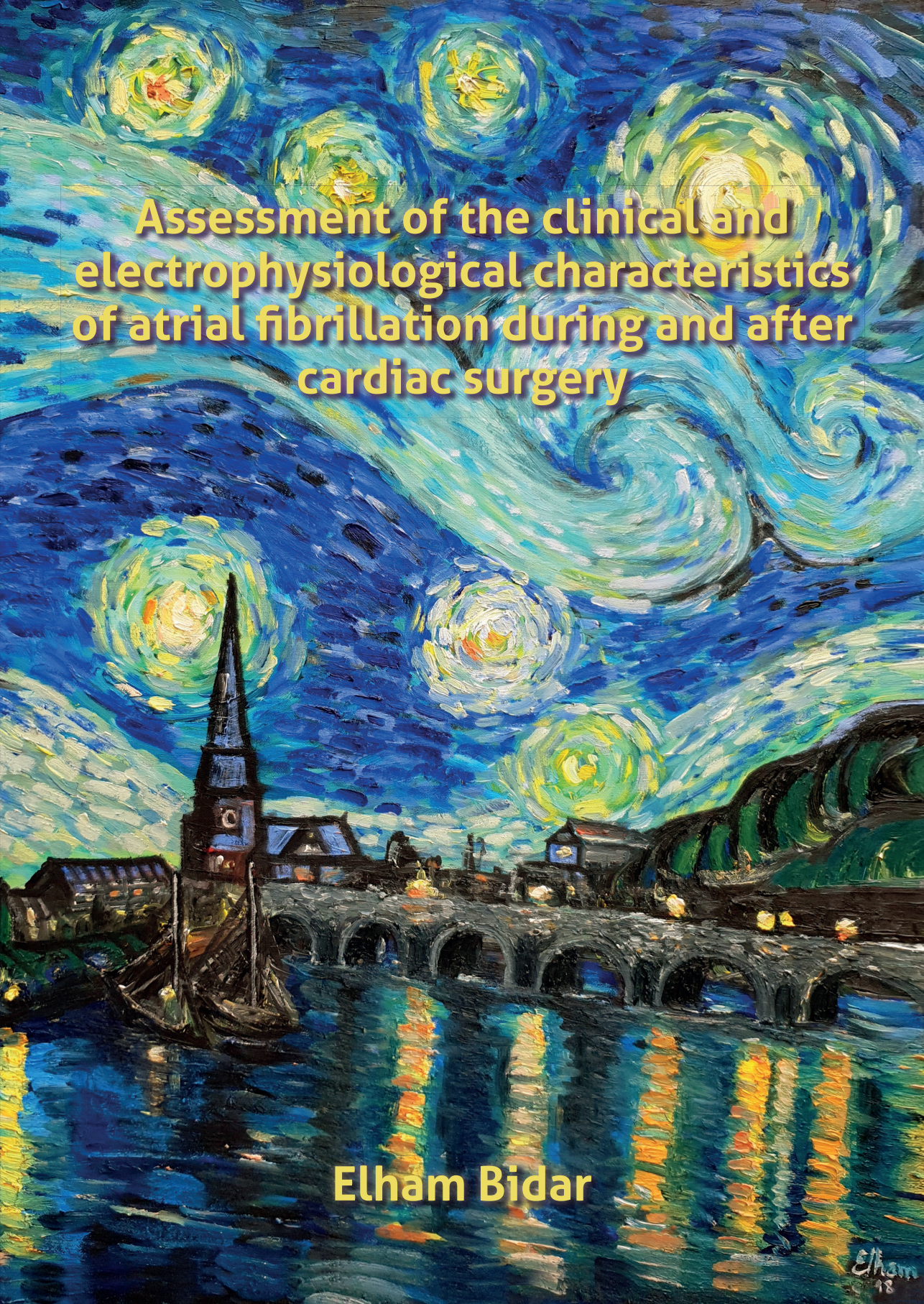
Assessment of the clinical and electrophysiological characteristics of atrial fibrillation during and after cardiac surgery



Elham Bidar

Assessment of the clinical and electrophysiological characteristics of atrial fibrillation during and after cardiac surgery

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Assessment of the clinical and electrophysiological characteristics of atrial fibrillation during and after cardiac surgery

DISSERTATION

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Dedicated to my parents.





1

General Introduction

Atrial fibrillation (AF) is the most common arrhythmia in human and its incidence is under-diagnosed because many episodes of AF are asymptomatic.[1] AF is associated with an increased chance of stroke and thromboembolic events.[2] Furthermore, because of its association with several age-related co-morbidities such as hypertension, diabetes mellitus, obesity and cardiac disease, its incidence is rising.[3] In general, AF is categorized into paroxysmal (self-terminating), persistent (non-self-terminating, but pharmacological cardioversion still possible) and permanent (not amenable to pharmacological cardioversion) forms.[4] In addition, postoperative AF (POAF) episodes occur after major surgery, mainly after cardiac surgery[5] in patients with a comparable risk profile as in non-surgical AF. [6, 7]

The degree of atrial wall remodelling and occurrence of triggers determine the number and duration of AF episodes. Co-morbidities and advanced age contribute to structural heart disease, which leads to atrial wall remodelling and AF perpetuation.[8, 9] This is illustrated for example in $CHADS_2VA_2Sc$ and HATCH scores [10, 11] both of which increase the chances of AF progression. The resulting multifactorial aetiology of AF includes abnormalities in calcium handling, ion-channel remodelling, fibrosis, oxidative stress, inflammation and others.[12]

Assessment of the atrial electrical activation during AF (Figure 1) has revealed that the fibrillation conduction pattern becomes more complex with AF persistence and is a reflection of the underlying structural changes.[12-14] Moreover, different underlying diseases lead to distinctly different patterns of structural remodelling and fibrillation patterns in animal models.[15] Two very interesting observations in human AF and AF animal models are dyssynchronous activation of the endo-epicardial surface (endo-epicardial dissociation) of the thin atrial wall, which leads to transmural conduction of wavelets (breakthrough). These conduction patterns have been shown to increase with complex substrates for AF in goat models[16] and in humans, with high inter-individual variability (Figure 2).[14]

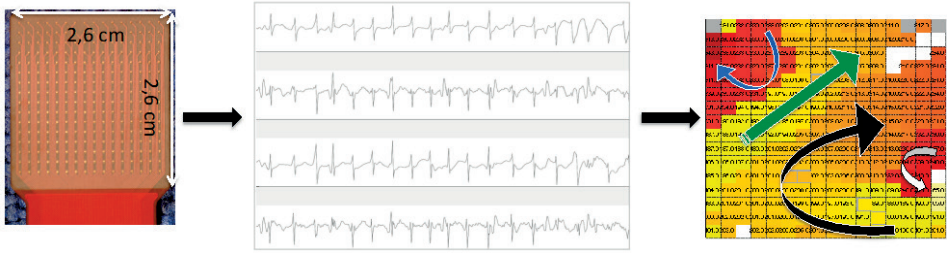


Figure 1 Different steps in epicardial mapping of fibrillation waves: From left to right: a unipolar electrode array (26 x 26 mm) is used to record epicardial electrical activation by placing the electrode on the atrial wall surface during (induced) AF; unipolar electrograms are recorded and processed using an automated algorithm to filter out farfield deflections and detect steepest local deflections; finally, using the conduction velocity and wave tortuosity a wave map is created from the activation map (coloured arrows depict individual waves).

Furthermore, AF itself can cause a gradual progression of structural changes such as myofiber rearrangement[17] and endomysial fibrosis[18] that contribute to AF perpetuation.

As expected, the traditional view of AF as a "one size fits all" disease does not suffice in classifying this complex disorder. This has become clearer from particularly two important findings of continuous rhythm monitoring devices (i.e. implanted pacemakers with atrial leads or implantable loop recorders). First, it has been shown that there is great discrepancy between the clinical classification of AF, which is often based on symptomatology, and the true temporal persistence of AF.[19] In other words, patients classified in identical clinical categories may in reality have a wide variety in duration and incidence of AF episodes, which can lead to underestimation of the true AF burden. This finding may have important implications in clinical risk stratification, treatment strategies and their outcome measures in the abovementioned categories. Second, and perhaps even more importantly, subclinical atrial high rate episodes (AHRE) detected from implanted pacemakers, lasting up to 6 minutes contribute to enhanced risk of stroke.[1, 20, 21] Consequently, even short lasting AF episodes may require oral anticoagulation treatment underscoring the need for rhythm monitoring in patients at risk for stroke. Thus, advanced monitoring strategies have led to a quest for re-evaluation of the clinical classifications of AF.



Figure 2 Two representative examples of activation patterns during electrically induced AF, acquired from patients without a history of AF: On the left, a 59 year old male patient with hypertension who underwent coronary artery bypass graft (CABG); On the right a 69 year old patient with hypertension who underwent CABG. Different colours depict different waves, arrows depict wave propagation direction, asterisks depict breakthrough waves. Clearly a more complex propagation pattern with wave narrowing and breakthroughs are seen in the older patient on the right (see also Chapter 4).

In this context, patients without a history of AF undergoing cardiac surgery represent a unique population. These patients carry on the one hand various degrees of potential substrates for AF caused by a variety of co-morbidities such as hypertension, cardiac

failure and myocardial infarction. On the other hand, AF occurs in these patients during the acute postoperative phase by a large number of triggers including acute hemodynamic instability causing atrial stretch, a systemic inflammatory response to cardiopulmonary bypass, high levels of sympathetic activation, and others.[5,22-26]

Notably, while POAF is thought of as a transient arrhythmia after cardiac surgery, it is associated with increased long-term mortality and risk of stroke.[6, 7] This indicates that POAF may not be confined to the acute phase triggers but may show late recurrences, which is plausible if there is an underlying substrate. Also, whether the substrate for late POAF develops as a result of surgery or is pre-existent may differ from patient to patient. On the one hand, POAF occurs more frequently after cardiac surgery as opposed to general surgery, emphasizing the importance of cardiac surgical manipulation.[27] On the other hand, analysis of right atrial appendages before and after surgery does not show histopathological differences.[28] Furthermore up to 90% of patients with severe pre-existing myolysis develop POAF.[28] These findings alongside the abovementioned co-morbidities in patients undergoing cardiac surgery, suggest a pre-existing substrate that predisposes patients to POAF as opposed to an acute change during the operation (Figure 3).

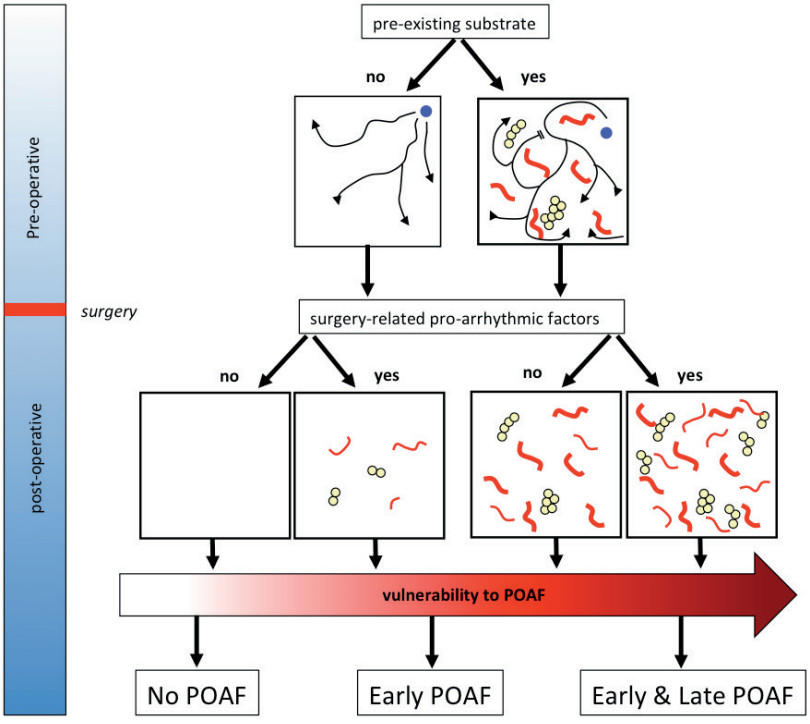


Figure 3 Schematic representation of a pre-existing structural substrate and its influence on vulnerability to POAF. Curved arrows depict electrical propagation, POAF= postoperative atrial fibrillation

Scope of this thesis

In this thesis, we describe a number of studies undertaken to characterize the electrophysiological properties of the AF substrate during and after cardiac surgery, including a thorough quantification of true AF burden for an extended period of time after surgery. For this purpose we used continuous rhythm monitoring devices to detect AF episodes during follow-up periods of 1 month up to 3 years after cardiac surgery.

Previous studies quantifying late POAF mostly discuss clinical AF recurrences in populations who had a history of AF or show symptomatic and long lasting AF episodes. Here, we studied the relation between clinical predisposition at baseline and the electropathological substrate for AF on the one hand and AF recurrences including short lasting subclinical AF episodes on the other hand. Next to the invasive substrate quantification during surgery, we also highlight less invasive methods of substrate quantification such as P-wave morphology in electrocardiograms.

In the light of the above-mentioned inter-individual variability in AF substrates, detailed computational models can incorporate specific structural changes and atrial remodeling, to assess their effects on the propagation properties. In the last chapters of this thesis we describe the complex 3-dimensional electropathological substrate for AF in humans using a highly detailed computer model of AF, which showed the occurrences of transmural propagation of breakthrough waves as a result of endo-epicardial electrical uncoupling. To test this, we developed an invasive mapping technique, in which a clamp like electrode was inserted into the right atrium prior to venous cannulation during cardiac surgery to map the endo- and epicardium simultaneously. Using these techniques, we detected a new dimension in the electropathological substrate of AF.

In summary, we discuss the following subjects in the different chapters of this thesis:

- The prevalence of new onset AF in the acute postoperative phase (early POAF) and during prolonged follow-up (late POAF) using continuous rhythm monitoring devices (Chapters 3-4)
- Effect of co-morbidities on incidence of early and late POAF in the patients undergoing open chest cardiac surgery (Chapters 2-4,7)
- The underlying electropathological substrate assessed during electrically induced AF for POAF and late POAF in patients without a history of AF (Chapter 4).
- The 3-dimensional substrate for AF in patients undergoing open chest surgery (Chapter 5-6).
- ECG parameters for substrate detection and POAF prediction in patients undergoing cardiac surgery (Chapter 4).

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Part 1

Incidence and pathophysiology of late postoperative atrial fibrillation



2

Post-operative Atrial Fibrillation –Pathophysiology, Treatment and Prevention

E Bidar S Bramer B Maesen J G Maessen U Schotten

J Atr Fibrillation 2013

Abstract

Atrial fibrillation occurring after cardiac surgery has been the subject of intensive research over the past decades. However, the incidence remains high, despite numerous preventive and treatment strategies. In addition, several reports show that the impact of postoperative atrial fibrillation (POAF) is high. It is an independent risk factor for mortality after several years. These findings make clear that the pathophysiology of POAF is not fully understood and POAF-associated risks to some extent might be underestimated. On the one hand, excessive triggers during the acute post operative phase after cardiac surgery might initiate AF even in atria with low vulnerability. On the other hand, many patients undergoing surgery have an atrial substrate at the time of operation promoting AF not only in the postoperative phase but also in the days and weeks thereafter. Progress in our understanding of the AF mechanisms in general has provided valuable insights into processes involved in atrial structural remodeling due to advanced age, hypertension, obesity, and congestive heart failure. These patient characteristics strongly contribute to cardiac disease, predict POAF and likely have an impact on the risk of thrombus formation in the weeks and months after cardiac surgery. For a better understanding of the mechanisms involved, it is important to not only recognize the occurrence of POAF by continuous monitoring after surgery, but also to identity the extent of atrial vulnerability to AF in these patients.

Introduction and Incidence

Postoperative atrial fibrillation (POAF) is an important complication after cardiac surgery, which increases short-term hospitalization costs [1] and more importantly, decreases long-term survival. [2, 3] This makes POAF an important target for prevention and treatment.

Great discrepancy remains between reported incidences of POAF in different studies. Reported incidences vary between 10-60% depending on the type of surgery, with higher incidences in valve surgery compared to coronary artery bypass surgery (CABG). [4] This is certainly affected by the more invasive structural changes arising from valvular diseases such as atrial dilatation and fibrosis, but also by the more prolonged and invasive nature of the surgical interventions in valve surgery.[5] The incidence of POAF is however also influenced by the definition of AF. The minimal duration of AF needed to qualify as POAF varies in reports between minutes of AF,[6, 7] to sometimes only qualification as AF if it requires therapy.[1]

In general, AF is defined as an episode with irregular RR-intervals without a traceable p-wave, during at least 10 seconds.[8, 9] It is important to acknowledge even the short episodes of AF,[6] because of the progressive nature of the arrhythmia,[10, 11] but also because even a low AF burden significantly increases the stroke rate.[12] The unpredictability of AF onset and duration poses a great challenge to the intermittent rhythm detectors such as ECG or Holter monitoring after discharge.[13] Reports on long-term follow up after cardiac surgery suggest that POAF is an independent predictor of mortality, which might well be related to the fact that it is a recurrent arrhythmia.[2, 3, 14] Of note, some of the AF episodes may remain unnoticed as they can be asymptomatic both during hospitalization and after discharge.[15-17]

Indeed, several studies in patients undergoing cardiac surgery have shown recurrence of AF after discharge.[18, 19] In a randomized trial of 124 patients on the effects of Amiodarone after cardiac surgery, 12% of the patients in the placebo group were in AF at a mean of 12 days after discharge.[20] In a retrospective study of 305 patients undergoing cardiac surgery, the annual incidence of symptomatic AF during a 4 year follow up was 5.1% in patients who had developed POAF.[21] Interestingly, multivariate analysis showed reduced left ventricular ejection fraction, which can cause atrial structural remodelling, to predict recurrences of POAF independently.[21] In line with this, other predictors of POAF after discharge that have been reported are valve surgery, history of myocardial infarction and pulmonary hypertension.[17]

The value of continuous monitoring seems essential in detecting the true POAF burden,[13] because the importance of asymptomatic “silent AF” in patients with a comparable risk profile as the POAF population, has recently been emphasized.[12] Therefore, to be able to treat or at least to restrain the consequences of POAF, a better understanding of the pathophysiology of POAF is mandatory.

Pathophysiology

Even in normal atria in sinus rhythm inter-atrial and site-specific conduction delays occur, leading to spatial non-uniformity of conduction anisotropy.[22] In the presence of triggers with sufficient incidence, AF can be induced both in normal and in abnormal atria. The wave pattern and type of AF however, may vary in complexity [9] depending on the severity of the underlying substrate.[23] Although inducibility of AF by pacing in normal atrial structure is dependent on the protocol of pacing, [24] it has predictive value for the occurrence of POAF.[25, 26] This suggests higher susceptibility for AF at least in some of the patients who subsequently develop POAF.[27] Furthermore, AF occurring as a consequence of cardiac surgery in patients without a history of AF postulates a significant pathophysiological role for the surgical intervention itself.

Early pro-arrhythmic environment

In a recent review, we discussed the acute and chronic factors contributing to initiation of POAF, and emphasized that different mechanisms are responsible for AF in the acute post operative setting.[28]

Inflammation in the postoperative phase has been subject of extensive research as it has been linked to several local and systemic pro-arrhythmic effects. First of all, direct atrial trauma, e.g. the venous cannulation through the right atrium, has been shown to induce an inflammatory reaction leading to inhomogeneity in conduction in a canine model.[29] The canine sterile pericarditis model, in which application of sterile talc and subsequent pericarditis enhanced AF susceptibility, supports this hypothesis.[30] Administration of prednisone in this model reduced inflammation and as expected prevented AF.[31] Similarly colchicine was able to reduce the incidence of POAF, as a result of a reduction of the post-cardiotomy syndrome in humans. [32] Secondly, systemic inflammatory effects expressed as increased C-reactive protein levels, and therefore complement activation during cardio pulmonary bypass and during the acute post operative phase, were demonstrated to coincide with the peak POAF incidence, advocating a direct immune reaction mediated by the complement system.[33] Indeed, the use of cardio pulmonary bypass is correlated with POAF incidence in most studies.[5, 34] Thus as expected, oral corticosteroids reduce not only the postoperative inflammatory markers, but also the incidence of POAF as demonstrated by an extensive meta-analysis.[35]

Furthermore, cardiopulmonary bypass might lead to insufficient cooling of the atria during the cardioplegic arrest.[36] This may induce a temporary substrate to initiate AF as a consequence of ischemia reperfusion injury.[36, 37] Indeed, oxidative stress has been shown to cause a transient pro-arrhythmic effect in the postoperative setting.[38] This can explain the anti-arrhythmic effects of statins in POAF prevention. Despite the anti-inflammatory effects of the HMG-CoA enzyme inhibitors, statins had no effect in predetermined substrates for AF, such as enlarged left atria.[39] In line with the effect of oxida-

tive stress in the direct postoperative occurrence of AF, administration of ascorbate acid preserved the length of the effective refractory period (ERP) during rapid pacing in a canine model, and reduced POAF especially in the very early postoperative phase in humans.[40] Similarly, the antioxidant N-acetylcysteine reduced the incidence of POAF in the early postoperative phase.[41] These findings suggest that independent of a pre-existing vulnerability to AF, surgery itself can have several pro-arrhythmic consequences on the atrial tissue based on ischemic and inflammatory effects.

Postoperatively, as a counterbalance to anaesthesia induced hypotension, systemic inflammatory response and cardiac stunning after aortic cross clamping fluid administration is required to keep up the cardiac output. Especially in hypertrophic ventricles, e.g. in aortic valve stenosis, significant volume therapy is applied for hemodynamic stabilization in the acute post-operative phase. In this setting, atrial enlargement seems to be an important factor in predicting POAF.[32] Acute atrial stretch decreases conduction velocity, increases conduction block and thereby the vulnerability of the atrial tissue to re-entry.[42-44] In addition, premature atrial beats initiate postoperative AF,[45] partly aggravated by high sympathetic activation.[6] Possibly they are also due to increased L-type calcium currents (I_{ca}^{2+}) in patients developing POAF.[46] Indeed, milrinone, a phosphodiesterase inhibitor inotropic agent, increased the incidence of POAF significantly, presumably through a protein kinase-A activation leading to triggered activity. [47]

It can be concluded that transient local and systemic changes in the acute postoperative phase after cardiac surgery are linked to POAF. They cause conduction disturbances and may enhance triggers for AF both of which together will enhance the susceptibility to AF.

Histopathological substrate

In addition to postoperative acute phase triggers, several long-term mechanisms have been identified to also predict POAF. These mechanisms are known to produce a more sustained substrate for AF, which favors AF maintenance rather than initiating it. The complexity of AF in these patients is therefore higher and recurrences are more likely after discharge, compared to AF in the less pronounced substrates, which are confined to solely acute phase POAF.

First, POAF is a disease of advanced age.[1, 48] The atrial wall becomes fibrotic with age[49] and this has been identified as one of the most important structural substrates for AF perpetuation in the non-operative setting.[10, 23] Prolonged signal averaged p-wave duration may reflect atrial fibrosis resulting in conduction delays and has been reported to be a predictor of POAF.[50-52] However, pre-operative AF was not excluded in all these studies.[50, 51] Nevertheless this finding suggests an increased AF vulnerability in patients with intra-atrial conduction delays particularly in a pro-arrhythmic environment.

Several co-morbidities have also been shown to increase the chances of POAF development, such as chronic obstructive pulmonary disease,[48, 53] hypertension, obesity

and systolic dysfunction.[1, 53] The role of these co-morbidities in the perpetuation of AF has long been established.[8, 54] Obesity has been associated with ERP shortening in left atria, diastolic dysfunction and left atrial dilation, all of which predispose to AF.[5]

In congestive heart failure, Sanders et al. demonstrated increased vulnerability to AF due to prolonged P-wave duration, prolonged ERP duration at the right atrial wall and significantly longer sinus node recovery time.[27] Accordingly, prolongation of conduction time with a higher percentage of double potentials and longer iso-electric intervals is linked to severely disturbed substrates. [10, 23] These pro-arrhythmic changes seem to occur due to chronic dilated atria, as a consequence of congestive heart failure or longstanding valve pathology for example. In line with these findings, left ventricular diastolic dysfunction was determined as an additional predictor of POAF.[55] On the biochemical level, stretch activated channels (SAC's) increase intracellular Na^+ concentrations. As a consequence, the Na^+/Ca^{2+} exchanger extrudes less Ca^{2+} to the extracellular space, thereby enhancing Ca^{2+} binding to the actin-myosin response. In this setting intracellular calcium overload causes a down regulation of $I_{ca}{}^{2+}$-gene expression, subsequently shortening the ERP.[56] Also chronic stretch has been associated with altered matrix metalloproteinase expression and angiotensin II mediated fibrosis.[10] Thus as expected preoperative atrial enlargement has been shown to increase risk for POAF. [57] Furthermore, preoperative dispersion of refractoriness and a prolonged PR interval predicted POAF after CABG.[58] Atrial structural changes have also been attributed to the uncontrolled ventricular rate and congestive heart failure leading to atrial stretch, apoptosis and myolysis.[59] Although apoptosis has not consistently been found in the atrial tissue of patients developing POAF, myolysis has been advocated as a pre-existing structural substrate in these patients.[60, 61]

Another important structural abnormality, which is closely linked to the propagating abilities of the atrial wall, is the gap-junctional connexin (Cx) distribution. Higher and more heterogeneously distributed levels of Cx 40 have been demonstrated in POAF patients.[62] Also local inflammation caused a reduction in Cx 40 and 43 expressions in the epicardial level, compared to normal distribution in non-inflammatory circumstances.[63] The exact role of connexin expression changes in POAF still needs to be defined.

From these findings it can be concluded that at least in some of the patients developing POAF after cardiac surgery, severely altered atrial architecture already is present before the operation. These structural alterations make the atria prone to not only POAF but also to AF in general. This is important because POAF might be an expression of the atrial vulnerability that is detected due to continuous monitoring in a period with excessive triggers, a "poor man's exercise" effect. This strongly implies close monitoring of these patients later on. Figure 1 gives a possible course of POAF development and perpetuation after cardiac surgery and after discharge.

Treatment strategies also provide additional information for the possible mechanism that is responsible for POAF. The positive effects of class III anti arrhythmic drugs for example, suggest a role for a re-entry mechanism, in which shortening of the excita-

ble gap might be the key element in their effectiveness, while beta-adrenergic blockers advocate a more prominent role for the sympathetic activation and triggers for AF.[5, 64]

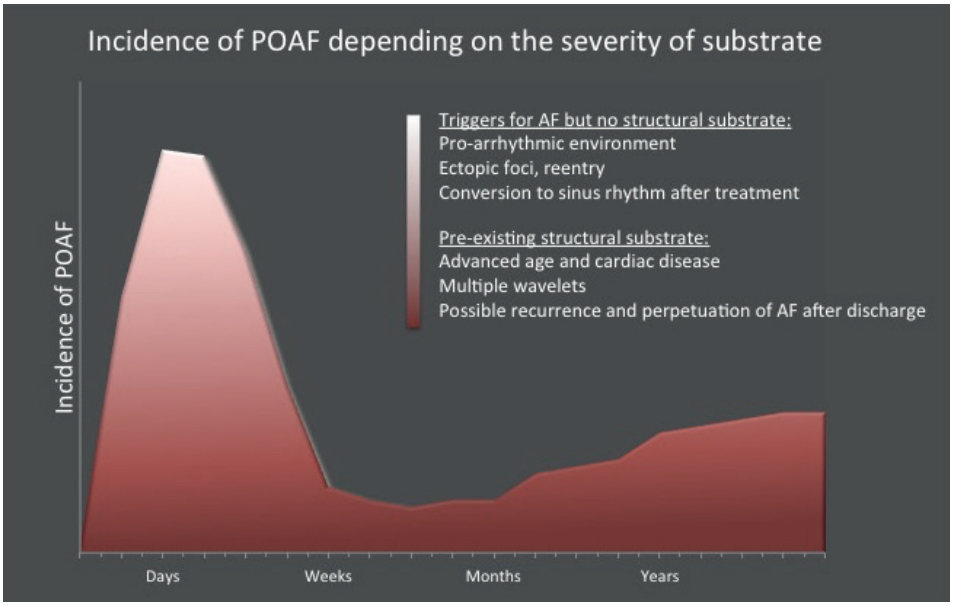


Figure 1 A schematic sketch of incidence of POAF in the early postoperative phase (i.e. the first post-operative week) and during the late postoperative phase (i.e. weeks to years following cardiac surgery) after discharge. In severely aggravated atrial substrates, POAF might continue to exist and reoccur. Red area under the curve represents patients with a preexistent structural substrate, e.g. atrial enlargement or heart failure, which is not easily reversible. White area under the curve represents patients with less severe structural substrate but who are exposed to the pro-arrhythmic environment of the acute-postoperative phase.

Prevention

Beta-Blockers

It has become clear from multiple meta-analyses, reviews, and large cohort studies, that the peri-operative use of β-blocking agents reduces the incidence of atrial fibrillation after cardiac surgery.[65-67] Furthermore, it is evident that the peri-operative use of β-blockers reduces mortality.[66] This knowledge has led to unambiguous recommendations of the use of β -blockers as standard of care in the prophylaxis of POAF in patients without contra-indications.[8, 68-70]

Sotalol

Sotalol has a greater efficacy in preventing POAF than standard β-blockers,[65] but has possibly more unfavorable adverse event profile. The extent of side effects of sotalol,

such as prolongation of the QT-interval, compared to standard β-blockers is debated. Because sotalol exposes patients to the risk for torsade des pointes, its use requires close monitoring, and under these conditions may be considered for the prevention of POAF. [8, 54, 68, 70]

Amiodarone

Amiodarone with its class III anti-arrhythmic effects is a strong preventive drug in the acute postoperative setting.[20, 71] Prophylactic amiodarone, with or without concomitant use of β-blockers also has a positive effect on duration of hospital stay, postoperative stroke, and postoperative ventricular tachyarrhythmia.[20, 65, 71-73] However, in one trial the effects of amiodarone were not superior to placebo in patients with enlarged atria and in patients undergoing valve surgery. These are important characteristics of patients with a strong structural substrate[43, 71] suggesting its effectiveness relies on the prevention of triggers in the early pro-arrhythmic environment. Common adverse effects of amiodarone are bradycardia and hypotension,[74, 75] which lead- together with extra cardiac side effects- to cessation of the treatment in up to 20% of all patients.[76] The pre-operative administration of amiodarone should be considered in patients with high risk for the development of POAF, according to the international guidelines,[8, 54] and should certainly be considered in patients with a contraindication for the use of β-blockers.[68, 70]

Biatrial pacing

Bi-atrial pacing significantly reduces the incidence of POAF,[65, 73] although it has been reported to be difficult to apply. Some studies demonstrated even pro-arrhythmic side effects and also unintentional diaphragmatic or left ventricular pacing are common.[52, 77-79] However, when sensing and capture thresholds of the pacemaker leads are followed accurately, particularly simultaneous biatrial pacing effectively prevents POAF. [7, 80-84] The main effects of postoperative atrial pacing on the atria are still unclear. It has been proposed that simultaneous biatrial pacing reduces dispersion of refractoriness and reduces the P-wave duration and dispersion. [52, 85] Also, overdrive pacing might prevent ectopic activity.[82] At the ventricular level, overdrive pacing after an ischemic episode has been shown to reduce infarct size, based on prevention of ischemic reperfusion injury.[86] More research is required to define the exact mechanisms of AF prevention by pacing at the atrial level, and to determine the population in which pacing is effective.

ACE-inhibitors

Angiotensin concerting enzyme inhibitors (ACEI's) may be as effective in preventing POAF as they are in permanent AF in general population.[87] Although administration of ACEI's have been associated with reduced POAF incidence,[48, 88] recent reports show conflicting results. Most importantly increased adverse effects are reported in some

studies, including hypotension, renal failure, higher mortality and a paradoxical increased risk of POAF incidence,[89, 90] or at least no reduction of new onset AF after cardiac surgery.[91] More research is required to find true effects of ACEI's in the acute and late postoperative setting for the prevention of POAF.[8]

Benefits from other prophylactic measures, such as the administration of corticosteroids, Colchicin, or vitamin C, are postulated in some reports,[92] but lack sufficient evidence for standard practice. The use of statins as a prophylactic measure has shown conflicting results [8] although a meta-analysis showed significant POAF reduction in statin treated arm.[93] Intravenous administration of magnesium might reduce the incidence of POAF, although conflicting results on this issue are reported.[65] In patients without renal dysfunction the probability of adverse effects is very low. In these patients some [68] but not all guidelines recommend the perioperative use of magnesium. Further research on the usefulness, and applicability of these, and other preventive strategies is warranted.

Treatment

In the majority of patients, POAF will spontaneously convert to sinus rhythm within 24 hours after surgery. Correction of predisposing factors such as hypoxia, anemia, and electrolyte imbalance, should be the first step in the management of POAF. The superiority of a certain drug regarding rate control remains to be proven. Therefore the decision of the drug to be administered should be based on the side effect profile, contraindications, and local familiarity with the drug.[94]

In case of hemodynamic instability cardioversion to sinus rhythm by direct current (ECV) or pharmacologically with ibutilide or amiodarone, should be pursued. [95] Also if patients are highly symptomatic or when rate control is difficult to achieve, electrical direct current cardioversion is recommended.[8, 54]

Oral anticoagulation

Since the risk of stroke is increased in patients with POAF,[3] starting with oral anticoagulation within 48 hours of the onset of AF, is recommended.[8, 54, 68 96] In contrast to patients with AF in the general population, it has yet to be proven for patients with POAF that anticoagulation will decrease the risk of stroke. It is recommended to continue anticoagulation for at least 4 weeks after conversion to sinus rhythm,[95, 97] although convincing evidence is lacking.

Conclusions

The pathophysiology of POAF is not completely understood. In general, AF initiation and perpetuation has been attributed to (or a combination of) ectopic focal discharges and reentry primarily represented by multiple wavelets.[10] In the postoperative setting, it is conceivable that in different patients, different mechanisms perpetuate AF. This is reflected by the fact that the preventive and therapeutic strategies are only helpful in some patients in the early phase after cardiac surgery. In patients with highly diseased atrial tissue e.g. due to chronic atrial stretch or advanced age, AF might not only occur in the early postoperative phase, but also during the days and weeks thereafter. Indeed, data on late POAF is accumulating and shows a potential role for prolonged monitoring in high-risk patients.[2, 14, 98, 99]

Future research needs to address the incidence of 'late POAF' in the weeks and months after discharge. It is also of interest how this incidence depends on the heart disease and other clinical factors. Finally, the therapeutic implications of 'late POAF' need to be defined. As a first step towards these objectives more studies systematically studying 'late POAF' in different indication groups are urgently needed.

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3

A prospective randomized controlled trial on the incidence and predictors of late phase post-operative atrial fibrillation up to 30 days and the preventive value of bi-atrial pacing

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Abstract

Background Postoperative atrial fibrillation (POAF) is considered to be a transient arrhythmia in the first week after surgery.

Objectives The aim of this study was to determine the 30-day incidence and predictors of POAF and the value of postoperative overdrive biatrial pacing in prevention of POAF.

Methods Patients (n=148) without a history of AF undergoing aortic valve replacement (AVR) or coronary artery bypass graft (CABG) were randomized into a pacing group (n=75) and a control group. Patients were treated with standardized Sotalol postoperatively. Rhythm was continuously monitored for 30 days by a trans-telephonic event recorder.

Results POAF occurred in 73 patients (49.3%) of whom 60 patients (40.5%) showed POAF during postoperative days (POD) 0-5 and 37 patients (25%) during POD 6-30. Prolonged aortic cross clamp time (ACCT) was an important univariate predictor of 30-day and of late POAF (POD 6-30) (p=0.017, p= 0.03 respectively). Best-fit model analysis using 15 predetermined risk factors for POAF showed different positive interactive effects for early POAF (i.e. baseline C-reactive protein (CRP) levels with a history of myocardial infarction or low body mass index (BMI)) and late POAF (i.e. high BMI, diabetes mellitus, baseline CRP, early POAF, creatinine levels, type of operation, smoking and male gender). Biatrial pacing reduced the late POAF incidence in patients with ACCT > 50 minutes (p=0.006).

Conclusion POAF is not limited to the first week after cardiac surgery but also occurs frequently in the postoperative month. It is desirable to regularly follow POAF patients for AF recurrences after discharge.

Introduction

Historically, postoperative atrial fibrillation (POAF) has been defined as a transient arrhythmia in the first week after cardiac surgery, with a peak incidence between the second and third postoperative days. A growing body of evidence has identified POAF as an important risk factor for increased late mortality. [1, 2] Data on the incidence of POAF after discontinuation of in-hospital continuous telemetric monitoring are rare but increasingly important because POAF may show later occurrences. [3]

In addition, despite the several treatment and preventive strategies, the reported incidence of POAF remains high. [4, 5] Overdrive atrial pacing has shown conflicting results in previous studies when tested for POAF prevention. [6-9] To our knowledge, long-term effects of strategies to prevent POAF have not yet been studied. We hypothesize that episodes of AF frequently recur after the first postoperative week and aimed to determine the preventive value of synchronized biatrial overdrive pacing on the 30-day POAF incidence.

Methods

Population

Between October 2009 and July 2011, patients undergoing elective coronary artery bypass graft (CABG) or aortic valve replacement (AVR), without a known history of AF or any treatment for that purpose were enrolled in the study. Exclusion criteria were a history of AF, sick sinus syndrome or AV-block. The local medical ethical committee approved this trial.

Study protocol

All patients underwent elective CABG or AVR using cardiopulmonary bypass, through a median sternotomy, with the use of cold crystalloid antegrade cardioplegic support. Perioperatively two pairs of unipolar temporary atrial pacemaker wires (Flexon ™) were placed on the epicardium of the right atrial wall and on the Bachmann bundle in all patients (figure 1). Patients were randomized into a pacing and non-pacing group and all were treated with Sotalol during the first postoperative week, unless contraindicated (dosage and discontinuation left to the discretion of the attending resident and the cardiologist).

The rhythm of patients was monitored by daily review of the continuous telemetric monitoring (POD 0-3). Twelve lead ECGs were obtained on the first, second and fourth postoperative days. In addition, from the moment of cessation of in-hospital telemetric monitoring, continuous trans-telephonic monitoring was started for a total of 4 weeks. For this purpose an external one-lead trans-telephonic loop recorder (Vitaphone 3100 BT ™) with an autotrigger for AF, was used. It detects conversion of sinus rhythm (SR)

into AF and AF into SR. Clinical and rhythm-monitoring data were collected and analysed by blinded investigators.

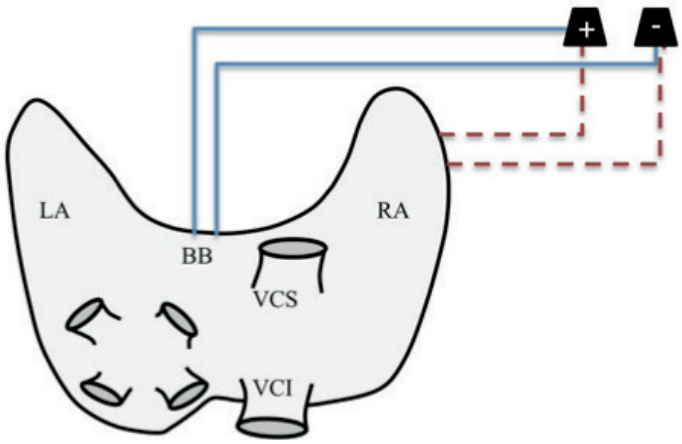


Figure 1. Schematic representation of the electrode placement. The right atrial (red line) and the Bachmann bundle (blue line) wire placement. BB= Bachmann's bundle; RA= right atrium; LA= left atrium; VCS= superior caval vein; VCI= inferior caval vein

Pacing protocol

After arrival at the cardiovascular intensive care unit, pacing wires in the pacing group were connected to the output of an external pacemaker and pacing protocol was initiated. The sensing and stimulus threshold of all wires were tested prior to chest closure and on a daily basis after surgery. The output was set at 2 times greater than the stimulation threshold of the pacing site with the highest threshold (i.e. Bachmann's bundle or right atrium). The sensitivity was set at half of the sensing threshold of the location with the lowest threshold. Pacing was maintained for 72 hours in AAI mode, 10 beats per minute (bpm) above the intrinsic heart rate (minimum of 80 and maximum of 120 bpm). Pacing was stopped during AF or sinus tachycardia > 110 bpm, and resumed after conversion to normal sinus rhythm (SR) to complete the 72-hour protocol. Uni-atrial right atrial pacing in the non-pacing group (POD 0) in response to bradycardia was not considered a protocol violation (n=7). In case of loss of capture and/or failure of sensing, the anode and cathode connections to the pacemaker were exchanged. The same was done when phrenic nerve pacing occurred. All pacemaker wires were removed after 72 hours.

Outcomes

Atrial fibrillation was defined as an irregular RR interval during at least 10 seconds, without a detectable p-wave. [10, 11] The event rate and duration of POAF was compared between study groups for early POAF (POD 0-5), late POAF (POD 6-30) and total POAF

(POD 0-30). Secondly, we aimed to determine demographic and clinical risk factors confounding the net effect of pacing on all outcome measures.

Statistical analysis

Metric variables are characterized by means and standard deviations, if they are normally distributed as tested by the Shapiro-Wilk test. Baseline patient characteristics between both randomized groups were tested by the Student t-test (if normally distributed), the Mann-Whitney test (if not) or the log-likelihood chi-square test (for categorical data).

Univariate analysis to examine the relationship of risk factors or variables with early POAF, late POAF and overall 30 day POAF are provided by means of absolutes and percentages, log-likelihood chi-square (χ^2_L), p-values of χ^2_L, odds ratios (OR) and 95% Confidence Intervals (C.I.) of the OR. Multivariate analysis on the three POAF incidence measures (early, late and total POAF) was performed by Cox regression analysis. At first, a univariate Cox regression analysis was performed using the experimental groups factor (non-pacing vs. pacing), in addition to a per protocol analysis for three groups (non-paced vs. sufficiently paced vs. insufficiently paced). Next, a direct-effects Cox regression model with only statistically significant effects on each of the three outcome measures was searched for by means of the backward elimination log-likelihood chi-square technique using a predetermined list of 15 risk factors for POAF in addition to the experimental factor. All first-order interactive effects of these risk factors between themselves and that of each risk factor with the experimental groups factor (nonpacing vs pacing) were group-wise and hierarchically tested by backward elimination log-likelihood chi-square. Finally, for each of the three measures separately a final Cox regression model was searched for containing only statistically significant effects. A p-value of less than 0.05 was considered to be statistically significant. All types of analysis were performed using SPSS-pc version 20.0.

Results

Patient characteristics

Of 163 patients who had given informed consent to participate, 15 patients (9.2%) were excluded due to surgical complications or difficulty of placement of the Bachmann bundle wires. Patients (n= 148) were followed for an average of 22.26 (± 9.98) days (range 4 - 42). Protocol violations occurred in the pacing group (i.e. pacing stopped before the end of the 72 hour protocol left to the discretion of the attending physician: 48 hours pacing n= 6; 24 hour pacing n= 8 and no pacing at all n= 6). Due to its potential pro-arrhythmic effects Sotalol was discontinued during the early postoperative phase in 55 patients (37.0 %) by the attending cardiologist. Two patients required amiodarone for

persistence of AF and no patients underwent electrical cardioversion. None of the patients died during the follow-up. Baseline characteristics in both groups were comparable except for COPD and DM. (Table 1)

Table 1. Patient characteristics

	Pacing (n= 75)	Non-Pacing (n= 73)	p
Age	66.5y (9.81 44-87)	68.3y (9.14 44-82)	P=0.198[b]
Male	61(81.3)	59(80.8)	P=0.937[a]
BMI	26.6 (3.82)	27.8 (3.57)	P=0.050[c]
LVEF <50%	18(24.0)	15(20.5)	P=0.614[a]
Hypertension	70(93.3)	67(91.8)	P=0.719[a]
COPD	2(2.7)	8(11.0)	P=0.038[a]
Preop β-blocker use	57(76.0)	54(74.0)	P=0.776[a]
Diabetes Mellitus	14(18.7)	24(32.9)	P=0.047[a]
History of smoking	23(30.7)	20(27.4)	P=0.661[a]
Hypercholesterolemia	70(93.3)	68(93.2)	P=0.965[a]
Myocardial infarction	13(17.3)	14(19.2)	P=0.771[a]
Creatinine	92.3 (27.44 50-243)	94.1 (24.52 56-194)	P=0.525[b]
ACCT	49.1 (15.52 25-95)	49.9 (17.52 19-115)	P=0.808[b]
CABG	66(88.0)	61(83.6)	P=0.439[a]
Number of anastomoses	3.1(0-6)	2.8(0-5)	P=0.141[b]9

BMI: body mass index; ACCT: aortic cross clamp time; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction. a = Log-likelihood chi-square test , b = Mann-Whitney test, c = Student t-test; Means with standard deviations and minima-maxima in brackets or numbers with percentages for both randomized groups.

POAF incidence

POAF occurred in 73 patients (49.3%) within the total 30-day follow-up period. The day-to-day prevalence of AF is shown in figure 2a and stratified by pacing and control group in figure 2b. In the early postoperative period (POD 0-5), 40.5% of the patients (n= 60) developed POAF, while the prevalence was 25.0% (n= 37) in the POD 6- 30. The durations of AF episodes during each day were added together and the total time in AF per day (AF burden) was calculated. Early POAF caused a larger AF burden (average 32.51 min, 0- 451 min) compared to late POAF (average 10.6 min, 0- 450 min, p< 0.001). Notably, AF burden of early POAF in patients (n= 24) developing additional late POAF was significantly larger (63.34 min in early POAF) compared to the AF burden in patients (n= 36) who only had early POAF (35.06 min in early POAF, p= 0.013). In thirteen patients (8.8%) the first episode of AF was detected during POD 6-30 (average duration 13.09 min).

Univariate analysis

In the univariate analysis only aortic cross clamp time (ACCT) was a statistically significant predictor of overall POAF (POD 0- 30) (p= 0.01). We found no significant predictors of early POAF. On the other hand, early POAF itself was a strong predictor of late POAF (p< 0.001). Also, patients with ACCT> 50min and patients who underwent AVR showed significantly higher incidence of late POAF.

Multivariate analysis

A high level of baseline CRP combined with a history of myocardial infarction or with low BMI was associated with higher chances of getting early POAF (p= 0.030 and p= 0.022 respectively) (Table 2). Seven interactive effects and one direct effect were found for the prediction of late POAF. In patients with ACCT> 50min, pacing reduced late POAF (p= 0.006) while it did not in the overall patient population. Pacing in patients with high pre-operative levels of creatinine (> 129 umol/L) increased the risk of late POAF (p= 0.041). These results have been corrected for the remaining 5 interactive effects (Table 3).

The highest significant interactive effect for prediction of total 30-day POAF was the combination of high (> 1.0 mg/L) level of baseline CRP and a history of MI (p= 0.008). In addition, a high (> 60min) ACCT (p= 0.017) and smoking tended to be associated with overall POAF (p= 0.051) (Table 4). No effects of Sotalol in the prevention of POAF were seen in the final models.

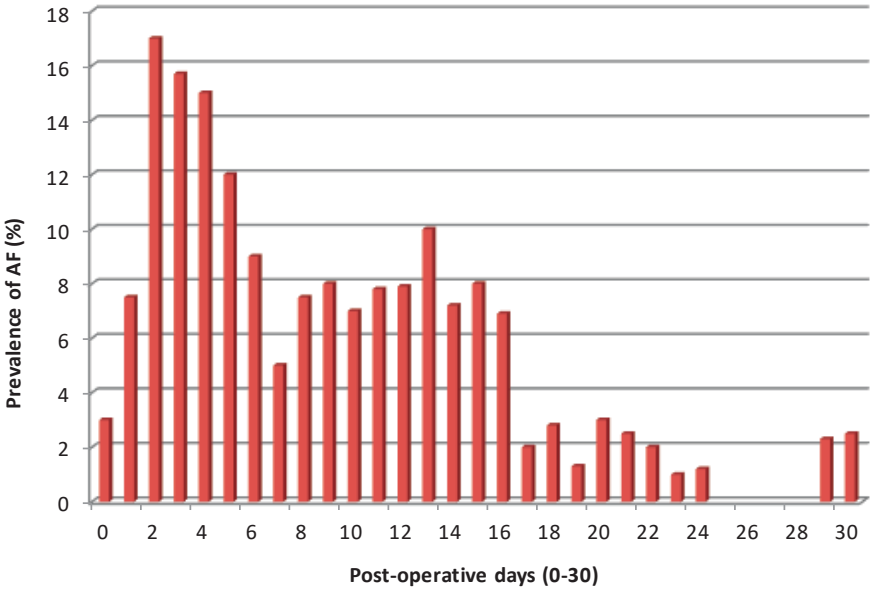
Per protocol analysis

To determine the true effect of 72 hour pacing on POAF, a per-protocol analysis was performed. For this purpose we compared patients who were biatrially paced for a total of 72 hours post surgery (n= 52), with the non-pacing group (n= 73). In this approach the patients who were insufficiently paced were excluded (n= 23, 15.5%). No significant effect of pacing on POAF was seen in this analysis.

Table 2: Multivariate analysis for early POAF

Predictors	Ln. Regression	S.E.	Loss in χ^2_L	p	Cox reg	95% C.I.
BMI	0.086	0.057			1.090	0.974-1.220
CRP	0.830	0.419			2.293	1.009-5.213
MI	-0.367	0.493			0.693	0.264-1.820
Pacing	0.013	0.266	0.002	0.961	1.013	0.602-1.706
BMI*CRP	-0.034	0.016	5.217	0.022	0.967	0.937-0.998
MI*CRP	0.248	0.110	4.708	0.030	1.281	1.033-1.589

Results of the final, best-fitting Cox-regression model for early POAF (POD 0-5): The model comprises one (non-significant) direct effect for Pacing and two interactive effects. n=148. BMI: body mass index; CRP: C-reactive protein; MI; myocardial infarction;



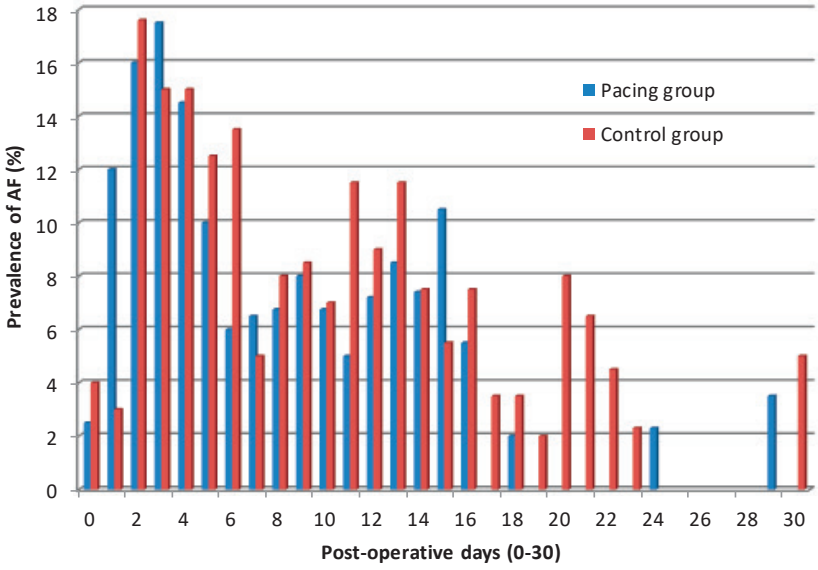


Figure 2a(top). Daily prevalence of POAF and **Figure 2b(bottom)** Incidence of POAF as stratified by pacing and control group.

Table 3. Multivariate analysis for late POAF

Predictors	Ln. Regression	S.E.	Loss in χ^2	p	Cox reg	95%C.I.
BMI	0.048	0.060			1.050	0.934-1.180
ACCT	0.038	0.014			1.039	1.010-1.068
Baseline Creatinine	-0.054	0.020			0.947	0.912-0.984
CABG(0)→AVR(1)	3.736	2.282			0.024	0.000-2.089
Diabetes Mellitus	-18.859	5.060			0.000	0.000-0.000
Smoking	-2.881	2.039			0.056	0.001-3.049
Baseline CRP	-0.382	0.148			0.682	0.510-0.912
Early POAF	0.441	0.214			1.555	1.022-2.366
Pacing (0→1)	-1.339	1.946			0.262	0.006-1.882
Gender	2.088	0.760	11.352	0.001	8.068	1.818-5.805
BMI * DM	0.605	0.159	14.372	<0.001	1.830	1.341-2.498
ACCT * Pacing	-0.061	0.023	7.453	0.006	0.941	0.899-0.984
Creat* Operation	0.061	0.026	6.083	0.014	1.063	1.011-1.118
Creat * Smoking	0.040	0.022	3.826	0.050	1.041	0.997-1.087
DM * early POAF	1.011	0.503	4.210	0.040	2.747	1.025-7.361
Creat * Pacing	0.035	0.018	4.178	0.041	1.035	1.000-1.072
CRP * Early POAF	0.132	0.049	6.486	0.011	1.141	1.036-1.256

Results of the final, best-fitting Cox-regression model for late (6-30 days follow-up) post- operative AF. The model comprises one direct effect for Gender and six interactive effects including one involving a specification for Pacing. N=148. (Abbreviations as in Tables 1 and 2)

Table 4. Multivariate analysis for total 30-day POAF

Predictors	Ln. Reg	S.E.	Loss in χ^2_L	p	Cox reg	95% C.I.
History of MI	-0.891	0.512			0.410	0.150-1.120
Baseline CRP	-0.087	0.042			0.917	0.844-0.995
Pacing (0-1)	-0.052	0.242	0.046	0.829	0.949	0.591-1.524
ACCT	0.017	0.007	5.658	0.017	1.017	1.003-1.031
(Ex)smoker (0-1)	0.527	0.264	3.818	0.051	1.694	1.011-2.841
MI*Baseline CRP	0.325	0.118	7.089	0.007	1.384	1.098-1.744

Results of the final, best-fitting Cox-regression model for total (0-30 days) follow-up postoperative AF. The model comprises one (non-significant) direct effect for Pacing and two interactive effects. N=148. (Abbreviations as in Tables 1 and 2)

Discussion

Previous studies have demonstrated that POAF is associated with an increase in long-term mortality. [1, 2, 12, 13] This observation suggests that POAF does not only occur during the first postoperative days but also in the weeks and months thereafter. If this is the case, early discontinuation of oral anticoagulation may have adverse effects. Notably,

continuation of warfarin after discharge showed protective effects against long-term mortality in one report. [1]

However, information on incidence and prevalence of 'late' POAF is very limited. To our knowledge, this is the first trial using continuous monitoring to detect late episodes of POAF after discharge. We demonstrate that POAF is not transient in the first week, but has 25% prevalence between day 6 and day 30 after the operation.

Early POAF

We demonstrate an important predictive effect of baseline CRP levels in patients with a previous MI and in low BMI patients for early POAF incidence. This is in line with the established role of systemic and local inflammation in early POAF. Higher baseline CRP levels before cardiac surgery have been hypothesized to start early complement activation during cardiopulmonary bypass, aggravating the acute postoperative systemic inflammation, which may lead to POAF. [14] Local inflammation has shown pro-arrhythmic effects in the sterile pericarditis model in dogs, in which sustained atrial flutter was inducible. [15] Also in a canine model of direct atrial trauma, activation maps revealed inhomogeneous conduction, which was diminished by treatment with methylprednisolone. [16]

Our results are in line with previous findings suggesting a postoperative transient pro-arrhythmic environment e.g. due to inflammation, oxidative stress, [17] acute atrial stretch due to hemodynamic changes, [18] and high sympathetic activity [19] consequently elicits AF in a fairly large population with limited structural heart disease. [10]

Furthermore, we demonstrate that the combination of low BMI with higher baseline CRP levels predicts early POAF, while high BMI levels predict late POAF. The vulnerability of low BMI patients has been demonstrated by increased short and long term mortality in patients undergoing CABG. [20] On the other hand, several pro-arrhythmic electrophysiological and mechanical changes in obese patients may contribute to a pro-arrhythmic substrate for AF [21] and high BMI has been shown to predict POAF.[22]

Late POAF

Early POAF consisted of longer episodes in patients who later on had additional late POAF, compared to patients who developed early POAF only. Also predictors for late POAF differed from factors predicting early POAF. Late POAF predictors include renal dysfunction (measured by creatinine levels) in smokers or in patients undergoing AVR, obesity and DM, early POAF both in combination with DM and high baseline CRP levels (>3mg/L) and finally male gender. Although some of the interactions may not have a causal effect in the postoperative setting, these morbidities have been identified as risk factors for AF in general. [23-26]

Despite the fact that the substrate for POAF is partly caused by the surgery itself, [27] the similarity in risk factors of late POAF and AF in general suggest common mecha-

nisms enhancing AF susceptibility in this group of patients. [28] Furthermore several structural abnormalities which potentially contribute to AF in general, have also been demonstrated in POAF patients, e.g. atrial enlargement, [29] fibrosis, [30] heterogeneous connexin distribution [31] and myolysis.[32]

Pacing in POAF

Overdrive pacing has been successfully used to treat sick sinus syndrome [33] and paroxysmal AF. [34] Biatrial pacing (i.e., 80-100 bpm, during 5 minutes) also produces favorable hemodynamic changes and shortens the P-wave duration. [35, 36] In the postoperative setting, biatrial overdrive pacing has been hypothesized to reduce dispersion of refractoriness and prevent ectopic activity. [9, 35, 37] Although previous studies showed promising effects of this strategy in early POAF, [4] their results have not been fully comparable, because of differences in pacing protocol and definitions of AF varying between minutes [35] to hours of AF. [38] Also the pacing sites have not been consistent. In our study, the pacing wires were placed on the right atrial free wall and on the Bachmann bundle. Some studies used posterior left atrial wall instead of the Bachmann bundle, [9] and the right atrial free wall is used in most reports.[39] However, the Bachmann bundle is not only easily accessible by the surgeon, but also seems to be the preferred site for pacing in atrial fibrillation.[40, 41] This is partly explained by the anatomical position of the bundle as a major pathway between right and left atrium. [42] In addition, biatrial pacing in POAF has shown superior results when compared to other pacing modalities (eg. right or left atrial pacing alone).[39]

In this study, biatrial pacing reduced the risk of late POAF incidence in patients with ACCT > 50 minutes, but did not affect early POAF. This effect may be explained by prevention of higher levels of oxidative stress which occur due to atrial ischemia in prolonged ACCT.[43] The effects of reperfusion injury are carried out beyond the first week and may affect late POAF more significantly. However, more research is required to address this question.

Study Limitations

The incidence of late POAF may be underestimated due to the required patient compliance in Vitaphone 3100 ™ device handling. Despite this limitation, we detected a high incidence of POAF after discharge. Known AF predictors such as hypertension, heart failure and age had no predictive value in this relatively small study. This is due to a high prevalence of hypertension and low prevalence of heart failure in this population (i.e. more than 90% of our population had hypertension and less than 4% had an LVEF <35%) and low variation in age amongst participants.

Conclusions and clinical implications

POAF is not limited to the early postoperative phase, but recurs in some patients at least in the first postoperative month. In current clinical practice oral anticoagulation (OAC) is often discontinued after conversion of POAF to SR. [24, 44, 45] According to our results and previous studies, it is desirable to regularly follow POAF patients for AF recurrence and treat the high-risk patients accordingly.

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4

Assessment of clinical and electrophysiological predictors of late recurrences of postoperative atrial fibrillation detected by implantable loop recorder

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Abstract

Background Postoperative atrial fibrillation (POAF) is a common complication of cardiac surgery. While early POAF occurs during the acute postoperative phase, late POAF can re-occur in the months thereafter, increasing the risk of stroke and mortality. Given the clinical risk profile of cardiac surgery patients, a predisposing structural and electrophysiological substrate for AF is likely to exist. Using epicardial mapping to determine the complexity of AF, we assessed the clinical and electro-pathological profile predicting early and late POAF.

Methods Patients without a history of AF undergoing cardiac surgery were included. Prior to cardiopulmonary bypass, electrically induced AF was mapped epicardially using a high-density 256-unipolar electrode plaque on the right atrial (RA) wall. Electrophysiological parameters such as the number of waves per cycle, fractionation index and breakthrough/cycle (BT/cycle) were quantified. P-wave analysis of the preoperative 12-lead electrocardiogram was conducted in all patients and correlated to POAF development. After surgery, patients were followed for 3 years using a continuous rhythm monitoring implantable loop recorder for AF detection and a remote monitoring system. Early POAF was defined as AF detected during the first 5 postoperative days, late POAF was defined as an irregular RR interval detected on a 2-minute ECG lead between postoperative day (POD) 6 until end of follow up. Clinical and electrophysiological data were compared between patients developing early and/or late POAF and those without POAF.

Results All patients (N= 79, 75% male) had hypertension and underwent either coronary artery bypass graft (72.2%), aortic valve replacement (22.8%), or mitral valve replacement (5.1%), with an average aortic cross clamp time of 60 minutes. POAF occurred in 46 patients (58.2%); early POAF in 27 patients (34.2%) and late POAF in 37 patients (46.8%), with an average duration per episode of 218.6 ±284min vs 91.3 ±173.3min respectively (p =0.04). Daily early POAF burden was significantly longer when additional late POAF occurred (370 ±276.9 vs 165.7 ±169.8 min, p=0.05). Age and $CHA_2DS_{25}VASc$ score were significantly higher in POAF patients and early POAF was a predictor of late POAF. P-wave amplitude was significantly lower in patients with early POAF; PQ time was prolonged in late POAF and P-wave duration shorter in patients developing both early and late POAF. Multivariate analysis of clinical an electrophysiological data revealed age as an independent predictor in all POAF and CHA_2DS_2VASc score as an independent predictor of early POAF. In addition, RA volume, RA waves/cycle and age were independent predictors of late POAF.

Conclusion After cardiac surgery, late POAF recurrences are common, with a higher CHA_2DS_2VASc score, advanced age and RA volume as predictors. Besides, a pre-existing electrophysiological substrate predisposes patients to POAF and its recurrences. Patients with high CHA_2DS_2VASc score developing early POAF should be followed intensively for late POAF recurrences.

Introduction

Postoperative atrial fibrillation (POAF) after cardiac surgery is prevalent in up to 50% of patients in the first postoperative days and reoccurs in up to 30% in the following year.[1,2] Early POAF occurring during the first postoperative days is a predictor of AF after discharge, [2-4] and predicts increased late mortality and stroke rate in the months to years following the initial operation.[5-9] In addition, long-term protective effects of anti-arrhythmic drugs[5] and oral anticoagulation[8] in patients developing POAF suggests that indeed late POAF recurrences contribute to increased risk of stroke.[10] However, data on incidence and burden of POAF in the years following cardiac surgery are scarce.

The clinical risk profile of patients developing POAF includes risk factors such as valvular heart disease, coronary artery disease, advanced age, hypertension, and heart failure, [11, 12] closely resembling that of AF in the general population.[13, 14] Although the surgical trauma and the acute postoperative phase contribute to a transient phase of prevalent early POAF,[15] the predisposing co-morbidities in POAF suggest that atrial structural remodelling predisposes to POAF and presumably contribute to its recurrences on a longer term.[10] Direct contact epicardial mapping of the atrial wall is a well-established technique for assessing the substrate for AF, varying from a low complexity of fibrillation patterns in acutely induced AF in normal atria[16] to more complex patterns with higher number of simultaneous wavelets and breakthrough waves in persistent AF.[17] The relation between substrate complexity and late POAF incidence is yet unknown.

We hypothesized that POAF occurs more frequently in patients with a pre-existing substrate, which also predisposes patients to late POAF. We also aimed to determine the electrophysiological substrate of early and late POAF assessed by direct contact epicardial high-density mapping of the right atrium during cardiac surgery.

Methods

Study population

Between May 2012 and September 2014, patients without a history of AF, undergoing open chest cardiac surgery using cardiopulmonary bypass were included. All available electrocardiograms, rhythm monitoring data and data obtained from the general practitioner were reviewed for AF episodes prior to hospitalization. Patients had to be 18 years of age and able to sign informed consent. Exclusion criteria were sick sinus syndrome and AV-block. The local ethical committee approved of this protocol.

Epicardial mapping protocol

Under general anaesthesia, after sternotomy, epicardial atrial pacemaker wires (Flexon™) were placed on the right atrial appendage. Atrial fibrillation was induced by atrial burst pacing (max 800 beats per minute (bpm) and/or incremental/decremental pacing. Induction attempts were stopped in case of hemodynamic instability, or when AF was not inducible after 10 minutes of atrial burst pacing. A custom-made high-density square electrode array (FlexMEA, Maastricht Instruments BV, Maastricht, The Netherlands – 26x26mm, 256 electrodes, electrode diameter 0.1mm and inter-electrode spacing 1.5mm) was used for direct contact epicardial mapping. Unipolar AF electrograms were recorded from the right atrial wall using an amplifier (filtering bandwidth 0.1–400Hz, sampling rate 1kHz). After epicardial mapping was completed, cardiopulmonary bypass was initiated.

All files were analysed using an automated analysis described previously.[18] In short, electrograms were filtered through a 0.5Hz high-pass filter with cancellation of far-field ventricular complexes followed by a probabilistic algorithm detecting steepest negative local deflections per electrode, accounting for AFCL distribution. From the local deflections, waves were constructed using wave conduction likelihood method based on the normal distributions of conduction velocity (CV) and conduction deviation. We considered a CV <20cm/s as conduction block. Non-local deflections were considered farfield activity if they were larger than 25% of the median of intrinsic deflections. Fractionation index was calculated as the ratio between these large non-intrinsic and intrinsic deflections.

ECG P-wave analysis

The day prior to the operation a 10-second ECG was digitally recorded in all patients with a sampling frequency of 250Hz, and analysed in Matlab (The Mathworks, Inc., Natick, Massachusetts, United States). The ECGs were filtered using a bandpass filter 1-100Hz. Parameters used for analysis included: averaged P-wave duration, dispersion, area, amplitude and PQ-time.

AF detection during follow up

After the operation all patients underwent continuous telemetric monitoring in the nursing ward until discharge (minimum 3 days). At least 2 ECGs were recorded during the first postoperative week. Following the closure of the sternotomy, a Reveal XT™ (Medtronic Minneapolis, MN, USA)[19] was inserted at the left parasternal area. This implantable loop recorder (ILR) classifies brady- and tachy-arrhythmias based on a specific algorithm for detection of irregular RR intervals lasting at least 2 minutes. All patients received a remote monitoring system (CareLink®) at postoperative day 3 for a period of 3 years. Patients were instructed to interrogate the ILR once in two weeks.

The interrogated episodes were stored in a protected central database (Medtronic Minneapolis, MN, USA). Each interrogated event contained episodes that were stored between the last session and the current interrogation. Only episodes containing an ECG recording were included in the analysis. Events stored as text only were excluded. Patients were contacted at 3 months, 1 year and 2 years and at detection of AF episodes and asked for any symptoms of palpitations, changes in medication or hospitalisations. Recurrent AF episodes were discussed with the patient's cardiologist and treatment or initiation of oral anticoagulation was left at the discretion of the cardiologist.

In this study, early POAF was defined as an irregular RR-interval, without evident P-waves, detected during the first postoperative days (POD) usually on telemetric monitoring or ECG lead. Late POAF was defined as an AF episode detected by the ILR on a one lead ECG of at least 2 minutes, between POD 6 until the end of the 3-year follow-up period.

Statistics

Analysis was performed using SPSS (IBM SPSS statistics version 21.0). Data are expressed as mean ± SD or percentages. Patients developing POAF at different time points were compared to patients without POAF using an unpaired Student's-t-test or analysis of variance (ANOVA). For differences between early and late POAF a paired Student's-t-test was used if normally distributed or Wilcoxon Rank sum test if not. Categorical data were analysed using Pearson's chi-square test. P-values <0.05 were considered statistically significant. For multivariate analysis we first conducted a univariate logistic regression analysis of 10 predetermined clinical and electrophysiological variables using total POAF, early POAF, late POAF and early AND late POAF as dependent variables. Afterwards we used the variables with $p<0.05$ in a multivariate logistic regression analysis (backward elimination, assessing goodness-of-fit with a Hosmer-Lemeshow test). For the multivariate analysis we excluded the electrophysiological data from the epicardial mapping (due to loss of power) but conducted a subgroup multivariate analysis including these data.

Results

Clinical data

Seventy-nine patients were included and received a Reveal XT™ (Medtronic Minneapolis, MN, USA) of whom 6 were explanted during follow-up due to pain or infection. Patients were on average 65 years of age, all had hypertension, with an average CHA_2DS_2VASc score of 2.4±1.3. In this population 72.2% underwent CABG alone with an aortic cross-clamp time of 60±25min. Right atrial volume was on average 52±15.7ml.

Pre-operatively, most patients were treated with a beta-blocking agent (72.2%) and statins (84.8%) (Table 1). Postoperatively all patients received standardised beta-blockers for POAF prevention unless contraindicated, although this was left at the discretion of the treating physicians.

Table 1: Basic clinical characteristics

Clinical parameter	N = 79
Age (years)	65 (±9.0)
BMI	27.5(±4.5)
RA-volume (ml)	51.87(±15.68)
RAVI	25.2 (±8)
LA-volume (ml)	79 (±24.5)
LAVI	40.2 (±14.4)
LVEF	60%(± 5%)
Creatinine	90.1(±21.2)
COPD	11(13.9%)
HATCH score	1.7(±1.1)
CHA_2DS_2 VASc	2.4(±1.3)
- *CHF*	10 (12.70%)
- *Hypertension*	79 (100%)
- *Age>75/ 65-75*	13 (16.46%)/ 23 (29.11%)
- *Diabetes*	16 (20.25%)
- *Stroke/TIA*	6 (7.59%)
- *Vascular disease*	15 (18.99%)
- *Sex*	20 female
CABG	57 (72.2%)
AVR± CABG	18 (22.8%)
MVR± CABG	4 (5.1%)
ACCT	60min (±25)
ICU-stay (days)	1.5 (±1.6)
B-blockers	57(72.2%)
ACE inhibitors	27(34.2%)
Statins	67(84.8%)

BMI=body mass index; RA= right atrium; CABG= coronary artery bypass graft; AVR=aortic valve replacement; MVP=mitral valve repair/replacement; LAVI/RAVI=left and right atrial volume index; LVEF= left ventricular ejection fraction; CHA_2DS_2 VASc score = CHF, congestive heart failure/ hypertension/ age/ diabetes/ sex/vascular disease; HATCH score= hypertension/ age>75years/ transient ischemic attack (TIA) or stroke/ chronic obstructive pulmonary disease (COPD) /heart failure; ACCT=aortic cross clamp time.

POAF-prevalence

During a follow-up of 3 years (range 5 days - 36 months), 3605 device interrogations were sent to the Carelink® central database for analysis (mean 48 per patient, range 3-

150). Forty-six patients (58.2%) developed POAF. Early POAF was detected in 27 patients (34.2%). Interestingly, two thirds of this group (18 patients, 22.8% of total) had additional late POAF episodes. In addition, 19 patients (24.1%) developed only late POAF without any early POAF episodes. Nine patients (11.4%) developed only early POAF without any late POAF episodes (Table 2).

Table 2. POAF incidence n=79(%)

	late POAF –	late POAF +	Total
early POAF –	33 (41.77)	19 (24.05)	52 (65.82)
early POAF +	9 (11.39)	18 (22.78)	27 (34.18)
	42 (53.16)	37 (46.84)	79 (100)

Cross tabulation between early and late POAF.

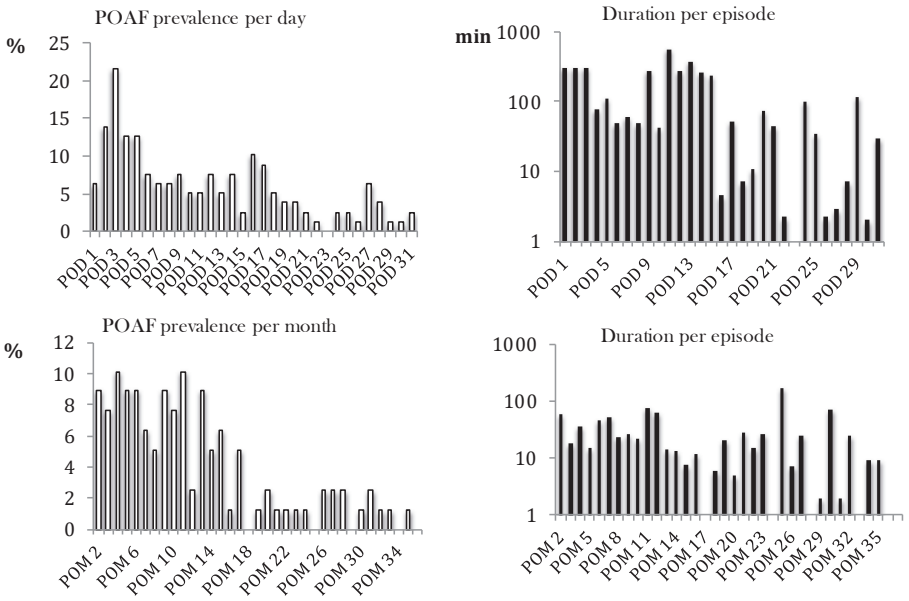


Figure 1. Prevalence of POAF in the first postoperative month (top left) and the following months excluding the first month (bottom left) and the average duration per episode on a logarithmic scale in the first postoperative month (top right) and the following months (bottom right). POD=postoperative day, POM=postoperative month.

The temporal variation in POAF incidence is presented in figure 1. As expected, the peak incidence of POAF occurred during the first few days after the operation with a notable decline after POD 5. However, after this period, there is a steady incidence of 5-10% in the following 17 months, slowly declining in the months thereafter, presumably due to decreased intensity of rhythm follow-up (inherent memory limitations of ILR, patient compliance and loss to follow-up). On the other hand, the average duration per episode on a daily basis remained consistent ranging between 10-100 minutes until the end of

the follow-up period. On average, the duration per episode in early POAF was longer than in late POAF (219 ±284min vs 91±173min, p=0.02) (Figure 2). Daily early POAF burden was also significantly longer in patients developing additional late POAF, compared to early POAF only (370±277 vs 166±170 min, p=0.05). In late POAF, 3 patients developed >24 hours of AF. Patients were contacted after recurrent late POAF episodes were diagnosed with the loop recorder.

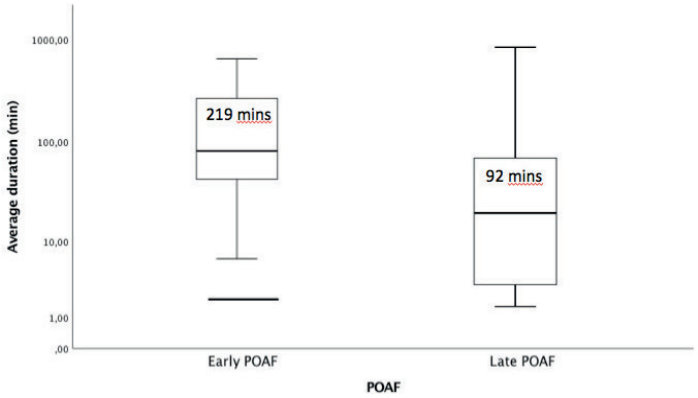


Figure 2. Boxplot of average duration of early and late POAF.

Interestingly, as depicted in figures 3a and b, the first episode of AF occurred between 10-40 weeks up to 100 weeks in 1 patient. Sixteen patients (20%) received oral anticoagulation by their treating cardiologist.

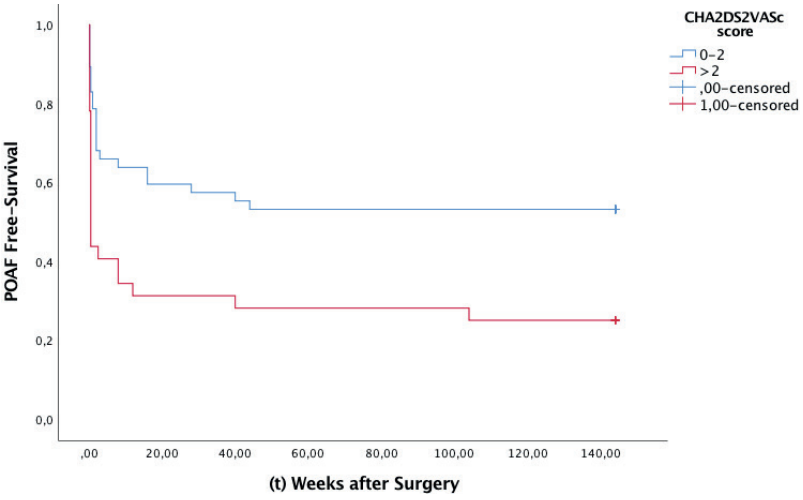


Figure 3a. Kaplan-Meier survival comparison between patients with CHA_2DS_2VASc score of 0-2 (n=47) and 3-6(n=32). P=0.002.

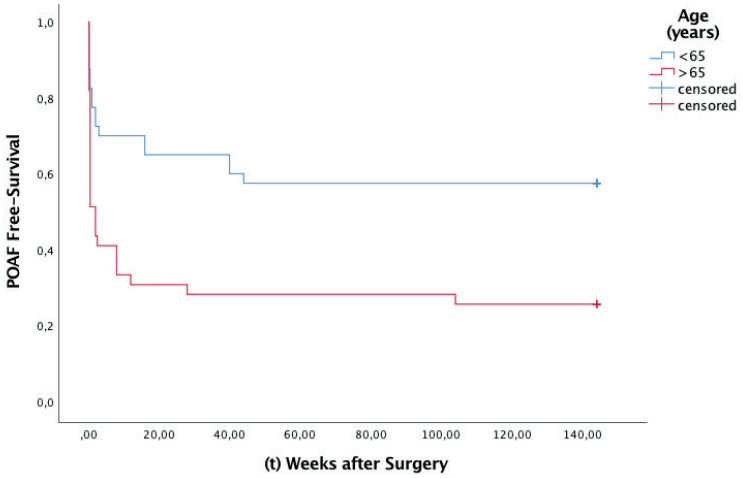


Figure 3b. Kaplan-Meier survival comparison between patients with Age>65 years (n=40) and <65 years(n=39). P=0.004.

Clinical characteristics of patients developing POAF

To assess a potential substrate for AF in POAF patients, we analysed the predisposing co-morbidities known to affect AF substrates in the general population. Univariate characteristics of different POAF subgroups are presented in table 3.

Age was consistently higher in all POAF subgroups (in years, 68.3±8.5 vs 60.9±8.3 in total POAF; 69.6±9.2 vs 62.9±8.3 for early POAF and 68.7±8.4 vs 62.1±8.8 for late POAF, $p<0.05$ for all). CHA_2DS_2VASc score was higher in total POAF (2.8±1.4 vs 2.0±1.2, P =0.01) and in early POAF (3.2 ±1.4 vs 2.2 ±1.2, p =0.01). In addition, HATCH score was also higher in early POAF (2.1±1.1 vs 1.5±1.1, p =0.04). Early POAF itself was a predictor of late POAF (p =0.01). In multivariate analysis age remained an independent predictor of total POAF, late POAF and of early and late POAF, while CHA_2DS_2VASc score was the only independent predictor of early POAF (Table 4).

Atrial electrophysiological characteristics of patients developing POAF

To test the hypothesis that the underlying structural substrate for POAF results from atrial conduction disturbances we performed direct contact mapping of electrically induced AF in the right atrium. In 9 patients sustained AF was not inducible after completing the AF induction protocol of incremental and burst pacing during 10 minutes. Also epicardial mapping could not be performed in another 17 patients because of hemodynamic instability during AF (n=4), for logistic reasons due to changes in operation time schedule (n=7) or poor quality of the electrograms due to electrical noise (n=6).

A total of 53 mapping files were obtained from the right atrium ranging between 7 to 45 seconds. Basic electrophysiological characteristics are presented in table 5. AFCL was significantly longer in patients who subsequently developed POAF (181 ±3 vs 166±2, p=0.03). In accordance with the pre-existing clinical substrate for POAF, fibrillatory propagation in the right atrium was clearly more complex in all POAF groups.

Univariate analysis is presented in table 3. Patients with POAF showed a significantly higher number of RA waves/cycle (POAF 5.0 ±1.4 vs 4.0 ±1.6; early POAF 5.3 ±1.5 vs 4.3 ±1.5; late POAF 5.1 ±1.6 vs 4.2 ±1.4 for patients that did not develop POAF, all p <0.05). The preoperative ECG showed significantly smaller P-wave amplitude for the early POAF group (0.07 ±0.03 vs 0.08 ±0.02, p =0.03), a prolonged PQ time for late POAF (171.7 ±19.1 vs 160.5 ±18.0 ms, p= 0.01) and a smaller P-wave area (3.0 ±0.8 vs 3.6 ±1.1, p =0.04) and amplitude (0.06 ±0.03 vs 0.08 ±0.02, p <0.05) and RAFI (total POAF 2.1 ±1.0 vs 1.7 ±0.7; early POAF 2.5 ±0.8 vs 1.7 ±0.7; early AND late POAF 2.4 ±0.8 vs 1.8 ±0.8 p <0.05 for all comparisons).

Table 3. Clinical, electrophysiological and ECG characteristics results of analysis of variance (ANOVA)

	POAF– (n=33)	POAF+ (n=46)	P	Early POAF– (n=52)	Early POAF+ (n=27)	P	Late POAF– (n=42)	Late POAF+ (n=37)	P	E&L POAF– (n=61)	E&L POAF+ (n=18)	P
BMI	27.91	27.28	0.55	27.62	27.39	0.84	27.40	27.70	0.78	27.32	28.30	0.43
Age (years)	60.88	68.33	0.00	62.92	69.63	0.00	62.14	68.70	0.01	63.48	71.11	0.00
AoCCT (min)	60.34	60.22	0.98	58.98	62.70	0.55	58.68	62.03	0.58	58.13	67.39	0.19
CRP	3.93	3.71	0.87	3.84	3.74	0.94	3.54	4.11	0.67	3.64	4.33	0.67
CHA_2DS_2VASC	2.03	2.83	0.01	2.15	3.15	0.00	2.29	2.79	0.14	2.28	3.22	0.01
HATCH score	1.48	1.89	0.10	1.54	2.07	0.04	1.67	1.78	0.64	1.66	1.94	0.34
RA volume (ml)	46.46	55.50	0.04	53.19	49.36	0.40	48.18	55.70	0.08	53.38	47.00	0.20
RA BT/cycle	1.05	1.3	0.18	1.13	1.33	0.31	1.09	1.30	0.24	1.12	1.50	0.12
RA waves/cycle	4.1	5.0	0.05	4.31	5.30	0.04	4.19	5.06	0.04	4.34	5.62	0.01
RA FI	1.6	2.2	0.02	1.66	2.53	0.00	1.84	2.02	0.43	1.80	2.40	0.04
P Duration(ms)	113.58	112.06	0.66	114.00	110.00	0.27	111.33	114.44	0.36	113.39	110.00	0.43
P dispersion	40.56	40.72	0.97	41.85	38.04	0.50	39.69	41.83	0.67	41.31	37.95	0.59
PQ-time (ms)	162.71	167.61	0.27	165.57	165.30	0.95	160.45	171.69	0.01	164.77	168.38	0.52
P area	3.46	3.45	0.95	3.52	3.30	0.40	1.12	0.91	0.43	3.57	2.96	0.04
P amplitude	0.08	0.08	0.24	0.08	0.07	0.03	0.081	0.083	0.42	0.08	0.06	0.00

ANOVA of patients developing early POAF, late PAOF, early AND late (E&L) POAF: BMI=body mass index; AoCCT=aortic cross clamp time; CRP= C-reactive protein; CHA_2DS_2 VASc score = congestive heart failure/ hypertension/ age/ diabetes/ sex/vascular disease; HATCH score= hypertension/ age>75years/ (TIA) transient ischemic attack or stroke/ (COPD) chronic obstructive pulmonary disease/heart failure; RA=right atrium; BT=breakthrough wave; FI= fractionation index; LA=left atrium; ECG= electrocardiography; P= P-wave

The number of breakthrough waves (BT) per AFCL (BT/cycle) was not significantly different between these groups but a trend towards more BT with POAF recurrence was seen. The substrate complexity parameters remained significantly different between

POAF and non-POAF groups in the final multivariate model. In addition to age, RA volume, and CHA_2DS_2VASc score, independent predictors for POAF were RA waves/cycle in total and for late POAF and RA FI for early POAF.

Table 4a-d. Results multivariate logistic regression analysis.

A. POAF (n=46)	Adjust OR (95%CI)	P
Age	1.11 (1.04 – 1.20)	0.03
Subgroup analysis		
RA volume	1.10 (1.03-1.18)	0.008
CHA_2DS_2VASC	3.38 (1.47-7.75)	0.004
RA waves/cycle	2.06 (1.09 – 3.90)	0.026

B. Early POAF (n=27)	Adjust OR (95%CI)	P
CHA_2DS_2VASC	1.80 (1.22 – 2.66)	0.003
Subgroup analysis		
CHA_2DS_2VASC	2.19 (1.17 - 4.08)	0.014
RA-FI	4.17 (1.41 - 12.36)	0.010

C. Late POAF (n=37)	Adjust OR (95%CI)	P
Age	1.10 (1.03 - 1.16)	0.003
Subgroup analysis		
Age	1.15 (1.03 - 1.30)	0.02
RA volume	1.08 (1.02 – 1.14)	0.01
RA waves/cycle	1.88 (1.07 – 3.32)	0.03

D. E&L POAF (n=18)	Adjust OR (95%CI)	P
Age	1.13 (1.04 - 1.22)	0.005

BMI=body mass index; AoCCT=aortic cross clamp time; CRP= C-reactive protein; CHA_2DS_2 VASc score = congestive heart failure/ hypertension/ age/ diabetes/ sex/vascular disease; HATCH score= hypertension/ age>75years/ (TIA) transient ischemic attack or stroke/ (COPD) chronic obstructive pulmonary disease/heart failure; RA=right atrium; BT=breakthrough wave; FI= fractionation index; LA=left atrium; ECG= electrocardiography;

By adding the RA waves/cycle to the clinical predictors of late POAF (age, RA volume and early POAF) the predictive value of the Receiver Operator Curve- model increased from area under the curve of 0.78 to 0.86 (Figure 3).

Table 5. Electrophysiological characteristics of epicardial mapping

	Mean (n=53)	POAF (n=30)	No-POAF (n=23)	p
AFCL(ms)	177 (±31)	181 (±30)	166 (±24)	0.05
CV(m/s)	0.58 (±0.1)	0.57 (±0.1)	0.58 (±0.1)	0.7
BT/CL	1.1 (±0.6)	1.3 (±0.6)	1.0 (±0.5)	0.09
RA-FI	1.9 (±0.8)	2.2 (±0.9)	1.6 (±0.7)	0.02
waves/CL	4.6 (±1.6)	5.0 (±1.5)	4.1 (±1.6)	0.05

RA= right atrium; AFCL= Atrial fibrillation cycle length; ms= milliseconds; CV= conduction velocity (meters/seconds); BT= breakthrough waves; CL= cycle length; FI=fractionation index.

Discussion

Previous reports on incidence of late POAF or the effect of interventions on AF recurrences did not exclude patients with a history of paroxysmal AF [7, 20] and focused on clinically symptomatic AF, relying on electrocardiogram recordings in patient reporting symptoms of AF. [2, 4, 21] However, a high percentage of subclinical AF may exist in high-risk patients [22] and "snapshot" monitoring strategies are insufficient for quantifying AF burden.[23] To our knowledge, this is the first prospective study with prolonged continuous rhythm monitoring with ILR, in patients without a clinical history of AF undergoing cardiac surgery. We found subclinical late POAF recurrences in 47% of patients during a 3-year follow-up. In our population, late POAF duration was 1.5 hours per episode on average. Atrial high rate episodes (AHRE), lasting minutes to hours, detected by cardiac implantable electronic devices have been reported to be associated with an increased risk for ischemic stroke in general population.[22, 24, 25] The ASSERT trial for example, included 2580 patients with hypertension without a history of AF and demonstrated AHRE in 35% of patients during continuous rhythm follow-up of 2.5 years.[26] As expected, the risk of stroke in these patients was higher especially in patients with elevated $CHADS_2$ score (>2.1).[25, 26] In line with this, AHRE in the absence of a history of AF has been associated with significantly higher incidence of silent ischemic brain lesions detected on computed tomography scans.[27] Furthermore, 15 minutes of AF or rapid pacing have been shown to increase amounts of platelet activation and thrombin generation compared to sinus rhythm,[28] emphasizing the potential prothrombotic effects of short lasting episodes of atrial arrhythmias.

Hence, there is a significant amount of data supporting oral anticoagulation (OAC) treatment in patients with short lasting AF episodes. Of note, a sub-analysis of the ASSERT trial recently showed that only episodes of subclinical AF lasting longer than 24 hours were associated with an increased risk of stroke[29] and elevated stroke risk in AHRE in different reports may have been driven by longer episodes.[25] Patients developing late POAF in our study had an average CHA_2DS_2VASc score of 2.8, which is known to

go along with an increased risk of stroke also in short lasting AF episodes.[30] Still, more research is required to determine the risk-benefit ratio of oral anticoagulation in late POAF.

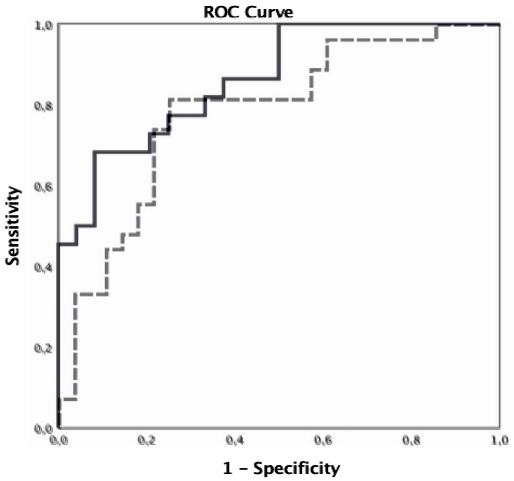


Figure 3. Receiver Operator Curve- model of predictors of late POAF. Dashed line: Age, RA volume, early POAF, AUC 0.78; Black line: Age, right atrial volume, early POAF and RA waves/cycle AUC: 0.86

We further determined the underlying clinical and electropathological substrate for POAF. In our patient population, a higher CHA_2DS_2VASc score was an independent predictor of early POAF and advanced age and large RA volume were independent predictors of late POAF. In addition, others have reported predisposing factors to POAF including COPD, obesity, systolic dysfunction, and valvular disease. [7, 11, 31] These co-morbidities may contribute to atrial remodelling through fibrosis[32] and heterogeneous gap-junction protein distribution[33] resulting into a structural substrate for AF.[34, 35] In line with this, patients developing POAF showed more complex propagating properties, including higher RA/FI and higher number of RA waves/cycle compared to patients without POAF.

The complexity of atrial activation pattern during AF is a reflection of the underlying structural substrate for AF.[17, 36-38] Also in patients without a history of AF some degree of remodelling may already exist as previously demonstrated by Konings et al., in patients undergoing ablation for Wolf-Parkinson-White (WPW) syndrome.[16] Similarly, RA local conduction slowing and enhanced AF inducibility were seen in patients without a history of AF with RA dilatation as a result of an atrial septal defect [39] or as a result of chronic hypertension.[40] Patients with persistent AF, on the other hand, show a much more complex wave pattern with a high number of simultaneous fibrillation waves and high number of breakthrough waves as compared to the WPW patients.[17, 38]

These findings alongside our epicardial mapping results suggest that some patients without a history of AF may have a predisposition to AF as a result of their underlying

co-morbidities. Of note, perioperative characteristics such as aortic cross clamp time and ICU stay did not differ in patients developing POAF. Patients developing additional late POAF showed significantly higher early POAF burden. This suggests that at least in this population, the pre-existing substrate resulted in prolonged early POAF development, also predisposing to late POAF that potentially requires rhythm follow-up.

Considering the pre-existing substrate, POAF can thus be predicted by substrate quantification in patients undergoing cardiac surgery. The 12-lead ECG has been shown to capture AF complexity and propagation properties of the atria. Previously, specific ECG parameters such as P-wave dispersion[41] and prolonged P-wave duration on signal averaged ECG [42, 43] have been described to predict POAF. Also, the number of peaks within the P-wave and the terminal force in lead V1 has been shown to detect patients with a history of AF. The P-wave area has been described as a predictor for AF and risk of stroke in general population.[44] However, these results are not solely based on the standardised 12 lead ECG and not all previous studies excluded patients with a history of AF including patients with lower left ventricular ejection fraction.[41-43] In the current study, using the standardised (filtered) preoperative ECGs, we found that P-wave amplitude and P-wave area were significantly lower in patients developing both early and late POAF. Although the filtered 12 lead ECG is known to smoothen most irregularities and peaks compared to signal averaged high-resolution ECGs,[45] these findings are easily available on a broad scale. The clinical use of the p-wave analysis for POAF prediction will have to be shown in future studies.

Conclusion

We found that 47% of cardiac surgery patients in our population developed late POAF at least once during 3 years of follow-up with an average duration of 1.5 hours per episode. Advanced age, CHA_2DS_2VASc score, RA volume and complex epicardial propagation patterns were important predictors of early and late POAF. Our data indicate that patients developing early POAF are likely to have an underlying structural substrate for AF, which predisposes them to late POAF recurrences. Because late POAF has been related to increased mortality and stroke, patients with high CHA_2DS_2VASc score developing early POAF should be followed intensively for late POAF recurrences. Furthermore, due to the existence of a clinical and electro-pathological substrate, predictive efforts should be evaluated in the future studies. 12-lead ECG P-wave characteristics may help to identify patients at risk for late POAF.

Study limitations

One important limitation in using Reveal XT™ device is the fact that the device has a short storage capacity. At the same time, the device has a relatively low specificity and positive predictive value for AF detection (85.6% and 79.3% respectively).[46] The problem arises when the device is used for longer periods and AF episodes are overwritten by more recent episodes. This limitation, along with the patient dependent interrogation, leads to relatively high false positive episodes and low frequency of device interrogations towards the end of follow-up. However, we regularly contacted the patients to keep the time between interrogations short and analysed more than 3000 interrogations of the implanted devices with an average of 48 interrogations per patient. Another important limitation in this study is the fact that patients did not have continuous rhythm monitoring prior to the surgery. Therefore, although all medical records of all patients were reviewed, it is plausible that at least some of the patients developing late POAF may have had episodes of (asymptomatic) AF prior to surgery.

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Part2

Importance of endo-epicardial dissociation of electrical activity for perpetuation of human atrial fibrillation



5

A Novel Computer Model of Endo-epicardial Electrical Dissociation and Conduction during Human Atrial Fibrillation

A novel computer model of human AF

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Abstract

Background: Recent studies have demonstrated dissociation of electrical activity between the subepicardial layer and the endocardial bundle network frequently leading to transmural conduction (breakthrough) during experimental and human atrial fibrillation (AF). However, this phenomenon has not been studied in mathematical models.

Objective: The goal of this study was to assess the effect of epicardial fibrosis on endo-epicardial dissociation and breakthroughs during AF.

Methods: We developed a 3-dimensional model of the human atria, based on MR images and histo-anatomical studies, consisting of a thin epicardial layer and an endocardial bundle network. We studied the effect of fibrosis in the epicardial layer on endo-epicardial dissociation and breakthrough. The simulation results were validated by simultaneous endo-epicardial mapping of AF in the right atrium of 4 patients with longstanding persistent AF and in 3 patients without a history of AF.

Results: In both measured and simulation data, endo-epicardial dissociation occurred that frequently resulted in breakthroughs. The AF cycle length, conduction velocity, and endo-epicardial dissociation were comparable in the mapping studies and the simulations. Fibrosis increased the average number of fibrillation waves per cycle. Endo-epicardial dissociation increased from 28.4±1.52% to 57±2.62% and 60.3±2.87% ($p<0.05$), while breakthroughs increased from 1.16±0.45 to 3.80±1.13 to 8.60±1.75 in control, moderate, and severe fibrosis ($p<0.05$). In both mapping data and simulations endo-epicardial dissociation correlated with prevalence of breakthrough.

Conclusion: Using a detailed model of human atria, we successfully simulated endo-epicardial dissociation resulting from increased fibrosis, culminating in breakthroughs, which emphasizes the 3-dimensional character of AF in humans.

Keywords: Atrial fibrillation, computer models, transmural conduction, endo-epicardial dissociation, breakthrough waves.

1 Introduction

The progression of atrial fibrillation (AF) is mediated by a complex process of ion channel remodeling and structural alterations including atrial fibrosis.[1] Both processes together result in an increase in conduction block in the atrial wall resulting in narrower wavefronts and increasing dissociation of electrical activity between the epicardial layer and the endocardial bundle network.[2-5] Verheule et al. demonstrated that transition from persistent to permanent AF in goats is characterized by an increase in endomysial fibrosis, particularly in the outer millimeter of the atrial wall, leading to loss of side to side connections in the subepicardial layer [6] explaining the decline in the electrical coupling between the subepicardial layer and the endocardial bundle network.[7] As such, increased fibrosis may contribute to dissociation of electrical activity between these two layers (endo-epicardial dissociation of electrical activity) giving rise to transmural propagation in both directions. These transmurally propagating waves become visible as "breakthroughs" and add to the overall complexity of fibrillatory conduction, and thereby to the stability of AF.[8] Endo-epicardial dissociation greatly increases the effective surface area available to fibrillation waves to propagate and causes the atrial walls to behave as a 3-dimensional substrate.[8]

While experimental studies have demonstrated a clear association between structural remodeling, endo-epicardial dissociation of electrical activity, and breakthrough incidence, the causal role of endomysial atrial fibrosis for the occurrence of 3-dimensional conduction is still not clear.[4, 6]

We hypothesized that isolated epicardial fibrosis is sufficient to enhance dissociation and increase breakthrough incidence. To test this hypothesis, we developed a novel highly detailed computer model of the atria, which includes an epicardial layer and an endocardial bundle network based on a large variety of human imaging and anatomical studies. The epicardial layer had varying wall thickness and two to three sub-layers with different fiber orientations depending on the atrial region. [9] To validate the model and the observed correlation between endo-epicardial dissociation of electrical activity and breakthrough rates, we performed simultaneous endo-epicardial high-density mapping in human right atria during cardiac surgery.

2 Methods

2.1 Patient characteristics

In total 7 patients, 4 with longstanding persistent AF (persAF) and 3 without a history of AF (sinus rhythm group, SR), were included. All patients underwent on-pump cardiac surgery through median sternotomy at Maastricht University Hospital (MUMC), Maas-

tricht, The Netherlands. The local medical ethical committee approved this study and written informed consent was obtained from each patient.

Table 1: Patient characteristics

Gender	BMI	Age (years)	Operations	LA-d(mm)	EF(%)	Rhythm
Male	23,5	75	AVR	45	35	persAF
Female	24	72	MVR	100	50	persAF
Male	30	66	CABG	69	60	persAF
Male	26,5	77	AVR	72	30	persAF
Male	30	71	CABG	37	60	SR
Male	18,7	70	CABG	28	60	SR
Male	24,2	60	AVR	40	30	SR

Pt#= patient number; AVR= aortic valve replacement; MVR= mitral valve replacement; CABG= coronary artery bypass graft; LA-d= left atrial diameter in mm; EF= left ventricular ejection fraction; persAF= longstanding persistent AF; SR= sinus rhythm.

2.1.1 Simultaneous Endo-epicardial mapping

Simultaneous endo-epicardial mapping of the right atrium was performed as described previously.[8, 10, 11] In short, we developed a tongs-shaped mapping device (Figure 1) with both arms ending in a square plaque containing 64 unipolar electrodes (8 × 8; inter-electrode distance 1.5 mm), directly facing each other when approximated.

2.2 Computational model of AF

2.2.1 Anatomical structures in the computer model

Magnetic resonance imaging (MRI) data of a subject with a normal atrial anatomy was used to reconstruct global atrial shape. Endocardium and epicardium were traced manually and combined into a 'myocardial envelope': a closed surface containing the atrial myocardium. Anatomical features from detailed anatomical studies were added manually to the model using Blender (The Blender Foundation, Amsterdam, The Netherlands) as a 3D editing tool.[12-16] Twenty pectinate muscles (PM) in the right atrial free wall in addition to Bachmann's Bundle (BB), interatrial bundles, and the crista terminalis (CT) were added based on published anatomical descriptions.[12, 13, 15]

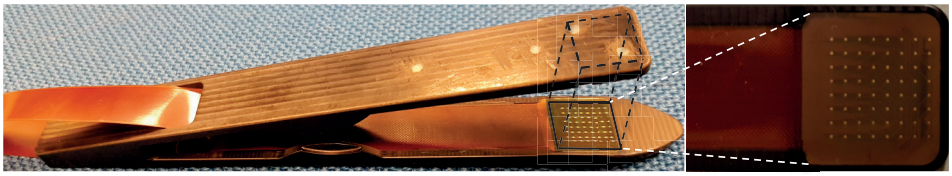


Figure 1. The Endo-epicardial electrode, the endocardial arm is designed in a convex end to facilitate insertion into the right atrium of the beating heart. Both arms contain identical plaques of 8 x 8 unipolar electrodes exactly opposing each other when approximated.

As illustrated in figure 2, the model contained four pulmonary veins, caval veins, left and right atrial appendages (LAA and RAA), and a LAA trabecular network, as well as the coronary sinus. The BB connected regions between superior caval vein and RAA in the right atrium to the superior wall of the left atrium. The coronary sinus (CS) originated in the right atrium and extended along the left atrial posterior wall. A number of fiber tracts connected the CS to the posterior wall of left atrium. These connections were created based on the anatomical study performed by Chauvin et al.[14] One to three layers of fiber orientations were added to the model based on several anatomical studies (see supplemental material).[12, 13] Comparison with results of a recently published submillimeter diffusion tensor magnetic resonance imaging study showed good agreement of the prevailing local fiber orientations in our model with human atria.[9]

Fibrosis was simulated by zeroing transversal conductivity in a random selection of model elements, while keeping longitudinal conductivity unaltered. It was only introduced in the epicardial layer. Two different degrees of fibrosis (moderate (50%) and severe (70%)) were selected, simulated, and compared with no fibrosis (i.e. all adjacent elements transversely coupled, control).

Simulations were performed with the propag-5 software [17, 18] and run on 2560 cores of a Cray XE6 supercomputer. Ionic currents and calcium handling for each model node was described by the Courtemanche-Ramirez-Nattel model.[19]

To exclude possible bias resulting from preferential conduction patterns, caused by AF induction at a certain site, ten episodes of AF were initiated at different locations for each group (see supplemental materials).

2.3 Signal processing

In patients, electrograms lasting 30-75 seconds were recorded at a sampling rate of 1 kHz using a band-pass filter of 0.5-500 Hz. To detect local activation times, data were analyzed using an automated algorithm described in detail previously (see supplemental methods).[20] In simulations, local activation times were calculated using maxima of positive deflections in simulated action potentials (APs) for each model node. From the local activation times obtained, we calculated the atrial fibrillation cycle length (AFCL) and the local conduction velocity (CV). Fibrillation waves were defined as groups of local activations surrounded by lines of block as described previously.[20] From these data, the number of fibrillation waves and the number of breakthroughs in both endocardial and epicardial layer were calculated.

2.4 Calculation of endo-epicardial dissociation of electrical activity

In human recordings, the electrodes on the epicardial and the endocardial planes were directly facing each other, allowing us to quantify activation time differences for each opposing electrode pair.

To calculate the endo-epicardial activation time differences in simulations, model nodes were categorized as epicardial, endocardial or endocardial bundle. We created pairs of opposing nodes by finding the nearest epicardial node for each endocardial bundle node. In order to obtain data from computer simulations that are comparable with the clinical recordings, an array of 64 segments (8 × 8 with inter-segment distance of 1.5 mm) was created in the epicardial and endocardial layers. Activation times were then obtained from the model node that was nearest to each segment centre.

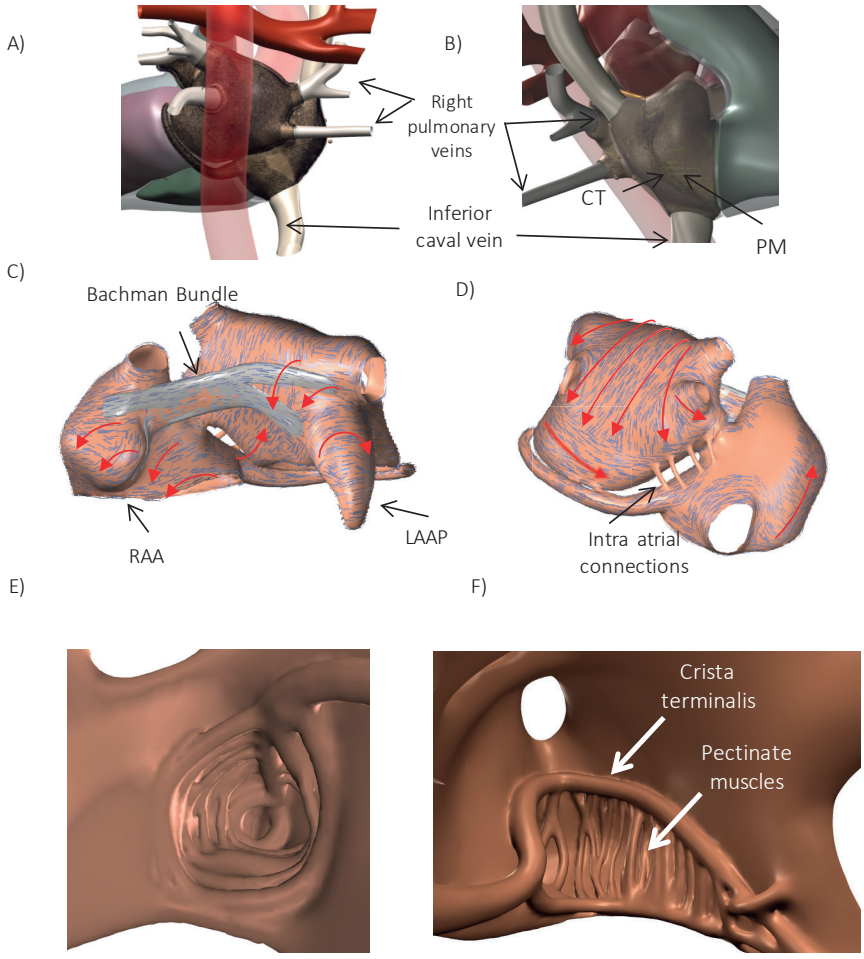


Figure 2. Anatomical model of the atria used for simulations. A) Posterior view B) Sagittal view. C) Fiber orientation in anterior view. D) LA posterior wall fiber orientations. E) Trabeculated network in LAA. F) Trabeculated network of 20 pectinate muscles in the right atrium (interior view)

The extracted activation time differences in both clinical and *in-silico* recordings were used to assess the degrees of endo-epicardial dissociation of electrical activity. The

smallest activation time differences of each electrode and either the directly opposing electrode or one of the 8 electrodes surrounding the opposing electrode were considered. For the simulations, quantification was performed using the same algorithm. Endo-epicardial dissociation was calculated from histograms of endo-epicardial activation time differences as previously described by Eckstein et al.[10]Briefly, two distinct populations of activation time differences representing dissociated and non -dissociated activity were identified by fitting a two-component Gaussian function (for activation time differences), or a Gaussian/uniform mixture distribution (for differences in direction) to the histograms. [10]

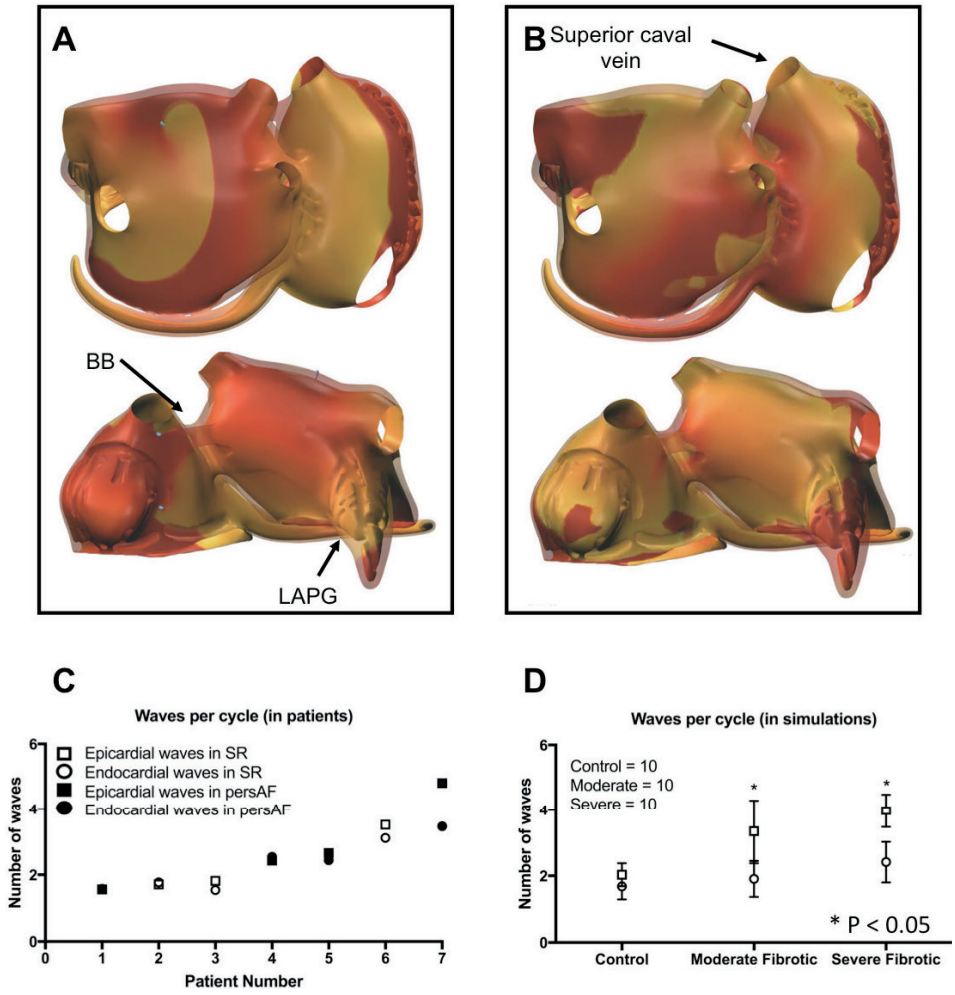


Figure 3. A) Potential map in LA and RA (control). B) Potential map in LA and RA (severe fibrosis). C) Number of waves per cycle in patients recordings (N=4 for persAF patients and N=3 for SR patients). D) Averaged number of waves in computer simulations (N=10 for control, Moderate Fibrotic, and Severe Fibrotic groups).

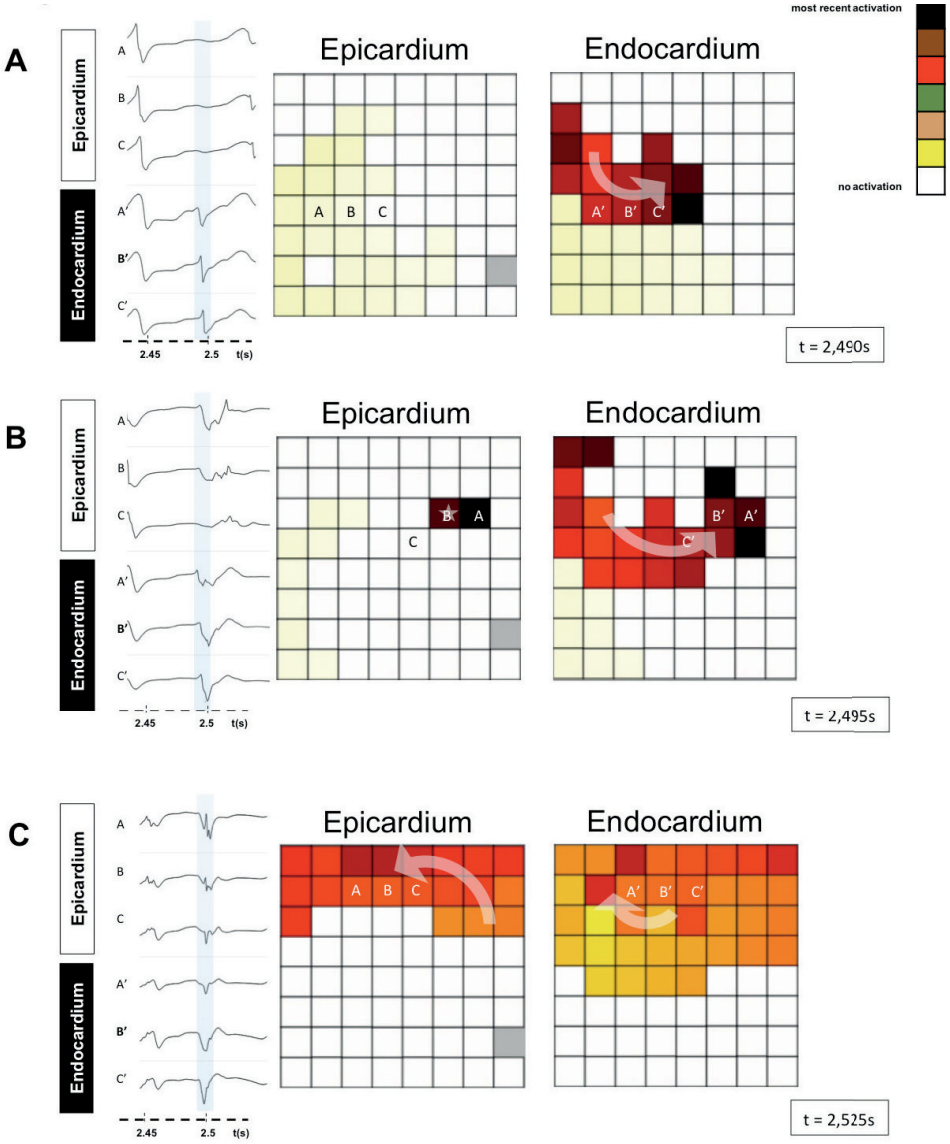


Figure 4. An example of a BT occurrence in the epicardial layer: A) A new wave enters the endocardial layer (Red) (A',B',C'). The epicardium is not activated (A,B,C). The left panels show the local electrograms. B) Epicardial breakthrough (b) as a result of endo-epicardial dissociation. C) The breakthrough in the epicardial layer spreads further in an endo-epicardially synchronized manner.

3. Results

3.1 Patient characteristics

Simultaneous high-density endo-epicardial mapping of AF was performed in 4 patients with longstanding persistent AF and 3 patients without a history of AF in whom the arrhythmia was acutely induced by rapid pacing. Patient characteristics are presented in table 1. The left atrial diameter was significantly larger in the AF (P=0.016) than in the SR group. We included 13 recordings from the 7 patients, ranging between 30-75 seconds (38.34±15.7s). Conduction velocity was higher in the endocardial plane compared to the epicardium (0.66 ±0.08m/s vs 0.58 ±0.06m/s respectively, p=0.05).

3.2 Basic AF characteristics in human mapping files and simulations

Both endocardial and epicardial AFCL were similar in the patient recordings and simulations. The AFCL ranged between 139ms to 261ms in the patients (140.3±6.14 for SR patients and 194.3±3.7 in persAF patients). In the simulations AFCL was 145±65ms, 152±3ms, and 197±13ms in control, moderate, and severe fibrosis, respectively. The AFCL in severe fibrosis was significantly longer than in control. Endocardial and epicardial CVs ranged between 50.9cm/s and 74.1cm/s in human recordings (64.2±4.64cm/s for SR patients and 67.9±23.38 for persAF patients), compared to 55.3±3.5cm/s, 49.0±4.68cm/s, and 42.6±1.7cm/s in control, moderately, and severely fibrotic simulations respectively.

3.3 AF conduction pattern complexity

We assessed AF conduction pattern complexity, in terms of number of fibrillation waves in both human recordings and simulations. In Figure 3A and B, examples of fibrillation patterns in a control simulation and a severe fibrosis simulation are depicted. In the presence of fibrosis, fibrillation patterns in RA, LA anterior wall, and pulmonary veins area were more complex compared to control.

Quantitative results extracted from 7 patients and 30 simulations are illustrated in figure 3C and D. The measured number of waves in both endocardium and epicardium in patients corresponded well to each other, with a trend to an increased number of waves in persAF patients compared to SR patients. The average number of waves per cycle was 2.46±1.11 in SR patients and 3.07±0.91 in persAF patients. The same phenomenon was observed in computational simulations, where the number of waves per cycle in the epicardium increased significantly from 2.03±0.34 to 3.34±0.96 and 3.98±0.51 in control, moderately fibrotic, and severely fibrotic models, respectively.

3.4. Endo-epicardial dissociation in human mapping recordings and simulations

An example of a breakthrough occurrence in the epicardial layer, using simultaneous endo-epicardial recording in a patient, is depicted in figure 4. As illustrated in this figure, a fibrillation wave (red) entered the endocardial layer (A', B', C' in panel A) while the epicardial layer was not activated (A, B, C). Five milliseconds later, a breakthrough appeared in the epicardial layer (panel B). During the next 30ms the wave spread simultaneously in the epi- and endocardial layer (panel C). An example of directly opposing electrograms in the endo- and epicardial planes of human right atrium is illustrated in figure 5.



Figure 5. Simultaneous mapping of endo-epicardial layers of human right atrium during AF. Epicardial activation=dotted line, endocardial activation=dashed line. Depicted are 6 electrograms 3 on each side of the atrial wall exactly at the same time and space. While at point A, H and I an almost synchronized activity was seen with earlier activation at the endocardial front, in B and C endo- and epicardial activations are out of phase.

As shown in this figure, at the beginning of the recording endocardial and epicardial deflections occurred simultaneously (A) while 80ms later only the endocardial recordings showed steep deflections. It is conceivable that at time point A the deflections in the endocardial layer reflected far field potentials from the epicardial layer. From time point C onwards the deflections occurred nearly simultaneously again in both layers. The same phenomenon was observed in simulated APs where a clear endo-epicardial

dissociation of electrical activity preceded the breakthroughs, while the endo-epicardial electrical activity synchronized after the breakthrough (figure 6).

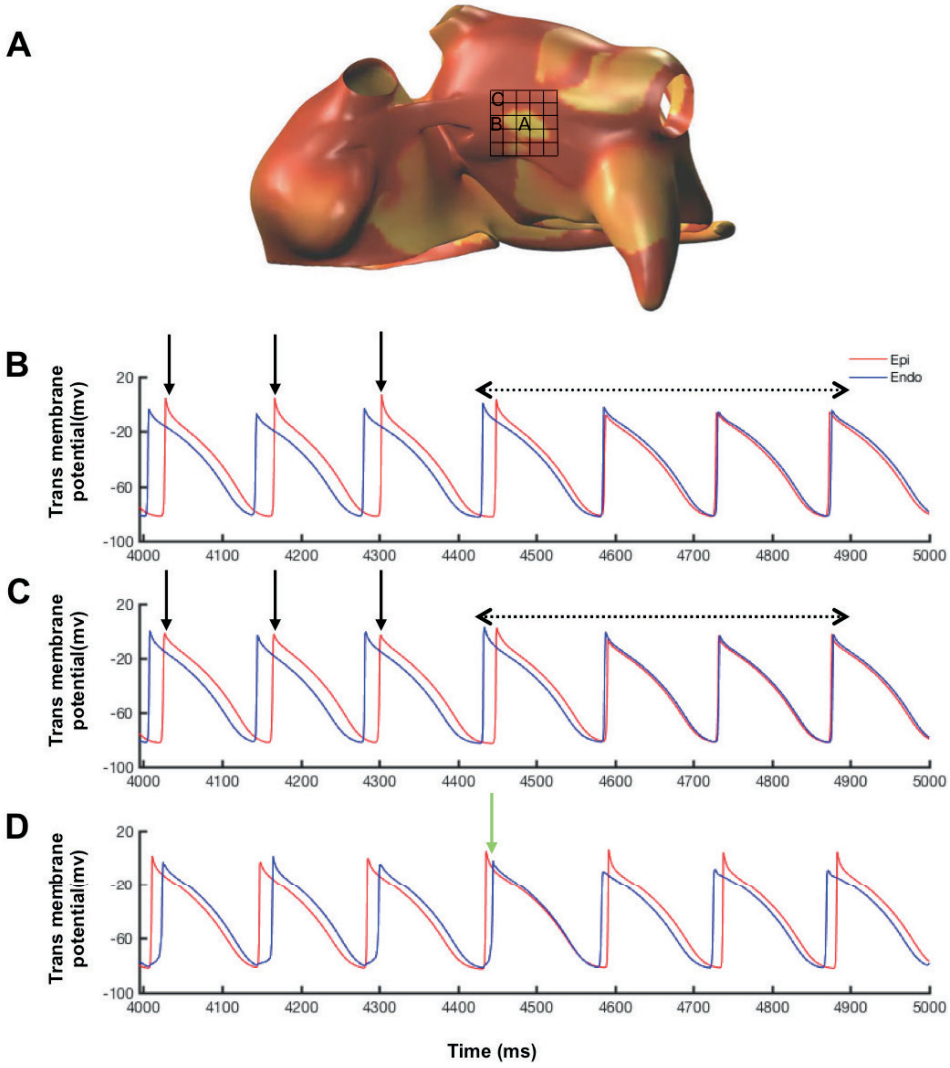


Figure 6. Simultaneous endocardial and epicardial recorded simulated action potentials during occurrence of an epicardial BT. A) An example of a BT and the location of recorded simultaneous endo-epi AP. B) Recorded simultaneous endo-epicardial APs at the center of a BT. Black arrows indicates moments of epicardial BTs occurrence (electrode A). The dotted line shows the disappearance of endo-epicardial electrical dissociation due to the occurrence of the last BT. B) Recorded simultaneous endo-epi AP at a neighboring electrode close to the BT occurrence position (electrode B). C) Recorded simultaneous endo-epi AP at an electrode further from the BT occurrence position. Green arrow shows the effect of the BT on flipping of endo-epi electrical activity dissociation (electrode C).

Histograms of activation time differences in a SR and a persistent AF patient are illustrated in figure 7A and B. For each electrode, the shortest activation time differences at the opposing 9 electrodes were considered. The same calculations were performed in the computational studies.

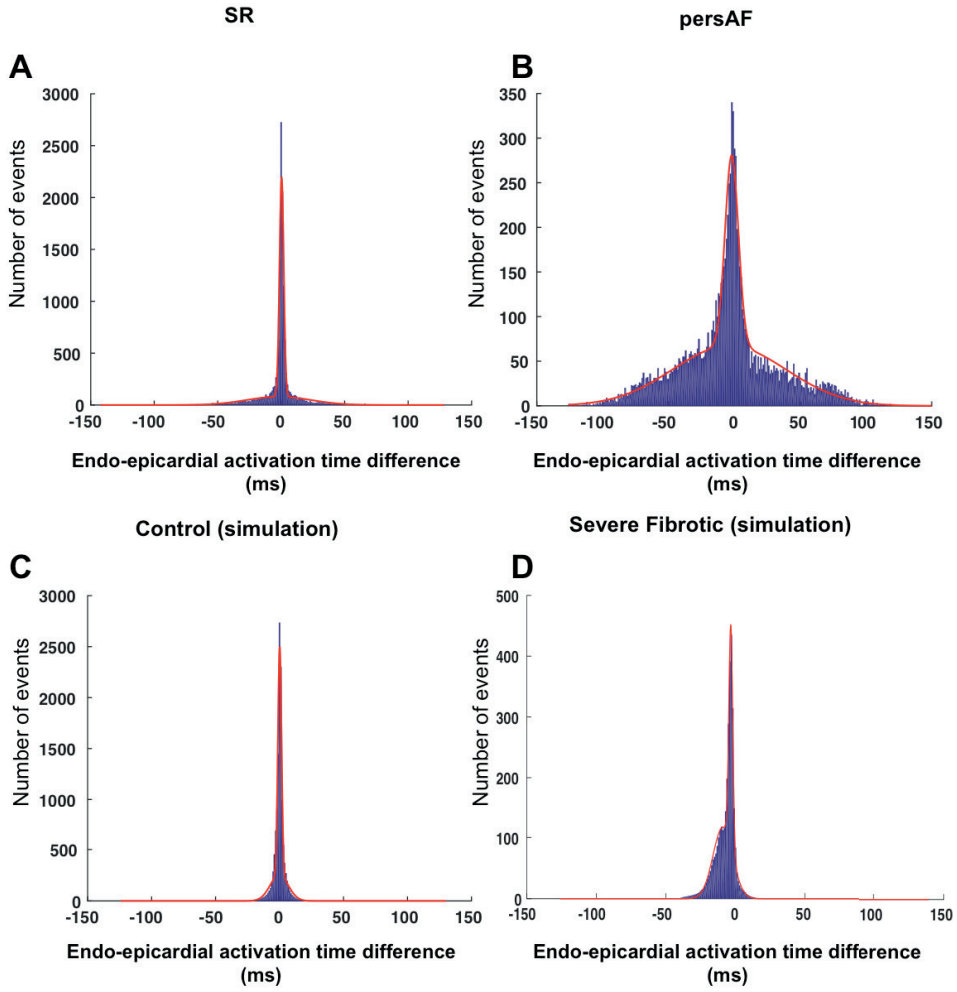


Figure 7. Activation time differences between endo and epicardial layers in patients (upper panels) and simulations (lower panels), A) A histogram of endo-epicardial activation time differences in a SR patient. B) Histogram of endo-epicardial activation time differences in a persAF patient. C) Histogram of endo-epicardial activation time differences in a control simulation. D) Histogram of endo-epicardial activation time differences in a severe fibrotic simulation. X-axis depict difference in activation time (ms) and y axis depict number of events.

Examples of activation time difference histograms in control and simulations with severe fibrotic tissue are depicted in figure 7C and D. Examples of simulated breakthroughs are shown in figure 8. While most breakthroughs occurred at the location of endocardial bundles (figure 8A and B), some breakthroughs occurred in areas without underlying endocardial bundles (figure 8C), suggesting that isolated epicardial fibrosis is sufficient to cause endo-epicardial dissociation even within the thin epicardial surface. Figure 8D and E depict the endo-epicardial dissociation in patients and simulations, which ranged from 28.4±1.52% to 57±2.62% and 60.3±2.87% in control, moderately fibrotic, and severely fibrotic models, respectively. Both in the clinical recordings and in the simulations, the degree of endo-epicardial dissociation ranged approximately between 20% and 80%. In the patients, there was a trend towards more endo-epicardial dissociation in the patients with persistent AF. In the simulations, fibrosis clearly increased the degree of endo-epicardial dissociation.

Interestingly, the increase in endo-epicardial dissociation of electrical activity was associated with an increase in the incidence of breakthroughs both in the patient data as well as in the simulations. In simulations, the average number of breakthroughs per cycle increased from 1.16±0.45 to 3.80±1.13 and 8.60±1.75 in control, moderately fibrotic, and severely fibrotic models, respectively. The calculated numbers of breakthroughs per cycle in all simulation groups were higher than the breakthroughs per cycle in patients (figure 8F and G). This is due to the fact that the breakthroughs in patients' recordings were calculated only within the recording locations, whereas in simulations the whole atrial surface was considered. Both in the mapping recordings and in the simulations, there was a positive correlation between the average number of breakthroughs per cycle and the degree of endo-epicardial dissociated activity (Pearsons correlation $r=0.61$ and $p < 0.05$, figure 9A for the patient recordings and $r=0.72$, $p < 0.05$ for the simulations). In the simulations, this correlation was partly driven by the differences between normal and fibrotic groups and partly driven by the differences within the 3 groups ($r_1 = 0.61$, $p<0.05$ and $r_2 = 0.5$, $p<0.05$).

4. Discussion

To the best of our knowledge, this is the first realistic atrial model that can simulate three-dimensional electropathological changes including endo-epicardial dissociation and transmural conduction, closely resembling the human 3D substrate for AF. To implement endo-epicardial dissociation of electrical activity and transmural conduction in a realistic computer model of AF, we developed a highly detailed 3D anatomical model of the human atria.

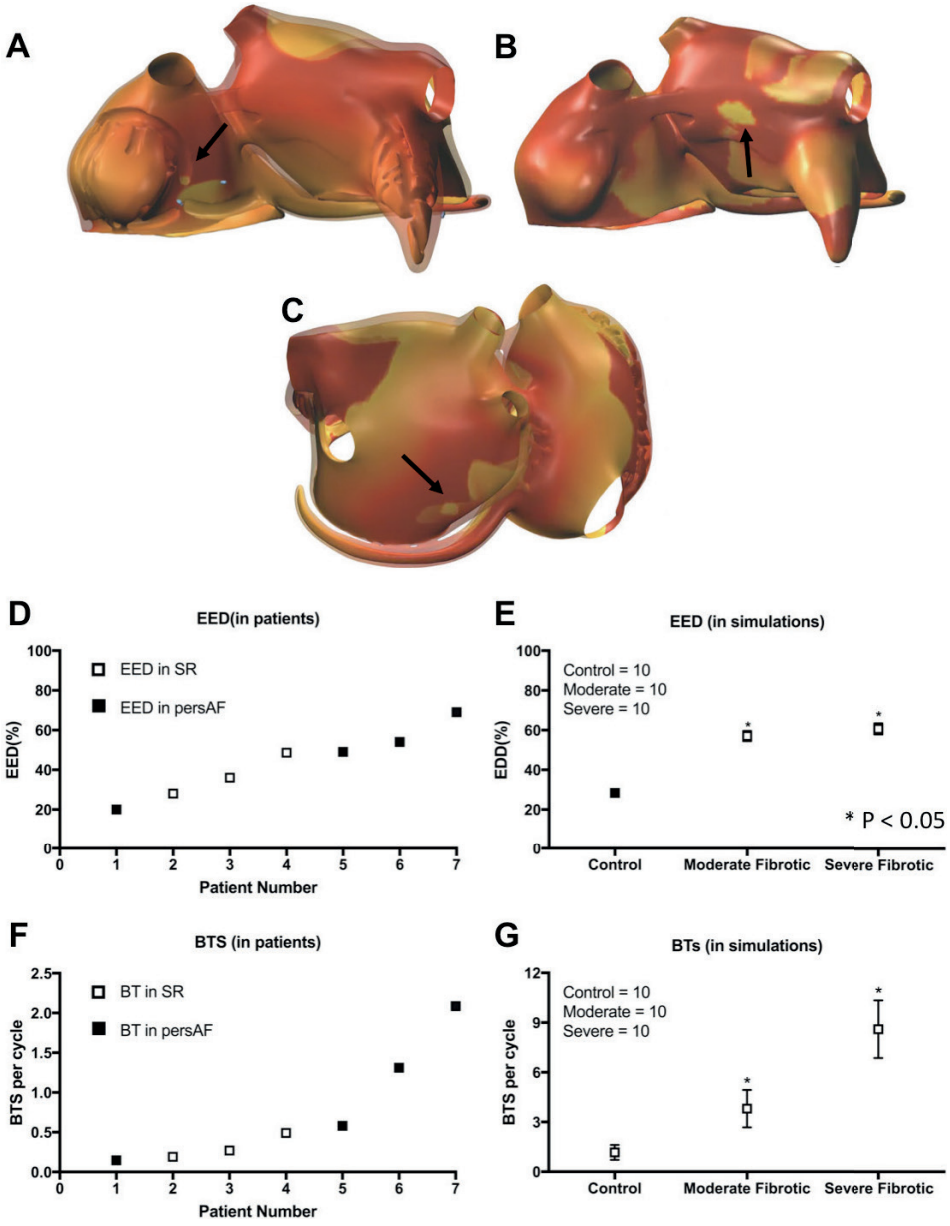


Figure 8. Examples of BTs. A) in control simulation. B) severe fibrosis. C) slight fibrosis. D) Endo-epicardial dissociation (EED) in clinical recordings. E) Endo-epicardial dissociation in simulations. F) Number of BTs per cycle in human recordings. G) Number of BTs per cycle in simulations.

Our results derived from the new computer model resembled well the basic electrophysiological characteristics obtained from simultaneous endo-epicardial recordings in humans. Parameters such as AFCL, CV, and degree of endo-epicardial dissociation were very similar in the model as compared to the AF recordings. Importantly, the introduction of isolated atrial fibrosis in the epicardial layer resulted in an increase in endo-epicardial dissociation of electrical activity and the incidence of breakthrough. Additionally, breakthroughs and endo-epicardial dissociation of electrical activity showed a good correlation in both patients and simulations. In simulations as well as in patients' recordings, breakthroughs made a significant contribution to AF complexity. These findings confirm the importance of the 3D electrophysiological substrate contributing to AF perpetuation.

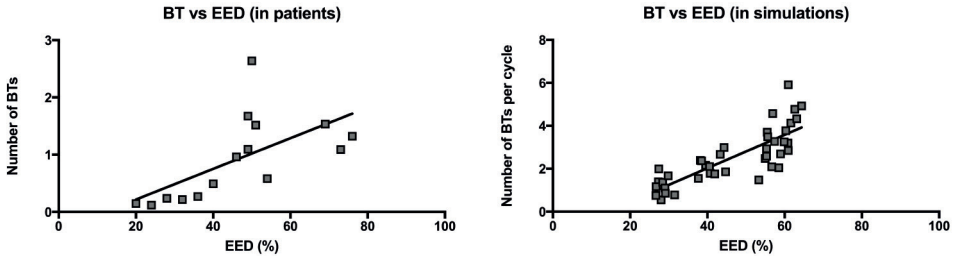


Figure 9. A)(Left) Correlation between EED and breakthrough incidence in patient recordings. Pearsons correlation r=0,61 for both endo and epicardial BT, p<0,05. B) (Right) Correlation between EED and breakthrough incidence in simulations. Pearsons correlation r=0,72 and p < 0.05.

4.1. Comparison to other computer models

Numerous modeling studies have been performed to understand the mechanisms underlying AF. Models developed for this purpose can be divided into two categories with respect to geometrical properties. The first category consists of surface models, which treat the atria as a two-dimensional sheet folded into the shape of the atria.[21-23] Models in the second category are volumetric models that incorporate a greater degree of detail on regional variation in wall thickness and fiber orientation.[24-29] Models of both categories have provided valuable insights into AF mechanisms and perpetuation such as ectopy[24], AP heterogeneity[28, 30] and fibrosis[31]. A few studies have investigated the effect of atrial anatomy, wall thicknesses, and endocardial bundles (modelled by higher local wall thickness) on fibrillatory patterns and AF maintenance.[24, 29, 30] Recently, Labarthe et al. investigated the effect of transmural heterogeneities on the complex mechanisms involved during electrical propagation in the atria using a bilayer atrial model.[32] However, by design, none of these models showed transmural conduction of fibrillation waves driven by endo-epicardial dissociation of electrical activity. The novelty of our

model is that, due to the presence of the above-mentioned details, it allows us to investigate this phenomenon, and to assess the effect of structural remodeling in this context.

The global anatomy in our model was based on MRI data from a human subject with normal atrial anatomy. Many anatomical details of the atrial bundle structures such as PMs, BB, CT, posterior bundles connecting left and right atrium, CS, and bundles running beneath the LAA were added to this global anatomy based on anatomical and histological observations.[12, 30] Furthermore, to investigate mechanisms that contribute to AF perpetuation more precisely, a higher level of anatomical detail, such as fiber orientation, must be integrated in the model.[13, 30] Indeed, the integrated fiber orientation in this model was also based on histological studies.[9, 12, 13, 33] Importantly, based on submillimeter diffusion tensor MRI, Pashakhanloo et al. reported that the main features of fiber orientations were well preserved among subjects .[9] The preferential fiber directions described in this study are well reflected by our 3D model. All above-mentioned properties, included in this model, have been observed as factors determining the propagation of fibrillation waves.[30]

4.2. The importance of endo-epicardial dissociation in AF

The mechanisms underlying AF have complex dynamics and involve tight interactions across multiple temporal and spatial scales.[34] Electrical remodeling, which occurs in the very early stages of AF, facilitates the progression from paroxysmal to permanent AF. This progression is also associated with irreversible structural remodeling such as loss of electrical side-to-side connections due to fibrosis.[8] Verheule et al. showed that AF-induced structural remodeling in the goat is characterized by an increase in endomysial fibrosis exclusively in the epicardial layer of the atrium.[6] This loss of connectivity can also occur between endocardial bundle networks and the epicardial layer. Therefore, it leads to endo-epicardial electrical dissociation, which is a prerequisite for transmural conduction.[8, 10, 35]

Endo-epicardial dissociation of electrical activity has previously been described by Schuessler et al. in isolated canine right atria using simultaneous endo-epicardial mapping.[36] More recently, optical mapping in isolated right atrial walls from explanted human hearts showed that intramural micro-reentry circuits may drive AF.[37] Gutbrod et al., in line with our findings in the goat model [7, 10], showed clear evidence of endo-epicardial dissociated activity and breakthrough waves in left atria in sheep, also using optical mapping.[38] De Groot et al. confirmed this with direct contact endo-epicardial mapping in human right atria during cardiac surgery, with 65% of breakthrough waves explained by activation on the opposing layer.[5] This is in good agreement with our findings in human right atrium where a higher degree of endo-epicardial dissociation was correlated with a larger number of breakthrough waves resulting in a 3D conduction pattern and enhanced overall complexity of AF.[8]

5. Study Limitations

First of all, our clinical mapping data were restricted to the right atrial free wall, largely because of safety reasons. In the goat model, however, we did not observe qualitative differences in endo-epicardial dissociation of electrical activity between right and left atria and the data in this study were just used to demonstrate that the data provided by the model are quantitatively comparable to the situation in patients. Secondly, we did not implement ectopic focal discharges as drivers for AF. A previous modeling study of our group has, however, shown that the quantitative relation between endo-epicardial dissociation of electrical activity and breakthrough rate does not critically depend on whether AF is driven by reentrant mechanisms or by ectopic focal discharges.[39] Finally, simultaneous endo-epicardial mapping would be desirable in a larger number of patients to establish differences in the degree of endo-epicardial dissociation between patients with and without a history of AF.

6. Conclusion

We created a novel computer model for AF by implementing an epicardial layer and endocardial bundle network with realistic assumptions on fiber directions based on histological studies and recent MRI studies on the submillimeter level. Simultaneous high-density endo-epicardial mapping in patients with AF confirmed the validity of the main quantitative characteristics of AF and endo-epicardial dissociation during AF in this model. Modeling results showed that isolated epicardial fibrosis is sufficient to explain increasing endo-epicardial dissociation of electrical activity and breakthrough incidence in complex substrate for AF.

7. Clinical Relevance

Our findings may have major clinical implications for the interpretation of mapping results to identify targets for AF ablation. Our study demonstrates that conduction patterns recorded on the epicardial or endocardial surface of the atrium does not necessarily reflect the overall conduction pattern in the atrial wall. Also, future computer models of AF will have to account for endo-epicardial dissociation and conduction, particularly when mechanisms of AF are addressed or when used for estimation of efficacy of individualized therapy.

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Supplemental material

1. Simultaneous Endo-epicardial mapping in the patients

During cardiac surgery, prior to the insertion of the venous cannula in the right atrium, the endocardial arm of the tongs-electrode was introduced into a purse-string suture.

In patients in SR, AF was induced through burst pacing by epicardial pacing wires. When AF was achieved and maintained for 30 seconds, the arms of the electrode were approximated to both sides of the atrial wall and a recording was started. By design, the electrodes were parallel at 3 mm distance. However, the surgeon could adjust the distance depending on the quality and amplitude of the electrogram signals.

2. Local activation detection in patient recordings

To detect local activation time we used automated algorithms described previously. (1) In this method, local deflections are detected after filtering out baseline drift and cancellation of ventricular far fields. Negative deflections in the electrograms were detected using a template matching procedure. Deflections representing local activations were identified by optimizing the match of the obtained intervals to the AF cycle length probability density function using a probabilistic algorithm as described previously. (1)

3. Fiber orientations in the developed atrial model

In the editing software, splines were drawn to define fibre orientations in different regions of the atrium. For the left atrial wall, two sets of splines were used to confer different fibre orientations on the endocardial and epicardial half of the wall. Each model element took its orientation from the nearest spline. In the right atrial wall the orientation was governed by the nearest endocardial bundle, and was made perpendicular to it, but parallel to the epicardial surface. An additional set of splines was used to confer a circumferential fiber orientation in the pulmonary and caval vein ostia. Endocardial bundles in the RA wall and LAA received a fiber orientation aligning with the bundle. The bundles consisted of myocardium to which different conduction properties could be assigned. One to three layers of fibre orientations were added to the model based on several anatomical studies. (2, 3)

4. Electrophysiological model for the simulations

Simulations were performed with the propag-5 software (6, 7) and run on 2560 cores of a Cray XE6 supercomputer. Electrical activity was simulated with a mono-domain reaction-diffusion equation. Simulations were performed using an atrial model at 0.2mm resolution. Within the myocardial envelope, a 1mm layer of myocardium was placed to represent the thin right atrial wall. A 3mm layer was used for the thicker left atrium.

Ionic currents and calcium handling for each model node was described by the Courtemanche-Ramirez-Nattel model.(8) To reproduce electrical remodelling as observed in

atrial fibrillation, conductivities for I_{to}, I_{caL}, and I_{k1} were set at 40%, 35%, and 200% of their normal values respectively. (9)

5. AF initiation

To initiate AF, a single pacing site in combination with an associated temporary block line was used (Figure 1). Ten episodes of AF were initiated at different locations for each group.

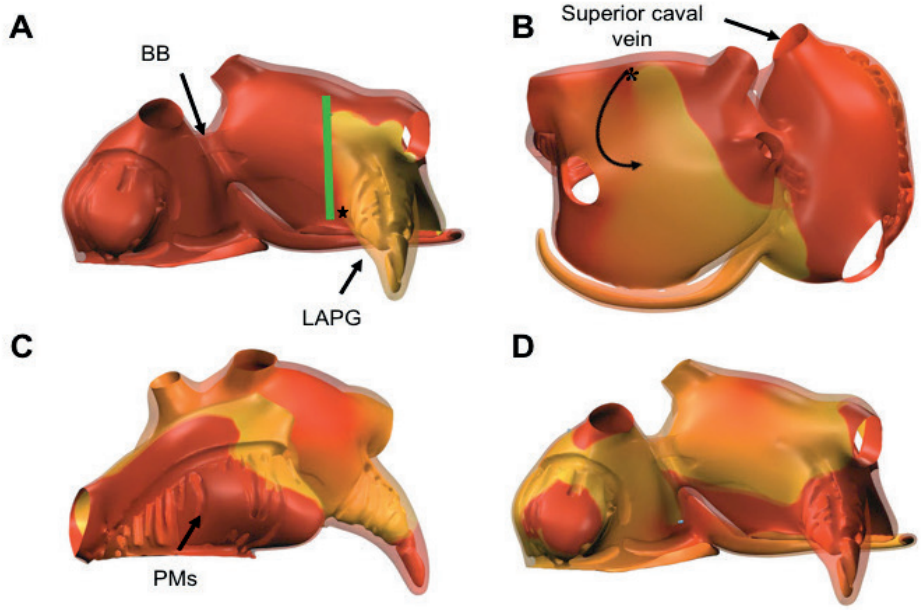


Figure S2. AF initiation. A) An Example of a spiral wave initiation. Pacing point (black star) and temporary line of block (green line). B) Initiated spiral wave (black asteriks) and its trajectory (black arrow). C) Potential map at right atrial free wall. D) Potential map at anterior view.

6. Detection of Waves in simulations

A wave was defined as a contiguous area in which all nodes have trans-membrane voltages above a threshold of –60mV. The number of waves was calculated at each millisecond of simulated time.

7. Detection of Breakthroughs in the simulations

A breakthrough (BT) was defined as a wave that appears in the epicardial layer or the endocardial bundle network and cannot be related to the propagation of other waves in that layer. To detect BTs, wave sizes at each time step were calculated. If a wave smaller than a threshold (9 nodes in this study) appeared within the opposing layer and this wave had an overlap with a wave in endocardial layer, this was considered as a BT candidate. Each BT candidate was monitored and if its size increased in twofold, it was confirmed as a BT.

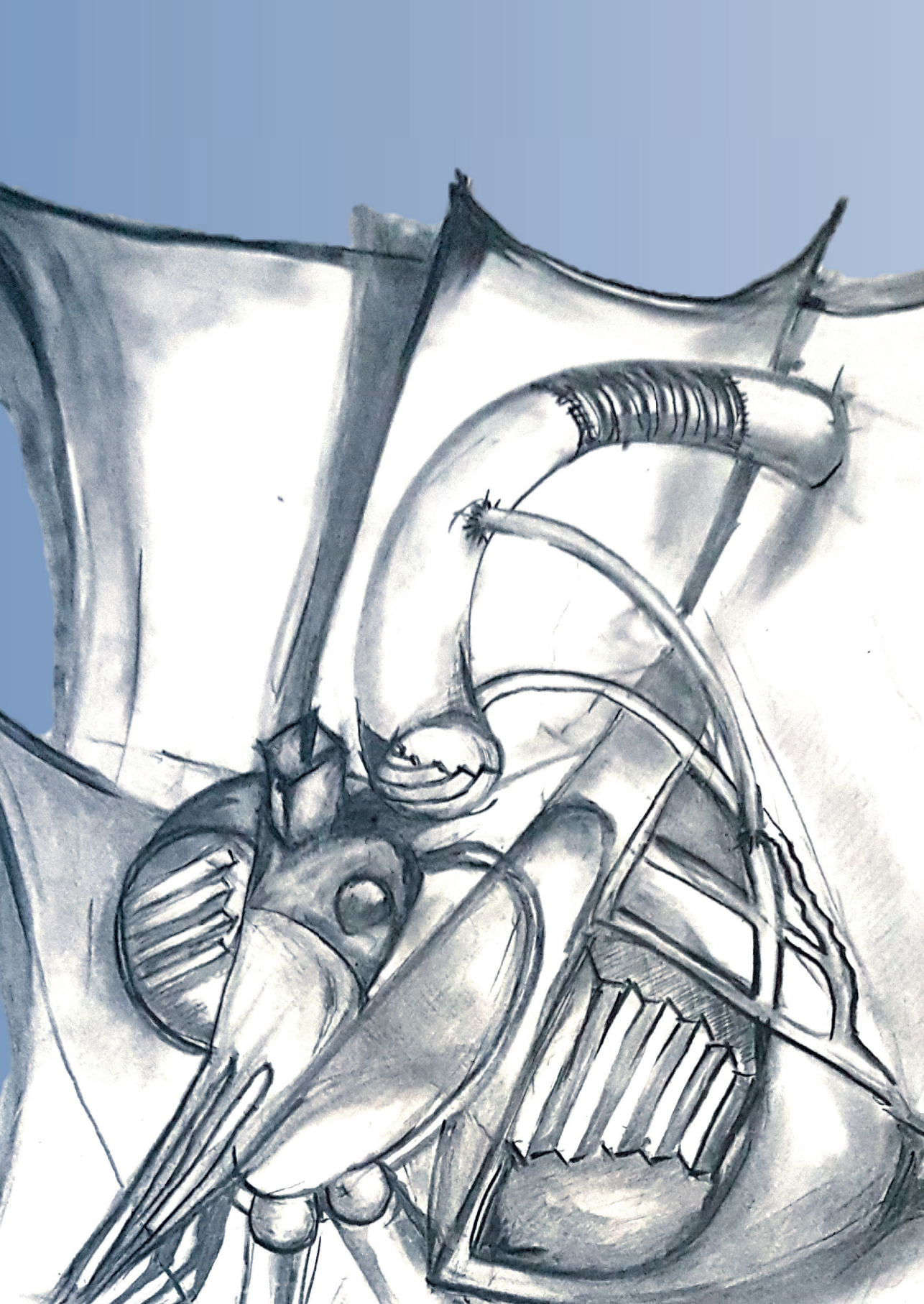
8. Statistics

All human data are expressed as means with standard errors (±SE). We used a mixed model analysis (SPSS 20.0) to test for differences between wave characteristics in the endo- and epicardial planes in AF and SR groups.

For the 3D model, all statistical analyses were performed using SPSS software (IBM Corp. Released 2013). Statistical tests were performed to compare the 3 groups of simulations (control, moderate, and severe fibrosis). The average number of waves, breakthroughs, and EED percentage during the whole simulation period were calculated for each individual simulation. The results of the 3 groups were compared using one-way ANOVA with a Bonferroni correction.

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6

Application of Phase Coherence in Assessment of Spatial Alignment of Electrodes during Simultaneous Endocardial-epicardial Direct Contact Mapping of Atrial Fibrillation

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Abstract

Aims: Mapping and interpretation of wave conduction patterns recorded during simultaneous mapping of the electrical activity on both endocardial and epicardial surfaces is challenging because of the difficulty of reconstruction of reciprocal alignment of electrodes in space. Here, we suggest a method to overcome this difficulty using a concept of maximized endo-epicardial phase coherence.

Methods: Endo-epicardial mapping was performed in six humans during induced atrial fibrillation (AF) in right atria using two sets of 8x8 electrode plaques. For each electrode, mean phase coherence (MPC) with all electrodes on the opposite side of the atrial wall was calculated. Localization error was defined as a distance between the directly opposing electrode and the electrode with the maximal MPC.

Results: Overall, there was a linear correlation between MPC and distance between electrodes with R^2=0.34. Localization error obtained for electrodes of the plaque in 6 patients resulted in a mean 2.3±1.9 mm for 25 s electrogram segment length. 84% of the measurements resulted in error smaller than 3.4mm. The duration of the recording used to compute MPC was negatively correlated with localization error, however the effect reached plateau for segment durations longer than 15 s.

Conclusion: Application of the concept of maximized endo-epicardial phase coherence to electrograms during AF allows reconstruction of reciprocal alignment of the electrodes on the opposite side of the atrial wall. This approach may be especially useful in settings where the spatial position of endo- and epicardial electrodes for intracardiac mapping cannot otherwise be determined.

What's new?

- Phase coherence between electrograms recorded during AF decays with a distance between electrodes.
- This property may be used to localize the closest electrode to an electrode with known position by calculating its coherence with remaining electrodes and locating the position of maximum coherence.
- This technique may also be used to localize an electrode with respect to a set of electrodes with known positions by calculation of the relative distances between the electrodes by using phase coherence as a surrogate distance parameter.
- Localization of an electrode located on other side of the atrial wall in RA during AF can be achieved with a mean error of 2.3±1.9 mm (recording length at least 25 sec).
- The duration of AF recordings should be at least 15s to minimize localization error.

Introduction

Despite decades of intense research efforts, detailed mechanism of Atrial Fibrillation (AF) initiation, perpetuation and termination remain unclear [1]. Most of the findings revealing patterns of wave conduction perpetuating AF regard atrial wall as a two dimensional medium, measuring electrical activity either on epicardial or endocardial surface of the chamber. However, complexity of atrial architecture augmented by structural remodeling of the atrial wall has been demonstrated to cause dissociation of electrical activity between endocardial bundle network and epicardial layer [2-7]. This three-dimensional complexity of electrical activity during AF requires development of novel methods of mapping and wave conduction analysis.

Simultaneous mapping of endocardial and epicardial electrical activity was already achieved in experimental setting using epicardial plaques of electrodes along with intra-atrial balloon arrays [4] or 'clamp like' devices comprising two plaques of electrodes for mapping of both surfaces of the atria [3]. The latter solution enables mapping of the wave conduction on both epicardial and endocardial surface providing information about relative spatial position of the electrodes on both sides of the atrial wall. However, requirement of the incision in order to introduce the clamp limits its experimental utility. The former approach doesn't require an incision of the atrial wall for mapping, however is limited with respect to positioning of the electrodes (location of the electrodes of the intracardiac array with respect to electrodes of epicardial plaques). This limitation makes assessment of the endo-epicardial dissociation and interpretation of the wave conduction patterns challenging. Exact spatial positioning of the electrodes could be achieved using impedance-based three-dimensional anatomical mapping systems, however their effectiveness may be limited in open chest experiment due to exposure

of the heart hampering impedance measurement. Here, we suggest a simple method to reconstruct reciprocal spatial alignment of the electrodes during AF using a concept of maximized endo-epicardial phase coherence [8].

Methods

Data acquisition

Electrical activity of endocardial and epicardial surface of atria was recorded using clamp-like mapping tool (see Figure 1). The device has two jaws ending in a square plaque (1.5x1.5 cm) carrying 64 (8x8) unipolar electrodes that directly oppose each other when the device is closed. Using this device, we conducted simultaneous endo-epicardial mapping of the right atrial wall in 6 patients with persistent AF undergoing open chest surgery. Prior to the insertion of the venous cannula for the cardiopulmonary bypass in the right atrial appendage, the endocardial jaw of the electrode was introduced into the purse-string suture that was placed for the venous cannula. By design, the electrode arrays were parallel to each other at a 3 mm distance between the arrays. However, the surgeon was able to adjust the distance guided by the quality and amplitude of the electrograms. In the beating heart, a 25-second endo-epicardial recording was made before the electrode was extracted and the venous cannula was inserted for cardiopulmonary bypass. Unipolar electrograms were recorded at 1kHz sampling rate, band-pass filtered between 0.1 and 500Hz, digitized and stored for off-line analysis.

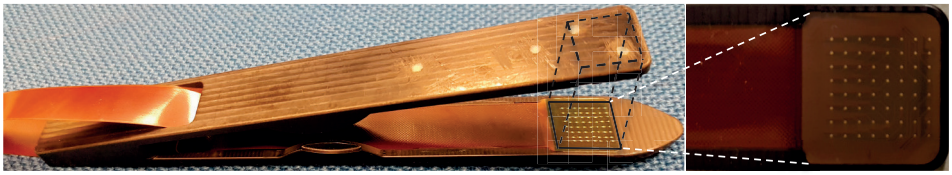


Figure 1 Clamp-like mapping device used in the study to simultaneously map both endocardial and epicardial electrical activity of the atria during AF.

Calculation of electrograms phase

Electrograms phase of was obtained using a concept of sinusoidal recomposition (see online Appendix A) followed by Hilbert transform. Phase of the electrogram was defined as:

$$\varphi(t) = \arctan\left(\frac{-u(t)}{H(u)(t)}\right) \quad (1)$$

where u(t) is recomposed electrogram and H(u)(t) is a recomposed electrogram after application of Hilbert transform.

Assessment of coherence of two electrograms using a concept of mean phase coherence

Mean phase coherence (MPC) [8] between an electrogram at position *(i,j)* on endocardial surface and electrogram at position *(m,n)* on epicardial surfaces was defined as:

$$MPC = \left| \frac{1}{T} \sum_{t=1}^{T} e^{j(\varphi_{i,j}^{Endo}(t) - \varphi_{m,n}^{Epi}(t))} \right| \quad (2)$$

where t is a time index, T is a number of time samples of the electrogram, $\varphi_{i,j}^{Endo}(t)$ is a phase of the electrogram on endocardial surface and $\varphi_{m,n}^{Epi}(t)$ is a phase of the corresponding electrode on epicardial surface. In a case both electrograms have identical phase in time, MPC is equal to one. In case of uncorrelated electrical activity between electrograms, MPC will be close to zero [8]. Schematic and an example of mean phase coherence (MPC) calculation are shown in Figure 2.

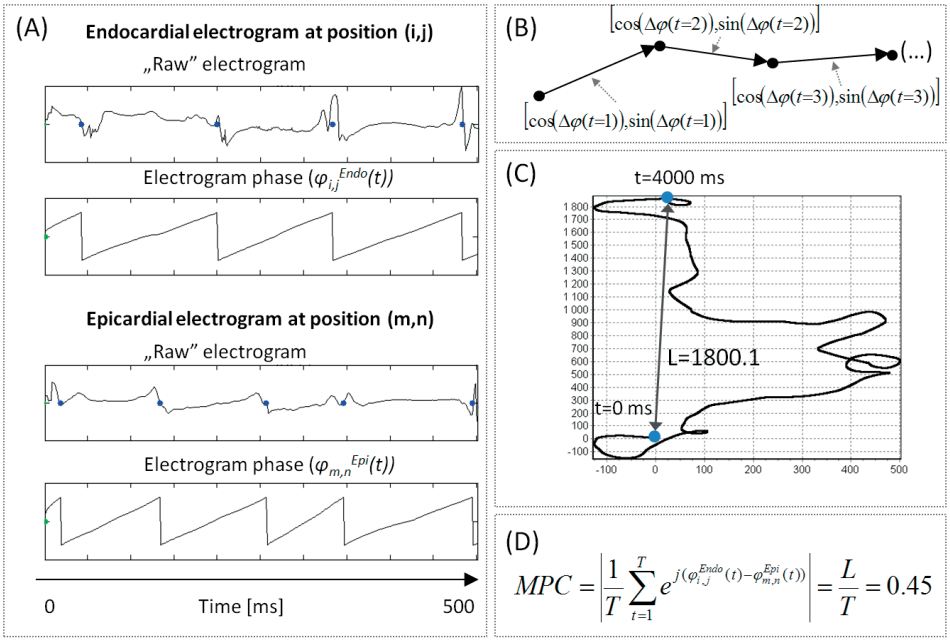


Figure 2 Schematic and an example of MPC calculation. Electrograms with corresponding phases recorded on endocardium and epicardium (*A*). For each timepoint, a unit vector with orientation set by phase difference between both signals is added in the complex plane plot (*B*) ($\Delta\phi$ denotes the phase difference between electrograms at a given timepoint). Such constructed curve for 4 s of example electrogram (*C*). Mean phase coherence is defined as a distance (denoted as *L*) between starting point of the curve (0, 0) and an endpoint divided by a number of time samples (*D*). Such defined parameter ranges from 0 if the endpoint is at the same location as a starting point, to 1 in case all contributing vectors are aligned along straight line (which corresponds with a constant phase difference)

Determination of the electrode position based on mean phase coherence

For each electrode of the plaque, MPC was calculated between an electrogram of given electrode and all electrograms recorded at electrodes on the opposite surface. Positioning error was defined as a distance between actual position of the electrode within a plaque and the position of the maximum in obtained distribution of MPC values (see Figure 3.a).

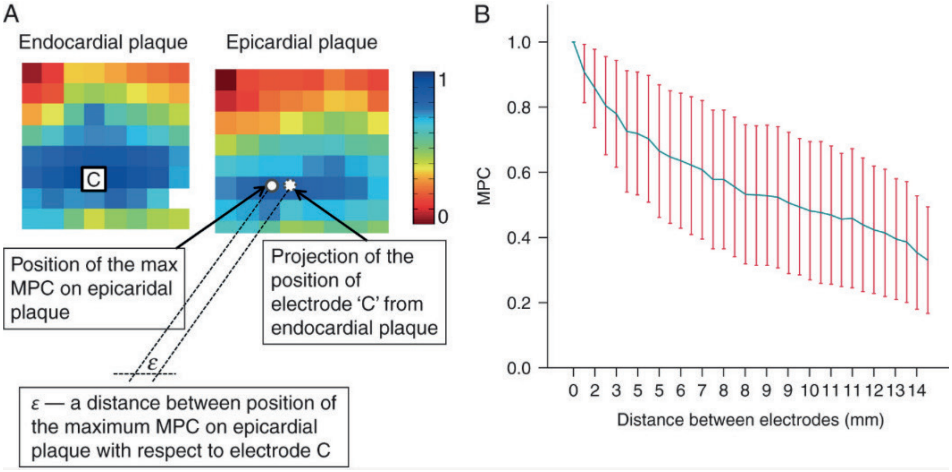


Figure 3 (A): Spatial distribution of mean phase coherence between arbitrarily selected electrode on endocardial plaque (marked as C). Each square corresponds with a measurement electrode. MPC decays with a distance from reference electrode C. Maximum of the MPC on epicardial plaque and projection of the electrode C marked with white circles. A distance between position of the maximum and position of the projected electrode is interpreted as a measurement error. (B): MPC value as a function of distance from electrode calculated or all pairs of electrodes for all patients (N=48140 electrode pairs). Despite significant spread of values (error bars denote one standard deviation) MPC exhibits a decay with increasing distance between electrodes.

Results

In order to assess relationship between MPC and a distance between electrodes, MPC was calculated between all pairs of the electrodes within the plaque (with electrode pairs belonging to either endocardial or epicardial plaque). Combined result for all patients (N=48140 pairs of electrodes) and length of the analyzed electrogram segment 25 sec is shown in Figure 3.b. Overall, there was a linear correlation between MPC and the distance between electrodes with R^2=0.34.

Mean localization error at an electrode (see Figure 3.a for definition) was defined as the distance between the electrode with the maximum endo-apicardial mean phase coherence and the directly opposing electrode. The result for each patient is shown in

Figure 4.a (result for analyzed electrogram segment length 25 sec). The mean error varied between patients with lowest for patient #5 with ε=1.2±1.1 mm and highest for patient #6 with ε=3.8±2.0 mm. On average, the localization error was 2.3±1.9 mm.

The duration of the electrogram used to compute MPC was negatively correlated with localization error (see Figure 4.b). However, the effect reached plateau for segment lengths longer than 15 s.

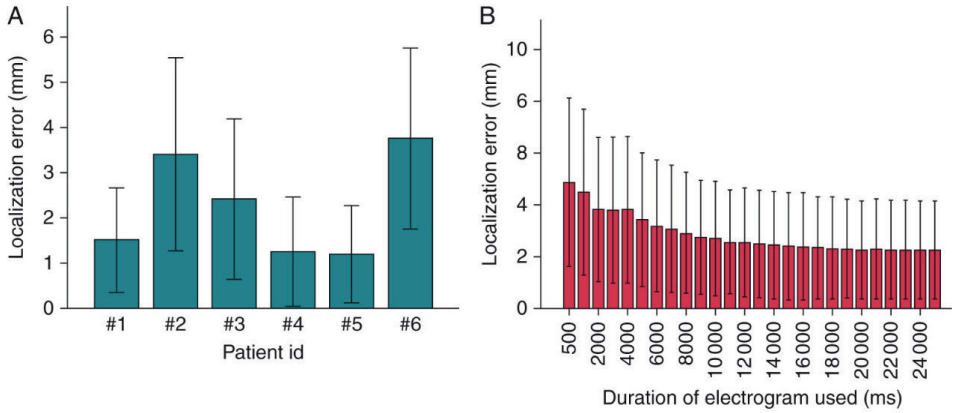


Figure 4 (A): Electrode localization error (a distance between position of reference electrode and a maximum MPC on the other side of the atrial wall) for all 6 patients included in this study and electrogram segment length 25 sec. (B): Electrode localization error for various lengths of the analyzed electrograms segment.

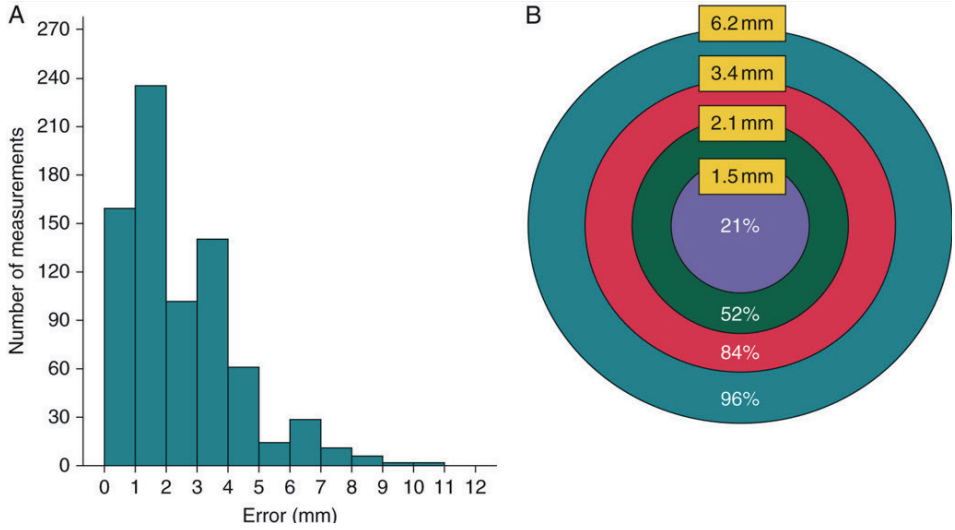


Figure 5 (A): Histogram of localization error ε. (B): cumulative frequency of the localization error ε falling within a circles of specified radius with respect to reference electrode. In 21% percent of cases, ε was between 0-1.5 mm, in 52% of cases ε was between 0-2.1 mm, etc. Results for analyzed electrogram segment duration 25 s.

The histogram of localization error ε for all patients combined is shown in Figure 5.a. Majority of the measurements were related with error ε<5 mm. A schematic presenting cumulative frequency of the localization error ε falling within a circles of specified radius with respect to reference electrode is shown in Figure 5.b. 84% of the measurements resulted in error smaller than 3.4 mm.

Discussion and conclusions

The main findings of the study may be summarized as follows:

- Phase coherence between electrograms recorded during AF decays with a distance between electrodes (see Figure 3.b).
- This property may be used to localize the closest electrode to an electrode with known position by calculating its coherence with remaining electrodes and locating the position of maximum coherence.
- This technique may also be used to localize an electrode with respect to a set of electrodes with known positions by calculation of the relative distances between the electrodes by using phase coherence as a surrogate distance parameter.
- Localization of an electrode located on other side of the atrial wall in RA during AF can be achieved with a mean error of 2.3±1.9 mm (recording length at least 25 sec).
- The duration of AF recordings should be at least 15 s to minimize localization error.

The presented technique may be particularly useful during detailed contact mapping of the atrial electrical activity with plaques of electrodes covering the epicardial surface, and arrays of the intracardiac electrodes covering endocardial surface (such as described in [4]). This configuration might be used in an experimental setting in which endo-epicardial dissociation and conduction is investigated. Also, during endo-epicardial approaches for AF ablation in hybrid electrophysiology labs this technique might prove useful to merge electrograms recording data sets recorded from various arrays of electrodes. These procedures require an open chest or at least a minimal invasive epicardial approach, making usage of 3D mapping systems or fluoroscopy to localize the electrodes difficult [9]. We suggest, in such setting, application of the proposed method to localize electrodes of the intracardiac catheter with respect to epicardial plaques of electrodes. Thus, for each electrode of the intracardiac catheter, the closest corresponding electrode of epicardial plaques will be located enabling proper spatial mutual positioning of the endocardial and epicardial electrodes. The relative distances between electrodes determined from the relative differences in phase coherence may further facilitate electrode alignment.

Since proposed method is based on the decay of electrogram phase coherence with distance between electrodes, robust results may only be achieved in case of irregular

atrial activity. Organized arrhythmia (such as atrial flutter) may result in lack of relationship between coherence and distance thus rendering the method inapplicable.

Limitations

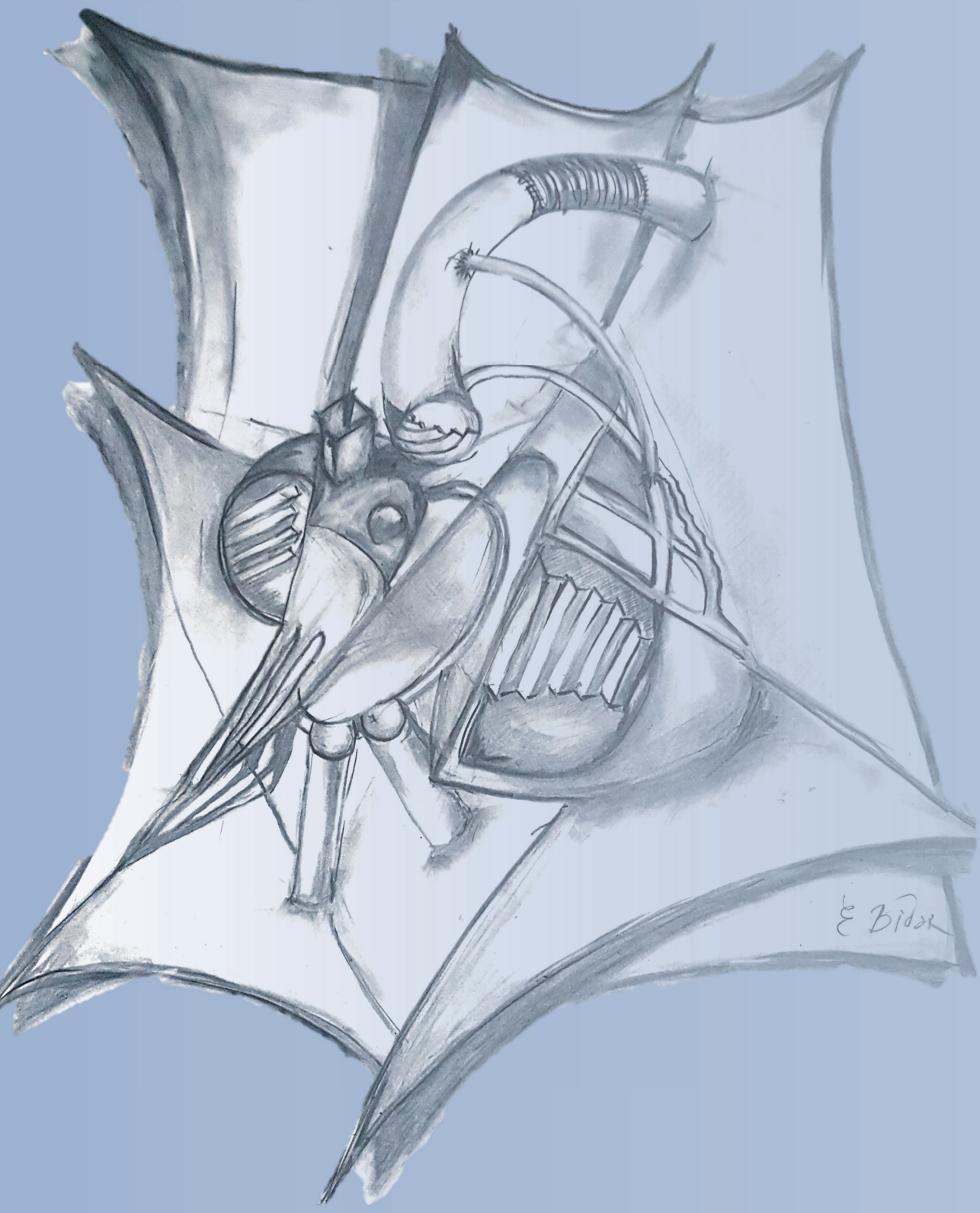
This study has following limitations: (i) due to difficulty in obtaining simultaneous endo-epicardial, high density recordings in human atria, electrograms were recorded only in one location in right atria. Measurements at different locations may have yield different coherence decay distributions, due to different myocardial architecture and presence of fibrosis, (ii) proposed method works best if intracardiac electrode is located in the area below epicardial plaque. In case electrode is located in a location falling into a gap between two different epicardial plaques, reconstruction of its exact positioning may require interpolation using the locations of maximum coherence on both plaques.

Acknowledgments

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E Bidak

7

General discussion

In the first 3 chapters of this thesis we aimed to determine the long-term incidence of postoperative atrial fibrillation (POAF) using prolonged rhythm-monitoring strategies. We hypothesized that while the incidence of early POAF peaks during the first postoperative days following the operation, suggesting an important causative role of acute inflammatory or autonomic alterations, late POAF also occurs frequently thereafter and might be more dependent on pre-existing organ damage. To exclude confounding electrophysiological effects of AF itself we included patients without a history of AF. We found that patients with a specific risk profile show mostly subclinical AF episodes lasting up to 1.5 hours per episode in the months to years after surgery. We divided the postoperative period into an early and late phase considering enhanced effects of the acute postoperative triggers in the first days after surgery. This early phase coincides with the hospitalization period of most patients undergoing cardiac surgery, which is reflected by the follow-up period in most previous studies on POAF. However, identifying the risk profile and the underlying substrate of late POAF contributes to prediction and prevention strategies of these episodes. Thus the presence of an underlying substrate for AF and the possible range of substrate complexity in AF should be thoroughly studied (Figure 1). For this purpose, electrophysiological mapping techniques are very useful. In Chapters 5 and 6 we carried out an in-depth analysis of the effects of fibrosis on the 3-dimensional propagation properties of the atria, which is an important contributor to AF maintenance in diverse AF substrates with different co-morbidities.

It is important to recognize that there are differences in AF substrates resulting from different underlying diseases. We further tested this hypothesis by assessing the electrophysiological characteristics of POAF patients as a reflection of a preexisting atrial structural substrate.

Acute postoperative triggers for POAF

POAF is the most common complication after cardiac surgery, affecting up to 60% of patients. To fully understand the high prevalence of POAF, it is very important to consider the multitude of pro-arrhythmic mechanisms after cardiac surgery.

AF initiation and perpetuation are facilitated by a complex interplay between triggers and an underlying structural substrate.[1-3] In other words there are specific pro-arrhythmic areas in the atria causing focal discharges (triggers), while structural changes influencing impulse propagation may perpetuate AF (substrate). While triggers can initiate an AF episode, the AF substrate determines the stability and duration of an AF episode after initiation. In structurally normal atria, a single trigger is likely to cause only a short AF episode, and maintenance of AF requires a high frequency of triggering events. In contrast, in atria with extensive structural remodelling, a single ectopic beat can initiate an AF episode that does not terminate spontaneously, [4] because it is maintained by the AF substrate.

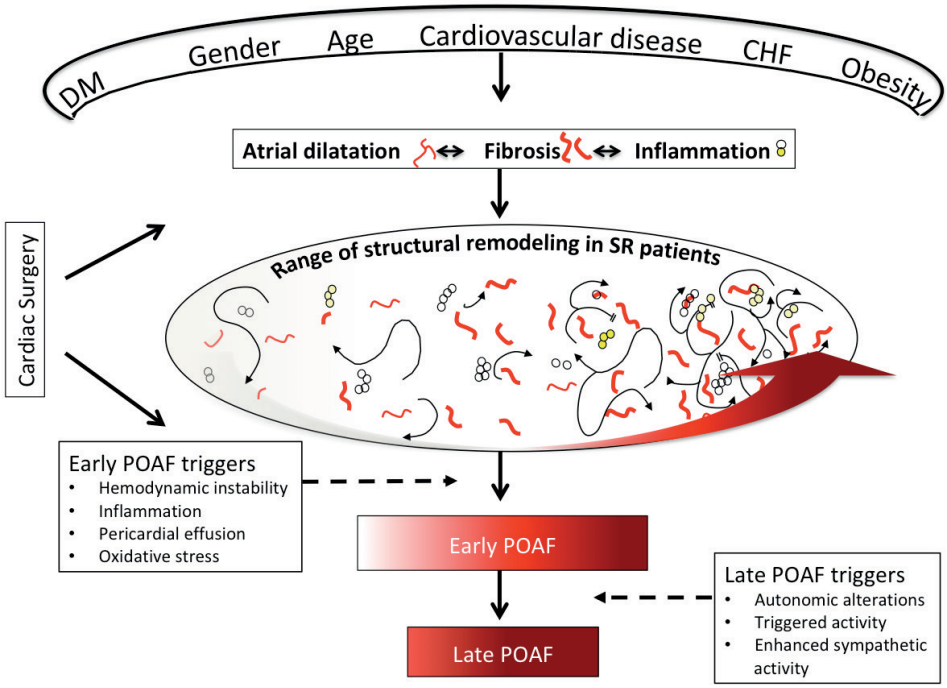


Figure 1. Schematic depiction of the pathophysiology of early and late POAF, effect of co-morbidities on development of a structural and electrophysiological substrate (curved arrows) for POAF and the subsequent triggers in the acute postoperative phase and later on. DM: diabetes mellitus; CHF: congestive heart failure; POAF: postoperative atrial fibrillation; SR: sinus rhythm.

The triggers for AF often originate in specific regions, most notably the muscular sleeves of the pulmonary veins, but also the ligament of Marshall, the coronary sinus, and the ostia of the caval veins. These regions may have specific pro-arrhythmic characteristics (i.e. differences in cellular electrophysiology, autonomic ganglia, overlapping and complex myofiber orientation),[1, 5-7] but the mechanism underlying ectopic activity (i.e. triggered activity vs. micro reentry) is not certain. Triggered activity often results from calcium (Ca^{2+}) oscillations. Calcium overload or abnormal Ca^{2+}handling causes these oscillations, which are mediated by Ca^{2+}-induced-Ca^{2+} release from the sarcoplasmic reticulum and lead to delayed after depolarisations (DADs) after a normal action potential as a result of activity of the sodium-calcium exchanger (NCX).[8] Specific conditions increasing the likelihood of these events are enhanced sympathetic activity, tachycardia and ischemia.[1, 4, 8] Furthermore pericarditis,[9] acute atrial stretch and oxidative stress [10] can all cause abnormalities in Ca^{2+} handling that may provoke afterdepolarisations.

As discussed in chapter 2, many of these conditions are present during the acute postoperative phase. Common examples include volume overload with increased right atrial pressures, which may last for days and sometimes weeks before euvolemia is achieved. Other examples are infections, pericardial effusions, systemic inflammation as

a result of cardio-pulmonary bypass, possibly leading to hypovolemia, and pro-arrhythmic inotropic agents such as Dobutamine or Milrinone used to stabilize hemodynamics in the intensive care unit. Hence the first few days after cardiac surgery contain an agglomerate of triggers for AF. Notably, the incidence of arrhythmias after cardiac surgery attributable to the surgical process or postoperative period is much lower for ventricular arrhythmias than for atrial arrhythmias. This may be due to the differences in ion-channel expression between the atrium and ventricle. Expression of the inward rectifier potassium channel I_{K1} for example, is 5-10 fold higher in the ventricles, which makes atrial myocytes more excitable than ventricular myocytes.[1]

While during the acute postoperative phase, patients are continuously under medical supervision, after discharge the effectiveness of medical treatment heavily depends on patient compliance. It is plausible that modulators increasing risk for late POAF such as heart rate variability and autonomic dysregulation [11] may be enhanced in case of non-adherence of the patient to beta-blockers [12, 13] or other antihypertensive and anti-arrhythmic drugs.

Substrate for POAF

Considering the acute postoperative phase, it is easily conceivable that early POAF may occur because the high incidence of triggers acts as 'a stress test' on the underlying AF substrate. However, we also demonstrated that POAF is not confined to the acute post-operative phase and a large number of patients are at risk of developing late POAF after discharge from the hospital. In addition, we propose that a pre-existing AF substrate predisposes patients to late POAF development. We demonstrated that predictors of POAF and late POAF include: obesity and diabetes mellitus (DM), smoking and aortic valve disease, male gender, C-reactive protein (CRP) levels combined with myocardial infarction (chapter 3), advanced age, higher CHA_2DS_2VASc (Congestive heart failure (CHF), hypertension (HT), age, DM, sex, vascular disease) and HATCH (i.e. HT, age >75 years, transient ischemic attack/stroke, COPD, and HF) scores and right atrial dilatation (chapter 4). We also investigated the pre-existing substrate for POAF by quantifying the atrial electrical propagation during AF using direct contact high-density mapping of the right atrial wall. To examine the complexity of fibrillation in patients developing POAF, we compared our results in chapter 4 to previously published data. Figure 2 illustrates the RA waves/cycle/cm^2 in patients described in chapter 4 (i.e. patients with co-morbidities, but no AF history) compared to patients undergoing Wolf-Parkinson-White ablation (i.e. no risk factors for AF) and persistent AF.[14, 15] As expected, due to several co-morbidities, patients undergoing cardiac surgery showed more complex fibrillation patterns compared to WPW-patients, also when they did not develop subsequent POAF (figure 2).

Hence the range of atrial remodelling depends on the underlying co-morbidities. Predictors of late POAF are similar to those in AF patients in the general population. The Framingham study, following 2090 men and 2641 women without a history of AF, showed that independent predictors of AF after 38 years of follow-up were diabetes, HT, CHF and valvular disease.[16] Accordingly, almost 60% of incident AF in general population has been attributed to the same elevated risk factors in addition to obesity and smoking.[17] Furthermore higher HATCH-scores are associated with an increased risk of new onset AF [18] and AF progression.[19] Indeed, aggressive management of factors such as weight, blood pressure, and lipid management, glycemic control, breathing management during sleep, smoking and alcohol cessation beneficially affect outcome as demonstrated by higher success rates of AF ablation compared to a control group.[20]

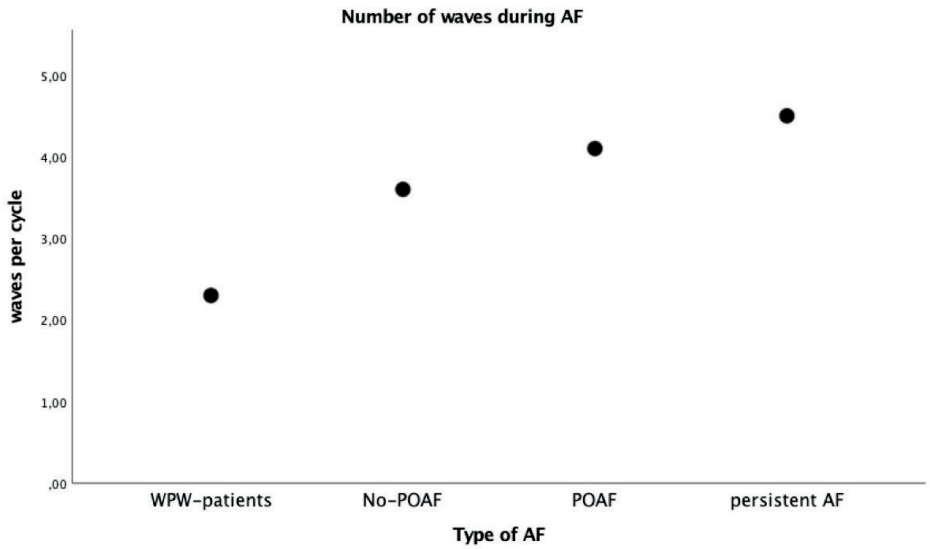


Figure 2. The median number of waves/cycle/cm^2 as measured by Allessie et al.[15] was 2.3 waves/cm^2 in WPW patients and 4.5 waves/cm^2 in persistent AF patients. In comparison recordings from patients with hypertension undergoing cardiac surgery showed a median of 4.1 waves/cm^2 in patients who developed POAF compared to 3.6 waves/cm^2 in those without subsequent POAF (see Chapter 4).

On the structural level, there are important proarrhythmic changes resulting from co-morbidities. One key structural abnormality demonstrated in different models of AF has been increased connective tissue deposition and fibroblast proliferation leading to fibrosis. The reaction of the myocardium to stressors such as pressure or volume overload and ischemia is mediated through cardiac fibroblast activation, synthesis of extracellular matrix proteins as a protective mechanism which in its turn disrupts electrical coupling between myocytes.[21] Fibrosis can display several distinct patterns.[22] As an

adaptive mechanism in response to increased stretch or wall stress due to volume or pressure overload, a type of fibrosis occurs that has been named reactive, interstitial or endomysial fibrosis, characterized by an increase in extracellular matrix volume surrounding individual myocytes. This type of fibrosis occurs in the absence of increased myocyte apoptosis or necrosis. By contrast, replacement fibrosis or scar formation occurs in response to myocyte death. In the ventricular myocardium, the exact distribution pattern of fibrous tissue strongly determines the impact on conduction.[23] Accordingly patients with AF also have enhanced level of both types of fibrosis.[21, 24]

Nevertheless the relation between AF and atrial fibrosis remains highly complex and non-linear. [25-27] Perpetuation of AF is not solely determined by fibrosis; another structural abnormality that has been recognized in recent studies is fatty infiltration.[28] Adipocytes intermingling with myocytes are likely to lead to a disruption of propagation similar to fibrous tissue. Many areas of fatty infiltration are also surrounded by fibrous tissue.[29] In addition, adipocytes release factors that can be profibrotic, but can also be protective, for example by reducing production of reactive oxygen species in myocytes.[30] Finally, mechanical stress resulting from pressure overload (concentric) and volume overload (eccentric), alongside profibrotic stimuli such as transforming growth factor (TGF)-β and macrophage mediated inflammation all contribute to myocyte hypertrophy.[31] Myocyte hypertrophy may compromise contractile function and become proarrhythmic.[32]

However, direct causality of diseases in AF is difficult to prove due to co-existence of morbidities, especially in the elderly population. For this purpose, animal models (discussed below) have been useful, assessing the relation between each disease and the specific structural changes at the atrial level.

'Lone AF'

'Lone AF', i.e. AF without underlying structural heart disease can be mimicked in animal models by rapid atrial pacing (RAP), in which a burst pacemaker stimulates the atria at high frequency. The goat model of RAP illustrated the progressive nature of AF, as evidenced by the gradual loss of efficacy of anti-arrhythmic drugs[33] paralleling observations in AF patients. During the first hours to days of RAP in goats, electrical remodeling, i.e. shortening of effective refractory period (ERP) occurs.[34] In the ensuing weeks to months, atrial structural remodeling slowly develops including myocyte hypertrophy and structural changes[35] hallmarked by gradual endomysial fibrosis in the outer epicardial layer of the atria.[36] Electrical propagation during AF in this model is characterized by multiple simultaneously propagating wavelets. Over time, fibrillation patterns become more complex and dissociated, with a larger number of waves. We have previously demonstrated that conduction does not only become more dissociated within the epicardial plane [36] but also between the epicardial layer and the underlying endocardial trabecular network.[37] In the goat model of AF, endo-epicardial dissociation explains a majority of breakthrough (BT) events, i.e. waves which suddenly appear on the surface

of one layer are conducted transmurally from the opposing layer. An increased incidence of BTs had also been described in patients with longstanding AF.[38]

In chapter 5, we demonstrate with simultaneous epi-endocardial mapping that epi-endocardial dissociation, leading to BTs, also occurs in patients. Interestingly, while there was a clear correlation between transmural electrical uncoupling and increased BT, these changes were not observed only in persistent AF patients but also in patients without a history of AF. This further underscores the range of atrial structural remodeling resulting from underlying cardiovascular diseases. Notably, previous mathematical models of atrial propagation have not been able to replicate this behavior.[39, 40] After taking the 3-dimensional structure of the atrial wall including fiber orientation into account, we present in Chapter 5 a computer model that, for the first time, was able to demonstrate endo-epicardial dissociated activation closely related to increased BT with enhanced levels of endomysial fibrosis. Indeed, this computer model replicated the propagation pattern observed in animal models and our patient population.

Heart Failure

Heart failure (HF) is also strongly associated with AF development in patients and [41] atrial fibrosis is significantly more pronounced in patients with heart failure.[42] In a canine model, Li et al, compared 6-8 week of RAP (with controlled ventricular rate) to CHF induced by 5 weeks of rapid ventricular pacing (RVP). They found that in contrast to the RAP group, HF led to slow and heterogeneous conduction with pronounced atrial fibrosis.[43] The pattern of fibrosis in this model suggests replacement fibrosis, and indeed, in the first days after the initiation of RVP, a dramatic phase of apoptosis, necrosis and inflammatory infiltration was observed. After cessation of ventricular pacing for 5 weeks in the same model, although recovery of clinical symptoms of heart failure and hemodynamics occurred, tissue fibrosis remained unchanged with consistently enhanced vulnerability to AF.[44]

Interestingly, in patients with ventricular hypertrophy and diastolic heart failure due to aortic valve stenosis, a similar effect is seen. In these patients, both focal replacement fibrosis (scar) resulting from necrosis as well as cellular hypertrophy and connective tissue deposition (reactive fibrosis) are present and can be quantified by cardiovascular magnetic resonance.[45] However, 1 year after aortic valve surgery, contrary to the replacement fibrosis, cellular hypertrophy and diffuse reactive fibrosis regress accompanied by functional and structural changes.[45] These findings alongside the abovementioned findings from HF and AF models, suggest that reactive extracellular matrix deposition and myocyte hypertrophy are reversible while fibrosis replacing necrotic tissue remains present after treatment, as a potential substrate for AF.

Mitral regurgitation and atrial dilatation

Atrial dilatation without HF is another pro-arrhythmic entity in the pathophysiology of AF, which is common to many animal models of AF (e.g. RAP, CHF) and has also been examined as a separate factor in several models. In patients with atrial septal defect RA dilatation is accompanied by electrophysiological changes such as conduction slowing and double potentials in the terminal crest.[46] Furthermore, in a canine model of left atrial dilatation due to mitral valve avulsion, increased atrial size correlated to AF inducibility and duration with histological findings including chronic inflammation and fibrosis.[47] These structural changes were not associated with altered conduction during pacing at slow rates. However, during extra-stimulation protocols, the dilated LA displayed direction-dependent conduction abnormalities that were not observed in the non-dilated RA of the same animals, nor in either atrium of a control and RAP comparison group.[48] Also in a model of AV block without HF in goats, atrial dilatation with local conduction disturbances was associated with myocyte hypertrophy. Interestingly no fibrosis or Cx re-distribution was found [49, 50] suggesting that in this model fibrosis was not a prerequisite for AF perpetuation.

In both MR and AV block models, atrial effective refractory period (ERP) was prolonged, which also contrasts the RAP and HF models described above. To further elucidate, Sparks et al. investigated the effects of atrio-ventricular (AV) asynchrony and consequent atrial dilatation in humans.[51] They compared patients with implanted pacemakers who were first paced in VVI mode (ventricular pacing only) for 3 months followed by DDD mode (atrio-ventricular pacing) to patients who were paced in DDD mode continuously. In line with previous findings, they found that after 3 months of VVI pacing, both atria increased in size and showed prolongation of ERP and P-wave duration.[51] All these changes were transient and normalized after 3 months of DDD pacing comparable to baseline and the control group.[51]

In this thesis, RA volume was an independent predictor of late POAF (chapter 4), which may have contributed to a substrate for AF beyond the effects of other predictors such as age and CHA_2DS_2VASc score. Interestingly, an indirect effect from the pericardium may also contribute to the right atrial dilating properties. There is a close correlation between the right atrial pressure and pericardial pressure before pericardium is opened.[52] In this sense, the pericardium is a determinant of RA contractility and stiffness as a response to RV afterload.[53] In a rabbit model of passive pericardial constraint, increasing atrial volume only resulted in ERP shortening and AF perpetuation when the pericardium was removed contrary to when the pericardium was still intact,[54] suggesting that atrial stretch as opposed to atrial pressure contributes to vulnerability to AF. During cardiac surgery, closing the pericardium is not always required and depends on the preference of the surgeon. Although closure of the sternum itself constraints cardiac dilatation, the direct pericardial support potentially contributes to normalizing RA function by preventing stretch.

Advanced age

In general AF is known to be age-dependent[1, 3, 55] and advanced age is one of the most important predictors of POAF, as discussed in chapters 2, 3 and 4. In animal models of aging, changes in cellular electrophysiology have been described [56, 57], along with a redistribution of gap junctional proteins, interstitial/ endomysial fibrosis, and fatty infiltration.[58] Thus, aging can lead to an accumulation of structural changes that can lead to pro-arrhythmic propagation patterns.

Hypertension

Hypertension has also been shown to correlate with interstitial fibrosis leading to heterogeneous atrial conduction.[59, 60] In a sheep model of longstanding hypertension (15 months), inflammatory infiltrates in the atrial wall correlated with increased AF inducibility and interstitial fibrosis.[59] Accordingly, renal denervation for uncontrolled hypertension increases atrial conduction velocity and reduces fractionated activity.[61] A previous study from our group suggests, however, that a protective effect of renal denervation also occurs in the absence of hypertension. [62]

Obesity

In a sheep model of obesity, animals were fed a high-calorie diet over 36 weeks and underwent electrophysiological and histological study.[63] In this model, obesity led to left atrial enlargement, increased tissue levels of transforming growth factor- β1 (TGF-β1) with increased fibrosis and left atrial fatty infiltration and subsequent pro-arrhythmic effects with heterogeneous conduction and enhanced susceptibility to AF.[63]

Inflammation

Another important AF substrate modifier in the context of cardiac surgery is local and systemic inflammation. Inflammation may be pro-arrhythmic through several profibrotic cytokines and atrial structural changes.[64] Increased inflammatory biomarkers such as tumor-necrosis factor- α (TNF-α) have been associated with AF and notably with lone AF.[65] TNF- α has been shown to increase fibrosis and the profibrotic TGF-β activity in the atrial wall.[66]

During cardiac surgery, spatial non-uniformity in refractoriness caused by hypoxia and oxidative stress due to insufficient cardioplegic support and insufficient cooling of the atria has been hypothesized as an important substrate for development of POAF.[67] In line with this, we found prolonged aortic cross clamp time as an independent predictor of late POAF (chapter 3). Notably, the source of inflammation in patients undergoing cardiac surgery is not only the surgical procedure including cardiopulmonary bypass, but additional low-grade inflammation may co-exist with the underlying cardiac disease itself. For example, in the pathophysiology of coronary artery disease, inflammation particularly with increased CRP level plays an essential role contributing to plaque de-

stabilisation following endothelial dysfunction.[68, 69] Also chronic inflammation is a major component in the cascade of native aortic valve degeneration. [70] Hence low-grade systemic inflammation goes hand-in-hand with several cardiovascular diseases in the setting of cardiac surgery. In accordance, we found baseline CRP levels combined with myocardial infarction as an independent predictor of POAF (Chapter 3).

In canine sterile pericarditis models, which resemble the acute post cardiac surgery setting, dispersion in gap junction distribution with heterogeneous conduction properties has been demonstrated.[9, 71] Also comparable to the systemic effect of cardiopulmonary bypass, [72] systemic inflammation has been associated with early AF recurrences after rhythm control in patients with recent onset persistent AF. [73] As expected, corticosteroids have been shown to reduce POAF incidence in a meta-analysis of 50 randomised controlled trials [74] indicating the role of inflammation in POAF. However, in a large randomised controlled trial, administration of a statin perioperatively reduced postoperative low-density lipoprotein and CRP levels but did not affect early POAF incidence.[75]

Although these animal models provide insight into pathophysiological mechanisms contributing to a structural substrate for AF, it is important to recognize that animal models have been used to study a single disease with a sudden onset for a limited duration, whereas patients most often have several disease factors developing gradually and with a more extended duration.

Conclusion

Patients without a history of AF with several co-morbidities may still carry a complex underlying substrate for AF as a result of atrial structural changes. In patients undergoing cardiac surgery, specific co-morbidities aggravating AF susceptibility already co-exist with the underlying cardiac diseases. Both CHA_2DS_2VASc as well as HATCH score are important predictors of POAF. In the acute postoperative phase after cardiac surgery, this AF substrate is unmasked due to a strong agglomeration of triggers leading to early POAF. On the other hand, patients with underlying substrates, perhaps depending on the duration of the underlying diseases and treatment compliance, also develop late POAF. Importantly, different underlying diseases may affect propagation properties differently and complex AF substrates are an accumulation of different co-morbidities and their intensity. It is therefore plausible that atrial propagation is negatively affected by progressive atrial structural changes towards a critical amount of substrate formation, which then maintains AF when initiated by triggers. These factors show a high inter-individual variability contributing to the difficulty to develop relevant classifications for AF. This variable and progressive AF substrate also indicates the desirability of minimally invasive characterization of the AF substrate, such as by P-wave analysis (Chapter4) for an optimal, individualized treatment strategy.

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Valorization

This thesis highlights the incidence and clinical relevance of late POAF and adds evidence to the notion of opportunities for intensified monitoring of postoperative patients to increase their health and avoid complication related costs.

Late POAF

Atrial fibrillation after cardiac surgery is the most prevalent complication adding to substantial morbidity and clinical costs.[1] Patients developing POAF shorter than 48 hours are discharged without oral anticoagulation and usually without prolonged rhythm monitoring. Although symptomatic late POAF episodes may be diagnosed due to patient's complaints, short subclinical episodes are often left undiagnosed and untreated. Two important clinical questions regarding POAF recurrences are relevant for late POAF, namely the importance of continuous rhythm monitoring and treatment of short lasting AF episodes with oral anticoagulation.

The importance of prolonged continuous rhythm monitoring in AF has recently been emphasized in several reports. Intermittent rhythm monitoring strategies such as Holter monitoring or periodical electrocardiograms is insufficient to uncover the true AF burden.[2, 3] Duration of AF per episode and AF density (i.e temporal clustering of the episodes) are highly unpredictable in all types of AF.[2] This is clearly reflected in clinical misclassification of AF, where only 47% of paroxysmal AF and 32% of persistent AF are correctly categorized.[4] In addition, a large amount of silent strokes result from AF. To quantify the incidence of silent stroke in AF patients, one study conducted cerebral magnetic resonance imaging (MRIc) of AF patients and compared them to sinus rhythm patients.[5] The authors showed that 89% of patients with pAF and 92% of pers AF patients (n= 90 in each group) had underlying silent cerebral ischemia (SCI). Interestingly, 46% of SR group also had SCI. Although significantly less than AF patients, this remains a high percentage of undiagnosed subtle brain damage, which at least partly may correlate to asymptomatic AF. [5, 6, 7] Indeed, asymptomatic AF is usually detected after a stroke episode [8] and using continuous monitoring, asymptomatic AF has been shown to explain a large group of cryptogenic strokes with a median AF detection rate of 41 days after the stroke,[9] further emphasizing the importance of long-term continuous monitoring due to heterogeneous AF density. In line with these findings, we found that the majority of patients without a history of AF also show recurrences of POAF lasting minutes to hours, after discharge from the hospital.

Interestingly, patients with late POAF in addition to early POAF had higher $CHADS_2VAS_2c$ scores. This raises the question of treating short lasting AF episodes, which is still debated. However, accumulating evidence inclines towards anticoagulation treatment for patients with short lasting subclinical AF episodes. First, AF maintains a systemic hypercoagulable state [10] and considering the trias of Virchow, at least in patients with endothelial damage, even short paroxysm of AF may expose the patient to

risk of stroke. In accordance, subclinical AF episodes in diabetic patients doubled the chances of subclinical infarct (up to 60%) and stroke compared to diabetics without AF.[11] Also, recent studies have shown higher hypercoagulability markers, a so called "pro-thrombotic" state, in young paroxysmal AF patients with $CHADS_2VAS_2c$ of 0 compared to patients without AF emphasizing the hypercoagulable state caused by AF.[12] Furthermore, 15 minutes of AF in paroxysmal AF patients significantly increases the levels of platelet activation, thrombin activation and inflammation in the atria compared to patients without AF.[13] In addition, as discussed in chapter 4, subclinical AF episodes detected by continuous rhythm monitoring lasting more than 5-6 minutes are associated with ischemic stroke or systemic embolization.[3, 14] These findings imply that both clinical AF, as well as clinical ischemic stroke, are not sufficient or reliable outcomes for decision making regarding patients long-term treatment. For this reason it is desirable to closely follow patients prone to AF during the months and years after the operation. If AF is detected, intensified monitoring may be adequate and as soon as an AF episode is diagnosed on ECG or Holter anticoagulant therapy should be considered. Furthermore, rhythm follow-up enables to investigate the effects of therapy on individual patients. This is nowadays possible because of the ease and efficiency level of continuous rhythm monitoring devices. Interestingly, detecting AF episodes using an i-phone electrocardiogram application was recently shown to be very feasible and effective and may be the next step in the evolution of effective arrhythmia management.[15] In addition, important outcomes such as silent stroke should also be considered in the decision making process.

Minimal invasive substrate detection in AF

In addition to continuous rhythm monitoring, adequate substrate quantification may contribute to patient selection for further follow up, treatment and perhaps in tailored treatment aimed at underlying substrate. We found that patients developing early and late POAF carry underlying structural substrate as a result of several co-morbidities making minimal invasive techniques to quantify this substrate very attractive. In chapter 4 we used the electrocardiogram to determine P-wave characteristics predicting POAF. Contrary to the direct contact epicardial mapping, the P-wave derived from the ECG gives a reflection of propagation of the entire atrial activation. Lower P-wave amplitude and duration was a characteristic of patients developing early and late POAF. Implementing signal averaged P-wave analysis to detect and predict AF episodes is a low cost low invasive and potentially very accurate technique. Still more research is required to expand the field of ECG based P-wave guided risk stratification in detection and prevention of POAF and AF in general.

In addition, transmural electrical conduction and a 3D substrate is pronounced in remodelled atria and is an important measure of substrate complexity for AF (chapter

5). In chapter 6 we describe a method to simplify endo-epicardial mapping during AF using phase analysis. Phase analysis of electrograms does not require the time-consuming process of activation time annotation and is more and more used to analyse fibrillation electrograms. The coherence of phase between neighboring electrodes allows quantifying the degree of electrical dissociation between these electrodes and thus this technique can also be used for quantifying endo-epicardial electrical dissociation. By calculating the phase of the unipolar electrograms for each electrode, we found that during a measurement of at least 15 seconds, maximum mean phase coherence is highest between closest electrodes on the opposing side (average of 2,3 mm localization error). As expected, we found that there was almost never complete phase coherence between endo-epicardially opposing electrodes, (figure 4 of chapter 6) further emphasizing our findings in chapter 5 where endo-epicardial activation time differences were never completely zero. We also found that phase coherence decays with distance between electrodes. This suggests that dissociated activity is heterogeneously distributed between endo- and epicardium and is not a temporary phenomenon (considering at least the mapped area). If dissociation would be a transient phenomenon, then phase coherence at least with distant electrodes (further than the dissociated region) would reach a plateau and remain constant. This is clearly not the case as seen in figure 3 of chapter 6. Nevertheless, maximum mean phase coherence detects the opposing electrode in longstanding AF patients with endo-epicardial files lasting 15 seconds or longer. In other words, there is a correlation between phase of electrograms and the distance between the electrodes. This technique may contribute to electrode localization on the opposing sites of the atrial wall even in electrically remodeled areas and thus become particularly of interest in quantifying individual substrates for AF for tailored treatment approaches.

In conclusion, for an effective and tailored AF treatment, detection of the severity of the underlying substrate correlating with true AF burden is mandatory. Future research should take primary outcomes such as subclinical short lasting AF episodes and silent strokes into consideration. Modern technology offers solutions for these challenges including enhanced rhythm follow-up with low burden devices independent of patient compliance (ILRs) and minimal-invasive substrate detection and stratification based on low cost low burden diagnostic systems (ECGs).

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Summary

Atrial fibrillation occurs in the first few days after cardiac surgery (postoperative atrial fibrillation, POAF) as a result of acute-phase triggers. Although historically thought of as a transient arrhythmia, accumulating evidence suggests that POAF is an independent predictor of poor survival years after surgery. In addition, there is an association between POAF occurring in the acute postoperative phase and thromboembolic complications such as stroke occurring months to years after discharge. This suggests that POAF may not be confined to the acute postoperative phase but may be a recurrent subclinical arrhythmia.

To determine the incidence of AF episodes after discharge, we used continuous rhythm monitoring devices to follow patients without a history of AF following their open chest cardiac surgical procedure. In Chapter 3 and 4, we describe our results from continuous rhythm monitoring for a month and for 3 years respectively. Firstly, we found that more than 25% of patients developed AF in the month following discharge form hospital, the so-called late POAF (Chapter 3). Predictors of late POAF included co-morbidities such as prior myocardial infarction, diabetes mellitus, obesitas and baseline CRP levels. In chapter 4 we further extended the rhythm-monitoring period to 3 years with an implantable loop recorder in patients without a history of AF. We demonstrated that up to 50% of patients developed AF episodes lasting 1,5 hours on average during the months to years following surgery. Patients who developed late POAF were older and had higher CHA_2DS_2VASc and HATCH scores with right atrial volume as an independent predictor of late POAF. Our findings in these chapters suggest that the risk profile for POAF and notably for late POAF resembles the risk profile of AF in general including a structural substrate for AF.

The complexity of the atrial structural substrate is reflected by the complexity of electrical conduction during induced AF. Patients with several cardiovascular co-morbidities (high CHA_2DS_2VASc scores), show enhanced level of pathological atrial wall changes leading to complex fibrillating patterns during AF. To explore the electrophysiological substrate for POAF, we measured the complexity of fibrillating patterns of electrically induced AF on the right atrial wall (Chapter 4). For this purpose we induced AF during cardiac surgery by burst pacing and mapped the electrical activation of the right atrium using a 256 unipolar electrode plaque. In line with the previous findings, we found more complex activation patterns (i.e. higher number of waves and fractionation index) in patients who subsequently developed POAF and also those with late-POAF. This illustrates the effects of age and several co-morbidities on the atrial wall, which may not have led to (symptomatic) AF prior to surgery but may be prone to development of a stronger substrate with time.

Interestingly, enhanced complexity of the electrophysiological substrate in animal models involves higher number of wavelets and higher number of breakthrough waves, i.e. waves migrating to the opposing layer of the atrial wall due to dyssynchronous activation of the endocardium compared with epicardium. To investigate the mechanism of transmural propagation of the atrial wall described in animal models, we developed a

highly detailed 3 dimensional computer model of the human atria. In this computer model, specific atrial anatomical structures were implemented and the mechanism of fibrosis related dissociation between endo-epicardial layers was demonstrated. We found a clear association between endo-epicardial dissociated activity due to increased levels of fibrosis and the number of breakthrough waves. To validate this model, we developed a crocodile shaped clamp electrode containing a double layer of unipolar electrode plaques. The electrode was designed to be inserted into the right atrium with one arm and to be approximated on the atrial wall on both sides. Using this technique, we were able to quantify for the first time in human, the amount of electrical uncoupling between the two layers of the atrial wall. We found that the endo-epicardial dissociation is enhanced with complex substrates for AF. In addition, there is indeed a clear correlation between endo-epicardial dissociation and the number of waves migrating to the opposing layer of the atrial wall, the so-called breakthrough waves. To further elucidate on these findings, we describe in Chapter 6 a method to detect the location of electrodes on the opposing side of the atrial wall by measuring the phase of depolarization during AF. We were able to demonstrate that mean-phase coherence between 2 electrodes, decays with distance between them. This method may be helpful in detecting the 3-D substrate of AF less invasively.

In conclusion, using continuous rhythm monitoring strategies combined with baseline substrate quantification in patients without a history of AF we found up to 50% late POAF recurrences. Patients developing late POAF were older with additional comorbidities and showed a more complex fibrillation pattern during electrically induced AF compared to those who did not develop POAF. In addition, we sought for the effects of atrial structural substrate on endo-epicardial dissociation and found a correlation between enhanced electrical dyssynchrony and breakthrough waves in a computer model of human atria. We also demonstrated the 3D substrate for AF in human by direct contact endo-epicardial mapping. Future research should determine the clinical consequences of late POAF and the range of the underlying structural substrate, which predisposes patients to AF development.

Samenvatting

Het hart bestaat uit 2 boezems en 2 kamers. De boezems vullen de kamers van bloed waarna de kamers bloed rondpompen naar de rest van het lichaam. Een ritmestoornis waarbij de boezems (atria) niet meer contraheren en het bloed niet meer adequaat naar de kamers kunnen pompen wordt boezemfibrilleren of atrium fibrilleren (AF) genoemd. De klachten die hiermee samenhangen zijn hartkloppingen, kortademigheid en pijn op de borst. Boezemfibrilleren is soms ook aanwezig zonder enige symptomen en wanneer het niet ontdekt en niet behandeld wordt, verhoogt het de risico op herseninfarcten en hartfalen.

Na een open hartoperatie ontstaat AF met name in de eerste paar dagen na de operatie. Dit wordt postoperatief AF (POAF) genoemd. Hoewel altijd gedacht werd dat POAF van voorbijgaande aard was, bleken patiënten die de ritmestoornis wel ontwikkelen, in de jaren na ontslag uit het ziekenhuis ook eerder te overlijden vergeleken met patiënten die dit niet ontwikkelen. Om te achterhalen waarom patiënten die POAF ontwikkelen slechtere overleving laten zien, hebben wij in dit proefschrift onder andere onderzoek gedaan naar 2 vragen.

Ten eerste is de vraag of POAF een voorbijgaande ritmestoornis is, of komt het maanden tot jaren na ontslag uit het ziekenhuis toch weer terug, een zogenaamde late POAF. Ten tweede is de vraag welke patiënten hier het meest vatbaar voor zijn.

De eerste vraag hebben wij onderzocht door patiënten die niet bekend waren met boezemfibrilleren te volgen nadat zij een open hartoperatie hadden ondergaan. Dit hebben wij gedaan op twee manieren. Eerst hebben wij speciaal ontworpen draagbare apparaten gebruikt die het ritme van de patiënten continu kunnen detecteren gedurende een maand (Hoofdstuk 3). Daarnaast hebben wij een tweede groep patiënten gedurende 3 jaar gevolgd via een chip die onder de huid werd geïmplanteerd met dezelfde ritme detectie functie (Hoofdstuk 4). In hoofdstukken 3 en 4 hebben wij de resultaten van deze twee technieken beschreven. Continue ritme monitoring liet in beide studies zien dat meer dan 30% van de patiënten die nooit tevoren symptomen van AF hadden, na ontslag uit het ziekenhuis alsnog POAF ontwikkelden. Nadat wij patiënten 3 jaar gevolgd hadden, zagen wij dat maar liefst 50% van de patiënten jaren na de operatie wederom kortdurende episoden van POAF ontwikkelden. De conclusie van deze studies was dat POAF geen voorbijgaande ritmestoornis is zoals vooraf gedacht werd.

Een tweede vraag die logischerwijs op de eerste vraag volgt, is welke kenmerken bepalend zijn voor late POAF ontwikkeling. Wij hebben dus uitgebreid onderzoek gedaan naar de zogenaamde voorspellers van POAF en de vatbaarheid van patiënten hiervoor.

De belangrijkste voorspeller van POAF en late POAF is hogere leeftijd (Hoofdstuk 4). Het is bekend dat door hogere leeftijd de structuur van de boezemwand langzaam verandert wat een belangrijk effect heeft op de regelmaat van boezem activatie en dus de ritme van het hart. Oudere patiënten hebben bovendien specifieke ziektebeelden zoals hypertensie, suikerziekte en overgewicht, ziektebeelden die ook rechtstreeks effecten uitoefenen op de kans op AF.

Een belangrijk neveneffect van de structuur veranderingen van de boezems is dat de elektrische geleiding over de boezems ook onregelmatig en chaotisch verloopt ten opzichte van een relatief eenvoudige patroon van activatie bij normale boezems. Om deze elektrische eigenschappen van de "zieke" boezems te achterhalen hebben wij gebruik gemaakt van speciaal ontworpen elektrodes die tijdens open hartoperaties op of in het hart werden gepositioneerd terwijl boezemfibrilleren werd opgewekt met behulp van een pacemaker. Wij vonden dat vooral in patiënten met POAF, de elektrische geleiding veel complexer en meer chaotisch was dan bij patiënten zonder POAF. Met andere woorden, door ouderdom en de ziektebeelden die ermee samengaan, hebben patiënten dusdanig beschadigde boezems ontwikkeld (een zogenaamd substraat voor AF), die (onder stimulatie) vatbaar kunnen zijn voor het ontwikkelen van boezemfibrilleren. Dit betekent dus ook dat gezien de vatbaarheid, deze patiënten niet alleen boezemfibrilleren ontwikkelen tijdens opname in het ziekenhuis, maar eveneens het risico lopen om later na ontslag uit het ziekenhuis opnieuw boezemfibrilleren te ontwikkelen.

Om de effecten van ouderdom en ziektebeelden op de elektrische geleiding van de boezems verder te onderzoeken hebben wij een anatomisch computer model ontwikkeld waarin wij deze eigenschappen konden nabootsen. We vonden dat afhankelijk van de ernst van de beschadiging van de boezems er ook een toenemend asynchrone geleiding plaatsvindt over de binnen en buitenwand van de boezems. Dit leidt er vervolgens toe dat steeds meer elektrische activatie vanuit de binnenzijde van de boezemwand ook naar buitenzijde kan geleiden en andersom. Hoe minder synchroon de buiten- en binnenzijde van de boezems geactiveerd worden, hoe meer elektrische activatie tussen de twee lagen wordt voortgeleid. Met andere woorden, naar mate de boezems beschadigd raken als gevolg van verschillende ziektebeelden (substraat), verbreekt de synchronisatie tussen de binnen en buitenwand van de boezems en ontstaat een 3 dimensionale elektrische geleiding die bijdraagt aan de complexe patroon van de elektrische geleiding.

In hoofdstukken 4 en 6 beschrijven wij enkele technieken waarin met behulp van minimaal invasieve methodes een eventueel substraat voor boezemfibrilleren gedetecteerd kan worden. Zo werden in hoofdstuk 4, P-golf eigenschappen in een standaard ECG besproken die kenmerkend waren voor patiënten die late POAF ontwikkelden. Deze technieken kunnen relatief eenvoudig voorspellen bij welke patiënten reeds een substraat bestaat en aldus behandeling voor late POAF aan te bevelen is. Uiteraard zijn deze technieken nog in kinderschoenen en zou meer onderzoek hiernaar de klinische toepasbaarheid ervan kunnen vergroten.

Concluderend kunnen wij stellen dat boezemfibrilleren na een hartoperatie een uiting is van de onderliggende ernst van de beschadiging van de boezemwand (substraat). Dit leidt ertoe dat boezemfibrilleren na een open hartoperatie zich niet beperkt tot het ziekenhuisopname maar in de maanden tot jaren na ontslag uit het ziekenhuis ook kan terugkeren. Verder onderzoek zal moeten uitwijzen op welke wijze de uitingen van dit substraat behandeld of zelfs voorkomen zouden kunnen worden.

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About the Author

Elham Bidar (Born August 4th 1986) became a refugee of war at the age of 6 when he fled Kabul, Afghanistan with his family travelling to Peshawar, Pakistan (1992). He attended several primary schools and after 3 years, he moved to Saint Petersburg, Russia where he lived until Feb-1998, subsequently migrating to The Netherlands. After acquiring the Dutch citizenship he obtained the secondary school diploma from Trevianum School in Sittard, The Netherlands (1999-2005, Gymnasium β). He studied medicine at the Medical Faculty of Maastricht University and graduated with Honours in 2011. During his internship he joined the research group of Cardio-Thoracic Surgery under the supervision of Prof. Dr. J. G. Maessen and after graduation he started a joint PhD program between the dept. Cardio-Thoracic Surgery and Physiology under supervision of Prof. Dr. U. Schotten, which resulted in this thesis. He started his training of Cardio-Thoracic Surgery in Maastricht (Jan-2014) en is currently in the final year of his training (until May-2019) under the supervision of Dr. S Kats and Prof. Dr. J.G. Maessen. He is married to Karina Kambulova and has 2 sons (6 and 4 years).

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E Bidar, B Maesen, F Niemann, S Verheule, U Schotten, J G Maessen **Incidence and predictors of "Late phase" versus "Early phase" post-operative atrial fibrillation**, Heart rhythm Scientific Sessions, 2013, Denver Colorado, US

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E Bidar, E Natour, M Makhoul, et al. **Cannula Position in Post-Cardiotomy ECMO: Configurations Options for a Better Patient Management**. European journal of heart failure, Vol. 19, p.12-12. ISSN 1388-9842.

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E Bidar, B Maesen, U Schotten, J G Maessen, **Add-on value of Bi-Atrial Pacing in combination with standardized Sotalol treatment for the prevention of postoperative Atrial Fibrillation after Cardiovascular Surgery** *Best oral presentation* at Antwerp Medical Students' congress (AMSC) 2009, European Medical Students' Association; Antwerpen, Belgium

A Gharaviri, E Bidar, M Potse, S Verheule, S Zeemering, R Krause, A Auricchio, U Schotten **Validation of a novel computer model of endo-epicardial electrical dissociation and transmural conduction during atrial fibrillation**, EP Europace, Issue suppl_1, https://doi.org/10.1093/europace/euy015.256

M Gilbers, E Bidar, B Maesen, J G Maessen, U Schotten, **Translational research: the use of our current knowledge in understanding postoperative atrial fibrillation' Oral presentation**, European association of cardiothoracic surgery, October 2018, Milan, Italy

Stellingen

behorend bij het proefschrift

'Assessment of the clinical and electrophysiological characteristics of atrial fibrillation during and after cardiac surgery'

Elham Bidar

20 November 2018

1. Postoperative atrial fibrillation (POAF) is not a transient arrhythmia and patients developing POAF should be monitored for AF recurrences after discharge. *(This thesis)*

2. POAF is a reflection of the vulnerability of the underlying structural substrate of AF that results from advanced age and co-morbidities. *(This thesis)*

3. Non-invasive substrate characterization such as by P-wave analysis can predict AF development. *(This thesis)*

4. Besides rhythm history and clinical history of a patient, also the severity of the underlying substrate should be considered in management strategies of AF. *(This thesis)*

5. Although computer models become more and more realistic, they are still far from being applicable to clinical decision-making.

6. For persistence, fibrillation waves travel towards excitable tissue, even if it leads them to the other side.

7. Assessment of social justice in a society should resemble the assessment of health: a "one size fits all" mentality does not suffice due to people's individualities.

8. By counterbalancing selfishness, empathy and altruism have contributed to survival of human race and form the basis of freedom by limiting algorithmic behaviour.

9. The natural distribution is neither just nor unjust; nor is it unjust that persons are born into society at some particular position. These are simply natural facts. What is just and unjust is the way that institutions deal with these facts. *(John Rawls, A theory of Justice)*

10. There is no blue, without yellow and without orange. *(Vincent van Gogh)*