choice, but the European Society of Cardiology (ESC)[3] prefers screening for aneurysms not only in the thoracic aorta, but also throughout the arterial tree (including cerebral arteries) with CT or MRI. The question remains whether the more expensive and potentially harmful CT-examinations should be used and are necessary in all patients referred for screening. A relatively new concept which is entering clinical care is the "Choosing wisely" campaign initiated by the American Board of Internal Medicine Foundation (ABIM). The goal is to provide evidence-based care which is free from harm and truly necessary. Overuse of low-value services is a significant problem[8, 9]. To choose an appropriate imaging approach for screening in patients at risk for aortic pathology, the advantages and disadvantages of each imaging modality must be carefully considered. In our center we use predominantly CT and TTE. The exact value of these examinations in screening for TAAs is not well known. Expected associated abnormalities, both cardiac and in the great arteries, may guide the choice of imaging modality. However, the prevalence of associated cardiac abnormalities and aneurysms in the great vessels has not been studied previously. The aim of this study was to describe current clinical practice of screening for thoracic aortic pathology in a tertiary center. We studied which imaging techniques were used for screening and aimed to establish the accuracy of TTE in comparison with CT to detect aortic dilation in patients who underwent both examinations. We also investigated which additional abnormalities of the heart, aorta or other great vessels were discovered.

Methods

All consecutive adults scheduled for screening of thoracic aortic disease in a specialized tertiary cardiology outpatient clinic between 2012 and 2016 were retrospectively included in this study. Patients are referred for aortic screening or follow-up and treatment of already existing (syndromes with) aortic pathology. Patients underwent no previous imaging investigations for screening of the thoracic aorta elsewhere. Inclusion criteria for our study were: (1) age ≥ 15 years, (2) first visit to the outpatient clinic of thoracic aortic disease and (3) screening as reason of referral. The decision which imaging modality was indicated for patients was based on clinical experience and preference of the treating physician (JR, JC or RM). Demographic, clinical and family data together with information about genetic testing[10] were obtained from the electronic patient files. Hypertension, hypercholesterolemia and diabetes mellitus were defined as current use of medication for that particular disease. The study complied with the Declaration of Helsinki and was approved by the medical ethical committee of the Erasmus Medical Center. Informed consent was not obliged.

Aortic diameters

On CT, the aortic diameters were measured following a standard protocol at the level of the sinus of Valsalva (SoV), ascending aorta, aortic arch and descending aorta. Both the ascending aorta (AA) and descending aorta (DA) were measured at the maximum diameter (mostly at the level of the left atrium or pulmonary bifurcation). On TTE, the diameters of the SoV and AA (largest diameter) were measured and compared with CT measurements.

Transthoracic echocardiography

Standard two-dimensional TTE was performed by experienced sonographers, following a standard protocol. All studies were acquired using harmonic imaging on an iE33 or EPIQ7 ultrasound system (Philips Medical Systems, Best, The Netherlands) equipped with an x5-1 matrix-array transducer (composed of 3040 elements operating at 1-5 MHz). The aorta was measured in the standard parasternal long-axis view and acquisition of the long-axis view performed from a different intercostal space or at a different distances from the sternal border to improve the visualization of the ascending aorta[11]. The measurements were performed from leading edge-to-leading edge during diastole. The presence of a bicuspid aortic valve was assessed on TTE and classified as yes, no or unclear. Aortic stenosis was defined as peak aortic velocity ≥2.5 m/s. Aortic regurgitation was graded by sonographers as mild, moderate or severe according to the EAE/ASE guidelines[12]. Septal wall thickness of ≥13 mm was identified as ventricular hypertrophy and a left ventricular diameter of ≥60 mm was identified as ventricular dilation. The transthoracic echocardiogram was analyzed using Curad off-line software (version 3.5.3.0, Wijk bij Duurstede, The Netherlands).

Computed tomography

Contrast-enhanced CT scans of the entire aorta were obtained with standard acquisition protocols on a variety of scanners including both the thoracic and abdominal aorta until the femoral artery. Overall 202/226 (89%) of the scans were performed on a second or third generation dual source scanner (Flash, Drive and Force, Siemens Healthineers, Elrangen, Germany) most commonly with a high-pitch acquisition in 183/226 (81%) scans. For 193/226, the phase of the RR interval was available and ranged between 20% and 70%. The aortic diameters were measured using the double-oblique technique perpendicular to the vessel axis and the SoV was measured as the cusp-to-commissure distance, because this is the method most often used[4]. Arterial anomalies were divided into aneurysm, stenosis and dissection located in the thorax or abdomen. We used the following definitions for clinical relevant aneurysms: aortic root ≥40 mm[13], ascending and descending aorta ≥40 mm[13], pulmonary artery ≥30 mm[14], abdominal aorta ≥30 mm[15], splenic, celiac, hepatic, gastroduodenal, pancreaticoduodenal, gastric or mesenteric arteries ≥20 mm[16,17], iliac artery ≥25 mm[18] and femoral artery ≥20 mm[19]. In addition, congenital abnormalities such as a partial anomalous pulmonary venous return (PAPVR) were determined. Variants in human anatomy like aberrant subclavian artery (lusoria artery) were also identified.

Statistical methods

All data are presented as mean with standard deviation when normally distributed, and in case of non-normal distribution as medians with interquartile ranges. Data distribution was checked using histograms and the Shapiro-Wilk test. Comparison of normally distributed continuous variables was done using the Student's t-test or, in case of a skewed distribution, the Mann-Whitney test. Categorical variables are presented as frequencies with percentages. Comparison of categorical variables was done using the chi-square test and in case of an expected count <5 in one of the cells of the crosstable the Fisher's exact test was used. Differences between the diameter of the aorta at TTE and CT were tested with a paired t-test and visualized with Bland-Altman plots[20]. The limits of agreement were calculated using the mean and standard deviation of the difference. Multivariable linear regression analysis was used to identify associations between aortic diameter and age, sex or aortic diameter on CT images. The sensitivity and specificity of TTE in diagnosing an aortic dilation (≥40 mm) of the SoV or AA was calculated with CT as reference method. The IBM SPSS statistics 21.0 software (IBM, Armonk, New York) was used for data analysis. All statistical tests were two-sided and a *P* value below 0.05 was considered significant.

Results

Study population

A total of 437 patients visited the outpatient clinic of thoracic aortic disease for the first time. Their age ranged from 15 to 82 years. In 81% (354/437) of all patients, the indication

was screening. The other patients were referred because of an incidentally detected aortic enlargement (n = 72) or for follow-up of aortic disease discovered elsewhere (n = 11). Screening patients were divided in two groups: patients with only TTE and patients with both TTE and CT in our center. Due to limited numbers, patients who underwent only a CT (n = 4) or MRI (n = 1) were excluded.

The 349 (44% male, mean age 41 ± 15 years) remaining patients form the basis of this study. They were referred by the clinical geneticist (67%), general practitioner (24%), another specialized physician (7%) or an external cardiologist (2%). The reasons for screening were family history of thoracic aortic pathology in 208 patients (60%), family history of aneurysms or dissections in other vessels than the thoracic aorta in 27 patients (8%), family history of sudden cardiac death in 12 patients (3%), family history with a bicuspid aortic valve in 22 patients (6%), suspicion of a syndrome associated with aortic pathology in 60 patients (17%) and a newly diagnosed genetic mutation associated with aortic pathology in 20 patients (6%).

Of the 349 patients, 123 (35%) patients underwent only TTE during their visit and 226 (65%) patients underwent both TTE and CT imaging. In four patients CT imaging was performed without contrast. Of all patients with CT imaging, the majority (95%) underwent CT imaging of both thorax and abdomen, while 12 patients had CT imaging of the thorax only. The baseline characteristics are shown in table 1. In general, patients who had TTE only were younger, had lower blood pressure, less hypertension and less family members with an aortic aneurysm or dissection. In 108 (31%) of the patients genetic testing was performed, equally divided between the 2 patient groups. In total, 35 patients had a genetic mutation of which most were found in the FBN1 gene (n = 5), SMAD3 gene (n = 6) and TGFB3 gene (n = 5). These genetic mutations were either the reason for screening or found as a result of screening. In 132 of the 349 patients (38%) the family history was negative, 107 patients (31%) had a first-degree or second-degree family member with a TAA, 57 patients (16%) had a first-degree or second-degree family member with a thoracic aortic dissection and 53 patients (15%) had both aneurysm and dissection in their family history. As expected based on guidelines and clinical experience of physicians, patients with a family history of aortic aneurysm or dissection underwent a CT more often than patients without such a family history (69% vs 50%, $p < 0.001$).

Table 1. Baseline characteristics screening patients

	Total (n=349)	Patients with echocardiography alone (n=123)	Patients with echocardiography and CT imaging (n=226)	p-value
Age (y)	41 ± 15	32 ± 12	46 ± 15	0.000
Female	194 (56%)	71 (58%)	123 (54%)	0.553
Height (cm)	176 ± 11	178 ± 12	175 ± 11	0.034
Weight (kg)	77 ± 17	73 ± 18	79 ± 16	0.009
Systolic blood pressure (mmHg)	130 ±19	125 ± 16	133± 19	0.000
Diastolic blood pressure (mmHg)	81 ± 12	78 ± 11	83 ± 13	0.001
Hypertension	44 (13%)	4 (3%)	40 (18%)	0.000*
Hyperchlesterolemia	7 (2%)	0 (0%)	7 (3%)	0.055*
Diabetes mellitus type II	7 (2%)	2 (2%)	5 (2%)	1.000*
Betablockers	25 (7%)	5 (4%)	20 (9%)	0.098
Diuretics	27 (8%)	2 (2%)	25 (11%)	0.001*
ACE inhibitors	12 (3%)	0 (0%)	12 (5%)	0.010*
Angiotensine receptor blockers	19 (5%)	2 (2%)	17 (8%)	0.024*
Cholesterol-lowering medication	27 (8%)	3 (2%)	24 (11%)	0.006*
Antiplatelet agents	15 (4%)	0 (0%)	15 (7%)	0.002*
Anticoagulants	6 (2%)	2 (2%)	4 (2%)	1.000*
Known genetic mutation	35 (10%)	12 (10%)	23 (10%)	0.900
Familial history of aortic aneurysm	160 (46%)	46 (37%)	114 (50%)	0.019
Familial history of aortic dissection	110 (32%)	23 (19%)	87 (39%)	0.000

Values are given in mean ± SD or n (%). * Fishers's Exact Test

Aortic diameter

In total, in 47 patients (13%) the proximal aorta (SoV or AA) was ≥40 mm on TTE or CT and in 2 patients (0.6%) it was ≥50 mm. In patients who underwent both TTE and CT, the diameter of the SoV was significantly larger on CT compared to TTE (33.9 mm vs 32.9 mm, p <0.001). However, the difference at the level of the AA was not significantly different (32.4 mm vs 32.0 mm, p = 0.089). Figure 1 shows Bland-Altman plots of measurements of the aorta with TTE and CT both at the level of the SoV and the AA. The diameter at the level of the SoV could not be measured with echo in one patient due to insufficient image quality and with CT in four patients due to the absence of contrast. The ascending aorta could not be imaged with echo in nine cases because of unfavorable aortic anatomy in the chest or high BMI. At SoV level, the difference between TTE and CT was ≥5 mm in 14% with a maximum difference of 8 mm, while at AA level a difference of ≥5 mm was found in 14% with a maximum difference of 11 mm. With multiple linear regression analysis, age was positively associated with the difference in diameter between CT and echocardiography for both the level of the SoV (p = 0.004) and ascending aorta (p = 0.006). However, for both levels the absolute aortic diameter was negatively associated

with the difference in diameter between CT and echocardiography (p <0.001). This implies that with a smaller aortic diameter, we are more likely to find a large difference between the two modalities. For the ascending aorta, male gender was also associated with a larger difference between the two modalities (p = 0.020). Sensitivity of TTE for detecting aortic dilation was 61% (SoV) and 57% (AA) and specificity was 96% (SoV) and 100% (AA).

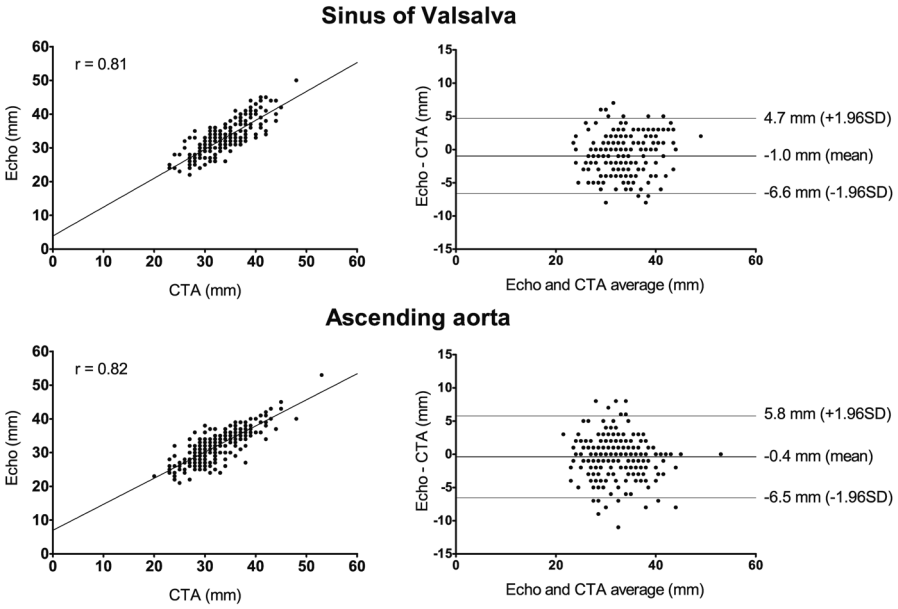


Figure 1. Bland-Altman plots of difference between echocardiography and computer tomography at the level of the sinus of Valsalva and the ascending aorta
Bland-Altman plots comparing aortic measurements performed using the leading-edge-to-leading-edge with echo and inner-edge-to-inner-edge with CT at the level of the sinus of Valsalva (mean difference -1.0 mm, n=217) and ascending aorta (mean difference -0.4 mm, n=221).

Additional findings on echocardiography and computed tomography

In table 2 the outcomes of TTE and CT are summarized. In eight patients (2%) a BAV was found. Valve abnormalities including BAV (5%), ventricular hypertrophy (1%) and ventricular dilation (1%) were relatively rare.

Table 2. Imaging findings of echocardiography and computed tomography in screening patients (n=349)

	Echocardiography (n=349)	Computed tomography (n=226)
Bicuspid aortic valve	8 (2%)*	-
Aortic stenosis (>2.5 m/s)	2 (1%)	-
Aortic regurgitation (>mild)	2 (1%)	-
Other valve disease (>mild)	6 (2%)	-
Ventricular hypertrophy (septal wall ≥13mm)	5 (1%)	-
Ventricular dilation (LV diameter ≥60mm)	4 (1%)	-
Diameter sinus of Valsalva (mm)	32 ± 6	33 ± 6
Diameter ascending aorta (mm)	29 ± 8	32 ± 5
Diameter aortic arch (mm)	-	26 ± 4
Diameter descending aorta (mm)	-	23 ± 4
Any arterial anomaly or variant	-	35 (16%)
Clinical relevant arterial anomaly	-	10 (4%)

Values are given in mean ± SD or n (%).
* In addition to this eight patients, we found six patients with unclear aortic valve morphology because of insufficient image quality of whom two have a high suspicion of a bicuspid aortic valve.

In the 226 patients who had a CT scan, 38 arterial abnormalities were described by radiologists in 35 patients (15%) in addition to aortic aneurysms of the SoV or AA (figure 2). Twenty-one of these arterial abnormalities were found in the abdomen (60%). Including only clinically relevant aneurysms, we found 11 abnormalities in 10 patients (4% of all patients): dissection of the renal artery in one patient, dilation of the pulmonary artery (≥30 mm) in six patients, dilation of the aortic arch in one patient, dilation of the abdominal aorta (32 mm) in one patient and one patient had a dilation of the femoral artery (36 mm) as well as a dilation of the abdominal aorta (32 mm). This last patient needed preventive surgery for the femoral artery aneurysm. Of the 10 patients with clinically relevant peripheral arterial abnormalities, six patients also showed a SoV or AA of ≥40 mm. All patients with clinically relevant abnormalities are shown in table 3. The presence of an aneurysm of the proximal aorta was associated with vascular abnormalities, both "all abnormalities" ($p = 0.004$) and "clinically relevant abnormalities" ($p = 0.013$). The presence of a known genetic mutation or family history of aortic disease was not associated with vascular abnormalities ($p = 0.138$ and $p = 0.259$ respectively).

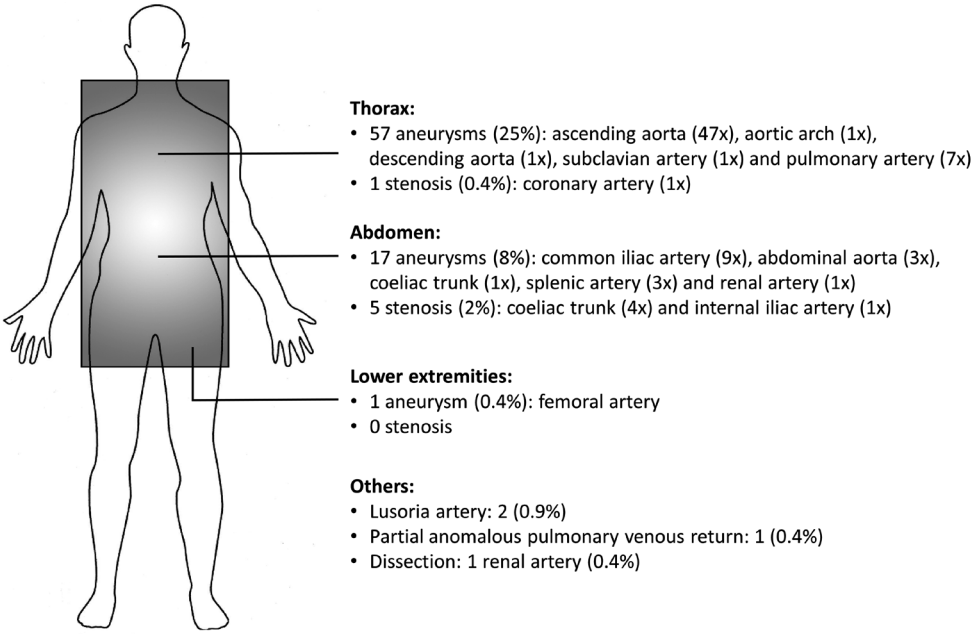


Figure 2. Vascular abnormalities or variants found with CT
Vascular abnormalities or variants found in scanned area (grey rectangle) with CT while patients came for thoracic aortic pathology screening. Thorax alone was scanned in 12 patients and in 214 patients both thorax and abdomen were scanned. When we only include the clinical relevant aneurysms, we found 11 abnormalities (4% of all patients).

Table 3. Ten patients with a clinically relevant arterial abnormality diagnosed with CT

Nr	Age, gender	Aortic diameters CT (mm)				Genetic mutation	Familial aneurysm	Familial dissection	Arterial abnomality
		SoV	AA	Arch	DA				
1	28, M	27	24	20	17	COL3a1	0	0	Dissection renal artery
2	58, F	30	30	27	23	No	1	0	Dilation pulmonary artery (32mm)
3	66, F	42	43	39	24	No	1	0	Dilation pulmonary artery (45mm)
4	69, M	35	34	31	26	SMAD 3	0	0	Dilation pulmonary artery (33mm)
5	48, M	44	42	30	28	No	1	1	Dilation pulmonary artery (35mm)
6	60, M	39	42	27	29	No	1	1	Dilation pulmonary artery (40mm)
7	75, F	*	48	33	29	No	1	1	Dilation pulmonary artery (41mm)
8	63, F	33	38	40	27	No	1	1	Dilation aortic arch (40mm)
9	62, M	32	34	28	28	No	0	0	Dilation abdominal aorta (32mm)
10	62, M	44	45	39	29	No	1	0	Dilation femoral artery (36mm) and abdominal aorta (32mm)

SoV = sinus of Valsalva, AA= ascending aorta, DA = descending aorta.
*Sinus of Valsalva could not be measured due to non-enhanced CT scan.

Discussion

In our tertiary center, the majority of the patients referred for aortic screening received both TTE and CT (65%). In our cohort, dilation (≥40 mm) of the aortic root or ascending aorta was found in 13%, intracardiac abnormalities were detected in 7% and relevant other arterial abnormalities in 4%.

Accuracy of TTE and CT to establish aortic dilation

The mean difference of the proximal aortic diameter measured with TTE vs CT was small, but large differences were found in individual patients with a difference of up to 8 mm for the SoV and up to 11 mm at the level of the ascending aorta. Although the specificity of TTE for detecting aortic dilation was good, the sensitivity was only 55-60%, which implies that by imaging the ascending aorta in one plane only on 2D TTE, the true maximal diameter may easily be missed. This is in agreement with previous literature[21, 22]. One previous study looked at the ability of TTE to identify an aneurysm of the aortic root or ascending aorta in patients with a bicuspid aortic valve[23]. In this paper, TTE sensitivity to detect aortic dilation (defined as SoV ≥35 mm and AA ≥38 mm) was 75% for the SoV and 47% for the AA with MRI as reference standard. The authors concluded that TTE often misses aortic dilation in patients with a bicuspid aortic valve. Our study confirms this in a more mixed population of patients referred for thoracic aortic screening.

We used the cusp-to-commissure method, because by CT or MRI the aortic root is measured most often between the inner edges from commissure to opposite sinus[4]. There is still no consensus in the guidelines how to measure the aortic root at the level of the SoV. One study showed that the cusp-to-commissure diameter is best comparable with echocardiography[24], while others show that the RCC-NCC cusp-to-cusp diameter show the best agreement with echocardiography[25]. When performing echocardiography the exact orientation of the measurement at the level of the SoV relative to the 3 sinuses highly depends on the orientation of the echo probe during the examination and the orientation of the aortic root itself in that individual. Therefore often we don't know if the ultrasound image cuts through the cusp or commissure and this explains the discrepancies in aortic measurements between echo and CT[26].

In patients at risk for thoracic aortic pathology, the aim is to accurately identify aortic dilation and therefore an accurate and reliable imaging modality is warranted. In our opinion, CT or MRI meets these requirements better than TTE and should be used at least once for screening in all patients at risk for thoracic aortic aneurysm and/or dissection. Particularly in subjects with a more extended family history of aneurysms or dissection in the more distal thoracic aorta, which is not visible with TTE, advanced imaging such as CT or MRI should be considered.

Should TTE be a part of routine screening?

An argument in favor of using TTE as screening tool would be the ability to detect intracardiac abnormalities, including valve pathology and ventricular hypertrophy or dilation. In our study, concomitant cardiac abnormalities were rarely found on TTE. A bicuspid aortic valve was present in 2% of the patients, which is comparable to the general population[27, 28]. In our specific group of patients, at risk for thoracic aortic pathology, we expected it to be higher. The prevalence of aortic valve regurgitation in our group was also comparable to the prevalence found in the Framingham Heart Study (0-2.3% depending on age)[29]. Aortic stenosis was found even less often compared to data from a systematic review on aortic stenosis[30]. Other new findings were not discovered. In our view, the low frequency of concomitant intracardiac findings is not a valid argument to choose TTE as a primary screening tool.

Additional vascular abnormalities on CT

In patients referred for screening who underwent CT, we found peripheral arterial pathology in 15%, predominantly located in the abdomen. Eleven of these pathologies (4% of all patients) were clinically relevant. We showed that aneurysms of the SoV and/or ascending aorta are associated with abnormalities in other intrathoracic, abdominal or more peripheral arteries. This is well known for patients with *SMAD-3* or *TGB3* mutation. In patients with abdominal aortic aneurysms, femoral or popliteal aneurysm are reported in up to 14%[31]. However, data on the co-existence of peripheral pathology in the case of thoracic aortic aneurysms are scarce[3]. Of course, the clinical decision to perform CT or not in these patients implies a selection bias.

Which imaging technique in which patient?

Every patient referred for aortic screening should have an accurate measurement of aortic dimensions by CT or MRI. It has already been shown that the measurement of the thoracic aortic diameter is comparable between CT and MRI[32]. Based on further family history or specific genetic mutation, an individual estimation should be made on the risk of intracardiac or peripheral vascular pathology. This should guide the decision to add TTE and choose between CT and MRI. In our center we prefer using CT imaging instead of MRI, because the high spatial resolution allows simultaneous imaging of the smaller thoraco-abdominal arteries. Because connective tissue diseases like *SMAD3*[33] and Loeys-Dietz are recognized increasingly, imaging of both aorta and peripheral arteries is more frequently required. Indeed in current times the radiation dose is typically low and in our opinion the clinical relevance of correctly diagnosing aortic pathology warrants optimal imaging. Of course MRI has the great advantage of not exposing the patient to radiation at all and this technique should be used in children when possible. The 11 clinically relevant arterial abnormalities listed in table 3 are located in the larger arteries and would likely have been picked up by an MRI vasculopathy study, which would be an argument for MRI.

In patients where aortic dilatation is diagnosed follow-up is needed to identify further growth of the aorta. In patients where echocardiography is able to visualize the aortic root and ascending aorta sufficiently, echocardiography can be used as imaging tool during follow-up. However, when TTE cannot be used, MRI is preferred, especially in younger patients. Preferably, follow-up should be performed with the same modality using the same technique. When the aortic diameter approaches the thresholds for preventive intervention, more accurate imaging of the aorta using CT (or MRI) is indicated to identify the exact aortic diameter and aortic anatomy before intervention is considered.

In conclusion, we found that CT performs better than TTE in screening for aortic dilation. We advise to use CT (or MRI) for screening in all patients at risk for thoracic aortic disease. Extra-aortic arterial abnormalities were found relatively often with CT, increasing the diagnostic value of CT as an imaging tool. Intracardiac abnormalities were not common in patients who were sent for screening of thoracic aortic pathology. Although TTE is a suboptimal imaging technique for aortic screening, it may be used to detect intra-cardiac abnormalities in selected cases such as a family history of BAV. For ongoing surveillance of patients with aortic dilatation, further research is needed to determine the best imaging strategy for ongoing surveillance.

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CHAPTER 3



Variability in echocardiographic ascending aortic diameters due to image acquisition by different sonographers

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Brief communication

Aortic dilatation carries an increased risk of aortic dissection with high mortality and morbidity rates[1]. In order to diagnose aortic dilatation and determine the need for preventive intervention, reliable measurement of the aortic diameter is crucial[2, 3]. The ascending aortic (AA) diameter can be assessed with different imaging modalities: computed tomography (CT), cardiovascular magnetic resonance imaging (CMR) and echocardiography. Because echocardiographic images are handmade by the sonographer, echocardiography is more operator dependent than CT and CMR, which induces additional variability in aortic measurements. Previous literature only investigated variability in aortic measurements performed by two observers on the same echocardiographic images[4-6]. We aimed to evaluate the intra-observer and inter-observer variability of the ascending aortic diameter including the acquisition of the aortic images.

Twenty adult patients with a bicuspid aortic valve (BAV), and 20 Turner patients, who were scheduled for a follow-up visit of an ongoing prospective cohort study[5], and also 20 healthy controls were included. BAV was also present in 6 (30%) Turner patients. Patients with aortic valve replacement or aortic surgery were excluded. Baseline characteristics are shown in table 1. Standard 2D transthoracic echocardiography was performed in each participant by two experienced sonographers out of a group of four (EW, LH, AB, DB) depending on their availability. All studies were acquired using harmonic imaging on an iE33 or EPIQ7 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with an X5–1 matrix-array transducer (composed of 3040 elements operating at 1-5 MHz). The aorta was measured from either the standard parasternal long axis view or from a more cranial intercostal window[7]. Sonographer 1 and 2 successively obtained echocardiographic data sets. Subsequently, sonographer 1 acquired a second data set. In this manner, aorta data sets were obtained independently by two sonographers, who were blinded to each other's results. After the acquisitions, the sonographer measured the aortic diameters on their own data sets, resulting in intra-observer and inter-observer test-retest variability. The aorta was measured at four different levels according to the guidelines[7]: annulus, sinus of Valsalva (SoV), sinotubular junction (STJ) and ascending aorta (AA). To assess intra-observer and inter-observer variability the coefficient of variance (COV) and intraclass correlation coefficient (ICC) were calculated.

Table 1. Baseline characteristics

	All (n=60)	Turner syndrome (n=20)	Bicuspid aortic valve (n=20)	Healthy controls (n=20)
Age (years)	37 ± 13	38 ± 15	36 ± 11	35 ± 15
Gender, female (%)	35 (58%)	20 (100%)	5 (25%)	10 (50%)
Height (cm)	172 ± 16	155 ± 10	182 ± 10	181 ± 9
Weight (kg)	73 ± 14	66 ± 16	77 ± 13	76 ± 11
Systolic blood pressure (mmHg)	125 ± 16	124 ± 19	123 ± 15	127 ± 13
Diastolic blood pressure (mmHg)	80 ± 11	80 ± 14	80 ± 10	80 ± 8
Hypertension (%)	7 (12%)	4 (20%)	3 (15%)	0 (0%)
Hypercholesterolemia (%)	2 (3%)	1 (5%)	1 (5%)	0 (0%)
Diabetes (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Coarctation (%)	5 (8%)	0 (0%)	5 (25%)	0 (0%)
Bicuspid aortic valve (%)	24 (40%)	6 (30%)	20 (100%)	0 (0%)
Aortic diameter >40mm and/or ASI>2.1 cm/cm^2 (%)*	19 (32%)	6 (30%)	13 (65%)	0 (0%)
Aortic stenosis, Vmax >2.5 m/s (%)	9 (15%)	0 (0%)	9 (45%)	0 (0%)
Moderate or severe aortic regurgitation (%)	9 (15%)	1 (5%)	8 (40%)	0 (0%)
Aortic size index (mm/m^2)				
Annulus	12.4 ± 1.9	12.6 ± 1.7	13.2 ± 2.3	11.4 ± 1.2
Sinus of Valsalva	18.9 ± 3.4	20.2 ± 3.4	20.0 ± 3.4	16.6 ± 1.8
Sinotubular junction	15.9 ± 3.1	17.2 ± 2.8	17.2 ± 4.0	13.7 ± 1.7
Ascending aorta	18.1 ± 4.1	19.1 ± 3.7	21.0 ± 3.5	14.6 ± 1.8

Values are presented as mean (SD) for continuous variables and N (%) for categorical variables. Weight was missing in 3 BAV patients and 1 Turner patient.
*Based on first measurements of the first observer. ASI = aortic size index.

Table 2. Test-retest variability of the aortic root and ascending aortic diameter.

			Measurement 1	Measurement 2	Mean absolute difference	Max	Paired t-test p-value	Coefficient of variation†	ICC
Intra-observer difference (one observer)	Total	Annulus	22.7 ± 3.6	22.6 ± 3.9	1.0 ± 1.2	7	0.936	7.1%	0.910
		Sinus of Valsalva	34.7 ± 5.6	34.7 ± 5.6	0.8 ± 0.8	3	0.912	3.3%	0.979
		Sinotubular junction	29.3 ± 5.2	29.6 ± 5.3	1.3 ± 1.3	6	0.336	6.3%	0.936
		Ascending aorta	33.2 ± 7.5	33.2 ± 7.6	0.7 ± 0.9	4	0.552	3.3%	0.990
	No aortic dilatation	Annulus	21.9 ± 3.0	21.7 ± 3.2	0.9 ± 1.0	4	0.284	5.9%	0.911
		Sinus of Valsalva	32.6 ± 4.3	32.5 ± 4.3	0.8 ± 0.9	3	0.796	3.7%	0.961
		Sinotubular junction	27.1 ± 3.3	27.4 ± 3.3	1.2 ± 1.3	5	0.424	6.4%	0.857
		Ascending aorta	29.4 ± 4.0	29.0 ± 3.7	0.6 ± 0.8	4	0.086	3.4%	0.967
	Aortic dilatation	Annulus	24.5 ± 4.4	24.8 ± 4.7	1.3 ± 1.7	7	0.386	8.6%	0.892
		Sinus of Valsalva	39.5 ± 5.6	39.3 ± 5.5	0.8 ± 0.7	2	0.834	2.7%	0.981
		Sinotubular junction	34.1 ± 5.5	34.3 ± 5.7	1.5 ± 1.5	6	0.601	6.3%	0.925
		Ascending aorta	41.6 ± 6.2	41.9 ± 6.0	0.7 ± 1.0	4	0.268	2.9%	0.981
Inter-observer difference (two observer)	Total	Annulus	22.7 ± 3.6	22.2 ± 3.3	1.7 ± 1.3	7	0.035	9.1%	0.827
		Sinus of Valsalva	34.7 ± 5.6	33.8 ± 5.4	1.6 ± 1.6	8	0.001	5.9%	0.933
		Sinotubular junction	29.3 ± 5.2	29.2 ± 5.0	1.6 ± 1.1	4	0.650	6.8%	0.924
		Ascending aorta	33.2 ± 7.5	32.7 ± 6.5	1.9 ± 1.6	6	0.079	7.5%	0.938
	No aortic dilatation	Annulus	21.9 ± 3.0	21.9 ± 2.7	1.6 ± 1.1	4	0.007	8.4%	0.797
		Sinus of Valsalva	32.6 ± 4.3	32.6 ± 4.3	1.5 ± 1.6	8	0.011	6.2%	0.895
		Sinotubular junction	27.1 ± 3.3	27.2 ± 3.1	1.5 ± 1.3	4	0.814	7.3%	0.804
		Ascending aorta	29.4 ± 4.0	29.4 ± 3.7	1.5 ± 1.3	5	0.756	6.9%	0.860
	Aortic dilatation	Annulus	24.5 ± 4.4	24.4 ± 3.3	1.7 ± 1.7	7	0.926	10.0%	0.804
		Sinus of Valsalva	39.5 ± 5.6	38.1 ± 5.1	1.8 ± 1.5	5	0.038	5.6%	0.918
		Sinotubular junction	34.1 ± 5.5	33.8 ± 5.2	1.9 ± 0.7	3	0.659	6.0%	0.927
		Ascending aorta	41.6 ± 6.2	40.0 ± 5.0	2.8 ± 1.9	6	0.037	7.5%	0.853

* The ascending aorta could not be measured in one Turner patient and in one BAV patient the annulus measurement was missing for the second measurement of the first observer. † Coefficients of variation represent the standard deviation of the difference between two measurements, divided by the mean of the measurements, expressed as a percentage.

The intra-observer and inter-observer difference are displayed in table 2 and Supplemental figures 1 and 2. Out of the 238 intra-observer comparisons performed, we found 21 (9%) cases of more than 2 mm difference (annulus n=5, SoV n=3, STJ n=11, AA n=2). In two patients, both with BAV and aortic dilatation, a difference of more than 5 mm was found. Out of the 239 inter-observer comparisons performed, we found 51 (21%) cases of more than 2 mm difference (annulus n=11, SoV n=14, STJ n=11, AA n=15). A difference of more than 5 mm was found in three patients (1%). All of these three patients had BAV and two had aortic dilatations. The echocardiographic images of the five patients with intra-observer or inter-observer differences above 5 mm are shown in supplemental figures 3 and 4. Possible explanations found for these large differences were: different frame rates, slightly different cutting planes, dropout artifact, side lobe artefact, incorrect measurements due to calcification of the annulus and not following the guidelines. By linear regression analysis, the aortic diameter was not associated with the intra-observer test-retest variability. However, a larger absolute aortic diameter was associated with larger inter-observer test-retest variability at all four levels measured (annulus ß 0.13±0.04, p=0.003, SoV ß 0.10±0.03, p=0.005, STJ ß 0.06±0.03, p=0.029 and AA ß 0.11±0.03, p<0.001). Therefore, table 2 also shows the results of inter-observer and intra-observer variability separately for participants with and without aortic dilatation (diameter >40 mm and/or aortic size index >2.1 cm/cm^2).

The overall intra-observer test-retest variability we found (0.7-1.3 mm) is comparable to the intra-observer variability reported in literature caused by only the aortic measurement, which ranges from 0.1 to 1.5 mm [6, 8]. This means that the additional variability caused by the image acquisition is limited when the acquisition is performed twice by the same sonographer on the same day. The mean differences for inter-observer test-retest variability (1.6-1.9 mm) was found to be higher or in the higher range of inter-observer variability caused by only the aortic measurement ranging from 0.1 to 1.7 mm[6, 8]. The image acquisition by two different sonographers seems to cause an additional variation, which should be taken into account when using echocardiography for aorta measurements.

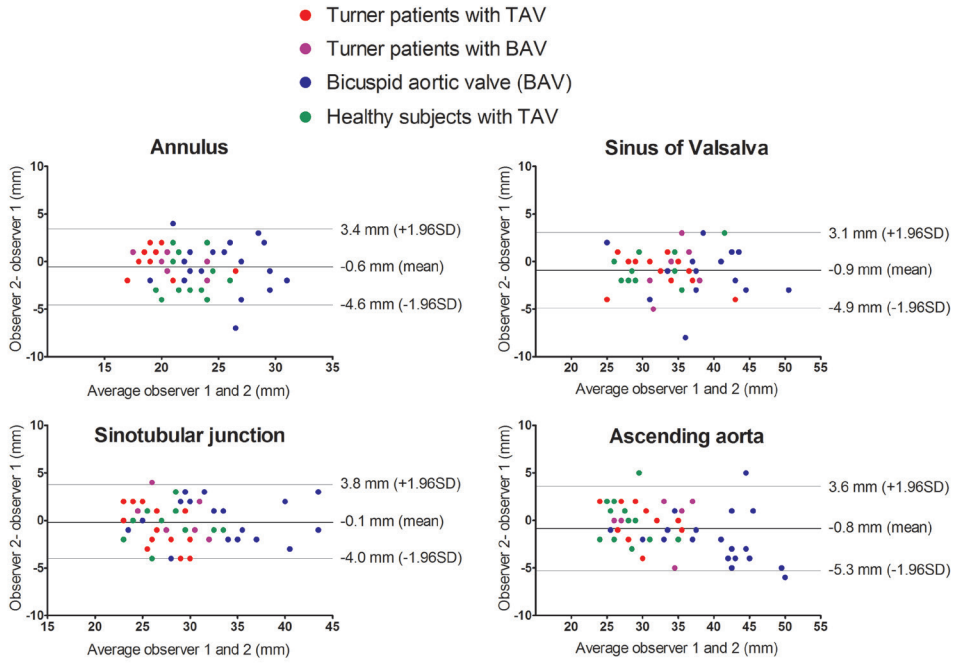
The ICC for inter-observer variability found in our study, ranging from 0.83 to 0.94, is slightly lower than the ICC reported for CT and CMR (ICC>0.95)[5, 6]. This suggests that CT and CMR do have superior test-retest performance, although echocardiography also shows good performance. The test-retest variability in our study was found to be less than 10% when expressed as a percent of the mean, which is usually considered to reflect good reproducibility. Therefore we can conclude that on average the intra-observer and inter-observer test-retest variability seems to be limited. However, there can be individual differences up to 8 mm. Hence, in case of large differences that suggest growth, there should be attention for causes of test-retest variability before it is seen as a real change in the aortic diameter. When no good explanation can be found for the large difference, the aortic diameter should be assessed with CT/CMR to verify the "true" diameter. We also found at all levels that a larger absolute aortic diameter was associated with higher inter-

observer test-retest variability. However, when the variability was expressed as percentage of the measured values (COV), the variability was comparable between patients with and without aortic dilatation. Although the COV is within the limits that are clinically tolerated, a large difference in absolute diameter may have major consequences, especially in patients who approach the threshold for preventive aortic surgery. In conclusion, the test-retest variability between two observers or two observations of one observer is less than 10%, but rarely larger differences can occur.

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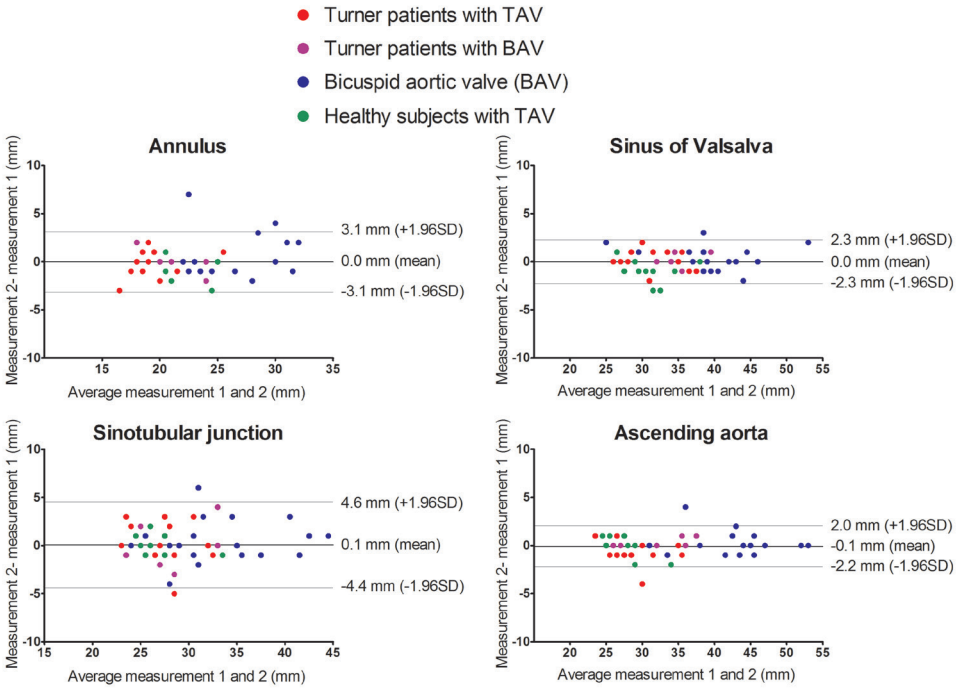
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Supplemental material

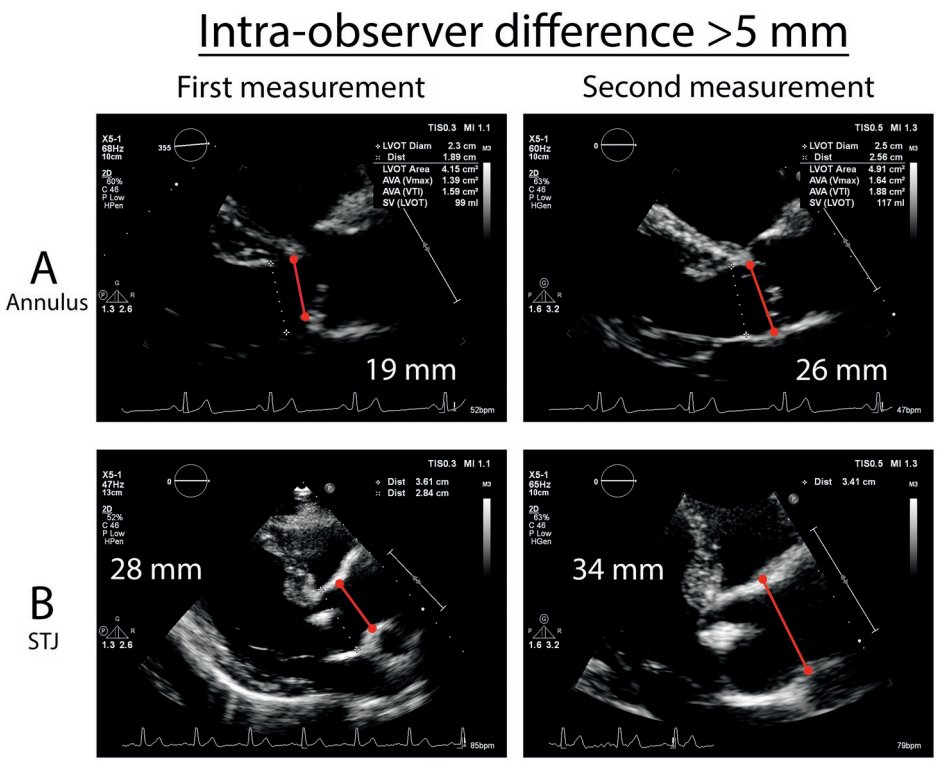


Supplemental figure 1. Bland-Altman plots presenting intra-observer test-retest variability of echocardiographic measurements of the aortic root and ascending aorta.

Variability of the aortic root and ascending aortic diameter between two measurements by the same observer for Turner patients (red), patients with bicuspid aortic valve (blue) and healthy controls (green).

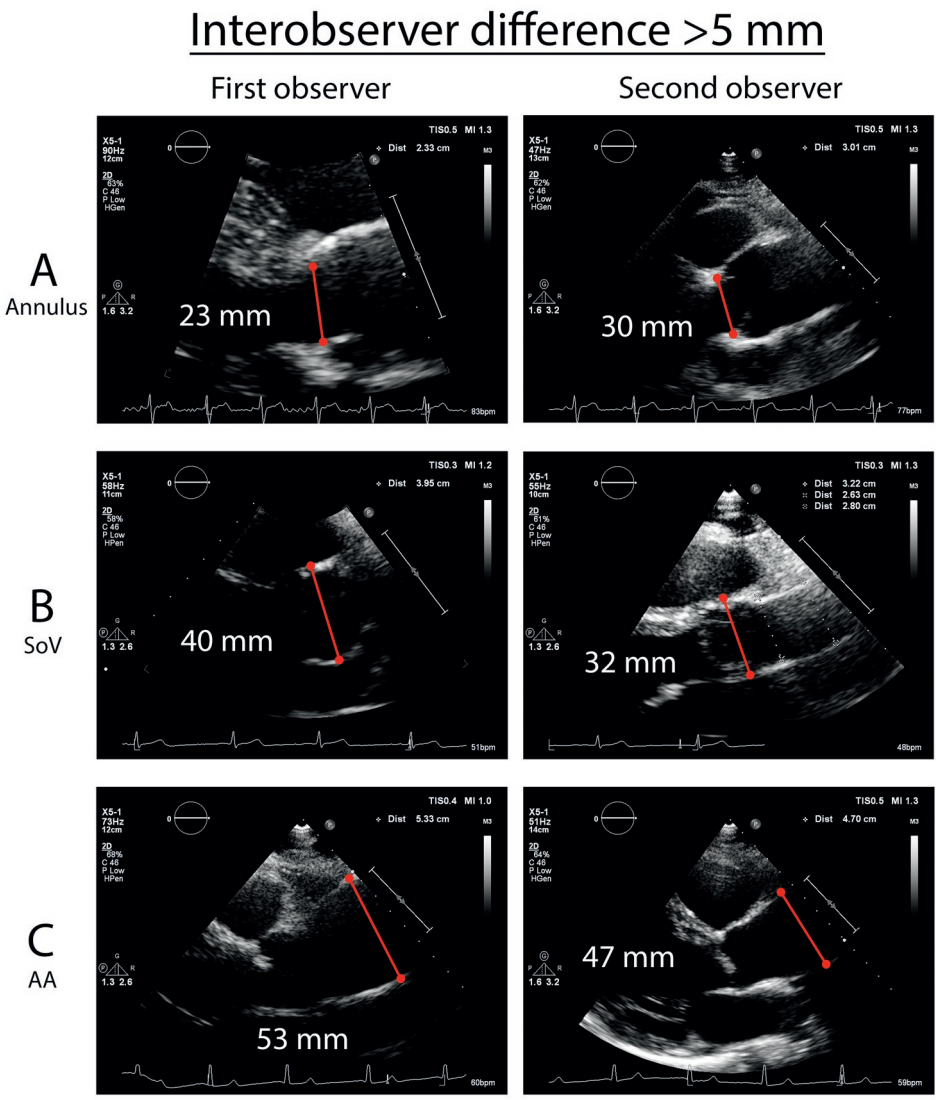


Supplemental figure 2. Bland-Altman plots presenting inter-observer test-retest variability of echocardiographic measurements of the aortic root and ascending aorta.
Variability of the aortic root and ascending aortic diameter between two observers for Turner patients (red), patients with bicuspid aortic valve (blue) and healthy controls (green).



Supplemental figure 3. Outliers (> 5mm) between first and second measurement of one observer.

STJ = sinotubular junction, SoV = sinus of Valsalva, AA = Ascending aorta.In the first subject (A), the difference of 7 mm at the annulus between the two measurements of the same observer was caused by one incorrect measurement. Calcification was probably considered to be annular tissue causing a smaller annulus diameter measurement. The measurement of 26 mm is probably closer to the true diameter. In the second subject (B), the difference between the two STJ measurements of one observer seems to be caused by the use of an incorrect method in the first image, namely the inner edge-to-inner edge method. Also, the second image is zoomed. In a zoomed image the frame rate is higher (65 Hz versus 47 Hz) and therefore the aortic measurement will be more accurate. A small dropout artifact at the posterior wall of the STJ could also have contribute to a larger diameter measured in the second image.



Supplemental figure 4. Outliers (> 5mm) between measurements of first and second observer. STJ = sinotubular junction, SoV = sinus of Valsalva, AA = Ascending aorta. The first subject (A) with large inter-observer difference (>5 mm) shows a large difference in frame rate. Also, the first observer measured the annulus too much to the right including a part of the posterior aortic valve leaflet. A slightly different cutting plane could have caused the large difference in SoV diameter between the observers (B). The SoV diameter measurements of both observers seem to be without errors. However, in the image of the first observer, the ascending aorta is not completely visualized, which makes it difficult to determine how the cross-sectional plane through the aorta is made. Therefore, the measurement error is probably due to two different cutting planes. In the third subject (C), the second observer underestimated the dimensions of the AA due to measuring a side lobe artefact and not the true wall. Again, the first observer acquired a zoomed image with a higher frame rate.

CHAPTER 4



Automated 3D segmentation and diameter measurement of the thoracic aorta on non-contrast enhanced CT

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Objectives

To develop and evaluate a fully automatic method to measure diameters of the ascending and descending aorta on non-ECG-gated, non-contrast computed tomography (CT) scans.

Material and methods

The method combines multi atlas registration to obtain seed points, aorta centerline extraction, and an optimal surface segmentation approach to extract the aorta surface around the centerline. From the extracted 3D aorta segmentation, the diameter of the ascending and descending aorta was calculated at cross-sectional slices perpendicular to the extracted centerline, at the level of the pulmonary artery bifurcation, and at 1 cm intervals up to 3 cm above and below this level. Agreement with manual annotations was evaluated by dice similarity coefficient (DSC) for segmentation overlap, mean surface distance (MSD), and intra class correlation (ICC) of diameters on 100 CT scans from a lung cancer screening trial. Repeatability of the diameter measurements was evaluated on 617 baseline-one year follow-up CT scan pairs.

Results

The agreement between manual and automatic segmentations was good with 0.95 ± 0.01 DSC and 0.56 ± 0.08 mm MSD. ICC between the diameters derived from manual and from automatic segmentations was 0.97, with the per-level ICC ranging from 0.87 to 0.94. An ICC of 0.98 for all measurements and per-level ICC ranging from 0.91 to 0.96 were obtained for repeatability.

Conclusion

This fully automatic method can assess diameters in the thoracic aorta reliably even in non-ECG-gated, non-contrast CT scans. This could be a promising tool to assess aorta dilatation in screening and in clinical practice.

Introduction

Aortic aneurysm with the risk of acute dissection is an important cause of mortality in the western world[1]. The prevalence of thoracic aortic aneurysms is estimated around 0.3 percent in the normal population[2, 3]. Most patients with a dilated aorta or aortic aneurysm are asymptomatic. The diagnosis can be made as during screening in the context of a positive family history or by coincidence on imaging examinations performed for other purposes like lung cancer screening[4]. However, acute dissection is often the first presentation, in which case over 50% of all patients die within 30 days[5]. Because of this silent process with high risks, screening programs using non-contrast computed tomography (CT) could be considered. In patients with aortic aneurysms, the aortic size has a profound impact on the risk of dissection[6, 7]. Detecting aortic dilatation at an early stage enables preventive surgery, which might save lives. CT imaging of the thoracic aorta could become available as part of a comprehensive assessment of CT imaging performed for screening purposes including also other organs (lungs, coronary calcium, vertebral bone density etc.)[4]. By measuring aortic dimensions in such screening cohorts we will also gain more information on normal values of aortic diameters, normal increase in diameters over time, and risk factors for dilatation, and a better insight in prognosis.

Besides its potential in screening, non-contrast CT is frequently used in diagnosis and follow-up of patients in clinical practice. It plays a central role in the imaging of the thoracic aorta because of the short time required for image acquisition, the ability to obtain a complete 3D view of the entire aorta, and its widespread availability. CT scans can be used for follow-up of patients with dilatation, especially in cases where echocardiography does not adequately visualize the dilatation. The ESC Guidelines and ACCF/AHA guidelines[8, 9] describe standard anatomical landmarks for reporting aortic diameters in CT in clinical practice.

Performing measurements of the aorta manually is labor intensive and subject to inter-observer variability. To assess aortic dilatation both in screening settings and in clinical practice, automated aorta segmentation and subsequent diameter analysis is therefore desirable. While automatic solutions for aortic measurements in CT angiography (CTA) exist[10-14], automatic aorta segmentation in non-contrast CT scans is more challenging due to the lack of contrast between blood pool regions and surrounding soft tissue[15-19]. The aim of the current study is to develop and validate an automatic method to robustly assess diameters of the ascending and descending aorta in non-ECG-gated, non-contrast CT without human interaction.

Materials and methods

Study Population & Image Acquisition

The CT scans used in this study are from the Danish Lung Cancer Screening Trial[20]. A Multi Detector CT scanner (Mx 8000 IDT 16 row scanner, Philips Medical Systems) was

used to acquire CT scans at 120 kV / 40 mAs at maximum inspiration breath hold and without cardiac gating. This protocol leads to an effective dose of around 1 mSv[21]. The scans were reconstructed with a sharp kernel (Philips D), in-plane isotropic resolution of 0.78 × 0.78 mm, and 1 mm slice thickness. Participants were current or former smokers between 50 and 70 years of age. For this study 742 participants were randomly selected, which were divided into three non-overlapping sets: (see supplemental table 1 for clinical characteristics of the entire data):

- Baseline scans of 25 subjects for parameter optimization of the proposed method
- Baseline scans of 100 subjects for evaluation of the method's accuracy (see table 1)
- Baseline and first year follow up scans of 617 subjects to evaluate the repeatability of the method

Therefore, aortic diameter measurements were performed in 1334 CT scans in total.

Table 1. Clinical characteristics of 100 subjects used in validation. Values are expressed as mean ± standard deviation and (range).

validation set (n=100)	Male	Female
Number of CT scans (n)	50	50
Age, years	58.5 ± 5.4 (50 - 70)	58.3 ± 4.8 (50 - 70)
Weight, kg	84.0 ± 12.0 (60 - 120)	67.6 ± 12.2 (48 - 103)
Height, cm	179.8 ± 6.3 (163 - 195)	167.0 ± 6.1 (155 - 179)
BMI	26.0 ± 3.6 (18.7 – 37.0)	24.3 ± 4.7 (16.2- 41.3)
Agatston score at ascending aorta and arch	231.3±416.7 (0 - 2190)	193.3±274.4 (0 - 1128)
Agatston score at descending aorta	53.5±116.2 (0 - 483)	81.4±316.4 (0 - 2139)

Manual annotation

Manual annotations were made using an in-house annotation tool developed in MeVisLab. One hundred CT scans were annotated by a physician (LB) for validation and an additional 25 scans by an experienced observer (ZSG) for method development. The annotation tool was similar to that described previously for carotid artery segmentation[22]. First, the window level/width was adjusted to 200 HU/600 HU, for all cases. Then, the aortic centerlines were drawn manually using the axial, coronal and sagittal views, starting from the sinotubular junction of the ascending aorta and ending at the diaphragm level of the descending aorta. Subsequently, the centerlines were checked and modified in reformatted cross-sectional views perpendicular to the drawn centerline. The obtained centerlines were used to generate curved multi-planar reformatted images of the entire aorta, with longitudinal views at six different angles equally spaced every 30° and cross-sectional views every 1 mm along the centerline. Longitudinal contours were drawn manually, whereupon cross-sectional contours were computed using spline interpolation through the intersection points of the longitudinal contours with the cross-sectional planes. Finally, after checking the cross-sectional contours in all cross-sections and adjusting them if required, the

contours were converted to a 3D binary image using variational interpolation[23]. An example of manual annotation is shown in figure 1. To manually locate the pulmonary artery bifurcation level, an experienced physician (DB) checked the scans in axial view and annotated the pulmonary artery bifurcation level where the left and right pulmonary arteries and the bifurcation from the pulmonary trunk were all visible.

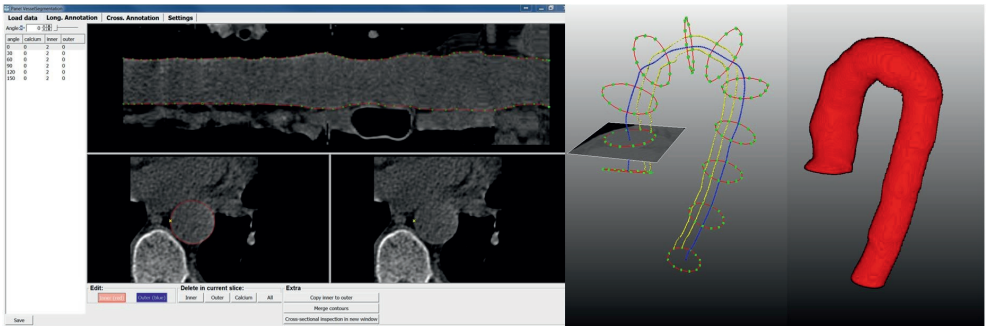


Figure 1. Screenshot of the manual annotation tool (left). Middle image shows two manually drawn longitudinal contours (yellow) and a few cross-sectional contours (red), which are perpendicular to the manual centerline (blue). A cross-sectional slice at the ascending aorta and the corresponding contour is shown as well. The corresponding 3D surface of the aorta is shown on the right.

Automatic aorta segmentation approach

To extract a full 3D segmentation of the aorta and a landmark point for the pulmonary artery bifurcation level, we applied a combination of image processing techniques. First, to avoid the segmentation to attract to the heart-lung or bone borders, we applied preprocessing as proposed in our previous work[24]. Subsequently, a multi-atlas registration method[25] was applied to localize the aorta, the pulmonary artery trunk, and the left and right pulmonary arteries. In this method, 25 preprocessed CT scans were non-rigidly registered to the scan in which the segmentation was required (target image). From these 25 registered images, the ten with the highest similarity to the target image were selected. The corresponding manual annotations of these ten scans were then deformed and combined using a per voxel majority voting procedure to obtain a coarse initial segmentation of the aorta and pulmonary arteries. The initial segmentation of the pulmonary arteries was then skeletonized and the slice where main pulmonary artery bifurcates into the left and right pulmonary arteries was extracted as the pulmonary artery bifurcation level. This level is used as the landmark level.

To start tracing the centerline of the aorta, aortic seed points were extracted as the center of mass of the coarse initial aorta segmentation at the axial slice 3 cm beneath the landmark level for the ascending aorta and 6 cm beneath the landmark level for the descending aorta. The aortic centerline was then extracted between these seed points by

a minimum cost path tracking algorithm[24]. In this algorithm, the cost function was based on the maximum output of a multi-radius medialness filter in coronal and axial views multiplied with a lumen intensity similarity metric. The centerlines were refined by re-computing the minimum cost path after curved multiplanar reformatting perpendicular to the previous centerline[26]. Failure in the centerline extraction was automatically detected by using the landmark level and the initial pulmonary artery segmentation. Centerlines that did not reach the landmark level or were inside the pulmonary artery segmentation were considered failed extractions and were excluded.
To obtain a first estimate of the aorta, the extracted centerline was dilated using a spherical structuring element with its radius defined by the estimated radius of the aorta obtained from the medialness filter. Subsequently, an optimal surface graph cut segmentation method (Available at https://bitbucket.org/opfront/opfront)[27], initialized by the dilated centerline, was used to accurately extract the surface of the aorta. The parameters for atlas registration, centerline extraction, and graph cut segmentation were tuned to maximize the similarity with manual annotations on 25 CT scans.

Aortic diameter measurement

Aortic diameters were assessed at multiple, fixed levels relative to the pulmonary artery bifurcation level. Based on the extracted pulmonary bifurcation level, thirteen cross-sectional slices were defined perpendicular to the extracted aortic centerline, located at 1 cm intervals around the bifurcation level from 2 cm below this level to 3 cm above for the ascending aorta and from 3 cm above to 3 cm below this level for the descending aorta. For the ascending aorta, the cross-sectional slice at 3 cm below the pulmonary artery bifurcation level was sometimes in the aortic root below the sinotubular junction which the aorta boundaries at the sinus of Valsalva are very unclear due to the lack of gating and contrast. Therefore, no measurements were performed at this level. Figure 2 shows an example of 3D segmentation with the corresponding centerline and four of the measured cross-sections. The cross-sectional average aortic diameter at each of the 13 cross-sectional slices was computed from manual and automatic segmentations. For the manual segmentations, diameter measurements were performed perpendicular to the manual centerlines and at levels relative to the manually indicated pulmonary artery bifurcation level. For the automatic segmentations, the automatically extracted centerlines and pulmonary artery bifurcation level were used instead.

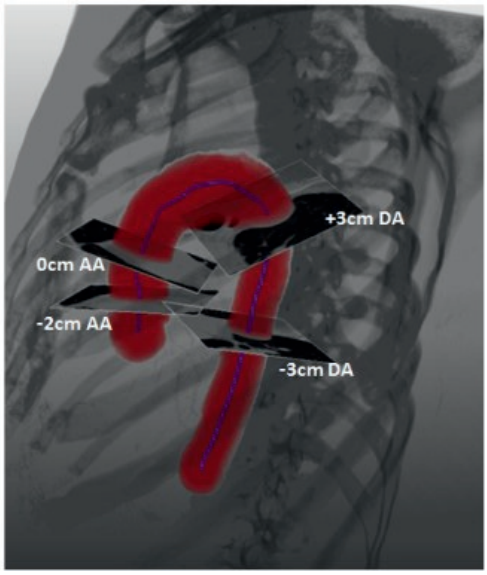


Figure 2. 3D automatic segmentation of the aorta and the corresponding automatic centerline showing cross-sections at the ascending aorta at the pulmonary artery bifurcation level (0 cm AA) and at 2 cm below this level (-2 cm AA) and at the descending aorta at 3 cm above (+3 cm DA) and below (-3 cm DA) the pulmonary artery bifurcation level.

Validation and statistical analysis

The method was validated on 100 CT scans with manual annotations. The segmentation accuracy was assessed by dice similarity coefficient (DSC) and mean surface distance (MSD). DSC[28] measures the degree of spatial overlap of the automatic segmentation with the manual segmentation, and it ranges between 0 and 1, where higher values indicate higher similarity. MSD shows the symmetric mean surface distance in millimeters between the manual and automatic segmentation surfaces, where lower value is better. The agreement between the manual and automatic segmentations was assessed from 3 cm beneath the landmark level at the ascending aorta to 6 cm beneath this level at the descending aorta. DSC, MSD, aortic diameters, and the error in the diameter were expressed as mean ± standard deviation (range).

The error in the extracted landmark level was assessed by the distance between the manually extracted pulmonary artery bifurcation level and the automatically extracted level in millimeters. The aortic centerlines were automatically checked for failed extractions. The agreement between the manual and automatic diameter measurements was assessed by (1) intra-class correlation (ICC) based on a single-rating, absolute-agreement, two-way mixed-effects model[29]; (2) R^2 Pearson correlation; and (3) Bland-Altman analysis.

Repeatability of the method was assessed by comparing the automatically extracted diameters of two scans of 617 subjects with time period of 1 year in between. Within 1

year, changes in aortic diameters are expected to be small, with 0.1-0.2 mm growth per year in a healthy population[3, 30]. All statistical analyses were done in MATLAB.

Results

Figure 3 shows examples of segmentation results. Out of all 1334 CT scans only in two cases the seed points at the descending aorta were extracted incorrectly. Centerline extraction further failed in seven cases, all of which were easily detected automatically. Average DSC for the entire aorta was 0.95 ± 0.01 (0.92-0.96) and MSD was 0.56 ± 0.08 (0.43–0.93) mm. The mean absolute distance between the manual and automatic landmark level of the pulmonary artery bifurcation was 2.55 ± 1.94 mm, with almost no bias (mean signed distance 0.45 ± 3.18 mm).

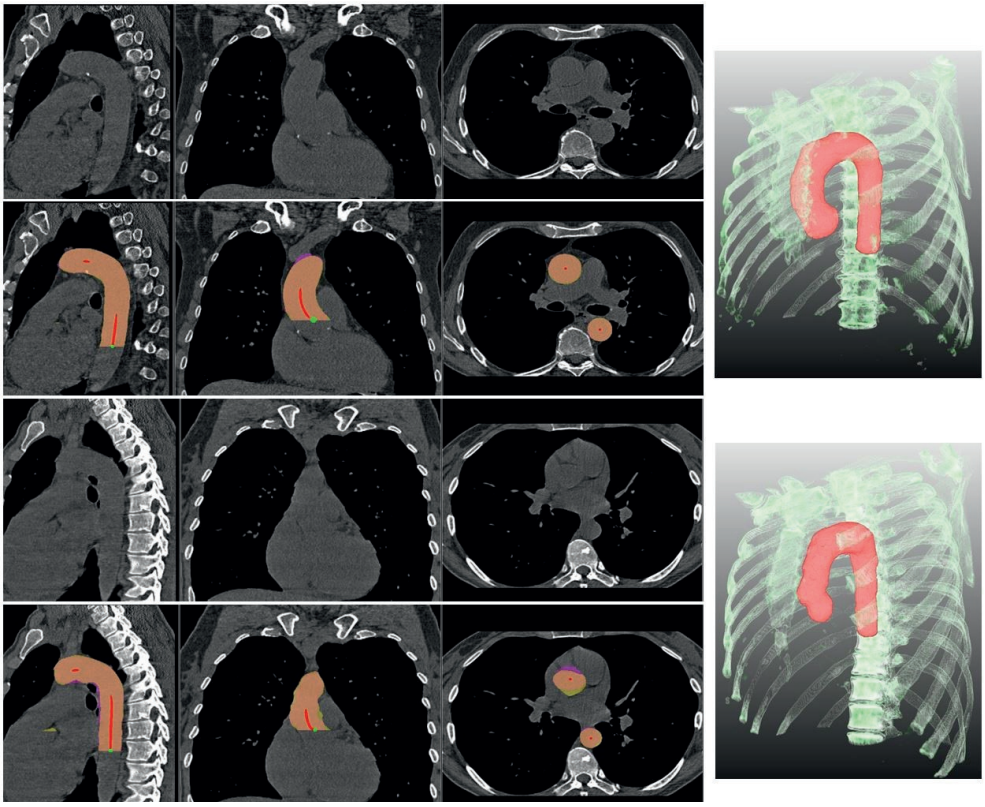


Figure 3. Two samples with the best (the first two rows) and the worst (the last two rows) automatic segmentation results. The columns from left show the sagittal, coronal and axial views, respectively. The right column shows the 3D visualization of the automatic segmentation in red. First and third row are the original CT scans, while the second and fourth row show the CT scan with the overlap of the corresponding manual and automatic segmentations with DSC=0.96 and MSD= 0.60 mm for the first sample and DSC=0.92 and MSD=1.44 mm for the second sample. Orange shows the regions where the manual and automatic segmentations overlap. Magenta is the region included in the automatic segmentation, but not in the manual segmentation and yellow is the region that is inside the manual segmentation, but not in the automatic segmentation. Centerline points are indicated in red and seed points in green.

Box plots for the average manual and automatic diameters for each measuring level are shown in figure 4. Diameters measured at the different levels, for men and women separately, are shown in table 2. High agreement between manually and automatically measured diameters was obtained, with an overall ICC and R^2 Pearson's correlation of 0.97. The level-wise correlations together with the correlations separated per gender are shown in table 3 (see supplemental figure 1 for scatter plots of each measuring level).

An average absolute diameter error of 1.09 ± 0.6 mm between manual and automatic diameters was obtained over all measuring levels, which showed a slight underestimation of the automated measurements compared to manual measurements (mean signed error -0.97 ± 0.8 mm). As shown in box plots of the level-wise diameter errors in figure 5, larger errors (more than 3 mm) were extracted in 8 out of 100 scans. In four cases, a large error occurred due to motion artifacts at the ascending aorta (beneath the landmark level), and in 3 cases, it occurred at the aortic arch due to branching arteries. In one case, the error was along the entire aorta due to a 6 mm difference between the automatic and manual landmark levels. Bland-Altman plots of manual and automated diameter measurements are given in figure 6.

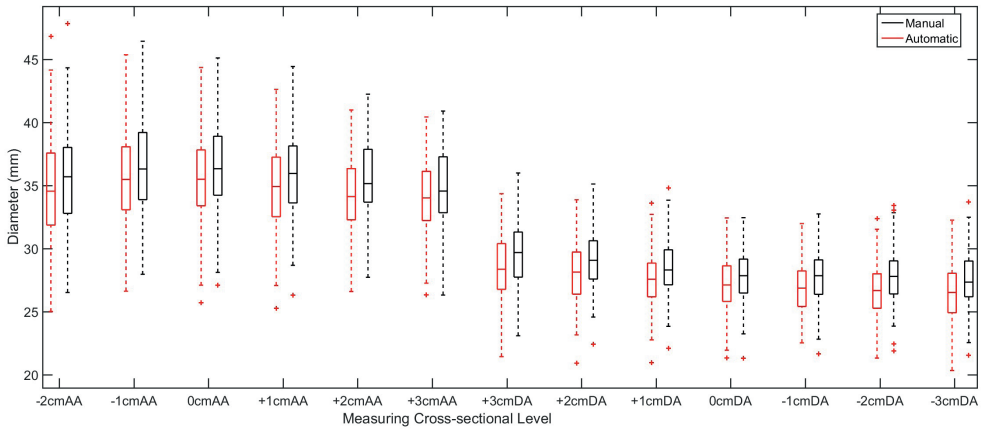


Figure 4. Average manual (black) and automatic (red) diameter per measuring level. From left to right, diameters measured at the different levels along the aorta from 2 cm below the pulmonary artery bifurcation level (0cm) at the ascending aorta (AA) to 3 cm below the pulmonary artery bifurcation level at the descending aorta (DA).

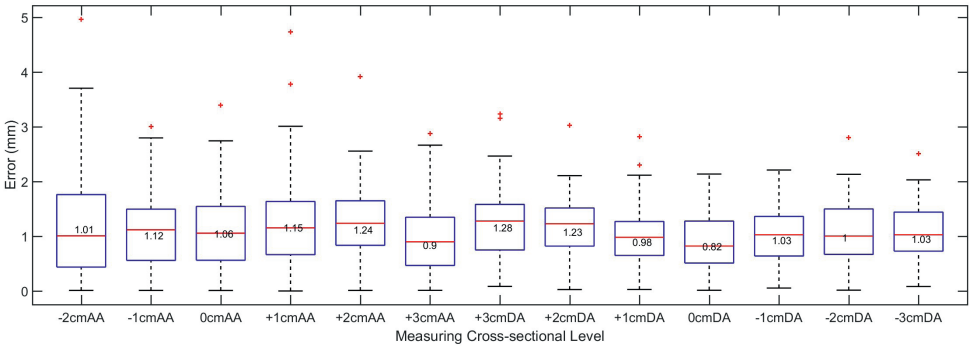


Figure 5. Absolute difference between the aortic diameters obtained from automated and manual 3D segmentations. From left to right, diameters measured at the different levels along the aorta from 2 cm below the pulmonary artery bifurcation level (0cm) at the ascending aorta (AA) to 3 cm below the pulmonary artery bifurcation level at the descending aorta (DA). The box plot shows the median (red line), interquartile range (boxes), the 99.3% coverage of the data (whiskers) and the outliers (+ symbol).

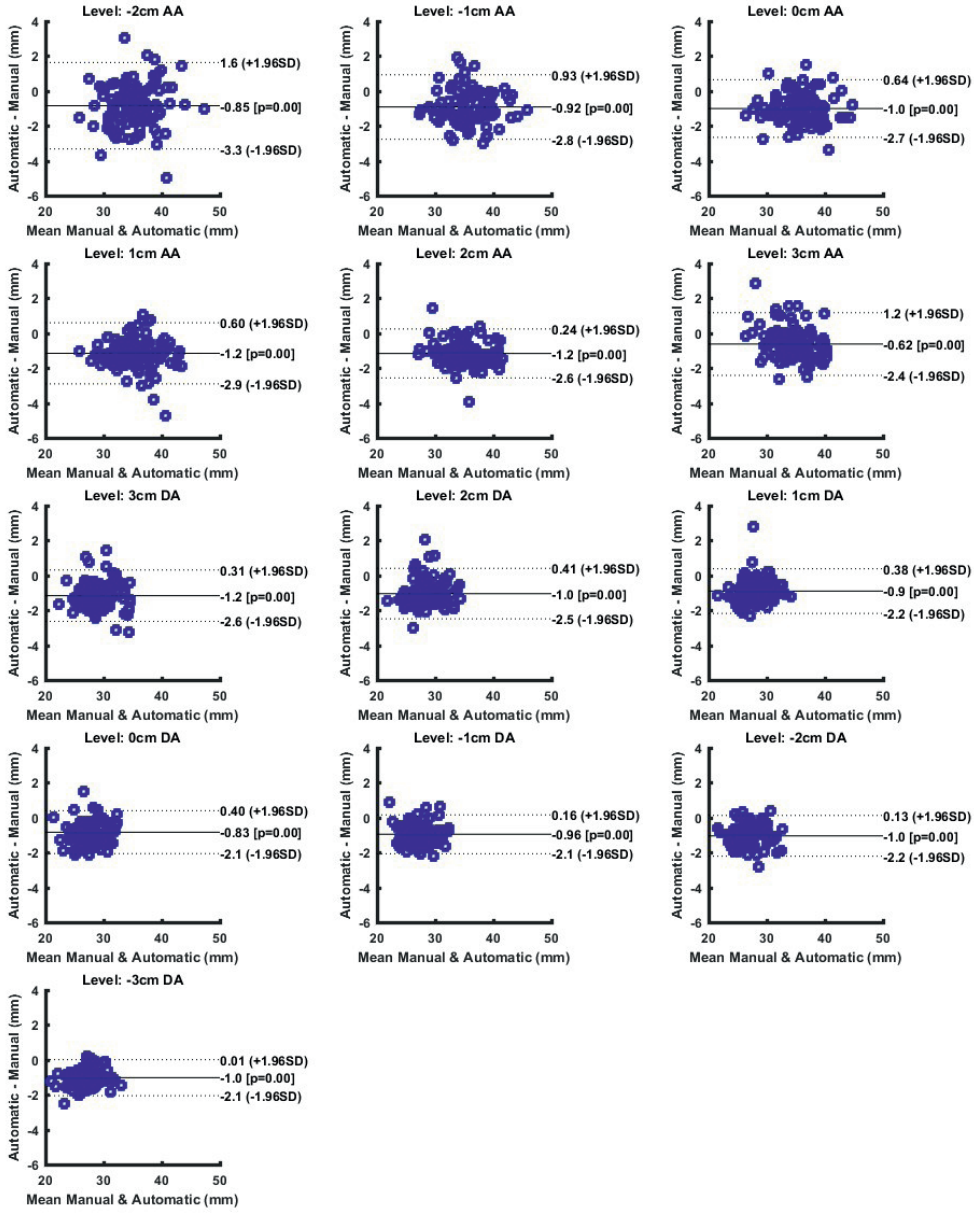


Figure 6. Bland-Altman plots for each measuring level from 2 cm below the pulmonary artery bifurcation in the ascending aorta AA) until 3 cm below this level in the descending aorta (DA). The measuring level, limits of agreement, and the mean difference are displayed on the plots.

Table 2. Average aortic diameters from the automatic and manual segmentations for each measuring level from the 100 CT scans. Values are expressed as mean ± standard deviation.

Measuring Level		Female (n=50)		Male (n=50)	
		Automatic	Manual	Automatic	Manual
Ascending Aorta	-2cm	33.3 ± 3.5	34.2 ± 3.5	36.2 ± 3.9	37.0 ± 3.7
	-1cm	34.2 ± 3.2	35.1 ± 3.4	36.9 ± 3.7	37.7 ± 3.6
	0cm	33.9 ± 3.3	35.0 ± 3.3	36.7 ± 3.5	37.7 ± 3.5
	+1cm	33.5 ± 3.0	34.7 ± 3.2	36.3 ± 3.6	37.4 ± 3.5
	+2cm	33.3 ± 2.7	34.3 ± 2.9	35.4 ± 3.3	36.7 ± 3.2
	+3cm	33.0 ± 2.9	33.4 ± 3.1	35.2 ± 3.0	36.0 ± 3.2
Descending Aorta	+3cm	27.6 ± 2.6	28.7 ± 2.5	29.5 ± 2.4	30.8 ± 2.5
	+2cm	27.3 ± 2.5	28.2 ± 2.4	29.0 ± 2.3	30.2 ± 2.1
	+1cm	26.7 ± 2.3	27.5 ± 2.2	28.5 ± 2.1	29.4 ± 2.0
	0cm	26.3 ± 2.3	27.1 ± 2.2	28.0 ± 2.0	28.9 ± 1.9
	-1cm	26.1 ± 2.1	26.9 ± 2.2	27.7 ± 2.1	28.9 ± 1.9
	-2cm	25.8 ± 2.2	26.9 ± 2.2	27.6 ± 2.0	28.6 ± 1.8
	-3cm	25.5 ± 2.3	26.7 ± 2.2	27.4 ± 2.1	28.3 ± 2.0

0cm is the pulmonary artery bifurcation level, where minus is level below this level and plus is level above the pulmonary bifurcation level.

Table 3. ICC and R^2 Pearson correlation between the automatic and manual diameters for the 100 CT scans.

	Measuring Level	ICC (n=100)	R^2 Pearson (n=100)	ICC Female (n=50)	ICC Male (n=50)
Ascending Aorta	-2cm	0.93	0.90	0.89	0.94
	-1cm	0.94	0.94	0.91	0.95
	0cm	0.94	0.95	0.92	0.94
	+1cm	0.92	0.94	0.89	0.92
	+2cm	0.92	0.95	0.91	0.90
	+3cm	0.94	0.93	0.94	0.93
Descending Aorta	+3cm	0.88	0.92	0.88	0.85
	+2cm	0.88	0.91	0.88	0.84
	+1cm	0.89	0.92	0.88	0.87
	0cm	0.90	0.93	0.90	0.87
	-1cm	0.89	0.94	0.90	0.83
	-2cm	0.87	0.93	0.86	0.83
	-3cm	0.89	0.95	0.86	0.88

ICC= Intra class correlation;
Measuring levels as in Table 2.

From the 617 subjects used to assess repeatability, 7 subjects had failed centerline or seed point extraction. From the remaining 610 subjects, ICC between the automatic diameters of the scan and rescan of each subject is shown in table 4. From these 610 subjects, 72

subjects (12%) had an absolute diameter difference larger than 3 mm between the two time points at any of the measuring levels. In 35 out of 72 cases (48.6%), the segmentations appeared visually correct in both time points. In 17 cases of these 35 cases, a 2 or 3 mm difference between the extracted landmark level in one of the time points, resulted in big diameter differences at 2 cm below the landmark level at the ascending aorta (in average 3.7 ± 0.5 mm). This is due to the aortic anatomy at the sinotubular junction where the aorta below this level is on average 3 mm larger than above[31]. In 5 out of 35 cases, there was more than 6 mm difference between the extracted landmark levels from the two time points, leading to a diameter measurement at very different levels along the entire aorta being compared (in average 3.4 ± 0.5 mm). The remaining 13 out of 35 cases appeared to have a slightly larger diameter at one of the time points (in average 3.7 ± 0.7 mm), possibly due to the aortic size changes during the cardiac cycle. In 37 out of 72 cases (51.4%), the average diameter difference (3.6 ± 0.6 mm) was due to segmentation error which mainly occurred at the aortic arch which was due to branching arteries, or was at the ascending aorta below the pulmonary artery bifurcation level which was due to heart motion artifacts caused by the non-ECG-gated data.

Table 4. Repeatability: ICC between the automatic diameters of the scan and rescan of 610 subjects.

	Ascending Aorta						Descending Aorta						
	-2cm	**-1cm**	**0cm**	**+1cm**	**+2cm**	**+3cm**	**+3cm**	**+2cm**	**+1cm**	**0cm**	**-1cm**	**-2cm**	**-3cm**
ICC	0.91	0.95	0.96	0.96	0.95	0.95	0.94	0.94	0.93	0.94	0.93	0.94	0.94

ICC= Intra class correlation; Measuring levels as in Table 2.

Discussion

We presented a fully automatic method to segment the thoracic aorta and measure aortic diameters. In our evaluation on 100 non-ECG-gated, non-contrast CT scans, the 3D segmentation algorithm performed well with an average segmentation overlap of 0.95 ± 0.01 and a mean surface distance between manual and automatic segmentations of less than 1 voxel (0.56 mm).

The agreement with diameters obtained from manual segmentations was high, with an overall ICC of 0.97 and an average per-level ICC of 0.91 ± 0.03, which is similar to the agreement reported between observers[32] (ICC = 0.94). The manual diameters were on average approximately 1 mm larger than automatic diameters. This bias is similar to inter-observer bias reported for mid-ascending aorta diameter measurement on CTA[33]. Scan-rescan repeatability was high, with an overall ICC of 0.98 and an average per-level ICC of 0.94 ± 0.01. The mean ascending aorta diameters measured at the pulmonary artery

bifurcation level were 36.7 ± 3.5 mm for males and 33.9 ± 3.3 mm for females. These values are similar to those reported by Kalsch et al.[3] (37.1 ± 4 mm for males and 34.5 ± 4 mm for females), while they were slightly greater than those reported by Wolak et al.[34] (33.5 ± 4 mm for males and 31.4 ± 3 mm for females). These differences may be due to differences in the study populations, CT scan protocol, and measurement approach.

A significant diameter increase of on average 0.11 ± 1.0 mm was measured in repeated scans after 1 year. This agrees well with reported natural yearly aortic diameter growth of 0.1–0.2 mm per year in the healthy population[3, 30]. In 12% of repeat scan pairs (72 subjects), diameter changes larger than 3 mm were observed. In the majority of these cases (44 subjects), large diameter differences occur at the ascending aorta beneath the landmark level which is due to the anatomy and the difficulty of measuring these regions. Due to motion artifacts in the non-ECG-gated scans, segmentation of the proximal part of the aorta including the aortic root is difficult even for experienced radiologists. However, although isolated aortic root aneurysms are seen in patients with Marfan syndrome[9], it is less common than aneurysms of the ascending aorta more distal to the aortic root. Therefore, the aortic root segmentation is less important in our application than the ascending aorta. In the remaining 28 cases, the large diameter difference was either in the aortic arch (15) or in the descending aorta (8) or at multiple locations due to error in the extraction of the pulmonary artery bifurcation level (5). Diameters measured at the aortic arch were visually correct; however, slightly larger diameters were measured at the location of branching arteries. In descending aorta, the large diameter differences were mainly due to segmentation error.

In contrast with our study, in literature, most methods for automatic aorta segmentation were evaluated on CTA in which the aortic lumen is much more clearly visible[10-14]. Few methods were proposed to segment the aorta in non-contrast CT[15-19]. Compared to these previous works, shown in Table 5, our proposed method is evaluated on a larger dataset and shows better performance.

Table 5. Performance comparison of methods for the aorta segmentation on non-contrast CT. Values are expressed as mean ± standard deviation.

Author Ref. #	Evaluation Data size	DSC	Jaccard coefficient	MSD (mm)
Kitasaka et al.[15]	7 CT	0.93 ± 0.03	--	0.90 ± 0.33
Avila-Montes et al.[16]	45 CT	0.84 ± 0.10	0.74 ± 0.13	--
Kurugol et al.[17]	45 CT	0.92 ± 0.01	0.85 ± 0.02	0.62 ± 0.09
Isgum et al.18	29 CT	--	0.78 ± 0.04	--
Xie et al.[19]	60 CT	0.93 ± 0.01	--	1.39 ± 0.19
Proposed Method	**100 CT**	**0.95 ± 0.01**	**0.90 ± 0.01**	**0.56 ± 0.08**

DSC = Dice Similarity Coefficient; MSD = Mean Surface Distance

We proposed to measure aortic dimensions at fixed intervals with respect to a single anatomical landmark level, the pulmonary artery bifurcation. In clinical practice, multiple anatomical landmarks including locations in the aortic arch are used instead for reporting aortic diameters in CTA[8, 9, 35]. However, consistently extracting these landmarks especially in non-ECG-gated CT is difficult. Moreover, the aorta diameter is poorly defined at the locations of the brachiocephalic artery, left-common carotid artery, and left-subclavian artery. Consistent measurements in the arch require landmark points in between branches that are not affected by this issue; however, detecting such points automatically and robustly in non-contrast CT scans is difficult. Furthermore, aortic dilatation is less common in the arch than in the ascending and descending aorta. Therefore, in this paper, we focus on the ascending and descending aortas which clinically are of more interest. In non-contrast CT, diameters have been mainly measured at the pulmonary artery bifurcation level[2, 3, 34, 36, 37]. The measuring levels used in our study approximately cover the same area used in CTA[8, 9, 35] but are easier to extract reliably in non-contrast and non-ECG-gated CT.

A limitation of our study is that the method was validated only on a relatively healthy screening population. Further investigation would be required to evaluate the performance on abnormal aortic shapes or large aneurysms. However, in all cases with aortic dilatation as indicated in the original radiology reports, the obtained segmentation was correct. In our data, calcification in the aorta was assessed by the Agatston score[38]. Visual inspection of the scans with Agatston score higher than 1500 for the entire aorta (58 out of 742 subjects) showed that the proposed method segmented the calcifications correctly inside the vessel wall in all cases.

The proposed automatic method is a promising technique to accurately and reproducibly assess subtle signs of aorta dilatation in non-ECG-gated, non-contrast CT scans without any human interaction and could be used for efficient screening for aortic dilatation as well as for monitoring of aortic change in clinical practice as part of a comprehensive CT analysis including lung screening.

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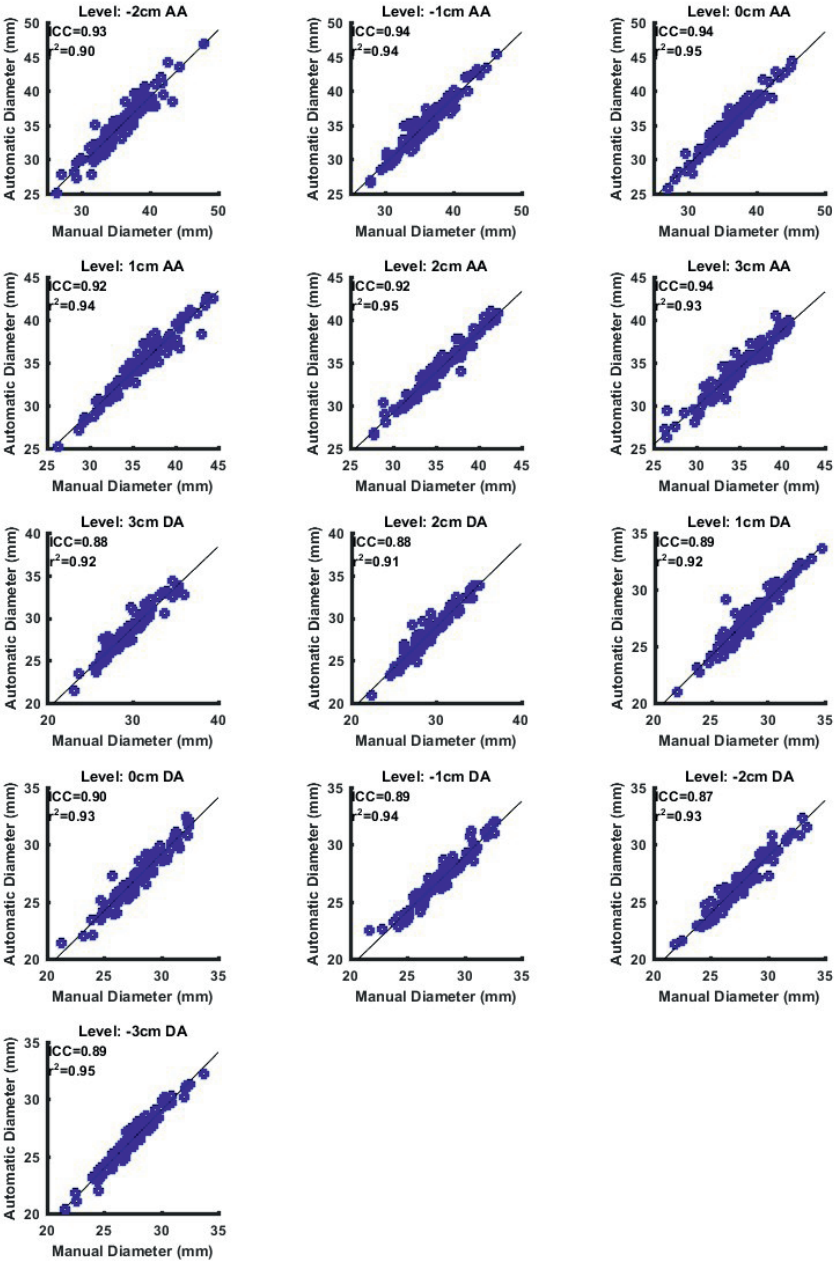
Supplemental material

Supplemental table 1. Clinical characteristics of the data in all three sets.

	method development (n=25)		**validation (n=100)**		**repeatability (n=617)**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
n	12	13	50	50	378	239
Age, years	57.4±4.0 (51.3-67.8)	58.3±5.2 (51.5-67.8)	58.5±5.4 (50.0-70.0)	58.3±4.8 (50.0-70.0)	58.9±5.2 (49.3-71.0)	58 ±5.3 (49.8-70.9)
Weight, kg	82.3±10.4 (66-102)	75.8±9.2 (60-90)	84.0±12.0 (60-120)	67.6±12.2 (48-103)	83.9±12.8 (57-130)	68.6±12.6 (42-126)
Height, cm	177.1±5.0 (167-185)	167.6±6.3 (158-180)	179.8±6.3 (163-195)	167.0±6.1 (155-179)	179.4±6.5 (163-200)	166.7±6.1 (150-182)
BMI	26.3±3.5 (23.3-33.4)	27.1±3.9 (20.1-35.2)	26.0±3.6 (18.7–37.0)	24.3±4.7 (16.2-41.3)	26.1±3.7 (17.3-40.9)	24.7±4.1 (16.4-41.2)
AS at AA & Arch	50.4±126.4 (0-435)	259.1±425.4 (0-1298)	231.3±416.7 (0-2190)	193.3±274.4 (0-1128)	304.3±749.6 (0-6492)	342.4±742.7 (0-5563)
AS at DA	53.3±99.1 (0-256)	37.8±98.7 (0-336)	53.5±116.2 (0-483)	81.4±316.4 (0-2139)	166.7±696.2 (0-9705)	224.1± 692.2 (0-5261)

n= number of participants; AS= Agatston Score; AA=Ascending Aorta; DA=Descending Aorta

Values are expressed as mean ± standard deviation and (range).



Supplemental figure 1. Scatter plots for each measuring level from 2 cm below the pulmonary artery bifurcation in the ascending aorta (AA) until 3 cm below this level in the descending aorta (DA). The measuring level, ICC, and the R^2 Pearson correlation are displayed on the plots.

Part II

The thoracic aorta in the general population

CHAPTER 5

5

Sex-specific distributions and determinants of thoracic aortic diameters in the elderly

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Objective

To provide population-based distributions of thoracic aortic diameters in men and women aged 55 years or older and to identify determinants of thoracic aortic diameters.

Methods

From 2003 to 2006, 2505 participants (1208 men, mean age 69.1±6.8 years) from the prospective population-based Rotterdam Study underwent non-enhanced cardiac CT. The diameter of the ascending (AA) and descending aorta (DA) was measured at the level of the pulmonary bifurcation.

Results

The mean diameter of the ascending and descending aorta was substantially larger in men (38±4 mm and 30±2 mm) than in women (35±3 mm and 27±2 mm). An ascending aortic diameter of larger than 40 mm was found in 228 (18.9%) men and 76 (5.9%) women and a descending aortic diameter larger than 40 mm was found in two men and no women. Male sex was found to be independently associated with larger DA diameter (standardized ß 0.24, CI 0.19;0.30), while a statistically non-significant trend was found for the AA diameter (standardized ß 0.06, CI 0.00;0.12). Age, height, weight and traditional cardiovascular risk factors were also associated with larger AA and/or DA diameters. Diabetes was associated with smaller AA and DA diameters. We found no evidence for effect modification by sex.

Conclusions

In persons aged 55 years or older, an ascending aortic diameter of 40 mm or larger was found in 18.9% of men and 5.9% of women. Given the importance of sex, sex-specific distribution values may prove useful in clinical practice, even when correcting for BSA or height.

Introduction

Individuals with a thoracic aorta dilatation of larger than 60 mm are at high risk for severe complications, such as aortic dissection and rupture,[1] which are related to mortality rates of up to 50% in the acute phase. These serious consequences have led to the development of the current guidelines stating that patients with an absolute thoracic aortic diameter of 55 mm or larger qualify for preventive aortic surgery.[2, 3] Yet, the definition of the threshold for aortic dilatation remains a topic of debate. Some argue that the absolute diameter provides a better risk-estimate than diameters corrected for height and weight, while others propose to correct for body measurements such as body surface area (BSA),[4] especially when it concerns women with short height. The current guidelines from the European Society of Cardiology (ESC)[2] define aortic dilatation as an absolute aortic diameter of larger than 40 mm. When aortic dilatation is found, follow-up visits are recommended to identify patients who will reach the threshold for preventive surgery due to further aortic growth. An important note regarding this definition of aortic dilatation is that this threshold is derived from cohort-data of relatively young individuals with an age range from 9 to 59 years.[5] Hence, this threshold of 40 mm [6] may not be directly applicable to older individuals, especially given increasing evidence suggesting that aortic diameters change with age.[7-9] Together with the finding that aortic complications mostly occur at older age,[10] this emphasizes the need for data on the distribution of aortic diameters among older persons.[11]

In addition, more insight is required into the existence of sex-specific thoracic aortic diameters, as well as into which determinants influence thoracic aortic diameters. These topics are crucial for further research into the clinical relevance of aortic diameters in the elderly and may even contribute to the development of sex-specific recommendations. Against this background, we investigated (1) sex-specific distributions of absolute and BSA-corrected thoracic aortic diameters in a large sample of middle-aged and elderly persons from the general population, and (2) examined determinants of thoracic aortic diameters.

Methods

Study population

The Rotterdam Study is a prospective population-based cohort study that started in 1990, initially including participants aged 55 years or older from the Ommoord district in Rotterdam.[12] Between 2003 and 2006, a random sample of 2524 participants underwent non-enhanced multidetector CT as part of a large project on arterial calcification. We excluded 17 CT-examinations due to image artefacts because of the presence of pacemakers or coronary stent implantations (n=5), poor image acquisition quality (n=4), or absence of the pulmonary artery bifurcation level in the images (n=8).

From two participants with complete data of aortic measurements, cardiovascular risk factor assessment at baseline was lacking. The remaining 2505 persons form the basis of the current analyses. In these 2505 participants, the ascending aortic diameter could be measured in 2500 (99.8%) and the descending aorta in 2462 (98.3%) participants. The Rotterdam Study complies with the Declaration of Helsinki and has been approved by the medical ethics committee, according to the Population Screening Act: Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. Participants were not involved in the design and conduct of the current research.

Assessment of aortic diameters

Non-contrast CT images were obtained using 16-slice (n=775) or 64-slice (n=1730) multidetector CT scanners (Somatom Sensation 16 or 64; Siemens, Forchheim, Germany). Two scans were obtained: A prospective ECG triggered cardiac scan started at the apex of the heart and ended at the tracheal bifurcation and an extra-cardiac scan that reached from the aortic arch to the intracranial vasculature. Aortic diameters were measured primarily on the cardiac scan at an R-R interval of 50%. When the ascending or descending aorta was not visible in the heart scan, the extra-cardiac scan was used (ascending aorta n=162 and descending aorta n=173). Detailed information on the scan protocol has been provided previously.[13] Both the ascending and descending aortic diameters were measured in millimetres in two directions at the bifurcation level of the pulmonary artery using the double-oblique method in a reconstruction perpendicular to the vessel axis. The largest diameter of the two measurements was used for further analysis. Given the lack of contrast material, we measured the aortic diameter with the outer edge-to-outer edge method. Assuming that calcified plaques are located in the intimal layer of the aorta, they were included in the measurement. The aortic diameters were measured by three observers. To assess interobserver variability each observer measured the aortic diameters of the first 100 participants. The intraclass correlation coefficient was 0.985 for the ascending aorta and 0.989 for the descending aorta. Mean differences between the three observers were determined by Bland-Altman plots (supplemental figure 1).[14] Since body size area (BSA) adjusted values are introduced by others,[4] we also presented the diameter adjusted for BSA. BSA was calculated using the Dubois and Dubois formula: BSA (m^2) = 0.007184 x Height(m)$^{0.725}$ x Weight(kg)$^{0.425}$.

Assessment of determinants

We gathered information on the following determinants: age, body measurements, systolic and diastolic blood pressure, smoking, alcohol consumption, coronary and aortic arch calcification volume, cholesterol levels, diabetes, history of cardiovascular disease (CVD) and medication use. Detailed information on the assessment strategy for each determinant is provided in the Appendix A.

Mortality due to aortic events during follow-up

For all Rotterdam Study participants, municipal records were checked for information on vital status. Mortality due to an aortic event (aortic aneurysm or dissection) is collected according to the WHO including ICD-10 code I71 and was available until 1 January, 2014.

Statistical analysis

Continuous variable are expressed as mean ± SD or as median ± IQR. Data distribution was checked using histograms and the Shapiro-Wilk test. Categorical variables are presented as frequencies with percentages. We calculated the sex-specific distributions with mean and 95th percentile of absolute and BSA-adjusted thoracic aortic diameters for the total group and for different age groups (55-64 years, 65-74 years and ≥75 years). As sensitivity analysis, we excluded the participants with a history of CVD.

Associations between the determinants and absolute ascending or descending aortic diameters were quantified with univariable and multivariable linear regression models. We certified that the following assumptions underlying linear regression were met: linearity and homoscedasticity with a plot of *ZRESID against *ZPRED, normal distribution of residuals with histograms and normal P–P plots, multicollinearity with the variance inflation factor (VIF) and independent errors with the Durbin-Watson test. In multivariable linear regression analyses, all determinants (ie, age, anthropometrics, sex, smoking, alcohol consumption, diabetes, blood pressure, medication use, lipids, calcification volumes, and history of CVD) were included in the model. For the analyses of calcification volumes, we used natural log-transformed values and added 1.0 mm^3 to the non-transformed calcification values (ln(calcification volume + 1)) to deal with calcium volumes of zero. In order to reduce the effect of multicollinearity, we removed a variable when a VIF of more than 10 was found. All models were adjusted for cohort and scanner type. We investigated statistical interaction of sex on all associations of determinants with the aortic diameters by adding interaction terms (sex x determinant) to the models. In addition, we determined to what extent only age and sex and age, sex and anthropometrics explained the variance in ascending and descending aortic diameters.

In 12.7% of the participants, ≥1 of the covariates were missing and they were handled by multiple imputation with five iterations.[15] IBM SPSS statistics software V.21.0 was used to analyse the data and a p-value of <0.05 was considered statistically significant.

Results

Study population

The median age of the 2505 participants was 67 (IQR 64-73) years, and 51.8% were women (table 1). CVD was prevalent in 303 participants (12%).

Table 1. Baseline Characteristics of Study Participants

Variables	Total (n=2505)	Men (n=1208)	Women (n=1297)
Age (years)	67 (64-73)	68 (64-73)	67 (64-73)
Height (cm)	168±9.5	175±7	161.5±6.3
Weight (kg)	78.4±13.7	84±12	73.0±12.8
Body surface area (m^2)	1.9±0.2	2.0±0.2	1.8±0.2
Hip circumference (cm)	103±8	102±6	105±9
Systolic blood pressure (mmHg)	147±20	146±20	147±21
Diastolic blood pressure (mmHg)	80±11	81±11	79±11
Smoking			
Never (%)	718 (29%)	188 (16%)	530 (41%)
Past (%)	1363 (54%)	796 (66%)	567 (44%)
Current (%)	424 (17%)	224 (19%)	200 (15%)
Alcohol consumption			
Never (%)	154 (6%)	30 (3%)	124 (10%)
Past (%)	182 (7%)	83 (7%)	99 (8%)
Current (%)	2169 (87%)	1095 (91%)	1074 (83%)
Coronary calcification volume (mm^3)*	5 (2-287)	138 (20-490)	18.8 (0-125)
Aortic arch calcification volume (mm^3)*	267 (49-881)	297 (55-1010)	238 (43-819)
Total cholesterol (mmol/L)	5.7±1.0	5.4±1.0	5.9±1.0
HDL cholesterol (mmol/L)	1.4±0.4	1.3±0.3	1.6±0.4
Diabetes mellitus (%)	338 (14%)	176 (15%)	162 (13%)
History of cardiovascular disease	303 (12%)	210 (17%)	93 (7%)
Myocardial infarction (%)	143 (6%)	103 (9%)	40 (3%)
PCI (%)	80 (3%)	60 (5%)	20 (2%)
CABG (%)	89 (4%)	77 (6%)	12 (1%)
Stroke (%)	102 (4%)	59 (5%)	43 (3%)
Medication			
Blood pressure lowering medication (%)	1046 (42%)	522 (43%)	524 (40%)
Antithrombotic agents (%)	625 (25%)	310 (26%)	315 (24%)
Serum lipid reducing agents (%)	608 (24%)	365 (30%)	243 (19%)

Values are presented as mean (SD) or median (IQR) for continuous variables and N (%) for categorical variables. Data represent imputed values. Missing values were present for height and weight (0.8%), hip circumference (0.7%), blood pressure (0.4%), smoking and alcohol consumption (2.9%), calcification in coronary arteries (1.4%), calcification in aortic arch (0.2%), serum lipids (1.6%), diabetes mellitus (0.4%), lipid-modifying agents (1.5%) and blood pressure lowering medication (1.5%). HDL indicates high-density lipoprotein. *Nontransformed median volume with interquartile range.

Sex-specific distributions of thoracic aortic diameters

Sex-specific distributions of absolute and BSA-adjusted aortic diameters are given for the total group and for different age groups in table 2. For the ascending and descending thoracic aorta, the mean diameters in men were 38±4 mm and 30±2 mm, and 35±3 mm

and 27±2 mm in women. The full distribution of the absolute diameters, including the 90th and 95th percentiles, are shown in figure 1. After exclusion of participants with a history of CVD, the results did not substantially change. An ascending aortic diameter larger than 40 mm was found in 228/1208 men (18.9%) and in 76/1292 women (5.9%). An aortic diameter larger than 45 mm was found in 26/1208 men (2.2%) and 7/1292 women (0.5%), among whom 4 (0.2%, 3 men) had a diameter larger than 50 mm. A descending aortic diameter of larger than 35 mm was found in 20/1169 (1.7%) men and 4/1293 women (0.3%), and larger than 40 mm in 2 (0.2%) men and no women. None of the participants had a descending diameter of 45 mm or larger. From the 304 participants (12.2%) with an aortic diameter of more than 40 mm, only 4 (1.3%, 3 men and 1 woman) participants died of an aortic event (supplemental table 1).

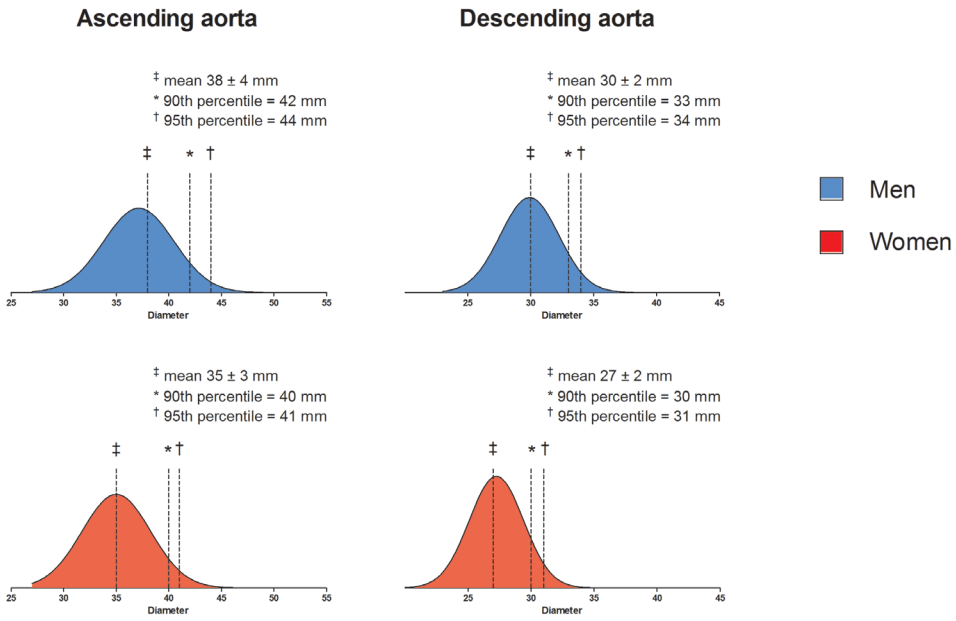


Figure 1. Distribution of the ascending and descending aortic diameters for both men (blue) and women (red), marking mean values, the 90th and 95th percentiles.

Table 2. Distribution of absolute aortic diameter and adjusted for BSA.

			Ascending aorta			Descending aorta		
	Age group		**Total**	**Men**	**Women**	**Total**	**Men**	**Women**
Absolute diameter (mm)	Total	Number	2500	1208	1292	2462	1169	1293
		Mean	36±4	38±4	35±3	29±3	30±2	27±2
		95th	43	44	41	33	34	31
	55-64 years	Number	724	341	383	721	335	386
		Mean	36±4	37±4	35±3	28±3	29±2	27±2
		95th	42	44	40	32	33	30
	65-74 years	Number	1238	610	628	1217	590	627
		Mean	37±4	38±4	35±3	29±3	30±2	27±2
		95th	43	44	41	33	34	31
	≥75 years	Number	538	257	281	524	244	280
		Mean	37±4	38±4	36±3	29±3	31±3	28±2
		95th	43	43	41	34	35	33
BSA-indexed diameter (mm/m2)	Total	Number	2500	1208	1292	2462	1169	1293
		Mean	20±2	19±2	20±2	15±2	15±2	16±2
		95th	24	22	24	18	18	19
	55-64 years	Number	724	341	383	721	335	386
		Mean	19±2	18±2	20±2	15±1	14±1	15±1
		95th	23	22	23	17	17	17
	65-74 years	Number	1238	610	628	1217	590	627
		Mean	19±2	19±2	20±2	15±1	15±1	15±1
		95th	24	23	24	18	18	18
	≥75 years	Number	538	257	281	524	244	280
		Mean	20±2	19±2	21±2	16±2	16±2	17±2
		95th	25	23	25	19	18	20

Mean value is given with the standard deviation.

Determinants of ascending and descending aortic diameters

The results for invariable analyses are presented in supplemental table 2 and the univariable associations of height, weight and BSA with aortic diameters are visualised in supplemental figure 2. Multivariable linear regression analysis showed that higher age, taller height and larger weight, higher diastolic blood pressure, lower systolic blood pressure, larger volume of calcifications in coronary arteries and aortic arch and the use of blood pressure-lowering medication were associated with larger absolute ascending and descending aortic diameters (figures 2 and 3). Conversely, the presence of diabetes and the use of lipid-modifying agents were associated with smaller ascending and descending aortic diameters. A smaller hip circumference was specifically associated with a smaller ascending aortic diameter. Male sex, current smoking, alcohol consumption and lower high-density lipoprotein (HDL) cholesterol were specifically associated with larger descending aortic diameters. None of the interaction terms between the potential

determinants and sex was significant. Age, sex and anthropometrics explained 15% of the variance in ascending aortic diameters while age and sex explained 34% of the variance in descending thoracic aortic diameters. Addition of anthropometrics and conventional cardiovascular risk factors increased this to 21% for the ascending aorta and to 39% for the descending aorta.

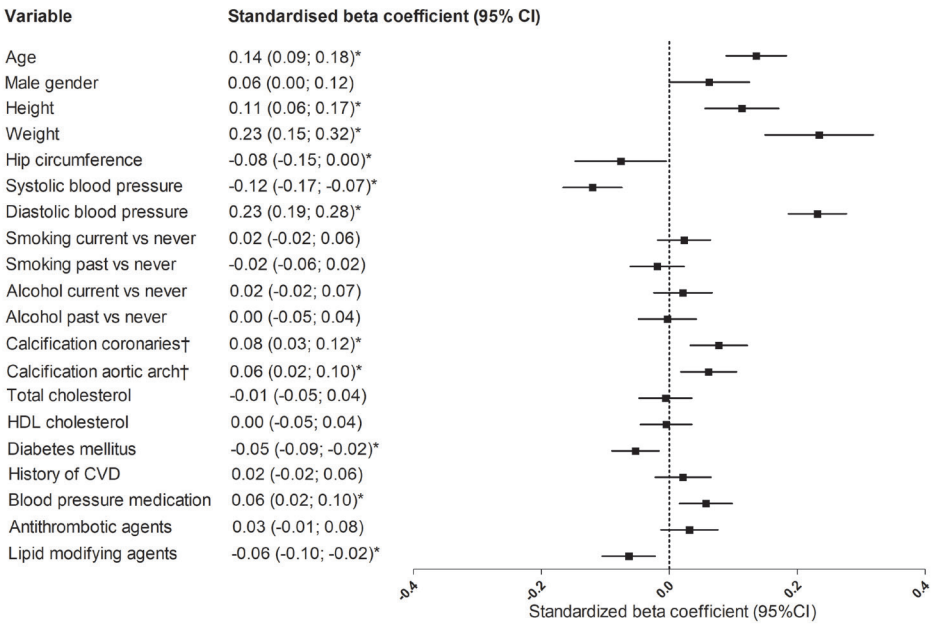


Figure 2. Determinants of ascending aortic diameters in multivariable analysis.
Models were further adjusted for cohort and scanner type. The variance of the ascending aortic diameter was explained by conventional cardiovascular risk factors for 21%.
95% CI= 95% confidence interval.
CVD = cardiovascular disease
* p-value <0.05
† Values represents transformed calcification volumes in mm^3: Ln(calcification volume+1 mm^3)

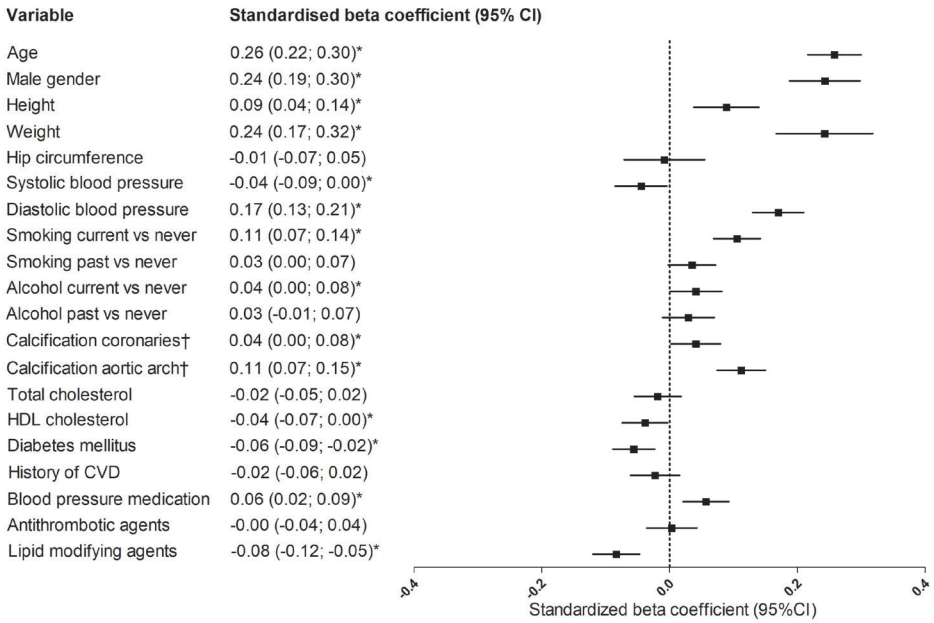


Figure 3. Determinants of descending aortic diameters in multivariable analysis.
Models were further adjusted for cohort and scanner type. The variance of the descending aortic diameter was explained by conventional cardiovascular risk factors for 39%.
95% CI= 95% confidence interval.
CVD = cardiovascular disease
* p-value <0.05

† Values represents transformed calcification volumes in mm^3: Ln(calcification volume+1 mm^3)

Discussion

Using data from a large population-based cohort, we provide new sex-specific distributions of absolute and BSA-corrected thoracic aortic diameters in middle aged and elderly persons. For the ascending and descending aorta, the mean diameters in men were 38 mm and 30 mm, and 35 mm and 27 mm in women. An ascending aortic diameter larger than 40 mm was found in 304 participants (12.2%, 228 men) and a descending aortic diameter larger than 40 mm was found in two participants. Although we found a thoracic aortic diameter of more than 40 in a considerable amount of persons aged 55 years or older, only 4 (1.3%) of them died as a result of an aortic event. This number seems rather low and raises the question whether a cut-off of 40 mm is an appropriate one. Yet, given the low number of events, this should be confirmed by larger studies.

Although the difference in mean aortic diameter between the age group of 55-65 years and ≥75 years was only 1 mm for both the ascending and descending aorta, the aortic

diameter above 55 years still increased. Our results show the 95th percentile for persons above the age of 75 years old to be 43 mm for ascending and 35 mm for descending aorta for men and 41 mm and 33 for women, an age group for whom distribution data are currently scarce.[11] Our data further establish the range of thoracic aortic diameters, which is similar to data found in a study performed in Germany.[16] Absolute aortic diameters measured in the Rotterdam Study are larger than previous studies performed in the USA,[9, 17] which also used non-enhanced CT imaging. They reported older participants (≥55 years) as subanalysis of the entire population studied and therefore contained smaller samples. The larger aortic diameters measured in our study may partly be explained by the larger average height of the study population. Native Dutch people are relatively tall.[18] BSA of our cohort (1.9±0.2 m^2) was comparable with the aforementioned two studies (both 1.9±0.3 m^2), but height was not reported by others and therefore could not be compared. BSA describes height and also weight, and since American individuals are more likely to be obese than Dutch individuals[19] this might suggest a taller height in our group. Nevertheless, both our cohorts as previously smaller cohorts show that an aortic diameter of >40 mm is not uncommon in middle-aged and elderly persons.

In our cohort, both weight and height were found to be important determinants of the aortic diameters, which supports previous findings on this matter.[7, 8] Whether the aortic diameter should be corrected for height, weight or BSA in defining aortic dilatation is an ongoing discussion. While some authors suggest to use only height,[20] others advocate the use of BSA, which takes into account both height and weight.[4] However, longitudinal data are needed to establish the abilities of indexed aortic diameters compared with the abilities of absolute aortic diameters in the prediction of aortic events. Interestingly, from our data, it appeared that absolute values are substantially larger for men than for women, yet BSA-corrected values are statistically larger for women than for men. This suggest that differences in body measures partly explain sex differences in aortic diameters, but that there is still a remaining sex-difference which results in a larger BSA-indexed values for women. Therefore, we conclude that distribution values should be provided for men and women separately, even when correcting for weight, height or BSA.

In line with previous literature,[9, 17, 21] smoking was associated with the diameter of the descending but not the ascending aorta. In addition, HDL cholesterol had a significant inverse relation with only the descending aorta. Based on figure 2 and 3, 39% of the variance in descending aortic diameter but only 21% of the variance in ascending aortic diameter was explained by age, sex, anthropometrics and traditional cardiovascular risk factors. Probably, other factors such as genetic predisposition are more important in the ascending aorta. Already 34% of the variation in descending aortic diameter and 15% of the variation in ascending aortic diameter was explained by age, sex and anthropometrics. Therefore there is only a small increase in explained variance caused by the addition of traditional cardiovascular risk factors to the model. Since this small increase in explained variance was shown in both the ascending and descending aorta, we provide no clear

evidence that the descending aorta is more susceptible to cardiovascular risk factors than the ascending aorta. Both the ascending and descending aortic diameter were associated with calcifications of the coronary arteries or aortic arch and use of lipid-modifying agents. This is in contrast to recent literature showing a significant relation of aortic plaques and calcium with only the descending aorta.[21, 22] In conclusion, although we found differences between the ascending and descending aorta in the association between smoking, alcohol consumption and HDL cholesterol, the effect of these cardiovascular risk factors seems of limited importance in explaining the overall variation in aortic diameter.

In addition, we found that blood pressure was associated with thoracic aortic diameters. We found a positive association of the diastolic blood pressure, but a negative association of the systolic blood pressure with aortic diameters. Whether hypertension is indeed a risk factor for aortic dilatation is still unknown,[23] but our results suggest that high diastolic blood pressure might be more important in the development of aortic dilatation than high systolic blood pressure. Current guidelines[2] advise to reduce blood pressure (both systolic and diastolic). The importance of high diastolic blood pressure on aortic diameters should be stressed and deserves more attention, also in research.

We found diabetes to be negatively associated with both the ascending and descending aortic diameters. This phenomenon has already been shown in the abdominal aorta, where it is described that diabetes is associated with less aortic dilatation of the abdominal aorta.[24, 25] This might be caused by advanced glycation associated with diabetes which inhibits through intermediate steps secretion of the matrix metalloproteinases.[25] Also, the fibrinolytic pathway, more specifically the plasminogen activator inhibitor-1, is mentioned as a candidate mechanism for hyperglycaemic inhibition of abdominal aortic disease.[26] More research is warranted to elucidate the role of these pathways in the development of both thoracic and abdominal aortic aneurysms.

Strengths of our study include the population-based setting and the relatively large sample size. By including participants with hypertension or a history of CVD, we measure the aortic diameter in the general population and not only in healthy people. Therefore the results can be generalised to a larger proportion of the older population.

Limitations

The use of ECG-gated CT scans allowed highly accurate measurements of the aorta. The use of contrast-enhanced CT would have made the measurements even more accurate. However, the use of contrast in predominantly healthy people from the general population is unethical and can cause unnecessary complications, such as an allergic reaction to contrast fluid.

Conclusion

We provide novel sex-specific distributions of thoracic aortic diameter for the middle-aged and elderly general population. Our distribution show high prevalence (12.2%) of

an ascending aortic diameter more than 40 mm, which is typically considered dilated. However, mortality due to aortic aneurysm or dissection in these participants seems rather low, and raises the question whether a cut-off of 40 mm is an appropriate one. Yet, given the low number of events, this should be confirmed by larger studies.

Sex was independently associated with descending aortic diameters and tended to be associated with ascending aortic diameters. This indicates that distribution values should be provided for men and women separately, even when correcting for BSA or height. Traditional cardiovascular risk factors are responsible for only a limited part of the variance in aortic diameters. We found no evidence for effect modification of these associations by sex.

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Supplemental material

Assessment of determinants

Data on current and former smoking habits and alcohol consumption were collected during a structured home interview. We assessed information on the use of blood pressure lowering medication, antithrombotic agents and lipid modifying agents including statins according to the ATC/DDD system (http://www.whocc.no). Clinical measurements were collected during regular visits at the research center.(1) Height, weight, waist and hip circumference were assessed. Blood pressure was measured at the right brachial artery using a random-zero sphygmomanometer with the participant in sitting position. The average of three consecutive measurements was used. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or the use of blood pressure-lowering medication. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were measured using an automated procedure. Diabetes was defined as the use of glucose-lowering medication and/or a fasting glucose level ≥7 mmol/L. Coronary artery calcification (CAC) and aortic arch calcification (AAC) volumes were quantified using commercially available software (Syngo CalciumScoring; Siemens). (2) A history of cardiovascular diseases (myocardial infarction, percutaneous coronary intervention, coronary revascularization, and stroke) was ascertained as described in detail previously.(3)

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Supplemental table 1. Characteristics of participants who died due to aortic aneurysm or dissection during follow-up

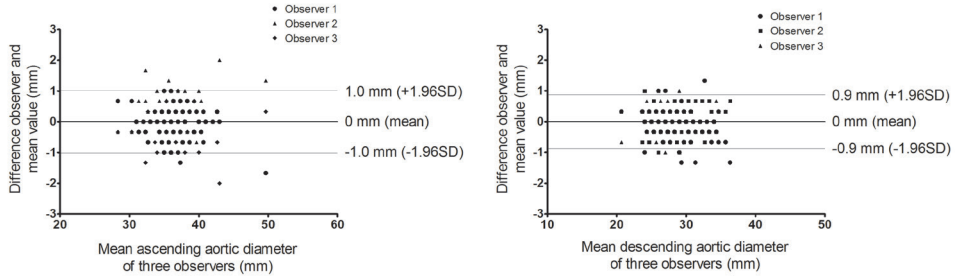
						Ascending aorta				Descending aorta			
Participant	**ICD-code***	**Gender**	**Age (years)**	**Height (cm)**	**Weight (kg)**	**Crude diameter**	**Height-indexed**	**Weight-indexed**	**BSA-indexed**	**Crude diameter**	**Height-indexed**	**Weight-indexed**	**BSA-indexed**
1	I71.1	Men	71	190.60	93.40	47	24.7	0.50	21.2	33	17.3	0.35	14.9
2	I71.1	Women	81	159.50	67.40	43	27.0	0.64	25.3	32	20.1	0.47	18.8
3	I71.2	Women	82	161.20	74.38	38	23.6	0.51	21.3	35	21.7	0.47	19.6
4	I71.3	Women	67	157.00	69.80	37	23.6	0.53	21.7	34	21.7	0.49	19.9
5	I71.4	Women	60	161.50	49.50	39	24.2	0.79	25.9	32	19.8	0.65	21.3
6	I71.8	Men	60	174.80	98.20	42	24.0	0.43	19.7	36	20.6	0.37	16.9
7	I71.8	Men	78	177.00	71.90	41	23.2	0.57	21.8	36	20.3	0.50	19.1
8	I71.8	Men	85	173.00	82.80	39	22.5	0.47	19.8	33	19.1	0.40	16.8

* I71.1 thoracic aortic aneurysm, ruptured, I71.2 thoracic aortic aneurysm, without mention of rupture, I71.3 abdominal aortic aneurysm, ruptured, I71.4 abdominal aortic aneurysm, without mention of rupture, I71.8 aortic aneurysm of unspecified site, rupture

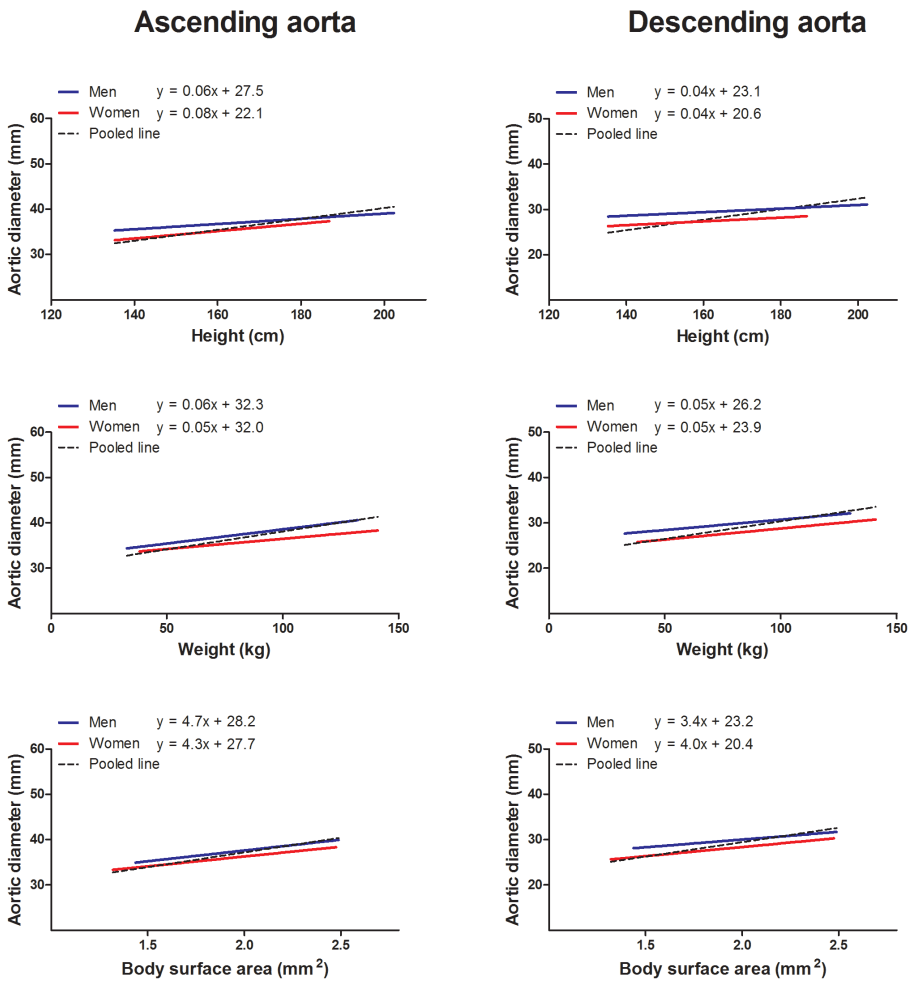
Supplemental table 2. Univariable analysis for ascending and descending aortic diameters

Variables	Ascending aorta Beta (95% CI)	Descending aorta Beta (95% CI)
Age (years)	0.04 (0.02; 0.06)*	0.08 (0.07; 0.10)*
Height (cm)	0.12 (0.11; 0.13)*	0.12 (0.11; 0.13)*
Weight (kg)	0.08 (0.07; 0.09)*	0.08 (0.07; 0.08)*
Hip circumference (cm)	0.04 (0.02; 0.05)*	0.03 (0.02; 0.05)*
Systolic blood pressure	0.01 (0.00; 0.01)*	0.02 (0.01; 0.02)*
Diastolic blood pressure	0.06 (0.05; 0.08)*	0.04 (0.03; 0.05)*
Smoking		
Past versus never	0.57 (0.28; 0.86)*	0.76 (0.55; 0.97)*
Current versus never	0.35 (-0.04; 0.73)	0.60 (0.32; 0.89)*
Alcohol consumption		
Past versus never	-0.60 (-1.23; 0.4)	-0.15 (-0.63; 0.33)
Current versus never	0.88 (0.44; 1.33)*	0.77 (0.43; 1.10)*
Calcification volumes in coronary artery	0.31 (0.25; 0.36)*	0.30 (0.26; 0.34)*
Calcification volumes in aortic arch	0.18 (0.12; 0.24)*	0.25 (0.21; 0.30)*
Total cholesterol (mmol/L)	-0.35 (-0.49; -0.20)*	-0.41 (-0.51; -0.30)*
HDL-cholesterol (mmol/L)	-1.48 (-1.84; -1.12)*	-1.74 (-2.00; -1.47)*
Diabetes mellitus	-0.20 (-0.62; 0.22)*	0.07 (-0.25; 0.38)
History of cardiovascular disease	1.08 (0.64; 1.52)*	0.74 (0.41; 1.07)*
Blood pressure lowering medication	0.83 (0.54; 1.12)*	0.74 (0.53; 0.96)*
Antithrombotic agents	0.90 (0.57; 1.23)*	0.71 (0.46; 0.95)*
Serum lipid reducing agents	-0.05 (-0.38; 0.28)	-0.15 (-0.40; 0.09)

95% CI= 95% confidence interval.
* p-value <0.05.



Supplemental figure 1. Bland-Altman agreement between three observers



Supplemental figure 2. Mean aortic diameter of the ascending and descending aorta plotted against height, weight and body surface area in men and women separately.

CHAPTER 6

6

Thoracic aortic diameter and cardiovascular events and mortality among women and men: The Rotterdam Study

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Submitted

Objective

To assess the independent association between crude and indexed ascending and descending aortic (AA and DA) diameters with major cardiovascular outcomes among women and men.

Methods

2178 women and men ≥55 years underwent multi-detector CT scan of thorax from the Rotterdam study. Crude and indexed diameters of the AA and DA, and dichotomous cutoff points (corresponding to 75th to 95th percentiles) were measured. Incidence of stroke, coronary heart disease (CHD), heart failure (HF), cardiovascular and all-cause mortality were outcomes under study during 13 years of follow-up.

Results

Among women, larger crude and almost all indexed DA diameters showed significant associations with the outcomes. Hazard ratios-HRs (95%CI) per 1 standard deviation-SD increase in crude DA diameter were 1.38 (1.03, 1.84) for stroke, 1.33 (1.01, 1.74) for HF, 1.47 (1.05, 2.05) for cardiovascular mortality, and 1.20 (1.02, 1.40) for total mortality. Among men, only weight-indexed DA diameters were associated with total mortality: 1.47 (1.21, 1.77). For AA, larger weight-indexed values were significantly associated with higher risk of mortality in both sexes: 1.19 (1.05, 1.36) in women and 1.38 (1.16, 1.65) in men). For crude DA diameter, the 75th percentile showed significant association with incident stroke among men while the 75th and 85th percentiles showed significant associations with incident HF and cardiovascular mortality respectively in women.

Conclusions

Our study suggests a role for descending aortic diameter as a marker for increased cardiovascular risk, in particular among women.

Abstract

Introduction

Dilatation of thoracic aorta has a silent nature. The risk of natural complications, including dissection or rupture, rises with increasing aortic diameter[1]. Therefore, indications for surgical interventions, recommended by the international guidelines, are mainly based on aortic diameter and derived from weighting the risk of potential natural complications against the risk of elective surgery[2, 3]. However, aortic diameter also increases with age. Changes of vessel size and structure (i.e. vascular remodeling) have a systemic nature involving hemodynamic and biological processes (oxidation, inflammation, matrix degradation, fibrosis)[4] that play a key role in cardiovascular disease (CVD) pathogenesis. While enlargement of the thoracic aorta is a frequent finding in clinical practice, few longitudinal data regarding its long-term prognosis for major CVD outcomes at population level, other than rupture or dissection, exist[5].

The limited available longitudinal data focuses mainly on the aortic root and suggest an association between aortic root diameter with CVD and mortality[5]. The association between ascending or descending aorta and cardiovascular events has only been investigated in two studies.[6, 7] Additionally, data regarding the sex-specific long-term prognostic value of dilatation of different segments of thoracic aorta for different cardiovascular outcomes are lacking. As the aortic diameter is significantly related to body measurements[8], use of aortic diameters indexed for body measurements could improve its prognostic value for cardiovascular outcomes. Assessing the cardiovascular risk associated with thoracic aortic size among asymptomatic women and men could lead to effective, sex-specific, prevention strategies.

Within the large population-based Rotterdam Study[9], we evaluated the association between computed tomography (CT)-assessed ascending and descending thoracic aortic diameters, both absolute and indexed, with cardiovascular events and mortality during 13 years of follow-up among women and men. We further assessed the predictive value of thoracic aortic diameters for cardiovascular events at dichotomous cutoff points corresponding to sex-specific percentiles of thoracic aortic diameters distribution.

Methods

Study Population

The Rotterdam Study (RS) is a prospective population-based cohort including individuals living in the well-defined Ommoord district in the city of Rotterdam, the Netherlands. The study started in 1990 (RS-I) including 7,983 individuals and was extended twice (RS-II and RS-III) to include subjects who turned 55 after the start of the study or migrated into the research area after the start of the study. By the end of 2008, the Rotterdam Study comprised 14,926 subjects aged 45 years or over[9]. Between 2003 and 2006, 2524 participants, who visited the research center for their regular follow-up visits (fourth visit of RS-1 and second

visit of RS-II), were invited to undergo non-enhanced multi-detector CT scan of thorax. For this longitudinal analysis, we excluded participants with prevalent stroke, coronary heart disease (CHD) or heart failure (HF) at the time of the CT. This left 2178 participants for the analyses in the current study. All participants provided written informed consent. The Rotterdam study complies with the declaration of Helsinki and has been approved by the medical ethics committee, according to the population screening act: Rotterdam study, executed by the ministry of health, welfare and sports of the Netherlands.

Ascending and descending thoracic aortic diameters

Ascending and descending thoracic aortic diameters were measured in millimeters by non-contrast ECG-gated CT images obtained using 16-slice (n= 642) or 64-slice (n=1536) multidetector CT scanners (Somatom Sensation 16 or 64; Siemens, Forchheim, Germany). We used the double-oblique method in two directions at the bifurcation level of the pulmonary artery. A full report of the scan protocol was described in detail earlier[10]. For the current analyses, in addition to the crude aortic diameters, the aortic diameters of all participants were also corrected for height, weight, body mass index (BMI) and body surface area with use of the aortic size index (ASI): ASI (cm/m^2) = aortic diameter (cm) / body surface area (m^2). Body surface area was calculated using the Dubois and Dubois formula[11]: BSA (m^2) = 0.007184 x $Height(m)^{0.725}$ x $Weight(kg)^{0.425}$. Coronary artery calcification (CAC) and aortic arch calcification (AAC) were quantified using commercially available software (Syngo CalciumScoring; Siemens)[12].

Cardiovascular risk factors

Previous medical history and comorbidities including hypertension, diabetes mellitus, current health status, smoking and alcohol consumption (never, past and current) and use of medications (blood pressure lowering, lipid lowering, and antithrombotic medications) were assessed by a trained interviewer at the home visit using a computerized questionnaire. A detailed explanation of the methods for measurement of the covariables can be found in the supplemental material.

Cardiovascular events and mortality

Cardiovascular events in this study included stroke, CHD, HF, cardiovascular mortality and all-cause mortality. All Rotterdam Study participants are intensively and constantly followed to identify the development of all adverse outcomes. A detailed explanation of the methods for outcome assessment can be found in the supplemental material.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or as median ± interquartile range (IQR) and categorical variables as numbers (percentages, %). Continuous variables were compared using independent t-test in case of normal distribution or Mann-

Whitney test in case of skewed distribution. Chi-square was used for comparison among categorical variables. Diameters of ascending and descending aorta were indexed by height in meters, weight in kilograms, BSA and BMI. We further standardized the crude and indexed ascending and descending aortic diameters for use in statistical analyses.

A Cox proportional hazard model was used to evaluate the association between time to each major adverse event and each aortic diameter (crude, indexed values). We reported the hazard ratios (HR) with 95% confidence intervals (CI). The analyses were adjusted for age, waist to hip ratio (WHR), smoking, alcohol consumption, total and high-density lipoprotein (HDL) cholesterol, hemoglobin, hypertension, diabetes mellitus, lipid lowering medications, anti-thrombotic medication, and CAC and AAC. Additionally, height and weight were used as covariates in the models that did not include them for indexing the aortic diameters. For each of the final models, proportional hazards assumption was evaluated through Schoenfeld residuals, Goodness-of-fit through linktest and Cox Snell residuals, linearity of covariables through martingales, and influential observations through deviance residuals and Cook distance. As a sensitivity analysis, we further performed competing risk analysis for cardiovascular mortality and non-cardiovascular mortality using non-parametric and semiparametric (Fine and Gray) methods evaluating cause specific hazard and cumulative incidence function.

We further examined associations of crude AA and DA diameters with the outcomes at dichotomous cutoff points corresponding to 75th, 80th, 85th, 90th, and 95th percentiles. The associated discriminative capacity for each cutoff point was evaluated using Harrell's C statistics. We further developed Cox proportional hazard models and examined the associations between percentiles based cutoff points for each crude aortic diameter and the risk for each cardiovascular outcome. These models were adjusted for the same covariates described above.

The analyses were performed with STATA (version 14.0, Stata Corp, College Station, TX). A two-sided P value of <0.05 was considered statistically significant.

Results

Participants and characteristics

In total, 2,178 participants of the Rotterdam Study were included in this analysis. Mean age was 68.6 ± 6.6 years, and 55% of the participants were women (Table 1). The ascending aortic (AA) diameter could be measured in 99.8% (2174/2178) and the descending aortic (DA) diameter in 98.5% (2146/2178) of the participants. Significant differences were observed in anthropometric measures, with height, weight, waist circumference and WHR being larger in men and BMI and hip circumference being higher in women. Men smoked more often, had a higher alcohol consumption as well as larger values for diastolic blood pressure, and CAC. Serum levels of total and HDL cholesterol were higher in women (Table 1). During 13 years of follow-up (median: 10.6 years; range between 0.18-13.6 years), 64

women and 64 men were diagnosed with stroke, 53 women and 88 men developed CHD, and 72 women and 68 men developed HF. In total, 229 women and 255 men died during follow-up of which 46 and 39 deaths were due to cardiovascular causes among women and men respectively.

Table 1 Baseline characteristics of the participants

Variable	Total N= 2178	Women N=1186	Men N= 992	p-value
Age, years	68.6 (6.6)	68.7 (6.7)	68.6 (6.4)	0.7493
Weight, Kg	77.92 (13.58)	73.0 (12.7)	84 (12.1)	<0.001
Height, cm	167.9 (9.6)	161.6 (6.3)	175.3 (7.2)	<0.001
Body mass index	27.61 (4.16)	27.87 (4.58)	27.30 (3.56)	<0.002
Waist, cm	93.66 (11.6)	89.38 (11.0)	98.78 (10.1)	<0.001
Hip, cm	103.5 (7.8)	104.8 (8.9)	102.0 (5.9)	<0.001
Waist hip ratio	0.91 (0.09)	0.85 (0.07)	0.97 (0.07)	< 0.001
Systolic blood pressure, mmHg	147 ± 19.9	147.0 ± 20.3	146.4 ± 19.5	0.504
Diastolic blood pressure, mmHg	80.6 ± 10.6	79.5 ± 10.5	81.9 ± 10.6	<0.001
Smoking, n (%)				<0.001
Never	661 (30.4%)	494 (42%)	167 (17%)	
Past	1145 (52.6%)	512 (43%)	633 (64%)	
Current	372 (17%)	180 (15%)	192 (19%)	
Alcohol consumption, n (%)				<0.001
Never	136 (6.2%)	114 (10%)	22 (2%)	
Past	155 (7.1%)	89 (7%)	66 (7%)	
Current	1887 (86.7%)	983 (83%)	904 (91%)	
Coronary artery calcium (log+1)	3.35 (2.40)	2.7 (2.30)	4.1 (2.29)	<0.001
Aortic arch calcium (log+1)	4.9 (2.32)	4.8 (2.33)	5.0 (2.30)	0.164
Total cholesterol mmol/lt	5.8 ± 0.9	6.0 ± 0.9	5.5 ± 0.9	<0.001
HDL cholesterol mmol/lt	1.5 ± 0.4	1.6 ± 0.4	1.3 ± 0.3	<0.001
Hemoglobin gr/dl	8.9 ± 0.7	8.6 ± 0.6	9.3 ± 0.7	<0.001
Glucose mmol/lt	5.7 ± 1.2	5.6 ± 1.2	5.8 ± 1.2	0.010
Comorbidities, n (%)				
Prevalent hypertension	1318 (60.5%)	714 (60%)	604 (61%)	0.743
Prevalent diabetes mellitus	269 (12.4%)	140 (12%)	129 (13%)	0.482
Medication use, n (%)				
Blood pressure lowering medication	792 (36.4%)	439 (37%)	353 (36%)	0.486
Lipid lowering medication	421 (19.3%)	250 (21%)	171 (17%)	0.024
Antithrombotic agents	340 (15.6%)	161 (14%)	179 (18%)	0.004

Values are presented as mean (standard deviation) or median (25^{th}-75^{th} percentile) or numbers (%).

Crude and indexed ascending aortic diameters in association with cardiovascular outcomes and mortality

When analyzed continuously, larger crude AA diameter showed a significant association with stroke in only men (HR per 1 standard deviation (SD) increase; 95% CI: 1.35; 1.05, 1.75). Larger crude and height-indexed AA diameters showed a significant association with incident of HF among women (HR per 1 SD; 95% CI: 1.32; 1.03, 1.71 for crude and 1.37; 1.09, 1.71 for height-indexed diameter). Weight-indexed (HR per 1 SD; 95% CI: 1.35; 1.03, 1.77) and BSA-indexed (HR per 1 SD; 95% CI: 1.34; 1.005, 1.79) AA diameters showed a significant association with cardiovascular mortality in only women (Table 2, figure 1A). Weight-indexed and BMI-indexed AA diameters showed a significant association with all-cause mortality among both women (HR per 1 SD; 95% CI: 1.19; 1.05, 1.36 for weight-indexed and 1.20; 1.06, 1.36 for BMI-indexed) and men (HR per 1 SD; 95% CI: 1.38; 1.16, 1.65 for weight-indexed and 1.31; 1.13, 1.53 for BMI-indexed).

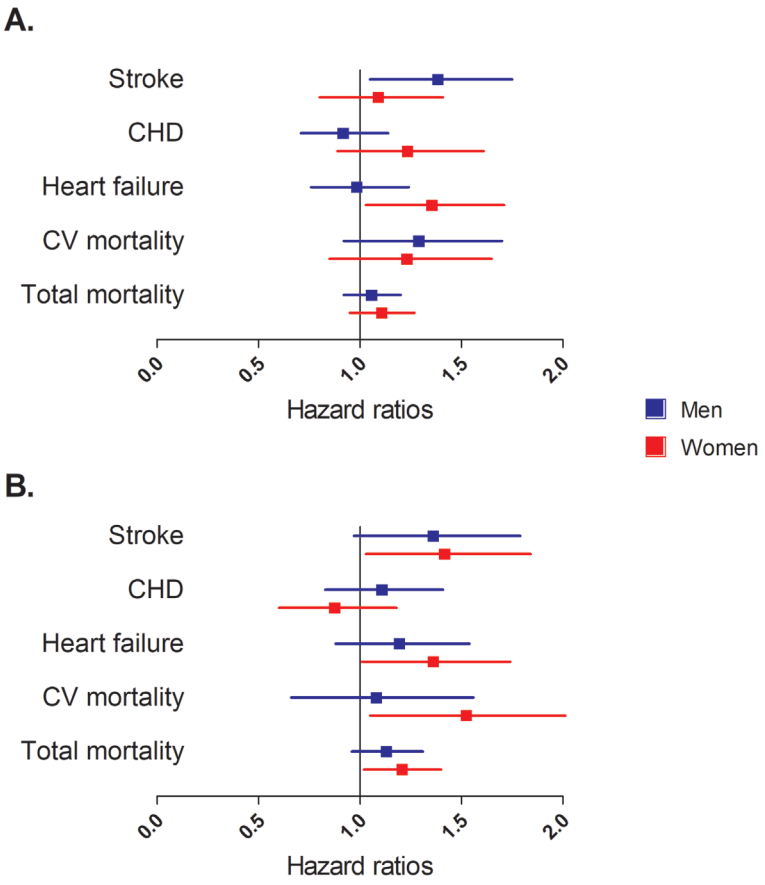


Figure 1. Forest plot of hazard ratios for the association of crude ascending (A) and descending (B) aortic diameters with cardiovascular outcomes and mortality among 992 men and 1186 women. CHD= coronary heart disease, CV= cardiovascular.

Table 2. Standardized hazard ratios for crude and indexed ascending aortic diameters and risk of cardiovascular outcomes and mortality

	Stroke	Coronary Heart Disease	Heart Failure	CV Mortality	Total Mortality
Women					
Crude diameter	1.06 (0.80, 1.41)	1.20 (0.89, 1.61)	**1.32 (1.03, 1.71)**†	1.19 (0.85, 1.65)	1.10 (0.95, 1.27)
Height Indexed	1.06 (0.82, 1.38)	1.17 (0.90, 1.54)	**1.37 (1.09, 1.71)**†	1.18 (0.87, 1.60)	1.06 (0.93, 1.22)
Weight Indexed	1.24 (0.96, 1.59)	1.15 (0.87, 1.51)	1.01 (0.80, 1.29)	**1.35 (1.03, 1.77)**†	**1.19 (1.05, 1.36)** †
BSA Indexed	1.22 (0.95, 1.57)	1.18 (0.90, 1.54)	1.24 (0.98, 1.56)	**1.34 (1.005, 1.79)** †	1.13 (0.99, 1.29)
BMI Indexed	1.19 (0.92, 1.53)	1.15 (0.87, 1.51)	0.96 (0.75, 1.22)	1.29 (0.99, 1.69)	**1.20 (1.06, 1.36)** †
Men					
Crude diameter	**1.35 (1.05, 1.75)**†	0.90 (0.71, 1.14)	0.95 (0.76, 1.24)	1.25 (0.92, 1.70)	1.05 (0.92, 1.20)
Height Indexed	1.29 (0.99, 1.66)	0.91 (0.72, 1.15)	0.97 (0.79, 1.50)	1.22 (0.9, 1.66)	1.0 (0.88, 1.14)
Weight Indexed	1.41 (0.95, 2.10)	0.91 (0.66, 1.27)	0.95 (0.66, 1.38)	1.42 (0.92, 2.17)	**1.38 (1.16, 1.65)** †
BSA Indexed	1.25 (0.93, 1.68)	0.93 (0.71, 1.21)	0.99 (0.75, 1.30)	1.37 (0.97, 1.94)	1.12 (0.97, 1.29)
BMI Indexed	1.37 (0.98, 1.91)	0.91 (0.69, 1.21)	0.93 (0.68, 1.28)	1.32 (0.90, 1.93)	**1.31 (1.13, 1.53)** †

† **Bold type:** Statistically significant association (P< 0.05).
All models were adjusted for age, waist-hip ratio, smoking, alcohol consume, total and high-density lipoprotein cholesterol, hemoglobin, hypertension, diabetes mellitus, cardiovascular disease, lipid lowering, antithrombotic and blood pressure lowering medications and coronary and aortic arch calcifications. Weight and height were used as covariates for adjustment if they were not integrated into the indexed outcome.
CV = cardiovascular, BSA = body Surface area, BMI = body mass index.

Crude and indexed descending aortic diameters in association with cardiovascular outcomes and mortality

There was a stronger association between larger crude and indexed DA diameters with the risk of stroke, HF, cardiovascular mortality and all-cause mortality in women than men. The HRs per 1 SD (95% CI) for crude DA diameter were 1.38 (1.03, 1.84) for stroke, 1.33 (1.01, 1.74) for HF, 1.47 (1.05, 2.05) for cardiovascular mortality, and 1.20 (1.02, 1.40) for all-cause mortality in women. Among men, only weight-indexed (HR per 1 SD; 95% CI: 1.47; 1.21, 1.77), BSA-indexed (HR per 1 SD; 95% CI: 1.19; 1.02, 1.38) and BMI-indexed (HR per 1 SD; 95% CI: 1.38; 1.17, 1.62) DA diameters were associated with all-cause mortality (Table 3, Figure 1B).

Competing risk analyses for cardiovascular and all-cause mortality

Findings from the competing risk analyses showed significant associations for crude and all indexed DA diameters with cardiovascular mortality in women and for weight-indexed and BMI-indexed DA diameters with non-cardiovascular mortality in men. Neither crude nor indexed AA diameter showed any significant associations with cardiovascular or non-cardiovascular mortality among women or men in these analyses (supplemental table 1).

Associations of aortic diameters with cardiovascular outcomes at dichotomous cut points corresponding to 75th, 80th, 85th, 90th, and 95th percentiles

Supplemental tables 2-5 show the cutoffs for crude values significantly associated with each outcome using the percentiles approach. In general, the area under the curve (AUC) for the examined percentiles were good (0.74-0.86) (supplementel tables 6-9). For the ascending aorta, a crude diameter ≥ 41 mm (95th percentile) was associated with increased risk for CHD (HR; 95% CI: 2.76; 1.077, 7.09) and HF (HR; 95% CI: 3.25; 1.43, 7.38) among women and a crude AA diameter ≥ 40 mm (75th percentile) was associated with increased risk for stroke (HR; 95% CI: 2.05; 1.20, 3.50) among men as well as the cutoffs based on the 80th, 85th and 90th percentile. For descending aorta in women, crude diameter ≥ 31 mm (95th percentile) was associated with stroke (HR; 95% CI: 2.0; 1.03, 3.90) and a crude diameter ≥ 29 mm (75th percentile) was associated with HF (HR; 95% CI: 1.92; 1.16, 3.18) together with the cutoffs based on the 80th, 85th and 90th percentiles. The Kaplan Meier curves are shown in figure 2. A crude diameter ≥ 30 mm (85th percentile) was associated with cardiovascular mortality (HR; 95% CI: 2.37; 1.23, 4.55) as well as the cutoffs based on the 90th and 95th percentile. In men, crude DA diameter ≥ 31 mm (75th percentile) was associated with stroke (HR; 95% CI: 1.89; 1.11, 3.23).

Table 3. Standardized hazard ratios for crude and indexed descending aortic diameters and risk of cardiovascular outcomes and mortality

	Stroke	Coronary Heart Disease	Heart Failure	CV Mortality	Total Mortality
Women					
Crude diameter	**1.38 (1.03, 1.84)** †	0.84 (0.60, 1.18)	**1.33 (1.01, 1.74)**†	**1.47** (**1.05, 2.05**) †	**1.20 (1.02, 1.40)** †
Height Indexed	**1.33 (1.04, 1.72)** †	0.87 (0.65, 1.16)	**1.38 (1.10, 1.73)**†	**1.39** (**1.05, 1.85**) †	1.12 (0.98, 1.28)
Weight Indexed	**1.40 (1.10, 1.79)** †	0.94 (0.70, 1.25)	0.99 (0.77, 1.27)	**1.48** (**1.13, 1.95**) †	**1.22 (1.07, 1.39)** †
BSA Indexed	**1.48 (1.16, 1.89)** †	0.90 (0.67, 1.19)	1.24 (0.99, 1.56)	**1.52** (**1.16, 1.99**) †	**1.17 (1.03, 1.34)** †
BMI Indexed	**1.37 (1.06, 1.76)** †	0.93 (0.70, 1.25)	0.94 (0.73, 1.22)	**1.46** (**1.09, 1.95**) †	**1.23 (1.08, 1.41)** †
Men					
Crude diameter	1.32 (0.97, 1.79)	1.08 (0.83, 1.41)	1.16 (0.88, 1.54)	1.02 (0.66, 1.56)	1.12 (0.96, 1.31)
Height Indexed	1.26 (0.95, 1.67)	1.08 (0.84, 1.38)	1.16 (0.89, 1.51)	1.00 (0.68, 1.49)	1.05 (0.91, 1.20)
Weight Indexed	1.21 (0.80, 1.83)	1.11 (0.80, 1.55)	1.08 (0.76, 1.55)	1.26 (0.76, 2.09)	**1.47 (1.21, 1.77)** †
BSA Indexed	1.14 (0.83, 1.57)	1.12 (0.86, 1.46)	1.16 (0.88, 1.54)	1.21 (0.81, 1.81)	**1.19 (1.02, 1.38)** †
BMI Indexed	1.21 (0.85, 1.73)	1.07 (0.80, 1.43)	1.04 (0.76, 1.43)	1.17 (0.75, 1.83)	**1.38 (1.17, 1.62)** †

† **Bold type:** Statistical significance association (P< 0.05).
All models were adjusted for age, waist-hip ratio, smoking, alcohol consume, total and high-density lipoprotein cholesterol, hemoglobin, hypertension, diabetes mellitus, cardiovascular disease, lipid lowering, antithrombotic and blood pressure lowering medications and coronary and aortic arch calcifications. Weight and height were used as covariates for adjustment if they were not integrated into the indexed outcome.
CV= cardiovascular, BSA=body Surface area, BMI: body mass index.

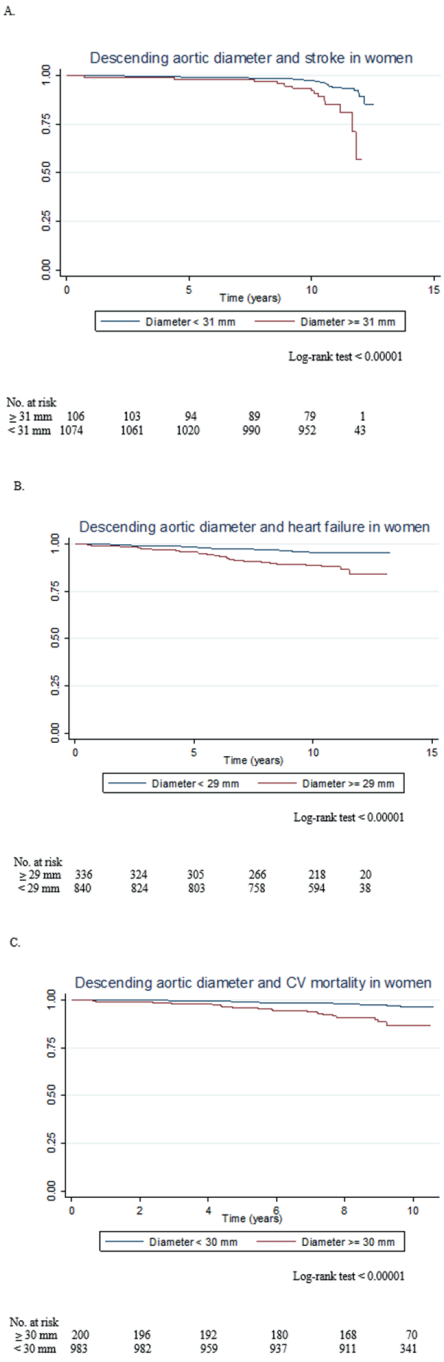


Figure 2 Kaplan Meier curves for descending thoracic aortic diameter and cardiovascular outcomes in women using the crude sex-specific percentile derived cutoff values specified in each graph. (A) stroke, (B) heart failure, (C) cardiovascular mortality.

Discussion

Within the large population-based Rotterdam Study, we found gender differences in the association of thoracic aortic diameters with the risk of cardiovascular outcomes during 13 years of follow-up. The gender differences were more pronounced for descending aorta, as the descending aortic diameters were strongly associated with stroke, HF, cardiovascular mortality in women. The risk for several cardiovascular outcomes increased significantly at cutoff points that were below the 95th percentile of the distribution of aortic diameters. So far, few studies have shown associations between aortic root diameters and adverse cardiovascular outcomes[5, 13, 14], and the evidence regarding ascending and descending aortic diameters remains limited. Gondrie et al[6] showed that ascending and descending thoracic aortic diameters were associated with a borderline increased risk for CVD. Recently, the investigators from the Framingham Heart Study reported on the predictive value of enlarged descending aortic diameters for incident cardiovascular events in a younger population[7]. Both papers, however, were based on a composite cardiovascular outcome and did not evaluate associations in a gender specific manner. To our knowledge, our study is the first to determine the associations between ascending or descending aortic diameters and multiple cardiovascular outcomes among women and men separately.

In the current study, we report a stronger association between descending aortic diameter and cardiovascular outcomes or mortality than that of the ascending aortic diameter. This is in line with the literature regarding closer link between descending aortic aneurysms and atherosclerosis[15]. This relationship might be attributed to the possible different connective tissue content in the descending compared to the ascending thoracic aorta[16]. In a meta-analysis including 11 studies, Katsanos et al[15] showed a larger prevalence of complex atheromatous plaques in the descending aorta among patients with stroke compared with controls. Wehrum et al[17] showed that retrograde blood flow in the proximal region of descending aorta was found in patients with stroke and this retrograde blood flow increased in patients with concomitant complex plaques, low strain, and/or large aortic diameter. A larger prevalence of atheromatous plaques and a retrograde flow might explain the increased risk of stroke in participants with larger descending aortic diameters.

Sex-differences in atherosclerosis have been mainly found in the coronary vessels[18]. Consequently, the differences between women and men in prevalence of CVD and its risk markers have received considerable attention in patients with coronary heart disease[19-21]. Our data revealed stronger associations between thoracic aortic diameters, in particular descending aorta, and the cardiovascular outcomes or mortality among women compared to men. As our population comprised post-menopausal women, hormonal changes during and after menopause may partly explain these findings. As women age and in particular go through menopause, the prevalence of hypertension increases[22], which might partly explain the larger burden of stroke and HF in older women.

However, the descending aortic diameter was independently associated with stroke, HF and cardiovascular mortality after taking into account hypertension among women in our study. Histopathological research of the descending aortic wall structure might help to further examine the differences between women and men with regard to the outcomes.
While both crude and indexed descending aortic diameters were associated with mortality, the associations for ascending aorta were stronger for indexed values. This suggests that it is important to adjust the ascending aortic diameters for body measurements to adequately predict cardiovascular outcomes. The importance of indexed values was also illustrated by Cuspidi et al[14], who showed that the aortic root indexed by height, but not by BSA or crude diameters, were associated with the composite outcome of fatal or non-fatal cardiovascular events.
The most recent European[23] and American[24] guidelines on primary prevention of CVD do not discuss the cardiovascular risk associated with increased thoracic aortic diameters. The European Society of Cardiology (ESC) guidelines consider patients with abdominal aortic aneurysms, but not those with thoracic aortic aneurysms, to be at very high cardiovascular risk[23]. We showed that the thoracic aortic diameter is associated with an increased risk of cardiovascular outcomes and mortality. In addition, we demonstrated that the risk for several cardiovascular outcomes significantly increases at a cutoff point below the sex-specific 95th percentiles of the population distribution. This implies that not only patients with aortic dilatation (aortic diameter >95th percentile) are at risk for major adverse outcomes, but a large group of individuals with mildly enlarged aortic diameters in the general population are at increased risk for cardiovascular outcomes and mortality. Strengths of our study include the population-based setting and the relatively large sample size which made the sex-specific analyses with multiple outcomes possible. The use of ECG-gated CT scans allowed for highly accurate measurements of the aorta. Computed tomography is a commonly used imaging technique in clinical practice, which allows to measure the aortic diameter even when this is not the primary reason for the investigation. Furthermore, our analyses included an asymptomatic population free of prevalent CVD at baseline. Besides presenting the associations with continuous aortic diameters, we also showed the predictive value of several clinically relevant percentile cut off points to identify individuals at increased risk for cardiovascular events. The limitations of our study also merit acknowledgment. The Rotterdam study consists of participants of 55 years or older and predominantly from an European ethnicity. This might limit generalization of our results to younger and non-European populations. The performance of non-contrasted CT scan limits the visualization and differentiation of the components of the non-calcified atheromatous plaque at the level of the vascular wall. This does not allow us to evaluate the role that atherosclerosis at the level of the descending aorta can play in increasing the risk of stroke.

Conclusion

Our study suggests a role for the descending thoracic aortic diameter as a marker for increased cardiovascular risk, in particular among women. The cutoff point for increased cardiovascular risk for several of the cardiovascular outcomes, was below the 95th percentile of the distribution of thoracic aortic diameters.

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Supplemental material

Assessment of determinants

Data on current and former smoking habits and alcohol consumption were collected during a structured home interview. We assessed information on the use of blood pressure lowering medication, antithrombotic agents and lipid modifying agents including statins according to the ATC/DDD system (http://www.whocc.no). Clinical measurements were collected during regular visits at the research center. Body surface area (BSA) was calculated using the Dubois formula[1]: BSA (in m^2) = 0.007184 x height (in m)$^{0.725}$ x weight (in kg)$^{0.425}$. In addition, waist and hip circumference were assessed. Blood pressure was measured at the right brachial artery using a random-zero sphygmomanometer with the participant in sitting position. The average of three consecutive measurements was used. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or the use of blood pressure-lowering medication. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were measured using an automated procedure. Diabetes was defined as the use of glucose-lowering medication and/or a fasting glucose level ≥7 mmol/L. Coronary artery calcification (CAC) and aortic arch calcification (AAC) volumes were quantified using commercially available software (Syngo CalciumScoring; Siemens).

Cardiovascular and mortality outcomes

The major adverse outcomes included in this study were stroke, coronary heart disease (CHD), heart failure (HF), cardiovascular mortality and all-cause mortality. All Rotterdam Study participants are intensively and constantly followed to identify the development of all adverse outcomes. Stroke was defined according to World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer or leading to death, with no apparent origin other than vascular. History of stroke, cardiovascular disease (CVD) or HF at baseline was assessed during the baseline interview and verified by reviewing medical records. After enrollment, participants were continuously monitored for incident of stroke, CVD or HF through automated linkage of the study database with medical records from general practitioners. Additional information was obtained from hospital records. Potential strokes identified in medical records were reviewed by research physicians, and verified by an experienced stroke neurologist. Transient ischemic attacks or subarachnoid hemorrhages were not included. Follow-up was complete until January 1st, 2016[2]. Incidence of CHD included incidence of fatal or non-fatal myocardial infarction (MI), other CHD mortality, coronary artery bypass graft, or percutaneous transluminal angioplasty during follow-up until January 1st, 2015, confirmed by ECG or medical records[3]. The diagnosis of HF was classified as definite, probable, possible or unlikely. Definite HF was defined as a combination of the presence of typical symptoms or signs of HF, such as

breathlessness at rest or during exertion, ankle edema, and pulmonary crepitation, confirmed by objective evidence of cardiac dysfunction (chest X-ray, echocardiography)[3]. This definition is in accordance with the criteria of the European Society of Cardiology (ESC)[4]. HF is classified as probable when at least two typical symptoms suggestive of HF are present, and at least one of the following: history of CVD (e.g., MI, valvar heart disease, hypertension), positive response to initiated treatment for HF, or objective evidence of cardiac dysfunction, while symptoms cannot be attributed to another underlying disease, such as chronic obstructive pulmonary disease. In accordance with the ESC guidelines, only definite and probable cases are used in the Rotterdam Study definition. HF follow-up information was available until January 1st, 2015. Information on the vital status of all participants was obtained on April 20, 2017 from the central registry of the municipality in Rotterdam and through digital linkage with records from general practitioners working in the study area. Cardiovascular mortality was available until January 1st, 2015. The cause of death was established by abstracting information from the medical records of the general practitioners or nursing home physicians and hospital discharge letters. Cardiovascular mortality was defined according to the World Health Organization including ICD-10 codes I00-I99, as described in detail elsewhere[5].

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Supplemental table 1. Competing sub- hazard ratios for crude and indexed thoracic aortic diameters and risk of cardiovascular and non-cardiovascular mortality.

	Ascending aorta				Descending aorta			
	Cardiovascular mortality		Non-cardiovascular mortality		Cardiovascular mortality		Non-cardiovascular mortality	
	Sub-Hazard	95% CI	Sub-Hazard	95% CI	Sub-Hazard	95% CI	Sub-Hazard	95% CI
Women								
Crude diameter	0.99	0.72, 1.36	1.09	0.88, 1.35	**1.58**	**1.10, 2.26** †	0.97	0.78, 1.20
Height Indexed	1.00	0.76, 1.33	1.07	0.88, 1.31	**1.48**	**1.10, 1.99** †	0.95	0.79, 1.15
Weight Indexed	1.14	0.84, 1.55	1.12	0.91, 1.38	**1.38**	**1.04, 1.84** †	1.03	0.85, 1.25
BSA Indexed	1.10	0.81, 1.49	1.08	0.88, 1.34	**1.50**	**1.12, 2.00** †	0.97	0.80, 1.17
BMI Indexed	1.11	0.82, 1.50	1.14	0.93, 1.39	**1.36**	**1.02, 1.82** †	1.06	0.87, 1.29
Men								
Crude diameter	1.06	0.85, 1.32	0.92	0.78, 1.09	0.86	0.65, 1.14	1.05	0.87, 1.26
Height Indexed	1.07	0.88, 1.30	0.87	0.74, 1.03	0.89	0.69, 1.16	0.97	0.81, 1.15
Weight Indexed	1.13	0.83, 1.53	1.20	0.96, 1.50	0.99	0.71, 1.40	**1.37**	**1.08, 1.74** †
BSA Indexed	1.15	0.93, 1.41	0.95	0.79, 1.15	0.99	0.75, 1.30	1.07	0.89, 1.28
BMI Indexed	1.13	0.85, 1.50	1.18	0.97, 1.43	0.99	0.72, 1.34	**1.33**	**1.08, 1.64** †

† **Bold type:** Statistically significant association (P< 0.05). BSA = Body Surface area, BMI = Body mass index.
All models were adjusted for age, waist-hip ratio, smoking, alcohol consume, total and HDL cholesterol, hemoglobin, hypertension, diabetes mellitus, cardiovascular disease, lipid lowering antithrombotic and anti-hypertensions medications and coronary and aortic arch calcifications. Weight and height were used as covariates for adjustment if they were not integrated into the indexed outcome.

Supplemental table 2. Associations of crude ascending thoracic aortic diameters with cardiovascular outcomes at dichotomous cut off points corresponding to 75th, 80th, 85th, 90th, and 95th percentiles among women

	Diameter	Stroke	Coronary heart disease	Heart failure	Cardiovascular mortality	Total mortality
P75	37 mm	1.60 (0.92, 2.76)	1.28 (0.71, 2.30)	1.20 (0.70, 2.10)	1.53 (0.80, 2.91)	1.16 (0.86, 1.55)
P80	38 mm	1.76 (0.97, 3.19)	1.22 (0.63, 2.36)	1.71 (0.98, 2.99)	1.64 (0.81, 3.31)	1.17 (0.84, 1.63)
P85	39 mm	1.76 (0.97, 3.19)	1.22 (0.63, 2.36)	1.71 (0.98, 2.99)	1.64 (0.81, 3.31)	1.17 (0.84, 1.63)
P90	40 mm	1.028 (0.46, 2.29)	1.29 (0.59, 2.79)	1.36 (0.70, 2.64)	0.81 (0.28, 2.29)	1.10 (0.75, 1.62)
P95	41 mm	-	**2.76 (1.077, 7.09)**	**3.25 (1.43, 7.38)**	0.53 (0.072, 3.88)	1.21 (0.67, 2.19)

Models include: age, weight, height, waist-hip ratio, hypertension, Smoking, alcohol, Prevalence of diabetes mellitus, lipid lower medications, anti-thrombotic medications, total cholesterol, hdl cholesterol, hemoglobin, cohort, type of scanner, and coronary and aortic arch calcifications. † **Bold type:** Statistically significant association ($P < 0.05$).

Supplemental table 3. Associations of crude ascending thoracic aortic diameters with cardiovascular outcomes at dichotomous cut off points corresponding to 75th, 80th, 85th, 90th, and 95th percentiles among men

	Diameter	Stroke	Coronary heart disease	Heart failure	Cardiovascular mortality	Total mortality
P75	40 mm	**2.05 (1.20, 3.50)**	0.91 (0.55, 1.51)	1.06 (0.61, 1.85)	1.76 (0.87, 3.55)	1.22 (0.91, 1.62)
P80	40 mm	**2.05 (1.20, 3.50)**	0.91 (0.55, 1.51)	1.06 (0.61, 1.85)	1.76 (0.87, 3.55)	1.22 (0.91, 1.62)
P85	41 mm	**1.93 (1.02, 3,67)**	0.48 (0.22, 1.07)	0.52 (0.22, 1.26)	1.31 (0.52, 3.30)	1.20 (0.83, 1.73)
P90	42 mm	**1.93 (1.02, 3.67)**	0.48 (0.22, 1.07)	0.52 (0.22, 1.26)	1.31 (0.52, 3.30)	1.20 (0.83, 1.73)
P95	43 mm	1.99 (0.98, 4.04)	0.40 (0.14, 1.11)	0.65 (0.25, 1.72)	1.25 (0.42, 3.74)	1.13 (0.73, 1.76)

Models include: age, weight, height, waist-hip ratio, hypertension, Smoking, alcohol, Prevalence of diabetes mellitus, lipid lower medications, anti-thrombotic medications, total cholesterol, hdl cholesterol, hemoglobin, cohort, type of scanner, and coronary and aortic arch calcifications. † **Bold type:** Statistically significant association (P< 0.05).

Supplemental table 4. Associations of crude descending thoracic aortic diameters with cardiovascular outcomes at dichotomous cut off points corresponding to 75th, 80th, 85th, 90th, and 95th percentiles among women

Diameter		Stroke	Coronary heart disease	Heart failure	Cardiovascular mortality	Total mortality
P75	29 mm	1.21 (0.70, 2.10)	0.59 (0.31, 1.13)	**1.92 (1.16, 3.18)**	1.50 (0.79, 2.82)	1.13 (0.85, 1.51)
P80	29 mm	1.21 (0.70, 2.10)	0.59 (0.31, 1.13)	**1.92 (1.16, 3.18)**	1.50 (0.79, 2.82)	1.13 (0.85, 1.51)
P85	30 mm	1.71 (0.94, 3.11)	0.95 (0.48, 1.89)	**1.85 (1.08, 3.17)**	**2.37 (1.23, 4.55)**	1.36 (0.99, 1.85)
P90	30 mm	1.71 (0.94, 3.11)	0.95 (0.48, 1.89)	**1.85 (1.08, 3.17)**	**2.37 (1.23, 4.55)**	1.36 (0.99, 1.85)
P95	31 mm	**2.0 (1.03, 3.90)**	0.84 (0.36, 1.95)	1.46 (0.76, 2.82)	**2.62 (1.28, 5.36)**	1.38 (0.96, 1.98)

Models include: age, weight, height, waist-hip ratio, hypertension, Smoking, alcohol, Prevalence of diabetes mellitus, lipid lower medications, anti-thrombotic medications, total cholesterol, hdl cholesterol, hemoglobin, cohort, type of scanner, and coronary and aortic arch calcifications. † **Bold type:** Statistically significant association ($P < 0.05$).

Supplemental table 5. Associations of crude descending thoracic aortic diameters with cardiovascular outcomes at dichotomous cut off points corresponding to 75th, 80th, 85th, 90th, and 95th percentiles among men

	Diameter	Stroke	Coronary heart disease	Heart failure	Cardiovascular mortality	Total mortality
P75	31 mm	**1.89 (1.11, 3.23)**	0.99 (0.62, 1.58)	1.37 (0.80, 2.33)	0.93 (0.45, 1.92)	1.13 (0.88, 1.50)
P80	32 mm	1.15 (0.66, 2.03)	1.24 (0.76, 2.04)	1.31 (0.76, 2.25)	1.06 (0.50, 2.25)	1.21 (0.91, 1.60)
P85	32 mm	1.15 (0.66, 2.03)	1.24 (0.76, 2.04)	1.31 (0.76, 2.25)	1.06 (0.50, 2.25)	1.21 (0.91, 1.60)
P90	33 mm	1.39 (0.73, 2,68)	0.98 (0.51, 1.88)	1.32 (0.69, 2.52)	0.93 (0.36, 2.38)	1.22 (0.87, 1.72)
P95	34 mm	0.74 (0.28, 1.95)	1.07 (0.47, 2.43)	1.0 (0.40, 2.49)	103 (0.29, 3.63)	1.09 (0.69, 1.74)

Models include: age, weight, height, waist-hip ratio, hypertension, Smoking, alcohol, Prevalence of diabetes mellitus, lipid lower medications, anti-thrombotic medications, total cholesterol, hdl cholesterol, hemoglobin, cohort, type of scanner, and coronary and aortic arch calcifications. † **Bold type:** Statistically significant association (P< 0.05).

Supplemental table 6. Area under the curve for crude ascending thoracic aortic diameter cut points (corresponding to 75th, 80th, 85th, 90th, and 95th percentiles) in association with the risk of cardiovascular outcomes in women

	Diameter	Stroke	Coronary heart disease	Heart failure	Cardiovascular mortality	Total mortality
P75	37 mm	0.7748	0.8044	0.7753	0.8508	0.7573
P80	38 mm	0.7788	0.8035	0.7820	0.8506	0.7569
P85	39 mm	0.7788	0.8035	0.7820	0.8506	0.7569
P90	40 mm	0.7663	0.8035	0.7771	0.8485	0.7568
P95	41 mm	-	0.8078	0.7858	0.8478	0.7561

Models include: age, weight, height, waist-hip ratio, hypertension, Smoking, alcohol, Prevalence of diabetes mellitus, lipid lower medications, anti-thrombotic medications, total cholesterol, hdl cholesterol, hemoglobin, cohort, type of scanner, and coronary and aortic arch calcifications. † **Bold type:** Statistically significant association ($P < 0.05$).

Supplemental table 7. Area under the curve for crude ascending thoracic aortic diameter cut points (corresponding to 75th, 80th, 85th, 90th, and 95th percentiles) in association with the risk of cardiovascular outcomes in men

	Diameter	Stroke	Coronary heart disease	Heart failure	Cardiovascular mortality	Total mortality
P75	40 mm	0.7755	0.7595	0.8034	0.8618	0.7421
P80	40 mm	0.7755	0.7595	0.8034	0.8618	0.7421
P85	41 mm	0.7631	0.7664	0.8081	0.8535	0.7409
P90	42 mm	0.7631	0.7664	0.8081	0.8535	0.7409
P95	43 mm	0.7662	0.7694	0.8070	0.8538	0.7408

Models include: age, weight, height, waist-hip ratio, hypertension, Smoking, alcohol, Prevalence of diabetes mellitus, lipid lower medications, anti-thrombotic medications, total cholesterol, hdl cholesterol, hemoglobin, cohort, type of scanner, and coronary and aortic arch calcifications. † **Bold type:** Statistically significant association (P< 0.05).

Supplemental table 8. Area under the curve for crude descending thoracic aortic diameter cut points (corresponding to 75th, 80th, 85th, 90th, and 95th percentiles) in association with the risk of cardiovascular outcomes in women

Diameter		Stroke	Coronary heart disease	Heart failure	Cardiovascular mortality	Total mortality
P75	29 mm	0.7663	0.8057	0.7876	0.8537	0.7577
P80	29 mm	0.7663	0.8057	0.7876	0.8537	0.7577
P85	30 mm	0.7702	0.8035	0.7860	0.8597	0.7603
P90	30 mm	0.7702	0.8035	0.7860	0.8597	0.7603
P95	31 mm	0.7752	0.8032	0.7816	0.8682	0.7605

Models include: age, weight, height, waist-hip ratio, hypertension, Smoking, alcohol, Prevalence of diabetes mellitus, lipid lower medications, anti-thrombotic medications, total cholesterol, hdl cholesterol, hemoglobin, cohort, type of scanner, and coronary and aortic arch calcifications. † **Bold type:** Statistically significant association ($P < 0.05$).

Supplemental table 9. Area under the curve for crude descending thoracic aortic diameter cut points (corresponding to 75th, 80th, 85th, 90th, and 95th percentiles) in association with the risk of cardiovascular outcomes in men.

	Diameter	Stroke	Coronary heart disease	Heart failure	Cardiovascular mortality	Total mortality
P75	31 mm	0.7700	0.7554	0.8102	0.8573	0.7412
P80	32 mm	0.7595	0.7571	0.8114	0.8587	0.7407
P85	32 mm	0.7595	0.7571	0.8114	0.8587	0.7407
P90	33 mm	0.7615	0.7554	0.8090	0.8580	0.7403
P95	34 mm	0.7597	0.7553	0.8075	0.8579	0.7401

Models include: age, weight, height, waist-hip ratio, hypertension, Smoking, alcohol, Prevalence of diabetes mellitus, lipid lower medications, anti-thrombotic medications, total cholesterol, hdl cholesterol, hemoglobin, cohort, type of scanner, and coronary and aortic arch calcifications. † **Bold type:** Statistically significant association (P< 0.05).

CHAPTER 7

7

Growth of the thoracic aorta in the smoking population: The Danish Lung Cancer Screening Trial

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Abstract

Background

Although the descending aortic diameter is larger in smokers, data about thoracic aortic growth is missing. Our aim is to present the distribution of thoracic aortic growth in smokers and to compare it with literature of the general population.

Methods

Current and ex-smokers aged 50–70 years from the longitudinal Danish Lung Cancer Screening Trial, were included. Mean and 95th percentile of annual aortic growth of the ascending aortic (AA) and descending aortic (DA) diameters were calculated with the first and last non-contrast computed tomography scans during follow-up. Determinants of change in aortic diameter over time were investigated with linear mixed models.

Results

A total of 1987 participants (56% male, mean age 57.4 ± 4.8 years) were included. During a median follow-up of 48 months, mean AA and DA growth rates were comparable between males (AA 0.12 ± 0.31 mm/year and DA 0.10 ± 0.30 mm/year) and females (AA 0.11 ± 0.29 mm/year and DA 0.13 ± 0.27 mm/year). The 95th percentile ranged from 0.42 to 0.47 mm/year, depending on sex and location. Aortic growth was comparable between current and ex-smokers and aortic growth was not associated with pack-years. Our findings are consistent with aortic growth rates of 0.08 to 0.17 mm/years in the general population. Larger aortic growth was associated with lower age, increased height, absence of medication for hypertension or hypercholesterolemia and lower Agatston scores.

Conclusions

This longitudinal study of smokers in the age range of 50–70 years shows that ascending and descending aortic growth is approximately 0.1 mm/year and is consistent with growth in the general population.

Introduction

'Dilatation of the thoracic aorta is associated with an increased risk of aortic dissection[1], with high mortality rates of up to 50% in the first 30 days[2]. In addition to the absolute diameter, fast growth of 3-5 mm/year is mentioned in the guidelines on the diagnosis and treatment of aortic diseases as an important risk factor for dissection and is therefore an additional indication to perform preventive surgery[3,4]. However, data about risk factors for fast aortic growth is scarce. It has been shown that patients with a bicuspid aortic valve or Marfan syndrome show larger aortic growth rates than the general population[5]. Smoking is associated with larger diameter of the aortic arch and descending aorta[6-8] and with larger aortic growth of the abdominal aorta[9]. Whether smoking is associated with faster thoracic aortic growth is still unknown. With use of a large prospective longitudinal cohort study, the Danish Lung Cancer Screening Trial (DLCST), we aimed to investigate whether aortic growth is larger in current or former smokers when compared to the available cross-sectional studies of the general population. With our longitudinal data of the thoracic aortic growth we will also be able to identify risk factors for fast growth in this subgroup of the population.'

Methods

Study population

Participants were recruited from DLCST (www.ClinicalTrials.gov, registration number: NCT 00496977), a randomized controlled trial conducted between 2004 and 2010. Participants in the DLCST volunteered in response to local media advertisements. Current and former smokers aged 50-70 years with at least 20 pack-years and forced expiratory volume in first second (FEV 1) of >30% of predicted value were included. Participants with body weight above 130 kg, previous treatment for any kind of cancer within 5 years, tuberculosis within 2 years, and any serious illness with life expectancy <10 years were excluded. The primary aim of this RCT was to investigate the effect of computed tomography screening on lung cancer mortality. No statistically significant effects of CT screening on lung cancer mortality were found. The study was approved by the National Ethics Committee of Denmark (identification no. H-KA-02045, supplementary protocol 20148) and all participants gave written informed consent. The study design is explained in more detail before[10].

In the DLCST study 2052 participants were randomized to the screening group, which received annual multidetector computed tomography (MDCT) during a 5 year period. This MDCT scans provided the opportunity to perform a post-hoc analysis in which the aortic growth was measured over a long period. For this study we excluded participants with <1 year follow-up between the first and last CT scans (n=65), because this follow-up period was too short to accurately measure growth. Overall, 1987 participants were included in the current study.

Clinical characteristics regarding smoking status, history of stroke and ischemic heart disease, medical treatment for diabetes, hypertension or hypercholesterolemia and

Agatston calcium scores (of the ascending aorta + arch and of the descending aorta) were collected at baseline as previously defined and described[11]. The Agatston calcium score is a measure of arterial calcium on computed tomography. The calculation is based on the weighted density score given to the highest attenuation value (HU) multiplied by the volume of the calcification. The Agatston score of the ascending aorta, aortic arch and descending aorta were assessed by one observer using Vitrea v. 6.0 (Vital Images, Inc., MN, USA). A standardized procedure for calcium scoring with a threshold of 130 Hounsfield units (HU) was used to identify aortic calcifications.

Computed tomography imaging

All non-ECG-gated, non-contrast CT scans were performed in a single institution with a 16-row Philips Mx8000 MDCT scanner, Philips Medical Systems, Eindhoven, the Netherlands. Scans were performed in supine position after full inspiration in caudocranial scan direction including the entire rib cage and upper abdomen with 120 kV and 40 mAs. Scans were performed with spiral data acquisition with the following parameters: section collimation, 16 x 0.75 mm; pitch, 1.5; and rotation time of 0.5 s. The obtained data were reconstructed with a slice thickness of 1 mm and a hard reconstruction algorithm (Philips D kernel).

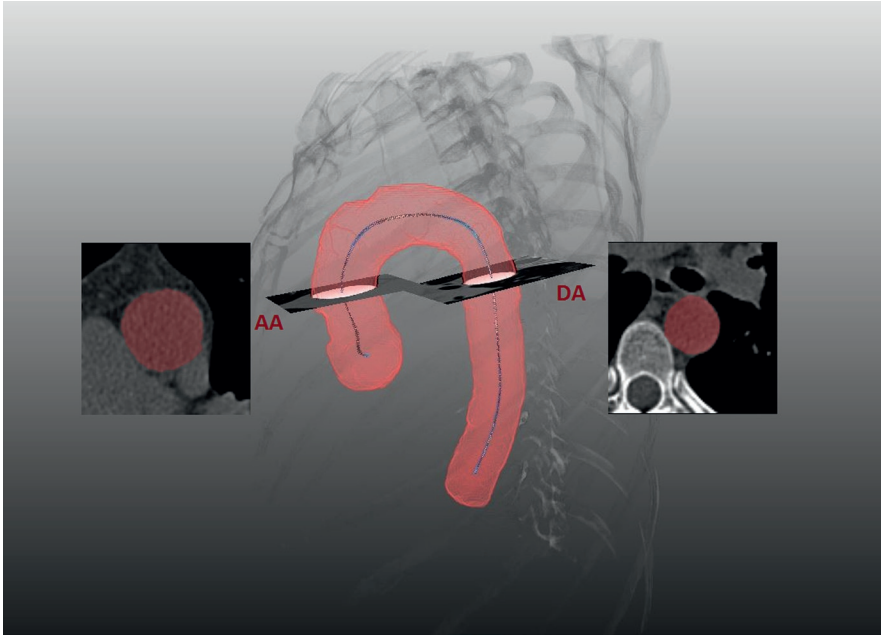


Figure 1. Measurements of the average ascending and descending aortic diameter.
A 3D image of the automatic tool which extracts the centerline (blue) and the surface of the aorta (red) to compute the ascending (AA) and descending aortic (DA) diameters at the level of pulmonary artery bifurcation. Cross-sectional views of the ascending and descending aorta are shown left (AA) and right (DA). Both cross-sections are overlaid with the automatically extracted aortic area (in red). The average diameters is computed as $Diameter = 2\sqrt{Area/\pi}$

Measurements of aortic diameter

Aortic diameters were measured with use of an automatic method, which is validated in 100 participants showing a good agreement with manual aortic diameter measurements[12]. The method combines multi atlas registration to obtain seed points, aorta centerline extraction, and an optimal surface segmentation approach[13] to extract the aorta surface around the centerline. From the extracted 3D aorta segmentation, the average diameters of the ascending aorta and descending aorta at the level of the pulmonary artery bifurcation were computed from the cross-sectional area measured at cross-sectional slices perpendicular to the extracted centerline (figure 1). The aortic wall with possible calcification was included in the measurements. In 29 participants, an error occurred in the automatic method for centerline extraction and therefore no aortic diameters were automatically computed. The ascending and descending aortic diameters for these cases were measured manually by drawing the centerline and cross-sectional vessel contour perpendicular to the centerline at the pulmonary bifurcation level as described in detail in our previous work[12]. In the remaining 1958 subjects with accurate centerline extraction we visually checked the following cases to identify inadequate measurements as a results of the automatic method: (1) all outliers of the aortic diameter at baseline and follow-up defined as 2.7 standard deviation above or beneath the median; (2) all subjects who showed aortic growth or decline of >3.5 mm; and (3) a random sample of 200 images (100 baseline and 100 follow-up scans in the same subjects). From the randomly selected 200 scans, only 3 (1.5%) at the ascending aorta and 4 (2%) at the descending aorta showed a slight over or under segmentation. Overall, in 68 subjects adequate measurements of the automatic method were not available due to inadequate segmentations. Also the aortic diameters for these 68 cases were measured manually for both the ascending and descending aorta diameter. As a result, ascending and descending aortic diameters and aortic growth was available in all 1987 participants.

Statistical analysis

Data are expressed as mean ± SD or as median ± interquartile range in case the distribution was not normal. Data distribution was checked using histograms. Categorical variables are presented as frequencies with percentages. To present the distribution of annual aortic growth, the annual growth rate was calculated by subtracting the aortic diameter measured on the baseline CT scan from the aortic diameter measured on the last scan during follow-up and subsequently dividing this value by the number of years between the baseline and last follow-up scan. The Student's t-test or Mann-Whitney test was used to compare means between two groups at baseline. Comparison of categorical variables was done using the Chi-square test or the Fisher's exact test. For the analyses of Agatston scores, we used natural log-transformed values and added 1.0 mm^3 to the nontransformed Agatston values (Ln(calcification volume + 1)) to deal with values of zero. For pack-years we used the log-transformed values.

To investigate whether change in aortic diameter was associated with baseline characteristics, linear mixed effects (LME) models were used. The ascending and descending aortic diameter were consecutively used as the dependent variable. Time was entered as a random effect. First, all baseline variables were entered concomitantly as independent variables to identify whether they were independently associated with the aortic diameter (while taking into account that the aortic diameter was measured twice in each participant by using the LME). All baseline characteristics (i.e. age, height, weight, sex, medical treatment, medical history, pack years, Agatston scores) were deemed clinically relevant based on previous research[7,8,14]. Second, interaction terms of each of the baseline variables with time were entered consecutively into the multivariable model, to assess the independent effect of each of these variables on the change of aortic diameter over time. We also examined the interaction term between time and large aortic diameter (ascending aorta >40 mm and descending aorta >30 mm) to assess whether participants with larger aortic diameters show larger changes in aortic diameter over time. All interaction terms, that were found to be significant were presented in the figures. We checked whether the assumptions underlying linear mixed effects modelling (linearity and homoscedasticity) were satisfied. The IBM SPSS® statistics 21.0 software was used to analyze the data and a p-value of <0.05 was considered significant.

Results

Study population

The baseline characteristics of the 1987 included participants are presented in table 1 for the total group and separately for males and females. The mean age of our cohort was 57.4 ± 4.8 years. Antihypertensive medication was used by 14.8% of the participants.

Aortic diameters and aortic growth

The distribution of the aortic diameters for both males and females can be found in supplemental figure 1. The ascending and descending aortic diameter at baseline were significantly larger in males (ascending aorta 36.0 ± 3.5 mm and descending aorta 28.2 ± 2.2 mm) than in females (ascending aorta 33.6 ± 3.2 mm and descending aorta 26.1 ± 2.2 mm). A baseline aortic diameter of ≥40 mm at the ascending aorta was found in 167 (8%) participants. For the descending aorta, a baseline aortic diameter of ≥40 mm was found in 1 (0%) participant and ≥30 mm in 257 (13%) participants. The distribution of annual aortic growth for both males and females is shown in figure 2 and was calculated during a median follow-up of 48 months (IQR 47-50 months). Annual growth did not statistically significantly differ between males and females for the ascending aorta (males 0.12 ± 0.31 mm/year and females 0.11 ± 0.29 mm/year) and descending aorta (males 0.10 ± 0.30 mm/year and females 0.13 ± 0.27 mm/year). In addition, the aortic growth did not differ significantly between current or former smokers for the ascending aorta (current

0.12 ± 0.30 mm/year and former 0.13 ± 0.29 mm/year) and descending aorta (current 0.11 ± 0.30 mm/year and former 0.11 ± 0.25 mm/year). In total, 621 (31%) participants showed decrease of the ascending aortic diameter in time and 604 (30%) of the descending aortic diameter. Eighteen people (1%) had an aortic growth of >1 mm/year, which in 9 persons only occurred in the ascending aorta (2 former and 7 current smoker), in 6 persons only in the descending aorta (all current smokers) and in 3 persons in both the ascending and descending aorta (one former and two current smokers). In two people (0.1%) >2 mm/year (both descending aorta) was found and only one (0.05%) showed >3 mm/year.

Table 1. Baseline characteristics

	Total (n=1987)	Males (n=1111)	Females (n=876)	p-value
Age, years	57.4 ± 4.8	57.8 ± 4.8	56.9 ± 4.8	<0.001
Height, cm	173.8 ± 8.8	179.4 ± 6.3	166.7 ± 6.0	<0.001
Weight, kg	76.5 ± 14.2	83.2 ± 12.1	68.0 ± 12.0	<0.001
Medical treatment				
Hypertension, N (%)	294 (14.8%)	158 (14.2%)	136 (15.5%)	0.416
Hypercholesterolemia, N (%)	168 (8.5%)	109 (9.8%)	59 (6.7%)	0.014
Diabetes, N (%)	39 (2.0%)	30 (2.7%)	9 (1.0%)	0.008
History of stroke, N (%)	34 (1.7%)	24 (2.2%)	10 (1.1%)	0.082
History of ischemic heart disease, N (%)	40 (2.0%)	36 (3.2%)	4 (0.5%)	<0.001
Current smoking, N (%)	491 (24.7%)	274 (24.7%)	217 (24.8%)	0.955‡
Pack-years*	34 (27-42.5)	36 (29-46)	31 (25.5-39)	<0.001†
Agatston score ascending aorta + arch*	36 (0-273)	33 (0-247)	39.5 (0-303.8)	0.795†
Agatston score descending aorta*	0 (0-38)	0 (0-45)	0 (0-25)	0.005†
Baseline ascending aortic diameter	35 ±4	36 ± 3	34 ± 3	<0.001
Baseline descending aortic diameter	27 ± 2	28 ± 2	26 ± 2	<0.001

Values are presented as mean (SD) or median (IQR) for continuous variables and N (%) for dichotomous variables. Missing values were present for age (n=1, 0.0%), weight (n=2, 0.0%) and Agatston scores of the aorta (n=8, 0.4%).
*Nontransformed median score with interquartile range
† Mann-Whitney test
‡ Fisher's exact test

Determinants of aortic growth

The association between the baseline characteristics and the aortic diameter is shown in supplemental table 1. Higher age, larger height and weight, hypertension and higher Agatston scores were associated with larger ascending aortic diameters, while female and diabetes were associated with smaller ascending aortic diameters. For the descending aorta, higher age, height, weight and Agatston scores were associated with larger aortic diameters, while female and hypercholesterolemia were associated with smaller aortic diameters.

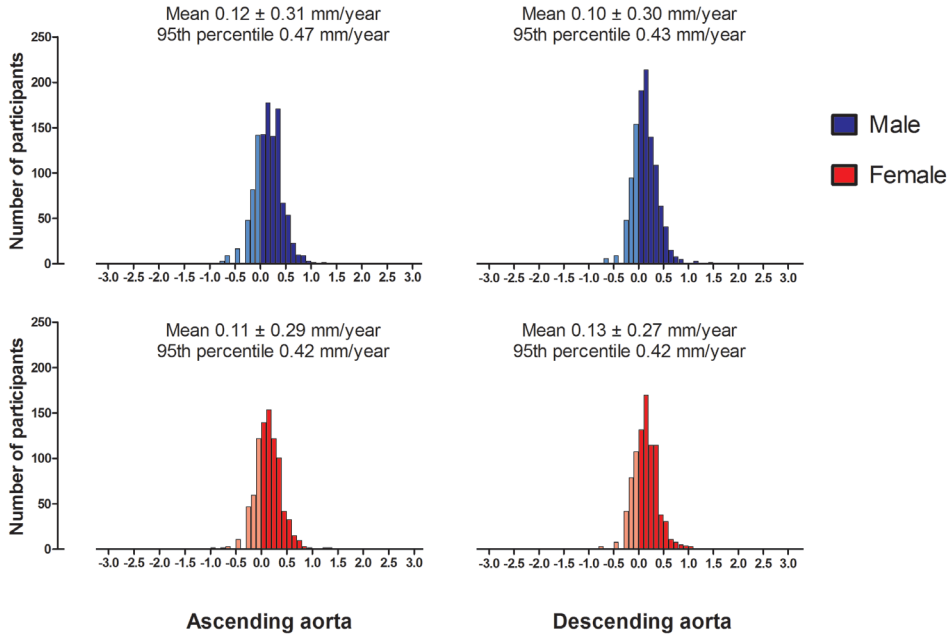


Figure 2. Annual growth of the ascending and descending aorta.
Lighter bars represent decrease in diameter and darker bars represent increase in diameter.
No differences were found between males and females in ascending aortic growth (p=0.394) and descending aortic growth (p=0.087).

Figure 3 shows the significance of the interaction terms between baseline variables and time from the linear mixed effects models. Larger height was associated with larger increase in aortic diameter over time. Higher age, hypertension, hypercholesterolemia and Agatston scores were associated with smaller increase in ascending aortic diameter over time. For the descending aorta, higher age, hypertension and higher Agatston score of the descending aorta were associated with smaller change of the descending aorta over time.

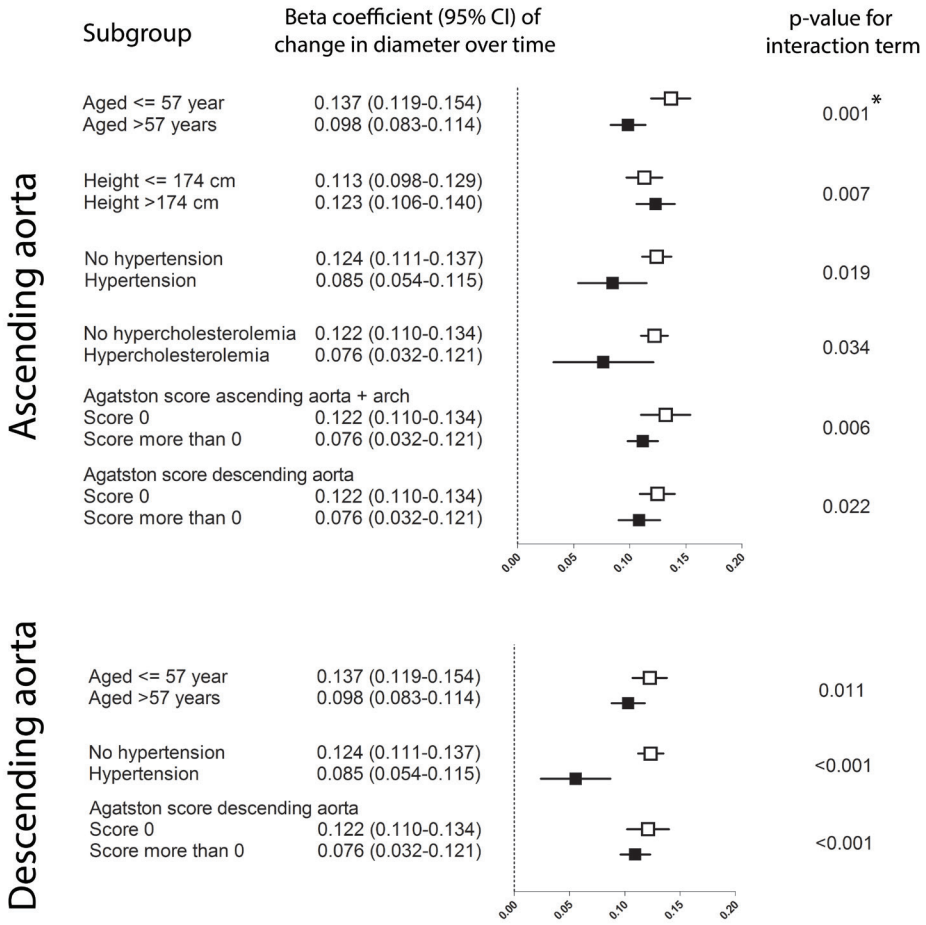


Figure 3. Mixed models including interaction terms between baseline variable and time in years.

All models were adjusted for sex, age, height, weight, hypertension, hypercholesterolemia, diabetes, history of stroke, history of ischemic heart disease, pack-years, Agatston score of the ascending aorta and aortic arch and the Agatston score of the descending aorta.

The continuous variables age and height were dichotomized at their median value. Age, height and Agatston scores were added as continuous variable in the interaction terms.

* Interpretation: A higher age is associated with less increase in the ascending aortic diameter over time (in years).

Discussion

This is the first study presenting longitudinal data on sex-specific growth of the ascending and descending aorta in a large population of current or former smokers with at least 20 pack-years. Males showed a growth of 0.12 ± 0.31 mm/year for the ascending aorta and 0.10 ± 0.30 mm/year for the descending aorta. In females, we found a growth of 0.11 ± 0.29 mm/year for the ascending aorta and 0.13 ± 0.27 mm/year for the descending aorta. Previous studies showed that smoking is associated with larger diameter of the aortic arch or descending aorta[6-8], suggesting faster growth. As such, it would be expected that the descending aortic growth will also be faster in our study compared to the general population. Nevertheless, our study showed comparable or even smaller growth rates compared to the two largest cross-sectional cohort studies who reported on the association between age and descending aortic diameter. Kalsch et al.[15] calculated an increase of 0.17 mm for males and 0.16 for females per 1 year increase in age. Wolak et al.[8] showed that the descending aortic diameter was 0.13 mm larger each 1 year increase in age, which is comparable to our results. Only one study, the Framingham Heart Study[14], measured the thoracic aortic growth longitudinally in a healthy population, but they solely measured the growth at the level of the aortic root. In addition, we have also found no association between pack years and descending aortic growth. Therefore, we can conclude that our data do not support the hypothesis that descending aortic growth would be larger in current or former smokers compared to the general population. Since there is no association found previously between the ascending aortic diameter and smoking, we did not expect any effect of smoking on the ascending aortic growth, which was also confirmed by our results.

The conclusions must be interpreted with caution taking into account the measurement variability of non-ECG-gated non-enhanced CT. In previous literature, the mean intra-observer variation between two measurements of the ascending aorta found in contrast CT scans is found to be 0.1-0.3 mm for manual measurements[16-18]. Possibly for non-contrast CT scans it is larger. The decrease in AA and DA diameter in 31% and 30% of the participants, respectively, is in part caused by this measurement variability. However, the absolute mean difference between the first and last CT scan, not divided by the amount of years in between the two scans, was 0.46 ± 1.05 mm for the ascending aorta and 0.44 ± 0.97 mm for the descending aorta. This is higher than we would expect based on the intra-observer variability of 0.1-0.3 mm and therefor our change in aortic diameter could not only be explained by measurement variability. Moreover, the use of identical CT scanners and automated segmentation for both baseline and follow-up measurements is an important strength of this study because it prevented us from additional inter-observer and inter-modality variability.

Determinants of aortic growth

From previous literature we know that body measurements are important in the assessment of aortic diameters[19, 20]. For instance, in Turner patients with typically a short

stature, the use of the aortic size index (ASI) is advised, which corrects for body surface area[21]. For the aortic growth, little data is available on the effect of body measurements. The Framingham Heart Study[14] included a slightly younger population (mean age 50 ± 14 years) with comparable BMI (25.5 ± 4.4 kg/m^2) and showed that BMI was correlated with change in aortic root diameter over time. We examined height and weight separately and showed that the effect of body measures on the ascending aortic growth is mainly based on height.

Higher age was associated with both less ascending and descending aortic growth. Aortic remodeling over the adult life is accompanied by reduced aortic elasticity[22] and reduced tortuosity with increased curvature[23]. Because of these changes, one may expect aortic growth will decrease at older age and aortic diameters will stabilize. Treatment for hypertension was associated with slower ascending and descending aortic growth. Since higher blood pressure is associated with larger descending aortic diameters[7], we would assume that participants with hypertension would show larger descending aortic growth. However, patients being treated for hypertension may represent the group with controlled blood pressure and the group of patients who are not receiving treatment may contain patients with uncontrolled blood pressure. Because we had no information about the exact blood pressure, which is a limitation of this study, we could not verify this assumption. This could also be the case with hypercholesterolemia because patients with treatment for hypercholesterolemia showed a smaller increase in aortic diameter. An ascending aortic diameter of >40 mm or descending aortic diameter of >30 mm was not associated with change in diameter over time in our cohort. Although patients with aortic aneurysms show larger growth rates[24], we may have had too few patients with aortic dilatation in our cohort to prove this.

A recent systematic review, which included all causes of thoracic aortic aneurysms, showed a mean growth rate in patients from 0.2 to 2.8 mm/year for ascending aorta and aortic arch, while those for descending and aorta ranged from 1.9 to 3.4 mm/year[24]. Detaint et al.[5] observed at the level of the ascending aorta an aortic growth of 0.12 ± 1.0 mm/year in Marfan syndrome and 0.42 ± 0.6 mm/year in BAV. These growth rates of patients with a bicuspid aortic valve or degenerative aortapathy are larger than found in our cohort with current and ex-smokers. In current guidelines for thoracic aortic diseases, different definitions are used for extensive growth (≥3 mm or ≥5 mm), which warrants preventive surgery. Our study showed only two cases with growth >2 mm/year and only one with >3 mm/year, which suggests that extensive growth, defined by the guidelines, is relatively rare in the general smoking population. Based on our 95th percentiles, annual aortic growth of 0.5 mm is the upper limit of normal in current or former smokers.

Limitations

One large limitation of our study is that we did not include our own reference group of healthy subjects. The literature only contained cross-sectional data with the mean thoracic

aortic growth rate of the general population and therefore we could not compare the distribution (95th percentile) of aortic growth rates in our group with a reference group. Another limitation is the lack of information about diseases related to aortic pathology, such as connective tissue disease and bicuspid aortic valve. This information was not available because the primary aim of this RCT was to investigate the effect of computed tomography screening on lung cancer mortality. Because this study was a post-hoc analysis, thoracic aortic growth was neither a primary nor a secondary outcome measure of the original trial. The limited age range of 50-70 years also prevents the generalization of our results to the total population. In addition, the limited aortic growth may have limited the power of our analysis. However, our cohort was large enough to find a significant aortic growth for both the ascending and descending aorta and also several determinants were found to be significant associated with the change in thoracic aortic diameter over time. Another limitation of this study is the use of non-ECG gated, non-contrast CT scans. Non-gated CT scans show significant more motion artifacts than ECG-gated CT scans[25], which likely effect aortic measurements. The use of contrast-enhanced CT is preferred for thoracic aortic measurements but could cause unnecessary complications. However, both baseline and follow-up measurements were made in the same manner.

An issue that warrants consideration in our study is the fact that we examined a total of 13 variables. If we were to account for multiple testing using a Bonferroni correction, only age would remain statistically significant for the ascending aorta, while hypertension and Agatston score would remain statistically significant for the descending aorta. However, our study was not data driven but hypothesis driven; the choice of variables we investigated was based on previous findings from the literature. These variables were thus already implicated in the disease process by earlier studies. Correcting for multiple testing in spite of this hypothesis driven approach could result in failure to recognize potentially interesting factors. In any case, our findings may be considered as indicative of a potential association, and these hypothesis generating findings merit validation in other large studies.

Conclusion

This longitudinal study of current and ex-smokers shows that the ascending and descending aorta grows on average 0.1 mm/year in both males and females in the age range of 50-70 years. The aortic growth rates are consistent (or even smaller) with the numbers available in cross-sectional studies of the general population. According to the 95th percentile, an aortic growth of >0.5 mm/year can be considered the upper limit of normal. Larger change of aortic diameters in time was associated with lower age, increased height, absence of medication for hypertension or hypercholesterolemia, lower Agatston score and a large thoracic aortic diameter.

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Supplemental material

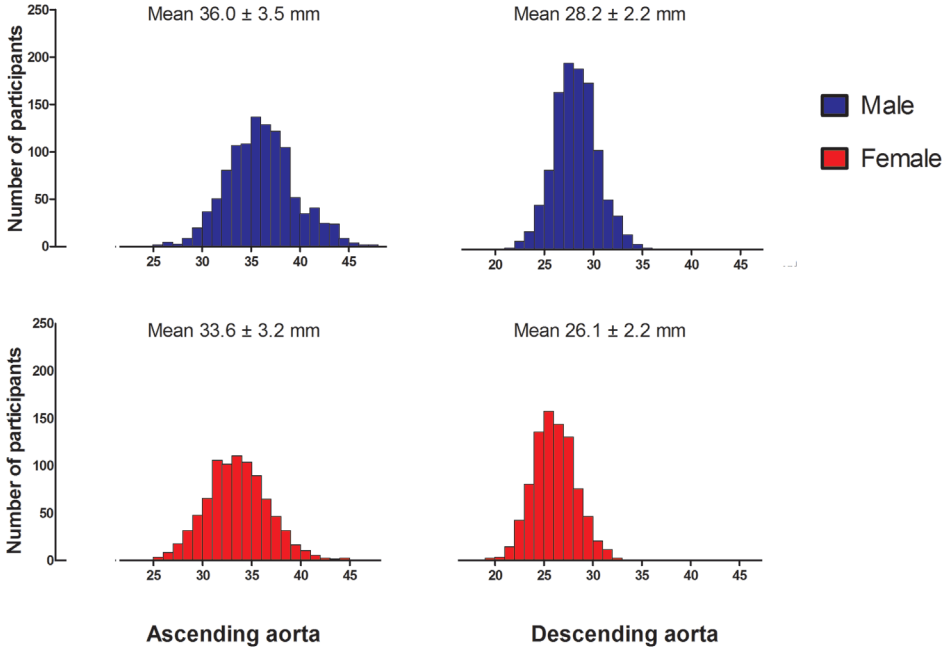
Supplemental table 1. Mixed models for ascending and descending aortic diameters

		Regression coefficient (95% CI)	*p-value*
Ascending aorta	**Time of measurement**	0.12 (0.11;0.13)	<0.001
	Female†	-0.94 (-1.35;-0.52)	<0.001
	Age, 10 years	1.37 (1.04;1.70)	<0.001
	Height, cm	0.06 (0.04;0.09)	<0.001
	Weight, kg	0.05 (0.03;0.09)	<0.001
	Hypertension	0.61 (0.20;1.03)	0.004
	Hypercholesterolemia	-0.40 (-0.95;0.15)	0.151
	Diabetes	-1.30 (-2.32;-0.28)	0.012
	History of stroke	0.72 (-0.35;1.79)	0.187
	History of ischemic heart disease	-0.37 (-1.43;0.69)	0.490
	Pack-years‡	0.03 (-0.41;0.47)	0.894
	Agatston score ascending aorta + arch‡	0.08 (0.02;0.14)	0.012
	Agatston score descending aorta‡	0.09 (0.03;0.16)	0.006
Descending aorta	**Time of measurement**	0.11 (0.10;0.12)	<0.001
	Female	-0.85 (-1.10;-0.59)	<0.001
	Age, 10 years	1.52 (1.32;1.73)	<0.001
	Height, cm	0.04 (0.02;0.05)	<0.001
	Weight, kg	0.04 (0.03;0.05)	<0.001
	Hypertension	0.15 (-0.11;0,41)	0.251
	Hypercholesterolemia	-0.52 (-0.86;-0.18)	0.003
	Diabetes	-0.28 (-0.91;0.35)	0.387
	History of stroke	-0.49 (-0.15;0.17)	0.149
	History of ischemic heart disease	0.29 (-0.36;0.95)	0.383
	Pack-years‡	0.10 (-0.18;0.37)	0.487
	Agatston score ascending aorta + arch‡	0.04 (0.00;0.08)	0.048
	Agatston score descending aorta‡	0.12 (0.08;0.16)	<0.001

* All baseline variables were entered concomitantly as independent variables to identify whether they were independently associated with the aortic diameter (while taking into account that the aortic diameter was measured twice in each participant by using the LME)

† Interpretation: the ascending aortic diameter is on average 0.94 mm smaller in females than in males.

‡ Log transformed



Supplemental figure 1. Baseline ascending and descending aortic diameters.
Males show a larger baseline diameter than females for both the ascending and descending aortic diameter ($p<0.001$).

Part III

The thoracic aorta in specific diseases

CHAPTER 8



Bicuspid aortic valve annulus: standardized method to define the annular plane and assessment of geometry changes during the cardiac cycle. Implications for TAVI planning

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Submitted

Background

Transcatheter aortic valve implantation (TAVI) is increasingly practised also in bicuspid aortic valve (BAV) patients. Determining the BAV annular plane is more challenging than for tricuspid aortic valves (TAV). Furthermore, it is unknown if the BAV annulus has a physiology similar to TAV. Our aim was to present a standardized methodology to determine BAV annulus and investigate its changes in shape and dimensions during the cardiac cycle.

Methods

BAV patients were prospectively included and underwent an ECG-gated cardiac CTA. The annulus plane was manually identified on reconstructions at 5% intervals of the cardiac cycle with a new standardized method for different BAV types. Based on semi-automatically defined contours, maximum and minimum diameter, area, area-derived diameter, perimeter, asymmetry ratio and relative area were calculated. Differences of dynamic annular parameters were assessed also per BAV type.

Results

Of the 55 patients included (age: 38.4±13.3 years; 58% males) 38 had BAV Sievers type 1, 10 type 0 and 7 type 2. The minimum diameter, perimeter, area and area-derived diameter were significantly higher in systole than in diastole with a relative change of 13.7%, 4.8%, 13.7% and 7.2% respectively (all $p<0.001$). The AR was ≥1.1 in all phases, indicating an elliptic shape, with more pronounced flattening in diastole ($p<0.001$). Different BAV types showed comparable dynamic changes.

Conclusions

The aortic annulus of BAV patients undergoes significant changes in shape during the cardiac cycle with a wider area in systole and a more elliptic conformation in diastole. Therefore, it is recommended that pre-TAVI measurements be performed in early systole.

Abstract

Introduction

With an estimated incidence of 0.9-2% in the general population, bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly[1]. BAV are prone to precocious stenosis and regurgitation, often requiring an intervention early in life[2]. Transcatheter aortic valve insertion (TAVI) is an established alternative to traditional open surgery for stenotic tricuspid aortic valves (TAV). BAV has been regarded as an absolute contra-indication for TAVI due to concerns related to the morphological anomalies of the aortic valve[3]. Yet, in the last few years the procedure has been performed with an increasing frequency in BAV patients demonstrating the feasibility and safety of the technique in this population[4] with short term results comparable to those obtained in patients with TAV[5].
Precise pre-procedural assessment of the annulus and aortic root dimensions and anatomy are fundamental to avoid under- or over-estimation of the valve size and subsequent complications after TAVI[6]. The broad variability in cusp morphology of BAV results in the cumbersome and, more importantly, sometimes impossible identification of the annulus plane as defined based on the standard anatomy of TAV. Therefore, a specific method for the definition of the annulus plane in BAV patients is lacking.
The annulus has been shown to have an elliptical shape that undergoes conformational changes during the cardiac cycle in normal as well as stenotic TAV using ECG-gated CT imaging[7,8]. Furthermore, most sizing parameters for the TAV aortic annulus show significant changes between diastole and systole[9]. If, and to what extent, such dynamic geometry changes also occur in the BAV annulus is unknown, but of paramount importance to establish the cardiac phase in which to perform the pre-procedural measurements and one of the prerequisites for increased use of TAVI in BAV. Furthermore, these measurements require a standardized and reproducible method to determine the BAV annulus plane. We describe a method to determine the BAV annulus plane and assessed the presence and magnitude of geometrical and dimensional changes of the annulus during the cardiac cycle using ECG-gated CT as well as investigated if different BAV subtypes present different patterns.

Materials and Methods

Study population and BAV classification

Sixty consecutive patients with a BAV were prospectively included as part of a clinical study at Erasmus Medical Centre between November 2014 and March 2016[10]. The local medical ethics committee approved the study and all patients provided written informed consent. As part of the study an ECG-gated contrast enhanced CT of the heart was performed.
The morphology of the aortic valve was classified as previously described by Sievers et al.[1] based on images obtained with echo, CT and MR.

CT scans

Contrast enhanced CT scans were acquired with a third generation dual-source CT scanner (Somatom Force, Siemens, Forchheim, Germany). All scans were performed with retrospective ECG-gating, 192x0.6mm collimation and 250ms rotation time. Reconstructions of 1.5mm thickness were performed throughout the entire cardiac cycle at 5% intervals resulting in 20 image datasets per patient. The heart rate of the patient during the scan was recorded.

Annulus analysis

A radiologist with >5 years of experience in cardiovascular radiology defined the annulus plane and semi-automatically measured the annulus dimensions on the CT scans for each of the 20 reconstructed phases.

Annulus plane definition

Images were exported to a commercially available workstation (IntelliSpace Portal, Philips, Best, The Netherlands) to allow for manual multiplanar reconstructions (MPR). The annulus plane was identified with a different methodology depending on the morphology of the bicuspid valve. In bicuspid valves with three equally/similarly sized cusps (Sievers type 1 and 2) the annulus plane was identified as the plane passing through the three hinge points (defined as the lowest insertion point of the valve leaflet on the aortic wall) as indicated by guidelines for TAV[11]. In case the fused cusps had different dimensions (Sievers type 1) or there were only two cusps (Sievers type 0) the annulus plane was identified with a newly developed approach consisting of multiple steps based on a combination of previously published definitions of the annulus: first, one of the planes passing through the hinge point of the non-fused cusp and the hinge point of the bigger one of the two fused cusps (or through the two hinge points in valves type 0) was identified; then, this plane was tilted until the minimum annulus area at that level was identified[12,13]; if this plane was considered to be too steeply angled in respect to the LVOT and the sinuses, a compromise between the plane with the smallest diameter and a plane perpendicular to the centerline at this level was reached[14,15] (figure 1 and 2). The plane was checked and adapted when necessary for each of the analysed phases to account for displacement of the annulus due to the contraction of the heart.

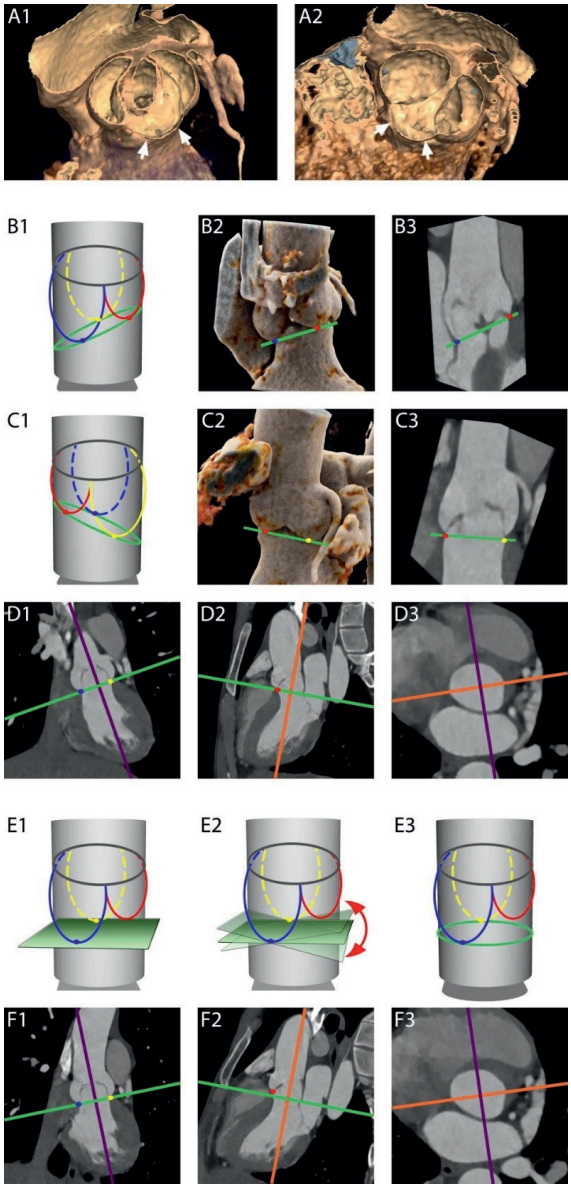


Figure 1. Determination of the annulus in patients with BAV type 1 with asymmetric cusps.
A – Volume rendered (VR) reconstructions in systole (**A1**) and diastole (**A2**) demonstrating the asymmetry of the sinuses due to the smaller dimensions of the right coronary cusp (RCC) (**arrows**). **B-D –** Wrong annulus plane definition based on the three hinge points. In **B1** and **C1** schematic representations of the LVOT, sinuses of Valsalva (**red, yellow, blue lines**) and sinotubular junction (**grey line**) where the annulus plane (**green line**) was identified as the plane passing through the three hingepoints (hinge point of the RCC in **red**; hinge point of the non-coronary cusp (NCC) in **blue;** hinge point of the left coronary cusp (LCC) in **yellow**). In **B2**-**B3** and **C2**-**C3** VR reconstructions showing the angulation between the centerline passing through the LVOT/aortic root and the line (**B2-B3** and **C2-C3**; **green lines**) passing through the hinge points of the LCC and the NCC (**B**) and RCC (**C**), respectively. In **D1** and **D2** MPR showing the position of the axis in the longitudinal planes when identifying the plane passing through the three hinge points (**D3**). **E-F –** Correct annulus plane definition. At first one plane passing through the two hinge points of the two biggest cusps is idenfied (**E1**); then this plane is tilted along the only still undetermined direction (**E2**) until the minimum cross-sectional area and/or a plane perpendicular to the centerline is obtained (**E3**). In **F1** and **F2** MPR showing the position of the axis in the longitudinal planes when determining the plane passing through the two hinge points and then make adjustements by tilting the violet and orange axis to identify the smallest possible area and a plane perpendicular to the centerline (**E3**).

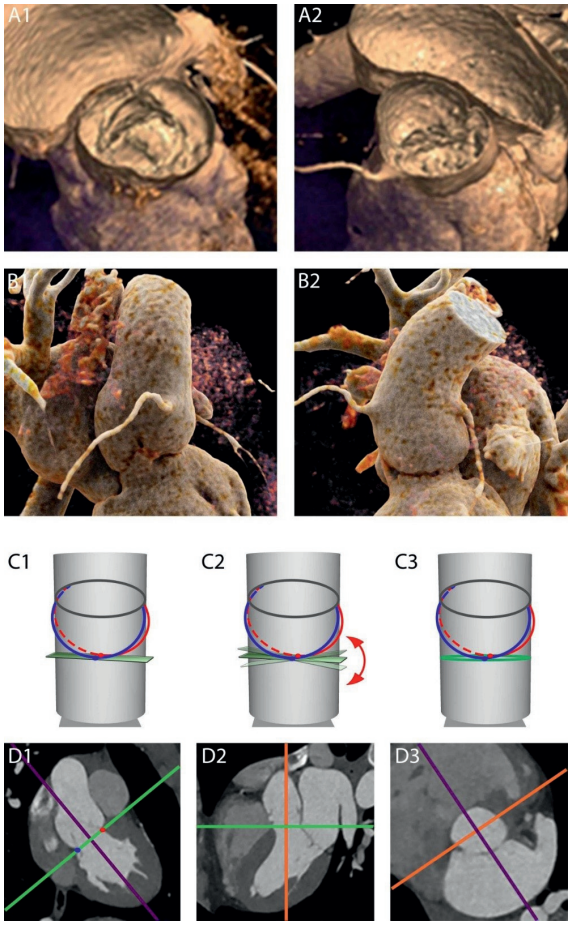


Figure 2. Determination of the annulus plane in patients with BAV type 0.
A – VR reconstructions in systole (**A1**) and diastole (**A2**) showing the presence of only two cusps. **B** – 3D anatomy of the aortic root.
C-**D** – One plane passing through the two hinge points of the two cusps is defined (**C1**); then this plane is tilted along the only still undetermined direction (**C2**) until the minimum cross-sectional area and/or a plane perpendicular to the centerline is obtained (**C3**). In **D1** and **D2** MPR showing the position of the axis in the longitudinal planes when determining the annulus plane (**D3**) as detailed above.

Annulus measurements

The annulus measurements were performed semi-automatically with the "edge finder" tool available in the reconstruction software (IntelliSpace Portal). With this tool, two seed points are placed somewhere inside the annulus and in the tissues surrounding the aortic root, respectively. Thereafter, the software automatically defines the contour of the annulus where there is a sharp transition of Hounsfield Unit values between the contrast enhanced lumen and surrounding tissues. For each phase, the automatically traced contour was checked and adjusted when deemed necessary. The contour was modified to encircle the inner edge of small calcifications and to extend over big calcifications in continuity with the adjacent outline. The maximum diameter, the diameter perpendicular to the maximum (referred to as "the minimum diameter"), the area and the perimeter were recorded (figure 3). The average diameter was calculated as the average of the maximum and minimum. The effective diameter was derived from the area[11]. The asymmetry ratio

(AR) and relative area (RA) were calculated as previously defined[7]. The AR was defined as the ratio between the maximum and the minimum diameter. The RA was calculated as the ratio between the area at each individual phase and the average area of all phases throughout the cycle.

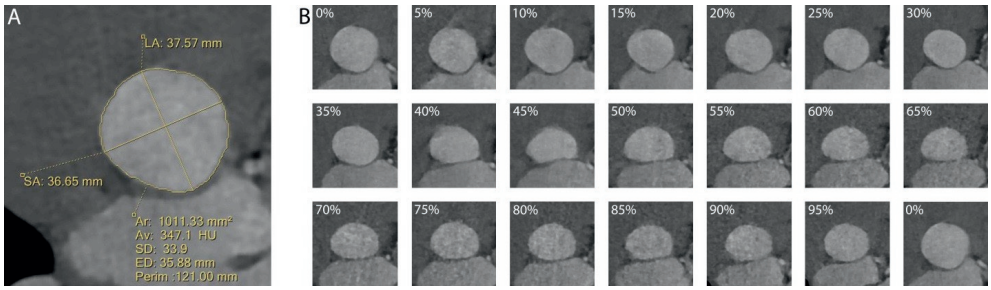


Figure 3. Annulus measurements
A – Measurement of the annulus parameters (maximum and minimum diameters, perimeter, area and area-derived diameter) based on the semi-automatically defined contour.
B – A case example showing all the 20 phases analyzed in a patient with BAV type 1 LR. The annulus shows a more circular shape in systole and a more elliptic shape during diastole.

Image quality assessment

The image quality of each phase at the level of the annulus was subjectively assessed based on a 2-point scale (insufficient quality; acceptable to perfect quality) based on the following criteria: the definition of the cusps and hinge points and subsequent reliability in the identification of these landmarks; the presence of motion artefacts; the adequate opacification of the LVOT and aortic root. The phases with insufficient quality were excluded from further analysis.

Intra and inter-observer variability

The same observer re-measured all phases of one third of the patients (n=18) at least one month after the first measurement. A second observer blinded to previous results, analysed 20 phases of 6 patients.

Statistical analysis

Continuous data are presented as mean ±standard deviation (SD). Student's t-test for paired samples and Wilcoxon signed-ranks tests were employed to assess differences during the cardiac cycle for all annular parameters. Data were examined with the Kolmogorov-Smirnov test to ensure normal distribution. A one-way ANOVA model with Bonferroni correction and Welch's test was used to investigate differences between valve types. A p value of <0.05 was considered as statistically significant.

Results

Patients and valve characteristics

Of the 60 eligible patients, 5 were excluded because of overall insufficient image quality (n=1), not all reconstruction phases available (n=3) and the presence of a large septal aneurysm (n=1).

In total 55 patients were included (mean age: 38.4±13.3(21-66); males: 32(58%)) of whom 10 had a Sievers type 0 BAV, 38 a type 1 BAV and 7 a type 2 valve. Patients' characteristics are summarized in table 1. In 9 patients with Sievers type 1, the new method for the definition of the annulus plane based on two hinge points was used. Ten patients had calcifications of the annulus that were of considerable amount in only one case.

Variation of annulus parameters during the cardiac cycle

Out of a total of 1100 phase datasets (55 patients with 20 reconstructed phases each), 71 (6.4%) were excluded due to insufficient quality. The excluded datasets were randomly distributed over the cardiac cycle (p=0.6). All of the measured annulus parameters presented statistically significant differences during the cardiac cycle (table 2 and figure 4). The minimum diameter, the average diameter, the area, the perimeter and the area-derived perimeter demonstrated the highest values during early systole (5-10% of the cardiac cycle) with a significant reduction in diastole of 13.7%, 6.7%, 13.7%, 4.8% and 7.2%, respectively (all p values <0.001). The RA was >1 during systole (0-30%) and in late diastole (90-100%) (p<0.001). The maximum diameter showed the highest value in diastole (p<0.001). The AR was ≥1.1 in all phases indicating an elliptic shape of the annulus throughout the entire cardiac cycle. The annulus demonstrated significant deformation with increased elliptic morphology during diastole (relative change of 13.9%; p<0.001).

Variation of annulus parameters during the cardiac cycle per type of BAV

When analysed separately, all three types of BAV showed analogous dynamic changes (table 3 and figure 5). All assessed parameters showed significant differences over time, with the exceptions of the maximum diameter for type 2 valves (p=0.15) and maximum diameter and perimeter for type 0 valves (p=0.2 and p=0.2 respectively) that did not show significant differences.

The AR was significantly different between BAV type 1 and 2 in early systole with valves type 1 showing a more elliptic annulus (p=0.024 at 10%; p=0.014 at 15%; p=0.023 at 20%; p= 0.016 at 25%). Patients with valves type 0 demonstrated a significantly more elliptic annulus than type 2 at phase 10% (p=0.047). The other parameters did not show significant differences between valve types at any of the time points.

Table 1. Patient characteristics

	Total (n=55)	Sievers type 0 (n=10)		Sievers type 1 (n=38)		Sievers type 2 (n=7)
		ap (n=6)	lat (n=4)	LR (n=30)	RN (n=8)	
Male*	32(58%)	4(67%)	3(75%)	17(57%)	4(50%)	4(57%)
Age (mean, SD, range) in years*	38.4±13.3(21-66)	41.7±18(24-62)	35±7.8(24-41)	39.8±14.2(21-66)	36.7±12.7(22-54)	33.8±8.5(22-43)
Height (mean, SD, range) in m*	1.7±0.2(1.3-2)	1.8±0.1(1.6-1.9)	1.8±0.1(1.6-1.9)	1.7±0.2(1.3-2)	1.7±0.2(1.4-2)	1.8±0.2(1.5-2)
Weight (mean, SD, range) in kg*	75±16(48-132)	76.7±15.9(55-95)	77.7±10(69-92)	75.5±16.5(48-132)	67.7±16.1(48-90)	77.7±18.4(52-106)
BMI (mean, SD, range) *	24.3±3.2(17.9-34)	24.1±1.1(22.3-25.8)	24.5±2.6(20.9-26.6)	24.9±3.8(17.9)	23.1±2.5(18.3-26.8)	23.2±2.6(20-27)
Blood pressure (the day of the CT scan)*						
- Max	124±16(94-170)	130±22(102-170)	138±27(107-161)	124±15(94-156)	119±8(109-130)	117±14(99-134)
- Min	81±11(64-117)	81±10(69-94)	94±24(66-117)	83±9.8(65-104)	76±7(67-91)	75±8(64-89)
Aortic valve dysfunction*						
- Insufficiency (at least mild)	9(16%)	1(17%)	0	3(10%)	2(25%)	3(42%)
- Stenosis (peak velocity>2.5cm/sec)	24(44%)	2(33%)	1(25%)	8(27%)	7(87%)	6(86%)
- Severe stenosis (peak velocity >4cm/sec)	6(11%)	1(17%)	0	1(3%)	3(4%)	1(14%)
Additional valve related events						
- Previous endocarditis	1(2%)	0	0	0	0	1(14%)
- Previous balloon-dilation	5(9%)	0	0	3(1%)	2(25%)	0
Congenital aortic valve or aortic diseases						
- Subvalvular stenosis	1(2%)	0	0	1(3%)	0	0
- Turner syndrome	9(6%)	0	1(25%)	6(20%)	1(12%)	1(14%)
- Coarctation	5(9%)	0	2(50%)	3(1%)	0	0
- Turner syndrome and coarctation	2(4%)	1(17%)	0	1(3%)	0	0

Percentages were rounded to the nearest integer. ap = BAV Sievers type 0 with the maximum diameter of the valve opening oriented along an anteroposterior axis. lat = BAV Sievers type 0 with the maximum diameter of the valve opening oriented along a latero-lateral axis. LR = BAV Sievers type 1 with fusion of the left coronary cusp (LCC) and the right coronary cusp (RCC). RN = BAV Sievers type 1 with fusion of the RCC and the non coronary cusp (NCC). * No statistically significant differences in age, sex, height, weight, BMI, blood pressure or aortic valve pathology were found between patients with valve types 0, 1 and 2.

Table 2. Changes of the annulus parameters values during the cardiac cycle

	Max value*	Min value*	Relative Difference[%]†‡ (±SD of the difference)	p Value‡ Min vs Max
Maximum diameter [mm]	30.2±4.5	28.4±4.2	3.6% (±3.9%)	<0.001
Minimum diameter [mm]	22.4±4.1	26.0±4.1	13.8% (±8.4%)	<0.001
Average diameter [mm]	27.8±4.1	25.4±4	6.7% (±3.5%)	<0.001
Perimeter [mm]	92.9±13.7	86.9±14	4.8% (±4.3%)	<0.001
Area [mm^2]	586.7±169.1	486.5±144.3	13.7% (±6.8%)	<0.001
Diameter based on area [mm]	27.1±4.0	24.6±3.7	7.2% (±3.7%)	<0.001
Relative area	1.1±0.1	0.9±0.1	13.8% (±8.3%)	<0.001
Asymmetry ratio	1.3±0.2	1.1±0.1	12.8% (±10.8%)	<0.001

*Values calculated based on all data available for each phase; †relative difference compared to the maximum value; ǂ values calculated based on the number of cases available per comparison of the means; values for relative area and asymmetry ratio were calculated with Wilcoxon signed-ranked test.

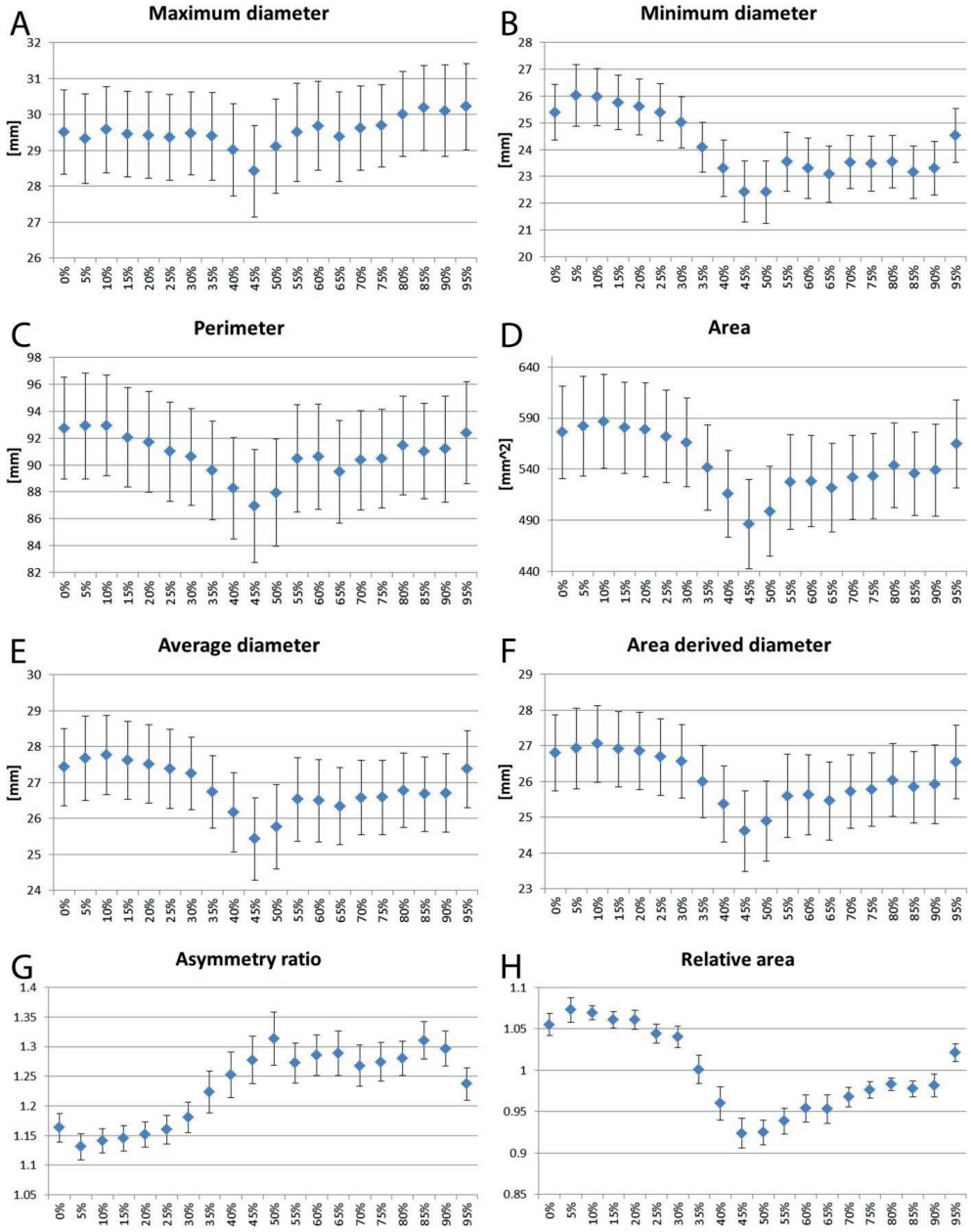


Figure 4. Mean annulus parameters per cardiac phase.
Vertical bars indicate 95% confidence intervals (CI).

Table 3. Changes of the annulus parameters values during the cardiac cycle per valve type

	Max value*	Min value*	Relative Difference[%]†‡ (±SD of the difference)	p Value‡ Min vs Max
Maximum diameter [mm]				
Sievers type 0	30.4±3.8	28.6±4.2	2.3% (±4,7%)	0.207
Sievers type 1	30±4.6	27.9±4.1	3.9% (±5.2%)	0.001
Sievers type 2	32.3±2.9	29.8±3.7	2.7% (±3.4%)	0.15
Minimum diameter [mm]				
Sievers type 0	25.8±4.1	20.6±3.9	19.5% (±4.5%)	<0.001
Sievers type 1	25.5±3.8	22.2±3.8	11.6% (±7.4%)	<0.001
Sievers type 2	29.6±2.2	23.5±3.3	19.4% (±9.6%)	0.028
Average diameter [mm]				
Sievers type 0	27.8±4.2	24.6±3.7	7.3% (±4.7%)	0.004
Sievers type 1	27.5±4.1	25±3.8	7% (±3.4%)	<0.001
Sievers type 2	30.6±2.2	27.1±2.8	7.6% (±4.8%)	0.028
Perimeter [mm]				
Sievers type 0	93.4±14.3	83.7±11.8	6% (±6%)	0.027
Sievers type 1	91.8±14.7	85.8±13.5	5% (±4.9%)	<0.001
Sievers type 2	102.5±8.1	93.7±11.9	3.5% (±5.9%)	0.229
Area [mm^2]				
Sievers type 0	584.4±167.8	438.7±123.1	17.9% (±6.5%)	0.001
Sievers type 1	574±172.7	475.4±140.9	13.2% (±6.6%)	<0.001
Sievers type 2	690.9±117.4	542.8±122.5	14.2% (±10.1%)	0.042
Diameter based on area [mm]				
Sievers type 0	27±23.4	23.4±3.3	9.5% (±3.5%)	<0.001
Sievers type 1	26.7±4.0	24.3±3.7	6.9% (±3.6%)	<0.001
Sievers type 2	29.6±2.6	26.1±3.0	7.5% (±5.3%)	0.038
Relative area				
Sievers type 0	1.1±0.1	0.9±0.0	16.4% (±6.0%)	<0.001
Sievers type 1	1.1±0.0	0.9±0.1	13.4% (±6.5%)	<0.001
Sievers type 2	1.1±0.1	0.9±0.1	17.2% (±7.5%)	0.004
Asymmetry ratio				
Sievers type 0	1.4±0.2	1.1±0.1	19% (±8.6%)	0.012
Sievers type 1	1.3±0.1	1.2±0.1	12.1% (±8.8%)	<0.001
Sievers type 2	1.3±0.2	1.1±0.0	17.6% (±11.7%)	0.043

*Values calculated based on all data available for each phase; †relative difference compared to the maximum value; ǂ values calculated based on the number of cases available per comparison of the means; values for relative area and asymmetry ratio were calculated with Wilcoxon signed-ranked test.

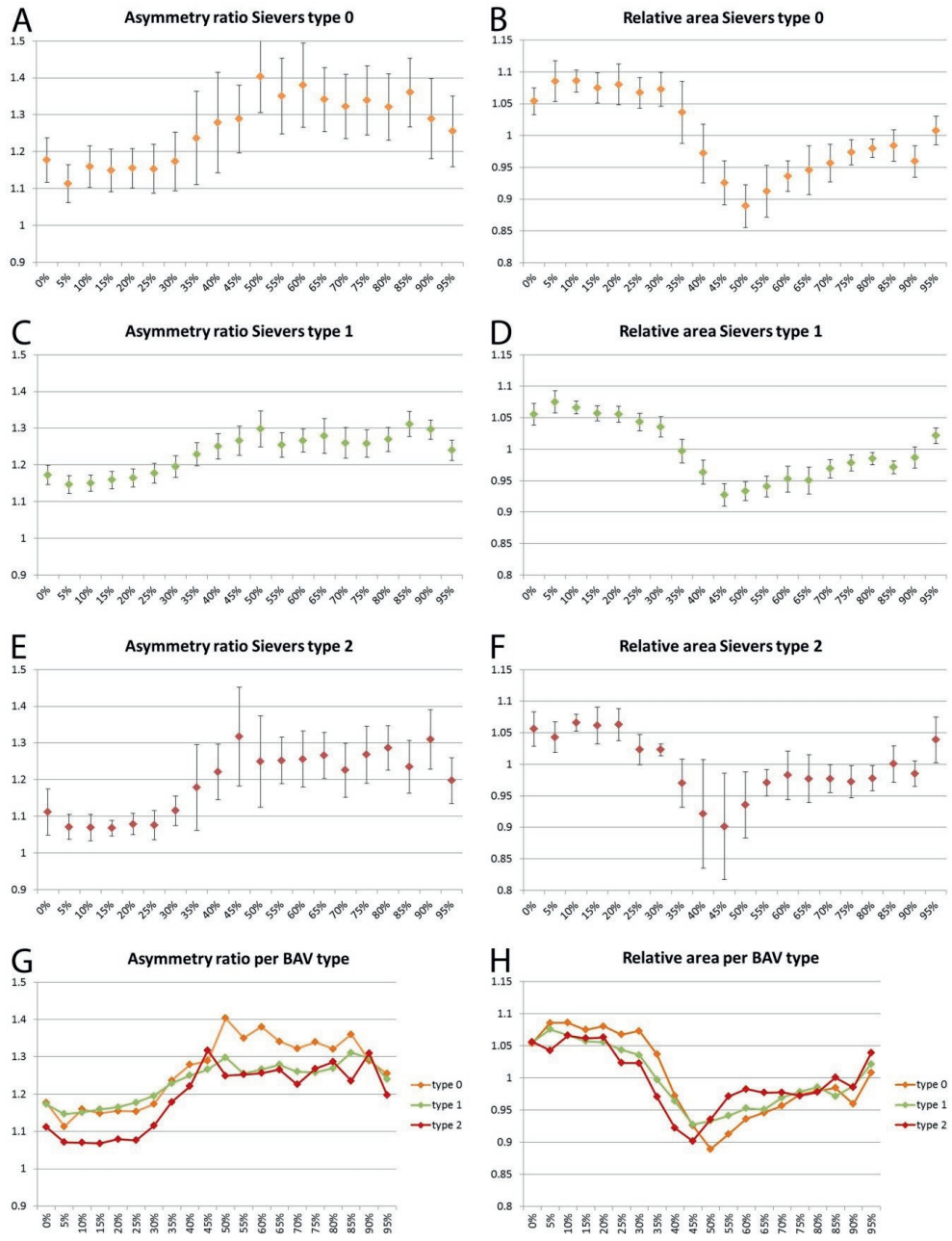


Figure 5. Mean AR and RA per phase and valve type.
Vertical bars indicate 95% CI.

Influence of heart rate on annulus dynamics

Scans were divided in 7 different categories based on heart rate (table 4). All groups showed a smaller area between 40-60% of the cardiac cycle (figure 6); however, the smallest values were reached earlier in the group with the slowest heart rate.

Table 4. Classificaton of scans based on heart rate.

Patients' heart rate	n
- 40-50	6
- 50-60	15
- 60-70	16
- 70-80	10
- 80-90*	4
- 90-100	4
- 100-110*	2

* Groups 80-90 bpm and 100-110 were not further analysed due to the absence of data for phase 55% and the low number of cases, respectively.

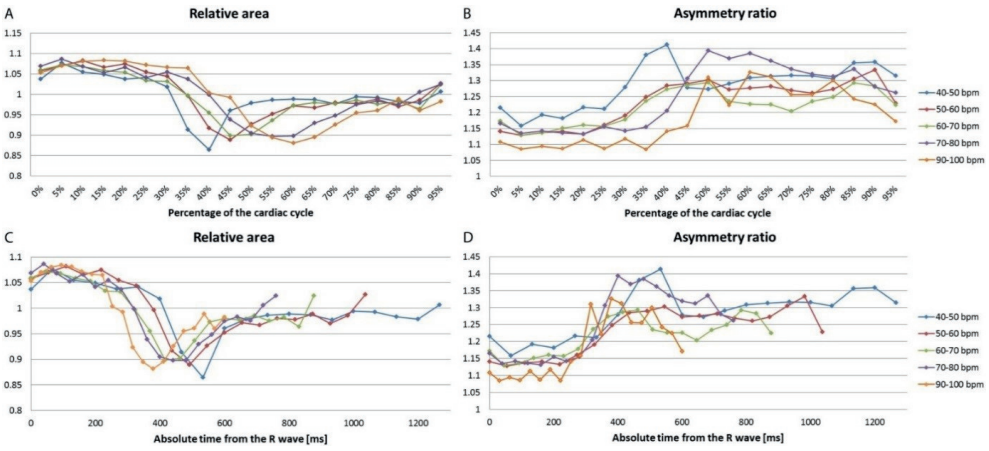


Figure 6. Mean AR and RA in groups with different heart rates during successive phases of the cardiac cycle expressed in terms of percentage (**A**-**B**) and absolute time (**C**-**D**).

Intra and inter-observer variability

Intra and interobserver variability were good with all mean differences respectively ≤0.5±0.6mm and ≤1±1.2mm for maximum and minimum diameter and ≤8.1±25.9mm^2 and ≤18.2±17.9mm^2 for the area.

Discussion

In this study we described a standardized way to determine the annulus plane in patients with a bicuspid aortic valve and demonstrated that the BAV annulus undergoes significant changes in shape and size during the cardiac cycle. Overall, the annulus showed a larger area with an almost circular shape in systole and a smaller area with an elliptic shape in diastole. Each of the BAV types showed analogous morphological changes. However, type 1 valves had a more elliptic annulus in early systole. Furthermore, as the heart rate at the moment of the CT scan increased, the minimum area was reached at a later phase of the cardiac cycle but earlier in absolute time.

The term BAV includes a spectrum of morphological alterations of the aortic valve that have in common the resulting presence of only two functional cusps. BAV are commonly divided based on the classification system introduced by Sievers et al.[1]. This classification is based on the valve phenotype and more specifically on the presence and number of raphe. A raphe represents the line of fusion between two cusps that are often unequal in size. Due to the absence of the normal three cusps and corresponding three apposition surfaces, the opening orifice of the valve is often asymmetric. Furthermore, the aortic root is asymmetrically and characteristically enlarged in 58% of cases[16]. The distortion of the valve opening in BAV patients has led to the exclusion of patients with this anomaly from most early studies assessing safety and results of TAVI, due to concerns about deformation and malposition of the implanted valve[3,17,18]. Although with limitations due to the inclusion of small populations, later investigations have shown that TAVI is in fact feasible also in the BAV population and, furthermore, has results comparable to those obtained in cohorts with TAV[4,5,19,20].

Correct and precise pre-TAVI assessment of aortic root diameters is fundamental to choose the most appropriate valve size and avoid complications, particularly paravalvular regurgitation, that has been shown to occur more frequently in the BAV population[4,21]. CT has been identified as the imaging modality of choice for this purpose. The most important entity to be assessed is the ring where the deployed valve will be anchored. These measurements will determine which valve size will be implanted among the limited number of available ones. This ring, commonly referred to as "annulus", contours the level with the smallest area along the junction between the LVOT and the aortic root but does not correspond to a well-defined anatomical structure[12,22]. Recent guidelines (intended for patients with TAV, albeit not addressing valve anatomy variations) indicate that the annulus should be identified on MPR as the plane passing through the three hinge points of the cusps[11]. Although this same technique has been previously applied also to datasets of patients with BAV[5], we did not find this method feasible for all patients. First, in patients with BAV valve type 0 there are only two cusps and therefore, in most cases, only two hinge points (or in few cases two of the three are very close). Since there are infinite planes that pass through two points, more criteria for the identification of the correct annulus

plane had to be introduced as detailed above in the Methods and figure 2. Furthermore, in patients with BAV type 1 (and possibly type 2) one of three cusps is often malformed and/or underdeveloped resulting in a distortion of the normal anatomy of the aortic root. Therefore, the plane passing through the three hinge points might not be representative of the desired plane where to deploy the valve. In these patients, at first the hinge points of the two bigger cusps were used as landmarks and subsequently the so obtained plane was oriented following the same steps as in patients with valves type 0 (figure 1). The application of this methodology, both in clinical and research settings, will likely improve the standardization of annulus measurements in BAV patients, and thereafter, provide accurate and appropriate sizing data as basis for future guidelines.

In patients with TAV it has been shown that the annulus has an elliptic shape that undergoes conformational changes during the cardiac cycle as well as significant variation in sizing parameters[8]. Knowledge of this phenomenon is fundamental in the pre-TAVI work-up to establish during which phase the annulus dimensions should be calculated. Although with some controversy attributable to the better quality and reproducibility of diastolic images[13], literature and guidelines suggest that measurements should be performed on images obtained in systole due to larger annular sizes in this phase[11,23]. Our study demonstrated the occurrence of significant changes in sizing parameters during the cardiac cycle in all types of BAV. The RA, minimum diameter and area showed the most pronounced differences (13.8% and 13.7%), with all highest values in the phases between 0% to 10%, while the maximum diameter demonstrated the smallest difference (3.6%). The relative difference of 7.2% found for the area-derived diameter corresponded to an absolute difference of 1.9mm between systole and diastole. Considering that each prosthetic valve size can be fitted in annuli presenting a range of diameters of 3mm at maximum (or 2mm depending on the type of valve employed), a 2mm difference could imply a different choice of valve size. For the patient with the highest relative difference in area-derived diameter (relative difference of 17%; minimum and maximum area-derived diameter of 24.5mm and 29.6mm respectively) measuring the annulus in a different phase could imply: employing a 29mm Medtronic CoreValve or not having an appropriate size for this type of valve; implanting a 26mm Edwards Sapien valve or risking paravalvular leakage with a possibly undersized 29mm valve of the same type.

Among the reasons that led to consider BAV patients as at high risk for TAVI procedures are some characteristics of the aortic annulus such as a more elliptic shape than in patients with TAV. This different conformation has been suggested as the cause for the higher rate of paravalvular regurgitation in BAV patients[17,19,24,25]. With an AR >1 at all phases and for all BAV types, but significantly more in early systolic phase for valves type 1, our study demonstrated that the annulus of BAV patients has an elliptic shape. However, the overall and per valve type maximum average AR in our study (maximum AR: 1.3±0.2 overall; 1.4±0.2 for valves type 0; 1.3±0.1 for valves type 1; 1.3±0.2 for valves type 2) are comparable to those found in patients with TAV[7,9,23].

Hemodynamic characteristics might influence the mechanics of the annulus. Therefore, we investigated the influence of the patients' heart rate at the moment of the CT examination. CT images were reconstructed based on the percentage of the cardiac cycle and therefore the absolute time span between phases depended on the heart rate of the patient at the moment of the acquisition. Our results suggest that in patients with a higher heart rate changes in area of the aortic annulus occur at a shorter absolute time, which, however, corresponds to a later phase of the cardiac cycle. Therefore, to ensure that the largest sizing parameters are detected for all heart rates, measurements should be performed in early systolic phase and within 200ms from the R wave.

A limitation of the present study is the impossibility to compare planes and measurements obtained with the new method to a reference standard. However, for the annulus, even in TAV patients, there is no reference standard. In fact, measurements performed in operating rooms are subject to limitations such as non-physiological conditions and the use of an imprecise measurement tool and, furthermore, values of implanted valves size are influenced by other additional factors. Second, due to the relatively limited number of patients per type of BAV valve, ANOVA models for repeated measurements were not applicable and comparison between valve types had to be performed per time points. Furthermore, the mean age of the study population was relatively low with a limited number of severely stenotic aortic valves. Another limitation that has to be considered is the thickness of the reconstructions (1.5mm), which might have influenced the precision of the measurements. Finally, the amount of calcium at the level of the annulus was not systematically and quantitatively scored. However, calcifications were considerable in one patient only.

Conclusions

We propose a new specific and systematic method for the definition of the annulus plane in patients with all types of BAV. The aortic annulus of patients with BAV undergoes dynamic changes during the cardiac cycle. In all three BAV types the annulus has an elliptical shape that undergoes conformational changes with a more flattened appearance in diastolic phase. Furthermore, the annulus presents significant dynamic variations in sizing parameters with the highest values in early systole. These changes occur earlier during the cardiac cycle for patients with a slower heart rate. Therefore, measurements for TAVI planning in patients with BAV should be performed in the early systolic phase to avoid underestimation of the annulus dimensions.

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CHAPTER 9

9

Biomarkers in patients with bicuspid aortic valve disease

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Background

Patients with a bicuspid aortic valve (BAV) are at risk of developing valve deterioration and aortic dilatation. We aimed to investigate whether blood biomarkers are associated with disease stage in patients with BAV.

Methods

Serum levels of high sensitive C-reactive protein (hsCRP), high sensitive Troponin T (hsTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and total Transforming Growth Factor-beta 1 (TGF-ß1) were measured in adult BAV patients with valve dysfunction or aortic pathology. Age-matched general population controls were included for TGFß-1 measurements. Correlation analyses and multivariable linear regression were used to determine the association between (2log-transformed) biomarker levels and aortic valve regurgitation, aortic valve stenosis, aortic dilatation or left ventricular function.

Results

hsCRP and hsTnT were measured in the total group of 183 patients (median age 34 years, 25th-75th percentile 23-46), NT-proBNP in 162 patients and TGF-ß1 beta in 108 patients. Elevated levels of NT-proBNP was found in 20% of the BAV patients, elevated hsTnT in 6% and elevated hsCRP in 7%. Higher hsTnT levels were independently associated with aortic regurgitation (odds ratio per doubling [OR_{2log}] 1.34, 95% CI 1.01;1.76) and higher NT-proBNP levels with aortic valve maximal velocity ($ß_{2log}$ 0.17, 95%CI 0.07;0.28) and aortic regurgitation (OR_{2log} 1.41, 95%CI 1.11;1.79). Both BAV patients with (9.9±2.7 ng/ml) and without aortic dilatation (10.4±2.9 ng/ml) showed lower TGF-ß1 levels compared to general population controls (n=85, 11.8±3.2 ng/ml).

Conclusions

Higher NT-proBNP and hsTNT levels were associated with aortic valve disease in BAV patients. TGF-ß1 levels were lower in BAV patients than in the general population, and not related to aortic dilatation. Longitudinal data are needed to further investigate the prognostic value of biomarkers in these patients.

Abstract

Introduction

A bicuspid aortic valve (BAV) is an aortic valve with only two cusps instead of three or with three cusps of which two or more are fused with a raphe in between the cusps. It is the most common congenital heart malformation with a prevalence of 0.5-2% in the general population[1, 2]. BAV is accompanied by aortic valve stenosis in about 65% and by aortic valve regurgitation in about 40%, although numbers vary between studies, depending on the age of the patients[3, 4]. Furthermore, approximately 50% of the BAV patients develop aortic dilatation throughout their lifetime[5]. To guide the optimal timing for surgical interventions in patients with BAV, accurate prognostication and monitoring of disease progression of aortic stenosis, aortic regurgitation or aortic dilatation, is of great importance. Circulating blood biomarkers might provide additional information to determine who is at highest risk for future complications. Currently, there is limited data on the use of biomarkers in patients with BAV and the data that is available mainly focuses on aortapathology[6]. It is of great interest to obtain further insight into alterations of growth factors and mediators in aortic valve degeneration, aortic dilatation or myocardial remodeling. The biomarkers Troponin-T and N-terminal pro B type natriuretic peptide (NT-proBNP) may be elevated as a result of pressure overload in aortic stenosis and volume overload in aortic regurgitation, which can help to identify patients with increased left ventricular wall stress who may benefit from earlier treatment. In older patients with degenerative aortic valve stenosis, higher C-reactive protein is associated with more severe aortic stenosis[7], but no evidence is available on aortic valve stenosis in patients with a BAV. Finally transforming growth factor-beta 1 (TGF-ß1) is found to be elevated in blood samples of patients with aortic dilatation or syndromes associated with thoracic aortic disease[8-11]. Yet, only small numbers ranging between 9 and 30 patients with a BAV were included in these studies. This cross-sectional study aimed to investigate the association between blood biomarkers (high sensitive C-reactive protein, high sensitive Troponin T, NT-proBNP and TGF-ß1) and the degree of aortic valve stenosis or regurgitation, left ventricular ejection fraction or aortic diameter in a large cohort of adults with BAV.

Methods

Study design and patient population

For this study we included the data of two cohorts of adults with BAV: the BioCon study, an observational prospective cohort study including consecutive adults with moderate to complex congenital heart disease enrolled between 2011-2013[12], and the BAV study, a multicenter observational cohort study performed between 2014 and 2016 including patients with BAV and/or Turner syndrome. We extracted adult patients from both cohort studies with BAV and at least one of the following: [1] aortic valve stenosis (maximal velocity >2.5 m/s), [2] aortic valve regurgitation (at least moderate), [3] aortic dilatation of

the sinus of Valsalva or ascending aorta (≥40 mm and/or aortic size index ≥2.1 cm/m^2), [4] aortic coarctation, [5] an aortic valve intervention (balloon dilatation, resection subvalvular stenosis or valve repair) or [6] Turner syndrome. Patients who previously underwent aortic valve or aortic replacement were excluded. All three types of a BAV according to the Sievers classification were included[13]. This classification is based on the number of raphes, which is a fused area between two cusps. BAV with no raphe are called type 0, valves with one raphe type 1 and valves with two raphes type 2. For research purposes, patients underwent physical examination, two-dimensional thoracic echocardiography (TTE) and venous blood sampling on the same day. Hypertension was defined as current use of antihypertensive medication. The study complied with the Declaration of Helsinki and was approved by the medical ethical committee of the Erasmus Medical Center (MEC10-165 and MEC14-225). Written informed consent was provided by all patients.

TGF-ß1 measurements in general population controls

Between 2014 and 2015, 145 healthy volunteers were prospectively recruited through an advertisement for healthy subjects and stratified into five age groups: 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 to 72 years[14]. TGF-ß1 levels were determined. To create an age-matched reference group, only the participants with an age under 50 years were included for the current study for TGF-ß1 measurements. The inclusion criteria required that subjects had normal results on physical examination, echocardiography and electrocardiography (ECG). Subjects were excluded when they met any of the following criteria: cardiovascular disease (including aortic dilatation, aortic valve stenosis, aortic valve regurgitation); cardiovascular risk factors consisting hypertension, diabetes mellitus, hypercholesterolemia; systemic disease or medication known to influence cardiac function; or the finding of cardiac abnormalities during examination. Professional athletes, morbidly obese subjects (BMI >40 kg/m2), pregnant women, and women with breast implants were also excluded. All participants underwent physical examination, TTE and venous blood sampling on the same day at the outpatient clinic.

Echocardiography

Standard 2D transthoracic echocardiography was performed by an experienced sonographer. All studies were acquired using harmonic imaging on an iE33 or EPIQ7 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with an ×5–1 matrix-array transducer (composed of 3040 elements operating at 1–5MHz). The aorta was measured during diastole with the leading edge-to-leading edge method from either the standard parasternal long axis view or from a more cranial intercostal window to improve visualization of the ascending aorta[15]. Aortic valve stenosis was defined based on a peak aortic velocity of >2.5 m/s[16] and aortic valve regurgitation was classified as no, mild, moderate and severe according to the EAE/ASE guidelines[17]. Aortic dilatation was defined as an aortic diameter ≥40 mm or aortic size index ≥2.1 cm/m^2 at the level of the sinus of Valsalva or ascending aorta. All measurements of left ventricular ejection fraction

(LVEF) based on strain analyses were performed blinded regarding subject ID with using the 2D CPA suite from Tomtec Imaging Systems (Unterschliessheim, Germany).

Laboratory testing

Venous blood sampling was performed for study purposes only. NT-proBNP was measured directly in fresh blood samples with the use of an electrochemiluminesence immunoassay (Roche Diagnostics, Basel, Switzerland) in the clinical chemistry laboratory of the Erasmus MC. The rest of the serum samples were aliquoted and stored by -80 degrees Celsius within two hours after withdrawal. High sensitive Troponin T (hsTnT) and high sensitive C-reactive protein (hsCRP) were measured in batches in thawed serum samples using an electrochemiluminesence immunoassays (Roche Diagnostics, Basel, Switzerland). Lower limit of detection was 3 ng/L for hsTnT, 0.3 mg/L for hsCRP and 0.6 pmol/L for NT-proBNP. TGF-ß1 measurement was only performed in the patients of the BAV study and healthy controls, and was performed by the laboratory medical immunology of the department of Immunology of the Erasmus MC. Serum concentration of human activated TGF-ß1 was measured by quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique according to the manufacturer's instructions (Duoset® ELISA, R&D Systems Europe, Ltd.). Before the assay, the latent TGF-ß1 contained in patients' serum was activated to the immunoreactive form using acid activation and neutralization. The lower limit of detection was 31.25 pg/ml. For the control subjects, the protocol of TGF-ß1 measurements was exactly the same as for the BAV patients.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), or median and interquartile range (IQR). Comparison of normally distributed continuous variables was done using the Student's *t* test or, in case of a skewed distribution, the Mann-Whitney test. Biomarker values below the limit of detection (LoD) were substituted with a value that was equal to 50% of this LoD, for analytical purposes. Because of a skewed distribution, all biomarker levels were 2log transformed for further statistical analysis. The upper limit of normal for NT-proBNP was 14 pmol/L (≈125 pg/mL), on the basis of the recommended cutoff for the diagnosis of heart failure in patients presenting with non-acute symptoms[18]. The upper limit of normal of hsTnT and hsCRP was defined as the 99th percentile of the reference distribution, which corresponded with 14 ng/L for hsTnT[19] and with 10 mg/L for hsCRP[20]. First, the Pearson (r_p) or Spearman (r_s) correlation coefficient between biomarkers, as well as between biomarkers and patient characteristics was determined. Second, regression analysis was performed with biomarker levels as independent variable and disease stage as dependent variable. For disease stage the following variables were used: maximum velocity (Vmax) across the aortic valve, aortic valve regurgitation (no, mild, moderate and severe), aortic diameter and left ventricular ejection fraction. When the dependent variable was continuous, linear regression analysis was used, and in case of an ordinal variable, ordinal

logistic regression analysis was used. Significant univariable associations were further analyzed in multivariable analysis. First, we adjusted for age and sex only and secondly also for Vmax, aortic regurgitation, diameter of the sinus of Valsalva and ascending aorta and ventricular function. Significant associations between biomarker levels and disease stage in multivariable linear regression analysis, were further analyzed using categories of disease stages. Aortic valve stenosis was categorized into no aortic valve stenosis (Vmax <2.5 m/s), mild aortic valve stenosis (Vmax 2.5-3.9 m/s) and severe aortic valve stenosis (Vmax ≥4.0 m/s). Aortic regurgitation was analyzed categorical as no, mild and moderate/severe aortic valve regurgitation. A sensitivity analysis was performed by excluding Turner patient. Third, we compared biomarkers levels between patients with either aortic valve stenosis or regurgitation and patients without aortic valve stenosis and regurgitation. Also biomarkers levels were compared between BAV patients with different Sievers classifications. Missing data were handled by multiple imputation with five iterations.[21] All tests were two-sided and a *p*-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The patient selection process is shown in Figure 1. A total of 183 patients were included with a median age of 34 (IQR 23-46) years of which 82 (45%) were female (Table 1). NT-proBNP measurement was available in 162 patients (89%). In a subset of 108 (58%) patients, total TGF-ß1 levels were determined. Patients in which TGF-ß1 was measured were significantly older, had larger aortic diameters and less patients had or were previously treated for an aortic coarctation compared to the total group of 188 patients. In the total group, a BAV Sievers type 0 was found in 27 (25%) subjects, Sievers type 1 in 144 (79%) subjects and Sievers type 2 in 12 (6%) subjects. Moderate or severe aortic valve regurgitation was found in 50 (27%) patients, aortic valve stenosis in 80 (44%) patients and aortic dilatation in 98 (54%) patients. Both aortic valve regurgitation (at least moderate) and aortic valve stenosis was found in 34 (19%) patients. LVEF of less than the lower limit (5th percentile) of the healthy group, which was 45%, was found in 69 (38%) of the BAV patients.

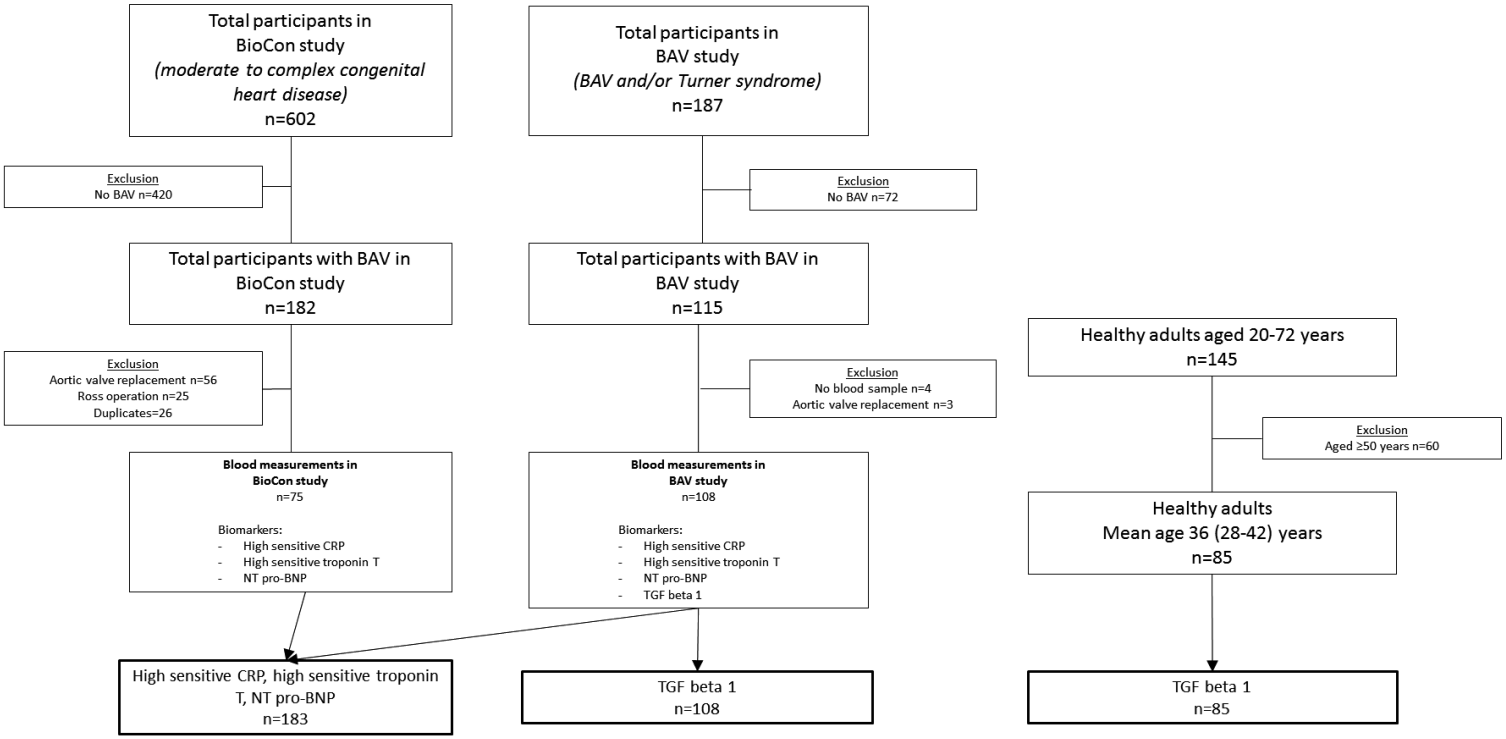


Figure 1. Flow charts of participants from the BioCon and BAV study in blood marker analysis. hsCRP = high sensitive C-reactive protein; hsTnT = high sensitive troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TGF beta 1 = transforming growth factor beta 1.

Table 1. Baseline characteristics

	hsCRP and hsTnT (total group)	NT pro-BNP	TGFß1 (only measured in BAV study)	Healthy controls for TGFß1 measurements
	n=183	n =162	n=108	n=85
Age (years)	34 (23-46)	31 (23-43)	38 (25-52)*	36 (28-42)
Female sex	82 (45%)	72 (44%)	42 (39%)	43 (51%)
Height (cm)	176 (164-183)	176 (165-183)	178 (162-186)	175 (167-182)
Weight (kg)	75 ± 15	75 ± 15	75 ± 15	73 ± 13
Systolic blood pressure (mmHg)	127 ± 17	127 ± 17	126 ± 16	123 ± 12
Diastolic blood pressure (mmHg)	79 ± 11	79 ± 11	78 ± 11	78 ± 8
Aortic diameter, sinus of Valsalva (mm)	35 ± 6	35 ± 6	37 ± 6*	31 ± 3*
Aortic diameter, ascending aorta (mm)	36 ± 8	36 ± 8	38 ± 7*	29 ± 3*
Left ventricular ejection fraction (%)	47 ± 8	47 ± 8	46 ± 8	52 ± 4*
BAV morphology				
Sievers type 0	27 (15%)	22 (14%)	27 (25%)	-
Sievers type 1	144 (79%)	128 (79%)	70 (65%)	-
Sievers type 2	12 (6%)	12 (7%)	11 (10%)	-
Comorbidities				
Aortic coarctation	59 (32%)	57 (35%)	15 (14%)*	0 (0%)
Aortic regurgitation >mild	50 (27%)	46 (28%)	32 (30%)	0 (0%)
Aortic valve stenosis (Vmax≥2.5 m/s)	80 (44%)	70 (43%)	44 (41%)	0 (0%)
Diabetes Mellitus	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Hypertension	40 (22%)	33 (20%)	25 (23%)	0 (0%)
Hypercholesterolemia	10 (6%)	6 (4%)	8 (7%)	0 (0%)
Turner syndrome	22 (12%)	14 (9%)	20 (19%)	0 (0%)
Previous aortic valve intervention				
Surgical aortic valve repair	5 (3%)	4 (3%)	1 (1%)	0 (0%)
Percutaneous balloon dilatation	18 (10%)	18 (11%)	12 (11%)	0 (0%)
Resection subvalvular stenosis	7 (4%)	7 (4%)	0 (0%)	0 (0%)

Values are presented as mean (SD) or median (IQR) for continuous variables and N (%) for categorical variables. Data represent non-imputed values. Missing values were present for blood pressure (1% in BAV patients), aortic diameter at the sinus of Valsalva (1% in BAV patients), ascending aortic diameter (2% in BAV patients and 1% in healthy controls) and LVEF (8% in BAV patients and 14% in healthy controls).
* Significantly different from the total group, p-value <0.05. Values of 0 (0%) could not be tested for significance.

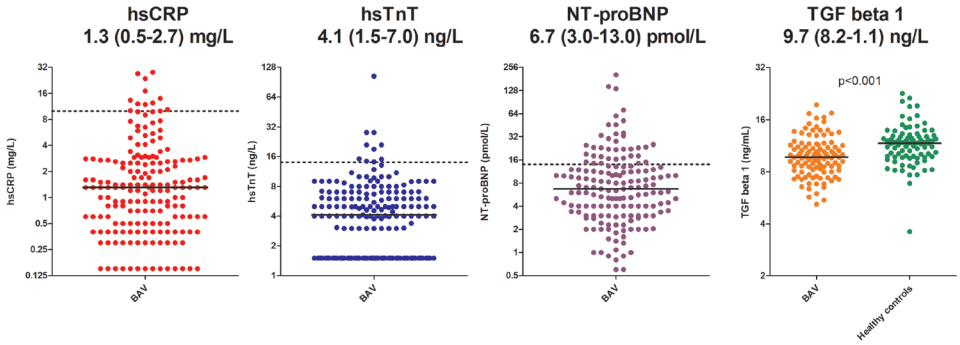


Figure 2. Biomarker levels in adults with BAV
Biomarker levels are presented at the Y-axis on the 2log-scale. The continuous line represents the median. The dashed line represents the upper limit of normal, defined as the 99th percentile of the reference distribution for hsCRP and hsTnT, corresponding with 10 mg/L and 14 ng/L. The upper limit of normal for NT-proBNP was 14 pmol/L (≈125 pg/mL), on the basis of the recommended cutoff for the diagnosis of heart failure in patients presenting with nonacute symptoms. hsCRP = high sensitive C-reactive protein; hsTnT = high sensitive troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TGF beta 1 = transforming growth factor beta 1.

Blood biomarkers

The levels of each biomarker are shown by scatterplots in Figure 2. An elevated NT-proBNP level was found in 37 (20%) patients, an elevated hsTnT level in 10 (6%) patients and an elevated hsCRP level in 12 (7%) patients. In our reference cohort of 85 volunteers, mean TGF-ß1 levels were 11.8±3.2 ng/mL and not significantly associated with age (r_p=0.13, p=0.227) or sex (11.6±2.7 ng/mL in men vs 12.0±3.6 ng/mL in women, p=0.640) (Supplemental Figure 1). A significantly lower TGF-B1 was found in both BAV patients with aortic dilatation (9.9±2.7 ng/ml) and BAV patients without aortic dilatation (10.4±2.9 ng/ml) compared to healthy controls with tricuspid aortic valve (TAV) (11.8±3.2 ng/ml)(Figure 3), also after correction for age. We found significant correlations between hsCRP and hsTnT (r_s=0.15, p=0.042), hsCRP and NT-proBNP (r_s=0.35, p<0.001), and NT-proBNP and TGF-ß1 (r_s=-0.24, p=0.025).

None of the biomarkers showed an association with aortic diameter or left ventricular function in multivariable analysis (Table 2). A two-fold higher hsTnT level was independently associated with an increased risk of one higher grade of aortic regurgitation by a factor of 1.34 (95% CI 1.01;1.76). When aortic valve regurgitation was categorized as no, mild or moderate/severe, hsTnT was only significantly higher in the patients with moderate/severe aortic valve regurgitation compared to patients with no aortic valve regurgitation (Figure 4).

A two-fold higher NT-proBNP level was independently associated with a mean 0.17 (95% CI 0.07;0.28) m/s higher Vmax. In addition, a two-fold higher NT-proBNP level was

independently associated with an increased risk of one higher level of aortic regurgitation by a factor of 1.41 (95% CI 1.11;1.79). When aortic valve stenosis was categorized into three groups, NT-proBNP levels were only significantly higher in patients with severe aortic valve stenosis (Vmax >4.0 m/s) compared to patients with no aortic valve stenosis (Figure 4). No significant differences in NT-proBNP levels were found between the three categories of aortic valve regurgitation. The comparison between patients with either aortic stenosis or aortic regurgitation and patients without both stenosis or regurgitation can be found in supplemental figure 2. Supplemental figure 3 shows the comparison in biomarker level between patients with different Sievers classification. When Turner patients were excluded from the analysis, the results remained the same.

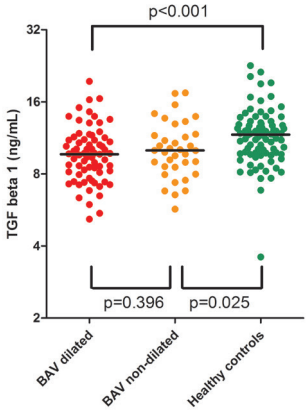


Figure 3. TGF beta 1 levels in BAV patients with and without aortic dilatation (≥40 mm and/or aortic size index ≥2.1 cm/m2) and healthy controls.
Biomarker levels are presented at the Y-axis on the 2log-scale. The continuous line represents the median. TGF beta 1 = transforming growth factor beta 1.

Table 2. Linear or ordinal logistic regression analysis of biomarkers and continuous variables representing disease progression.

		Correlation analysis		Univariable regression analysis		Multivariable regression analysis*	
		Correlation coefficient	p-value	ß or OR (95% CI)†	p-value	ß or OR (95% CI)†	p-value
Log2 hsCRP	Aortic valve stenosis (Vmax in m/s)	0.00	0.981	0.02 (-0.07;0.11)	0.300		
	Aortic valve regurgitation (no, mild, moderate, severe)	-0.02	0.827	0.99 (0.85;1.15)	0.716		
	Aortic diameter at the level of sinus of Valsalva (mm)	0.00	0.996	0.02 (-0.51;0.56)	0.938		
	Aortic diameter at the level of ascending aorta (mm)	0.01	0.855	0.01 (-0.64;0.67)	0.972		
	Left ventricular ejection fraction (%)	0.01	0.191	0.01 (-0.57;0.83)	0.725		
Log2 hsTnT	Aortic valve stenosis (Vmax in m/s)	0.11	0.132	0.09 (-0.04;0.22)	0.164		
	Aortic valve regurgitation (no, mild, moderate, severe)	0.16	0.035	1.29 (1.03;1.57)	0.030	**1.34 (1.01;1.76)**	**0.041**
	Aortic diameter at the level of sinus of Valsalva (mm)	0.29	<0.001	1.56 (1.17;1.95)	<0.001	0.07 (-0.61;0.76)	0.838‡
	Aortic diameter at the level of ascending aorta (mm)	0.19	0.011	1.39 (0.44;2.33)	0.004	-0.40 (-1.40;0.60)	0.431‡
	Left ventricular ejection fraction (%)	0.10	0.260	0.49 (-0.63;1.61)	0.384		
Log2 NT-proBNP	Aortic valve stenosis (Vmax in m/s)	0.19	0.016	0.16 (0.05;0.26)	0.003	**0.17 (0.07;0.28)**	**0.002**
	Aortic valve regurgitation (no, mild, moderate, severe)	0.14	0.070	1.22 (1.01;1.47)	0.035	**1.41 (1.11;1.79)**	**0.005**
	Aortic diameter at the level of sinus of Valsalva (mm)	-0.04	0.593	-0.18 (-0.81;0.46)	0.592		
	Aortic diameter at the level of ascending aorta (mm)	0.03	0.694	0.16 (-0.64;0.95)	0.693		
	Left ventricular ejection fraction (%)	0.17	0.035	0.94 (0.08;0.09)	0.033	0.36 (-0.73;1.44)	0.518‡
Log2 TGFß1	Aortic valve stenosis (Vmax in m/s)	-0.11	0.277	-0.38 (-0.88;0.12)	0.137		
	Aortic valve regurgitation (no, mild, moderate, severe)	-0.01	0.944	0.92 (0.37;2.30)	0.866		
	Aortic diameter at the level of sinus of Valsalva (mm)	0.19	0.045	3.01 (0.10;5.92)	0.043	1.32 (-1.06;3.70)	0.278‡
	Aortic diameter at the level of ascending aorta (mm)	-0.03	0.758	-0.60 (-4.37;3.18)	0.757		
	Left ventricular ejection fraction (%)	-0.13	0.205	-2.60 (-6.59;1.38)	0.200		

Bold = significant in multivariable analysis.

* Adjusted for age, sex, Vmax, aortic valve regurgitation, aortic diameters and LVEF. † Beta coefficient was given for linear regression analysis performed with Vmax, aortic diameter or LVEF as dependent variables. Odd ratio was given for ordinal logistic regression analysis performed with aortic regurgitation (no, mild, moderate, sever) as dependent variable. ‡ Not significant after adjustment for only age and sex.

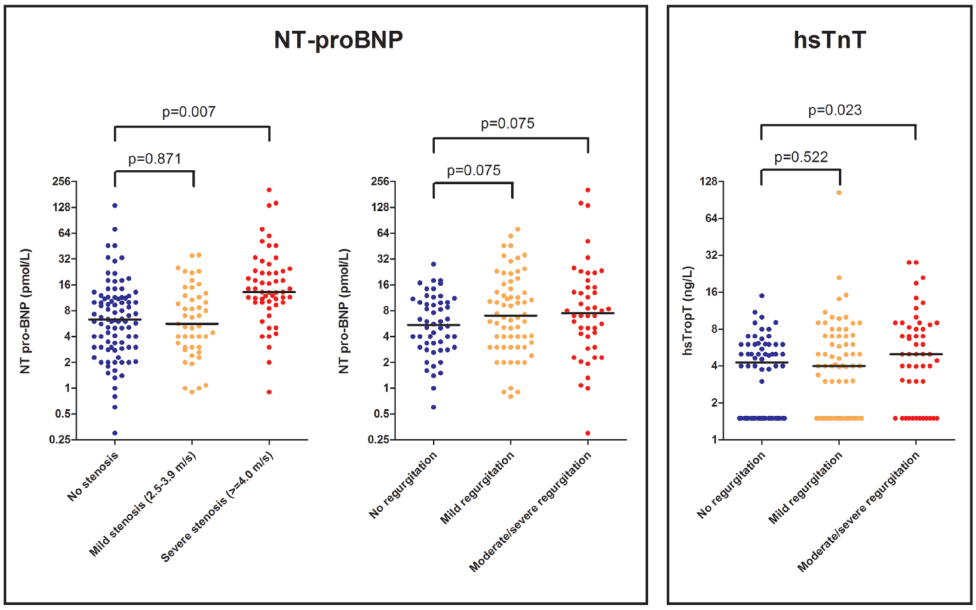


Figure 4. NT-proBNP and hsTnT levels in patients with different stages of aortic valve stenosis and aortic valve regurgitation.
Biomarker levels are presented at the Y-axis on the 2log-scale. The continuous line represents the median. NT-proBNP = pro-B-type; hsTnT = high sensitive troponin T.

Discussion

This cross-sectional study investigated the levels of hsCPR, hsTNT, NTproBNP and TGF-ß1 in a large cohort of adults with BAV. We can conclude that a substantial number of patients with BAV have elevated levels of NT-proBNP, hsTnT and hsCRP. TGF-ß1 levels were found to be lower in patients with BAV than in a healthy age-matched control population with TAV. A higher NT-proBNP was significantly associated with a higher maximum velocity across the aortic valve and more severe aortic valve regurgitation. In addition, higher hsTnT levels were associated with more severe aortic valve regurgitation. Specifically high levels of NT-proBNP were present in patients with severe aortic stenosis (≥4.0 m/s) and high levels of hsTnT were present in patients with moderate to severe aortic valve regurgitation.

In contrast to imaging biomarkers, blood biomarkers can be obtained in all patients and at relatively low cost, making them very suitable as diagnostic and useful in prediction models. This study already showed that patients with BAV have higher levels of NT-proBNP, hsTnT and hsCRP and lower levels of TGF- ß1, which can help us to understand the pathophysiology of complications in patients with BAV. In addition, this is the first study that evaluated associations between biomarkers and disease stage in this specific group of patients with BAV and demonstrated that particularly NT-proBNP and hsTNT may have

potential prognostic value in adults with a bicuspid aortic valve. Whether biomarker levels can predict deterioration of aortic valve pathology and can be used for clinical decision making in BAV patients should be further investigated in longitudinal studies.

NT-proBNP in bicuspid aortic valve patients

NT-proBNP is associated with ventricular dysfunction in patients with congenital aortic valve stenosis[22] and is elevated in older individuals with calcified aortic valve stenosis[23] or aortic valve regurgitation[24]. In older patients with aortic stenosis, the prognostic value of NT-proBNP has also been proven[25]. However, BAV patients differs genetically, histopathologically and in age from the patient group of aortic valve degeneration represented in literature[26, 27]. BAV patients are prone to develop aortic valve stenosis, aortic valve regurgitation or aortic dilatation at a relatively young age[28]. We showed that NT-proBNP levels are associated with aortic valve stenosis and regurgitation in BAV patients. NT-proBNP expression is induced by diastolic and systolic myocardial wall stretch[29]. This can be a result of both aortic valve stenosis and regurgitation due to increased left ventricular pressure afterload or volume overload respectively. Two studies[29, 30] that included relatively old patients with aortic valve stenosis, showed that NT-proBNP and BNP are already elevated in patients with normal LV end-diastolic pressure or left atrial pressure, compared to controls. This might suggest that NT-proBNP is already elevated before patients with aortic valve stenosis or regurgitation develop increased pressures and compensated hypertrophy. However, to answer the question whether NT-proBNP could help to identify BAV patients with future LVEF deterioration, longitudinal studies are required.

hsTnT in bicuspid aortic valve patients

Troponin T, a marker of myocardial injury, is not only elevated in acute coronary syndrome, but it can also be elevated in chronic heart failure[31] as a result of multiple suspected contributing mechanisms including cardiomyocyte damage from inflammatory cytokines or oxidative stress, apoptosis or a stretch-related meachanism[32]. Troponin T levels also have a predictive value of long-term outcome in patients with non-ischemic heart failure[33]. Again these studies are performed in older patients compared to the BAV patients included in our study and therefore probably represent another disease etiology. Although we did not find an association between hsTnT levels and LVEF, we did find that hsTnT levels were associated with more severe aortic valve regurgitation in BAV patients. One hypothetical explanation might be the reduced coronary blood flow during diastole found in patients with aortic regurgitation[34, 35], which can result in cardiomyocyte damage and therefore increased hsTnT levels. A reduced coronary blood flow is also found in patients with aortic stenosis[36], while aortic stenosis was not associated with increased hsTnT levels in our cohort.

hsCRP in bicuspid aortic valve patients

In older patients with aortic stenosis, Galante et al. found that inflammatory markers, such as CRP, were elevated[37]. Statins have been tested and suggested as new treatment to reduce the progression of aortic valve stenosis, because they reduce vascular inflammatory processes besides their already known cholesterol-lowering effect[38]. Nevertheless, large randomized controlled trials did not found an effect of statin therapy on cardiovascular events, mortality, or valve dynamics in patients with aortic valve stenosis[39]. In our study, CRP levels did not show an association with the severity of aortic valve stenosis in BAV patients, suggesting that inflammation is less likely to be involved as underlying process of aortic valve stenosis development in BAV patients. This finding confirms that indeed there is no clear role for statin therapy. A theory of dilatation of the aortic is presumed to be a process of inflammation, in this study we did not find an association between aorta diameter and the level of hsCRP. The reason for this could be that this process only plays a role in late stage of dilatation and the number of patients with a large aortic diameter might have been too small.

TGF-beta 1 in bicuspid aortic valve patients

There has been attention for biomarkers in BAV-associated aortic pathology, focusing on matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinase (TIMP) and TGF-ß[6, 40]. Although TGF-ß also seem to be important in TAA development in BAV[41], we did not find an association between serum TGF-ß1 levels and aortic diameter in BAV patients. Our results did show, however, that TGF-ß1 levels are decreased in patients with BAV, both with and without aortic dilatation. This is in line with a study investigating aortic tissue, since they found a higher proportion of TGF-ß sequestered in the extracellular matrix in BAV compared to a tricuspid aortic valve (TAV). This probably leads to less free TGF-ß being available to activate the TGFß-pathway[42]. The development of aortic dilatation in BAV patients does not seem to be associated with an increased TGF-ß signaling, such as in Marfan and Loeys-Dietz syndrome. This is confirmed by another study, which also presented a group of non-dilated BAV patients in whom TGF-ß was less expressed in aortic tissue[43]. This different activation of the TGF-ß pathway in aortic dilatation between BAV patients and patients with Marfan or Loeys-Dietz syndrome needs further attention. Contradictory, other studies presented results with higher TGF-ß1 in BAV patients[10, 11] or no difference in TGF-ß1 between BAV and TAV participants[9], but these studies contained only 30, 24 and 12 BAV patients. Also important to mention is that platelets are a major source of TGF-ß1 in the circulation. It has been shown that patients with BAV tent to have a higher mean platelet volume[44], indicating increased platelet activation. If this increased platelet activation had affected the TGF-ß1 measurements, BAV patients would have had higher TGF-ß1 levels. However, we found lower levels of TGF-ß1 in BAV patients, but no information on platelet levels was available to substantiate this assumption.

In addition, we provided reference values for TGF-ß1, based on 85 healthy volunteers without aortic dilatation with an age range from 20-50 years. The mean TGF-ß1 levels that we found (11.8±3.2 ng/ml) were both lower[45] or higher[8, 9] than previously published studies. This could possibly be due to differences in affinity of the antibodies in the immunoassays or inclusion of different reference groups (patient without BAV versus local population). Since the current literature presents a large variation in reference levels of circulating TGF-ß1, reference levels should be measured with the same technique, preferably measured in the same laboratory.

Limitations

Some limitations of our study need to be addressed. The lack of follow-up data prevented us to evaluate the longitudinal prognostic value of these biomarkers. In addition, patients who previously underwent aortic valve or aortic replacement were excluded and therefore BAV patients with the most severe disease stage were less likely to be included in this study. Finally, measurements of LVEF were based on strain analyses in both BAV patients and healthy controls, while the biplane method of disks is the currently recommended 2D method to assess LV EF[46]. A substantial variation between techniques has to be taken into account, with the values found in our study being lower compared to the values referred to as abnormal by the guidelines: LVEF of <52% for men and <54% for women are suggestive of abnormal LV systolic function[15].

Conclusion

A substantial number of patients with BAV have elevated levels of NT-proBNP, hsTnT and hsCRP and they show lower levels of TGF- ß1 compared to healthy controls with TAV. In BAV patients, higher NT-proBNP was associated with more severe aortic valve stenosis and regurgitation, while higher hsTnT levels were associated with more severe aortic valve regurgitation. No independent association between hsCRP or TGFß1 and the degree of aortic valve stenosis or regurgitation, left ventricular ejection fraction or aortic diameter was found. This is the first step towards the identification of a biomarker that can be used in prognostic staging and risk prediction.

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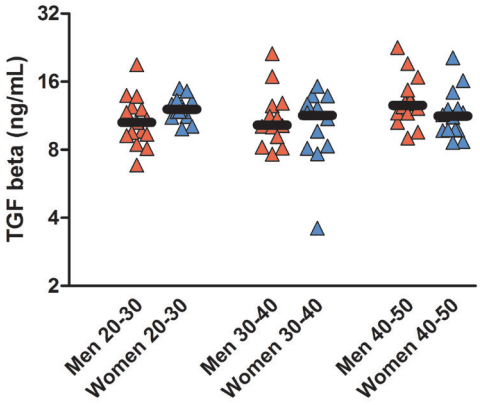
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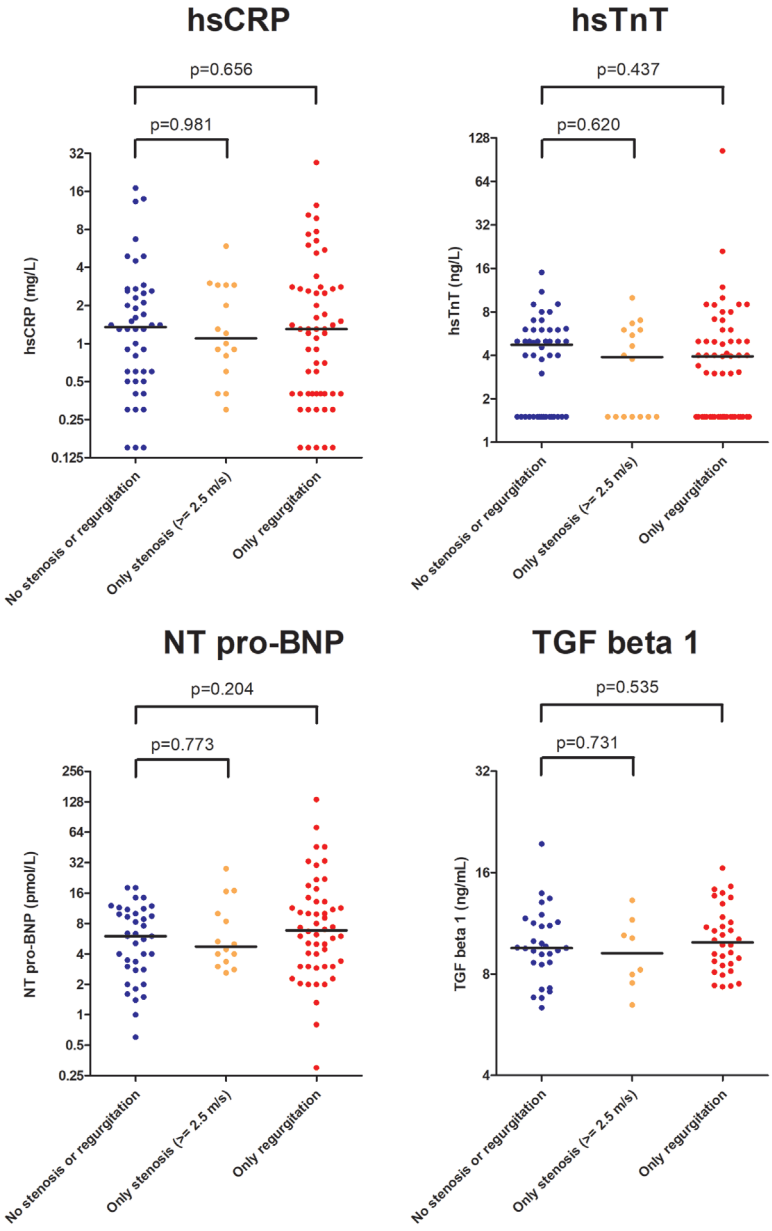
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Supplemental material



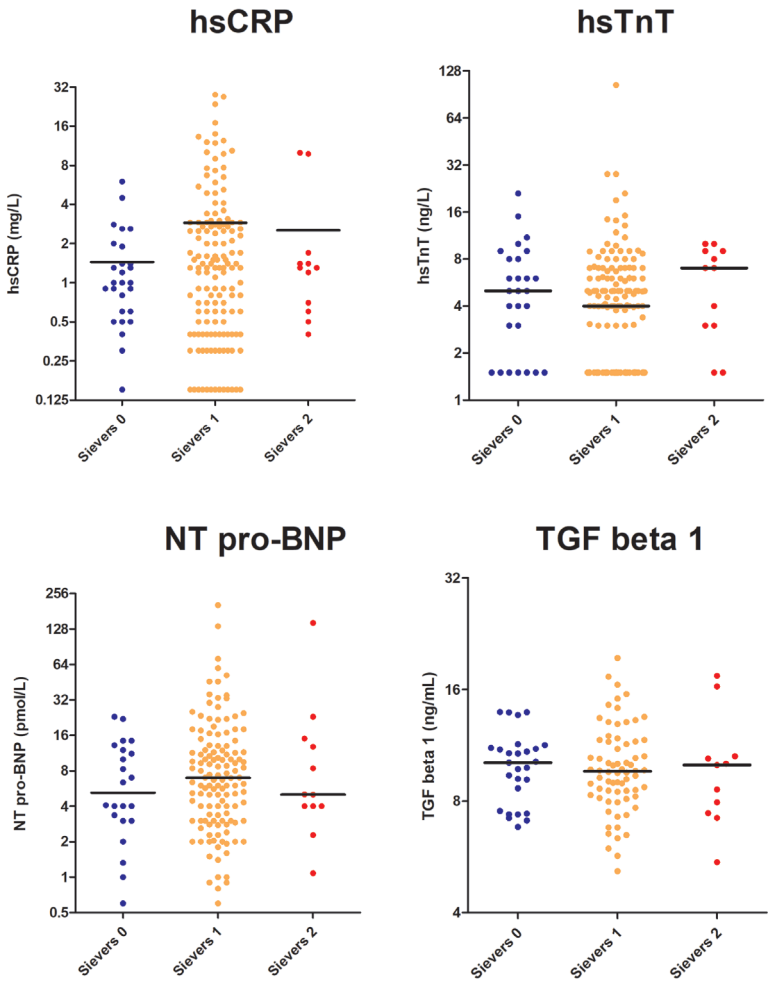
Supplemental figure 1. TGF beta 1 levels according to sex and age groups measured in healthy volunteers (n=85).

Biomarker levels are presented at the Y-axis on the 2log-scale. The continuous line represents the median. No differences were found between men and women for each age group. TGF beta 1 = transforming growth factor beta 1.



Supplemental figure 2. Biomarker levels in patients without aortic stenosis or aortic regurgitation, patients with only aortic valve stenosis and patients with only aortic valve regurgitation.

Biomarker levels are presented at the Y-axis on the 2log-scale. The continuous line represents the median. hsCRP = high sensitive C-reactive protein; hsTnT = high sensitive troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TGF beta 1 = transforming growth factor beta 1.



Supplemental figure 3. Biomarker levels separated by Sievers classification
Biomarker levels are presented at the Y-axis on the 2log-scale. The continuous line represents the median. No differences were found between Sievers classifications with use of the One-way anova for NT-proBNP and TGF beta 1 and the Kruskal-Wallis test for hsCRP and hsTnT levels. hsCRP = high sensitive C-reactive protein; hsTnT = high sensitive troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TGF beta 1 = transforming growth factor beta 1.

CHAPTER 10

Aortic dilatation and outcome in women with Turner syndrome

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Background

Women with Turner syndrome (TS) are at increased risk of aortic dissection, which is related to ascending aortic diameter. However, the relation between aortic diameter and outcome is not well determined. This study evaluates the prevalence of aortic dilatation, the growth rate of the aorta and the risk of aortic complications in adults with TS.

Methods

Single centre, retrospective study of all women with TS followed with a strict protocol in an outpatient TS clinic. Aortic diameters were analysed using advanced imaging. The primary outcome was a combined endpoint of aortic-related mortality, aortic dissection and preventive aortic surgery. The secondary endpoint was aortic growth and prevalence of aortic dilatation, defined as an aortic size index >20 mm/m^2 at baseline.

Results

At least one cardiac MR/CT was available in 268 women with TS, having median age of 28.7 (IQR: 21.3–39.7) years. Aortic dilatation was present in 22%. Linear regression identified independent factors associated with larger aortic diameters: age (coefficient=0.23; p<0.001), hypertension (coefficient=2.7; p<0.001), bicuspid aortic valve (coefficient=3.3; p<0.001), 45XO karyotype (coefficient=1.7; p=0.002), weight (coefficient=0.075; p<0.001) and growth hormone treatment (coefficient=1.4; p=0.044). During follow-up (6.8±3.2 years), five women (2%) reached the primary endpoint (two dissections, three aortic surgery). Women withmore than one scan (n=171; 1015 patient-years follow-up), the median aortic growth was 0.20 (IQR: 0.00–0.44) mm/year. In multivariate analysis, aortic growth was not associated with baseline aortic diameter or other variables.

Conclusions

Aortic dilatation is common and known associations were confirmed in large adult TS cohort However, aortic dissection, related mortality and preventive aortic surgery are rare. Growth hormone treatment in childhood was associated with aortic dimensions.

Introduction

Turner syndrome (TS) is a rare disorder, caused by partial or total absence of an X-chromosome. Prominent features are short stature, gonadal dysgenesis and congenital heart defects. Most commonly seen cardiovascular abnormalities are bicuspid aortic valve (BAV), partial anomalous pulmonary venous return, elongation of the transverse aortic arch, aortic coarctation and ascending aortic dilatation[1-3]. Depending on the definition, the prevalence of aortic dilatation ranges from 4% to 42%[4, 5]. In patients with TS, aortic dissection is reported to occur six times more often compared with the general population[1]. Reported associated factors of aortic dissection are the presence of BAV, aortic coarctation, dilatation of the aorta, hypertension and pregnancy. Dilatation of the aorta occurs predominantly at the level of the ascending aorta and is associated with dissection[6, 7]. European Society of Cardiology guidelines advise to correct for body surface area (BSA) in small body size patients[8]. For the ascending aortic diameter, this index is called the aortic size index (ASI). Preventive aortic surgery is advised when the ASI exceeds 27.5 mm/m^2, but this cut-off value is mainly derived from extrapolation of thoracic aortic dissection in women with non-TS with mostly normal height and higher age[8]. Other guidelines advise preventive surgery even with lower ASI (>25 mm/m^2), mainly based on registries of aortic dissection[9]. The relation between aortic diameters and clinical outcome in patients with TS is not studied in large prospective studies. Increase in aortic diameters over time is theoretically expected to be more rapid in patients with a dilated aorta based on Laplace's law and is also expected to be associated with the same factor that also are associated with aortic dilatation, but whether this is true for patients with TS is also not well investigated[10]. In this cohort study of women with TS, we describe the prevalence of ascending aorta dilatation, growth of the aorta over time and sought to identify factors associated with clinical outcome.

Methods

Population

In March 2003, a dedicated multidisciplinary adult TS outpatient clinic was established at Radboud University Medical Centre and a standard protocol for assessment and follow-up was initiated.[11] The diagnosis of TS was made based on karyotyping of at least 30 blood lymphocytes. All TS karyotypes were included and divided in two main groups 45X0 and mosaicism (non-45X0), in which the mosaicism group is divided in six groups (supplemental material). A strict follow-up protocol was followed[8]. As part of their multidisciplinary evaluation, patients were routinely investigated by a cardiologist with ECG, echocardiography and cardiac MRI (CMR) or when contraindicated CT and by an endocrinologist and gynaecologist. The yield of this standardised health screening in the initial 100 patients of our cohort was published previously[11]. All women with TS

visiting this specialised outpatient clinic were eligible for inclusion. For this retrospective study, we included all women with TS who had at least one CMR/CT at adult age and the images had to be available for review. For the study on aortic growth, all patients with at least two CMR/CT were included. BSA was calculated using the Dubois formula[12]. Ascending aortic dilatation was defined as an ASI≥20 mm/m^2. Z-scores for every patient were calculated based on the formula published by Campens et al[13]. Hypertension and hypercholesterolaemia were defined following guidelines and 'requiring medical therapy'. The Institutional Ethical Board (CMO Arnhem-Nijmegen) approved this study and concluded that no informed consent was needed as the treating doctors performed the study and the institution adopted an opt-out policy on scientific medical file research. All data were handled carefully and confidentially.

Advanced imaging

Baseline and follow-up aortic diameters were measured by a dedicated radiologist using CMR or when contraindicated CT. In all CMR/CT a standard imaging protocol was used. An Avanto 1.5 T whole-body MRI system was used (Siemens). Dedicated phased-array cardiac surface coils were placed over the thorax. All images were acquired with breath-hold. The ascending aorta was measured on axial TRUFI images in the axial plane.

For CT acquisition, a 320 slice scanner (Aquilion one, Toshiba) was used. The heart was fully covered within a wide volume scan with ECG gating during the whole heart cycle. The ascending aorta was measured in the axial plane, during diastolic phase. In both modalities, an inner edge to inner edge method was used to measure the ascending aortic diameter at the height of the right pulmonary branch[11]. Both the absolute measurements and measurements corrected for BSA (ASI) were collected.

Endpoints

The primary endpoint was an aortic event, defined as aortic-related mortality (proven or high suspicion of dissection or rupture), aortic dissection or (preventive) aortic surgery. Information on the vital status of all participants was obtained from the municipal base administration of personal data (GBA) of the Netherlands on 1 February 2017. The secondary endpoint was the increase in ascending aortic diameters which was assessed in the patients with more than one CMR/CT. Patients who reached the primary endpoint before having the second CMR/CT were excluded from this analysis. The annual change of the aortic diameter was calculated based on the aortic diameter measurements of the first and last scan, divided by the time span between these scans. Because of this, negative aortic diameter change could occur[14].

Statistical analysis

Results are expressed as mean±SD or as median±IQR if the distribution was skewed or the Shapiro-Wilk test showed abnormal distribution. A $p \leq 0.05$ was defined to be

statistically significant. The independent samples t-test was used to compare means (eg, aortic growth/year) between groups. In case of a skewed distribution, the Mann-Whitney test was used. The paired sample t-test was used to compare ascending aortic diameter change in time within cases. Univariate and multivariate linear regression analyses were used to explore associations with aortic diameter and aortic growth, or logistic regression analysis was used to explore associations with aortic dilatation and aortic growth using the same variables. Survival analysis could not be performed due to the limited number of events.

Results

In total, 270 patients with TS were eligible, of whom 2 had to be excluded due to poor-quality aorta images. The remaining 268 patients, median age of 28.7 (IQR: 21.3–39.7) years and mean height of 155.2±7.2 cm, had at least one CMR/CT with adequate imaging and were included in the current study. During follow-up, 171 patients with TS had at least one other CMR/CT (figure 1). For the other patients, additional CMR/CT imaging was not available due to various reasons (eg, care transfer, refusal by patient, lost to follow-up, short period since first scan). No differences were found in baseline characteristics between the patients with versus without more than one scan.

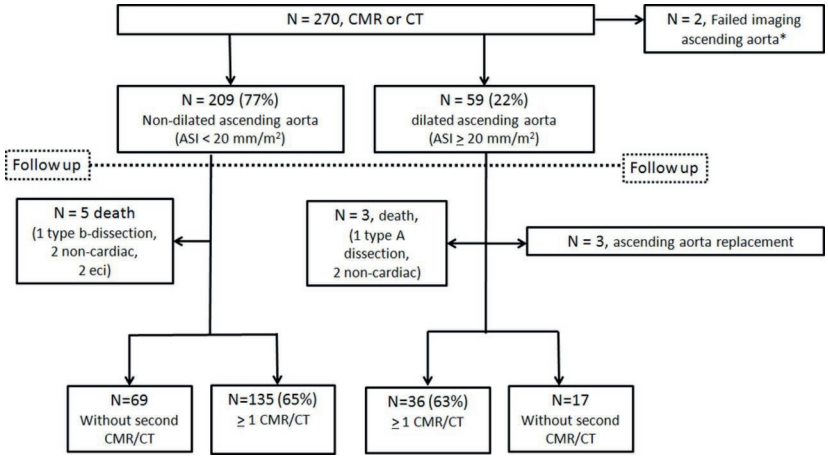


Figure 1. Flow diagram of patient inclusion. *Due to artefacts, the CMRs were not suitable for measuring the diameter of the ascending aorta. ASI, aortic size index; CMR, cardiac MRI.

Table 1. Characteristic of patients with TS with or without aortic dilatation at baseline

	Total (N=268)	Aortic size index <20 mm/m² (n=209)	Aortic size index >20 mm/m² (n=59)	P values
Mean age in years (IQR)	28.7 (21.3–39.7)	25.9 (20.5–34.8)	40.0 (29.0–47.3)	<0.001
Height in cm (SD)	155.1 (±7.2)	156.5 (±6.7)	150.4 (±6.9)	<0.001
Weight in kg (IQR)	59.0 (51.3–67.8)	60.0 (53.0–70.0)	53.0 (48–59)	<0.001
BSA in m² (IQR)	1.57 (1.47–1.70)	1.60 (1.51–1.71)	1.47 (1.37–1)	<0.001
BMI in kg/m² (IQR)	24.7 (22.0–27.7)	25.1 (22.2–28.0)	23.5 (21.5–26.0)	0.048
45X0 Mosaicism	40.0% 60.0%	36.7% 63.3%	51.9% 48.1%	0.052
Bicuspid aortic valve	22.0%	15.5%	45.8%	<0.001
Aortic coarctation	3.4%	2.9%	5.1%	NS
Growth hormone*	61.0%	66.8%	40.7%	0.001
Active smoking	9.5%	9.3%	10.2%	NS
Hypertension	16.9%	12.1%	33.9%	<0.001
Dyslipidaemia	4.5%	3.4%	8.5%	NS
Diabetes	3.8%	2.4%	8.5%	0.032

45X0 and mosaicism refers to the karyotype; aortic size index (mm/m²) is the ascending aortic diameter divided by BSA. *Patients treated during childhood with growth hormone. BMI, body mass index; BSA, body surface area; NS, non-significant; TS, Turner syndrome.

Baseline

Characteristics of all 268 included patients at baseline are shown in table 1. Dilatation of the ascending aorta (ASI>20 mm/m²) was present in 59 (22%) patients. Mean z-score was 0.91±1.50 and 22.8% had an z-score ≥2. The mean age of the patients with TS and a dilatated ascending aorta was significantly higher compared with patients with TS without dilatation 40.9 (IQR: 29.0–47.3) versus 25.9 (IQR: 20.5–34.8) years, p<0.001. The prevalence of hypertension was significantly higher in the women with dilatation (33.9% vs 12.1%; p<0.001). Figure 2 shows the uncorrected and corrected ascending aortic diameters at baseline for all patients according to age. At the age of 35 years, the upper 95% line crosses the ASI=25 mm/m² line. In total, 13 patients had an ASI>25 mm/m², mean age of 44.3±7.7 years versus 30.4±10.8 years in ASI<25 mm/m². Baseline uncorrected ascending aortic diameter was independently associated with age, hypertension, BAV, 45X0 karyotype, weight and growth hormone treatment (table 2). Although the p-value for aortic coarctation in univariate analysis was <0.10, we excluded it from the model. The reason for this were: the SE was larger than the coefficient, the number of women with aortic coarctation was low and multivariate analysis using backward selection with p<0.1 excluded coarctation out of the model. The significant adjusted odds ratios for ASI>20 mm/m² are presented in figure 3.

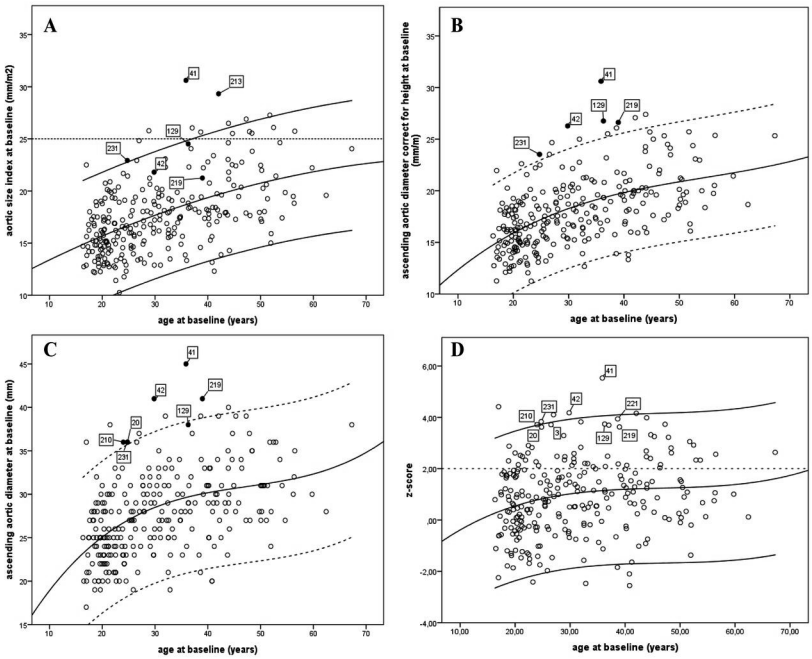


Figure 2. Ascending aortic diameter at baseline corrected and uncorrected versus age. (A) Aortic size index versus age; (B) ascending aorta diameter corrected for height versus age; (C) absolute ascending aortic diameter versus age; (D) z-score at baseline versus age. Cases 41, 42 and 231 underwent aortic preventive surgery. Case 231 had aortic valve dysfunction as primary indication. Case 129 is a patient who had presumably a type A dissection. Case 219 had a body mass index of 40.5 kg/m^2 and an ascending aorta of 41 mm. Case 213 is a patient who has an ascending aortic diameter of 39 mm and a body surface area of 1.33 kg/m^2. The centre line represents the mean of y-axis variable and the upper and lower line represent the 95% limit of the mean of y-axis variable.

A history of growth hormone treatment during childhood was reported in 161 (60%) patients. Compared with patients who were treated with growth hormone, the non-treated group was significantly older (mean age 39.3±10.7 vs 25.0±6.8 years; p<0.001). As a consequence of the relative recent introduction of synthetic growth hormone treatment, younger age patients were more likely to have been treated with growth hormone. The mean aortic diameter and ASI unadjusted for age were smaller for patients who were treated compared with the non-treated group (27.2±4.8 vs 29.1±5.2 mm; p=0.004 and 16.9±3.1 vs 18.9±4.1 mm/m^2; p<0.001). However, after correcting for variables shown in table 2, previous growth hormone treatment was still associated with a larger ascending aortic diameter.

Table 2. Univariate and multivariate linear regression analysis for the association of absolute ascending aortic diameter at baseline

	Univariate		Multivariate*		95% CI for coefficient
	Coefficient	P values	Coefficient	P values	
Age (years)	0.209	<0.001	0.230	<0.0001	0.17 to 0.29
Hypertension	4.024	<0.001	2.677	<0.0001	1.24 to 4.12
Bicuspid aortic valve	3.254	<0.001	3.307	<0.0001	2.07 to 4.55
Karyotype 45X0	1.823	0.005	1.702	0.002	0.64 to 2.77
Weight (kg)	0.056	0.014	0.075	<0.0001	0.04 to 0.11
Growth hormone treatment†	−1.879	0.003	1.404	0.044	0.04 to 2.77
Diabetes‡	3.96	0.015			
Aortic coarctation	3.1	0.076			
Height (cm) §	−0.07	0.115			
Active smoking	0.36	0.74			
Dyslipidaemia	1.77	0.24			
Body surface area	2.76	0.119			

*R^2=39.1%, indicating that only 39% of the aortic diameter differences could be explained by this model; coefficient = regression coefficient also called estimate; analysis of the residuals showed a normal distribution.
†Multicollinearity between age and history of growth hormone therapy (correlation −0.637).
‡In the best fit model, diabetes was excluded as it was not significant in multivariate analysis.
§Small differences in height in this cohort, mean 155.1 (±7.2) cm.

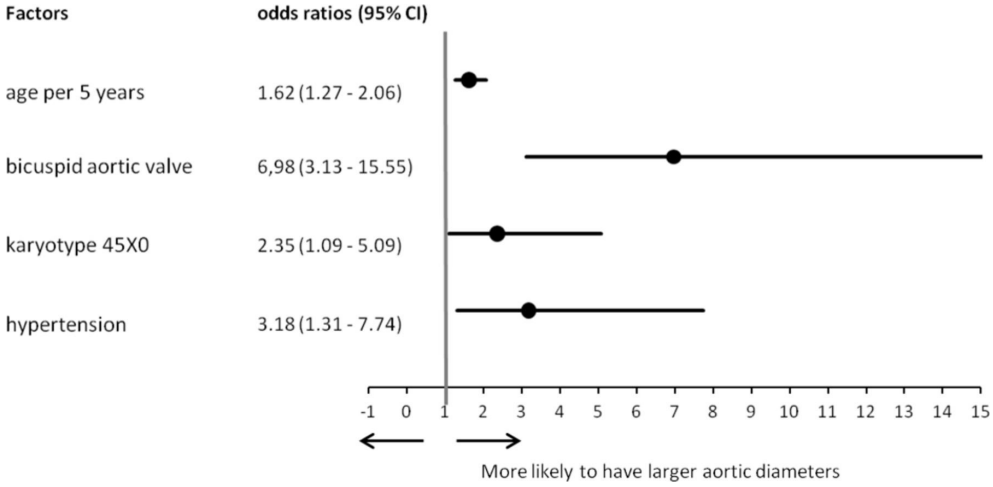


Figure 3. Forest plot of adjusted odds ratios for aortic dilatation at baseline in women with Turner syndrome. R2=38.1%. Aortic dilatation was defined as an aortic diameter >20 mm/m2 body surface area.

Follow-up

Survival status was available for all patients. In total, eight patients died during a mean follow-up of 6.8±3.2 years. These eight cases are described in table 3. In two patients, the cause of death was assumed to be related to aortic dissection (case 129; case 4). Case 129 was a 44-year-old patient with TS with an ascending aortic diameter of 65 mm (ASI=39.2 mm/m^2), who delayed her operation to get married and died suddenly. No autopsy was performed. Case 4 was also 44 years old and died from acute dissection of the descending aorta. This patient had normal ascending (30 mm; ASI=18.4 mm/m^2) and descending (25 mm) aortic diameters on CMR 3.5 years prior to this event. Preventive ascending aortic surgery was performed in three patients. In two patients, the indication for surgery was ascending aortic dilatation (45 mm; 48 mm or ASI=28 mm/m^2; ASI=25.5 mm/m^2, respectively) and in one patient the indication was severe aortic valve regurgitation with concomitant moderate ascending aortic dilatation (36 mm; ASI=22.9 mm/m^2). The primary endpoint was therefore reached in five patients. Because of the limited number of events, no analysis on predictors could be performed.

Aortic growth

In total, 171 (64%) patients had more than one CMR/CT during follow-up (figure 1). There was a significant increase in ascending aortic diameter per patient (1.2±2.3 mm; p<0.001) in a mean follow-up time of 5.9 (range: 1.1–11.3) years and a total of 1015 patient-years. Ascending aortic diameter increase per year was 0.20 (IQR: 0.00–0.44) mm/year. The median ascending aortic diameter change in the whole cohort was 0.43 (IQR: 0.00–0.43) mm/year. The mean time between the first and last CMR/CT was not significant different between the women with TS who had a dilated and non-dilated ascending aorta (6.2±2.4 vs 5.9±2.1; p=0.51). The median ascending aortic diameter change in the dilated group was 0.00 (IQR: −0.20 to 0.31) mm/year and 0.24 (IQR: 0.00–0.44) mm/year in the non-dilated group (p=0.021). No significant difference was found in ascending aortic diameter change between patients with (n=38) or without BAV (n=133) 0.16 (IQR: −0.02 to 0.37) mm/year versus 0.22 (IQR: 0.00–0.44) mm/year, p=0.75). There was a difference in patients with (n=29) or without (n=142) hypertension 0.00 (IQR:−0.22 to 0.30) mm/year versus 0.23 (IQR: 0.00–0.44) mm/year, p=0.04). Eight women showed an increase in ascending aorta diameter of ≥1 mm/year. Of the nine women who had an ASI>25 mm/m^2 at baseline, one underwent preventive aortic surgery and one experienced an aortic complication during follow-up.

Table 3. Causes of death in women with TS

Case no	Probable cause	Age of death (years)	Corrected aortic diameter (mm/m²)	Bicuspid aortic valve	Growth hormone treatment	Karyotype	Aortic coarctation	Hypertension
129	Type A aortic dissection*	44	39.2	Yes	No	45X0	Yes	Yes
2	Cancer	53	27.9	No	No	Unknown	No	Yes
3	Cachexia and dementia	58	27.0	no	No	Non-45X0	No	Yes
4	Type B aortic dissection	44	18.4	No	No	45X0	No	No
5	Intestinal ischaemia	67	19.4	No	No	Non-45X0	No	Yes
6	Cancer	50	19.7	No	No	Non-45X0	No	No
7	Unknown†	33	19.5	No	Yes	Non-45X0	No	No
8	Unknown	38	20.1	No	Yes	45X0	No	No

*Case 129 is also shown in figure 2A. This woman with TS was on waiting-list for preventive aortic surgery.
†History myocardial infarction on the age of 30 years; the corrected aortic diameter also called aortic size index (mm/m2) is the ascending aortic diameter divided by body surface area.
CMR, cardiac MRI or CT; TS, Turner syndrome.

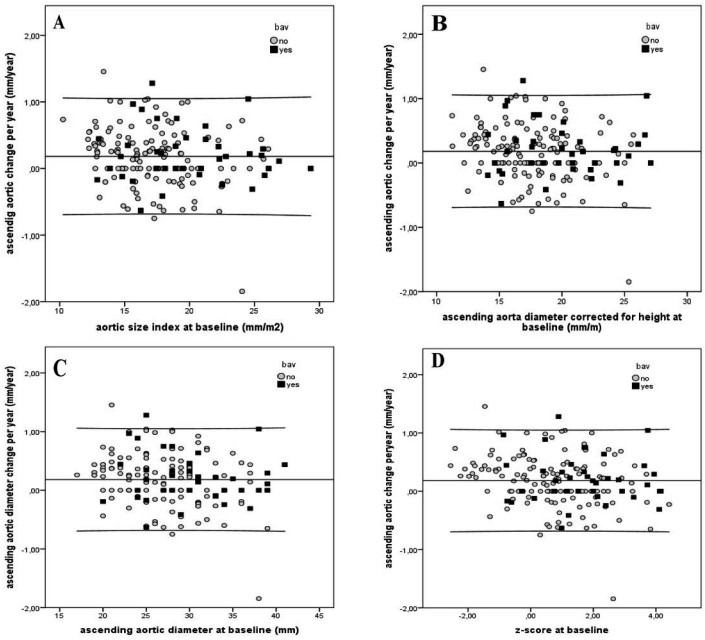


Figure 4. Corrected and uncorrected ascending aortic diameter change versus baseline corrected and uncorrected ascending aortic diameter. (A) Ascending aortic change versus aortic size index at baseline; (B) ascending aortic change versus ascending aorta diameter corrected for height at baseline; (C) ascending aortic change versus absolute aortic diameter at baseline; (D) ascending aortic change versus z-score at baseline. Case 129 (diameter change of 3.25 mm/m2) is not presented in these figures.

During the study period, four women became pregnant, and median change in aortic diameter was 0.05 (IQR: −0.17 to 0.97) mm/year versus 0.20 (IQR: 0.0– 0.43) mm/year for the other women (p=0.84). Figure 4 shows the change in ascending aortic diameter for all 171 patients, related to baseline ascending aortic diameter (both uncorrected and corrected for BSA). The three operated cases had a growth varying between 0.33 and 1.22 mm/year and the woman with presumed type A dissection had an ascending aortic growth of 3.25 mm/year (not presented in figure 4). Univariate linear regression identified two associations with aortic growth, hypertension, and aortic dilatation at baseline, which were not significant in multivariate analysis. Based on the upper quartile of ascending aortic change (0.43 mm/year), the TS cohort was divided in two groups. Logistic regression did not identify significant associations for aortic growth ≥0.43 mm/year. Figure 5 shows the unadjusted HRs in a forest plot of all tested variables.

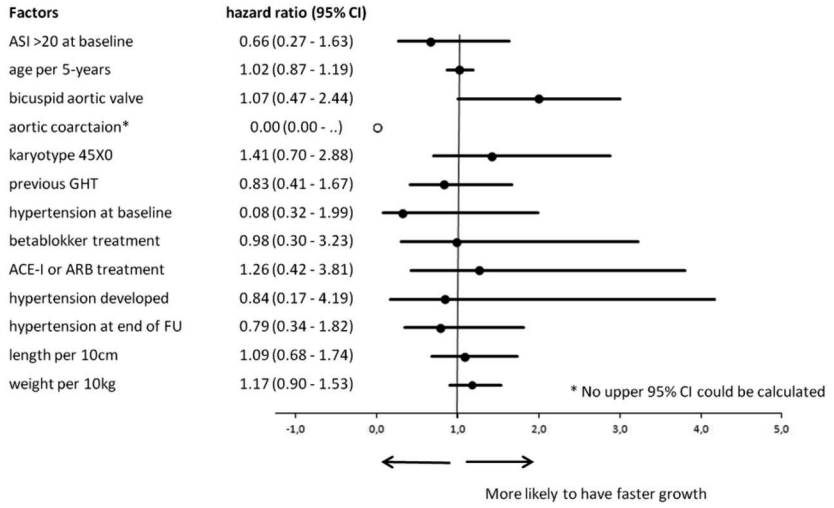


Figure 5. Forest plot of unadjusted HRs for aortic growth. Aortic growth was defined as aortic diameter increase >0.42 mm/year. ACE-I, ACE inhibitors; ARB, angiotensin II receptor blockers; ASI, aortic size index; FU, follow-up; previous GHT, previous growth hormone treatment during childhood.

Discussion

This study describes one of the largest TS cohorts to date, in which aortic dimensions are measured using advanced imaging during a relative long follow-up time. Aortic dilatation was present in one-fifth of women with TS at a mean age of 29 years. Classical factors associated with larger aortic diameters were age, hypertension, BAV, 45X0 karyotype, weight, and growth hormone treatment. During almost 7 years of follow-up, only 2% of the women suffered an aortic event and no unexpected ascending aortic complications occurred. The aortic growth rate was low (0.20 mm/year), but higher than reported in the normal population (0.12 mm/year)[13, 14]. Classical factors associated with larger aortic diameters, such as a BAV, were not associated with faster growth of the ascending aortic diameter. Also, an initial larger aortic diameter was not associated with faster growth.

Ascending aortic dilatation

As shown by others, current study shows that also in women with TS age has a clear impact on aortic diameter[15]. This association with age is also observed in the general population[13, 16]. This relation is not linear but rather more curved and levelling-off at older age. In the current TS guidelines, no correction is made for age, which seems indicated. At a median age of 29 years, 22% of the women with TS have a dilated aorta (ASI>20 mm/m^2). Maybe this high prevalence is partly caused by the ASI method. One of the pitfalls of the

ASI method is that the ASI becomes lower in obese patients (case 219) and relative larger in slim patients (case 213). Due to this 'overcorrection' of the aortic diameter, some women with TS will be labelled as having a normal aortic diameter. Correcting the aortic diameter using height instead of BSA could partly solve this problem. This is especially important when realising that ASI is the main indicator for preventive surgery. Recent publications have shown that z-scores used for people with a normal height are also fit for women with TS[13, 15]. The z-score was ≥2 in 22.8% of the women in this cohort. This is comparable with the ASI method. Indeed, both the z-score method and the ASI method correct for weight and height. It seems more appropriate to use ASI or z-score in women with TS with a normal BMI and be cautious in women with a very low or very high BMI.

The cross-sectional analysis confirmed the known factors associated with aortic dilatation[4]. In addition to these known associations, our data suggest that growth hormone treatment during childhood is associated with larger aortic diameter even after correcting for age and height. Due to multicollinearity with age and the chance of having being treated with growth hormone, this effect should be interpreted with caution. Dedicated research is warranted to investigate the long-term effect of growth hormone treatment on aortic diameters, aortic wall composition and vulnerability. Olivieri et al. found that a partial cusp fusion was associated with larger aortic diameters[17]. In the current study, we did not use this partial cusp fusion.

Aortic growth

Even though older patients with TS generally have a larger ascending aorta, we do not know if these larger dimensions also lead to higher risks of aortic complications. It seems logical that dilatation occurring at younger age is associated with more aggressive aortic pathology. In the literature, the mean age at which patients with TS present with aortic dissection is 32 years[4, 18-20]. The age of both patients with dissection in our series was 44 years, so also still relatively young. Others showed that especially younger adult women with TS who had a dilatated aorta are vulnerable and that after a certain age the risk of aortic dissection decreases[7].

Limited publication on aortic growth in women with TS are available. A prospective study would be the best study design. Our study is retrospective, but because of the standardised follow-up, the use of CMR/CT scans and the inclusion of all patients referred to our hospital without selection bias, we believe this to be the second-best option to study aortic growth. The observed increase in aortic diameters in the current study is low, but higher than reported in the general population[13]. Univariate analysis suggested that hypertension and baseline aortic dilatation were associated with aortic growth, but in multivariate analysis they were no longer significant. Possibly that treatment of hypertension protected these women against accelerated aortic growth. The low increase in aortic diameter and the relative short follow-up time could be an explanation for not finding any independent associations for aortic diameter change.

Mortensen et al. developed an aortic diameter prediction model using complex mathematical processing based on the follow-up of 78 women with TS over a period of almost 5 years. These cohesive models identified predictors of accelerated aortic growth (aortic coarctation, BAV, age, diastolic blood pressure, BSA and antihypertensive treatment)[7]. In our study, we could not confirm these findings. Heterogeneity of karyotypes present in patients with TS has been shown. In most cases, blood lymphocytes are used for the diagnosis and sometimes additional buccal cells are used. Different cell lines can show different karyotypes, making it possible that the karyotype of the aortic wall differ from the cell line used for diagnosis[21]. The aortic wall properties may therefore be not well presented by the used karyotypes.

Outcome

In 7 years of follow-up, the incidence of aortic complications was 2%. This low incidence of 0.3 %/year immediately illustrates the difficulty of identifying risk factors of aortic complications in women with TS. On the other hand, it is important information that the absolute risk is very low, although still higher than in women with non-TS[1]. Our data certainly do not support a more aggressive approach towards surgery. The indication for surgery is still matter of debate. Pape et al. showed, in a large cohort of patients, that in 50% of the patients with a dissection, the aortic diameter was below the advised surgical aortic diameter threshold[22]. This clearly shows that, aortic diameter as sole parameter on which preventive aortic surgery is advised in current guidelines is not sufficient enough to prevent future aortic dissections[8, 9, 23, 24]. Future research should focus on other parameters to better predict future aortic dissection risk.

Limitations

Although we have included all patients, selection bias due to referral cannot be excluded. However, if selection bias has taken place, the more severe cases would have been sent to our tertiary clinic and therefore the relatively positive and reassuring results would only have been more positive. Indeed, information on survival and events was 100% complete. The used z-score is based on echocardiographic measurements and could differ from a z-score based on CMR/CT measurements.

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Supplement material

Mosaicism group division

1) mosaicism 45,X/46,XX
2) isochromosome (45,X/46,X,i(Xq), 46,X,i(Xq) or 45,X/46,X,i(Xq)/47,X,i(Xq))
3) deletion (45,X/46,X,del(X) or 46,X,del(X))
4) polyploidy (45,X/46,XX/47,XXX or 45,X/46,XXX)
5) ring X material (45,X/46,X,r(X))
6) Y-material (45,X/46,XY, 45,X/46,XX/46,XY or 45,X/48,XXYY)

CHAPTER 11

11

Is the elasticity and structure of the thoracic aortic wall different in patients with Turner syndrome?

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Submitted

Abstract

Background

Turner syndrome (TS) is associated with aortic dilatation and dissection, but the underlying process is unclear. The aim of this study was to investigate the elastic properties and composition of the aortic wall in women with TS.

Methods

In this cross-sectional study, 52 women with TS aged 35±13 years (50% monosomy, 12 with bicuspid aortic valve (BAV) and 4 with coarctation) were investigated using carotid-femoral pulse wave velocity (CF-PWV) by echocardiography and ascending aortic distensibility (AAD) and aortic arch pulse wave velocity (AA-PWV) by magnetic resonance imaging. As control group, 13 women with BAV without TS and 48 healthy subjects were included. In addition, aortic tissue samples were investigated with routine and immunohistochemical stains in 5 additional women with TS who were operated for dilatation of the ascending aorta.

Results

Women with TS showed a higher AA-PWV (ß 1.08, CI 0.54;1.62) after correcting for age and comorbidities compared to controls. We found no significant difference in AAD and CF-PWV. In women with TS, the presence of BAV, CoA or monosomy (45,X) was not associated with aortic stiffness. Histopathological data showed more compact smooth muscle cell layers with abnormal deposition and structure of elastin and diminished or absent expression of contractile proteins desmin, actin and caldesmon, as well as the progesterone receptor.

Conclusion

Both aortic arch stiffness measurements on MRI and histomorphological changes point towards an inherent abnormal thoracic aortic wall in women with TS.

Introduction

Turner syndrome (TS) is a genetic condition caused by partial or complete absence of an X chromosome and occurs in 50 per 100.000 females at birth[1]. The main complication is aortic dissection, most often preceded by aortic dilatation[2], which carries a substantial mortality risk[3]. To prevent acute aortic dissection, preventive surgery is advised when the aortic diameter exceeds a diagnosis-specific cut-off value. Since patients with TS are known for their short stature, correction for body size area using the aortic size index is advised[4]. However, even patients with a normal aortic size index may develop aortic dissection[5]. Consequently, aortic dilatation alone is not sufficient for identifying patients with TS at high risk of aortic dissection. Other clinical parameters identifying high-risk patients are not very clear.[6] It has been proposed that other, more subtle changes such as increased stiffness of the aortic wall are present in patients with TS prior to dissection. Studies in patients with hypertension, diabetes or ischemic heart disease have shown aortic stiffness to be an independent predictor of all-cause mortality and cardiovascular events[7]. Although previous literature showed an increased aortic stiffness in patients with TS[8-10], it remains unclear to what extent this is explained by the commonly found bicuspid aortic valve (BAV) and coarctation of the aorta (CoA). Both BAV and CoA are also associated with aortic stiffness[11, 12] and it is known that dissection may occur in the absence of BAV and CoA[13]. Differences in aortic stiffness between monosomy (45, X) and mosaicism have also not yet been investigated. In addition, histomorphological examination of aortic tissue from patients might also be of help to identify possible pathological changes in the aortic wall and to interpret aortic stiffness imaging parameters. The aim of this current study was to investigate whether the aortic wall of patients with TS is different than that of healthy control subjects and if this can be explained solely by the bicuspid valve and/or aortic coarctation.

Methods

In this cross-sectional cohort study, we included all adult patients with TS who participated between October 2014 and March 2016 in a study previously described[14]. Inclusion criteria for patients with Turner syndrome were a 45, X or 45, X/46, XX mosaic karyotype. The patients were prospectively included and subjected to physical examination (including height, weight, systolic and diastolic blood pressure), electrocardiography, two- and three-dimensional echocardiography, computed tomography angiography (CTA) and magnetic resonance imaging (MRI) all on the same day. Measurements of the aortic diameter were performed double-oblique on CTA during systole, except for two patients. In those two patients contrast-enhanced magnetic resonance angiography (CEMRA) images were used, as CTA was not performed. Scan parameters of the CT imaging can be found elsewhere[14]. Two reference groups were selected: patients with BAV without Turner syndrome and healthy control women. We selected patients with BAV from the same prospective cohort

study from which the patients with TS were included. The inclusion criteria for BAV were age ≥18 year and one of the following features: (1) aortic stenosis (gradient >2.5 m/sec), (2) aortic regurgitation (at least moderate) or (3) ascending aortic diameter ≥40 mm and/or aortic size index >2.1. For carotid-femoral pulse wave velocity measurements, we included a statistically age-matched control group. They did not undergo CTA or MRI and therefore aortic diameters were measured during mid-systole with echocardiography in this group of healthy subjects using the leading edge-to-leading edge technique. The healthy control group for aortic distensibility and aortic arch pulse wave velocity (PWV) measurements were recruited from a previous MRI study on aortic stiffness of subjects with the same age[15]. The study was approved by the medical ethical committee (MEC14-225). Written informed consent was provided by all patients and controls.

A standard two-dimensional transthoracic echocardiogram was performed by an experienced sonographer. All studies were acquired using harmonic imaging on an iE33 or EPIQ7 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with an x5 – 1 matrix-array transducer (composed of 3040 elements operating at 1-5 MHz). The aorta was measured in the standard parasternal long axis view and on a more cranial view one intercostal space higher which often improve the visualization of the ascending aorta.

Pulse wave (PW) Doppler signals were obtained consecutively at the common carotid artery and the femoral artery (supplemental figure 1, panel A). PWV (expressed in m/s) was defined as: distance (in meters) between carotid artery and femoral artery/delta time (in seconds). The distance was measured outside the patient's body with a measuring tape. For both signals, the time interval was measured between the onset of the QRS complex and the onset of the systolic PW Doppler signal. Delta time was calculated as the difference between both time intervals. Validated software was used to analyze the pulse wave velocity (Curad Viewer version 3.5.3.0, Wijk bij Duurstede, The Netherlands).

Image acquisition was performed using a 1.5 T scanner (Discovery MR450,GE Medical Systems, Milwaukee, WI, USA) using a 32-channel phased-array cardiac surface coil. A retrospectively ECG-gated 2D balanced Steady-State Free Precession sequence during breath hold was obtained perpendicular to the ascending aorta at the level of the pulmonary trunk to measure aortic distensibility. Typical scan parameters were as follows: FOV 420 mm (phase FOV 60%), matrix size 256x192, slice thickness 6.5 mm, flip angle 45°, TR/TE 3.3/1.5 ms, and number of reconstructed phases 24 per cardiac cycle. The contour of the ascending aorta was manually traced in all phases (QMass analytical software version 8.1, Medis, Leiden, The Netherlands). The minimum and maximum ascending aortic cross-sectional areas were identified, and aortic distensibility (10-3 mmHg-1) was calculated using the following calculation: (maximum area-minimum area)/(minimum area x ΔP) x 1000, where delta P is the brachial pulse pressure in mmHg (supplemental figure 1, panel B).

A free-breathing, retrospectively ECG-gated 2D phase-contrast flow sequence was performed to measure aortic PWV. The slice plane was positioned at the level of the pulmonary artery perpendicular to the ascending and descending aorta. Typical scan

parameters were as follows: FOV 350 mm (phase FOV 90%), matrix size 192x160, slice thickness 7.0 mm, flip angle 20°, number of averages 3, TR/TE 4.3/2.3 ms, views per segment 1, velocity encoding value 200 cm/s, true temporal resolution ~11 msec, and number of reconstructed phases 100 per cardiac cycle. Aortic arch PWV was defined as: distance between ascending and descending aorta/Δ time (expressed in m/s). Delta time was measured with the same method explained by Devos et al.[9] (supplemental figure 1, panel C). The onset of the systolic wave front was determined from the resulting flow graph by the intersection point of the constant horizontal diastolic flow and the upslope of the systolic wave front, the latter of which was modeled by linear regression along the upslope from the flow values between 20% and 80% of the total range. To determine the length of the aortic segment between the two aortic levels, sagittal angulated T1-weighted black blood turbo spin echo images of the aortic arch were acquired during breath-hold. Typical scan parameters were FOV 400 mm (phase FOV 100%), matrix 256x256, slice thickness 5.0 mm, flip angle 155°. When the aortic arch was not properly visible on the black blood images a multiplanar reconstruction was made with contrast-enhanced magnetic resonance angiography (CEMRA) images to measure the distance (n=35, 47%). The CEMRA scan parameters are described elsewhere[14]. Qmass software was used for distensibility measurements and Qflow software was used for PWV measurements (Medis, Leiden, The Netherlands).

We studied the histomorphology of formalin-fixed paraffin-embedded (FFPE) specimens of the ascending aorta of 5 Turner syndrome patients who underwent preventive replacement of the ascending aorta because of dilatation. In one patient, we additionally performed electron microscopy examination to ultra-structurally investigate medial elastin fiber morphology and deposition of elastin. To clearly show the differences between aortic tissue of patients with TS and healthy tissue, aortic tissue from a healthy woman aged 45 years was obtained from the Heart Valve Bank in Rotterdam and investigated.

Routine staining with hematoxylin-eosin (HE), elastica van Gieson (EvG) and Alcian blue (AB) stains was performed on 3µm sections. The criteria as outlined in the recent consensus statement on surgical pathology of the aorta[16] were used for scoring and classification of abnormalities. In addition, immunohistochemical stains were carried out on a Ventana Benchmark Ultra automated staining platform (Roche Diagnostics, Tucson, AZ) to assess the vessel wall expression of smooth muscle actin (SMA), caldesmon, desmin, actin HHF-35, estrogen receptor (ER) and progesterone receptor (PR) as well as the proliferation marker MIB-1. Immunohistochemical methods including the antibody clones used are provided in the supplemental material (Appendix A). For electron microscopy, representative samples of the media were isolated from paraffin blocks, and incubated with a mixture of 1% glutaraldehyde and 4% formaldehyde. The sections were osmicated with 1% osmium in distilled water, dehydrated in 50% to 100% Acetone and embedded in a mixture of Embed-812, NMA, DDSA and DMP-30 (EMS diasum, Hatfield, Pennsylvania). Ultrathin sections (60-70 nm) were cut using an Ultramicrotome UC7 (Leica, Germany),

mounted on copper grids, and counterstained with uranyl acetate 0,5% for 30 minutes at 45°C and Ultrostain II (Leica, Germany) for 7 minutes at room temperature in the Leica AC20. Elastin lamellae were visualized at magnifications of x2800 and x7100 and analyzed under the electron microscope (Philips, Eindhoven, the Netherlands).

All characteristics are presented as mean ± SD when normally distributed, and in case of non-normal distribution, medians (interquartile ranges) are provided. Categorical variables are presented as frequencies with percentages. Comparison of normally distributed continuous variables between two groups was done using the Student's t-test or, in case of a skewed distribution, the Mann-Whitney test. Univariable linear regression analysis was performed with patient characteristics as independent variables and the measurement of aortic stiffness as dependent variable. In addition, multivariable analysis was performed using the Enter method to adjust for age, aortic size index, BAV, CoA and hypertension. To assess interobserver variability the intraclass correlation coefficient (ICC) was calculated for all measurements using 25 randomly selected subjects. The IBM SPSS® statistics 21.0 software was used to analyze the data. The statistical tests were two sided and a p-value below 0.05 was considered significant.

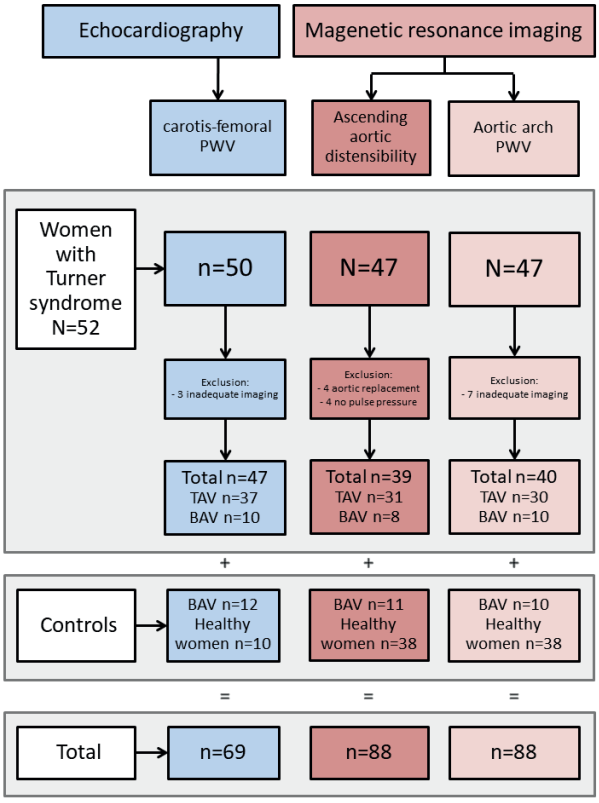


Figure 1. Flowchart of the patients with aortic stiffness measurements. All three measurements could be performed in 32 patients with Turner syndrome (25 TAV and 7 BAV) and in 8 control patients with BAV only.

Results

In total 52 women with Turner syndrome aged 35±14 years were included: 40 with a tricuspid aortic valve (TAV) and 12 patients with BAV. Twenty-five Turner women had X chromosome monosomy (45,X) and the other 25 Turner women had X chromosome mosaicism (n=2 missing). Renal function was normal in all. In 13 women (25%) the time between the first and last investigation was ≥1 day (median 7 days; IQR 5-42 days) due to technical or practical issues. We included 13 women with BAV without Turner syndrome and 10 healthy women for the control groups of carotid-femoral pulse wave velocity. The control group for aortic distensibility and aortic arch pulse wave velocity (PWV) measurements consisted of the same 13 women with BAV and an additional 38 healthy female subjects. In figure 1 a flowchart is presented with the number of measurements that could be performed in the participants. Table 1 shows the baseline patient characteristics of the Turner women and control groups separately. Surgical correction for CoA with end-to-end anastomosis was performed in 3 patients with TS. Five patients with TS were treated for hypertension with beta-blockers, angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors.

Figure 2 shows the comparison between patients with TS and controls for the carotid-femoral PWV, ascending aortic distensibility and aortic arch pulse wave velocity. We found no significant difference in carotid-femoral PWV between the groups. Within the women with Turner syndrome, patients with BAV (median 7.0, IQR 6.1-7.7 m/s) did not show a significantly different carotid-femoral PWV compared to the patients without BAV (median 6.7, IQR 5.8-8.5 m/s). In all four Turner women with CoA, the carotid-femoral PWV could be measured (5.3, 6.9, 7.6 and 7.8 m/s) and was not statistical different from Turner women without CoA (median 6.7, IQR 5.9-8.4 m/s). Also no statistical difference was found between patients with monosomy (median 6.5, IQR 5.7-7.7 m/s) or mosaicism (median 6.9, IQR 6.4-8.6 m/s). For carotid-femoral PWV measurements we found an ICC of 0.893 (0.772-0.951).

Table 1. Baseline characteristics.

	Turner syndrome		(n=52)	Bicuspid aortic valve without Turner syndrome (n=13)	Healthy controls echocardiography (n=10)	Healthy controls MRI (n=38)
	Total (n=52)	TAV (n=40)	BAV (n=12)			
Age (y)	35 ± 14	36 ± 14	35 ± 13	34 ± 11	35 ± 15	34 ± 14
Height (cm)	156 ± 9	157 ± 9	154 ± 7	169 ± 11	187 ± 6	166 ± 8
Weight (kg)	66 ± 16	68 ± 17	61 ± 11	69 ± 11	83 ± 10	61 ± 11
Systolic blood pressure (mmHg)	124 ± 17	124 ± 18	126 ± 16	116 ± 12	131 ± 10	118 ± 14
Diastolic blood pressure (mmHg)	80 ± 13	80 ± 12	83 ± 14	77 ± 7	79 ± 7	70 ± 9
Hypertension	8 (15%)	7 (18%)	1 (8%)	3 (23%)	0 (0%)	0 (0%)
Surgical correction for aortic coarctation*	3 (6%)	0 (0%)	3 (25%)	2 (15%)	0 (0%)	0 (0%)
Aortic dilatation (>40 mm and/or ASI>2.1 cm/cm^2)	11 (21%)	6 (15%)	5 (42%)	9 (69%)	0 (0%)	1 (3%)†
Aortic stenosis (echo V_{max} >2.5 m/s)	1 (2%)	0 (0%)	1 (8%)	11 (85%)	0 (0%)	0 (0%)
Aortic regurgitation (moderate or severe)	1 (2%)	0 (0%)	1 (8%)	5 (39%)	0 (0%)	0 (0%)
Absolute ascending aortic diameter (mm)	31 ± 5	30 ± 4	33 ± 6	40 ± 7	31 ± 3	27 ± 3
Aortic size index ascending aorta (mm/m^2)	19 ± 4	18 ± 3	21 ± 3	22 ± 3	15 ± 2	16 ± 2

Data are expressed as mean ± SD or number (percentage). ASI=aortic size index (aortic diameter divided by BSA), Vmax=maximum velocity. Missing values were present for height (n=1) and weight (n=1), blood pressure (n=6) and aortic size index (n=1). *One additional Turner patient has a coarctation of the aorta, but did not undergo surgical correction. † One healthy woman with an aortic diameter of 29 mm, height of 151 cm and weight of 40 kg, which resulted in an ASI of 2.2 cm/m^2.

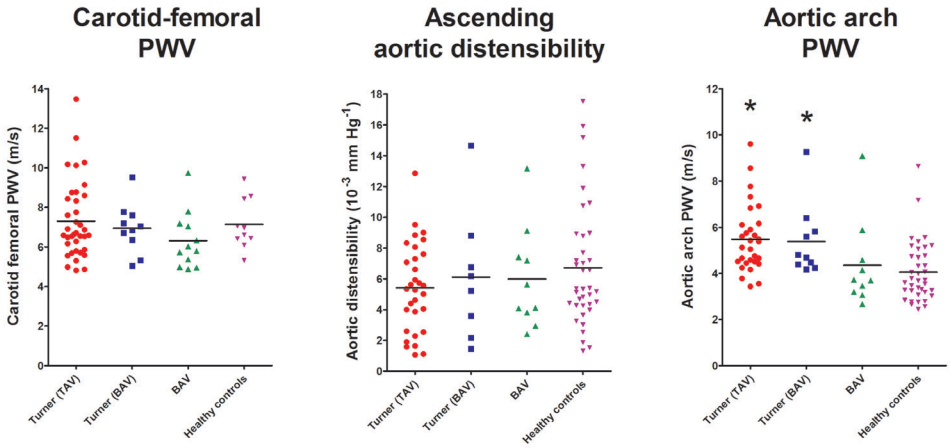


Figure 2. Uncorrected results of carotid-femoral pulse wave velocity, ascending aortic distensibility and aortic arch pulse wave velocity divided in four groups. The median level in each subgroup is indicated with the black line.
* Significant different from the healthy group according to the Wilcoxon one-sample test

We found no significant difference in ascending aortic distensibility between the groups. Within the women with Turner syndrome, patients with BAV (median 5.7, IQR 2.5-8.3 $mmHg^{-1}$) did not show a significantly different ascending aortic distensibility compared to the patients without BAV (median 5.3 IQR 2.6-7.6 $mmHg^{-1}$). Only in two Turner women with CoA de ascending aortic distensibility could be measured (1.5 and 6.2 x 10^{-3} $mmHg^{-1}$), which was lower and higher than Turner women without CoA (median 5.3, IQR 3.1-7.8). No statistical difference was found between patients with monosomy (median 5.2, IQR 3.9-7.1 $mmHg^{-1}$) or mosaicism (median 5.6, IQR 2.3-8.3 $mmHg^{-1}$). For ascending aortic distensibility measurements we found an ICC of 0.999 (0.996-0.999) for the minimum area and 0.999 (0.998-1.000) for the maximum area.

Patients with TS showed significantly higher aortic arch PWV compared to healthy controls (figure 2). In the multivariable analysis (table 2), the presence of Turner syndrome remained significantly associated with higher aortic arch PWV (ß 1.08, 95% CI 0.54-1.62, $p<0.001$). Within the patients with TS, patients with BAV (median 4.8, IQR 4.4-6.0 m/s) did not show a significantly different aortic arch PWV compared to the patients without BAV (median 5.3, IQR 4.5-6.1 m/s). In three Turner women with CoA, the aortic arch PWV could be measured (4.4, 5.8 and 6.4 m/s), which was comparable to the median of Turner women without CoA (median 4.9, IQR 4.5-5.9 m/s). No statistical difference was found between patients with monosomy (median 4.7, IQR 4.4-5.8 m/s) or mosaicism (median 5.5, IQR 4.5-6.2 m/s). For aortic arch PWV measurements we found an ICC of 0.970 (0.935-0.987) for the distance measurements and 0.704 (0.437-0.857) for the time measurements.

Table 2. Univariable and multivariable analysis of aortic stiffness measurements in the total group including patients with TS, BAV patients and control subjects.

		Univariable analysis		Multivariable analysis†	
		Beta (95% CI)	**P-value**	**Beta (95% CI)**	**P-value**
Carotid-femoral PWV (n=69)	**Turner syndrome**	0.54 (-0.34; 1.42)	0.223	0.03 (-0.65; 0.72)	0.924
	Age	0.09 (0.06; 0.11)	<0.001	0.06 (0.04; 0.09)	**<0.001**
	Baseline aortic size index	0.16 (0.05; 0.27)	0.004	0.14 (0.04; 0.25)	**0.007**
	Bicuspid aortic valve	-0.67 (-1.54; 0.21)	0.132	-1.03 (-1.95; -0.12)	**0.028**
	Aortic coarctation	-0.42 (-2.01; 1.16)	0.596	0.53 (-0.76; 1.82)	0.413
	Hypertension	2.41 (1.26; 3.56)	<0.001	1.082 (0.13; 2.03)	**0.027**
Ascending aortic distensibility (n=87‡)	**Turner syndrome**	-1.01 (-2.5; 0.51)	0.191	-0.87 (-1.99; 0.25)	0.126
	Age	-0.18 (-0.22; -0.14)	<0.001	-0.18 (-0.23; -0.14)	**<0.001**
	Baseline aortic sixe index	-0.15 (-0.36; 0.07)	0.181	0.11 (-0.11; 0.32)	0.327
	Bicuspid aortic valve	-0.09 (-1.97; 1.79)	0.926	-0.33 (-2.17; 1.52)	0.726
	Aortic coarctation	-1.38 (-5.00; 2.24)	0.451	-1.86 (-4.79; 1.07)	0.210
	Hypertension	-3.61 (-6.13; -1.09)	0.005	-1.25 (-3.35; 0.85)	0.238
Aortic arch PWV (n=87‡)	**Turner syndrome**	1.34 (0.72; 1.95)	<0.001	1.08 (0.54; 1.62)	**<0.001**
	Age	0.06 (0.04; 0.08)	<0.001	0.05 (0.03; 0.07)	**<0.001**
	Baseline aortic sixe index	0.14 (0.05; 0.24)	0.004	0.06 (-0.03; 0.16)	0.198
	Bicuspid aortic valve	0.18 (-0.62; 0.99)	0.651	-0.35 (-1.17; 0.47)	0.395
	Aortic coarctation	1.39 (0.27; 2.50)	0.015	0.66 (-0.35; 1.67)	0.195
	Hypertension	2.47 (1.42; 3.52)	<0.001	0.80 (-0.24; 1.85)	0.131

Bold = statistical significant in multivariabele analysis

† Corrected for all other variables mentioned in this table. ‡ One patient had a missing value for weight.

The five patients with TS who underwent surgery had an age range of 11-47 years at time of surgery. Supplemental table 1 shows a complete overview of the routine stains of each patient. Using the criteria outlined in the recent consensus statement, the patients were found to show only mild medial degeneration in 4 patients, and no medial degeneration in 1 patient, with mostly intralamellar and focal, mucoid matrix accumulation (figure 3). In addition to these findings, we found compact smooth muscle cell layers and a decrease in the intralamellar space, but only mild smooth muscle cell nuclei loss. Also, conspicuous granular deposition of elastin adjacent to lamellae was found in aortic tissue of women with Turner syndrome when compared to healthy controls (figure 3). Additional electron microscopic images confirmed these granular structures by showing 'bulges' on the surface of elastin fibers (figure 4). The elastin fibers themselves were positioned closer together, and were more irregular and thinner compared to a healthy control. Immunohistochemically, the most striking findings were seen in the middle section of the media with a complete lack of desmin expression in all 5 patients, underexpression of caldesmon and progesterone receptor in 4 out of 5, and weak expression of HHF35 in 3 out of 5 patients (figure 5). We observed apparent overexpression of estrogen receptor in the media of Turner syndrome patients, while SMA and MIB-1 were not differentially expressed.

Discussion

The results of our study show that women with Turner syndrome have a stiffer aortic arch compared to controls, independent of the presence of BAV or CoA. Ascending aortic distensibility and carotid-femoral pulse wave velocity were not statistical different between patients with TS and controls. We also found no effect of karyotype on aortic stiffness. Our imaging results confirm that the wall of the aorta is indeed different in patients with TS, even in the absence of cardiovascular pathology such as a bicuspid valve and this seems especially true for the aortic arch and ascending aorta. In addition, clear histomorphological changes are found in the ascending aorta, pointing towards an inherent abnormal aortic wall.

The observed increased aortic arch pulse wave velocity in our study was also observed by Devos et al.[9], however Schafer et al.[8] did not find these results in the younger group of patients with TS. This may indicate that aortic stiffness occurs later in the disease process. Besides increased aortic stiffness, patients with Turner syndrome also have a higher risk of aortic arch abnormalities, such as elongation of the aortic arch[17]. It might be that anatomical abnormalities in the arch, including wall abnormalities or anatomical variations influencing flow patterns, contribute to the occurrence of dissection in the descending aorta. The majority (54%) of the patients with TS developed dissection in the ascending aorta, while only 16.4% developed a dissection in the descending aorta[18]. Further research is required to determine whether descending aortic dissection can be a result of long-lasting abnormal flow patterns caused by aortic arch abnormalities or increased stiffness as in patients with TS. Consequently, these patients might benefit from more intensive follow-up and earlier preventive surgery.

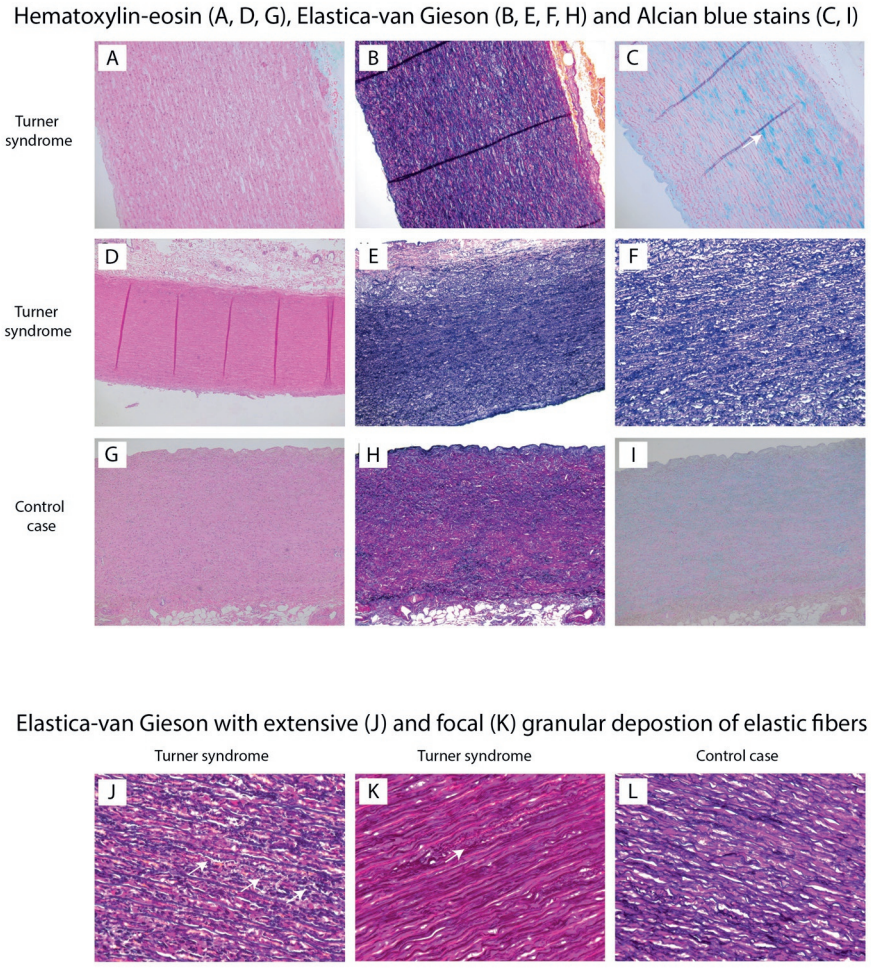


Figure 3. Routine stains of aortic tissue of patients with Turner syndrome and a healthy control. Top row: hematoxylin-eosin (A), Elastica-van Gieson (B) and Alcian blue stains (C) of a representative aortic explant of a Turner syndrome patient, with essentially intact lamellation, and only minimal elastin fragmentation (B) and mucin deposition (C, arrow). Second row: Turner case lacking significant degeneration in HE (D) or EvG (E and F), but with decrease in smooth muscle cell volume. Third row: control case lacking significant degeneration in HE (G), EvG (H), or Alcian blue stains (I). Bottom row: Elastica-van Gieson stains of two Turner patients with extensive (J) and focal (K) granular deposition of elastin fibers (arrows) and one healthy control (L).

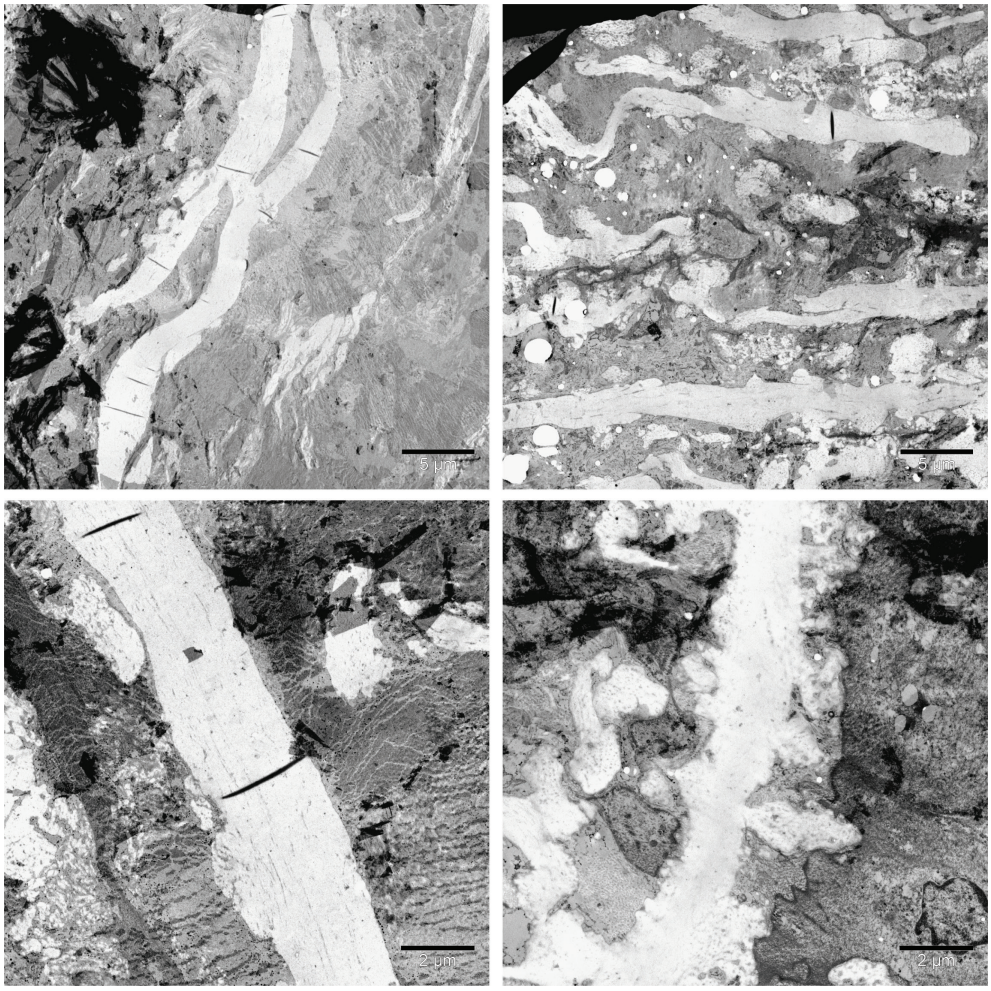


Figure 4. Representative electron microscopic images of the aortic media of a women with Turner syndrome (images on the right) and a healthy control (images on the left). Top row 2800 x magnification, below 7100 x magnification. This figure shows that the elastin lamellae of the women with Turner syndrome are positioned closer together, more irregular and thinner, and display numerous excrescences on the surface.

In addition, our histomorphological results showed abnormalities in the wall of the patients with TS. A hitherto undescribed and striking pattern which is not scored in the current consensus statement[16], was seen in most patients, with compact smooth muscle cell layers and granular deposition of elastin adjacent to lamellae and in the intralamellar tissue. The described compact smooth muscle cell layers and a decrease in the intralamellar space without strong evidence of smooth muscle cell loss indicates a smooth muscle cell

volume loss. This finding is supported by contractile fiber attenuation demonstrated by a complete lack of desmin expression, underexpression of caldesmon and HHF35, as well as weak expression of PR. Our results are in line with a murine study[19] that showed decreased smooth muscle cell content and expression of smooth muscle actin in mice with Turner syndrome. Hinton et al.[19] also found subtle smooth muscle cell misalignment abnormalities that were not present in our patients. The phenomena of decreased smooth muscle cell volume with contractile fiber attenuation and granular deposition of elastin may be key factors in medial destabilization in Turner syndrome patients. Because we only included patients who had undergone surgery for aortic dilatation, these changes could also be a result of aortic dilatation. However, it is not consistently present in aortic resection specimens from other types of connective tissue disease (such as Marfan's disease or Loeys-Dietz syndrome (own observation and Jain et al.[20]). Based on our findings, we suggest that both smooth muscle cell volume and (patterns of) elastin deposition should be included in future grading schemes to evaluate aortic tissue, rather than solely focusing on smooth muscle cell loss and elastin degradation, respectively.

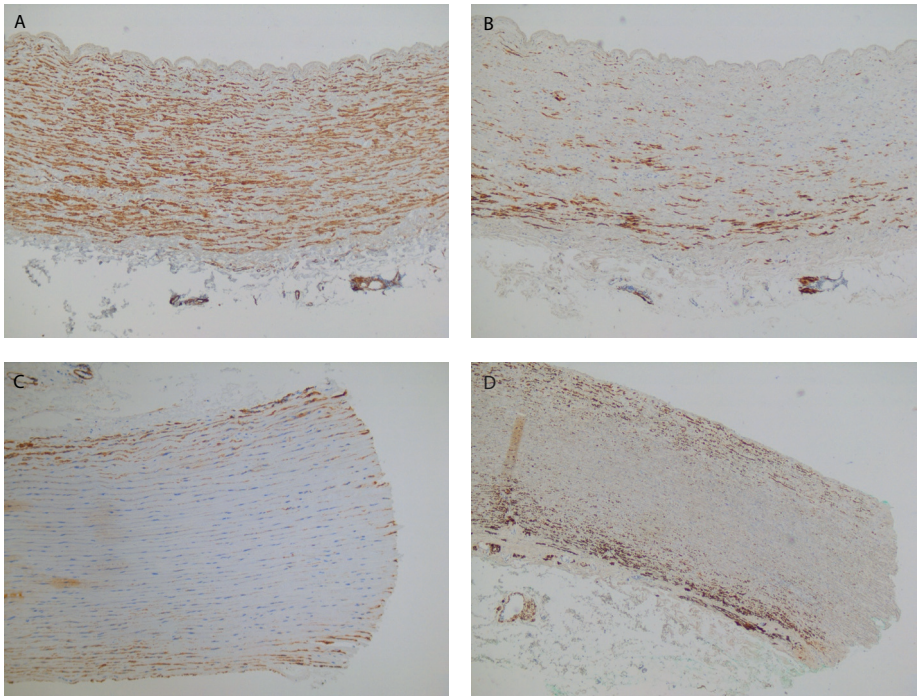


Figure 5. Immunohistochemical stains of patient with Turner syndrome and healthy control. Top row: immunohistochemical caldesmon (A) and desmin (B) stains of representative aortic explant of controls. Bottom row: immunohistochemical caldesmon (C) and desmin (D) stains of representative aortic explant of Turner syndrome patient, with appreciable loss of staining in the media for both proteins.

Although histomorphological data confirms that the wall is different in patients with TS, the elasticity measurement of the ascending aortic (ascending aortic distensibilty) was not statistical significant different between Turner syndrome and controls. This might indicate that elasticity measurements of the ascending aorta are impeded by non-optimal diagnostic power to determine these adverse structural changes within the aortic vessel wall of individual patients with TS. If that is the case, hopefully new imaging developments such as nuclear imaging[21] or computational fluid dynamics[22] will help to non-invasively visualize the changes in the aortic wall or the abnormal blood flow as a result of abnormal aortic wall behavior. Another reason for our non-significantly different ascending aortic distensibility between women with and without Turner syndrome, might be the limited number of participants. Since there seemed to be a tendency to a reduced ascending aortic distensibility in patients with TS, the size of the group might have prevented us from finding a significant difference. Others also have been investigated whether the presence of BAV can explain the increased aortic stiffness in patients with TS but the results are contradictory. Two studies[8, 23] showed reduced ascending aortic distensibility and increased aortic arch PWV independently of the presence of BAV, while Devos et al.[9] showed that only patients with BAV have a reduced ascending aortic distensibility. Our results are more in line with the first study, since we found no effect of BAV on stiffness. The influence of CoA on aortic stiffness in patients with TS has been investigated by Wen et al.[10], who showed that the aortic distensibility of the descending aorta was only lower among Turner with CoA. A history of hypertension and specific medical treatment and the effect of the treatment could have caused this ambiguous result in different studies. Our and former results should be interpreted with caution and verified in a larger cohort of Turner taken into account the assumed factors which affect the aortic elasticity.

The aortic stiffness over the entire aorta measured with carotid-femoral pulse wave velocity showed no significant difference between patients with TS and healthy controls, which is in line with previous literature[24]. Important to acknowledge is that carotid-femoral PWV uses a conventional measurement of the distance on the body surface. Patients with Turner syndrome are known to have a fairly abnormal course of the larger vessels with unrolling and tortuosity[9, 25]. Because of these aortic abnormalities, measurement of the aortic length on the outside of the body is likely to fail in patients with TS. We probably underestimate the length of the aorta and therefore the value of the carotid-femoral PWV will be measured lower than it actually is. In conclusion, the classic carotid-femoral PWV might not be efficient enough to identify abnormal aortic elasticity with this measurement in patients with TS due to methodological issues.

Conclusion

Women with Turner syndrome show a stiffer aortic arch independently of the presence of a BAV or CoA. No differences were found in aortic stiffness between patients with

monosomy or mosaicism. In addition, histomorphological changes are found in the ascending aorta. Our histomorphological investigation provided new insights into the structure of the aortic wall in patients with Turner syndrome. Further research should aim to investigate whether these structural changes are indeed related to the markedly different elastic properties of the ascending aortic in a larger cohort and how we can identify this difference in elastic properties more accurate with use of new imaging developments.

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Supplemental material

Appendix A. Immunohistochemical methods including the antibody clones

SMA
Clone: 1A4
Protocol: CC1-8 min(97 °C)/amplification 4 min/36 min incubation (at 36 °C)/OptiView detection

Caldesmon
Clone: E89
Protocol: CC1-32 min (97 °C)/16 min incubation (at 36 °C)/OptiView detection

Desmin
Clone: DE-R-11
Protocol: Protease 1 – 8 min /amplification/32 min incubation (at 36 °C)/UltraView detection

Actine
Clone: HHF35
Protocol: CC1-36 minuten (97 °C)/36 min incubation (at 37 °C)/UltraView detection

ER
Clone: SP1
Protocol: CC1-64 min (97 °C)/amplification /32 min incubation (at 36 °C)/UltraView detection

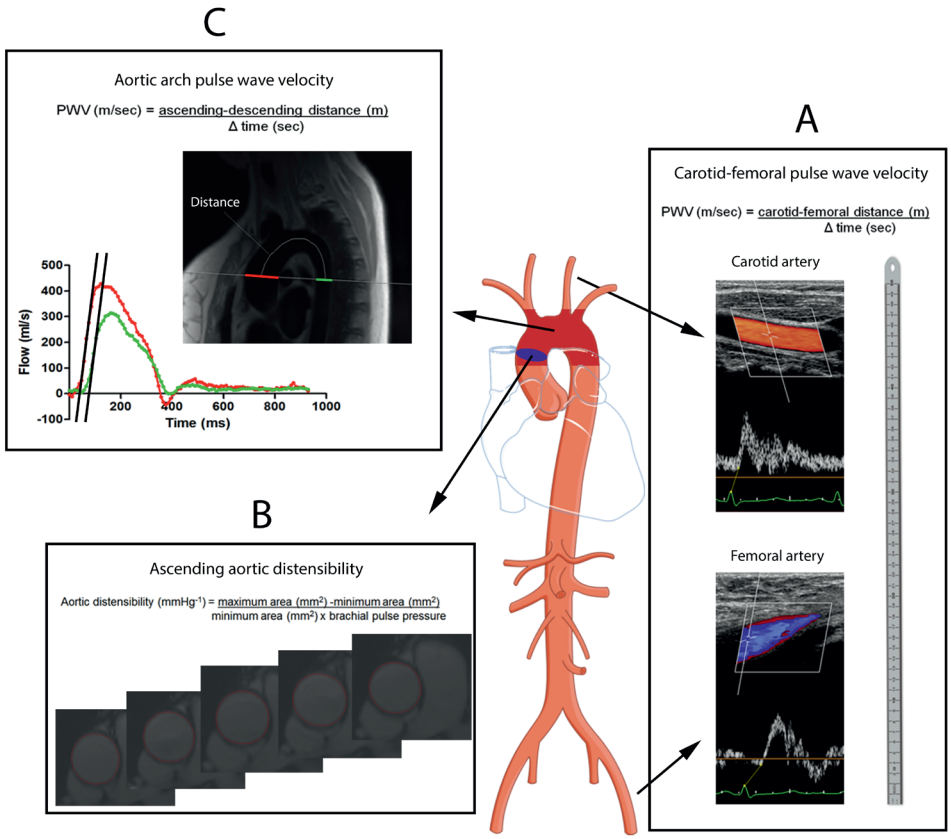
PR
Clone: 1E2
Protocol: CC1-36 min (97 °C)/amplification/12 min incubation (at 36 °C)/UltraView detection

Ki-67
Clone: 30-9
Protocol: CC1-36 min (97 °C) /28 min incubation (at 36 °C)/ UltraView detection

Supplemental table 1. Complete overview of the routine stains.

Nr.	Age	Diameter ascending aorta	BAV or CoA	Routine stains					
				Mucoid ECM accumulation intralamellar	Mucoid ECM accumulation translamellar	Elastic fibre fragmentation and/ or loss	VSMC nuclei loss	Laminar medial collapse	Overall Medial degeneration
1	26	50	BAV	**I**	**0**	**I**	**I**	**0**	**I**
2	24	49	BAV	**I**	**0**	**I**	**I**	**0**	**I**
3	11	42	BAV + CoA	**0**	**0**	**0**	**0**	**0**	**0**
4	40	52	-	**I**	**0**	**0**	**I**	**0**	**I**
5	47	39	-	**I**	**0**	**0**	**0**	**0**	**I**

Scale: 0 = None, I = Mild, II = Moderate, III = Severe.
BAV = bicuspid aortic valve; CoA = coarctation of the aorta.



Supplemental figure 1. Multiple measurements of aortic stiffness at various levels of the aorta using different imaging modalities.

CHAPTER 12

12

Aortic dimensions and clinical outcome in patients with SMAD3 mutations

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Circulation: Genomic and Precision Medicine. 2018 Nov;11(11):e002329.

Research letter

Pathogenic SMAD3 mutations are a known cause of early aortic dilatation and dissection. In combination with osteoarthritis at young age this is encapsulated in the Aneurysms-Osteoarthritis Syndrome[1]. Aneurysms-Osteoarthritis Syndrome has many similarities with Loeys-Dietz Syndrome, and is recognized by some as part of Loeys-Dietz Syndrome[2]. It is currently unknown how the rate of aortic dilatation in SMAD3 patients compares to other syndromic causes of aortic dilatation.

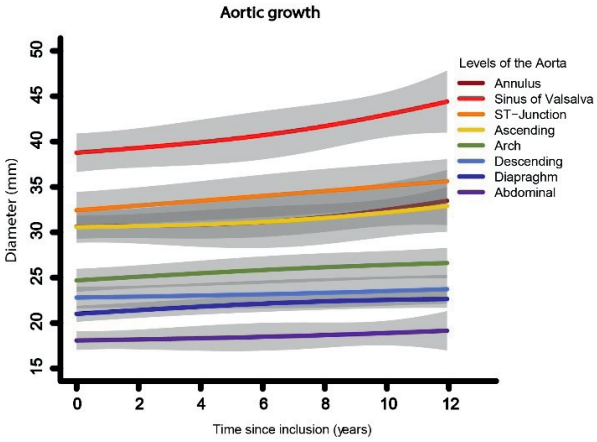
We have followed SMAD3 mutation carriers in our center per in-house protocol since December 2011. This protocol includes yearly ECG-gated contrast enhanced thoraco-abdominal computed tomography angiography. In 10 patients earlier scans were available (2003 to 2011), which were included only when aortic diameters could be reliably measured according to protocol standards. Aortic dimensions were repeatedly measured perpendicular to the vessel at 8 standardized levels using double-oblique multiplanar reconstruction by an experienced cardiovascular radiologist, blinded to clinical data and to previous measurements. To account for correlations between multiple measurements within each patient, average time trends were estimated using linear mixed models. Cubic splines were used to model nonlinear growth curves. Patient-specific intercepts and slopes allowed for individual deviations from the average growth. As described in our in house protocol patients with an aortic diameter of 42 mm or above are considered in the interdisciplinary heart team for intervention. The study protocol was approved by the medical ethics committee of our center.

Baseline characteristics are shown in figure (A). When looking at the average increase per year (figure B), significant growth was seen at 3 levels: the sino-tubular junction, the ascending aorta, and the level of the diaphragm. The average growth was largest at the sino-tubular junction with 0.4 mm/y (95% CI, 0.12-0.62, P=0.005), followed by the ascending aorta and diaphragm with 0.2 mm/y (95% CI, 0.04-0.38, P=0.018 and 95% CI, 0.10-0.27, P<0.001, respectively). The aorta did not show significant growth at the level of the annulus, sinus of Valsalva, aortic arch, the descending and the abdominal aorta. Age had an impact especially at the level of the aortic arch and abdominal aorta. During follow-up no mortality occurred; however, 14 (50%) patients needed elective valve-sparing root replacement. The median age at time of operation was 40.6 years (interquartile ratio, 22.76). Additionally, 14 vascular interventions, most often embolization of a side branch aneurysm, were needed in 9 patients. Five of these patients also underwent a valve-sparing root replacement. In total, 18 patients (64%) underwent at least 1 cardiovascular intervention during the duration of this study. Interventions were done at the discretion of the vascular surgeon, as there are no clear guidelines for intervention in this patient group.

Baseline Characteristics

SMAD-3 patients (n=28)	
Age, years	34 (15-69)
Gender (female)	17 (61)
Follow-up duration, years	10 (3-14)
Blood pressure medication	6 (21)
Most frequent genetic mutation*	9 (32)
Baseline aortic diameters, mm	
Annulus	31±5
Sinus of Valsalva	39±6
ST junction	33±6
Ascending aorta	31±4
Aortic arch	25±4
Decending aorta	23±3
Diaphragm	21±2
Abdominal aorta	18±3

Panel A



Panel B

Figure 1. Baseline characteristics and aortic growth. A, baseline characteristics, *most patients shared the same heterozygous mutation R287W, 859C>T, SMAD3 ex 9. Data are shown as mean±SD, median (25%–75%), or n (%). B, aortic growth: average of all aortic measurements per level of the aorta, shaded gray areas indicate the 95% CI for the estimate. ST indicates sino-tubular

The mean rate of increase in aorta diameter in the normal population is 0.07 mm and 0.09 mm per year of life in women and men respectively[3]. The natural course of this process is influenced by many factors such as age, sex, and blood pressure. In the past decade much attention has been paid to genetic aortopathies. In Marfan syndrome, for example, the aorta dilates fastest at the level of the sinus of Valsalva with a rate of ≈0.49±0.5 mm per year[4]. In comparison to Loeys-Dietz Syndrome, where the aorta can grow at rates of up to 10 mm/y, dilatation in our cohort may seem relatively mild[5]. However, in earlier studies mortality was high, and although no deaths occurred during our follow-up, it should be noted that this could be explained by the intensive management and preventive surgery at relatively mild dilatation of the aorta.

The current results differ from a previous report from our group especially in growth rate and location of fastest growth, which can be explained by longer follow-up duration, inclusion of milder cases discovered by family screening, and by using different analysis methods. Still, we can appreciate that SMAD3 mutation carriers show aortic dilatation at a rate similar to other genetic aortopathies, dilatation occurs predominantly at the sino-tubular junction and ascending aorta, but also in all other parts of the aorta and large arteries. With this study we provide evidence that SMAD3 mutations cause an aggressive form of aortic dilatation, warranting vigilant follow-up. The fastest growth rate (0.4 mm/y) was observed at the level of the sino-tubular junction. In 64% (18 of 28) of the

patients in this study a potentially fatal arterial pathology was discovered. However, for the management of SMAD3 patients this implies that the current protocol adequately addresses the clinical problem in these patients as no patients died from aortic rupture or suffered from aortic dissection during follow-up. Additionally this study provides an important measure of reference to other known causes of genetic aortopathies. More research is needed to determine predictors for fast growth and possible medical therapies in SMAD3 patients hopefully resulting in a better understanding and improved outcome.

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CHAPTER 13

13

Psychological well-being in patients with aneurysms-osteoarthritis syndrome

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Abstract

Aneurysms-Osteoarthritis Syndrome (AOS) is characterised by arterial aneurysms and dissection in combination with early-onset osteoarthritis, which can impact quality of life. We describe the subjective quality of life and investigate anxiety and depression in 28 AOS patients aged 15-73 years. Three questionnaires were used: 36-Item Short Form Survey (SF-36), Hospital Anxiety and Depression Scale (HADS) and Rotterdam disease specific questionnaire. Results of the SF-36 and HADS were compared to a reference Dutch cohort and the SF-36 questionnaire also to patients with Marfan syndrome. Compared to the general population, AOS patients scored significantly lower on the following SF-36 domains: physical functioning, vitality, social functioning, bodily pain, and general health. Physical functioning was also lower than in Marfan patients. Patients with AOS scored higher on the HADS depression scale, while anxiety did not show a significant difference compared to the general population. No difference in SF-36 and HADS domain scores were found between patient with and without orthopaedic symptoms and patients with or without previous aortic surgery. Additionally, we found that patients' worries for their future and heredity of their disease are important factors for anxiety, which should be addressed in clinical practice.

Introduction

An aneurysm or dilatation of the thoracic aorta can cause aortic dissection, which is a potentially life threatening event as over half of all patients with an acute thoracic aortic dissection die within 30 days [1]. In 20% of the patients an aortic aneurysm results from a heritable thoracic aortic disease (HTAD) [2, 3]. In 2011, a new HTAD was described, the so-called "aneurysms-osteoarthritis syndrome (AOS)", caused by a pathogenic variant in the *SMAD3* gene[4], which is part of the TGF-β pathway. Aneurysms-osteoarthritis syndrome has many similarities with Loeys-Dietz syndrome (LDS), and is therefore also referred to as LDS type 3. In AOS, aneurysms can occur within the aorta and other arteries (among which the splenic, iliac, hepatic and intracranial arteries). Furthermore, the arteries show tortuosity and aortic dissections or ruptures already occur in a mildly dilated aorta. In 18% of the patients aortic dissection is even the first manifestation of the disease[5]. In addition to the vascular findings, joint abnormalities are an important feature of this syndrome, which are often the reason for first presentation. These joint abnormalities include osteoarthritis and osteochondritis dissecans at a relatively young age[6]. Other characteristics associated with pathogenic variants in the *SMAD3* gene are widely spaced eyes, bifid uvula, umbilical or inguinal hernias varices, velvety skin, and striae[4]. These physical symptoms and the risk of life threatening dissection of the arteries might cause reduced quality of life, anxiety, and depression. Anxiety in AOS patients can also be caused by experiencing the consequences of the disease through relatives, since this autosomal dominant genetic disorder is often diagnosed in multiple family members. Therefore knowledge about psychological well-being and causes of impaired quality of life and anxiety or depression in AOS patients is important in order to develop specific management strategies. Although psychosocial well-being has been investigated for other vasculopathies such as Marfan syndrome[7] and Ehlers-Danlos[8], no attention has been paid yet to the quality of life and occurrence of depression or anxiety in patients with this life-threatening syndrome. Therefore, the aim of this study was to comprehensively describe the subjective quality of life and investigate anxiety and depression in AOS patients.

Materials and methods

Study population

All carriers of a pathogenic variant in the *SMAD3* gene undergoing follow-up in our tertiary center per in-house protocol since January 2009 were invited for this study. Family members which were 50% risk carriers with obvious AOS related symptoms (aortic dilatation or osteoarthritis at an early age) were also included. Demographic and clinical data were obtained from the electronic patient files. Diabetes mellitus was defined as current use of medication. As part of our protocol, all patients underwent echocardiography and whole-body computed tomography angiography (CTA). The aortic measurements of the sinus

of Valsalva, ascending aorta, aortic arch, and descending aorta were measured using the inner edge-to-inner edge method on the most recent CTA. Aneurysms and dissections were categorized by the following locations and definition: head and neck, thoracic, coronary, abdominal, leg and/or arm or pulmonary artery. Information on the following valvular, ventricular and arrhythmic abnormalities was collected: bicuspid aortic valve, aortic stenosis (Vmax >2.5 m/s), aortic regurgitation (at least moderate)[9], valvular disease other than from the aortic valve, congenital heart disorders, ventricular hypertrophy (septal wall>13 mm), left ventricular dilatation (diastolic diameter >60 mm) and atrial fibrillation (former, paroxysmal or current). The study complied with the Declaration of Helsinki and was approved by the medical ethical committee of the Erasmus Medical Centre (MEC17-057). Written informed consent was provided by all patients.

Questionnaires

All participants received three questionnaires: the Short Form-36 Health Survey (SF-36)[10], the Hospital Anxiety and Depression Scale (HADS)[11] and the Rotterdam disease specific questionnaire. The questionnaires were sent at first on the 14th of November 2017 and were collected until the 1st of February 2018. If participants did not respond at first, they received a maximum of two reminders. The SF-36 was used to determine patient-reported quality of life. It covers the following eight domains: physical functioning, role limitations due to physical health, bodily pain, general health, mental health, role limitations due to mental health, vitality (energy or fatigue related), and social functioning. The scale ranges from 0 through 100 points. A lower score per subcategory, reflects a lower quality of life on that life domain. In addition, two sum scores, the mental component summary (MCS) and physical component summary (PCS), were calculated[12]. These summary scores are standardised according to the general Dutch population[13], which means that all scores above and below 50 are above and below the average in the Dutch population. The HADS questionnaire determines the levels of anxiety and depression on two subscales with a total score ranking from 1 to 21. A score of 0-7 for either subscale is in the normal range, a score of 8-10 is possible abnormal and 11 or higher indicates the probable presence of anxiety or depression. The "Rotterdam disease specific questionnaire" was developed by our multidisciplinary team in the Erasmus Medical Center to investigate the impact of having AOS related aortic aneurysm on daily life, work participation, sexual functioning, pregnancy wish, and sports participation. Patients received 18 statements and were asked to grade how they felt on a continuous scale from 0 to 10, 0 being "I completely disagree" and 10 being "I completely agree".

Comparison with the general population and other aortic disease patients (Marfan syndrome)

For the HADS and SF-36 questionnaires we compared our data to the reference values of the age-matched general Dutch population[13, 14]. For the SF-36, a cohort of age and

sex matched Marfan patients was also available, which allowed us to compare AOS with another syndromic HTAD[15]. For the results of the Rotterdam disease specific questionnaire, there are no reference values available yet because this questionnaire was newly developed for this study's aim.

Statistical analysis

Continuous variables with a normal distribution were reported as mean with ± SD and the median and interquartile range was reported in case of non-normal distribution. Categorical variables were summarized as frequencies and percentages. Data distribution was checked using histograms. Because of the non-normally distribution of the values in the domains of the SF-36 and HADS questionnaires, the median and interquartile ranges are presented in table 1 and the *p*-value of the one-sample Wilcoxon signed rank test was presented in the text and figures. With the one-sample Wilcoxon signed rank test the median of a continuous variable in our cohort was compared with a hypothesized median of a reference group. Since our reference article showed their values only with mean ± SD, we assumed that the variables were distributed normally. Because mean and median are comparable in normally distributed variables, we used the mean of the reference as hypothesized median in our nonparametric test. To visually compare our data with reference data presented as mean ± SD, also our data were presented as mean ± SD in the figures although we could not proof normal distribution. However, only small differences were found between the calculated mean and median of the HADS and SF-36 domain scores. To further investigate if patients with orthopaedic symptoms or previous aortic surgery had higher levels on the SF-36 and HADS domains, we performed the Mann-Whitney U test. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, New York: IBM Corp).

Results

Study population

Of the 31 patients with AOS in our centre, 28 patients (90%) agreed to participate and returned the questionnaires. The other three patients were approached two times, but could not be reached (n=2) or decided not to participate due to time-constraints (n=1). There were no major differences between the 28 responders and 3 nonresponders. The baseline characteristics of the 28 study patients are presented in table 2. Our cohort contained 23 participants with a confirmed SMAD3 mutation representing 10 different genetic mutations with the most common heterozygous mutation (R287W, 859C> T, SMAD3 ex 9) present in 9 patients. The mean age was 44.0±17.3 years with an age range from 15 to 73 years. Of the 28 patients, 17 (61%) were women. Cardiac or vascular

abnormalities were present in 22 (79%) patients and orthopaedic symptoms were present in 24 (86%) patients. In 18 (64%) of the 28 patients both cardiovascular manifestations and orthopaedic symptoms were reported.

Table 1. Results of SF-36 and HADS in patients with AOS.

	Domain/scales	Score	Summary measures†	Score
SF-36	Physical functioning	45.0 (30.0-78.8)	PCS	34.3 (25.0-48.2)
	Role limitations due to physical health	37.5 (0.0-100.0)		
	Bodily pain	57.5 (35.0-75.0)		
	General health	40.0 (25.0-55.0)		
	Mental health	76.0 (57.0-88.0)	MCS	50.4 (39.4-59.9)
	Role limitations due to mental health	100.0 (33.3-100.0)		
	Vitality	50.0 (20.0-63.8)		
	Social functioning	62.5 (50.0-87.5)		
HADS	Depression scale	5.0 (2.0-9.8)		
	Anxiety scale	5.0 (2.0-7.8)		

Data is shown as median (25%-75%).
AOS = aneurysms-osteoarthritis syndrome; HADS = hospital anxiety and depression scale; MCS = Mental component summary; PCS = Physical component summary.
† Standardized scores with use of the general Dutch population 13.

Quality of life, anxiety and depression

The median values with interquartile range of the domains from the SF-36 and HADS questionnaires are presented in table 1. Our cohort scored significantly lower compared to the age-matched reference group of 1,742 Dutch citizens[13] on the following domains: physical functioning ($p<0.001$), role limitations physical health ($p=0.001$), bodily pain ($p=0.001$), general health ($p<0.001$), vitality ($p<0.001$), and social functioning ($p=0.002$). AOS patients showed a standardized PCS score of 34.3 (25.0-48.2) and a MCS score of 50.4 (39.4-59.9). When comparing the SF-36 with age-matched Marfan patients, only physical health was lower in patients with AOS ($p=0.005$). The mean values with standard deviation of the domains from the SF-36 questionnaire for AOS patients, Marfan patients and the reference group are visualized in figure 1.

Table 2. Baseline characteristics.

Baseline characteristics	AOS patients (N=28)
Sex (female)	17 (61%)
Age (years)	44.0 ± 17.3
Confirmed SMAD3 mutation carriers†	23 (82%)
BMI (kg/m2)	24.9 ± 3.4
Smoking (currently)	2 (7%)
Systolic blood pressure (mmHg)	128.2 ± 16.9
Diastolic blood pressure (mmHg)	80.4 ± 9.5
Medication use	14 (50%)
- Beta-blocker	8 (29%)
- Diuretics	0 (0%)
- ACE inhibitors	4 (14%)
- Angiotensin receptor blocker	2 (7%)
- Calcium channel blocker	0 (0%)
- Cholesterol lowering drugs (statins or other)	3 (11%)
- Platelet inhibitor	6 (21%)
- Oral anticoagulant	2 (7%)
Comorbidity	4 (14%)
- Diabetes Mellitus	0 (0%)
- Coronary artery disease	1 (4%)
Aortic aneurysm or dissection	19 (68%)
- History of aortic surgery	9 (32%)
- Thoracic aortic aneurysms (>40 mm)‡	5 (18%)
- Head and neck arterial anomaly	6 (21%)
- Coronary arterial anomaly	0 (0%)
- Abdominal arterial anomaly	5 (18%)
- Leg or arm arterial anomaly	0 (0%)
- Pulmonary artery dilatation (>40mm)	2 (7%)
Aortic diameter‡	
- Sinus of Valsalva	36.0 ± 3.5 (range 30-44)
- Ascending aorta	30.6 ± 3.6 (range 25-40)
- Aortic arch	26.5 ± 3.7 (range 21-34)
- Descending aorta	24.9 ± 3.4 (range 19-33)
Cardiac anomalies	9 (32%)
- Bicuspid valve	0 (0%)
- Aortic stenosis (Vmax > 250 m/s)	0 (0%)
- Aortic regurgitation (at least moderate)	0 (0%)
- Valve disease other than aortic (at least moderate)	1 (4%)§
- Congenital heart disease (i.e. VSD)	1 (4%)
- Ventricular hypertrophy (>13 mm)	2 (7%)
- Left ventricular dilatation (>60 mm)	2 (7%)
- Atrial fibrillation (former/paroxysmal or currently)	4 (14%)
Age first vascular or cardiac abnormalities (in years)	38.0 (26.5-56.0)
Orthopaedic abnormalities¶	24 (86%)
Age first orthopaedic abnormalities (in years)	20.0 (13.8-46.0)

Data is shown as median (25%-75%), mean ± S.D. or as N (%). Missing values for BMI (n=2).
† Five patients have a 50% chance of having AOS, since they are not yet genetically tested. They are included because they showed significant aortic, cardiac or orthopaedic symptoms associated with AOS.
‡ Aortic diameters of the sinus of Valsalva and ascending aorta and prevalence of thoracic aortic aneurysm (>40 mm) are presented for patients who have not undergone aortic surgery.
§ This patients showed moderate mitral valve regurgitation
¶ Orthopaedic abnormalities such as arthritis, arthrosis, osteochondritis dissecans, orthopaedic surgeries, osteosarcomas, instability of the joints, joint or muscle pain.

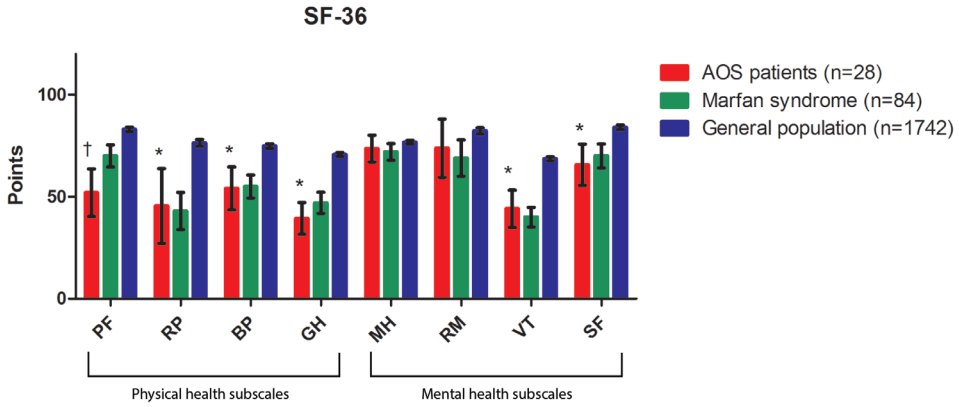


Figure 1. Comparison of eight SF-36 domains between AOS patients, Marfan patients and healthy control. Data is shown as mean (incl. 95% CI). The SF-36 scale ranges from 0 through 100 points. The lower the point count per subcategory, the more prevalent it is that the individual has a negative effect of that sub scale's premise. For social functioning and general health one patient was missing, because he forgot to fill in one page of the questionnaire.
* Significant lower compared to the mean of the general population (One-sample Wilcoxon signed rank test)
† Significant lower compared to both the mean of the general population and the mean of patients with Marfan syndrome (One-sample Wilcoxon signed rank test)
AOS = aneurysms-osteoarthritis syndrome; BP = bodily pain; GH = general health; HADS = hospital anxiety and depression scale; MH = mental health; PF = physical functioning; RM = role limitations due to mental health; RP = role limitations due to physical health; SF = social functioning; VT= vitality.

The HADS questionnaire showed no differences in anxiety (median 5.0 versus 5.1, p=0.569) between AOS patients and the general population. However, patients with AOS scored higher on the depression subscale (median 5.0 versus 3.4, p=0.036) compared to a sample of 199 Dutch adults[14]. In our population of AOS patients, 2 patients (7%) scored above the cut-off, indicative for clinical depression, while 1 patient (4%) scored in the range for clinical anxiety. The mean values with standard deviation of the domains from the HADS questionnaire are shown in figure 2 for the AOS patients and the reference group. No significant differences in SF-36 and HADS domain scores were found between patient with and without orthopaedic symptoms and patients with or without previous aortic surgery.

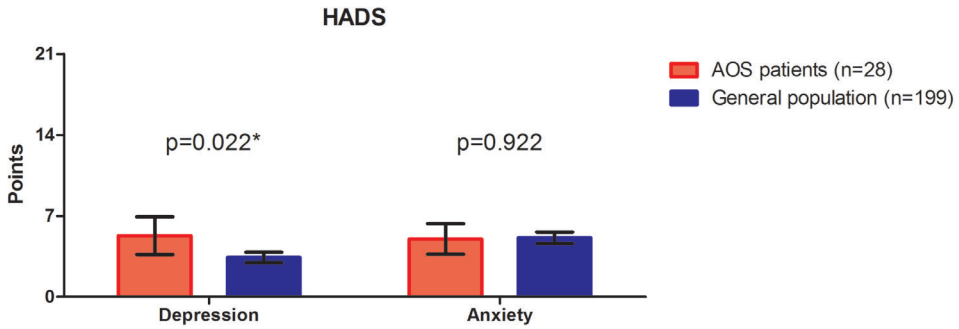


Figure 2. Comparison of two HADS domains between AOS patients and healthy control. Data is shown as mean (incl. 95% CI). The anxiety and depression sub scales have a point system of 0 through 21 points total. The higher the point count for any sub scale, the more likely that the individual suffers from anxiety or depression. *Significant higher compared to the general population (one-sample Wilcoxon signed rank test)

Disease specific anxieties/concerns

In the Rotterdam disease specific questionnaire, the majority of the patients reported fear and/or anxiety according to their future or the future of their siblings or offspring's (figure 3). Concerns about dying at an early age (median 3.5, IQR 1.0-7.0), future health (median 5.0, IQR 2.3-7.0), future surgery (median 6.5, IQR 1.0-9.0) and heredity of their disease (median 7.0, IQR 4.3-10.0) were mentioned. The risk of developing aortic dilatation or dissection or already having aortic pathology did not have a significant impact on participation in work, hobbies, sexual activities and physical activities.

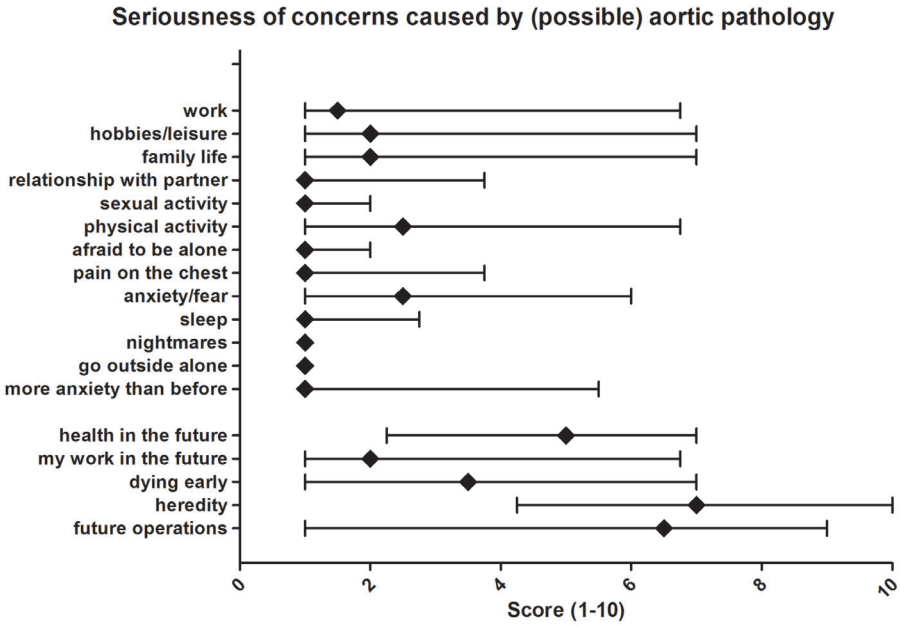


Figure 3. Results of the Rotterdam disease specific questionnaire. This figure shows the influence of (possible) aortic dilatation or dissection on different aspects of life. Data shown as median with interquartile range 25%-75%.

Discussion

The results of our study show that patients with AOS report a lower quality of life, mainly on the physical health subscales, and higher scores on the depression subscale compared to the general Dutch population. Disease specific anxiety was most often related to the future of their own health or the health of their close relatives.

Although anxiety, depression and quality of life have been described in other patients groups with aortic pathology[16-18], specifically after thoracic aortic surgery[19], it has not yet been described in AOS patients or Loeys-Dietz syndrome. In general, AOS is not a very well-known syndrome among cardiologist and other specialists, while pathogenic variants in the *SMAD3* gene are responsible for 2% of familial thoracic aortic disease[20]. This patient group is of great interest, because of their recently discovered extensive presentation including severe joint abnormalities and most importantly aggressive cardiovascular phenotype requiring vigilant follow-up[5]. Therefore it is important for all clinicians involved in the care for these patients to be aware of the psychological aspects in order to provide adequate care. We showed lower SF-36 scores, on almost all domains compared to the general population [13]. The median PCS score of our patients with pathogenic variants in

the *SMAD3* gene was 34.3, which means a much lower physical health than the general population, while the median MCS score (50.4) showed that mental health was comparable with the general population. However, on two subscales of mental health, namely vitality and social functioning, AOS patient did score lower than the general population. We know that middle aged Dutch patients with congenital heart disease show similar or even more favorable levels compared to normative data using the SF-36 survey[21]. This difference between patients with congenital heart disease and AOS patients can be explained by the moment at which the symptoms are present. Orthopaedic and cardiovascular symptoms associated with AOS start at a median age of 22 and 38 years respectively, which cause an acute change in patients' health with clear impact on quality of life. Whereas the patient with congenital heart disease are known with their defect from birth, AOS patients need to adapt and accept that they have this disease at later age. Compared to patients with Marfan syndrome[15], AOS patients scored only lower on the SF-36 questionnaire for the domain of physical functioning. This can be a result of the more extensive presentation of musculoskeletal complaints in patients with AOS including osteoarthritis, osteochondritis dissecans, scoliosis and pectus excavatum [6, 22]. This assumption is supported by data from patients with Ehlers-Danlos syndrome, a connective tissue disorder which presents with extreme musculoskeletal symptoms including hypermobility [23]. Ehlers-Danlos patients report even lower physical function score (39.6) and general health score (26.8) compared to AOS patients [8, 24]. We did not find a difference between patients with and without orthopaedic symptoms. However, this should be tested in larger cohorts, since our cohort might be too small to prove the association between orthopaedic symptoms and reduced quality of life. In conclusion, AOS patients and probably also patients with other heritable thoracic aortic disease, have lower quality of life than the general population, but there seem to be some differences between syndromes. By assessing quality of life, anxiety and depression, we found unfavorable outcomes and impairments, warranting attention and in some cases treatment. In our population of patients with pathogenic variants in the *SMAD3* gene, 4% scored above the cut-off for clinical anxiety, while 7% scored in the range for clinical depression. These percentages are comparable to or even slightly lower than the prevalence's in the general German population, which are 5.2% for anxiety and 9.6% for depression based on the HADS questionnaire[25]. However, the median of the continuous outcome of the depression scale was higher in OAS patients than in the general population. With the development of our own Rotterdam disease specific questionnaire, we were able to identify patients concerns due to their disease. Most importantly, patients report worries concerning the future of their own health or the health of their close relatives. These results emphasize the need for physicians to discuss patient's future and risk for family members and check in each patient whether someone is concerned about this. This is not only important for AOS, but for all inherited syndromes. Generic questionnaires such as SF-36 or EuroQol (EQ-5D) are commonly used for quality of life assessment. Although the use of validated questionnaires is extremely

important, these questionnaires do not distinguish between quality of life based on the disease itself or as a result of other problems like small or short-term injuries and life events. With the use of more disease-specific questionnaires, such as the Rotterdam disease specific questionnaire, in larger cohorts we will be able to identify the cause of physiological burden in a disease more precisely in the future. Nevertheless, before using these questionnaires in clinical practice, they should be validated.

Limitations

In this study, we used questionnaires to measure self-reported quality of life, anxiety, and depression, which may have caused documentation of more complaints than patients would have mentioned spontaneously. Also, it may cause some information bias, although we assume that the high response rate of 90% reduced the chance of bias. Because of our single center design, we included a small cohort, which prevented us from extensive identification of factors associated with quality of life, anxiety, or depression.

Conclusion

In conclusion, our population of AOS patients showed reduced quality of life in comparison with the general population on physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, and social functioning. Physical functioning was also lower than in Marfan patients. Although the prevalence of depression was similar to the general population, patients with AOS scored significantly higher on the depression scale, which physicians must be aware of to provide good medical care. Additionally, we found that patients' worries for their future and heredity of their disease are important factors for anxiety, which should be addressed in clinical practice.

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Part IV

Aortic disease with regard to sport and pregnancy

CHAPTER 14

14

Aortic disease and pregnancy

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Abstract

Purpose of review

During pregnancy, cardiac disease is the most important cause of maternal mortality, with aortic disease being the most important contributor. This review describes the impact of pregnancy, risk stratification for and the management of aortic diseases during pregnancy and delivery.

Recent findings

The most common aortic diseases with an increased risk of complications during pregnancy are genetic syndromes such as Marfan, Loeys-Dietz, vascular Ehlers-Danlos, Turner syndrome and bicuspid aortic valve. The key management of aortic dilatation consists of prepregnancy counseling, including imaging of the entire aorta and preventive treatment when indicated. The possible treatment options for aortic dissection during pregnancy are medication and surgical treatment. Percutaneous interventions are associated with a high risk.

Summary

The heterogeneity of aortic diseases underlines the need for an individual risk assessment and management. A dedicated plan for diagnosis, management, follow-up, labor and delivery should be formulated by an experienced multidisciplinary team.

Introduction

Diseases affecting the thoracic aorta, causing both aneurysm formation and aortic dissection, can be divided into syndromic, nonsyndromic and inflammatory. The most common genetic syndromes associated with thoracic aortic aneurysm and dissection are Marfan, Loeys-Dietz, vascular Ehlers-Danlos, Turner and aneurysm-osteoarthritis syndrome. Other genetic mutations, leading to familial thoracic aortic aneurysms and dissections, are TGFB 2, MYH11 and ACTA2[1]. Inflammatory diseases associated with thoracic aortic aneurysms are Takayasu arteritis and giant cell arteritis. Overall, the incidence of aortic dissection in the general population is estimated around 3.5-5.9 per 100 000 persons[2-4]. According to the Stanford classification[5] Standford type A dissection is more common than type B dissection in both younger and older patients[6]. The mortality rate ranges from 13% in patients with a type B dissection[7] to 33% in patients with a type A dissection[8]. During pregnancy, cardiac disease is the most important cause of maternal mortality, with aortic disease being the most important contributor[9]. The other way around, pregnancy itself is linked to a 25-fold increased risk of aortic dissection among young women[10]. However, one should keep in mind that case-reports focusing on a specific problem, such as aortic dissection, might give an overrepresentation of the problem. Although the incidence seems higher during pregnancy, the mortality rate is not found to be increased. Recently, a maternal mortality rate of 21% was found in pregnant women with aortic dissection[11], comparable with the mortality in nonpregnant patients.

Impact of Pregnancy

The increased risk of aortic dissection due to pregnancy is probably because of the impact of pregnancy, which can be divided into hemodynamic, hormonal and thromboembolic changes. Most of the hemodynamic changes are summarized in figure 1[12-14]. From the beginning of gestation, the total peripheral vascular resistance declines by 40-70%[13]. This normally causes a decrease in blood pressure, but blood pressure shows only a slight fall in the first trimester of pregnancy due to the increase in cardiac output of 50%. The latter is the result of an increase in heart rate (10-20 bpm) and stroke volume. As red blood cell mass increases less than blood volume, low hemoglobin known as 'anemia of pregnancy' arises[14,15]. After pregnancy, the hemodynamic changes return to prepregnancy levels after 3-6 months. Another important impact of pregnancy, probably due to hormonal changes, is found in the media wall of the aorta[16-17]. Using histochemical methods specific findings in pregnant women compared with healthy controls were fragmentation of the reticulum fibers, a diminished amount of acid mucopolysaccharides, loss of the normal corrugation of elastic fibers and hypertrophy and hyperplasia of smooth muscle cells. The last important factor is thromboembolic changes during pregnancy. A rise in factor VII, VIII, X, XII and XIII together with von Willebrand factor and fibrinogen is found during normal pregnancy[18-19].

Also, higher levels of plasminogen and activators and inhibitors of fibrinolysis are found[20]. In conclusion, both coagulation and fibrinolysis are activated during normal pregnancy. In summary, several factors will have an additional and reinforcing effect on already existing aortic disease and will contribute to the elevated risk of aortic dissection during pregnancy.

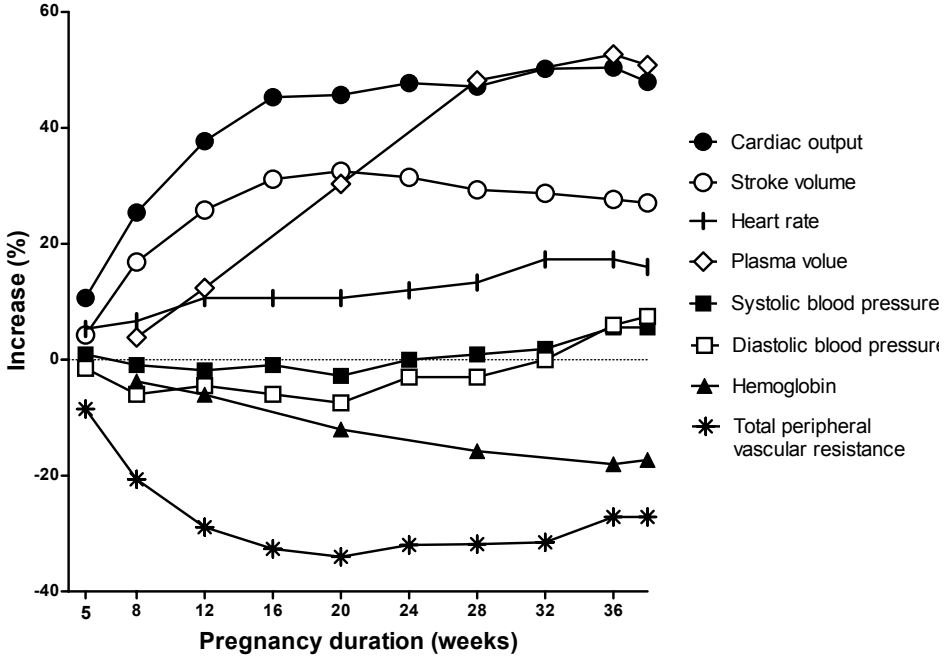


Figure 1. Changes in cardiac output, stroke volume, heart rate, plasma volume, systolic and diastolic blood pressure, hemoglobin concentration and total peripheral vascular resistance during pregnancy[13,14]. Modified from Karamermer Y, Roos-Hesselink JW. Pregnancy and adult congenital heart disease. Expert Rev Cardiovasc Ther 2007; 5:859–69.

Risk stratification

Counseling

Risk stratification to identify patients at high risk before pregnancy is essential. As 11% of all births worldwide are in the maternal age of 15-19 years[21], timely counseling is essential. An interview with detailed history, including family history, should be obtained with physical examination and advanced aortic imaging. It is of importance that imaging of the entire aorta is done by either magnetic resonance imaging (MRI) or computed tomography (CT) to be sure no abnormality is missed. In line with the guidelines for thoracic aorta diseases[22], it is of importance to measure both diameters and growth rate. During

counseling maternal and fetal risks should be discussed together with contraindications for pregnancy, medication use, long-term prognosis and heredity of genetic mutations. More recently the possibility of preimplantation genetic diagnosis before pregnancy was introduced[23]. Concerning management during pregnancy, labor and delivery, a clear plan should be formulated by a multidisciplinary team including a cardiologist, an obstetrician and an anesthesiologist.

Risk factors

There are different patient-related risk factors described for aortic complications in patients with thoracic diseases, to begin with pregnancy itself as well as the number of pregnancies in the past[10,24]. As most of the aortic dissection during pregnancy occurs in the third trimester or peripartum, these are the periods at highest risk[11,25]. Furthermore, two thirds to three quarters of patients have hypertension, which is often uncontrolled[22,26]. Also a family history of thoracic aneurysms or dissections is a risk factor. Several genetic factors are involved in thoracic aortic aneurysm and dissection[26,27]. Logically, having suffered from dissection in the past is also a risk factor for a new event[28]. Other risk factors are smoking, aortic size, rapid growth and specific aorta diseases mostly in the context of a syndrome[24, 28-31]. An overview of the risk factors is shown in table 1.

Table 1. Risk factors for aortic dissection

Factors associated with increased risk of aortic dissection
Aortic dimensions of the thoracic aorta
Rapid growth of the thoracic aorta
Pregnancy
Third trimester
Hypertension
Family history of thoracic aneurysms or dissections
Medical history of dissection
Smoking
Associated aortic disease
[a]Bicuspid aortic valve [b]Turner, Loeys-Dietz, Marfan and vascular Ehlers-Danlos syndrome

[a]Low risk
[b]High risk

Recently, Rajagopalan et al.[11] conducted a large systematic review on the outcome in pregnant women with acute aortic dissection. The group consisted of 75 patients. Approximately 49% of the patients had a systemic disease, and Marfan syndrome was the most common contributor (41%). Marfan syndrome is a connective tissue disorder with Fibrillin gene mutations on chromosome 15. In the Registry of Pregnancy and

Cardiac Disease (ROPAC)[32], four cases of aortic dissection were described, of which two had Marfan syndrome. Pregnant patients with Marfan syndrome have an increased risk of aortic dissection[28]. It seems that patients with a diameter of the aortic root below 40 mm have a low risk of dissection; however, data are limited and there is no safe diameter[24, 33-35]. Guidelines recommend prepregnancy surgery when the ascending aorta is at least 45mm, depending on individual characteristics[36]. In Turner syndrome, caused by loss of part or all of an X chromosome, the risk of aortic dissection is also increased during pregnancy[37]. As patients with aortic size index greater than or equal to 2.5 cm/m^2 are at highest risk for aortic dissection[38], prophylactic surgery should be considered before pregnancy in patients with an aortic size index of at least 2.7cm/m^2 [36]. Patients with Turner syndrome often have a bicuspid aortic valve, aortic coarctation or aortic dilatation[39-41]. Although there are no studies on the risk of dissection during pregnancy in women with Turner syndrome and cardiovascular abnormalities, it is likely that the risk is probably associated with these cardiovascular abnormalities. It is in fact well proven that bicuspid aorta valve (BAV) itself is a risk factor for aortic dissection[42]. Immer et al.[43] found that patients with an aortic dissection during pregnancy in combination with a bicuspid aortic valve disease had an increased aortic root diameter. Guidelines recommend prepregnancy surgery in patients with an aortic root of more than 50 mm[36]. The results of a review of 88 women with BAV and pregnancy, suggesting that the risk of pregnancy-associated dissection in the presence of BAV is low, are noteworthy[44]. However, there were only six patients with an aortic diameter more than 40 mm. Loeys-Dietz syndrome is caused by mutations in the genes encoding for TGFBR1 and TGFBR2. There are a few studies about aortic dissection in pregnant patients with Loeys-Dietz syndrome[45-48]. One of the studies is a review of 52 probands with 21 pregnancies in 12 women[46]. Aortic dissection was present in four women during pregnancy or postpartum. Another study is a cohort with 93 pregnancies in which one type A dissection occurred[47]. Canadian guidelines recommend a threshold for surgical intervention prepregnancy of 40-45 mm[49], whereas the European Society of Cardiology (ESC) guidelines advise a threshold of at least 45mm[36]. Vascular Ehlers-Danlos syndrome is associated with aortic and other arterial aneurysm and dissection. An arterial dissection/rupture occurred in 9.2% of 81 pregnant patients in a cohort in the United States[50]. A second study found a maternal mortality of 6.6% (n=5), of which three deaths resulted from aortic rupture at delivery or in the postpartum period[51]. Currently, because of the high risk of uterine rupture vascular Ehlers-Danlos syndrome is a contraindication for pregnancy. There are limited data on pregnancy and familial thoracic aortic aneurysm and dissection (FTAAD). FTAAD does have a genetic cause, but the specific mutation can be identified at present in fewer than 50% of cases. The most common gene causing FTAAD is ACTA2. Regalado et al.[25] performed a retrospective review of 53 ACTA2 women with a total of 137 pregnancies. Eight of these women had an acute aortic dissection during pregnancy or in the postpartum period, which indicates that ACTA2 mutation is associated with an increased risk for thoracic aortic dissections during pregnancy. The

threshold for elective operation for patients with FTAAD according to the guidelines is more than 50 mm[36]. The different thresholds for elective surgical intervention prior to pregnancy are listed by disease in table 2[22,36]. In addition to the diameter of the aorta, other risk factors mentioned above should be taken into account to identify patients at risk[52,53]. However, patients who have undergone aortic surgery are not entirely protected from aortic dissection related to pregnancy, as shown by a case series of Braverman et al.[54]. They report three cases of Loeys-Dietz syndrome with prior valve-sparing aortic root replacement. Two of the three women suffered acute aortic dissection in the early postpartum period.

Table 2. Thresholds for elective surgical intervention prior to pregnancy and indication for caesarean section*[22,36]

Disease	Indication pre-pregnant surgery	Indication caesarean section
Marfan syndrome	≥45 mm	≥45 mm
Turner syndrome	≥27 mm/m^2	≥27 mm/m^2
Bicuspid aortic valve	≥50 mm	≥45 mm
Loeys-Dietz syndrome	≥45 mm	≥45 mm
Vascular Ehlers-Danlos syndrome	Contraindicated	Always
Others	≥50 mm	≥45 mm

*Level C evidence applicable for all recommendations.

Risk classification

The modified World Health Organization risk classification composed by Thorne et al.[55] seems to be the best available risk assessment model for estimating cardiovascular risk in pregnant women with congenital heart diseases[56]. In this classification, the two contraindications for pregnancy are Marfan syndrome with an aorta diameter more than 45 mm and bicuspid aortic valve with an aorta diameter more than 50 mm. According to the ESC Guidelines of 2011, patients with (a history of) type B dissection or vascular Ehlers–Danlos syndrome type IV should also be advised against pregnancy[36]. Counseling by an obstetrician as well as a cardiologist is essential[57,58].

Management during pregnancy

Follow-up and medication

The ESC guidelines on pregnancy advise monitoring of patients with aortic disease at 4-12 week intervals throughout pregnancy and 6 months postpartum, preferably with echocardiography and when needed with cardiac magnetic resonance imaging (CMR)[36]. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines state that for all patients with known root or ascending aortic dilatation, monthly

or bimonthly echocardiographic measurements of the ascending aortic dimensions are recommended until birth and the first weeks after delivery. Patients with aortic arch or descending aorta dilatation or known aortic disease are recommended to have MRI[22]. A specific timeframe is not advised. MRI (without gadolinium) is recommended, as radiation should be avoided during pregnancy. During follow-up, strict blood pressure control is advised, and where necessary antihypertensive treatment should be initiated. Alpha-methyldopa and beta-blockers are first-line therapy[36], as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are contraindicated during pregnancy[59-61]. In patients with Marfan syndrome there is evidence that beta-blocker therapy has a positive impact on aortic growth and this is advised by the ESC guidelines[36,62]. However, some doubt the clinical benefit[63]. The use of statin to achieve a target low-density lipoprotein cholesterol of less than 70mg/dl and smoking cessation are also included in the guideline for patients with thoracic aortic disease[22]. However, statins are also contraindicated during pregnancy.

Acute dissection

Unfortunately, we are not able to prevent all aortic dissections with elective surgical intervention prior to pregnancy and proper follow-up. When aortic dissection occurs during pregnancy, this is an emergency. The possible treatment options are medication and surgical treatment. In the case of a Stanford type A aortic dissection, immediate surgical repair is required, whereas an uncomplicated type B aortic dissection can be treated conservatively. Intravenous beta-blockers have been recommended by guidelines in an acute situation of thoracic aortic dissection, based on the ability to decrease aortic wall stress. However, data are scarce. For the midterm, treatment with oral beta-blockers in patients with chronic type B dissection reduces the progression of aortic dilatation, the incidence of subsequent hospital admissions, and the incidence of late dissection-related aortic procedures[64]. Calcium channel blockers might also have a beneficial effect on outcome[65,66].

Surgery

In the case when a patient presents with acute disease during pregnancy, warranting a surgical intervention, a decision must be made about whether or not the baby can be delivered first. If the baby is not viable, aortic surgery with the fetus in place should be performed. The risk of surgical repair of the aortic valve or aorta during pregnancy has been studied recently by Yates et al.[67]. A group of 11 patients, who had no option to deliver their baby before surgery, received aortic root and/or valve replacement. There was no maternal death but fetal mortality was 27%. It was described that full maternal and fetal monitoring, attention to cardiopulmonary bypass, pulsatile perfusion, nearnormothermia and avoidance of vasoconstrictors may minimize surgical risks. This was in line with another study, which studied four case reports and found that pulsatile

bypass possibly can minimize maternal and fetal risks[68]. When the baby is viable, delivery first is advised, (directly) followed by cardiac surgery. If possible, waiting until 32 weeks of gestation is advised[69]. A new approach for complicated aortic dissection type B is the thoracic endovascular aortic repair (TEVAR). Although the long-term outcome of this type of intervention is not known, the midterm outcome is already reported in an international registry and looks promising[70]. The outcome of TEVAR during pregnancy is only described in two case reports[71,72]. Despite a favorable outcome in these two cases, further studies of management of aortic disease in pregnancy are clearly needed. Regarding the fact that not much is published about these interventions in pregnant women, only centers with experienced teams and expertise in pregnancy and heart disease should carry out surgical and catheter-based procedures.

Mode of Delivery

For patients on oral anticoagulants, vascular Ehlers-Danlos syndrome, ascending aortic aneurysms of more than 45 mm, or acute or chronic aortic dissection, caesarean section is recommended. In all other patients, vaginal delivery is considered the best option. In patients with an aortic aneurysm of 40-45 mm, a vaginal delivery with epidural anesthesia and expedited second stage can be planned, but caesarean section may also be considered[36]. Epidural analgesia is preferred together with vaginal delivery because of the positive influence on hemodynamic parameters[73]. Another recommendation for vaginal delivery is to put a patient on her left side or in a half sitting position during contractions to prevent aortocaval compression[74]. A global prospective observational registry, the ROPAC, investigated the relationship between mode of delivery and pregnancy outcome in women with cardiac disease[75]. They found no significant difference between vaginal delivery and caesarean section in maternal and perinatal mortality. However, caesarean section resulted in lower birth weight and a higher rate of preterm birth. In addition, there was a higher rate of postpartum heart failure in the caesarean section group. Concerning caesarean section indicated in patients with aortic dissection, Rajagopalan et al.[11] suggested that patients undergoing combined caesarean section with aortic repair had favorable fetal outcomes compared with aortic repair before or after delivery, but this study consisted of a small population.

Conclusion

The changes of the aorta during pregnancy itself, already existing aortic diseases and risk factors, such as hypertension and familial history or patient's history of dissection, all together will contribute to the elevated risk of complications during pregnancy. The heterogeneity of aortic diseases and inherent risks underlines the need for an individual risk assessment and management. Timely counseling is important and prophylactic

interventions may be needed. The management of acute complications during pregnancy includes medical therapy where appropriate and surgical or catheter-based interventions where needed. This should be done in centers with experienced teams, having expertise in both pregnancy and aortic diseases. Further research should be done on risk stratification and cutoff values for elective surgical interventions, as it is of importance to prevent acute events during pregnancy. Also, further research on the mode of delivery in patients with aortic disease is needed.

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CHAPTER 15

15

Exercise and sports participation in patients with thoracic aortic disease: a review

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Abstract

Introduction

Current guidelines recommend patients with thoracic aortic disease (TAD) including inherited aortopathies to avoid heavy exercise. However, evidence supporting the negative advice on exercise is scarce. We aimed to provide an up-to-date systematic review of the available evidence on risks and benefits of exercise and sports participation in TAD patients.

Areas covered

A systematic search was performed in Medline, Embase and Web of Science: thoracic aortic aneurysm *or* thoracic aortic dissection *or* inheritable aortopathies including Marfan Syndrome (MFS), Loeys-Dietz syndrome, Turner Syndrome, Ehlers-Danlos syndrome, bicuspid aortic valve (BAV) *and* sports, exercise *or* athletes. The resulting 1,652 manuscripts were reviewed by two independent observers. Eventually, 26 studies and 12 case-reports were included, reporting on thoracic aortic dimensions in athletes, exercise related acute aortic dissections, and exercise in BAV and MFS patients.

Expert commentary

Blood pressure elevation during exercise may be associated with an increased risk of acute aortic dissection; however, no controlled trials have longitudinally evaluated the effect of exercise on survival or the risk of aortic dissection in TAD patients. Mouse-model studies suggest beneficial effects of exercise in the setting of a dilated aorta in MFS. There is a clear need for prospective research in this field.

Introduction

The incidence of thoracic aortic disease (TAD) such as thoracic aortic aneurysms and dissections is estimated to be 9.1-16.3/100,000 per year [1]. However, thoracic aortic aneurysms are mostly asymptomatic and its prevalence is probably underestimated. About 20% of patients with thoracic aortic dilatation have a positive family history of aortic disease [2], which can be an expression of an underlying disorder such as bicuspid aortic valve (BAV) or connective tissue disorders, such as Marfan Syndrome (MFS), Loeys-Dietz syndrome, Ehlers-Danlos syndrome or Turner Syndrome. BAV patients are of particular interest because this condition is not uncommon with a prevalence of about 1% in the general population [3-5]. However, BAV patients seem to be at relatively low risk for aortic dissection [6]. On the contrary, Marfan Syndrome has a lower prevalence of 6.5/100.000, but these patients are at high risk of acute aortic dissection [7].
The hemodynamic changes associated with exercise, and specifically the increase in blood pressure, is potentially associated with an enhanced risk of aortic growth and acute aortic dissection in the context of a thoracic aortic disease (TAD). Current guidelines state that patients with TAD should avoid strenuous resistance or isometric exercise and competitive sports [8-10]. Due to the lack of data, however, these European, Canadian and American guidelines are characterized by low levels of evidence [8-10]. Recommendations for specific patient groups, such as patients with BAV, are in line with these guidelines. However, MFS patients are advised to only participate in low and moderate intensity sports with regular checks including echocardiography every 6 months, even if aortic root dilatation is absent [11-13].
The importance of daily exercise became clear in the 1950's when an inverse relationship between physical activity and cardiovascular risk was discovered[14]. Ever since, it has become well understood that a sedentary lifestyle is an important modifiable risk factor for cardiovascular disease and mortality[15]. Furthermore, regular exercise is known to prevent and reduce hypertension[16]. For TAD patients it is evenly important to not have a sedentary lifestyle, but also to prevent thoracic aortic growth and the occurrence of aortic dissection, creating a difficult paradox for clinicians. In this study, we sought to provide an up-to-date systematic review of the available evidence on exercise and sports participation in TAD patients including those with inherited aortopathies, and identify gaps in knowledge. We particularly aimed to find evidence on: 1) the aortic remodelling associated with regular exercise training and upper limits of dimensions in physically active individuals, 2) the risk of acute thoracic aortic dissections during exercise, and 3) the impact of exercise on the thoracic aorta in specific patient groups, especially in BAV and MFS patients.

Methods

Literature search

A broad systematic search was performed in Medline, Embase and Web of Science on August 2, 2018. The following search terms (including synonyms) were used: exercise,

sports, athletes, training and thoracic aortic aneurysm, thoracic aortic dissection. Additionally, search terms were included for various inheritable connective tissue disorders: Marfan syndrome, Loeys-Diets syndrome (including aneurysm osteoarthritis syndrome e.g. SMAD3 mutation), Turner syndrome, Ehlers-Danlos syndrome and bicuspid aortic valve. The exact search details are shown in supplemental material. Additional publications were obtained by hand searching, and reference lists were crosschecked to identify possible relevant papers overlooked by the original search. Duplicates were identified and removed.

Study selection

Titles and abstracts were screened for eligibility by two independent researchers (CT and LB). Only articles in the English language were included. Solely original data was included, therefore reviews and meta-analysis were excluded. Furthermore, book chapters, double publications on the same cohort and conference abstracts were excluded. Papers that could not be accessed in full text were also excluded. Only case reports on acute thoracic aortic dissection associated with exercise were included, while case reports on thoracic aortic dilatation and case reports on aortic dissections not related to exercise were excluded. Papers on thoracic aortic dilatation in athletes were only included if aortic diameters were reported. Of all potentially eligible papers the full text was reviewed. In case of disagreement a third reviewer was asked for counsel (JR) and eligibility was assessed by reasoning.

Results

Search results

Figure 1 shows the flowchart of the study selection. Our search identified a total of 1652 unique publications. After reviewing the titles and abstracts 1530 papers were excluded, and 122 potentially eligible papers were reviewed in full text. Finally, 26 studies and 12 case reports were included. We grouped the selected papers based on the abovementioned subjects of interest. Sixteen studies were found on thoracic aortic diameters in athletes. Three studies and twelve case reports were identified on the occurrence of acute aortic dissections during exercise. Three studies reported on exercise in MFS and four evaluated exercise in patients with BAV. Unfortunately, no papers were identified addressing the association between exercise and thoracic aortic dilatation or risk of dissection in patients with Loeys-Dietz syndrome, aneurysm-osteoarthritis Syndrome (AOS e.g. SMAD3 mutation), vascular Ehlers-Danlos syndrome or Turner syndrome.

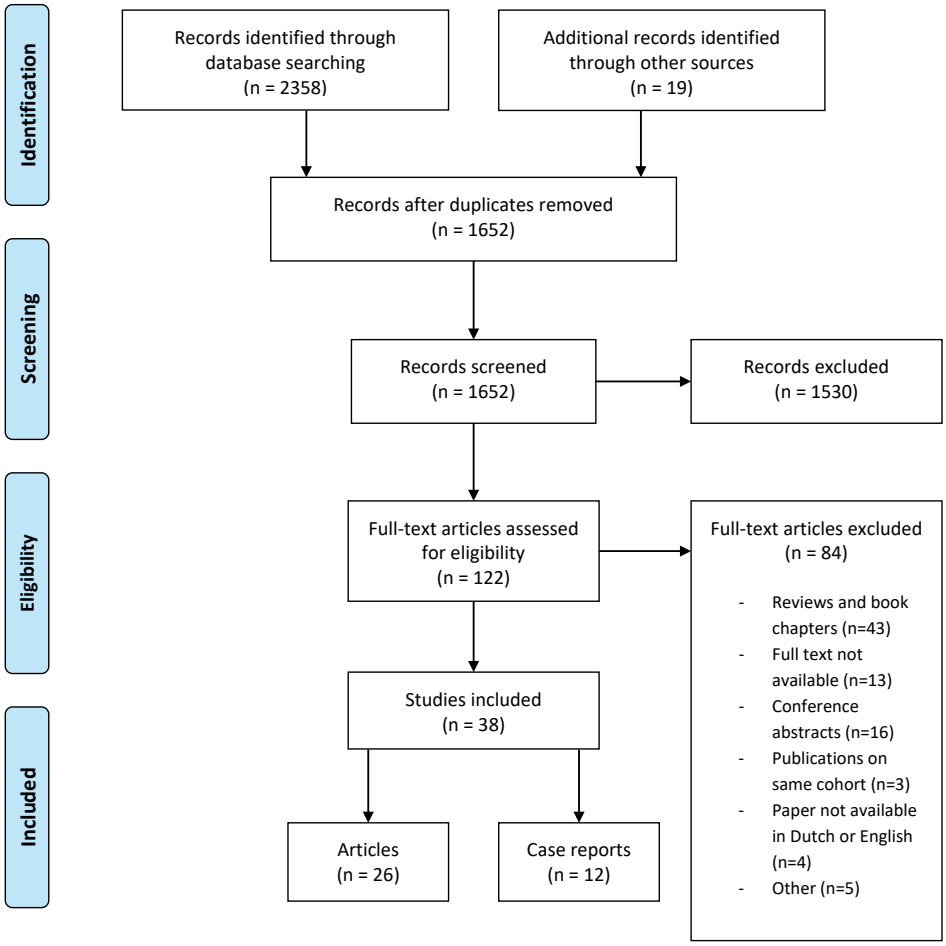


Figure 1. Flowchart of literature search and selection of studies

Thoracic aortic dimensions in athletes

We identified 16 papers published between 1981 and 2015 which evaluate aortic dimensions in athletes practicing a variety of sports disciplines, shown in table 1. Almost all papers were cross-sectional cohort studies (15/16), and one was a longitudinal cohort study. The number of included patients differed greatly, ranging from 9 to 1929 participants. Eleven studies compared aortic diameters in athletes to a sedentary control group, shown in figure 2[17-27]. Overall, outcomes of these studies show that athletes have significantly larger absolute aortic diameters than controls. However, the reported differences in absolute mean aortic root diameters are small: varying between 0.6 and 4 mm. Aortic diameter measurement was performed at the level of the aortic root in all studies, only two studies measured aortic diameter at multiple levels[23, 28]. One study

reported aortic root diameters corrected for body surface area (BSA) and found no significant difference between athletes and controls, although the absolute aortic root diameters were significantly different between the groups [26]. Three papers only included female athletes [17, 19, 20], and five papers only included male athletes [18, 21-24]. The 99th percentile of aortic root dimensions in male athletes was found to be 40 mm and 34 mm for female athletes[29]. Five articles reported the prevalence of aortic root dilatation[27, 29-32]. In these articles, different definitions of aortic dilatation were used, as shown in table 1. The reported prevalence of aortic dilatation among athletes was low (0.26-1.3%), except in one cohort of athletes from the US national volleyball team, in which 6% of female athletes had an aortic root diameter ≥34 mm, and 8% of male athletes had an aortic root diameter ≥40 mm[32]. However, these volleyball players were very tall with an average body height of 198.2 ± 8.0 cm in males and 184.1 ± 7.4 cm in females.

Four studies evaluated differences in aortic diameter between strength trained and endurance trained athletes[21, 27, 28, 31]. Three studies report a small but significant difference in absolute aortic root diameters, with slightly larger aortic root diameters in strength trained athletes than athletes who perform dynamic exercise. The mean differences reported ranged from 2.1-5 mm. However, mean aortic root measurements were all below 40 mm[27, 28, 31].

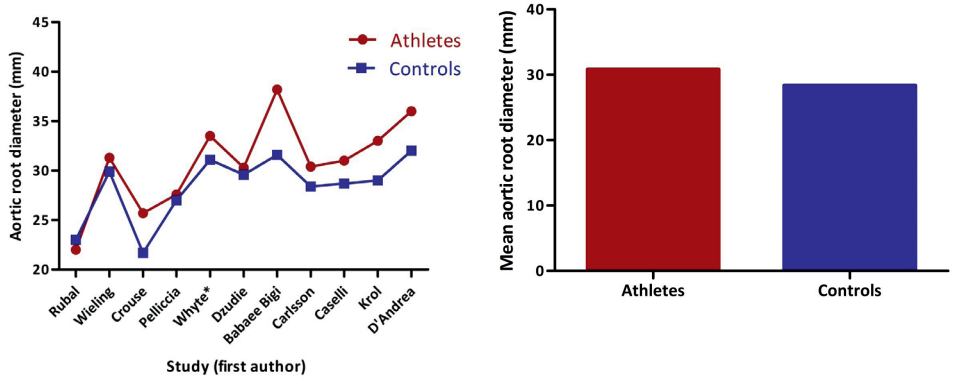


Figure 2. Studies that reported aortic root diameters in athletes and controls.
* This study reported only aortic annulus diameter, not aortic root diameter

Exercise-related acute thoracic aortic dissections

Table 2 presents all case reports and case series reporting the occurrence of thoracic aortic dissections during exercise. The papers were published between 1987-2016 and each describe 1 to 31 cases of acute thoracic aortic dissection occurring during sports activities. A total of 49 patients were described, of whom 42 suffered Stanford type A thoracic aortic dissections and 7 patients had Stanford type B dissections. Remarkably, only 2 out of 49 patients (4%)

were female. The age ranged from 12 to 76 years. However, many reports only included young patients, with half of the papers reporting on patients up to 20 years of age[33-38]. In the majority of cases (26/49) weightlifting was the type of sport associated with the occurrence of aortic dissection[34-37, 39-41]. MFS was diagnosed after presentation in four patients and one patient was known to have a connective tissue disorder other than MFS, which was not specified. Notably, family history was not obtained or reported in 7 of the 12 papers[34, 35, 39, 41-44].

Furthermore, three retrospective cohort studies on sports related acute aortic dissections type A (AD-A) were identified, shown in table 3. Only one paper focussed on the different types of sports practised during AD-A[45]. This study described 650 patients with a mean age of 62.3 years in patients with sports-associated AD-A and 63.7 years in non-sports associated AD-A. Of all AD-A's 4.1% was found to be associated with sports activities [45]. The type of sport most often reported was golf (32%), followed by swimming and cycling (each 16%), weight lifting (12%), and dancing (8%). Figure 3 illustrates the distribution of sports-related AD-A's reported in this study over the different sports categories. These exercise related AD-A's occurred in all age groups and there was no significant difference in sex distribution between sports related AD-A's (60% males) and non-sports related AD-A's (52% males)[45]. Two retrospective cohort studies were identified specifically studying the occurrence of AD-A during a specific exercise: sexual intercourse and alpine skiing[46, 47]. The first reports exercise and sexual intercourse associated AD-A's in a cohort of 365 patients and found a much higher percentage of 68% exercise associated AD-A's, with no significant difference between males and females. In this study, evidence of MFS was present in only 0.9% of patients. AD-A associated with sexual intercourse occurred only in males (17/245)[46]. The other retrospective cohort study by Schachner et al.[47] reported on AD-A's occurring during winter season and they found that 22% of all AD-A's were associated with alpine skiing, and the majority of these cases were unrelated to trauma (82%). There was no significant difference in sex distribution between skiing associated AD-A (88% males) and AD-A not associated with skiing (77% males).

Exercise in patients with BAV

We identified four papers reporting on the association between exercise and thoracic aortic diameters or thoracic aortic dilatation rate in BAV patients, which are shown in table 4. Of these, three papers came from the same research group[48-50]. Two of which compared athletes with BAV to athletes with a normal tricuspid aortic valve (TAV)[48, 49]. Both reported significantly larger aortic diameters at all measured levels in BAV athletes compared to TAV athletes. However, all reported mean diameters were below 36 mm. One cross-sectional study, which included 58 competitive athletes with BAV, showed no correlation between aortic dimensions and duration of training[48]. Two longitudinal studies presented by the same research group reported on mean aortic diameter growth rate in BAV athletes, presumably describing the same patients. The mean growth rates reported were: 0.78 mm/year at the aortic annulus (Ann), 0.61 mm/year at the Sinuses of Valsalva (SoV), 0.81 mm/

year at the sinotubular junction (STJ) and 0.98 mm/year at the proximal ascending aorta (AA)[49, 50]. The mean age of these two cohorts of BAV athletes were 19 ± 8.8 years and 25 ± 11 years. No significant increase of aortic diameter was reported in TAV athletes (mean age 25 ± 5 years) after five years of follow-up. Another longitudinal study by Spataro et al. found no clear association between sports participation and valve deterioration in BAV patients, with a mean follow-up duration 13 years[51]. Unfortunately, no aortic diameter measurements were reported and no conclusions can be drawn about the effect of exercise on the aortic diameter in this cohort of BAV athletes. Only one paper compared BAV athletes to sedentary BAV subjects. This article reported no difference in aortic growth rate between the two groups at all measured levels of the thoracic aorta: Ann, SoV, STJ and AA[50].

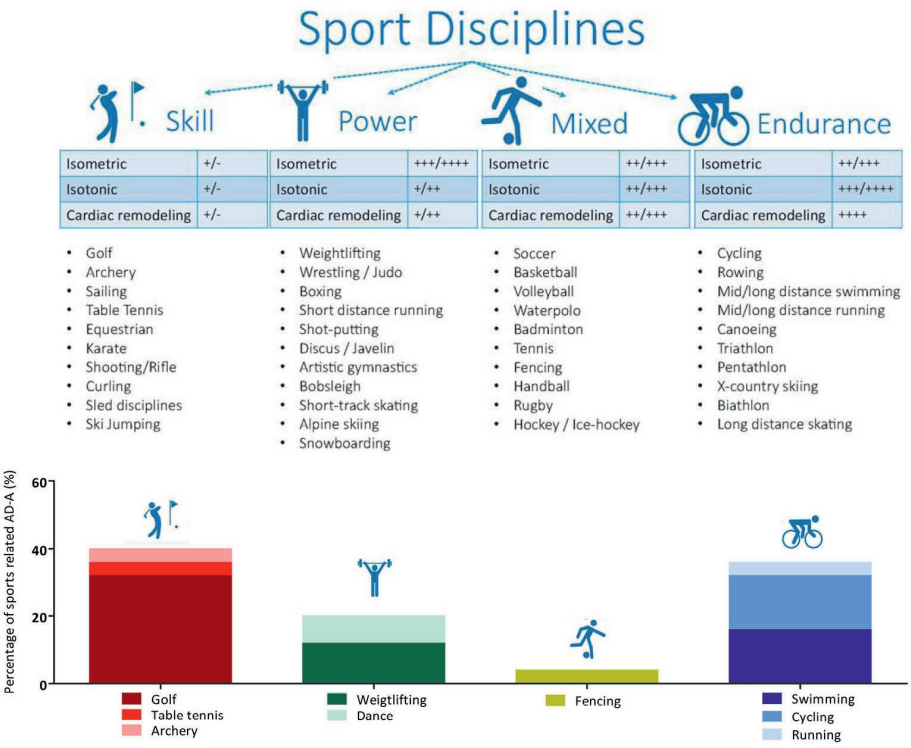


Figure 3. Classification of sports and sports related aortic dissections
Most sports require a combination static and dynamic exercise. In order to facilitate counselling about sports participation this simplified classification of the most common olympic sports disciplines was created, according to the relative isometric and isotonic components of exercise and resulting cardiovascular adaptation. Underneath the distribution of sports related aortic dissections type A (AD-A) over the four categories is displayed, based on data published by Itagaki et al. [45]. The classification of sports was reprinted from: A. Pelliccia; S. Caselli, European Association of Preventive Cardiology (EAPC) and European Association of Cardiovascular Imaging (EACVI) joint position statement: recommendations for the indication and interpretation of cardiovascular imaging in the evaluation of the athlete's heart, European Heart Journal, 2017, Volume 39, Issue 21, Pages 1949–1969, by permission of Oxford University Press. AD-A= Aortic Dissection Stanford type A.

Exercise in Marfan Syndrome

Table 4 presents the three papers on exercise in MFS, all published in 2017. Two papers describe mouse model studies investigating the effects of mild-moderate dynamic exercise on the aortic wall in MFS mice[52, 53]. Both were controlled trials with one or more dynamic exercise training groups and a sedentary group. The follow-up duration of both studies was five months. Both papers reported a reduction of aortic diameter growth rate in MFS mice performing mild to moderate dynamic exercise compared to sedentary MFS mice[52, 53]. Also, in mice performing dynamic exercise, the aortic wall became stronger compared to sedentary MFS mice. This was testified by the larger amount of mechanical stress on the aorta required to induce rupture of the aortic wall[52]. Exercise seemed to improve aortic wall elasticity in one study[52], but no significant improvement was found in the other[53]. Dynamic exercise was not found to increase lamina ruptures, indicating no additional structural damage in the tunica media[53]. An optimum of protective effects was found at a training intensity level of 55-65% of maximum oxygen uptake (VO2max), while higher intensity of dynamic exercise training seems to blunt the positive effects[52]. The third paper is a small prospective cohort study that evaluated the feasibility and effects of a three-week rehabilitation program in 19 MFS patients with a mean age of 46.7±7.8 years[54]. During the one-year follow-up, no adverse medical events were reported, physical fitness improved, and psychological distress decreased. These effects were already present after three weeks of rehabilitation, and mostly remained persistent throughout the one-year follow-up[54]. Unfortunately, no information on aortic diameters was provided.

Discussion

To our knowledge, this is the first systematic review describing the effect of exercise and sports participation in TAD patients. We were not able to identify any controlled or randomized trials evaluating the longitudinal effect of exercise on survival or risk of aortic dissection in TAD patients. When focusing on the association between exercise and thoracic aortic growth rate very limited data can be found. In total, we identified 38 papers of interest, of which 9 were case reports, 3 case series, 8 longitudinal cohort studies and 16 cross-sectional cohort studies. Two were mouse-model studies: one non-randomized controlled trial and one randomized controlled trial. Assessment of methodological quality of the included papers was planned, but ultimately not performed quantitatively, since the large variety of study designs made consistent and comparable quality assessment impossible and meaningless. Eventually it can be concluded that most papers would reach low scores.

Are aortic dimensions different in athletes?

Screening before participating in competitive sports provides a lot of easily accessible data resulting in a large number of studies performed in athletes. The absolute thoracic aortic diameters reported are larger in athletes compared to non-athletic controls, although

the differences are very small. This is consistent with the findings of a fairly recent meta-analysis reporting a small but significantly larger aortic root diameter in elite athletes than in non-athletic controls[55]. One study showed that after indexing aortic root diameter for BSA, the significant difference in aortic root diameter between athletes and controls was blunted[26]. Indicating the differences in aortic diameter might be attributed to a difference in body size between athletes and controls, which is known to be associated with thoracic aortic diameter[56]. The larger aortic diameters reported in athletes are therefore not necessarily caused by a pathological process, but presumably result from higher cardiac output and difference in body size. Whether this is associated with an increased risk of aortic dissection is yet to be determined. The findings mentioned above seem to be comparable in male and female athletes. However, they might not be applicable to less intensively trained and older individuals, and patients who already have TAD.

Is there an association between exercise and acute thoracic aortic dissections?

The incidence of sudden cardiac death among the younger population (< 40 years) is approximately 1.3 to 8.5 per 100,000 person-years[57]. Approximately 1-5% of sudden death in young athletes is caused by acute aortic dissections[58-60]. Over the past decades, there have been many reports, especially case-reports, that link exercise (mainly high intensity static exercise) to acute aortic dissection. Aortic dissection is an emergency situation with a reported in-hospital mortality of up to 33%[61]. This has made clinicians cautious when counselling TAD patients about exercise. We found a striking difference in the reported amount of acute thoracic aortic dissections related to exercise: Itagaki et al.[45] reported a relation to exercise in 4.1% of all AD-A's and Gansera et al.[46] in 68% of all AD-A's . This difference might partially be explained by a different definition of 'sports related aortic dissections'. Whereas one study classified non-sports exertion and Valsalva manoeuvres such as lifting or moving a heavy load, defecation, or sexual activity, into the non-sports group (Itagaki et al.), the other classified these into the sports group (Gansera et al.). The true amount of sports-related type A aortic dissections might be somewhere in between, such as the 22% of all winter season AD-A's related to alpine skiing, as reported by Schachner et al[47]. Apart from the theoretical physiological impact, we found no evidence supporting the theory of static exercise being more prone to inducing acute thoracic aortic dissections than dynamic exercise. The majority of the identified case reports described acute thoracic aortic dissection during weightlifting. However, this might be due to selection bias, since a larger series showed the type of sport associated with AD-A most frequently was golf (32%), which is classified as a low isometric and low isotonic sport (skill category, figure 3)[45]. It seems that aortic dissection can also occur during relatively mild intensity sports such as golf, but for interpreting the results of figure 3 keep in mind that this is based on only one study and more research is clearly warranted. Of course, the size and composition of the study population is crucial here. When a study includes all patients with dissection, the mean age will be relatively high, and golf will be a sport which is

prevalently practised. In younger cohorts, a totally different sports involvement pattern is likely to be found. Furthermore, this study was conducted in Japan where golf is known to be a very popular form of exercise. Therefore, in the absence of reliable information on rates of sports participation, no conclusion can be drawn on the association between dissection and a specific sports activity. Concerning the impact of sex, it was striking that almost all case reports describe males with acute aortic dissections related to exercise. However, this does not seem representative since the larger series both from Itagaki and Gansera reported no significant differences in sex distribution[45, 46]. Population based studies might provide additional information, but data on the prevalence of participation in different types of sports, aortic diameters and long-term follow-up are scarce.

How does exercise influence the thoracic aorta in BAV and Marfan patients?

Although bicuspid aortic valve is the most prevalent congenital heart disease and an important underlying etiology of thoracic aortic dilatation, the association between exercise and aortic diameter and growth rate has been investigated to a limited extent in this patient group. In BAV patients, Galanti et al. and Stefani et al. state that the aortic growth rate they reported in BAV athletes does not differ from aortic growth rate reported in the general BAV population[49, 50]. Indeed, the reported dilatation rate of 0.98 mm/year found in the athletes with BAV seems comparable to the reported aortic dilatation rate in various studies reporting aortic growth rate in the general BAV population[62, 63].Even though the BAV populations studied by Stefani et al and Galanti et al were relatively young (19 ± 8.8 years and 25 ± 11 years), and younger age is known to be associated with higher aortic growth rates[64]. These findings suggest that aortic growth rate is not significantly influenced by exercise in BAV patients.

Two recently published papers have investigated the effect of dynamic exercise on the thoracic aorta in mice with MFS. Both studies reported mild to moderate dynamic exercise had a positive effect on aortic growth rate and seemed to improve aortic wall structure. This suggests that exercise does not only have potential negative effects on the thoracic aorta in TAD patients, but might be actually be beneficial[52, 53]. Further research is needed to evaluate these potential positive effects of exercise on the thoracic aorta in MFS patients and patients with other thoracic aortic diseases. Especially, since mouse model studies on the aorta might not always be reliable[65]. One randomized trial has been performed in patients with an abdominal aortic aneurysm (AAA) in 2014[66]. In this trial 140 patients with AAA were randomized to either standard care or exercise training including dynamic as well as isometric exercise (rowing). No difference in abdominal aortic growth rate was reported between the groups. Although AAA has a different aetiology than thoracic aortic aneurysms and should therefore be seen as a different disease entity, the findings of this study are promising. A randomized study, such as the one illustrated above for AAA patients, would provide important additional information about the effect of exercise in TAD patients.

Conclusion

Although several case reports have described aortic dissection occurring during exercise, no high quality studies have been performed to illuminate the association between exercise and acute aortic dissection. In athletes, aortic diameters are only slightly larger than in controls. Evenly, aortic diameter growth rate does not seem to be enhanced by exercise in BAV patients. In mice with MFS a positive effect of mild to moderate dynamic exercise on the thoracic aorta diameter was found. There clearly is a gap in knowledge about the effects of exercise and sports participation in TAD patients. Currently there is no unequivocal evidence to support discouragement of exercise and sports participation in TAD patients. Hence, mild to moderate regular exercise should be encouraged, for its known positive effects on overall health. However, based on theoretical knowledge, participation in heavy static exercise should likely be avoided in TAD patients.

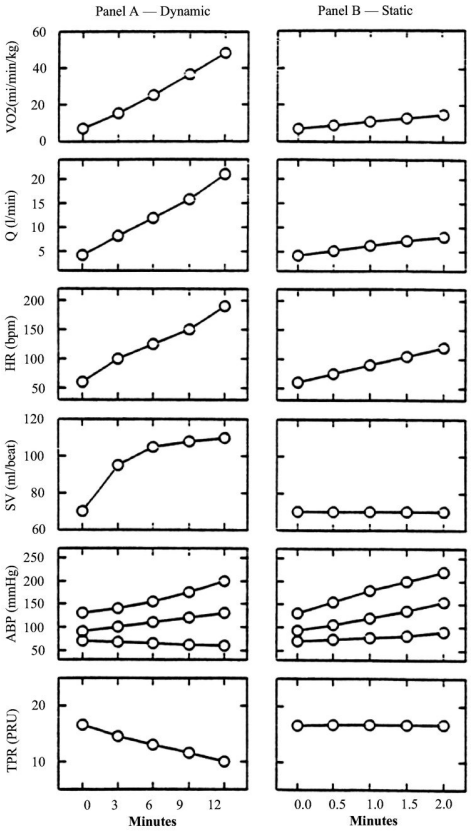


Figure 4. Hemodynamic response to exercise.
(A) Response to dynamic exercise of progressively increasing workload. This causes a volume overload as a result of increased cardiac output (Q) and arterial blood pressure (ABP), with a decrease in total peripheral resistance (TPR).
(B) Response to a static handgrip contraction. This causes a pressure overload as a result of increased blood pressure, but no decrease in total peripheral resistance.
ABP (mm Hg): systolic, mean and diastolic arterial blood pressures; HR: heart rate (beats/min); Q: cardiac output (liters/min); SV: stroke volume (ml/beat); TPR: total peripheral resistance (PRU); VO2: oxygen uptake (ml/min/kg).
Reprinted by permission from J.H. Mitchell and P.B. Raven, "Cardiovascular Adaptation to Physical Activity," in *Physical Activity, Fitness, and Health: International Proceedings and Consensus Statement*, edited by C. Bouchard, R.J. Shephard, and T. Stephens (Champaign, IL: Human Kinetics, 1994), 288.

Expert opinion

When a patient is diagnosed with TAD , discussing lifestyle modification is mandatory. Next to cessation of smoking, controlling hypertension and prevention of obesity, discussing exercise and sports participation is important. However, there is not enough evidence to strongly discourage exercise or recommend any particular type of exercise or sport. Theoretically, high blood pressure is unfavourable. Therefore, it is important to distinguish between dynamic (also isotonic) and static (also isometric) exercise [61], since both initiate a different hemodynamic response (illustrated in figure 4). On the other hand exercise and sports participation are also known to have many positive effects on cardiovascular and overall health. For the general population the Dutch and American health councils, as well as the World Health Organization recommend a target rate of 150 to 300 minutes per week of moderate to heavy intensity exercise[67-69], as participation in regular physical activity has shown to have many benefits.[67, 68].

Therefore, we believe it is mandatory to explain both the negative and positive effects of exercise to TAD patients. In order to create full understanding and ideally reach a shared decision, rather than imposing restrictions on sports participation. In order to prevent TAD patients becoming scared of physical activities and to minimize concerns, stress and anxiety further affecting TAD patient's quality of life, which was shown to be reduced compared to healthy controls[70].

Ideally future research would be (randomized) controlled trials longitudinally evaluating the effect of exercise on thoracic aortic aneurysm dilatation rate, the risk of thoracic aortic dissections, quality of life and survival of TAD patients. Secondly, the effect of different types and intensities of exercise on thoracic aortic growth rate acceleration needs to be evaluated. More research is especially needed in patients with Loeys-Dietz syndrome, aneurysm-osteoarthritis Syndrome (AOS e.g. SMAD3 mutation), vascular Ehlers-Danlos syndrome and Turner syndrome, on which we found no evidence at all.

Five-year view

In the upcoming five years we envision that more research will be carried out on the association between exercise and thoracic aortic growth and acute aortic dissection. Further exploring the potential beneficial effect of dynamic exercise on the aortic wall in humans is warranted. This knowledge will enable us to better understand and predict the risks of exercise and sports participation in TAD patients. This will hopefully enforce better counselling, with more detailed and well-founded advice to TAD patients.

Table 1. Aortic dimensions in trained individuals

					Study population			Outcome			
Ref. nr.	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Sex (% female)**	**Control group**	**Outcome measures**	**Prevalence aortic dilatation**	**Results**	**Conclusion**
17	Rubal	1981	Medicine and Science in Sports and Exercise	Cross-sectional cohort study	9	Female softball athletes	100	10 age-and body size-matched sedentary controls	Left ventricular parameters, aortic root diameter	Not reported	Mean aortic root diameter in athletes was 22 mm ±1 and 23 mm ±1 in controls.	There was no statistically significant difference in aortic root diameter between athletes and controls.
18	Wieling	1981	British Heart Journal	Longitudinal cohort study	23	Male oarsmen: seniors (n=14) and freshmen (n=9)	0	17 healthy age-matched controls	Left ventricular parameters, right ventricular diameter, aortic root diameter at end-diastole	Not reported	At the beginning of the season aortic root diameter was 31,3mm ±1,5 in senior oarsmen, 28,8mm ±2,0 in freshmen, and 29,9mm ±2,8 in control subjects.	At the beginning of the season aortic root diameter was greater in senior oarsmen than in freshmen, but did not differ from control subjects. No consistent increase was observed in aortic root diameter at the end of the season.
19	Crouse	1992	Research Quarterly for Exercise and Sport	Cross-sectional cohort study	15	Female basketball athletes	100	22 age-matched non-athletic controls	Left ventricular parameters and aortic root diameter	Not reported	Aortic root diameter was 25.7 mm ±3.3 in athletes and 21.7 mm ±2.4 in controls.	Aortic root diameter was significantly higher in athletes than in controls.
20	Pelliccia	1996	JAMA	Cross-sectional cohort study	600	Female athletes from Italian national teams	100	65 age-matched untrained females and 738 age-, ethnicity, sports discipline and training intensity matched elite male athletes	Left ventricular parameters, aortic root diameter	Not reported	The aortic root was 27.6 mm ±2.5 in athletes, 27.0 mm ±1.8 in controls, and 30.3 mm ±2.0 in male athletes.	The aortic root was significantly larger (2% larger) in athletes than in controls, and significantly larger in male athletes.
21	Whyte	1999	International Journal of Sports Medicine	Cross-sectional cohort study	29	Elite modern pentathletes (n=11) and triathletes (n=18)	0	13 sedentary controls	Left ventricular parameters, aortic annulus diameter	Not reported	Aortic annulus diameter was 28,8 mm ±5,1 in triathletes, 33,5 mm ±2,1 in pentathletes and 31,1 mm ±1,9 in controls.	There was no statistically significant difference in aortic annulus diameter between triathletes, pentathletes and controls. Whilst the large training volume elicits significant morphological adaptation in triathletes and modern pentathletes, all measures were within normal limits.

Table 1. Aortic dimensions in trained individuals (continued)

					Study population				Outcome		
Ref. nr.	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Sex (% female)**	**Control group**	**Outcome measures**	**Prevalence aortic dilatation**	**Results**	**Conclusion**
30	Kinoshita	2000	American heart Journal	Cross-sectional cohort study	1929	Athletes active in competitive sports	19	No control group	Aortic root diameter	Aortic root >40mm: 0,26-0,36% and 0,96% in basketbal and volleybal players	0,26-0,36% of athletes had aortic root dilatation >40 mm, 0,96% of basketbal en volleybal players had aortic root dilatation >40 mm.	A higher prevalence of aortic dilatation is to be anticipated among basketball and volleyball players, many of whom are very tall.
22	Dzudie	2006	European Journal of Echocardiography	Cross-sectional cohort study	21	Male handball players	0	21 age-, sex-, height- and weight-matched sedentary men	Left ventricular parameters and aortic root diameter	Not reported	Aortic root diameter was 29.6 mm ±3.6 in control subjects and 30.3 mm ±2.8 in handball players.	Aortic root diameter was slightly larger in control subjects than in handball players, but this difference was not significant.
23	Babaee Bigi	2007	American Journal of Cardiology	Cross-sectional cohort study	100	Male elite athletes	0	128 age- and height-matched healthy men	Aortic diameter, aortic regurgitation	Not reported	Aortic diameters were measured at Ann 25.1±2.9 in athletes and 21.8±2.4 in controls, SoV 38.2 ±4.1 in athetes and 31.6 ±3.2 in controls, STJ 34.1 ±2.8 and 29.5 ±3.1 in controls, AA 36.1 ±4.5 in athetes and 31.0 ±2.9 in controls.	Aortic root diameters in all segments of the aortic root were significantly greater in elite strength-trained athletes compared with an age- and height-matched population.
29	Pelliccia	2010	Circulation	Cross-sectional cohort study	2317	Highly trained athletes	44	No control group	Aortic diameter	Aortic root >40 mm: 1,3% of male athletes. Aortic root >34 mm: 0,9% of female athletes	Mean aortic root diameter was 32.2mm ±2.7 in male athletes with 99th percentile 40 mm, and 27.6 mm ±2.6 in female athletes with 99th percentile 34 mm.	Aortic root enlargement (40 mm in males and 34 mm in females) is particularly uncommon in highly trained athletes.
31	D'Andrea	2010	American Journal of Cardiology	Cross-sectional cohort study	615	Elite athletes: endurance-trained athletes (n=370) and strength-trained athletes (n=245)	33	No control group	Aortic diameter	Ascending aortic dilatation >95% CI of overall distribution: 1% of athletes	The mean aortic root diameter at the SoV was 31 mm (2.8–3.6) in endurance trained athletes and 36 mm (3.2–4.2) in strength trained athletes.	The aortic root diameters at all levels were significantly greater in strength trained athletes. Significant ascending aortic dilatation and aortic regurgitation proved to be uncommon in strength trained athletes.

Table 1. Aortic dimensions in trained individuals (continued)

					Study population				Outcome			
Ref. nr.	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Sex (% female)**	**Control group**	**Outcome measures**	**Prevalence aortic dilatation**	**Results**	**Conclusion**
24	Carlsson	2010	European Journal of applied physiology	Cross-sectional cohort study	10	Male endurance athletes	0	10 untrained men	Cardiac functional parameters, cardiac structural parameters (among which aortic root diameter)	Not reported	Aortic root diameter was 30.4 mm ± 3.2 in athletes and 28.4 mm ± 4.4 in controls.	Aortic root diameter was not significantly larger in athletes than in controls.
25	Caselli	2011	European Journal of Echocardiography	Cross-sectional cohort study	429	Athletes from Italian national teams	22	98 healthy controls	Left ventricular parameters and aortic root diameter	Not reported	Aortic root diameter was 31.0 mm±3.8 in athletes and 28.7 mm±3.3 in controls.	Aortic root diameter was significantly larger in athletes than in controls.
26	Krol	2011	Echocardiography	Cross-sectional cohort study	38	Members of the Polish Olympic team (rowing, cycling, speed-skating)	16	41 sex and age matched, healthy sedentary individuals	Left ventricular parameters, right ventricular parameters, aortic diameter (level of measurement not specified)	Not reported	Aortic diameters were 33 mm ±4 in het athletes and 29 mm ±2 in controls. After indexing for BSA the mean aortic size index for athletes was 1.6 cm/m2 ± 0.1 and 1.5 cm/m2 ± 0.2 for controls.	Aortic diameters were significantly larger in het athletes group than in controls. However after indexing for BSA there was no significant difference between the groups.
27	D'Andrea	2012	Journal of the American Society of Echocardiography	Cross-sectional cohort study	410	Elite athletes: endurance-trained athletes (n=220) and strength-trained athletes (n=190)	38	240 healthy controls	Aortic root diameter, aortic root distensibility and elasticity	Aortic root dilatation >95% CI of overall distribution: 1% of male power athletes	Aortic root diameter was 36 mm±5 in strength trained, 31 mm±6 in endurance trained athletes and 32 mm ±3 in controls.	Aortic root diameters and stiffness were significantly greater in strength trained athletes than in endurance trained athletes and controls. While aortic distensibility was higher in endurance trained athletes compared to controls.

Table 1. Aortic dimensions in trained individuals (continued)

					Study population				Outcome		
Ref. nr.	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Sex (% female)**	**Control group**	**Outcome measures**	**Prevalence aortic dilatation**	**Results**	**Conclusion**
28	Aparci	2013	Expirimental & Clinical Cardiology	Cross-sectional cohort study	60	Personnel Etimesgut Military Hospital: strenuous activity trainers (n=30) and ordinary activity trainers (n=30)	Unknown	No control group	Aortic diameters, left ventricular parameters, left atrial diameters	Subjects with abnormally enlarged aortic diameters (≥40 mm) were excluded	In the strenuous activity training group mean aortic diameters were: 35.6 mm (SoV) and 36.8 mm (AA), in the ordinary activity training group the mean aortic diameter was 33.5 mm (SoV) and 34.4 mm (AA).	Aortic root and ascending aortic diameter were significantly higher in the strenuous activity training group.
32	Davis	2015	Clinical Journal of Sport Medicine	Cross-sectional cohort study	70	Athletes from the US national volleyball team	47	No control group	Aortic diameter and Ghent criteria (signs of Marfan syndrome)	Aortic root diameter ≥40 mm: 8% of male athletes. Aortic root diameter ≥34mm: 6% of female athletes	34% of the athletes had at least 1 characteristic of MFS (Ghent criteria) but none had more than 2 characteristics.	Elite US volleyball players have a higher than expected prevalence of dilation of the aortic sinuses and ascending aorta. In the absence of MFS.

Ann; Aortic Annulus, SoV; Sinus of Valsalva, STJ; Sinotubular Junction, AA; Ascending Aorta

Table 2. Case reports and case series on acute aortic dissections during exercise

				Study population				Outcome					
Ref. nr.	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Age (years)**	**Sex**	**Stanford Classification**	**Max. aortic diameter**	**Type of sport**	**Aortopathy**	**Family history**	**Conclusion**
33	Bain	1987	The American Journal of Forensic Medicine and Pathology	Case-report	1	20	M	Type A	60 mm	Fitness	Marfan Syndrome	Positive for sudden death	This case demonstrates Marfan Syndrome presenting as sudden, unexpected death.
39	De Virgilio	1990	The Annals of Thoracic Surgery	Case series	4	22-57	M	Type A	Unknown	Weightlifting	Not suspected	Unknown	Individuals who have evidence of cystic medial disease or family histories of this disease should avoid weight lifting.
34	Schor	1993	Journal of Vascular Surgery	Case-report	1	18	M	Type B (periaortic hematoma)	Unknown	Weightlifting	Not suspected	Unknown	Weight lifting, with its profound cardiovascular effects, may be the major, if not sole cause of aortic dissection.
35	Baumgartner	1997	The Annals of Thoracic Surgery	Case-report	1	19	M	Type A	Unknown	Weightlifting	Marfan Syndrome	Unknown	Individuals with Marfan Syndrome, cystic medial disease or family histories of the disorder should be strongly urged to refrain from weight-lifting activities.
36	Elefteriades	2003	Journal of the American Mediucal Association	Case series	5	19-53	Unknown	Type A	40-52 mm	Weightlifting, push ups, heavy lifting	Not suspected	Positive for aortic disease in 1 patient	The risk of weight lifting as a cause of aortic dissection has generally been underappreciated.
40	Hogan	2005	Emergency Medicine Journal	Case-report	1	27	M	Type A	Unknown	Weightlifting	Non-Marfan's fibrillinopathy	Positive for aortic dissection	Aortic dissection should be considered in symptomatic patients with a family history of early cardiac deaths, suspect of a connective tissue disorder, or who practice weightlifting.
37	Hatzaras	2007	Cardiology	Case series	31	19-76	30 M, 1 F	Type A: 87% (n=27), Type: B 13% (n=4)	30-78 mm	Weightlifting or push-ups (n=16), heavy lifting (n=9), dynamic exercise like swimming or tennis or racquetball (n=5)	Unknown	Positive for aortic disease in 3 patients	Increased blood pressure due to heavy weight lifting raises aortic wall stress to a level that produces aortic dissection in individuals with pre-existing mild to moderate aortic enlargement.

Table 2. Case reports and case series on acute aortic dissections during exercise (continued)

				Study population				Outcome					
Ref. nr.	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Age (years)**	**Sex**	**Stanford Classification**	**Max. aortic diameter**	**Type of sport**	**Aortopathy**	**Family history**	**Conclusion**
38	Uchida	2009	Interactive CardioVascular and Thoracic Surgery	Case-report	1	12	M	Type B	Unknown	Swimming	Not suspected	Negative	Swimming coaches and pediatricians should recognize that swimming exercises like the butterfly stroke are a risk factor for aortic dissection in children.
42	Westaby	2011	Circulation	Case-report	1	28	M	Type B	Unknown	Soccer	Bicuspid aortic valve, aortic coarctation	Unknown	Aortopathy associated with a bicuspid aortic valve and coarctation may contribute to aneurysmal transformation and rupture.
43	Chattranukulchai	2013	British Medical Journal Case Reports	Case-report	1	38	M	Type A	52 mm	Bowling	Marfan Syndrome	Unknown	Early diagnosis of Marfan Syndrome is crucial as it has a positive influence on the outcome.
41	Ozyildirim	2015	The American Journal of Cardiology	Case-report	1	28	M	Type A	Unknown	Weightlifting	Unknown	Unknown	Weight lifting creates significant stress along the aortic wall and this produces predisposition to acute aortic dissection.
44	Cereda	2016	European Heart Journal	Case-report	1	25	F	Type A	100 mm	Volleybal	Marfan Syndrome	Unknown	Echocardiography has a potential role in preventing tragic sudden death in sport.

Table 3. Papers on sports related aortic dissections

Ref. nr.				Study population			Outcome				
	First author	Year	Journal	Study design	n (total)	Patient population	Sex (% female)	Definition	Missing (%)	Exercise related dissections (%)	Additional results
47	Schachner	2013	BioMed Research International	Retrospective cohort study	140, of which 77 (55%) during winter season	Patients with aortic dissection involving the ascending aorta during the winter season (from the beginning of November until the end of April).	21 (16/77)	Onset of symptoms during alpine skiing.	Not reported	22	In 14/17 (82%) patients symptoms occurred during recreational skiing without additional trauma. Only 1 patient (6%) had a skiing accident with consequent ascending aortic dissection.
46	Gansera	2015	The Thoracic and Cardiovascular Surgeon	Retrospective cohort study	365	Patients who underwent surgery for aortic dissection involving the ascending aorta.	32	Onset of symptoms occurred during physical exercises, such as sports or lifting of heavy weights.	24	68	Peri- or postcoital aortic dissection occurred in none of the females, but in 17 of 245 males. Mortality in females < 65 years was higher (20.2%), compared with their male counterparts (14.9%).
45	Itagaki	2017	Surgery Today	Retrospective cohort study	650	Patients who underwent surgery for aortic dissection involving the ascending aorta.	47 (323/615)	Onset of symptoms during a sports activity. Non-sports exertion, such as lifting or moving a heavy load, defecation, or sexual activity, were classified into the non-sports group.	5	4.1 (5% of all daytime type A dissections)	The sport most frequently associated with type A aortic dissections in this series was golf (n = 8; 32%), followed by swimming and cycling (each n = 4; 16%), then weight lifting (n = 3; 12%), dance (n = 2; 8%), and finally, long-distance running, fencing, table tennis, and archery, (each n = 1; 4%).

Table 4. Papers on exercise in patients with Marfan Syndrome and bicuspid aortic valve

					Study population					Outcome				
Ref. nr.	**Group**	**First author**	**Year**	**Journal**	**Study design**	**n (total)**	**Patient population**	**Genetic mutation**	**Sex (% female)**	**Control group**	**Outcome measures**	**Follow-up**	**Results**	**Conclusion**
51	BAV	Spataro	2008	International Journal of Sports Medicine	Longitudinal cohort study	81	Competitive athletes with BAV from Italian national teams divided into 2 groups: the low-risk group (n=51) and the high-risk group (n=30)	NA	10	No control group	Aortic regurgitation, aortic stenosis and left ventricular parameters, aortic root diameters.	13 ± 4.9 years (range 5–19 years)	Over the follow-up period, six of the initially low-risk athletes (7%) and all of the high-risk patients showed significant worsening of morphologic features of bicuspid aortic valve and/or incidence of symptoms. In high risk subjects the progression of valvular disease occurred independently from the former athletic activity.	Continued sport participation is not responsible itself of BAV worsening. However, long-term athletic training may be associated with progressive worsening of the valvular lesion and the appearance of clinical symptoms.
48	BAV	Stefani	2008	British Journal of Sports Medicine	Cross-sectional cohort study	58	Non-elite but competitive athletes with BAV	NA	0	75 non-elite but competitive athletes with TAV	Aortic regurgitation, aortic stenosis and aortic root diameters.	NA	Aortic root dimensions at all levels were significantly greater in athletes with BAV than in athletes with a normal TAV. No relation was found with age, body surface area, aortic regurgitation or years of training.	A short echocardiographic examination should be performed at least once during an athlete's sporting life.

Table 4. Papers on exercise in patients with Marfan Syndrome and bicuspid aortic valve (continued)

					Study population					Outcome				
Ref. nr.	Group	First author	Year	Journal	Study design	n (total)	Patient population	Genetic mutation	Sex (% female)	Control group	Outcome measures	Follow-up	Results	Conclusion
49	BAV	Galanti	2010	British Journal of Sports Medicine	Longitudinal cohort study	88	Athletes with BAV and mild aortic regurgitation	NA	Unknown	56 athletes with TAV	Left ventricle parameters and aortic diameters	5 years (30/88 subjects)	There was a progressive increase at each measured aortic level (Ann: 0.78 mm/year; SoV: 0.61 mm/year; STJ: 0.81 mm/year; AA: 0.98 mm/year). This increase became significant from the last 2 years of the 5-year follow up. In TAV athletes, there was no significant increase of aortic diameters (Ann 0.17 mm/year; SoV 0.12 mm/year; STJ 0.21 mm/year; AA: 0.32 mm/year)	In athletes with BAV, aortic dimensions increase significantly more than in TAV athletes, but do not differ from those in the general BAV population.
50	BAV	Stefani	2014	Cardiology Research and Practice	Longitudinal cohort study	292	Subjects with BAV who were evaluated at the Sports Medicine and Exercise Centre, divided into three different groups: athletes (n=210), sedentary (n=59), and ex-athletes (n=23)	NA	Unknown	No control group	BAV morphology classification, left ventricular parameters and aortic diameters	5 years	Typical BAV morphology was most frequent in all three groups (68% athletes, 67% sedentaries, and 63% ex-athletes). The aortic dimensions showed a progressive enlargement during follow-up, with no difference between athletes and sedentary subjects. There was a progressive increase at each measured aortic level (Ann: 0.78 mm/year; SoV: 0.61 mm/year; STJ: 0.81 mm/year; AA: 0.98 mm/year).	In BAV patients the ascending aorta is involved in normal progressive, not necessarily pathological, enlargement.

Table 4. Papers on exercise in patients with Marfan Syndrome and bicuspid aortic valve (continued)

					Study population					Outcome				
Ref. nr.	Group	First author	Year	Journal	Study design	n (total)	Patient population	Genetic mutation	Sex (% female)	Control group	Outcome measures	Follow-up	Results	Conclusion
54	MFS	Benninghoven	2017	Orphanet Journal of Rare Diseases	Longitudinal cohort study	19	Patients with MFS or similar syndrome in stable condition	Not specified	71	No control group	Adverse events, physical fitness and psychological assessment	1 year	No adverse medical events were reported. Physical fitness improved from admission to discharge. Psychological distress decreased. Admission to discharge effects mostly persisted through the one year follow-up but declined to smaller sizes.	The three week rehabilitation program improved physical fitness and psychological wellbeing. Medical assessments ruled out medical problems or adverse events caused by participation in the program.
52	MFS	Gibson*	2017	Journal of Applied Physiology	Non-randomised controlled trial (mouse-model study)	16	Male mice with MFS divided in a sedentary group (n=10), voluntary exercise group (n=3) and forced exercise group (n=3)	Fbn1C1039G/+	0	19 mice without MFS, divided in a sedentary group (n=4), voluntary exercise group (n=7) and forced exercise group (n=8)	Histological characteristics, isometric force, aortic wall elasticity and stiffness and combined benefit score for: elastin fiber length, elastin fragmentation, and elasticity	5 months	Both voluntary and forced exercise routines reduced aortic diameter, prevented aortic wall weakening, increased the breaking stress and improved aortic wall elasticity in MFS aorta. There is an optimum of protective effects at training intensity levels between 55% and 65% (of VO2max) which significantly reduces elastin fragmentation and disorganization within the aortic wall.	The present study provides helpful insights into the potential protective effects of a mild exercise routine in MFS patients in the absence of pharmacological interventions.

Table 4. Papers on exercise in patients with Marfan Syndrome and bicuspid aortic valve (continued)

					Study population					Outcome				
Ref. nr.	Group	First author	Year	Journal	Study design	n (total)	Patient population	Genetic mutation	Sex (% female)	Control group	Outcome measures	Follow-up	Results	Conclusion
53	MFS	Mas-Stachurska*	2017	Journal of the American Heart Association	Randomized controlled trial (mouse-model study)	19	Mice with MFS, randomized to a sedentary group n=9 and exercise group n=10	Fbn1C1039G/+	47	21 mice without MFS, randomized to a sedentary group n=11 and exercise group n=10	Left ventricular parameters, aortic root diameter, aortic pulsatility, aortic stiffness and histological characteristics of aortic wall tissue	5 months	In MFS mice subjected to exercise aortic root diameter was smaller than in their sedentary littermates and aortic dilatation rate was blunted, becoming comparable to the controls. Exercise training improved aortic stiffness in controls but not in MFS mice, but did not increase lamina ruptures in MFS mice, indicating no additional structural damage in the tunica media.	Moderate dynamic exercise prevented aortic root dilation and mitigates cardiac hypertrophy.

* Mouse-model study

MFS; Marfan Syndrome, BAV; Bicuspid Aortic Valve, TAV; Tricuspid Aortic Valve, Ann; Aortic Annulus, SoV; Sinus of Valsalva, STJ; Sinotubular Junction, AA; Ascending Aorta

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Supplemental material

Search date: August 2, 2018

Embase

'thoracic aorta aneurysm'/de **OR** 'Loeys Dietz syndrome'/de **OR** 'Ehlers Danlos syndrome'/de **OR** 'Turner syndrome'/de **OR** 'Marfan syndrome'/de ***OR*** 'bicuspid aortic valve'/de **OR** 'aneurysm osteoarthritis syndrome'/de **OR** 'Smad3 protein'/de **OR** 'smad3 gene'/de **OR** 'thoracic aortic dissection'/de **OR** 'thoracic aortic aneurysm and dissection'/de **OR** (((thoracic OR thorax) NEAR/3 (aortic OR aorta) NEAR/3 (aneurysm* OR dilatation* OR dissect*)) OR 'Loeys Dietz' OR 'Ehlers Danlos' OR Turner OR Marfan OR ((bicuspid) NEAR/3 (aort*) NEAR/3 (valve)) OR 'aneurysm osteoarthritis syndrome' OR 'Smad3'):ab,ti

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Medline

Aortic Aneurysm, Thoracic/ **OR** Loeys-Dietz Syndrome/ **OR** Ehlers-Danlos Syndrome/ **OR** Turner Syndrome/ **OR** Marfan Syndrome/ **OR** (bicuspid aortic valve).nm. **OR** Smad3 Protein/ **OR** (((thoracic OR thorax) ADJ3 (aortic OR aorta) ADJ3 (aneurysm* OR dilatation* OR dissect*)) OR Loeys Dietz OR Ehlers Danlos OR Turner OR Marfan OR ((bicuspid) ADJ3 (aort*) ADJ3 (valve)) OR aneurysm osteoarthritis syndrome OR Smad3).ab,ti.**)**

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Web of Science

((((thoracic OR thorax) NEAR/2 (aortic OR aorta) NEAR/2 (aneurysm* OR dilatation* OR dissect*)) **OR** "Loeys Dietz" **OR** "Ehlers Danlos" **OR** Turner **OR** Marfan **OR** ((bicuspid) NEAR/2 (aort*) NEAR/2 (valve)) **OR** "aneurysm osteoarthritis syndrome" **OR** "Smad3"**)**

AND

sport* **OR** exerci* **OR** athlet* **OR** training

Google Scholar (200 top relevant)

"thoracic aortic aneurysm|dilatation|dissection"|"Loeys Dietz"|"Ehlers Danlos"|"Turner syndrome"|Marfan|"bicuspid aortic valve"|"aneurysm osteoarthritis syndrome"|Smad3 sport|sports|exercise|athletics|athletes|training

Epilogue

Epilogue

Summary and general discussion
Dutch summary (Nederlandse samenvatting)
List of publications
PhD portfolio
About the author
Acknowledgements (dankwoord)



Summary and general discussion

Summary

A thoracic aortic aneurysm is often not recognized because of its silent presentation. It is associated with an increased risk of aortic dissection with high mortality and morbidity rates, and therefore early diagnosis of a thoracic aortic aneurysm is important. Recently, more insight into the genetic inheritance was gained. In 20% of patients with a thoracic aortic aneurysm, one or more first-generation relatives have an aortic aneurysm. As a result, screening of thoracic aortic disease in family members is performed more often and an aneurysm of the aorta is more frequently diagnosed. Additionally, the increasing use of advanced imaging techniques, permitted by major technical developments, enables us to diagnose an aortic aneurysm early. Currently imaging is very important in the diagnosis and therapeutic decisions in people with an aortic aneurysm. However, also new diagnostic modalities, such as blood and imaging biomarkers, are necessary to more accurately identify aortic pathology in patients at risk for aortic dissection. Therefore, this thesis focuses on the epidemiology, optimal diagnostic methods and outcome of thoracic aortic disease and studies its impact on living a normal life.

Part 1 - Imaging of the thoracic aorta

In part one we looked at the variability of the aortic measurements on different modalities and the utility of these modalities used for aortic measurements: echocardiography, computed tomography (CT) and magnetic resonance imaging (MRI). In **chapter 1** we determined the agreement between modalities and techniques to measure the aortic diameter in 100 patients with bicuspid aortic valve (BAV) and/or Turner syndrome. Measurement techniques differ in timing during the cardiac cycle and whether the aortic wall is included or excluded in the measurements. We concluded that the variability of techniques and modalities can cause large differences in diameter in one patient of up to 11mm for the sinus of Valsalva and sinotubular junction and up to 18 mm for the ascending aorta. Therefore, it is mandatory to use the same protocol each time the aorta is measured in a patient. We suggest using the leading edge-to-leading edge method, because this is most comparable between echo and CT or MRI and to measure during systole, since the aorta is better visualized on echocardiography and the largest diameter is measured. No large variation was found between the "cusp-to-cusp"and the "cusp-to commissure" method. Based on large differences found between modalities, CTA or MRI should be performed at least once in addition to 2DE for optimal imaging of the entire aorta and to check the reliability of echocardiography in a patient. This is confirmed by the study performed in **chapter 2.** In a cohort of 349 patient at risk for thoracic aortic disease, visiting our aortic pathology outpatient clinic, we identified the value of transthoracic echocardiography (TTE) in comparison with computed tomography (CT) to detect aortic dilation. It was found that echo underestimates the diameter compared to CT, which may cause false negative results. Sensitivity of TTE for detecting aortic dilation was 61%

(sinus of Valsalva) and 57% (ascending aorta) and specificity was 96% (sinus of Valsalva) and 100% (ascending aorta). In addition, we investigated which additional abnormalities of the heart, aorta or smaller arteries were discovered. With echocardiography, valve abnormalities including BAV (5%), ventricular hypertrophy (1%), and ventricular dilation (1%) were relatively rare. Arterial abnormalities described on CT by radiologists were found in 15% of the patients visiting for aortic screening, which increases the diagnostic value of CT as an imaging tool.

Since echocardiography is sonographer dependant, this could result in inter-observer variability in aortic measurements. Therefore, we investigated in **chapter 3** the measurement variability due to both the aortic image acquisition and the aortic measurement. In each patient, the image acquisition and subsequent aortic measurement were both performed twice by one sonographer and once by a second sonographer. We found that the aortic diameter measurements differ on average from 0.7 to 1.3 mm between images acquired by the same sonographer and from 1.6 to 1.9 mm between images acquired by different sonographers. One of our major findings was that echocardiographic measurements of aortic diameters show more variation between two observers in larger aortas. As a result, we prefer to use CT and MRI in patients with aortic diameters approaching the threshold for preventive aortic surgery because in general the inter-observer variability for CT and CMR (presented in chapter 1) is slightly lower than for echocardiography. Also we provide several reasons for the large (>5 mm) intra-observer and inter-observer differences between measurements, namely incorrect measurements due to annular calcification, drop-out artefacts, side lobe artefact, differences in frame rate or different cross-sectional cutting planes through the aorta. When a large difference is found between two follow-up echocardiographic aortic measurements in one patient, the physician is advised to re-evaluate the measurements on the first image to see if there are explanations for this large difference.

Another challenge of aortic measurements is that it is very time consuming, because the measurements need to be performed at multiple levels and perpendicular to the vessel. Therefore, an automatic method to measure the aorta, which is presented and validated in **chapter 4** for non-ECG-gated, non-contrast CT scans, is valuable for both clinical practice and study purposes. We showed that our automatic method had a high agreement with manual segmentations and we further used it to measure aortic growth in a large cohort, presented in another chapter (chapter 7).

Part II – The thoracic aorta in the general population

To assess the prevalence of aortic dilatation or fast aortic growth, it is necessary to have information on the "normal" aorta in the general population. In a large population-based study, the Rotterdam Study, we measured the aorta at the level of the ascending and descending aorta. Our cohort of the Rotterdam Study consist of approximately 2500 participants aged 55 years or older, which means that we specifically focused on the older

population. In **chapter 5**, we provided sex-specific distributions of thoracic aortic diameter and diameters adjusted for body surface area (BSA). We found that sex was independently associated with descending aortic diameters, which indicates that distribution values should be provided for men and women separately, even when correcting for BSA. Higher diastolic, and not systolic, blood pressure was associated with larger aortic diameters, while systolic blood pressure currently receives the most attention of physicians. We also found a high prevalence (12.1%) of ascending aortic diameters larger than 40 mm in our elderly population, which is often considered as dilated. Only 4 (1.3%) patients with a diameter larger than 40 mm died as a results of an aortic event. This number seems rather low, and raises the question whether a cut-off of 40 mm is an appropriate one. Yet, given the low number of events, this should be confirmed by larger studies. In addition, we used the follow-up data of the Rotterdam Study in **chapter 6** to evaluate the independent association between absolute and adjusted ascending and descending aortic (AA and DA) diameters with major cardiovascular outcomes among women and men and to provide optimal cutoff values associated with increased cardiovascular risk. The sex differences were more pronounced for the descending aorta, as this diameter was strongly associated with stroke, heart failure and cardiovascular mortality in women. For both sexes, the risk for several cardiovascular outcomes increased significantly at higher ascending aortic diameters. We concluded that a larger thoracic aortic diameter could be a marker for an increased overall cardiovascular risk, in addition to being known as a risk factor for aortic dissection.

Besides the thoracic aortic diameter, we also looked at thoracic aortic growth in a subgroup of the general population, namely smokers. Since smoking is known to be associated with increased descending aortic diameters and abdominal aortic growth, we investigated whether smokers also show larger thoracic aortic growth rates. In **chapter 7** we measured the ascending and descending aortic growth rates in almost 2000 current or former smokers of the Danish lung Cancer Screening Trial. We found a growth rate of approximate 0.1 mm/year, which is comparable to the data available in cross-sectional studies of the general population showing a thoracic aortic growth ranging from 0.08 to 0.17 mm/years. In addition, thoracic aortic growth was comparable between current and ex-smokers and aortic growth was not associated with pack-years. In conclusion, smokers do not show larger aortic growth rates compared to the general population. Since only cross-sectional data was available on thoracic aortic growth in the general population, we were the first to present longitudinal data with 95th percentiles of aortic growth in a subgroup (smokers) of the general population which was found to be 0.42-0.47 mm/year.

Part III – The thoracic aorta in specific diseases

In part III of this thesis we have looked in more detail at the following specific diseases associated with thoracic aortic pathology: bicuspid aortic valve, Turner syndrome and aneurysm-osteoarthritis syndrome.

In patients with BAV, we determined the annulus dimension changes during the cardiac cycle, presented in **chapter 8**. We concluded that the aortic annulus of BAV patients undergoes significant changes in shape during the cardiac cycle with a wider area in systole and a more elliptic conformation in diastole. Therefore, it is recommended that measurements of the annulus before transcatheter aortic valve implantation (TAVI) are performed in early systole to avoid underestimation of the annulus dimensions. In **chapter 9** we investigated four potential biomarkers for disease progression in patients with BAV. We found that NT-proBNP is associated with more severe aortic valve stenosis and regurgitation and hsTnT is associated with more severe aortic valve regurgitation. With this study we identified biomarkers associated with disease progression, which is the first step towards the development of a biomarker that can be used in prognostic staging and risk prediction.

In Turner women, information about the relation between aortic diameters and clinical outcome was scarce. Therefore, we evaluated the prevalence of aortic dilatation, the growth rate of the aorta and the risk of aortic complications in adults with Turner syndrome. This is described in **chapter 10**. We showed that aortic dilatation was present in 22% of the patients and the aortic growth was on average 0.20 mm/year, which is limited but slightly larger than the general population. Although aortic pathology is common in Turner patients, we found that aortic dissection and preventive aortic surgery only occurred in 2% during a follow-up of 7 years. Nevertheless, it is still more prevalent than in the general population and new tools, such as aortic elasticity measurements, to identify patients at risk would be helpful. Therefore, we further investigated aortic elasticity in 52 Turner patients measured by pulse wave velocity (PWV) on echocardiography and MRI and aortic distensibility on MRI. In **chapter 11**, we concluded that the aortic elasticity of the aortic arch was reduced in patients with Turner compared to healthy controls independently of the presence of aortic dilatation, BAV or aortic coarctation. Histopathological data of 5 patients who went for preventive surgery due to aortic dilatation showed changes in the ascending aortic wall. We found compact smooth muscle cell layers and a decrease in the intralamellar space, with granular deposition of elastin and diminished or absent expression of contractile proteins, which might be specific changes in the aortic wall of patients with Turner syndrome.

Besides Turner syndrome, we also looked at long-term outcome in 28 patients with aneurysm-osteoarthiritis syndrome (AOS) in **chapter 12**. The fastest aortic growth rate (0.4 mm/y) was observed at the level of the sino-tubular junction. In 64% (18 of 28) of the patients at least 1 cardiovascular intervention was performed. However, no death was observed during follow-up, probably due to the intensive management and preventive surgery at relatively mild dilatation of the aorta. With this study, we provided evidence that SMAD3 mutations cause an aggressive form of aortic or arterial dilatation, warranting vigilant follow-up and that this follow-up seems helpful in preventing complications. This risk of life-threatening dilatation and dissection of the aorta or arteries, together

with physical symptoms and experiences of family members with frightening events, can cause reduced quality of life, anxiety and depression. In **chapter 13**, we therefore describe this subjective quality of life and investigated the presence of anxiety and depression in 28 AOS patients. As expected, AOS patients reported reduced quality of life in comparison with the general population on several domains of the SF-36 questionnaire. In addition, patients with AOS scored significantly higher on the depression scale. Also, we found that patients' worries for their future and heredity of their disease are important factors for anxiety, which should be addressed in clinical practice.

Part IV - Aortic disease with regard to sport and pregnancy

Two situations that are very important in patients with aortic pathology are pregnancy and exercise. Both conditions are known to cause increased pressure on the aortic wall and therefore might be dangerous in these patients. In **chapter 14**, we reviewed the current literature on pregnancy in patients with aortic disease. Besides hemodynamic changes during pregnancy, hormonal and thromboembolic changes are also described. The key management of women with aortic dilatation, contemplating pregnancy, consists of pre-pregnancy counseling after imaging of the entire aorta and preventive treatment when indicated. Regarding the fact that not much is known about aortic interventions in pregnant women, only centers with experienced teams and expertise in pregnancy and heart disease should guide these high-risk women and should carry out surgical and catheter-based procedures when needed. **Chapter 15** provides an up-to-date systematic review of the available literature on risks and benefits of exercise and sports participation in thoracic aortic disease patients. It seems that the larger aortic diameter in athletes is primarily caused by the larger body size. The anxiety for aortic dissection during sports is mainly based on case reports and the high mortality rates of aortic dissection in general. However, there is no longitudinal data about the risk of aortic dissection due to exercise in patients with aortic dilatation. In conclusion, there is currently no unequivocal evidence to support discouragement of exercise and sports participation in patients with thoracic aortic disease. Hence, mild to moderate regular exercise should be encouraged, for its known positive effects on overall health. However, based on the theoretical physiological impact of heavy static exercise on the aorta and a lack of data supporting that this kind of exercise is safe in patients with aortic dilatation, participation in heavy static exercise should likely be avoided in TAD patients.

General discussion and future directions

How to measure the thoracic aorta?

Various techniques are used to measure the aorta, but it is mandatory to use the same protocol each time the aorta is measured in a patient. Based on this thesis, we suggest to use the leading edge-to-leading edge method, because this is most comparable between echo and CT or MRI. Also we suggest to measure during systole, since the aorta is better visualized on echocardiography and the largest diameter is measured. Our advice to measure during systole is contrary to the guidelines[1, 2], which advice to measure during diastole. The reasons they mention to measure the aorta during diastole are (1) the more stable aortic pressure in late diastole which increase reproducibility and (2) the ease of identification of end-diastole by the onset of the QRS complex. However, the argument about greater reproducibility has never been supported by evidence and the moment of systole can be easily identified as well. Future research should investigate the influence of varying aortic pressures on aortic diameter measurements during systole. Also more reference values of aortic diameters during systole are needed, because most studies report thoracic aortic diameter measurements during diastole.

Another important question when measuring the aorta is whether we should correct for factors, which are found to be associated with the aortic diameter. In adults, aortic dimensions are strongly positively correlated with age and body size[3-5]. Since taller or heavier people show larger aortic diameters[6], it is important to take height and weight into account when assessing aortic diameters. One way to adjust for height and weight is by using the aortic size index (ASI), which is the aortic diameter divided by the body surface area. One study showed that correcting for height alone is at least as good as correcting for body surface area in predicting the risks of rupture, dissection, and death in patients with thoracic ascending aortic aneurysms[7]. This might be a more reliable way of correcting for body structure, since the more unstable value of weight is not taken into account here. The Z-score (the number of SDs above or below the predicted mean normal diameter) is another useful way to quantify aortic dilatation. Among a population, 95.8% have Z-scores between −2 and 2. Therefore, an aortic diameter can be considered dilated when the Z-score is ≥2. Using the Z score allows comparison of a certain patient's aortic size with the mean in a specific population, taken into account several factors. The possibility to account for more factors, such as age, gender or ethnicity, is an advantage of the Z-score[8]. The Z score is particularly useful for evaluating growing children[9], which show rapid changes in physical development. In my opinion, both Z-scores and ASI can be used in clinical practice of adult patients, but the most important thing is that we all use the same method and the same cut-off values.

Which modality should be used to measure the aorta?

Which imaging modality should be used, is dependent on the situation. As discussed above, CT or MRI imaging should be performed in each patient at risk for aortic pathology. Nevertheless, the role of echocardiography should not be underestimated. Our studies focused on patients who specifically visit the outpatient clinic to screen for aortic pathology and since they are already at risk, they should receive CT or MRI to measure the aorta most accurately. However, echocardiography is probably safe to use for follow-up in cases of mild or no aortic dilatation (<45 mm) when echocardiography is able to visualize the aortic root and ascending aorta sufficiently. Also in developing countries, where CT and MRI might not be available, echocardiography is a very good alternative. In addition, echocardiography is important to investigate if aortic dilatation of the sinus of Valsalva causes aortic valve regurgitation[10]. Moreover, when screening for aortic pathology in the general population, echocardiography will be a preferred technique because of its greater availability and lower cost. Echocardiography costs around 120 euros in the Netherlands followed by 180 euros for CT and 380 euros for MRI. In my opinion, these different modalities give us the opportunity to use less expensive echocardiography when possible and to use more advanced and accurate imaging modalities when necessary. Based on this thesis and the current guidelines, an advice is presented in Figure 1 on when to use which imaging modality and how to measure the aorta on each imaging modality. The use of the cusp-to-cusp method for the sinus of Valsalva on CT and MRI is based on the guideline from Goldstein[2]. The experience of each hospital with certain imaging techniques must also be taken into consideration. In conclusion, we need to face the difficulties of multimodality and see it as an opportunity.



Echocardiography
Indications
- Screening healthy population
- Follow-up of mild or no aortic dilatation (<45 mm) in which echocardiography is able to visualize the aortic root and ascending aorta sufficiently
- First choice for assessment of aortic regurgitation in case of dilatation at the Sinus of Valsalva

Measurements
- Parasternal long axis view
- Leading edge-to-leading edge method
- During systole



Computed tomography
Indications
- Screening patients at risk
- Screening for patients with a risk of intra-cardiac or peripheral vascular pathology (connective tissue syndromes, for example Aneurysm-Osteoarthritis syndrome)
- Follow-up for moderate or severe dilatation of the aortic root or ascending aorta (with attention for repetitive radiation)
- Follow-up of aneurysm located in the distal portion of the ascending aorta, aortic arch, or descending thoracic aorta (with attention for repetitive radiation)
- Follow-up of patients with contra-indication for MRI imaging, for example claustrofobia

Measurements
- Double-oblique measurements
- Inner edge-to-inner edge in contrast CT scans and outer edge-to-outer edge in non-contrast CT scans
- During systole
- Sinus of Valsalva: sinus-to-sinus method



Magnetic resonance imaging
Indications
- Screening patients at risk
- Follow-up for moderate or severe dilatation of the aortic root or ascending aorta
- Follow-up of aneurysm located in the distal portion of the ascending aorta, aortic arch, or descending thoracic aorta

Measurements
- Double-oblique measurements
- Inner edge-to-inner edge in contrast MRI scans or when possible and otherwise outer edge-to-outer edge
- During systole
- Sinus of Valsalva: sinus-to-sinus method

Figure 1. Indications and measurement recommendations for thoracic aortic measurements on different imaging modalities.

When to screen for aortic dilatation?

With the increased use of imaging modalities, screening for thoracic aortic disease becomes more attractive. Screening can be offered to (1) people in the general population, (2) family members of patients with thoracic aortic disease, (3) patients who visit the hospital for diseases related to thoracic aortic disease or (4) patients who undergo imaging of the thorax for other reasons while information about the aorta is available.

First, screening of the thoracic aortic in the general population has not been investigated yet. The introduction of an ultrasound screening program for abdominal aortic aneurysms (AAA) has been proven to reduce AAA related mortality in men aged 65-74 years[11]. Also it has been proven to be cost-effective[12], but the same screening program was unlikely to be cost-effective in women[13]. The most important difference between abdomen and thorax is that abdominal aortic disease can be visualized relatively easy with echocardiography, while echocardiography is less feasible for thoracic aortic aneurysms, especially higher in the ascending aorta or in the arch, warranting additional expensive imaging such as CT or MR. Therefore, it will be more difficult to reach cost-effectiveness in TAA screening. When TAA screening will be investigated in the future, attention should be paid to sex differences in aortic diameters and risk for aortic dissection. In current literature, cut-off values are presented for men and women together[14], while we showed along with others[3, 5] that the normal thoracic aortic diameter in men is different from women and that the thoracic diameter is also accompanied by a different risk for cardiovascular diseases between sexes. These differences may result in different cut-off values for men and women when taking the decision to perform further diagnostics in screening programs carried out in the general population.

Secondly, family members of patients with thoracic aortic disease may be a relevant group for screening purposes, since 20% of patients with thoracic aortic aneurysm show 1 or more first-generation relatives with an aortic aneurysm[15]. A recent systematic review[16], published in 2018, concluded that first- and second-degree relatives of patients affected by both familial and sporadic non-syndromic thoracic aortic disease may benefit from personalized screening programs. They found no information about the cost-effectiveness of screening program in relatives of patients with non-syndromic thoracic aortic aneurysm, which needs further research.

Thirdly, patients can be screened for related diseases when they visit the physician. We know, for example, that approximately 20 percent of the patients with thoracic aortic aneurysms also have an abdominal aortic aneurysm (AAA)[17], which was more positively associated with arch and descending thoracic aortic aneurysms, probably because of their common pathophysiology[18]. A previous study showed that screening for abdominal aortic aneurysms can be performed accurately and within 5 additional minutes by a cardiologist already performing a transthoracic echocardiogram[19]. The other way around, it has been shown that 28% of the patients with AAA show also TAA, most often located at the descending aorta[20]. Therefore, it might be beneficial to screen patients with AAA

for TAA, although CT or MRI is necessary to accurately visualize the thoracic aorta. In our center, CT imaging is often performed in patients with AAA and the thorax is also scanned to exclude thoracic artic pathology.

Lastly, in patients receiving CT or MRI imaging we are able to look at other organs and structures than the primary organ for which the scan is made. However, it is important that these additional measurements do not take too much extra time. Currently, imaging modalities are increasingly used in different specialisms and this results in more organs or structures being visualized. For the physician it is almost impossible to accurately look at all the structures and perform all measurements which could be done on the images. Therefore, the development of automated programs will be extremely useful. New developments, such as machine learning and artificial intelligence, will make it possible to have more measurements carried out by the computer in the future. The automated methods developed by us and others[21] for aortic measurements, are already further improving machine learning in the case of aortic measurements on CT. Also other structures such as lung noduli or brains, when able to segment automatically, might be part of a large screening protocol of an imaging modality. Some people predict that the work of the radiologist will become unnecessary, but in my opinion this will not be the case. We will always need people to interpret and check the results and put the findings in patient's perspective[22]. These automatic measurements performed by computers will however reduce the amount of time performed on relatively simple measurements, enabling physicians to focus on the more important work, for example, interpretation of these new techniques. One major challenge is to find a way to deal with the large amount of information which will become available with artificial intelligence. Eventually, not only patients will benefit directly from the early detection of a disease or risk factor, but large data sets of measurements will help to extend research and will enable more individual patient care in the future.

How does the aorta behave in time?

When patients are diagnosed with a thoracic aortic aneurysm, a disease associated with thoracic aortic disease or familial thoracic aortic aneurysm and dissection (FTAAD), the guidelines advise that follow-up strategies should be individualized from annually to every 2 to 3 years. This depends on the abnormalities present, history of complications among family members, the present size, and the degree of change in size over time[2]. In patients with more aggressive connective tissue diseases, such as Marfan syndrome[23], Loeys-Dietz syndrome[24] and aneurysm-osteoarthritis syndrome[25], annual follow-up is indicated. However, aortic growth in aortic diseases or in the general population seems to be limited (Table 1). At the aortic root mean growth rates 0.09-0.49 mm/year are reported with the largest growth in Marfan patients. The ascending aorta grows on average 0.11-0.42 mm/year with the largest growth in patients with a bicuspid aortic valve and information about descending aortic growth is scarce in patients with thoracic aortic pathology.

According to these results, patients with small aorta's (<40 mm) during screening, are not likely to develop a large aorta in the near future. Case reports about rapid aortic growth in a short period of time are scarce[26, 27] and they are a result of specific causes such as aortitis or systemic lupus erythematosus. Also giant asymptomatic thoracic aortic aneurysm of more than 10 cm are scarce[28]. Therefore, follow-up visits can be planned with longer periods in between for patients at risk for thoracic aortic disease who have small aorta's or who have had stable diameters for at least two years. By planning a new follow-up visit after 3-5 years, we can reduce medical costs, but probably also the patient's psychological burden by the reduction of anxiety present with each visit. However, the patient's wishes should also be taken into account since patients can also be sent away for years but still live in fear because of the uncertainties. Although we found no clear sex-differences of thoracic aortic growth in the smoking population, a more recent study which included all types of TAA showed that women had a two-fold higher annual growth of thoracic aortic aneurysms than men[29]. This highlights that sex-differences in thoracic aortic disease needs further research.

Are we chasing the right target?

As shown earlier, the aortic diameter is the key measurement in the management and diagnosis of thoracic aortic diseases. The aortic diameter together with the presence of specific diseases causing aortic pathology, such as Marfan syndrome or BAV, are now used in guidelines[30,31] to decide which patients benefit from preventive aortic surgery. Also fast growth of the aortic diameter is mentioned as risk factor for aortic dissection, but this is predominantly investigated in abdominal aortic aneurysm and is still a topic of discussion[32]. However, the International Registry of Acute Aortic Dissection (IRAD) showed that the majority of patients with acute type A acute aortic dissection do not fall within current guidelines for elective aneurysm surgery[33]. Although patients with larger aortic diameters are at higher risk of developing aortic dissection[34], we can conclude that the aortic diameter itself does not give us enough information on the risk of aortic dissection. Future research should focus on other markers adding additional information to improve diagnostics and prognostics (Figure 2). For example, aortic stiffness or wall shear-stress might improve risk prediction of aortic complications. We showed that aortic stiffness of the aortic arch is increased in patient with Turner syndrome compared to healthy controls, while others have proved increased stiffness in patients with BAV, Marfan syndrome or an isolated familial thoracic aneurysm[35, 36]. In addition, aortic stiffness measured on MRI has been shown to be an independent predictor of progressive aortic dilatation in Marfan patients[37] and patients with dilatation of the ascending aorta[38]. However, the predictive value of aortic stiffness on aortic dissection has not yet been investigated. Several blood biomarkers are also currently gaining more attention as possible risk predictors. To understand the cellular and molecular mechanisms driving the pathogenesis in aortic dilation, research over the last decades has mainly focused on smooth muscle cells and

the role of biochemical signals to steer their differentiation and extracellular matrix modulation within the middle layer of the aorta[39]. One upstream signaling protein known to play an important is transforming growth factor ß (TGF-ß). However, paradoxical discoveries have implicated both enhanced TGF-signaling and loss of function TGF-receptor mutations in aneurysm formation[40], which highlights the complexities of TGF-signaling and biomarker assessment in general. The possible role of the endothelium in aortic dilation has also been investigated more recently. For example, the endothelial cells show altered endothelial-to-mesenchymal transition, migration and endothelial dysfunction in the ascending aorta of BAV patients[41]. Besides proteins in the blood stream, other potential biomarkers are microRNAs, which are small RNA molecules, approximately 22 nucleotides long which control the expression of the genes[42]. MicroRNAs can be detected in blood or urine samples and they are stable, which are important properties for biomarkers. With fast-progressing techniques, we are also able to unravel the total human genome, which will help us to identify people at risk for aortic pathology based on their genetic information. Although a lot of studies have focused on patients' blood levels of blood biomarkers[43] compared to healthy controls, studies assessing the prognostic value of biomarkers in patients with aortic disease are limited. Only the prognostic value of TGF-ß levels in Marfan patients[44] and C-reactive protein levels in patients with acute aortic dissection[45] has been investigated. In addition to the diagnostic or prognostic potential of blood biomarkers for aortic diseases, research into biomarkers is also important to help identify therapeutic targets that are currently unavailable for patients with aortic dilatation. In conclusion, with the patient characteristics currently used in guidelines (presence of specific aortic disease and large aortic diameter or fast growth) we are not yet capable to predict accurately which patients are at risk for aortic dissection. Further research is needed to identify new biomarkers, as discussed above, which can provide additional prognostic information. However, it should be acknowledged that by using current guidelines with intensive management and preventive surgery at larger aortic diameters, the long-term outcomes of specific aortic diseases have improved. This is well demonstrated by the studies with Turner patients and AOS patients in this thesis.

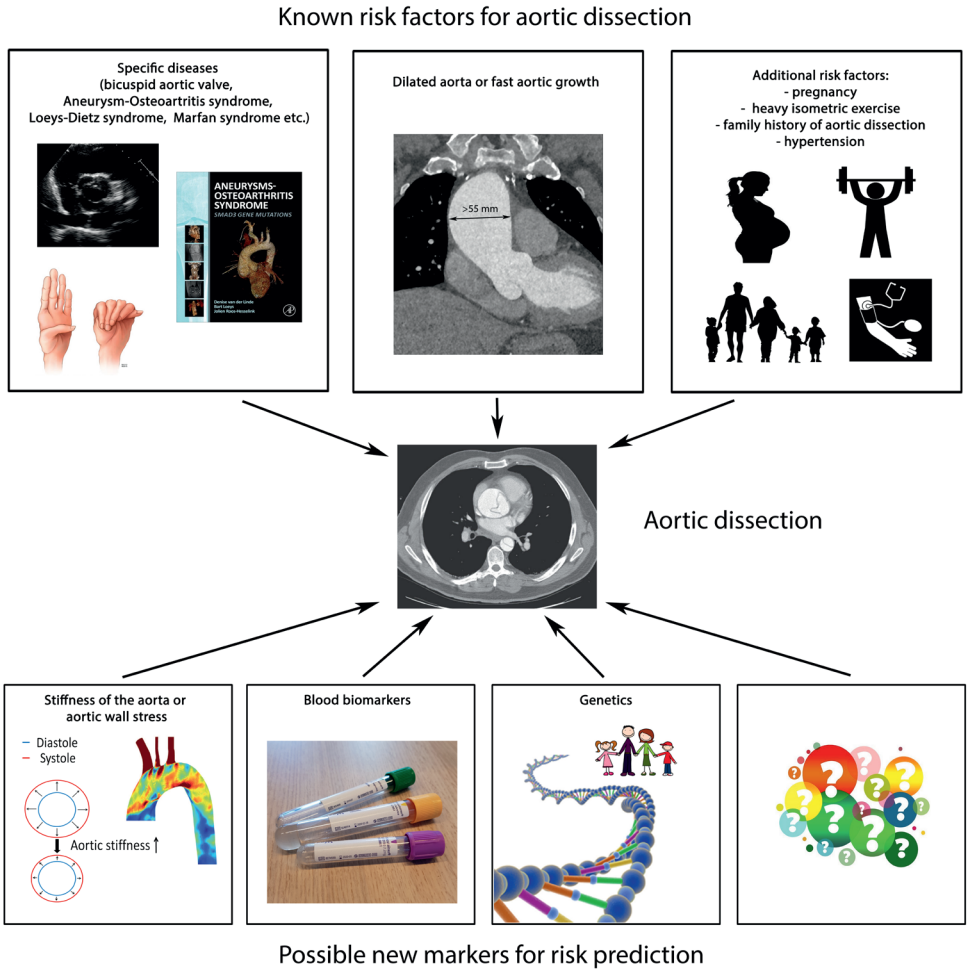


Figure 2. Imaging and biochemical biomarkers known or possibly useful in predicting patients at risk for aortic dissection or rupture.

What is the impact of aortic disease on the quality of life?

Since aortic dilatation is rarely accompanied by symptoms, patients are not able to monitor their own health as for example, patients with heart failure. This can be an enormous psychological burden, because the patient is not aware of the changes in their own health. A follow-up visit to measure their aortic diameter is very important to monitor disease progression. For that reason, patients are often very anxious when sitting in front of a physician. This is confirmed by studies showing lower scores on the SF-36 mental subdomain in patients with Marfan syndrome[46, 47] and psychosocial distress and coping difficulties in patients with genetic aortic diseases[48]. Quality of life also appears

to be decreased in individuals with Turner syndrome[49] and our own study about quality of life in AOS patients also showed lower mental health on the SF-36 questionnaire. In addition, our study highlights that the anxiety experienced by these patient groups was most often related to the future of their own health or the health of their close relatives. This anxiety will probably also be present in other genetic disorders, which should be acknowledged by the physician. However, none of the questionnaires used in research are designed specifically for patients with aortic disease, but they are rather commonly used for different chronic diseases. More disease-specific questionnaires will make it possible to ask patients more specifically about their psychological complaints. This will help the physician to offer more patient-tailored care. An excellent example is the well-developed disease-specific questionnaire, initiated in the USA for patients with sickle cell disease[50, 51]. Recently, the questionnaire has been validated in the UK[52]. It is important to formulate questions related to potential direct effects of a particular condition. Because sleeping disorders are common in sickle cell disease, they specifically ask for sleep patterns and complaints. For thoracic aortic disease, we should focus on anxiety for future operations and family members at risk and their feeling about life style changes due to their disease, such as no smoking and sport restrictions. Also syndrome-specific symptoms must be listed in the questionnaire, like joint complaints in Marfan and AOS patients and eye disorders in Marfan syndrome only. Nevertheless, before using these disease-specific questionnaires in clinical practice, they should be validated.

This thesis answered many questions in the imaging and clinical aspects of thoracic aortic disease. It also has become clear from the discussion that improved knowledge is needed in various areas of medical care provided to patients with thoracic aortic disease. Further research has to focus on better risk prediction, improving imaging of the thoracic aorta while dealing with new imaging techniques and the integration of quality of life assessment in clinical care. Also there should be attention for new treatment options, since surgery is still the only option for patients with severe aortic dilatation. The main goal is to optimize patient care and hopefully we can further reduce and prevent life-threatening events due to thoracic aortic disease in the future.

Table 1. Aortic growth in mm/year of different cohorts, both general population as patients with aortic diseases

Group of participants	Reference	Numbers	Imaging modality	Aortic root	Ascending aortic growth	Descending aortic growth
General population*	Rylski et al.[53]	195	Contrast CT	-	0.08 for men, 0.11 for women	0.08 for men, 0.08 for women
	Kalsch et al.[3]	4129	Non-contrast CT	-	0.15 for men, 0.15 for women	0.17 for men, 0.16 for women
	Vasan et al.[54]	3249	TTE	0.09 (SE 0.006) for men and 0.09 (SE 0.004) for women	-	-
Athletes*	Pellicia et al.[55]	2317	TTE	0.09	-	-
Smokers	Chapter 7	1987	Non-contrast CT	-	0.12±0.31 for men, 0.11±0.29 for women	0.10±0.30 for men, 0.13±0.27 for women
Bicuspid aortic valve	Detaint et al.[56]	353	TTE	0.21±0.2	0.42±0.6	-
Turner syndrome	Chapter 11	171	MRI or CT		0.20 (IQR: 0.00-0.44)	-
	Mortensen et al.[57]	80	Non-contrast MRI	0.38±0.7	0.24±0.6	-0.01±0.3
AOS	Chapter 13	28	Contrast CT	-	0.2 (95% CI 0.04–0.38)	-
Marfan syndrome	Detaint et al.[56]	50	TTE	0.49±0.5	0.12±1.0	-
	Meijboom et al.[58]	221	TTE	0.42 (SE 0.05) in men and 0.38 (SE 0.04) in women	-	-
Loeys-Dietz syndrome	-	-	-	-	-	-
Vascular Ehlers-Danlos	-	-	-	-	-	-
Degenerative TAA	Detaint et al.[56]	51	TTE	0.09±0.2	0.20±0.3	-

Beta from univariabel association when available, otherwise beta from multivariabel analysis. Studies which only included measurements on aneurysm level were excluded, for example Cheung et al.[59].

* cross-sectional data

AOS =Aneurysm-Osteoarthritis Syndrome; CT = computed tomography; MRI = magnetic resonance imaging; TTE = transthoracic echocardiograph

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Dutch summary

Dutch summary

Een aneurysma is een lokale verwijding van een slagader. Een aneurysma kan op allerlei plaatsen in het lichaam voorkomen, maar wordt het meest frequent gezien in de aorta (grote lichaamsslagader). Dit proefschrift focust zich op een aneurysma van de aorta in de borstkast. Aangezien de borstkast ook wel thorax wordt genoemd, spreken we van een thoracaal aorta aneurysma. De meerderheid van thoracale aorta aneurysma's komt voor in het eerste stukje (aortawortel) of in het opstijgende deel van de aorta (aorta ascendens), gevolgd door het dalende deel van de aorta (aorta descendens) en slechts een kleine hoeveelheid wordt vertegenwoordigd door een aneurysma in de aortaboog. Een aneurysma kan echter ook meerdere aortasegmenten omvatten. Omdat er verschillende definities voor aortaverwijding genoemd worden in de literatuur, zijn er verschillende cijfers bekend over het voorkomen van thoracale aorta aneurysma's. Studies die een thoracaal aorta aneurysma definieerden als een diameter van meer dan 50 mm, vonden een prevalentie van 0,16-0,34%. Bij het groter worden van een aneurysma neemt het risico op een scheur van de vaatwand toe. Zo'n scheur wordt een aorta dissectie genoemd en is een levensbedreigende situatie die zich meestal kenmerkt door hevige pijnklachten. Het verraderlijke van een thoracaal aneurysma is dat de verwijding zelf vaak geen klachten geeft. Klachten kunnen eventueel ontstaan wanneer het verwijde bloedvat druk uitoefent op omringende weefsels of wanneer verwijding van de aorta lekkage van de nabij gelegen aortaklep veroorzaakt. Echter deze symptomen komen maar zelden voor. Tegenwoordig weten we wel steeds meer over genetische afwijkingen die thoracale aorta aneurysma's veroorzaken. Dit heeft tot gevolg dat screening van thoracale aorta bij familieleden van mensen met een afwijking van de aorta of een bekende erfelijke aandoening vaker wordt uitgevoerd en daardoor verwijding van de aorta vaker wordt gediagnosticeerd. Daarnaast kunnen we tegenwoordig de thoracale aorta ook steeds gemakkelijker in beeld brengen door de technische ontwikkelingen van medische beeldvorming. Ook is de stralenbelasting van een CT-scan flink afgenomen. De drempel voor het uitvoeren van beeldvormend onderzoek bij patiëntenzorg maar ook bij wetenschappelijk onderzoek is hierdoor lager dan vroeger wat ook bijdraagt aan het eerder ontdekken van thoracale aorta aneurysma's. Een thoracaal aorta aneurysma kan dus worden gevonden bij het ontstaan van klachten, bij familiescreening of toevallig wanneer iemand een beeldvormend onderzoek krijgt vanwege een hele andere reden. Beeldvorming is momenteel heel erg belangrijk voor de diagnostiek en therapeutische beslissingen bij mensen met een aorta aneurysma. Er is echter nog onvoldoende informatie over hoe we de aorta het beste in beeld kunnen brengen met de verschillende technieken en hoe de thoracale aorta groeit in de gezonde populatie en in specifieke patiëntengroepen. In dit proefschrift hebben we daarom onderzoek gedaan naar het voorkomen en diagnostiek van een thoracale aorta aneurysma. Daarnaast hebben we onderzocht wat de impact is van het hebben van een aorta aneurysma of een erfelijke aandoening met kans op aneurysma op de kwaliteit van

leven. Als laatste hebben we een begin gemaakt met de vraag welke andere diagnostiek naast beeldvorming ons zou kunnen helpen bij het identificeren van een zieke thoracale aorta. Hierbij hebben we gekeken naar stofjes in het bloed (=biomarkers) en de elasticiteit van de aorta.

Deel 1 – Beeldvorming van de thoracale aorta

In **hoofdstuk 1** van dit proefschrift hebben we gekeken in hoeverre de aorta diameter kan variëren door (1) het gebruik van verschillende beeldvormende modaliteiten, namelijk echocardiografie, computertomografie (CT) en magnetic resonance imaging (MRI) en (2) het gebruik van verschillende manieren van meten van de aorta diameter. De aorta kan bijvoorbeeld gemeten worden op verschillende moment tijdens de hartcyclus en je kunt ervoor kiezen om de aortawand mee te nemen in de aorta diameter of juist niet. Voor dit onderzoek hebben we een groep van 100 patiënten onderzocht, die een tweeslippige hartklep (=bicuspide aortaklep, BAV) of het syndroom van Turner hadden. Beide aandoeningen kunnen gepaard met een thoracaal aorta aneurysma. Bij het Turner syndroom is één van de twee X chromosomen, die een vrouw normaal heeft, niet of niet volledig aanwezig. We hebben gevonden dat de verscheidenheid aan meettechnieken en modaliteiten grote verschillen in diameter kan veroorzaken, namelijk tot zelfs 11 mm aan het begin van de aorta (sinus van Valsalva en sinotubulaire junctie) en tot 18 mm ter hoogte van de aorta ascendens. Daarom zijn wij van mening dat hetzelfde protocol gebruikt dient te worden wanneer de aorta bij een patiënt meerdere keren gemeten wordt. We raden aan bij echocardiografie alleen de bovenste aortawand op de opname mee te nemen in de meting, omdat de diameter van de aorta dan het meeste overeenkomt met de diameter gemeten op CT of MRI. Daarnaast adviseren we om de diameter te meten tijdens de contractiefase van het hart (=systole), omdat de aorta dan beter zichtbaar is op echocardiografie en de grootste diameter van de aorta kan worden gemeten. Omdat er grote verschillen werden gevonden tussen de beeldvormende modaliteiten, is het geïndiceerd om in ieder geval éénmalig een CT of MRI te laten maken bij een patiënt om de gehele aorta in beeld te kunnen brengen en om de betrouwbaarheid van echocardiografische metingen bij een patiënt te controleren. Dit wordt bevestigd door een ander onderzoek wat we hebben uitgevoerd met 349 patiënten, die onze polikliniek bezochten voor screening van de aorta (**hoofdstuk 2**). In dit onderzoek onderzochten we de diagnostische waarde van echocardiografie (TTE) om een aorta aneurysma op te sporen door de resultaten te vergelijken met CT, wat het meest betrouwbare beeldvormende onderzoek is. Er werd vastgesteld dat de diameter van de aorta met behulp van echocardiografie wordt onderschat. Het maken van een echocardiografie geeft dus risico op een vals negatief resultaat. Daarnaast hebben we onderzocht welke extra afwijkingen van het hart, de aorta of kleinere slagaders worden gevonden bij echocardiografie en CT onderzoek. Bij echocardiografisch onderzoek werden hartklepafwijkingen gevonden, waaronder BAV in 5%. Daarnaast kwamen ventriculaire hypertrofie en ventriculaire

dilatatie beide maar bij 1% voor en waren dus relatief zeldzaam. Afwijkingen van de kransslagaderen (=arteriën) werden gezien op CT afbeeldingen bij 15% van de patiënten, waardoor de diagnostische waarde van CT toeneemt.
Een belangrijk nadeel van echocardiografisch onderzoek van de thoracale aorta is dat de beelden (en dus de beeldvorming van de aorta) afhankelijk zijn van de manier waarop en de locatie waar de echolaborant de geluidskop tegen het lichaam van de patiënt houdt. Wanneer een opname van de aorta vanuit een andere hoek gemaakt wordt, kan dit zorgen voor een kleinere of grotere aorta diameter. Variabiliteit in de opnamerichting van verschillende echolaboranten kan dus grote klinische consequenties hebben en daarom hebben we dit onderzocht in **hoofdstuk 3**. In een groep van 60 mensen, werden de echocardiografische beelden bij elke persoon gemaakt (en de aorta diameter gemeten) door twee verschillende echolaboranten. Daarnaast werd de eerste echolaborant gevraagd nog een keer opnames te maken en metingen te verrichten. We vonden dat de diameter van de aorta gemiddeld 0,7 tot 1,3 mm (afhankelijk van het niveau van de aorta) verschilt tussen afbeeldingen die zijn verkregen door dezelfde echolaborant. De diameter van de aorta verschilt 1,6 tot 1,9 mm tussen afbeeldingen die zijn verkregen door verschillende echolaboranten. De verklaringen die wij vonden voor deze verschillen tussen echolaboranten waren zaken die de beeldvorming bemoeilijkten zoals verkalkingen, 'drop-out' artefacten en 'side lobe' artefacten. Daarnaast verschilden de opnames in beeldsnelheid of hadden echolaboranten verschillende dwarsdoorsnedes door de aorta gemaakt. Wanneer een groot verschil wordt gevonden tussen twee echocardiografische aorta metingen bij één patiënt, adviseren wij de arts om de metingen op de eerder gemaakte afbeelding opnieuw te evalueren om te zien of er verklaringen zijn voor dit grote verschil. Eén van onze belangrijkste uitkomsten van het onderzoek was dat het verschil tussen de echocardiografische aorta metingen van twee echolaboranten groter werd naarmate de aorta diameter groter was. Daarom lijkt het ons van klinisch belang dat er bij patiënten met aorta diameters die de grens voor preventieve aorta chirurgie naderen, beeldvorming met behulp van CT of MRI wordt verkregen om de aorta diameter betrouwbaarder te kunnen meten.
Een andere uitdaging van het meten van de aorta diameter met bijvoorbeeld CT is dat het erg tijdrovend is, omdat de metingen op meerdere niveaus en loodrecht op het vat moeten worden uitgevoerd. Daarom kan een automatische methode voor het meten van de aorta waardevol zijn voor zowel de klinische praktijk als voor onderzoeksdoeleinden. Een automatische meetmethode voor niet-ECG-getriggerde CT-scans waarbij geen gebruik is gemaakt van contrast, wordt gepresenteerd en gevalideerd in **hoofdstuk 4.** Dit bestond al wel voor CT onderzoek met contrast maar niet voor CT onderzoek zonder contrast, omdat het veel lastiger is om de wand hierop goed af te beelden. We toonden aan dat onze automatische methode goed overeenkomt met handmatige metingen en we gebruikten deze methode om de aortagroei in een groot cohort te meten (**hoofdstuk 7**).

Deel II – De thoracale aorta in de algemene bevolking

Om te kunnen beoordelen of er afwijkingen zijn van de thoracale aorta diameter of groei, is het noodzakelijk om informatie te hebben over de "normale" aorta in de algemene populatie. In een groot populatieonderzoek, de Rotterdam Studie of het ERGO onderzoek (Erasmus Rotterdam Gezondheid Onderzoek), hebben we de thoracale aorta gemeten op het niveau van de aorta ascendens en aorta descendens. De groep bestond uit ongeveer 2500 deelnemers van 55 jaar of ouder, omdat de Rotterdam Studie zich vooral richt op de oudere populatie. In **hoofdstuk 5** hebben we verdelingen van de absolute diameter en diameters gecorrigeerd voor lichaamsoppervlak gegeven voor zowel mannen als vrouwen in de algemene bevolking. Er werden verschillen gevonden in de waarden van mannen en vrouwen, ook wanneer lengte en gewicht meegenomen waren in de analyse. Dit geeft aan dat het belangrijk is om referentiewaarden voor mannen en vrouwen apart op te stellen, zowel voor de absolute diameter als voor de waarde gecorrigeerd voor lichaamsoppervlakte. Daarnaast vonden we dat een hogere diastolische bloeddruk geassocieerd was met grotere aorta diameters, terwijl juist de systolische bloeddruk momenteel de meeste aandacht krijgt. We vonden ook vaak (in 12,1%) een diameter van de aorta ascendens groter dan 40 mm in onze oudere populatie. Dit wordt vaak beschouwd als de afkapwaarde en hierboven wordt gesproken van een verwijde aorta. Echter stierven er slechts 4 (1,3%) patiënten met een diameter groter dan 40 mm als gevolg van een aandoening aan de aorta. Dit aantal sterfgevallen blijkt vrij laag en roept dan ook de vraag op of de afkapwaarde van 40 mm voor de definitie van aorta aneurysma wel geschikt is voor de oudere populatie. Mogelijk horen waarden boven de 40 mm bij de normale ontwikkeling van de aorta gedurende het leven en moeten we het niet een verwijding noemen bij ouderen. We weten namelijk dat de normale aorta groeit tijdens het leven en dus wijder is op oudere leeftijd. Grotere studies zijn nodig om te bevestigen of 40 mm inderdaad ongeschikt is als afkapwaarde bij deze oudere patienten.

Hiernaast hebben we de deelnemers van de Rotterdam Studie gedurende ongeveer 13 jaar gevolgd. In **hoofdstuk 6** zijn deze gegevens gebruikt om te kijken of de thoracale aorta diameter (zowel absoluut als gecorrigeerd voor lichaamsoppervlakte) ons iets kan vertellen over het risico op belangrijke cardiovasculaire aandoeningen in de toekomst bij vrouwen en mannen. Na 13 jaar waren 229 (19%) vrouwen en 255 (26%) mannen overleden. Bij vrouwen was de diameter van de aorta descendens veel sterker geassocieerd met de uitkomsten beroerte, hartfalen en cardiovasculaire mortaliteit dan bij mannen. Op basis van deze gegevens concluderen we dat een grotere diameter van de aorta descendens een goede marker zou kunnen zijn voor een verhoogd risico op cardiovasculair aandoeningen bij vrouwen.

Naast de thoracale aorta diameter hebben we ook gekeken naar de thoracale aorta groei in een subgroep van de algemene bevolking, namelijk bij rokers. Omdat roken bekend staat als een risicofactor voor grotere thoracale aorta diameters en grotere groei van de abdominale aorta, hebben we onderzocht of rokers ook grotere thoracale aorta groei

laten zien over de tijd. In **hoofdstuk 7** hebben we de groei van de aorta ascendens en aorta descendens gemeten bij bijna 2000 huidige of voormalige rokers die deelnamen aan een Deens longkanker screeningsonderzoek. We vonden een groei van ongeveer 0,1 mm/jaar, wat vergelijkbaar is met de groei van de aorta in de algehele bevolking. Met behulp van cross-sectioneel onderzoek werd namelijk in de algemene bevolking een thoracale aortagroei van 0,08 tot 0,17 mm/jaar gevonden. Bovendien was in onze studie de thoracale aortagroei vergelijkbaar tussen huidige en ex-rokers en was de aortagroei niet geassocieerd met het aantal pack-years (= aantal jaren roken x aantal pakjes per dag). Concluderend vertonen rokers geen grotere thoracale aortagroei in vergeleken met de algemene bevolking.

Deel III – Thoracale aorta in specifieke ziektebeelden

In deel III van dit proefschrift hebben we meer in detail gekeken naar specifieke ziekten die gepaard gaan met thoracale aorta aandoeningen, namelijk de bicuspide aortaklep (BAV), het Turner syndroom en het aneurysma-osteoartritis syndroom.

Bij patiënten met BAV hebben we de gekeken naar de verandering van de vorm en het oppervlakte van de annulus tijdens de hartcyclus (**hoofdstuk 8)**. Deze oppervlakte wordt vaak gebruikt om de maat van een kunstklep te bepalen tijdens een operatie via de lies, ook wel 'transcatheter aortic valve implantation (TAVI)' genoemd. We vonden dat de annulus significante veranderingen in vorm ondergaat tijdens de hartcyclus met een ronder en groter oppervlakte tijdens systole en een meer elliptische conformatie tijdens diastole. Op basis van deze resultaten adviseren wij om het oppervlakte van de annulus (en dus de maat van de kunstklep) vroeg tijdens de systole te meten om onderschatting van het oppervlakte te voorkomen.

In **hoofdstuk 9** hebben we vier potentiële stofjes in het bloed (=biomarkers) onderzocht waarmee we een inschatting willen maken over de ziekteprogressie bij patiënten met BAV. We vonden dat NT-proBNP geassocieerd is met ernstiger aortaklepvernauwing en -lekkage en dat hsTnT geassocieerd is met ernstiger aortakleplekkage. Het aantonen van deze associaties is de eerste stap in de ontwikkeling van één of meerdere biomarkers die gebruikt kan worden bij prognostische stadiëring en risicovoorspelling.

In **hoofdstuk 10** hebben we bij volwassen vrouwen met het syndroom van Turner gekeken naar de prevalentie van thoracale aorta aneurysma's, de groeisnelheid van de thoracale aorta en het risico op complicaties van de aorta. We vonden een thoracaal aorta aneurysma bij 22% van onze volwassen patiënten en de thoracale aortagroei was gemiddeld 0,20 mm/jaar. Deze groei is niet heel snel maar wel groter dan in de algemene bevolking (0,08 tot 0,17 mm/jaar). Terwijl een verwijding van de thoracale aorta dus blijkbaar vaak aanwezig is, werd er bij slechts 2% een aortadissectie gevonden of preventieve aortachirurgie verricht tijdens een follow-up van 7 jaar. Dit is echter wel meer dan in de algehele populatie en daarom zijn we op zoek naar andere gegevens die ons zouden kunnen helpen om deze mensen met een hoog risico op complicaties op te sporen, bijvoorbeeld metingen van de

aorta elasticiteit of stijfheid. Wij hebben de aorta elasticiteit onderzocht bij 52 patiënten met Turner syndroom met behulp van echocardiografie en MRI in **hoofdstuk 11.** We vonden bij patiënten met Turner syndroom een verminderde elasticiteit van de aorta ter hoogte van de aortaboog ten opzichte van gezonde controle deelnemers. Daarnaast hebben we histopathologisch onderzoek verricht op aortaweefsel van 5 patiënten die preventief waren geopereerd vanwege aortadilatatie. Hierbij vonden we onder andere een korrelige afzetting van elastine en verminderde of afwezige expressie van contractiele eiwitten ter hoogte van de aorta ascendens. Dit zouden specifieke veranderingen in de aortawand van patiënten met het syndroom van Turner kunnen zijn, maar dat moet in toekomstig onderzoek verder onderzocht en bevestigd worden.

Naast het syndroom van Turner hebben we in **hoofdstuk 12** ook gekeken naar de aortagroei en lange termijn uitkomsten bij 28 patiënten met het aneurysma-osteoarthiritis syndroom (AOS). Dit syndroom heeft onze onderzoeksgroep in 2011 in het Erasmus voor het eerst beschreven. Tegenwoordig wordt dit ziektebeeld ook wel Loeys-Dietz syndroom type III genoemd. In deze studie werd de aorta bij deze patiënten op verschillende locaties gemeten, waarbij de meeste aorta groei werd gevonden ter hoogte van de sinotubulaire junctie (0,4 mm/jaar). Tussen 2011 en 2018 werd bij 18 van de 28 (64%) patiënten een arteriële afwijking ontdekt, welke chirurgische behandeling vereisten. Niemand overleed tijdens de studie. Dit zou mogelijk verklaart kunnen worden door de intensieve behandeling volgens een vast protocol met laagdrempelige preventieve chirurgie die wij deze patiënten in ons centrum bieden. Met deze studie hebben we bewezen dat het AOS syndroom snel dilatatie van de aorta of arteriën kan veroorzaken en dat intensieve follow-up van deze patiënten nodig is. Het risico op een levensbedreigende aneurysma of dissectie van de aorta of slagaders, zou een verminderde kwaliteit van leven, angst of depressie kunnen veroorzaken. Hierbij kunnen de fysieke symptomen en de gebeurtenissen die patiënten hebben meegemaakt met familieleden met AOS ook een rol spelen. In **hoofdstuk 13** beschrijven we daarom de subjectieve kwaliteit van leven en onderzochten we de aanwezigheid van angst en depressie bij 28 AOS-patiënten. Zoals verwacht, rapporteerden AOS-patiënten een verminderde kwaliteit van leven in vergelijking met de algemene bevolking op verschillende gebieden. Bovendien scoorden patiënten met AOS significant hoger op de depressieschaal. Daarnaast hebben we geconstateerd dat patiënten zich zorgen maken over hun toekomst en de erfelijkheid van hun ziekte. De resultaten benadrukken dat het van belang is om kwaliteit van leven, depressie en angst uit te vragen tijdens het spreekuur bij patiënten met AOS. Zo kunnen we hopelijk mensen identificeren die baat hebben bij intensieve psychologische begeleiding.

Deel IV – Sporten en zwangerschap bij aandoeningen van de thoracale aorta

Er zijn twee situaties bekend die extra aandacht verdienen bij patiënten met een thoracaal aorta aneurysma, namelijk zwangerschap en sporten. Beide geven een verhoogde druk op de aortawand en daarom wordt gedacht dat dit een extra risico geeft bij patiënten met

een aneurysma. In **hoofdstuk 14** bespreken we de huidige literatuur over zwangerschap bij patiënten met een thoracale aorta aandoening. Naast hemodynamische veranderingen tijdens de zwangerschap worden ook hormonale en trombo-embolische veranderingen beschreven. Counseling vóór de zwangerschap is het belangrijkste in de begeleiding van patiënten met een thoracaal aorta aneurysma. Hierdoor kan beeldvorming van de gehele aorta nog plaatsvinden en wanneer nodig preventieve behandeling ingezet worden voor de zwangerschap. Aangezien er weinig bekend is over operaties van de aorta bij zwangere vrouwen, zouden alleen centra met ervaren teams en goede expertise in zwangerschap en hartaandoeningen deze risicovolle vrouwen moeten begeleiden. **Hoofdstuk 15** biedt een up-to-date overzicht van de beschikbare literatuur over risico's en voordelen van lichaamsbeweging en sportparticipatie bij patiënten met thoracale aorta aandoeningen. Er wordt vaak een grotere aorta diameter bij atleten gevonden, maar dit lijkt voornamelijk te worden veroorzaakt door de grotere lengte van de atleten. Er bestaat een angst om mensen met een aorta aneurysma te laten sporten. Dit lijkt voornamelijk gebaseerd te zijn op enkele casussen van aorta dissectie tijdens sporten en de hoge sterftecijfers bij aorta dissectie in het algemeen. Er zijn namelijk geen gegevens in de literatuur bekend over het risico van aortadissectie als gevolg van inspanning bij patiënten met aortadilatatie. Sterker nog, er komt steeds meer bewijs in de algemene populatie en in andere patiëntengroepen dat sporten juist een positief effect heeft. Er is dus momenteel geen eenduidig bewijs om lichaamsbeweging en sportparticipatie te ontmoedigen bij patiënten met thoracale aortaziekte. Wij zijn van mening dat milde tot matige lichaamsbeweging juist ook moet worden aangemoedigd vanwege de bekende positieve effecten van beweging op de algehele gezondheid. Ondanks dat het causale verband tussen zware statische oefeningen en het ontstaan van aorta dissectie niet is aangetoond, zouden zware statische sporten theoretisch een impact kunnen hebben op de bloeddruk en daardoor op de aorta. Aangezien er geen onderzoeken zijn die hebben laten zien dat zware statische oefeningen veilig zijn voor patiënten met thoracale aorta aneurysma, lijkt het ons belangrijk om de veiligheid voorop te stellen en zware statische inspanning wel te ontraden.

Dit proefschrift beantwoordt veel vragen over de beeldvorming en klinische aspecten van thoracale aorta aneurysma's. Dit proefschrift draagt daarom bij aan de kennis op verschillende gebieden van de medische zorg aan patiënten met thoracale aortaziekte. Verder onderzoek dient zich te richten op betere risicovoorspelling, verbetering van de beeldvorming van de thoracale aorta en het optimaal gebruik maken van vragenlijsten over psychisch welbevinden in de dagelijkse klinische praktijk. Er moet ook aandacht zijn voor nieuwe behandelingsopties, omdat chirurgie nog steeds de enige optie is voor patiënten met ernstige verwijding van de aorta. Het belangrijkste doel is om de patiëntenzorg te optimaliseren en hopelijk kunnen we in de toekomst levensbedreigende

gebeurtenissen als gevolg van thoracale aorta aandoeningen verder verminderen en voorkomen.

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PhD portfolio

Name	Lidia R. Bons
Department	Cardiology
Research school	COEUR, Erasmus MC
PhD period	2016-2019
Title thesis	Thoracic Aortic Disease: Imaging and Clinical Aspects
Promotor	Prof. Dr. J.W. Roos-Hesselink
Co-promotor	Dr. R.P.J. Budde

PhD training (21.3 ECTS) **ECTS**

General courses

2016	COEUR day 'Life after COEUR – What is your plan?'	0.5
2016	PhD day 'Balance your PhD!'	0.3
2016	Basic course Clinical Investigators (BROK)	1.5
2016	Research Integrity course	0.3
2016	Biostatistical Methods I: Basic Principles, NIHES	5.7
2016	Photoshop and Illustrator CS6 Workshop	0.3
2017	Workshop Presenting Skills for junior researchers	1.0
2017	COEUR day on 'Valuable Science'	0.5
2017	Biostatistical Methods II: Classical Regression Models, NIHES	4.3
2018	PhD day 'A healthy PhD!'	0.3
2018	Biomedical English Writing and Communication course	3.0

Cardiology courses

2016	COEUR Right Ventricular Failure	0.2
2016	COEUR Research in subarachnoid hemorrhage and intracranial aneurysms: current status and future plans	0.4
2017	COEUR Cardiovascular Imaging and Diagnostics	1.5
2017	COEUR Congenital heart disease	0.5
2017	COEUR Aneurysmal Disease	0.5
2019	COEUR Vascular Clinical Epidemiology	0.5

Teaching (7.5 ECTS)

Lectures

2016-2019	BAV study consortia meetings	1.5

2016	Lecture 'Pregnancy in Turner Syndrome', Turner syndrome patient information day, Amersfoort , The Netherlands	0.6
2016	Lecture 'Congenital heart disease' for volunteers of the Dutch Heart Foundation, The Hague, The Netherlands	0.6
2018	Lecture 'Turner syndrome and heart diseases', Turner syndrome patient information day, Rotterdam, The Netherlands	0.6
2018	ACE kick-off meeting aortic disease	0.6
2018	Lecture 'The Rotterdam Study' at the cardiogenetics meeting	0.6
2018	Lecture 'Clinical diagnosis and (pre)clinical visualization of aortic aneurysms' at the ACE meeting Translational imaging	0.6
2018	Lecture 'The diameter and growth of the thoracic aorta in the healthy population' at the plenary meeting of the radiology department	0.3
2019	Lecture 'The Rotterdam Study' at the Cardiometabolic Epidemiology meeting	0.6
2019	Lecture 'AOS syndrome and quality of life', AOS syndrome patient information day, Rotterdam, The Netherlands	0.6

Supervision

2017	Supervising 2nd year medical students in writing a systematic review	0.3
2018	Supervising 2nd year medical students in writing a systematic review	0.3
2018	Supervising a 4th year medical students in performing research	0.3

Symposia and conferences (15.6 ECTS)

Oral presentations

2017	Davos wintermeeting SIQC, Davos, Switzerland	1.2
2017	Dutch Society of Cardiology (NVVC) Autumn congress, The Netherlands	0.6
2017	Cardiogenetic Symposium, Antwerp, Belgium	1.2
2018	Davos wintermeeting SIQC, Davos, Switzerland	1.2
2018	Dutch Society of Cardiology (NVVC) Spring congress, The Netherlands	0.6
2018	Dutch Society of Cardiology (NVVC) Autumn congress, The Netherlands	0.6
2019	European Congres of Radiology	1.5

Poster presentations

2017	EuroGUCH congress Lausanne, Zwitserland	0.9
2017	27th International Symposium on Adult Congenital Heart Disease Cincinnati, USA	1.2
2017	EuroEcho-Imaging Lisbon, Portugal	1.5
2018	EuroGUCH Munster, Germany	0.9

2018	ESC congress Munchen, Germany	1.8
2019	EuroGUCH Zagreb, Croatia	0.9

Attended

2016	Dutch Society of Cardiology (NVVC) Autumn congress, The Netherlands	0.3
2016	Symposium 'Tijd voor kwaliteit', Rotterdam, The Netherlands	0.3
2016	Dutch Society of Cardiology (NVVC) Junior kamerdag, Utrecht, The Netherlands	0.3
2017	Dutch Society of Cardiology (NVVC) Spring congres, The Netherlands	0.3
2017	Dutch Society of Cardiology (NVVC) Junior kamerdag, Amsterdam, The Netherlands	0.3

Award

2018	Best oral presentation in 'Gender', NVVC spring congress

About the author

Lidia Rianne Bons was born in Spijkenisse, The Netherlands, on the 3rd of February, 1991. After graduating from secondary school in 2009 (Gymnasium, Maerlant College, Brielle), she commenced medical school at the Erasmus University in Rotterdam. During her medical school, she played Volleybal at national level resulting in a national championship in 2013 with her club team Sliedrecht Sport. She also worked as a medical student at the Neurosurgical department and participated in clinical research at the department of Cardiology of the Erasmus MC in Rotterdam. After she obtained her medical degree in 2016, she started her PhD project at the department of Cardiology of the Erasmus MC supervised by prof. dr. Jolien W. Roos-Hesselink and dr. Ricardo P.J. Budde. She was closely involved in patient care at the outpatient clinic for aortic disease, at which she consulted patients once a week and participated in a multidisciplinary team for patients with Turner syndrome. During her PhD project she had the opportunity to present her work at international conferences and to publish manuscripts in peer-reviewed journals. In addition, she was engaged in supervising second year medical students and a MSc Clinical Research student. As of June 2019, Lidia is working as a doctor at an elderly home in Rotterdam.

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