Optimizing procedural sedation and analgesia: from patient selection to post-procedural care

Marloes Homberg

Stellingen behorende bij het proefschrift

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from patient selection to post-procedural care

M.C. Homberg, 7 juli 2026

1. De brede implementatie van procedurele sedatie en analgesie bij non-invasieve procedures heeft verdere ontwikkeling en verfijning van non-invasieve technieken mogelijk gemaakt. (dit proefschrift – Chapters 3,4, 6 and 7)

2. Procedurele sedatie en analgesie is een zelfstandig onderdeel van de anesthesiologische zorg. (dit proefschrift – Chapter 7)

3. Een betere voorspelling van respiratoire complicaties tijdens procedurele sedatie en analgesie verhoogt de patiëntveiligheid. (dit proefschrift – Chapter 3)

4. Het gebruik van high flow nasal oxygen kan het gevoel van veiligheid en comfort bij zowel patiënten en zorgverleners versterken. (dit proefschrift – Chapter 5)

5. Procedurele sedatie en analgesie wordt frequent toegepast op remote locaties, waar de werkomstandigheden gepaard gaan met een verhoogd risicoprofiel. (dit proefschrift – Chapter 1)

6. Niet de benaming 'sedatie' of 'narcose' bepaalt de veiligheid van anesthesie.

7. Overmatige focus op objectieve vitale parameters miskent de voorspellende waarde van de klinische blik.

8. E-health sluit nog steeds een deel van de bevolking structureel uit.

9. Het combineren van klinisch werk met het uitvoeren van onderzoek beïnvloedt de voortgang van het onderzoek.

10. Durven is even je evenwicht verliezen. Niet durven is jezelf verliezen. (naar Kierkegaard 1843)

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Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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1

General introduction

PROCEDURAL SEDATION AND ANALGESIA AND THE ANESTHESIA CARE PROVIDER

Non-operating room anesthesia (NORA) has rapidly grown due to the development of novel interventional techniques in radiology, gastroenterology, cardiology and pulmonary medicine and other areas.[1, 2] The core responsibilities of the anesthesia care provider are therefore broadened and no longer limited to providing care in traditional operating rooms.[1, 2] New interventional techniques and NORA are continuously in rapid development. NORA includes general anesthesia, procedural sedation and analgesia and regional anesthesia.[1] This thesis will focus on procedural sedation and analgesia (PSA) as provided by anesthesia care providers specifically in non-operating room situations.

PSA denotes the administration of hypnotic and/or analgesic agents to enable the safe and effective completion of diagnostic or therapeutic procedures. The aim is to alleviate procedure-related anxiety and pain while continuously monitoring a patient to promptly detect and manage potential adverse effects.[3, 4] Achieving adequate patient tolerance, encompassing anxiolysis and/or amnesia and/or analgesia, is critical for the successful and safe completion of such interventions. Consequently, the administration of sedative and analgesic agents requires the acquisition of specific competencies and technical skills aimed at optimizing procedural conditions and enhancing patient comfort. PSA is provided by both non-anesthesia care providers as well as by anesthesia care providers. The required depth of PSA and the condition of patients in combination with local (hospital) policy determine if a non-anesthesia care provider is competent and allowed to administer PSA. Guidelines describe the role and competencies required for the clinicians to safely perform PSA.[3, 4, 5] When deeper sedation, higher-risk patients, or more complex procedures are present, PSA is typically performed or supervised by anesthesia care providers, who possess advanced skills in airway management, pharmacological knowledge, and the management of sedation-related complications.

As the procedures as well as the patients are often complex, a standardized and effective pre-procedural evaluation is critical for both optimizing outcomes and ensuring the operational efficiency of PSA. Basic standards for pre-anesthesia care must apply to all patients receiving care from an anesthesia provider, regardless of the location (operating or non-operating room) or approach.[3, 6] Following PSA, patients should be monitored until both cardiorespiratory function and consciousness have returned to baseline.[3, 7, 8] Recovery from moderate to deep PSA is comparable to that needed after general anesthesia, although patients typically regain consciousness more rapidly and have a shorter overall recovery time with the moderate to deep PSA. Discharge from hospital must be guided by objective criteria, preferably the Post-Anesthetic Discharge Scoring System (PADSS), although this tool has not been formally validated for PSA.[4, 8] Symptoms such

as pain, nausea, or dizziness should be absent or acceptable, and procedure-specific risks need to be taken into account.

THE LEVELS OF PSA

The American Society of Anesthesiologists (ASA) has defined levels of sedation depth in its practice guidelines for non-anesthesiologists administering sedation and analgesia.[5] In 2024 an update on the Dutch guideline for PSA in adults also describes the levels of sedation.[4] The Dutch guideline describes the following levels of sedation depths [4]:

Anxiolysis:

A drug-induced state in which patients respond normally to verbal commands. The primary aim is to reduce the patient's anxiety and stress levels while generally preserving full consciousness.

Light Sedation:

A state in which consciousness is mildly depressed. Cognitive function and physical coordination may be impaired; however, airway reflexes, spontaneous ventilation, and cardiovascular function remain unaffected. The patient responds consistently and appropriately to verbal stimuli, and verbal communication remains possible. This level of sedation is often achieved through orally administered agents or low-dose parenteral medication and carries minimal risk in patients without significant comorbidities.

Moderate Sedation:

A drug-induced depression of consciousness during which patients purposefully respond (i.e., not reflexively) to verbal commands, either alone or accompanied by light tactile stimulation. No airway interventions are required, spontaneous ventilation is adequate, and cardiovascular function is usually maintained.

Deep Sedation:

A drug- or technique-induced depression of consciousness during which patients cannot be easily aroused but will purposefully respond after repeated or painful stimulation. The ability to maintain independent ventilatory function may be impaired, and patients may require assistance in maintaining airway patency. Spontaneous ventilation may be inadequate, though cardiovascular function is usually preserved.

General Anesthesia:

A drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. Independent ventilatory function is frequently impaired, and patients often require assistance in maintaining airway patency. Positive pressure ventilation may

be required due to depressed spontaneous ventilation or drug-induced suppression of neuromuscular function. Cardiovascular function may also be impaired.[4]

The Dutch guideline retains the terms anxiolysis and light sedation (AL-PSA) and moderate-to-deep sedation (MD-PSA). The different levels of sedation should be seen as a continuum, in which a patient may inadvertently be transitioned to a lighter or deeper level of sedation.[4] Therefore, anesthesia care providers aiming to achieve a specific level of sedation must be able to appropriately manage patients whose sedation depth becomes deeper than initially intended.[4] Similarly, the European Society of Anaesthesiology and the European Board of Anaesthesiology provide guidelines for PSA in adults, describing sedation stages according to the Ramsay Sedation Scale.[3] The Ramsay Sedation Scale (RSS) is a validated tool for assessing and monitoring the depth of sedation[9] (Table 1). Another commonly used scale, particularly in clinical research, is the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale.[10]

Table 1 Ramsay Sedation Scale

Definition	Score
Anxious, agitated, and/or restless	1
Cooperative, orientated, and tranquil	2
Responding to commands only	3
Brisk response to light glabellar tap or loud auditory stimulus	4
Sluggish response to light glabellar tap or loud auditory stimulus	5
No response to stimulus	6

PHARMACOLOGICAL DRUGS FOR SEDATION AND ANALGESIA

For patients, the primary goal of PSA is to safely avoid discomfort during and after the procedure. Factors such as amnesia, post-procedural pain, and nausea are often cited as most important in determining patients' overall comfort.[4] This can be accomplished with several drugs which have all their specific indications, adverse effects and risk-benefit ratio. Many drugs for PSA can produce light to deep sedation depending on the dose, the rate of administration, the use of adjunctive drugs, and the patient's individual sensitivity (such as age and comorbidities). An overview of commonly used pharmacological drugs for PSA is provided in Table 2. These drugs differ in sedative depth, analgesic properties, and adverse-effect profiles, and their selection should be individualized based on patient characteristics, procedural requirements, and clinician expertise.

Table 2 Common drugs for PSA

Agent	Drug class	Sedation	Key Advantages	Key Limitations	Typical Use
Propofol	GABA agonist	Light–deep	Rapid onset, short recovery, flexible administration (bolus, infusion, TCI)	Hypotension, respiratory depression	Frequently used agent for light–deep PSA
Midazolam	Benzodiazepine	Light-moderate	Anxiolysis and amnesia, reversible with flumazenil	Accumulation with repeated dosing	Mainly used in non-anesthesia settings
Remimazolam	Benzodiazepine	Light–moderate	Less hypotension and hypoxemia, organ-independent elimination, reversible	Slower onset, limited depth, higher cost	Short procedures, elderly or frail patients, limited data for prolonged sedation
Dexmedetomidine	α2-agonist	Light–moderate	Minimal respiratory depression	Bradycardia, hypotension, therefore modest clinical benefit	Selected cases prioritizing respiratory stability.
Esketamine	NMDA antagonist	Moderate	Potent analgesia, minimal cardiorespiratory depression [11]	Psychotomimetic effects [12], increased PONV [13]	Dissociative sedation, when apnea or hypotension must be avoided
Fentanyl	Opioid	—	Rapid onset, potent analgesia	Respiratory depression, nausea	Painful procedures
Alfentanil	Opioid	—	Very rapid onset, short duration	Respiratory depression	Brief interventions
Remifentanil	Opioid	—	Very rapid onset and offset, easily titratable, organ-independent elimination	Respiratory depression, higher cost	Longer procedures or precisely titrated analgesia

For all studies on sedative drugs, it should be noted that the majority of trials included patients with ASA class I–II, and that older adults were underrepresented.[4] In most hospitals, moderate to deep sedation is performed using continuous intravenous (i.v.) or intermittent propofol administration. Remimazolam may be the appropriate drug for sedation in older patients and with procedures based on a shorter duration, as it then significantly reduces the incidence of hypoxemia and hypotension.[14, 15] In clinical practice, the benefits of dexmedetomidine appear less pronounced than would be expected based on its pharmacological properties. Many studies evaluating dexmedetomidine are small, of moderate to poor methodological quality, or confounded by the co-administration of other agents during procedural sedation and analgesia.[16, 17, 18, 19] The use of short-acting opioid adjuvant during PSA improves patient comfort. The choice of an opioid adjuvant should be guided by the clinician's experience, the clinical setting, and the type, duration, and

expected pain intensity of the procedure. When the reduction of apnea or hypotension is prioritized over the increased risk of PONV, esketamine is preferred over an opioid as an adjuvant to propofol sedation. Overall, patient factors, procedural demands, and clinician expertise remain the dominant determinants of optimal PSA. In practice, drug selection is mainly influenced by clinician familiarity and local institutional practices.

SEDATION RELATED ADVERSE EVENTS

The majority of sedation-related adverse events are mild and manageable, such as postoperative nausea and vomiting (PONV), mild hemodynamic instability, and short episodes of respiratory compromise. [20] Nevertheless, respiratory complications remain the leading cause of adverse events leading to escalation of care, particularly in interventional cardiology and bronchoscopy, and during prolonged or deep sedation. Hypoxemia (SpO_2 < 90% for ≥2 minutes) has been reported in up to 29% of patients undergoing moderate-to-deep sedation, with the highest rates observed in the cardiac catheterization laboratory (54%) and during bronchoscopy (56%).[20] Longer procedures were associated with an increased incidence of hypoxemia.[20] The incidence of pulmonary aspiration is low [21], and this might largely be attributed to the application of fasting guidelines. A limitation of this review is that much of the available evidence consists of retrospective, self-reported cases, which are inherently subject to under-reporting.[22] More data are available on aspiration during gastrointestinal endoscopy. For example, an incidence of 1 in 714 has been reported during anesthesia-assisted colonoscopy.[23] In the specific case of gastric endoscopic submucosal dissection (ESD) one study reported a considerably higher incidence of 1.9%.[24]

Although earlier studies reported higher rates of adverse events in NORA locations, more recent data indicate that the overall incidence of quality-assurance events is lower in NORA than in the operating room.[25, 26] However, cardiac suites exhibit disproportionately higher rates of both cardiac- and airway-related events compared with other NORA settings.[25, 26] To ensure standardized reporting, adverse events during procedural sedation and analgesia (PSA) can be classified according to the Tracking and Reporting Outcomes of Procedural Sedation (TROOPS) framework, which distinguishes sentinel events (death, cardiopulmonary resuscitation, unexpected intubation, or unplanned ICU admission), moderate events (unexpected interventions such as bag-mask ventilation or vasoactive medication), and minor events (self-limiting complications without escalation, such as brief hypoxemia or PONV).[27]

PROCEDURES

This thesis investigates sedation practices in two major clinical indications: 1. catheter ablation for atrial fibrillation and 2. percutaneous thermal liver tumor ablation. Both procedures are commonly performed under deep sedation, but each presents its own specific considerations and challenges.

Catheter ablation for atrial fibrillation:

Atrial fibrillation (AF) is highly prevalent with a lifetime risk of about 1 in 3–5 individuals over the age of 45 years.[28] Between 2010 and 2019, the global prevalence of AF has risen markedly from 33.5 million to 59 million individuals living with AF.[28] Catheter ablation (CA) for atrial fibrillation (AF) has become one of the most common procedures in the electrophysiology (EP) laboratory, often integrated within the cardiac catheterization lab environment [29]. In patients with AF, CA is performed either under procedural sedation and analgesia (PSA) or under general anesthesia (GA).[29, 30] With deep sedation, the level of consciousness approaches that of general anesthesia.[31] In addition to alleviating pain and anxiety, an important goal for anesthesia during AF ablation is to minimize patient movement as this improves catheter stability.[31] A potential adverse effect of deep sedation is a reduced ability to maintain ventilatory function, meaning that patients may require support to keep the airway patent. In this context, high-flow nasal oxygen (HFNO) has emerged as a promising noninvasive strategy to mitigate respiratory compromise during sedation.[32, 33, 34] HFNO delivers warmed and humidified oxygen at high flow rates (typically 30–60 L/min) with adjustable fraction of inspired oxygen (FiO_2) up to 1.0, thereby providing a small but potentially clinically relevant degree of positive airway pressure. Compared to low-flow nasal, HFNO may theoretically improve oxygenation, reduce work of breathing, and may help decrease the incidence of hypoxemia and other sedation-related respiratory complications during AF ablation. It is important to note that AF ablation itself carries procedure-related risks. Procedure-related complications of AF ablation include vascular access complications, pericardial effusion and tamponade, thromboembolic events, pulmonary vein stenosis, phrenic nerve injury, and, more rarely, esophageal injury including atrio-esophageal fistula.[35]

Percutaneous thermal liver tumor ablation:

Liver cancer is one of the most common types of cancer. In 2020 an estimated 905,700 people were diagnosed with, and 830,200 people died, from liver cancer globally.[36] The principal treatment for both primary and secondary liver tumors is surgical resection, for which not all patients are suitable.[37] This may be due to the location of the tumor, prior surgery, (severe) comorbidities, poor hepatic reserve, advanced cancer stage or the patient's age[37]. In many of these cases, thermal liver ablation can be a good alternative.[37, 38] Thermal ablation in patients with liver tumors is generally performed by an interventional radiologist (IR) under computed tomography–scan or ultrasound guidance and

procedural sedation and analgesia (PSA) or general anesthesia (GA). In recent years, the number of treatments performed with thermal ablations has risen considerably.[39] During percutaneous thermal liver tumor ablation, procedural sedation and analgesia (PSA) aims to provide adequate analgesia and anxiolysis while minimizing patient movement to facilitate precise needle placement and safe delivery of thermal energy. Several procedure-specific challenges may complicate PSA, including respiratory motion affecting imaging guidance, diaphragmatic irritation, and pain during energy delivery. In this context, PSA carries potential risks, including hypoventilation, airway obstruction, hypoxemia, and hemodynamic instability, which may compromise both patient safety and procedural efficacy. Furthermore, during CT-guided ablation, restricted access to the patient's head can limit airway maneuvers and complicate airway management. Also, percutaneous thermal liver tumor ablation has procedure-related risks. Intraperitoneal or intrahepatic bleeding, liver capsule irritation with post-procedural pain, thermal injury to adjacent structures including the diaphragm, stomach, colon or gallbladder, bile duct injury or stricture, pleural effusion, and pneumothorax may occur.[40]

OUTCOME

The risks associated with PSA are influenced by multiple factors, including the clinical context, the training and dedication of the caregiver, and the complexity of the procedure. The patient's underlying health status further contributes to the overall safety profile of sedation.[3, 7] Importantly, providing sedation during NORA is associated with an increased risk of adverse events.[26, 41] Most critical incidents or near misses in these settings arise from operator error or the absence of appropriate rescue systems.[42] Inadequate staffing or insufficiently trained personnel may also increase the risk of serious complications. Even in the presence of an anesthesiologist, morbidity and mortality risk may increase if non-anesthesia care providers in departments such as radiology or endoscopy are unfamiliar with anesthesia or cardiovascular resuscitation.[41, 42] Careful patient selection, strict adherence to evidence-based guidelines, and adequate training of all healthcare professionals (non-anesthesia care providers as well as the anesthesia care providers) involved are therefore essential to minimize complications and ensure both safety and efficacy of PSA.[3, 7, 8]

Minimally invasive procedures can be associated with significant pain and discomfort. Adequate analgesia is therefore a critical component of PSA. By providing sufficient analgesic effect, sedative requirements can be reduced, thereby lowering the risk of dose-related adverse events such as respiratory depression and hemodynamic instability. Moreover, appropriate analgesia is particularly important in procedures requiring deep sedation, where it not only enhances patient comfort but also contributes to procedural safety and overall clinical success.[43] Post-procedural care constitutes an essential compo-

nent of PSA. Patients may experience adverse effects such as nausea or vomiting, in addition to procedure-related pain or discomfort. Targeted pharmacological interventions and supportive measures are required to ensure optimal patient comfort, safety, and recovery. This aligns with findings from studies on non-operating room anesthesia (NORA), which reported that the most common minor complications were post-operative nausea and vomiting, inadequate pain control, and hemodynamic instability, with complication rates being higher in interventional cardiology and radiology suites.[26]

Post-procedural pain, similar to acute postoperative pain, remains a significant clinical challenge.[44] Its negative consequences resemble those of postoperative pain and are among the leading causes of delayed hospital discharge.[45] Post-procedural pain substantially contributes to patient discomfort and suffering, highlighting the importance of effective pain management as a cornerstone of high-quality care.[46] This challenge is amplified in the outpatient setting, where procedures are not necessarily less painful than inpatient surgery, yet patients are discharged earlier, underscoring the need for tailored pain management strategies.

RESEARCH QUESTIONS AND THIS THESIS

The use of PSA by anesthesia care providers, particularly in non-operating room settings, remains associated with complications such as nausea, vomiting, pain, and hypoxemia, underscoring the need to further improve safety and quality in these procedures. The research presented in this thesis aims to evaluate the safety and quality of PSA administered by anesthesia care providers, with particular attention to complications and clinical outcomes in NORA settings. In addition, it seeks to identify opportunities to improve the quality of the procedure and thus improvement of patient care. The research was conducted in two common clinical indications: (1) catheter ablation for AF and (2) percutaneous thermal liver tumor ablation. Both procedures are performed under deep sedation where respiratory complications represent a major challenge during catheter ablation for AF, while pain is the predominant concern during percutaneous thermal liver tumor ablation.

The aim of this thesis is to study and evaluate the safety and quality of PSA, with particular attention to complications and clinical outcomes in NORA settings. To address this aim, the following research questions (RQ's) were formulated:

1. What is the status on optimization of practices of procedural sedation and analgesia during atrial fibrillation ablation?
2. Is it possible to determine the incidence and severity of respiratory complications during procedural sedation and analgesia in atrial fibrillation ablation, and to identify predictive factors for their occurrence?
3. Does high-flow nasal oxygen affect oxygenation and the incidence of hypoxemia during procedural sedation for atrial fibrillation catheter ablation?
4. What is the prevalence and severity of acute post-procedural pain following percutaneous thermal liver tumor ablation under procedural sedation and analgesia?

OVERVIEW OF THIS THESIS

Chapter 2 addresses RQ1 and presents a narrative review on optimization of PSA during AF ablation performed in the electrophysiology (EP) laboratory. This review aims to provide a comprehensive overview and critical discussion of current practices, with a particular focus on key components such as staff qualification, patient evaluation, intra-procedural monitoring, sedative and analgesic medication strategies, and post-procedural care.

Chapter 3 focuses on RQ2 and studies the incidence and severity of respiratory complications during PSA, and aims to identify predictive factors for the development of peri-procedural respiratory complications in patients undergoing AF ablation performed in the EP laboratory.

Chapters 4 and **5** deal with RQ3. In **Chapter 4** the design of a single-center randomized clinical trial comparing HFNO with standard LFNO during deep sedation in patients undergoing radiofrequency catheter ablation for AF, performed in the EP laboratory, is presented. **Chapter 5** presents the results and outcome of this single center RCT in which the effects of HFNO (n = 51) and standard low-flow nasal oxygen (n = 50) on oxygenation and hypoxemia are compared.

In **Chapter 6** the prevalence and severity of post-procedural pain following computed tomography (CT) or ultrasound-guided percutaneous liver ablation with PSA are investigated. Potential predictors, including procedural, psychological, and sedation-related factors, are examined in a single-center study.

Chapter 7 summarizes all findings and discusses them in view of the general aim (see page 16) and in relation to the methods used. The discussion will end with suggesting possible future directions.

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2

Optimization of procedural sedation and analgesia during atrial fibrillation ablation

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ABSTRACT

This mini-review aims to provide an overview and discuss procedural sedation and analgesia for atrial fibrillation (AF) ablation with a focus on the qualification of staff, patient evaluation, monitoring, medication and post-procedural care. Sleep-disordered breathing (SDB) is highly prevalent in patients with AF. The impact of often used STOP-BANG questionnaire to detect SDB in AF patients is limited due to its restricted validity. Dexmedetomidine is a commonly used drug in sedation, but has shown not to be superior to propofol in sedation during AF ablation. Alternatively, remimazolam has characteristics that make it a promising drug for minimal to moderate sedation for AF ablation. High-flow nasal oxygen (HFNO) has been shown to reduce the risk of desaturation in adults receiving PSA. An optimal sedation strategy during AF ablation should be based on AF patient characteristics, the level of sedation needed, the procedure (duration and type of ablation) and the education and experience of the sedation provider. Patient evaluation and post-procedural care are part of sedation care. More personalized care based on the use of various sedation strategies and types of drugs as related to the type of AF ablation is the way to further optimize care.

Key points:

Procedural sedation and analgesia for atrial fibrillation (AF)-ablation is a safe procedure after careful evaluation, performed by trained professionals, with adequate monitoring and adequate post-procedural care.

Sleep-disordered breathing (SDB) is highly prevalent in patients with AF, although detection of SDB with use of STOP-BANG questionnaire is overrated.

Careful selection of medication is needed in view of use of modality of anesthesia with catheter ablation for AF and this can minimize risks and adverse events.

INTRODUCTION

Catheter ablation for atrial fibrillation (AF) has emerged as an important rhythm-control strategy and is by far the most common cardiac ablation procedure performed worldwide.[1] Radiofrequency ablation (RFA) with 3D electro-anatomical mapping to guide the catheter and cryoablation are techniques for AF ablation.[1] The best modality of anesthesia with catheter ablation for AF is still a matter of debate.[2] Although general anesthesia is the standard in the majority of clinical centers, procedural sedation and/or local anesthesia is a good alternative and used in those clinical centers where general anesthesia is not easily available.[2] Sedation is not inferior to general anesthesia in terms of ablation time and freedom from atrial arrhythmia at 1 year and is accompanied by reduced resource utilization and therefore costs.[3]

Procedural sedation and analgesia (PSA) involves the use of hypnotic and/or analgesic medications to enable diagnostic or therapeutic procedures effectively, whilst the patient is closely monitored for potential adverse effects.[4] Depth of sedation is graded into: 1. minimal sedation, 2. moderate sedation, 3. deep sedation and 4. general anesthesia (see Table 1) based on the recommendations of the American Society of Anesthesiologists (ASA).[5] Although the wording conscious sedation is commonly used, this term is misleading and should not be used as it is contradictory as effective sedation decreases consciousness.[4] For AF cryoablation minimal or moderate sedation has been shown to be efficient in the majority of patients.[6] For RFA with 3D electro-anatomical mapping deep sedation or general anesthesia is mandatory as the success of the procedure depends on minimal patient movement.[6]

Table 1. Levels of sedation as suggested by the American Society of Anesthesiology[4]

	Level 1 Minimal	**Level 2 Moderate**	**Level 3 Deep**	**Level 4 General anesthesia**
Responsiveness	Normal responses to verbal stimuli. Cognitive function and coordination may be impaired.	Purposeful responses to verbal/tactile stimuli and verbal commands.	Not easily arousable. Purposeful responses to repeated verbal/tactile or painful stimuli.	Not arousable. No response to painful stimulation.
Airway	Normal	Airway is patent	Ability to maintain a patent airway may be impaired. Airway support may be required.	Ability to maintain a patent airway. Airway support is required.

Table 1. Levels of sedation as suggested by the American Society of Anesthesiology[4] (*continued*)

	Level 1 Minimal	**Level 2 Moderate**	**Level 3 Deep**	**Level 4 General anesthesia**
Ventilation	Normal	Spontaneous ventilation is adequate	Ability to maintain spontaneous ventilation may be impaired. Respiratory support may be required.	Ability to maintain spontaneous ventilation is impaired Respiratory support and positive pressure ventilation is required.
Hemodynamic function	Normal	Unaffected	Usually unaffected	May be impaired

Previously published table. European Society of Anesthesiology and European Board of Anaesthesiology guidelines for procedural sedation and analgesia in adults. J Hinkelbein Jochen. Eur J Anaesthesiol 2018;35:6–24.

In clinical practice it is not always possible to predict how an individual patient will respond to sedative agents, and for instance moderate sedation can unintentionally lead to deep sedation.[5] Providers are responsible for resuming a well-tolerated level of sedation while ensuring patient safety. Complications during AF ablation are sedation and/or procedure related. The complications related to sedation are mostly a consequence of the effects and side effects of the sedation agents. The most common drug-related side effects are apnea, airway obstruction, hypoventilation and hypotension. A recent study on drug-related complications in a cohort of patients undergoing deep sedation for AF ablation showed that out of 3211 patients 1 patient (0.03%) required endotracheal intubation (eIT) and 47 patients (1.5%) required noninvasive ventilation (NIV).[7] Those patients which needed eIT and/or NIV experienced an increased duration of sedation procedures, an increased CHA2DS2 –VASC score and were characterized by a higher body mass index (BMI).[7] The CHA2DS2 –VASC score is widely used to estimate cardioembolic risk in patients with atrial fibrillation.[8] In this CHA2DS2 –VASC score one point is related to each of the following individual parameters: congestive heart failure, hypertension, age between 65 and 74 years, diabetes mellitus, vascular disease (myocardial infarction/peripheral arterial disease) and female gender (one point for each parameter) whereas two points are related to previous Stroke/Transient ischemic attack and to age ≥ 75 years.[8]

The rate of procedure related complications during deep sedation for AF ablation is approximately 2.9% and has decreased over the years.[9] It needs to be stressed that although sedation and procedure related complications are rare, complications like cardiac tamponade, stroke, pulmonary vein stenosis, vascular access related complications (e.g. bleeding, hematoma, femoral pseudoaneurysm formation) and pneumothorax occur rapidly, are often very serious and may be life-threatening.[9]

As sedation is dynamic and the clinical course of patients may vary considerably, we will discuss the following topics in more detail: 1. qualification of staff involved in PSA with AF ablation, 2. patient selection, 3. peri-operative care during AF ablation.

QUALIFICATION OF STAFF INVOLVED IN PSA FOR AF ABLATION

The growing demand for PSA for AF ablation cannot be fully covered and performed by anesthesiologists in a number of countries. It is a clinical reality that not only anesthesiologists but also other healthcare practitioners like cardiologists, nurse practitioners, physician assistants, nurses and sedation practitioners (SPs) provide PSA for AF ablation. In view of the complexity of the procedure and/or treatment it is mandatory that sedation is performed by a sedation provider with adequate qualification and full focus on PSA.

Fundamental knowledge of sedative agents, analgesics, cardio-active and antagonist drugs is mandatory and are standards to maintain.[10] The most common risk associated with PSA is respiratory compromise including hypoventilation and apnea potentially resulting in hypoxemia.[10] The sedation provider is expected to have airway management skills including mask ventilation, use of supraglottic airway devices and the use of advanced airway devices like laryngeal mask airway (LMA) and endotracheal intubation.[10] As there is a need for formal training programs, some professional national and international anesthesiology societies developed guidelines and a curriculum like the ASA's Safe Sedation Training. The latter is an educational program designed to guide moderate and deep sedation for non-anesthesiologist and healthcare providers.[10] For example in the Netherlands SPs are certified anesthesia nurses trained at the anesthesia department, and in line with the European Society of Anesthesiology and Intensive Care (ESAIC) guidelines on PSA of adults.[4] Nevertheless, moderate to deep sedation by SPs is often performed under indirect supervision of an anesthesiologist.[2]

It has been demonstrated that this setting of trained SPs as in the Netherlands is safe as sedation and sedation-related events have been reported to be managed effectively.[11] In case of complex sedation or high-risk procedures, the SPs can request for direct supervision of an anesthesiologist. Legal requirements for PSA differ all over the world.[2, 7] For example, the United States Food and Drug Administration (FDA) only approves the use of propofol for performing deep sedation by trained sedation providers due to its risk profile.[12] On the other hand in countries like France, Spain or Italy, it is not permitted to perform deep sedation without the presence of an anesthesiologist.[2]

Qualifications of staff involved in PSA with AF ablation under moderate to deep sedation are of utmost importance for optimal care and need to be well described for the sedation

provider in each institution. Training and (in)direct supervision of a sedation provider by an anesthesiologist are closely related to the complexity of the case and/or procedure. Guidelines and practice recommendations as published by ESAIC and/or ASA should be implemented in local practice and provide essential basic information.

Table 2 Summary of suggested training expectations for sedation providers of moderate and deep sedation.[10]

Training expectation	Moderate sedation	Deep sedation
Anesthetic provider	Anesthesia trained professionals (anesthesiologist, CRNA, or AA), nonanesthesiologist providers, and supervised sedation practitioners (registered nurses and physician assistants)	Anesthesia trained professionals (anesthesiologist, CRNA, or AA), nonanesthesiologist providers (doctor of medicine or osteopathy, qualified dentist, oral surgeon, or podiatrist)
Approved sedatives	Opioids, benzodiazepines, and dexmedetomidine	Opioids, benzodiazepines, dexmedetomidine, propofol, and ketamine
Emergent life support	ACLS & mastery of moderate sedation and recognition of deep sedation	ACLS & mastery of deep sedation and recognition of general anesthesia
Airway management skills	Face mask and positive pressure ventilation	Bag mask ventilation, oro- and nasopharyngeal airway, laryngoscopy and ET intubation
Preprocedural evaluation	History and physical	History and physical Formal perioperative evaluation
Monitoring and Documentation	Pulse oximetry, BP, EKG, HR, depth of sedation, capnography	Pulse oximetry, BP, EKG, HR, depth of sedation, capnography

AA, anesthesiologist assistant; ACLS, advanced cardiac life support; BP, blood pressure; CRNA, certified registered nurse anesthetists; EKG, electrocardiogram; ET, endotracheal tube; HR, heart rate. Previously published table. Moderate and deep sedation training and pharmacology for nonanesthesiologists: recommendations for effective practice. T.T. Tran Thi. Curr Opin Anesthesiol 2019;32:457–463.

PATIENT EVALUATION

Pre-procedural patient evaluation contributes to the likelihood of satisfactory sedation and decreases the likelihood of adverse outcomes for both moderate and deep sedation.[10, 13] The following recommendations are widely accepted: 1. patient evaluation for elective PSA in advance to allow optimal patient preparation, 2. perform a standard pre-anesthesia assessment, 3. reviewing previous medical records and interview the patient, 4. including focused physical examination, and 5. review available laboratory test results.[13] Based on the outcome of the interview and the physical assessment additional examination might be needed. For example kidney function is necessary pre-procedural for AF ablation and a medication dosage reduction can be indicated if kidney function is impaired and further reduction caused by contrast-induced nephropathy avoided.

Furthermore, patients receiving sedation for AF ablation usually require pre-procedural cardiac echocardiography and evaluation for OSAS. As AF ablation is an elective procedure there is time to perform a pre-procedural evaluation in advance and to optimize the condition of the patient if indicated.

Patients with a significant comorbidity (like those with suspected high risk of either obstructive sleep apnea syndrome (OSAS), or severe cardiovascular diseases, or morbid obesity, or chronic renal failure, or chronic hepatic disease as well as elderly or patients with an ASA Physical Status III and IV require evaluation and management of procedural sedation and analgesia by anesthesiology professionals like nurse anesthetists, screeners, residents or anesthesiologists.[4, 13] In case of pre-existing renal failure or/and chronic hepatic disease adverse events can be reduced by careful selection of medication, adjustment of dose and careful titration for example in patients with reduced clearance. A BMI > 30 kg/m^2 has been shown to be an independent predictor for severe persistent hypoxemia during sedation for AF ablation.[7] OSAS is the most common subtype of sleep-disordered breathing (SDB) and is highly prevalent in AF-patients.[14] Detection of SDB is by use of the STOP-BANG questionnaire.[15] Nevertheless impact of this questionnaire is limited due to its restricted validity to detect SDB in AF patients.[16, 17] Most patients with AF do not report daytime sleepiness, a typical SDB-related symptom.[14] Diagnostics for SDB should not only be performed to reduce adverse sedation events but SDB is also a predictor of a twofold higher risk of AF recurrence after ablation.[18]

In conclusion: Careful patient evaluation contributes to patient safety as it signals the risk factors for sedation related adverse events. Severe OSAS and morbid obesity are relative contra-indications for moderate to deep sedation during AF ablation; then general anesthesia is a safe alternative. As the threshold of parameters resulting in the need for general anesthesia do not exist this is a target for future research.

PERI-PROCEDURAL CARE DURING AF ABLATION

Peri-procedural sedation care during AF ablation can be subdivided into three areas of interest:

1. Monitoring,
2. Medication,
3. Post-procedure care.

Monitoring

Standard monitoring of patients undergoing PSA includes noninvasive blood pressure (NIBP), pulse oximetry, ECG and expiratory capnography ($ExCO_2$). Some authors recommend the use of depth of sedation monitoring (e.g. processed EEG).[4, 13] During moderate or deep sedation continuous evaluation of ventilation using $ExCO_2$ is mandatory. End expiratory CO_2 monitoring is able to detect apnea earlier as compared to use of pulse oximetry.[4] The use of $ExCO_2$ has shown to reduce the incidence of hypoxic events by early detection of apnea.[19] During $ExCO_2$ monitoring waveform abnormalities can be observed and the measurement of $ExCO_2$ can be unreliable. If it is technically not possible to measure reliably $ExCO_2$, for example using high-flow nasal oxygen, peri-procedural transcutaneous carbon dioxide level ($TcCO_2$) is a noninvasive option to monitor CO_2.[19] $TcCO_2$ measurement is an alternative used during PSA as a replacement for laboratory measurement of blood CO_2 levels.[19, 20] However invasive arterial blood pressure monitoring can be indicated in selected cases. Foerscher recently observed and reported that arterial blood pressure monitoring is indicated for blood pressure control and/or arterial blood gas analysis in 27.8% of the population in a study in patients undergoing left arterial ablation.[7] The results of this study also showed a significant blood pressure drop (MAP < 60 mmHg) in 12.3% of the cases.[7]

The level of sedation can be rated by the Ramsay Sedation Scale (RSS) or Modified Observer's Assessment of Alertness/Sedation (MOAA/S)(see Table 3). Processed EEG like Bispectral index (BIS) monitoring is used to measure the level of sedation. It has been demonstrated that EEG based titration of hypnotic agents leads to a stable level of sedation.[4] This stable situation consequently results in increased patient as well as staff satisfaction and reduces the duration of the procedure resulting in enhanced productivity. The latter seems important giving the long waiting times for patients planned for elective ablation.

Table 3. Sedation scales commonly used in PSA: Ramsay sedation scale and MOAA/S scale
Improvements in monitoring of patients undergoing AF ablation are still possible using noninvasive methods like $TcCO_2$ for monitoring ventilation. These noninvasive methods allow early detection of hypoventilation. Correct adjustment of the depth of sedation does easily solve these ventilation problems and thus prevents the occurrence of any sedation related complications.

Table 3 Sedation scales commonly used in PSA

	Ramsay Sedation Scale (RSS)	MOAA/S Scale
0		Does not respond to painful trapezius squeeze
1	Patient is anxious and agitated or restless, or both	Responds only after painful trapezius squeeze
2	Patient is cooperative, oriented and tranquil	Responds only after mild prodding or shaking
3	Patient responds to commands only	Responds only after name is called loudly and/or repeatedly
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus	Lethargic response to name spoken in normal tone
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	Responds readily to name spoken in normal tone
6	Patient exhibits no response	

Medication

Hypnotic agents

Midazolam and/or fentanyl is commonly used with minimal to moderate sedation.[2, 10] For deep sedation propofol (continuous or target controlled infusion (TCI)) is most often used as sedative, alone or in combination with midazolam.[2, 10] In a recent survey the current status and evolution of the use of sedation strategies for AF ablation was presented and there it was indicated that over the last decade propofol is more frequently used for deep sedation (57,2%) as compared to midazolam (48,1%).[2] In the same review it is documented that with minimal sedation midazolam is preferred to be used (in 58,6%) over propofol (19,2%).[2]

Other commonly used drugs in sedation of patients with AF ablation are dexmedetomidine and ketamine. Dexmedetomidine (dexmed) is an alpha2-adrenoreceptor agonist with sedating and analgesic effects without respiratory depression.[21] Decreased heart rate via sinus and AV node depression and hypotension caused by decreased vascular resistance occur with the use of dexmed.[21] In patients with underlying heart disease dexmed may cause left ventricular dysfunction.[21] In a recent study, Servatius et al. compared the effects of propofol vs. dexmedetomidine in 160 patients undergoing RFCA.[22] Dexmed was shown not to be superior to propofol in this randomized controlled study.[22] Hypercapnia occurred less frequently with dexmed, but with propofol the sedation strategy was shown to be efficient in all patients and patient satisfaction was significantly higher.[22]

Ketamine is a phencyclidine-derived anesthetic which can be used in deep sedation.[10] It is a unique anesthetic because it can be used as a sedative and as an analgesic.[21] Because

of its hypertensive side effects attention is needed in particular in patients with hypertension and/or coronary artery disease. With use of ketamine not only respiratory drive but also heart rate and airway reflexes are generally (better) preserved as compared to that noted after use of other drugs/sedatives.[10] Ketamine induced side effects like dissociation and hallucinations can cause patient movement, psychotomimetic emergence and hyper-salivation and they do relatively often occur.[10] Sub-therapeutic doses of ketamine provide analgesia in AF-patients who are already sedated with propofol for example. A derivative of ketamine, esketamine might become an interesting option providing more potent sedative and analgesic effects and less psychotropic side effects.[23]

Remimazolam is a more recently used drug, that undergoes rapid metabolism and degradation due to abundant presence of plasma and tissue esterases. The safety profile of remimazolam is comparable to midazolam although sedation depth is reached much faster.[24] With respect to remimazolam, all present studies and RCT's are performed during sedation for endoscopies and therefore the results cannot be generalized to sedation for AF ablation. In a meta-analysis of 5 RCT's with 1,248 participants, Jhuang et al investigated the effectiveness and adverse events (AEs) of remimazolam during procedural sedation.[25] Compared with the use of midazolam, the utilization of remimazolam resulted in an increased procedure success rate, a reduction in the application of rescue medication, a decrease in time to recovery and a better cognitive recovery of Hopkins Verbal Learning Test-Revised.[25] Theoretically, the use of remimazolam for mild to moderate sedation in AF ablation can be beneficial. Hence the use of remimazolam in AF ablation and mild to moderate sedation is an important target for future research.

Analgesic drugs

Most commonly, hypnotic agents are combined with opioids for optimal pain relief. The opioid remifentanil is a fast acting drug which can be titrated accurately by TCI and this drug is characterized by a fast washout in minutes after ending infusion (T1/2 el 12-30 minutes) whereas the duration of action of opioid fentanyl is 30-60 minutes (T1/2 el 6-8 hours).[10] Remifentanil is rapidly hydrolyzed and degraded and cleared due to abundant presence of plasma and tissue esterases.[24] Fentanyl is metabolized via CYP3A4 pathways and is renally cleared and this makes that the dosage should be adjusted in case of liver or renal failure. Information on the preference of the use of opioids for moderate and deep sedation is rather limited and can at present not exactly be determined as in a recent survey fentanyl and remifentanil were combined and analyzed as one group.[2]

Combination and use of drugs via one bolus of midazolam, continuous infusion of propofol and boluses fentanyl is often used for deep sedation of patients during AF ablation.[7] The combined use of TCI of propofol and remifentanil is expected to increase among anesthesia sedation providers as TCI facilitates precise control over the level of sedation.[7]

POST-PROCEDURE CARE

The ESAIC guidelines on procedural sedation recommend that patients after PSA must be monitored in a recovery room for at least 30 minutes.[4] Post-sedation monitoring (with at least NIBP, ECG and pulse oximetry) is essential to supplement continuous visual observation by an experienced trained nurse. Patients may deteriorate considerably after PSA and AF ablation, mostly patients with a significant disease burden or with complications of the AF ablation. Post procedure management includes pain management, HD optimization and recognizing and treatment of post-procedure complications. Most major complications were reported to occur intraprocedurally or within 6 hours after the procedure.[26] Congestive heart failure and transient ischemic attack were the most common major complications.[26]

OPTIMIZING CARE

Literature concerning patients with OSAS undergoing moderate and deep sedation is lacking, also for AF ablation procedures. SDB-screening prior to PSA can result in the reduction of respiratory complications during sedation.[27] In case of severe OSAS general anesthesia is an alternative for deep sedation. As the threshold of parameters resulting in the need for general anesthesia do not exist this is a target for future research. Further studies are needed to determine if moderate and deep sedation can safely be performed in SDB patients. $TcCO_2$ monitoring should be considered in patients with risk for hypercapnia and acidosis like those with obesity, chronic obstructive pulmonary disease and SDB (all common in AF-patients). Supporting spontaneous ventilation during sedation with high-flow nasal oxygen (HFNO) or NIV may result in optimization of ventilation. HFNO has been shown to reduce the risk of desaturation in adults receiving PSA.[28] Further studies are needed to show if HFNO/NIV during deep sedation indeed reduces hypercapnia and this should be linked to the identification of those patients who will benefit from HFNO/NIV. Titration of propofol and remifentanil with TCI may facilitate precise control over the level of sedation. TCI is available in many countries but is not yet approved in the United States by Food and Drug Administration (FDA).[24]

CONCLUSION

An optimal sedation strategy during AF ablation should be based on AF patient characteristics, the level of sedation needed, the procedure (duration and type of ablation) and the education and experience of the sedation provider. Careful medication selection can minimize risks and adverse events. Patient evaluation and post-procedural care are part of sedation care. New (combinations of) drugs, noninvasive monitoring like $TcCO_2$ and optimizing ventilation during sedation may further optimize sedation care during AF ablation. More personalized care based on the use of various sedation strategies and types of drugs as related to the type of AF ablation is the way to further optimize care. Guidelines and practice recommendations as published by ESAIC and/or ASA should be implemented in local practice. Training and (in)direct supervision of a sedation provider by an anesthesiologist is closely related to the complexity of the case and/or procedure.

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Peri-procedural respiratory complications in patients undergoing pulmonary vein isolation with procedural sedation and analgesia: incidence and predictive factors

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ABSTRACT

Background and Objectives: Catheter ablation (CA) in patients with atrial fibrillation (AF) can be performed under procedural sedation and analgesia (PSA). Risk factors for respiratory complications during PSA are unclear. We aimed to determine the incidence and severity of respiratory complications during PSA and identify predictive factors for development of per-procedural respiratory complications.

Methods: Patients with AF receiving PSA in the MUMC$^+$ for CA were included. Respiratory complications were defined as the need for an oral/nasal airway, a non-rebreathing mask, high flow oxygen, a hypoxemic event or conversion to general anesthesia.

Results: In total 232 procedures (42.2% cryoballoon ablation; 57.3% RF ablation) were performed. Most patients were male (62.1%), with a mean age of 64±9.3 (mean ± SD), an activity level ≥4 METS (94.8%) and paroxysmal AF (68.5%). Respiratory complications occurred in 42.2%. A multiple logistic regression model including sedation duration, age >50 years, neck circumference >40 cm, visceral fat percentage, self-reported tiredness, apnea-hypopnea index (AHI), a medical background of diagnosed sleep apnea (OSAS) and chronic obstructive pulmonary disease (COPD) identified patients at risk with an AUROC 0.72, 95% CI: 0.65-0.78.

Conclusion: In patients with AF undergoing CA under PSA, per-procedural respiratory complications occur in 42.2% of the cases. Duration of the PSA, a neck circumference >40 cm, visceral fat percentage, tiredness, AHI, OSAS and COPD may help to identify patients at risk for per-procedural respiratory complications. Although age >50 years is a recognized risk factor, this cut-off had limited discriminative value in our cohort, as most patients were older than 50.

INTRODUCTION

Catheter ablation (CA) for atrial fibrillation (AF) has become one of the most common procedures in the cardio-electrophysiology lab.[1] In patients with AF, CA is performed either under procedural sedation and analgesia (PSA) or under general anesthesia (GA).[1, 2, 3] The worldwide European Heart Rhythm Association (EHRA) survey in 2021 showed that GA was the most commonly used anesthetic technique (40.5%), followed by conscious sedation (32.0%) and deep sedation (27.5%).[4] Under deep sedation, the level of consciousness approaches that of general anesthesia, and in most centers an anesthesiologist, a second physician, or a specially trained nurse is required to be present.[1, 5, 6] In addition to alleviating pain and anxiety, an important goal for anesthesia during AF ablation is to minimize patient movement as this improves catheter stability.[4] Therefore, general anesthesia or deep sedation has frequently been preferred over conscious sedation.[4]

Patient-related risk factors of perioperative respiratory complications include advanced age, chronic obstructive pulmonary disease (COPD), poorly controlled asthma, heart failure, poor systemic health status defined as an ASA classification of 2 or higher, cigarette smoking within 8 weeks before surgery, preoperative anemia (hemoglobin concentration lower than 10 g/dL), low preoperative peripheral oxygen saturation (SpO_2), functional dependence, patients with a current respiratory tract infection, and obstructive sleep apnea (OSA).[7, 8, 9] Obesity, COPD and sleep-disordered breathing (SDB) are common concomitant conditions in AF-patients.[10, 11] Although the STOP-BANG questionnaire is a broadly used screening tool for SDB, and therefore used during pre-assessment in the anesthesia outpatient clinic, it is known not to be very accurate in patients with AF.[12, 13] These conditions may affect the incidence of respiratory complications during PSA.

Interdisciplinary teamwork, patient selection, close communication, accurate planning, establishing protocols and pathways for help may facilitate safe, efficient procedural care and non-operating room anesthesia (NORA).[3] In NORA, the anesthesia technique may range from minimal sedation to general anesthesia. The occurrence of hypoxemia is one of the most common issues of sedation in non-intubated patients.[14] A considerable number of patients undergoing PSA for CA are at risk of hypoxemia during PSA.[15] Increased duration of medical procedures has shown a positive correlation with hypoxemia during PSA.[15] In patients undergoing PSA during procedures in the heart catheterization room, a 54% incidence of hypoxemia was found.[15] However, patients with coexisting cardiovascular or pulmonary disease are more at risk for hypoxemic cardiac or cerebral events.[7, 8, 16]

Nevertheless, the identification of patient-related factors, in particular in view of respiratory complications during moderate or deep sedation, is known to be very limited. In a multidisciplinary approach, involving electrophysiologists and anesthesiologists, patient selection is needed to outweigh the risks and benefits related to PSA and GA. All the

more important, as AF ablation has increased enormously in recent years. And therefore the demand for anesthesia support for AF ablations does not match the anesthesia availability.[1] The primary aim of this study was to determine the incidence and severity of per-procedural respiratory complications during CA in patients with AF under PSA. The secondary aim of this study was to identify predictive factors for the development of per-procedural respiratory complications during RFCA in patients with AF under PSA. Ultimately, this knowledge could help optimize patient selection for PSA during CA.

METHODS

Study design and ethical approval

This retrospective single-center study was performed at the Maastricht University Medical Centre (MUMC$^+$) in the Netherlands. This is a secondary data analysis of the ongoing ISOLATION cohort study (NCT04342312) and ISOLATION 'light' registry [17]. The ISOLATION cohort study and ISOLATION 'light' registry were approved by the ethical review boards MUMC$^+$ (METC numbers 19-052, 2019 1022) and Radboud-UMC (METC number 2019-5629). This study was conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All participants provided written informed consent.

Study population

Patient selection for PSA during CA is based on a combination of guidelines and practice. PSA is provided and monitored by anesthesia care providers (ACPs) at MUMC$^+$ since 2013. Known exclusion criteria for PSA during CA at MUMC$^+$ are: Body Mass Index (BMI) > 32 kg/m^2, Obstructive Sleep Apnea (OSA) diagnosed or high risk based on STOP-Bang questionnaire, reflux and diaphragmatic hernia. Also a poor pulmonary condition, an electrophysiologist request for GA or a lack of informed consent for PSA is a reason for excluding patients from PSA. Patients with AF receiving anesthesia in the MUMC$^+$ for CA were included in this study between October 2020 and July 2023. Patients were excluded from this study if they received GA, PSA was performed but not registered into the patient data management system (PDMS), or the patient did not undergo the remote sleep test for SDB (the Virtual-SAFARI approach).[18]

Systematic screening for common comorbidities and triggers for AF is part of the ISOLATION study and is integrated in a standardized care pathway. Patients are screened for hypertension, obesity, hyperlipidemia, diabetes mellitus, and chronic obstructive pulmonary disease (COPD) according to current AF guidelines.[4] The standard work-up for ablation in the participating centers consists of a systematic collection of clinical information, vital signs, 12-lead ECG, blood tests, echocardiography, imaging to assess pulmonary vein anatomy (either computed tomography or cardiac magnetic resonance imaging), and pre-anesthesia assessment by a physician assistant of the department of anesthesiology.

The pre-anesthesia assessment is standard anesthesia care. Previous medical records are reviewed, the patient is interviewed, a focused physical examination is performed, and available (laboratory) tests are reviewed. This patient evaluation contributes to the likelihood of satisfactory sedation and decreases the likelihood of adverse outcomes for moderate and deep sedation. Additionally, results of the following additional diagnostics are included in the ISOLATION study: determination of body composition, pre-procedural rhythm monitoring, extended surface electrocardiogram, biomarker testing, genetic analysis, and questionnaires.[17]

Interventions and outcome measures

CA was always performed under sedation by an ACP. Types of CA were cryoballoon ablation or radiofrequency AF ablation. ACPs involved in moderate to deep sedation are sedation practitioners working under either direct or indirect supervision (direct support available within 5 minutes) from an anesthesiologist. PSA included a combination of a continuous infusion with propofol in combination with a short-acting opioid like remifentanil or alfentanil. Acetaminophen was administered to prevent post-procedural pain if necessary in combination with piritramide or morphine. Patients were continuously observed. Noninvasive blood pressure, peripheral oxygen saturation (SpO_2), a 5-lead electrocardiogram, bispectral index (BIS), respiratory rate and waveform capnography were monitored. ACPs assessed the depth of sedation periodically throughout the procedure by utilizing the Modified Ramsay Sedation Scale (RSS).[19, 20] Oxygen was administered with a flow of 2-5 L/min. In case of hypotension, a vasoactive drug was administered. In case of an upper airway obstruction, airway repositioning, tactile stimulation or airway (nasal or oral) was applied. In our center, the use of a nasal or oral airway is not part of routine care. These devices are only inserted in response to clinically significant airway obstruction or desaturation, not as prophylactic use. The setting complies with international sedation guidelines.[5, 6]

After reaching an appropriate level of sedation, femoral venous access for CA was obtained using ultrasound guidance. A decapolar catheter was placed in the coronary sinus (Webster CS catheter, Biosense Webster, Inc, Diamond Bar, CA, United States). Transesophageal echocardiography-guided double trans-septal access was performed: the first access was realized using a SL-0 sheath (Abbott, Inc, Chicago, IL, United States) and a Brockenbrough technique. Intravenous heparin was administered after the trans-septal access, targeting an activated clotting time (ACT) > 300 s.

Catheter ablation by cryoballoon is described in detail elsewhere.[21] In brief, the trans-septal sheath was exchanged over a guidewire for the 15F Flexcath Advance sheath and continuously flushed with heparinized saline and the cryoballoon catheter (Arctic Front™ cryoballoon, Medtronic, Inc.) was introduced into the left atrium and a spiral mapping catheter (20 mm diameter; Achieve, Medtronic, Inc.) was advanced into the target

pulmonary veins to record electrical activity. A stable occlusion was verified by contrast dye injection. The minimum cryoballoon cut-off temperature was set at –60°C. A time-to-effect based ablation protocol was utilized for both cryoballoon systems. The procedural endpoint was the disappearance of PV signals verified via the circular mapping catheter after the freeze cycle.

Catheter ablation by radiofrequency is described in detail elsewhere.[22] In brief, a second trans-septal access was realized using a deflectable sheath (Vizigo sheath, Biosense Webster, Inc) and an over the wire technique. A high-density mapping catheter (OctaRay catheter, Biosense Webster, Inc) was used to perform an electro-anatomical reconstruction of the left atrium (LA) (CARTO 3 System Version 7, Biosense Webster, Inc). The ablation catheter (ThermoCool® SmartTouch® Surround Flow (STSF), Biosense Webster, Inc) was used for pulmonary vein isolation by a wide area circumferential ablation. Target range for CF was 10–25 g. Target ablation index was 500–550 using 45 Watts or 380–400 using 35 Watts for the anterior and posterior segments, respectively. The inter-lesion distance was set to 5–6 mm. Routine use of an esophageal temperature probe is avoided in sedated patients due to its potential to cause peri-procedural respiratory complications. After the procedure, a systematic trans-thoracic echocardiography was performed to rule out pericardial effusion. Figure-of-8 stitch and 4 hours compressive bandaging was placed at the site of femoral puncture to avoid bleeding. Patients were then transferred to the recovery room for monitoring. After clinical observation on the short stay unit, patients were discharged on the same day in case of an uneventful procedure and recovery.

The Tracking and Reporting Outcomes Of Procedural Sedation (TROOPS) comprehensive research tool was used to define per-procedural respiratory complications during sedation.[23] Events were grouped under the broader category of "respiratory complications," this stratified classification allows for a more nuanced interpretation. Respiratory complications were defined as mild when transient hypoxemia or airway obstruction was relieved by the use of a nasal airway, intermediate when relieved by an oral airway, a non-rebreathing mask or high-flow oxygen, and severe when a prolonged hypoxemic event occurred (peripheral oxygen saturation <90% lasting ≥120 seconds) or when airway obstruction necessitated conversion to general anesthesia with a laryngeal mask airway (LMA) or tracheal intubation. The definition for a hypoxemic event was based on a retrospective observational study on hypoxemia during procedural sedation in adult patients.[15] To express the severity of respiratory complications, in addition to the incidence of hypoxemia, we determined the area under the curve (AUC_{Desat}), the lowest mean saturation and the duration of the lowest saturation. For each hypoxemic event AUC_{Desat} (by multiplying duration in minutes and drop in saturation under 90%) were determined in seconds %.[24] Figure 1 shows the descriptions of respiratory complications and the severity assessment of hypoxemic events.

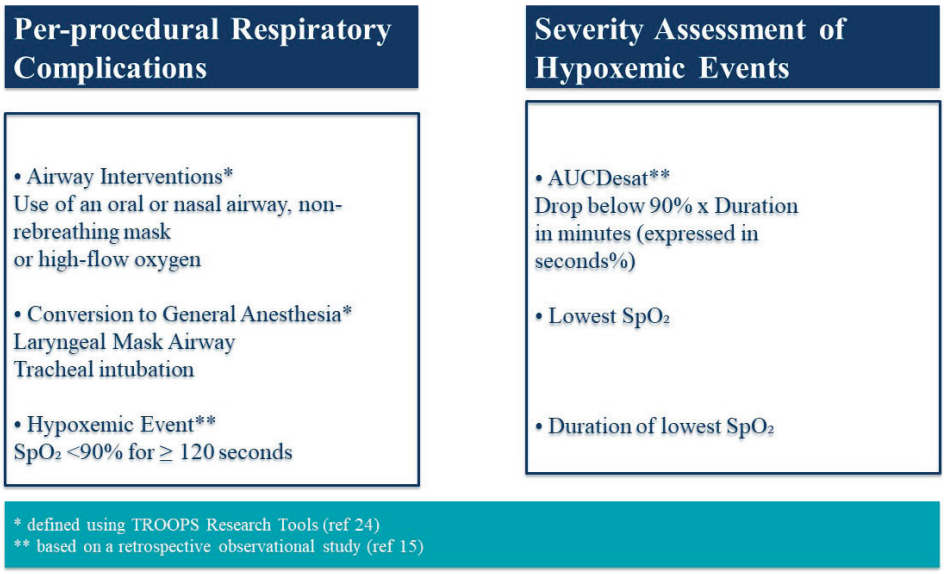


Fig. 1. Descriptions of respiratory complications and the severity assessment of hypoxemic events.

Clinical assessment

Vital signs were continuously monitored using the Philips Medical Systems Intellivue MX800 1&2 and automatically stored in a patient data management system (PDMS). Administrated medication during PSA and recovery stay, duration of sedation, and CA were entered into the PDMS. For this study, the prospective dataset from ISOLATION study and ISOLATION 'light' registry were completed with anesthesiology data from PDMS and the pre-operative anesthesia evaluation form. All data required for this study was extracted from the hospital electronic health systems and incorporated in the online database Castor EDC.

Statistical methods

Patients' characteristics were described using descriptive statistics. The distribution of continuous variables was assessed using histograms. Depending on the distribution, we used the independent-samples t-test (in case of normal distribution) or the Mann-Whitney U test. Categorical and binary variables were tested using Pearson's chi-squared test. The associations between patient- or procedure-related factors and respiratory complications were estimated using univariable and multivariable logistic regression. The alpha used for variable selection was set at 0.30, a rule often used for detection of risk factors or predictors. We used backward elimination with all factors associated with respiratory complications. The discriminative ability of patient- and procedure-related characteristics was evaluated by calculating the area under the receiver operating characteristics (ROC) curve (AUROC). An AUROC above 0.7 was considered to indicate a sufficient level of dis-

crimination. Missing data were imputed using multiple imputations with fully conditional specification. Imputation was performed in SPSS version 28.0.0.0. Statistical analysis was performed using R version 4.1.3.

RESULTS

Patient characteristics

We included 232 participants. Most sedations were performed in men (62.1%). The mean (± SD) age was 64±9.3, BMI 27.0±3.0, with an activity level ≥4 METS (94.8%) and paroxysmal AF (68.5%). Most patients had an American Society of Anesthesiologists (ASA) classification II (84.1%). A cryoballoon ablation was performed in 42.2% and RF ablation in 57.3% of the cases. Patient characteristics at baseline of all procedures, without respiratory complications group and with respiratory complications group are summarized in Table 1, with additional details provided in Supplemental Table 1 (see page 54).

Table 1 Baseline characteristics of all procedures, without respiratory complications group and with respiratory complications group. Values are number (percentages) unless stated otherwise.

Characteristic	Total	No complications	Respiratory complications
	n=232	n=134	n=98
Sex			
Male	144 (62.1)	78 (58.2)	66 (67.3)
Female	88 (37.9)	56 (41.8)	32 (32.7)
Age, years – mean (SD)	64 (±9.3)	63 (±9.7)	64 (±8.7)
BMI, kg/m² – mean (SD)	27.0 (±3.0)	26.4 (±3.0)	27.4 (±2.9)
Activity level <4 METS	12 (5.2)	8 (6.0)	4 (4.1)
ASA classification			
I	2 (0.8)	1 (0.7)	1 (1.0)
II	195 (84.1)	115 (85.9)	80 (81.6)
III	35 (15.0)	18 (13.4)	17 (18.4)
Type of AF			
Paroxysmal	159 (68.5)	97 (72.4)	62 (63.3)
Persistent	73 (31.4)	37 (27.6)	36 (36.7)
Type of ablation			
Cryoballoon	98 (42.2)	64 (47.8)	34 (34.7)
Radiofrequency	133 (57.3)	69 (51.5)	64 (65.3)
Comorbidities			
CAD	19 (8.2)	9 (6.7)	10 (10.2)
CHF	25 (10.8)	15 (11.2)	10 (10.2)
Diabetes mellitus	15 (6.5)	7 (5.2)	8 (8.2)
OSAS	21 (9.1)	16 (11.9)	5 (5.1)

Characteristic	Total	No complications	Respiratory complications
COPD	10 (4.3)	8 (6.0)	2 (2.0)
Body composition			
Fat percentage, mean (SD)	30.0 (±7.6)	29.7 (±1.9)	30.1 (±7.1)
Muscle percentage, mean (SD)	30.0 (±3.9)	30.4 (±4.2)	30.2 (±3.4)
Visceral fat percentage, mean (SD)	11.0 (±3.8)	10.7 (±4.0)	12.2 (±3.3)
SDB indices			
AHI, mean (SD)	13.4 (±10.5)	12.6 (±9.4)	14.5 (±11.7)
ODI, mean (SD)	5.6 (±6.1)	5.4 (±5.7)	6.5 (±6.6)
Desaturation nadir, % (SD)	91.4 (±6.2)	91.8 (±1.3)	91.7 (±1.4)
Saturation <90%, min (SD)	2.2 (±7.0)	2.1 (±7.1)	2.3 (±6.9)
STOP-BANG questionnaire			
Snoring	63 (27.2)	37 (27.6)	26 (26.5)
Tiredness	123 (53.0)	67 (50.0)	56 (57.1)
Observed apnea	41 (17.6)	26 (19.4)	15 (15.3)
High blood pressure	106 (45.7)	54 (40.3)	52 (53.1)
BMI >35 kg/m^2	0 (0)	0 (0)	0 (0)
Age >50 years	214 (92.2)	119 (88.8)	95 (96.9)
Neck circumference >40 cm	68 (29.3)	31 (21.1)	37 (37.6)
Male sex	144 (62.1)	78 (58.2)	66 (67.3)

BMI: body mass index; METS: Metabolic Equivalent of Task Score; ASA-classification: American Society of Anesthesiologists physical status classification; PVI: pulmonary vein isolation; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; SBD: sleep breathing disorder; AHI: apnea hypopnea index; ODI: oxygen desaturation index; SD: standard deviation.

Outcomes and predictive factors

The incidence of respiratory complications during CA in patients with AF under PSA was 42.2%, with 0.4% classified as minor, 35.0% as intermediate, and 15.1% as severe. An oropharyngeal airway (Guedel) was required in 63 patients (27.2%), whereas a nasopharyngeal airway (Shiley™) was required in 1 patient (0.4%). A non-rebreathing mask was used in 2 (0.9%) cases. In 16 (6.9%) cases high flow oxygen (Optiflow®) was applied. In 3 (1.3%) cases there was a crossover to general anesthesia. A laryngeal mask airway (LMA) was placed 2 (0.9%) times. Endotracheal intubation because of intra-oral bleeding was performed in 1 case (0.4%) (due to intra-oral blood during the procedure). In 13.8% of the cases a hypoxic event (saturation <90% for more than 120 seconds) occurred. AUC_{Desat} was 42 ± 68 seconds % (mean ± SD) in a range 4-360. The outlier was 360 seconds % during the Covid pandemic. This patient had respiratory complaints 2 weeks prior the procedure (not confirmed as a Covid infection). The difference in lowest saturation was 3.9% (90.1% ± 4.4 vs 86.2% ± 6.9). The lowest saturation was not significantly decreased in patients with respiratory complications. There is no significant difference in duration of desaturation. An overview of the respiratory complications is provided in figure 2. In several cases more than 1 respiratory complication occurred during PSA.

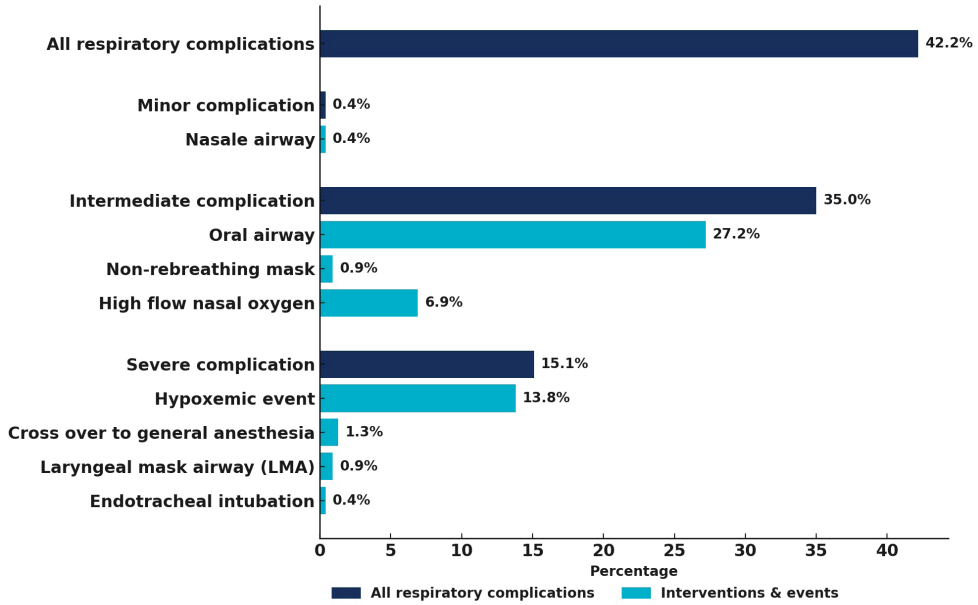


Fig. 2. Respiratory complications, with subcategories (minor,intermediate,severe) and interventions in percentages. In several cases more than one respiratory complication occurred.

Supplemental table 2 (see page 54) shows the results of the univariable logistic regression analysis. The presence of a longer sedation duration was associated with respiratory complications. Also, patient factors as a higher percentage of visceral fat, a higher BMI, an age >50 years and a neck circumference >40 cm resulted in a significant increase of respiratory complications. OSAS in the medical history, COPD, apnea hypopnea index (AHI) and oxygen desaturation index (ODI) did not have a significant effect on respiratory complications. Neither age, activity level, ASA classification or congestive heart failure affected the incidence of respiratory complications. Mean BIS values were similar between cryoballoon and radiofrequency ablation (61.2±14.4 vs. 62.6±12.1; range 28–95 vs. 38–95). In logistic regression analysis, BIS values were not associated with respiratory complications (OR 1.00, 95% CI 0.98–1.02; $p = 0.79$), whereas RF ablation remained an independent predictor (OR 1.74, 95% CI 1.02–3.00; $p = 0.04$). Anesthesia duration was significantly shorter in the cryoballoon ablation group compared with radiofrequency ablation (95.7±20.9 vs. 181.5±40.7 minutes; mean difference 85.9 minutes, 95% CI 77.7–94.0; $p < 0.001$). The incidence of respiratory complications was lower with cryoballoon ablation than with radiofrequency (34.7% vs. 48.1%; OR 1.75, 95% CI 1.02–3.01; $p = 0.04$). Within the radiofrequency group, patients who developed respiratory complications had longer anesthesia duration compared with those without (188.1 ± 45.9 vs. 175.4 ± 34.5 minutes; OR 1.01, 95% CI 1.00–1.02). Supplemental table 3 (see page 56) shows the univariable logistic regression analyses if we exclude the use of nasal or oral airway as a complication. BMI, visceral fat percentage and duration of sedation remain predictive factors for respi-

ratory complications. Table 2 shows the results of the multivariable logistic regression analysis. The AUROC of the model with all retained variables was 0.72, 95% CI: 0.65-0.78.

Table 2 Multivariable logistic regression analysis

Variable	OR	95% C.I.	p-value
Tiredness	0.61	0.33-1.09	0.09
Age >50 years	0.20	0.04-0.70	0.02
Neck circumference >40 cm	0.65	0.34-1.25	0.19
Visceral fat percentage	1.08	0.99-1.17	0.07
AHI	1.02	0.99-1.05	0.15
OSAS (medical history)	0.24	0.07-0.70	0.01
COPD	0.25	0.05-0.94	0.05
Anesthesia duration	1.01	1.00-1.01	0.02

All factors with a p-value of < 0.30 were used for the multiple logistic regression analyses. The model should be sensitive for factors associated with respiratory complications. AUROC 0.72, 95% CI: 0.65-0.78.

DISCUSSION

In this explorative study, the incidence of respiratory complications during CA in patients with AF under PSA was 42.2%. This high incidence of respiratory complications occurred despite a careful pre-screening protocol at the outpatient clinic. Patients with the clinical diagnosis Obstructive Sleep Apnea (OSA) prior or high risk based on STOP-Bang questionnaire were excluded for PSA based on the pre-anesthesia assessment. For the participants with a medical background of obstructive sleep apnea (OSA) who took part in the study, it was documented that this condition was no longer a current medical issue (e.g., as a result of weight loss or surgical intervention). The relatively low prevalence of previously diagnosed OSA in our study population (9.1%) likely reflects the exclusion criteria applied during patient selection for PSA in AF ablations. Certain patients with a previously established OSA diagnosis may have been identified through SDB testing prior to the baseline visit. Among patients without previously diagnosed OSA, 67 (28.9%) were identified with moderate to severe SDB (AHI >15). Since this prevalence is lower than would be expected in a general AF population, the incidence of respiratory complications would very likely be higher in an unselected AF cohort, and our findings may therefore underestimate the true complication rates. Possibly, the strategies currently used during pre-anesthesia assessments may work in the general population, but may show some limitations in patients with AF, which may explain the high incidence of respiratory complications in our study. Previous studies have shown that the STOP-BANG questionnaire is not very accurate in detecting SDB in patients with AF.[10, 25] Additionally, the VIRTUAL-SAFARI study showed that SDB is largely underdiagnosed in patients scheduled for AF ablation.[12] As a questionnaire-based pre-selection for SDB screening remains challenging in this population.[12] Interestingly, only 15 (6.5%) of the patients had severe SDB (AHI >30 dur-

ing remote sleep test). The majority of patients with severe SDB (53% of 15 patients) had respiratory complications. Based on these findings, we continue to consider severe SDB a contraindication for deep sedation during CA for AF. In our experience, SDB screening was frequently incomplete at the time of the pre-anesthesia evaluation. This suggests a need to revise the current workflow, particularly in high-risk patients. Routine sleep testing prior to the pre-anesthesia assessment may help optimize patient selection for procedural sedation. Ideally, the anesthesia assessment should be scheduled only after completion of SDB screening in patients with a high clinical suspicion of SDB.

The incidence of respiratory complications found in our study seems substantially higher than those reported by van Schaik et al., who reported an overall incidence of respiratory complications of 29%.[17] Both studies used a retrospective observational design and were performed in a tertiary university hospital, with sedation services provided by the Department of Anesthesiology. There are some important differences between these studies related to procedures and patient selection. For optimal comparison of the data of our study and that of van Schaik it is best to focus on data related to those procedures performed in the heart catheterization room.[15] In the heart catheterization room 1393 procedures were performed under moderate to deep sedation. Then, however, still differences in outcome can be noted: an incidence of complications in our study of 42% and that reported by van Schaik of 54%.[15] It needs to be emphasized that the respiratory complications described in the study by van Schaik et al. were all hypoxemic events (defined as a peripheral saturation (SpO_2) < 90% lasting for at least two minutes).[15] On the other hand, in our study the incidence of hypoxemic events was 13.8%. There are some possible explanations for the observed difference. First, and maybe the most important difference might be sedation procedure related: due to the fact that in our study an oral airway was regularly used (27.6%) whereas in van Schaik 's study this was only very incidentally used (0.1%). The use of an oral airway is considered to have no negative effects, it is, furthermore, very well accepted by the patient and considered only a minor complication.[23] Another difference, related to patient selection is noted between van Schaik 's study and our study, is the BMI-range. In our study BMI was 27.0 ± 3.0 (mean ± SD) with a range 20-33 whereas a BMI of 26.0 ± 5.0 (mean ± SD) with a range 13-60 was reported by van Schaik et al.[15]

The incidence of respiratory complications is high although the risk of potential harm appears low. The clinical effects of short term hypoxemia are unknown. In theory severe hypoxemia can lead to anaerobic metabolism and circulatory changes, resulting in ischemia.[16] A negative impact on neurobehavioral tests 24 hours after surgery in patients that showed desaturations on cerebral level is reported.[26] AUC_{Desat} is an end point for assessment of risk of adverse clinical outcomes in clinical sedation studies.[24] All hypoxemic events were mild desaturations with AUC_{Desat} <150 (seconds %) with the exception of 1 case of moderate desaturation (AUC_{Desat} <900 seconds %). Comparison of our data

related to the presence of hypoxemic events with other studies is limited because the AUC_{Desat} is often not specifically described. It should furthermore be acknowledged that AUC_{Desat} does not differentiate between short but severe desaturations and prolonged yet mild events, and this implies distinct physiological and clinical consequences. Given the potential for severe hypoxemia to cause harm, even in isolated or transient episodes, it remains essential to implement strategies that prevent desaturation, ensure adequate oxygen delivery, and minimize the risk of long-term adverse outcomes. Further research is warranted to define clinically meaningful thresholds and to better understand the long-term implications of intra-procedural hypoxemia.

The identification of patient-related factors, in particular in view of respiratory complications during moderate or deep sedation, is known to be very limited. We were able to identify several new predictive factors which are associated with the development of per-procedural respiratory complications during CA in patients with AF under PSA. An age >50 years, the diagnoses OSAS and COPD in the medical history are predictive factors for development of per-procedural respiratory complications. Also neck circumference >40 cm and visceral fat percentage are predictive factors. The factor tiredness from the STOP-BANG questionnaire and AHI are patient characteristics which are closely related with the development of respiratory complications. The duration of sedation is an important predictive procedure related factor of influence. Cryoballoon ablation was associated with significantly shorter anesthesia duration and a lower incidence of respiratory complications compared with radiofrequency ablation. Depth of sedation as assessed by BIS monitoring, was comparable between the cryoballoon and radiofrequency groups and was not associated with the occurrence of respiratory complications. This suggests that it is not the absolute depth of sedation that drives respiratory risk, but rather the prolonged duration of deep sedation. Accordingly, longer anesthesia exposure in the radiofrequency group appears to be a key procedural factor contributing to the higher incidence of respiratory complications during PSA. We checked whether the predictive factors remain the same when we would exclude the use of an oral airway as a complication. BMI, visceral fat percentage and duration of sedation remain predictive factors (Supplemental Table 2).

Our study shows that neck circumference and visceral fat percentage are risk factors for respiratory complications. Measuring the neck circumference is an easy measurement that does not require advanced technology. In our study patients reported their neck circumference. Neck circumference and visceral fat percentage are factors closely related to the BMI and this should be taken into account. The latter suggest that these patient characteristics correlate with body composition. It is more likely that patterns of body fat distribution influence the function of the respiratory system via the direct mechanical effect of fat accumulation in the chest and abdominal region.

COPD is recognized as a risk factor for AF. A COPD care pathway can be successfully embedded within an existing AF outpatient clinic infrastructure, using (micro)spirometry and remote analysis of results. Although one in five patients showed results suggestive of an underlying chronic respiratory disease, only 62% of these patients opted for a referral.[27] From the patient's perspective this is understandable given the significant overlap in the symptomatology of COPD and AF. However, the latter also implies that a subset of patients undergoing CA for AF may have been undiagnosed and untreated for COPD.

Strengths and Limitations: The strength of our study is the availability of prospective data from the ISOLATION cohort study and ISOLATION 'light' registry. In these datasets a major amount of patient factors were registered. Therefore we were able to identify and exclude risk factor for respiratory complications. Especially all factors related to SDB as all patients had remote sleep test for SDB and most of them filled out the STOP-BANG questionnaire. By combining data from the ISOLATION baseline characteristics we were able to identify new risk factors. Another strength of our study is the fact that the PSA population of AF patients for CA is basically a rather homogeneous population. Limitations of this study include a selection bias because of the institutional pre-anesthesia assessment and the retrospective study design. Although the data of prospective data from the ISOLATION cohort study and ISOLATION 'light' registry are used, the anesthesia data are collected retrospectively. An age >50 years is identified as a risk factor for respiratory complications. However this is 92.2% of the patients in our population. It might be possible that due to the small group size in the age group <50 years other factors due to coincidence have been underexposed. Unfortunately the group of participants under 50 years of age is too small to determine a cut-off point at a lower age. Due to the exclusion criteria for PSA during CA a selection bias is part of our study. For instance patients with a BMI > 32 are not included in this study. As a result of the local selection criteria we were unable to determine a BMI-threshold for PSA during CA. The type, dosage, or combination of short-acting sedatives and analgesics used may have influenced the occurrence of respiratory complications. In this observational study, no restrictions were imposed on the choice or administration of these medications. As a result, there was considerable variability in sedation regimens, which reflects the pragmatic, real-world nature of our dataset. Due to the retrospective design of the study the total dose of sedative and analgesic agents is not available. However, continuous infusion was used to minimize the risk of overdose. Furthermore, all sedatives and analgesics were titrated to clinical effect, which makes fixed-dose reporting difficult to interpret due to substantial interindividual variability in pharmacodynamic response. Finally, our multivariable model yielded an area under the receiver operating characteristic curve (AUROC) of 0.72, indicating acceptable, but not strong, predictive accuracy. This moderate performance underscores the limitations of clinical variables alone in capturing the multifactorial risk for respiratory complications during sedation. Future research should improve model performance and support more individualized risk stratification.

Looking forward, it remains to be seen how these findings will apply to emerging ablation technologies, particularly pulsed field ablation (PFA). Especially during single-shot PFA applications direct diaphragmatic or phrenic nerve stimulation may transiently disrupt breathing patterns. In addition, the sensory response to PFA energy appears more intense than that of cryoballoon or radiofrequency ablation, often necessitating deeper sedation levels. These observations are currently anecdotal and beyond the scope of the present study. They emphasize the need for future research into sedation strategies and respiratory safety in the context of PFA.

CONCLUSION

First, the incidence of respiratory complications during CA in patients with AF under PSA is 42.2% and thus relatively high. Second, the following predictive factors were identified for development of per-procedural respiratory complications in these patients: a neck circumference >40 cm, visceral fat percentage, the factor tiredness from the STOP-BANG questionnaire, AHI, the diagnoses OSAS and COPD in the medical history. Although age above 50 years is generally associated with an increased risk of respiratory complications, this threshold demonstrated limited discriminative value in the present cohort, as the vast majority of patients undergoing AF ablation exceeded it. An important procedure related predictive factor is the duration of the PSA. Prospective studies are needed to test, whether a refinement of pre-anesthesia assessment can help to better identify patients at high risk of experiencing respiratory complications during CA procedures under PSA.

SUPPLEMENTAL TABLES

Supplemental Table 1 Additional baseline characteristics of all procedures, without respiratory complications group and with respiratory complications group. Values are number (percentages) unless stated otherwise.

Characteristic	Total	No complications	Respiratory complications
	n=232	n=134	n=98
Cerebrovascular disease	16 (6.9)	11 (8.2)	5 (5.1)
Peripheral vascular disease	20 (8.6)	12 (9.0)	8 (8.2)
Dyslipidemia	42 (18.1)	17 (12.7)	25 (25.5)
Decreased kidney function	9 (3.9)	4 (3.0)	5 (5.1)
Smoking status			
Active	43 (18.5)	23 (17.2)	20 (20.4)
Previous <1 year	1 (0.4)	1 (0.7)	0 (0)
Previous >1 year	38 (16.4)	23 (17.2)	15 (15.3)
Never	150 (64.7)	87 (64.9)	63 (64.3)
Alcohol consumption			
None	55 (23.7)	34 (25.4)	21 (21.4)
<5 units/week	116 (50.0)	66 (49.3)	50 (51.0)
5–15 units/week	50 (21.6)	27 (20.1)	23 (23.5)
>15 units/week	11 (4.7)	7 (5.2)	4 (4.1)

Supplemental Table 2 Univariable logistic regression analysis.

Variable		OR	95% CI	P-value
Sex	Male	1.48	0.86-2.57	0.16
Age		1.01	0.98-1.04	0.50
BMI		1.12	1.03-1.23	0.01
Activity level		1.49	0.46-5.73	0.52
ASA classification	ASA2	0.68	0.03-17.39	0.79
	ASA3	1.05	0.04-28.22	0.97
Atrial fibrillation	Persistent	1.52	0.87-2.67	0.14
CAD				
Cerebrovascular disease	TIA	0.44	0.06-1.98	0.33
	Ischemic stroke	1.03	0.20-4.76	0.97
	Hemorrhagic stroke	6.4e-07	u.e	0.99
Congestive heart failure		0.90	0.38-2.08	0.81
Diabetes mellitus		1.61	0.56-4.75	0.37
Decreased kidney function		1.75	0.45-7.22	0.41
COPD		0.49	0.10-1.52	0.22
OSAS	Medical history	0.40	0.13-1.05	0.08

Variable		OR	95% CI	P-value
Smoking	Actively	1.20	0.60-2.37	0.60
	Previously (<1 year)	6.5e-07	u.e.	0.99
	Previously (>1 year)	9.0e-01	0.43-1.85	0.78
Alcohol consumption	<5 units/week	1.23	0.64-2.39	0.54
	5-15 units/week	1.38	0.63-3.02	0.42
	>15 units/week	0.93	0.22-3.45	0.91
SBD	AHI	1.02	0.96-1.01	0.18
	ODI	1.03	0.99-1.07	0.20
	Desat nadirs	0.94	0.78-1.01	0.46
	Saturation <90% (minutes	1.03	0.88-1.20	0.72
STOP-BANG	Snoring	0.95	0.52-1.70	0.86
	Tiredness	1.33	0.79-2.26	0.28
	Observed apneas	0.75	0.36-1.49	0.42
	High blood pressure	1.68	0.99-2.84	0.05
	BMI>35kg/m2	-	-	-
	Age >50 years	3.99	1.27-17.6	0.03
	Neck circumference >40 cm	2.01	1.14-3.59	0.02
	Male	1.48	0.86-2.57	0.16
Fatpercentage		1.01	0.97-1.04	0.71
Muscle percentage		0.98	0.92-1.05	0.64
Visceral fat percentage		1.11	1.04-1.20	0.004
Rest metabolism		1.00	1.00-1.00	0.01
LVEF		1.01	0.97-1.05	0.61
NTproBNP		1.00	0.99-1.01	0.78
GFR		1.00	0.98-1.02	0.92
Anesthesia duration		1.01	0.99-1.00	0.006

BMI: body mass index; METS: Metabolic Equivalent of Task Score; ASA-classification: American Society of Anesthesiologists physical status classification; PVI: pulmonary vein isolation; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; SBD: sleep breathing disorder; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; LVEF: left ventricular ejection fraction; GFR: glomerular filtration rate; OR: Odds Ratio; SD: standard deviation; u.e: unable to estimate.

Supplemental Table 3 Per-procedural respiratory complications were defined if a non-rebreathing mask or high flow oxygen was indicated, or a hypoxemic event (a peripheral saturation <90% lasting for at least 120 seconds) or a conversion to general anesthesia with laryngeal mask airway (LMA) or tracheal intubation.

Variable		OR	95% CI	P-value
Sex	Male	1.78	0.90-3.71	0.11
Age		1.01	0.98-1.05	0.44
BMI		1.16	1.04-1.31	0.009
Activity level		u.e	u.e	0.99
ASA classification	ASA2	u.e	u.e	0.99
	ASA3	u.e	u.e	0.99
Atrial fibrillation	Persistent	1.03	0.51-2.01	0.94
CAD		1.45	0.45-4.04	0.50
Cerebrovascular disease	TIA	1.33	0.19-5.98	0.74
	Ischemic stroke	0.65	0.03-3.93	0.69
	Hemorrhagic stroke	u.e	u.e	0.99
Congestive heart failure		1.28	0.44-3.24	0.62
Diabetes mellitus		0.59	0.09-2.23	0.50
Decreased kidney function		1.13	0.16-4.87	0.88
COPD		0.34	0.02-1.84	0.31
OSAS	Medical history	u.e	u.e.	0.99
Smoking	Actively	1.76	0.78-3.82	0.16
	Previously (<1 year)	u.e	u.e.	0.99
	Previously (>1 year)	1.21	0.48-2.85	0.67
Alcohol consumption	<5 units/week	2.08	0.88-5.50	0.11
	5-15 units/week	2.17	0.79-6.32	0.14
	>15 units/week	0.69	0.03-4.50	0.74
SBD	AHI	1.00	0.97-1.03	0.96
	ODI	1.00	0.94-1.05	0.91
	Desat nadirs	0.76	0.60-0.97	0.02
	Saturation <90% (minutes)	1.05	0.87-1.22	0.53
STOP-BANG	Snoring	0.67	0.30-1.40	0.31
	Tiredness	0.91	0.48-1.73	0.76
	Observed apneas	0.78	0.30-1.79	0.58
	High blood pressure	1.81	0.95-3.50	0.07
	BMI>35kg/m2	-	-	-
	Age >50 years	u.e.	u.e.	0.99
	Neck circumference >40 cm	1.88	0.96-3.66	0.06
	Male	1.78	0.90-3.71	0.11

Variable	OR	95% CI	P-value
Fatpercentage	1.02	0.96-1.06	0.44
Muscle percentage	0.96	0.89-1.04	0.35
Visceral fat percentage	1.16	1.07-1.28	0.0006
Rest metabolism	1.00	1.00-1.00	0.06
LVEF	1.00	0.96-1.05	0.96
NTproBNP	1.00	0.99-1.01	0.71
GFR	1.01	0.98-1.04	0.48
Anesthesia duration	1.01	0.99-1.00	0.05

BMI: body mass index; METS: Metabolic Equivalent of Task Score; ASA-classification: American Society of Anesthesiologists physical status classification; PVI: pulmonary vein isolation; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; SBD: sleep breathing disorder; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; LVEF: left ventricular ejection fraction; GFR: glomerular filtration rate; OR: Odds Ratio; SD: standard deviation; u.e: unable to estimate.

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4

High flow nasal cannula versus standard low flow nasal cannula during deep sedation in patients undergoing radiofrequency atrial fibrillation catheter ablation: A single center randomized controlled trial.

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ABSTRACT

Background: To our knowledge there are few trials studying the effect of high flow nasal cannula (HFNC) during deep sedation. Our hypothesis is that high flow nasal cannula (HFNC) will prevent hypoxemia and desaturation as compared to low flow nasal cannula (LFNC) during prolonged deep sedation in patients with atrial fibrillation undergoing radiofrequency catheter ablation (RFCA).

Methods: A single center, randomized controlled trial with HFNC as intervention and LFNC as control group. A total of 94 adult patients per group undergoing elective radiofrequency atrial fibrillation catheter ablation under deep sedation will be included. The primary outcome is the lowest oxygen saturation (SpO_2). Secondary outcomes: The duration of lowest SpO_2, cross-over from oxygen therapy in both directions, incidence of SpO_2 below 90% > 60 seconds, adverse sedation events, adverse effects of HFNC, mean CO_2, peak CO_2, patients' experience with oxygen therapy. The study will take place during the 2-day admission period for RFCA. Patients can fill out their questionnaires in the first week after treatment.

Discussion: HFNC is increasingly used as a technique for oxygen delivery in procedural sedation and analgesia. We hypothesize that HFNC is superior to the standard treatment LFNC in patients under deep sedation with respect to the incidence of desaturation. To our knowledge there are no adequately powered clinical trial studies on the effects of HFNC in prolonged deep sedation.

Trial registration: ClinicalTrials.gov, NCT04842253. Registered on 04 April 2021

INTRODUCTION

Background and rationale

A decrease in oxygen saturation (SpO_2) may occur in patients during deep sedation resulting in an elevated risk for perioperative adverse events including hypoxemia.[1, 2, 3] The use of pulse oximetry is important as it can detect hypoxemia early.[4] The incidence of hypoxemia, defined as SpO_2 below 90%, is approximately 168 per 1000 patients in a general procedural sedation and analgesia population.[5] The clinical significance of episodic desaturations resulting in hypoxemia remains debatable. However, many perioperative incidents are often short-term and limited in nature, but still a predictor of a serious complication resulting in permanent injury.[6] Peri-interventional incidents, e.g. hypoxemia, may be associated with procedure-related and procedure-unrelated complications due to unstable sedation and patient movement potentially resulting in permanent injury. Using HFNC during deep sedation is a non-harmful way to prevent patients from desaturations and hypoxemia and may reduce the risk of perioperative events.

High flow nasal cannula (HFNC) is increasingly used as a technique for oxygen delivery in patients undergoing procedural sedation and analgesia (PSA).[7] Humidified HFNC therapy is a form of non-invasive respiratory support. The HFNC technique permits flows of up to 70 L/min of humidified gas to be delivered to the lungs via a nasal cannula. With the use of HFNC the amount of oxygen can be titrated more precisely in contrast to low flow nasal cannula (LFNC).[8] Delivering oxygen at high flow rates has multiple physiological effects that may be beneficial for patients undergoing PSA. First, high inspiratory flow during HFNC increases upper airway pressure resulting in a reduced incidence of upper airway obstruction during sedation.[9] Second, HFNC improves functional residual capacity potentially reducing ventilation-perfusion mismatch.[10] Third, humidification improves mucociliary clearance of secretions which reduces work of breathing.[11] HFNC may prevent the peri-procedural complications typically associated with LFNC.

Several randomized controlled trials have been conducted to test the physiological effects of HFNC.[8, 9, 12, 13, 14, 15] The randomized controlled trials were conducted across a variety of critical care populations including patients with acute respiratory failure[13, 14] or after major surgery.[15, 16] However, adequately powered trials of HFNC in patients undergoing PSA are lacking.

Until now, only three small randomized controlled trials of HFNC in patients undergoing PSA have been published. Sago et al. randomized 30 patients undergoing dental surgery into three treatment groups.[9] Patients received a fraction of inspired oxygen concentration of 40% either via HFNC at a rate of 50 L/min and 30 L/min, or via a standard nasal cannula at 4 L/min. Participants randomized to the HFNC groups had higher blood oxygen levels recorded than the low flow group. Participants who received a flow rate

higher than 30 liters per minute under PSA maintained upper airway patency. Douglas et al. randomized 60 participants undergoing bronchoscopy to receive HFNC at 50 L/min with 100% oxygen or to receive 10-15 liters oxygen per minute with a face mask.[12] Desaturation occurred in 4 out of 30 patients allocated to the HFNC group as compared to 10 out of 30 allocated to the standard oxygen group. No statistical difference for the primary outcome (defined as SpO_2< 90%) was found between the treatment groups. Riccio et al. included 59 morbidly obese patients undergoing colonoscopy to receive the same fraction of inspired oxygen concentration of 36% either via HFNO at a flow rate of 60 liters per minute or via nasal cannula at 4 liters per minute.[17] No difference in oxygen saturation and the incidence of desaturation periods was reported. From these studies, it can be concluded that HFNC per se did not result in a substantially improved oxygen status. However, it needs to be noted that this conclusion is based on short procedures requiring PSA with a duration of less than 75 min.

In a number of indications, PSA is applied for longer periods. One of these indications is radiofrequency catheter ablation (RFCA) in AF patients with a duration of PSA of more than 3 hours. AF ablation has become one of the most common procedures in the electrophysiology lab with rapidly increasing volumes. A recent survey by the European Heart Rhythm Association (EHRA) shows, that in 2019 32% of all procedures are performed under conscious sedation and 27,5% of all procedures under deep sedation.[18] The most commonly used hypnotic drugs were propofol and midazolam, whereas the most commonly used opioids were remifentanil and fentanyl.[18] The potential positive effects of HFNC in this growing patient population is unclear.

In the Maastricht University Center patients undergoing RFCA are managed by deep sedation with a combination of low dose remifentanil and propofol, as patient movement may result in shifts of the electro-anatomical maps required for the navigation of the ablation catheter and might cause serious complications including air embolisms and cardiac tamponade. Deep sedation is associated with an increased incidence of upper airway collapsibility and disturbed central respiratory drive[19], which results in forced breathing movements during obstructive respiratory events resulting in pronounced intrathoracic pressure swings leading to electro-anatomical map shifts. Additionally, if LFNC is used (standard of care) a sudden drop of oxygen saturation (SpO_2<90%) occurs in 1.5% of patients.[20] Increased pressure in the upper airway during HFNC might reduce upper airway collapsibility during sedation[21] and facilitates active gas exchange during times of hypoventilation[22] allowing stable and long PSA procedures**.** Additionally, HFNC may enhance carbon dioxide clearance by an entrained and highly turbulent supraglottic flow vortices created by high flow nasal oxygen and cardiogenic oscillations.[22]

METHODS

Objectives

The aim of this study is to test the hypothesis that oxygen supplementation via HFNC as compared to LFNC can prevent hypoxemia and desaturation in patients with atrial fibrillation undergoing RFCA and prolonged deep sedation of 3 hours and more.

Trial design

This study is a single center, randomized controlled trial and is designed to evaluate the superiority of HFNC compared with LFNC. Based on a power-calculation it is aimed to include 188 participants. The allocation ratio is 1:1. Patients will be randomized to the intervention group (HFNC during deep sedation) or the control group (LFNC during deep sedation). Figure 1 summarizes the study design.

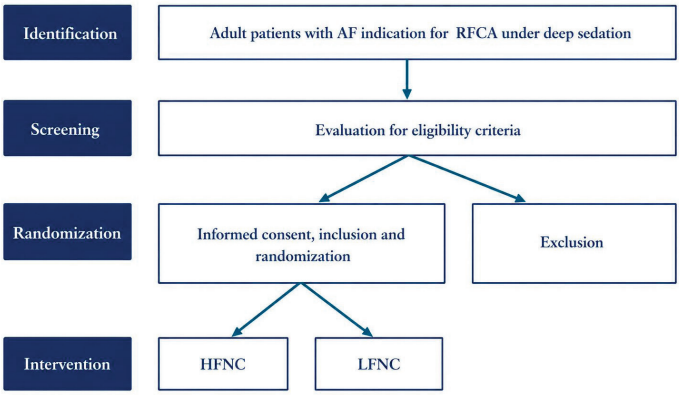


Fig.1 Flow diagram of the study design

Participants

Study setting

Participants will be recruited at Maastricht University Medical Center, Maastricht, the Netherlands. Treatment of participants will take place in the same institution.

Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria: Adult (age > 18 years), undergoing an elective RFCA for atrial fibrillation in the MUMC$^+$ Cardiac Catheter Labs, under deep sedation administered by a physician assistant (PA) anesthesiology or nurse anesthetist (NA). In this study deep sedation is performed without a protected airway / mechanical ventilation.

Exclusion criteria

Patients will be excluded from the study if they meet one or more of the following criteria:

- Age < 18 years
- Incapacitated patients or inability to provide informed consent
- Body mass index (BMI) > 32 kg/m^2
- Diagnosed sleep apnea syndrome (SAS)
- Chronic obstructive pulmonary disease (COPD):
    - o GOLD stage IV, or
    - o GOLD stage III with frequent or recent exacerbations
- Diagnosed pulmonary or cardiac condition requiring chronic oxygen therapy
- Complete nasal obstruction
- Active epistaxis
- Untreated (pre-existing) pneumothorax
- Recent upper airway surgery
- Recent base of skull fracture
- Anticipated difficult airway
- Active COVID-19 infection

Who will take informed consent?

The patient receives a written information letter and is additionally informed about the study. At the catheter ablation outpatient clinic a physician assistant will obtain the informed consent after preoperative screening. The information about the study is explained and the patient has the opportunity to ask questions about the study. After this, the patient is invited to participate in the study. When the participant gives permission for participation, the informed consent form is signed. Patients will receive a copy.

Additional consent provisions for collection and use of participant data and biological specimens

Participants are informed that with signing the informed consent, they give permission for the research team to share relevant data with regulatory authorities. On the consent form, the participant will be asked if they give permission to store the data for follow-up studies. Participants will also be asked for permission to contact them for future studies. This trial does not involve collecting biological specimens.

Interventions

Explanation for the choice of comparators

We decided to compare HFNC to a control group with LFNC during deep sedation in patients with atrial fibrillation undergoing radiofrequency catheter ablation. LFNC is

standard care during deep sedation.[23] It is expected that HFNC is superior to LFNC during deep sedation.

Intervention description

All randomized patients will receive standard care with regard to medications used for sedation and physiological monitoring or other interventions to support respiratory function that are considered necessary to be initiated during the procedure by the clinicians. Standard care is consistent with the ESA guideline on Procedural Sedation and Analgesia in Adults.[23]

Deep sedation is defined as "A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation". Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate."

The physician assistant (PA) anesthesiology or nurse anesthetist (NA) administers a combination of analgesics and sedatives to target the level of deep sedation. There will be no restrictions of any dose ranges of the different medications used by the PA/NA. The actual doses of medication used will be registered. The PA/NA will record the doses of sedative medications used during procedures. Oxygen therapy is administrated as indicated by randomization. The device used for oxygen supplementation will be different.

For HFNC supplemental oxygen will be given with the Optiflow™ device (Fisher and Paykel Healthcare, Auckland, New Zealand). The Optiflow™ device has a heated breathing tube and chamber, and a nasal cannula will be used. The gas temperature will commence at high settings (37°C) and titrated downwards if the patient complains of irritation. The gas flow rate will be started at 10 liters per minute prior to sedation. The gas flow rate of 10 liters per minute is usually well tolerated by awake patients. The gas flow will be increased after sedation has been administrated to 50 liters per minute. The gas flow can be titrated according to patients' requirements. The flow rate is accommodated according to SpO2. The FiO2 will be set at 40%.

For LFNC supplemental oxygen will be given with Microstream® Smart CapnoLine® O_2. Oxygen supplementation is recommended to start at 5 liters per minute. The flow rate is accommodated according to SpO2. The clinician responsible for the sedation will in case of an upper airway obstruction combine the Microstream® Smart CapnoLine® O_2 with a nasal or oral airway. The use of a nasal or oral Guedel airway is preferred above multiple airway repositioning to protect the clinician against unnecessary exposure to X-rays.

The cardiologic treatment RFCA for atrial fibrillation in combination with the required deep sedation often causes cardiac hemodynamic fluctuations due to changes in heart

rate. A low dose norepinephrine is used to prevent the occurrence of hypotension. The dose of norepinephrine is titrated to prevent hypotension due to arrhythmias. Temporary pacing is also permitted, due to the nature of the procedure. RFCA and deep sedation are part of the usual medical treatment.

Participants will receive oxygen via a nasal cannula.

There will be no invasive procedures performed. There will be no extra diagnostic procedures performed.

Criteria for discontinuing or modifying allocated interventions
Participants in the study will receive the best possible medical care at all times.

Protocol deviations are permitted in the following situations:

- Cross-over from LFNC to HFNC in the event of persistent desaturation, defined as an oxygen saturation (SpO_2) < 90% lasting more than 180 seconds and not improving despite:
    - o airway repositioning,
    - o tactile stimulation,
    - o an increase in supplemental oxygen, or
    - o the use of an oral or nasal Guedel airway.
- Cross-over from HFNC to LFNC, in combination with an oral or nasal airway, in cases of upper airway obstruction due to airway collapse.

Cross-over from HFNC to low flow nasal oxygen is also permitted when the participant is unable to tolerate HFNC because of discomfort.

Strategies to improve adherence to interventions
To improve adherence to the study protocol the physician assistants (PA) anesthesiology and nurse anesthetist (NA) are trained and instructed on the study protocol, use of Optiflow and Sentec Vsign. Data from during sedation will be obtained from the online automatic patient data management system, PDMS.

Relevant concomitant care permitted or prohibited during the trial
Participating in this study will not require alternation to usual care pathways (including use of any medication).

Provisions for post-trial care

The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

Outcomes

Primary outcome

Primary outcome is the lowest SpO_2. During PSA continuous SpO_2 measurements will be recorded using Sentec Digital Monitoring with Vsign 2 sensor. Percentage hemoglobin saturated with oxygen will be measured continuously during the procedures as part of routine clinical practice through the anesthetic monitoring. SpO2 monitoring will be measured by the sensor that is placed on the earlobe and recorded continuously.

Timeframe: The time from the first administration of sedative medication to stopping of the sedative medication (= the end of the procedure).

Measure method: Continuous SpO_2 measurements will be recorded using Sentec Digital Monitoring with Vsign 2 sensor. SpO_2 will be measured by the Vsign sensor that is placed on the earlobe and will be recorded continuously.

Secondary outcomes

The following secondary outcomes will be assessed:

- The duration of the lowest oxygen saturation (SpO_2)
  - o Timeframe: The time from the first administration of sedative medication to stopping of the sedative medication (= the end of the procedure)
  - o Measurement: Duration (in seconds) of the lowest recorded SpO_2.
- Cross-over of oxygen therapy
  - o Timeframe: The time from the first administration of sedative medication to stopping of the sedative medication (= the end of the procedure).
  - o Measurement: Occurrence of cross-over (yes/no).
- Incidence of hypoxemia and desaturation (SpO2 under 90% for > 60 seconds).
  - o Timeframe: The time from the first administration of sedative medication to stopping of the sedative medication (= the end of the procedure).
  - o Measurement: Incidence of SpO_2 < 90% lasting > 60 seconds.
- Area under the curve (AUC) of oxygen desaturation
  - o Defined as the cumulative difference between the 90% SpO_2 threshold and the actual measured SpO_2, summed per second when desaturation persists for more than 60 seconds.

  - Timeframe: The time from the first administration of sedative medication to stopping of the sedative medication (= the end of the procedure)
  - Measurement: Difference between SpO_2 90% (threshold) for > 60 seconds and the actual oxygen saturation summed every second during which the oxygen saturation was below threshold.
- Incidence of adverse sedation events
  - Adverse events will be recorded using the Tracking and Reporting Outcomes of Procedural Sedation (TROOPS) tool.[24]
  - Completion of the tool includes documentation of the adverse event, intervention, outcome, and overall severity.
  - The physician assistant or nurse anesthetist (PA/NA) will complete the tool at the end of the procedure.
- Incidence of adverse effects related to high-flow nasal oxygen
  - Including pressure-related skin injury and epistaxis due to mucosal damage.
  - Skin integrity of the nasal region will be assessed by the PA/NA at the end of the procedure.
  - Observations will be documented in a case report form.
- Patient experience with sedation
  - Assessed using the Iowa Satisfaction with Anesthesia Scale (ISAS), a validated questionnaire that is used to measure patient experience with the sedation during a procedure.[25, 26]
  - Timeframe: Before discharge from hospital (day of treatment +1).
- Mean transcutaneous carbon dioxide ($TcCO_2$)
  - Timeframe: The time from the first administration of sedative medication to stopping of the sedative medication (= the end of the procedure).
  - Measurement: $TcCO_2$ will be continuously measured during the whole procedure using Sentec Digital Monitoring with Vsign 2 sensor. $TcCO_2$ monitoring provides continuous, accurate (mean bias -0.1mmHg) and precise (95 limits of agreements within 6mmHg) estimates of arterial CO_2 when the sensor is placed on the earlobe.
- Peak transcutaneous carbon dioxide ($TcCO_2$)
  - Timeframe: The time from the first administration of sedative medication to stopping of the sedative medication (= the end of the procedure).
  - Measurement: $TcCO_2$ will be continuously measured and recorded.
- Patient-rated comfort of oxygen delivery
  - A 5-point Likert scale will be used to rate the patients' comfort of oxygen delivery. Participants will be asked to rate their perceived overall comfort with the oxygen delivery device. A 5-point Likert scale is used with ratings of "very uncomfortable", "uncomfortable", "neutral", "comfortable", "very comfortable".[27, 28]
  - Timeframe: Before discharge from hospital (day of treatment +1)

- PA/NA-rated difficulty of maintaining oxygenation
  - o A 5-point Likert scale will be used to rate the PA/NA-rated difficulty maintaining oxygenation status (25, 26). The AC will be asked to rate their perceived level of difficulty using a 5-point Likert scale with ratings of "very difficult", "difficult", "neutral", "easy", "very easy".[27, 28]
  - o If rated very difficult or difficult, the PA/NA will specify the reason.
  - o Timeframe: As soon as possible after the end of the procedure.
  - o Measurement: PA/NA rating of difficulty maintaining oxygenation status during the procedure using a 5-point Likert scale.
- PA/NA-rated user-friendliness of the oxygen delivery device
  - o A 5-point Likert scale will be used to rate the user-friendliness of the oxygen delivery device (by PA/NA).[25, 26] The AC will rate their perceived level of difficulty of maintaining oxygenation using a 5-point Likert scale with ratings of "very difficult", "difficult", "neutral", "easy", "very easy". If rated "very difficult" or "difficult" the PA/NA specifies their answer.[27, 28]
  - o Timeframe: As soon as possible after the end of the procedure.
  - o Measurement: PA/NA rating of user-friendliness of the oxygen delivery device during the procedure using a 5-point Likert scale.
- Cardiologist-rated satisfaction with catheter stabilization in relation to sedation
  - o The cardiologists will rate their perceived level of satisfaction with sedation using a 5-point Likert scale with rating of "very unsatisfied", "unsatisfied", "neutral", "satisfied", "very satisfied".[27, 28]
  - o If rated unsatisfied or very unsatisfied, the cardiologist will specify the reason.
  - o Timeframe: As soon as possible after the end of the procedure.
  - o Measurement: Satisfaction of cardiologists with sedation-related catheter stability using a 5-point Likert scale.

Participant timeline

Participant timeline is summarized in SPIRIT (Fig. 2).

STUDY PERIOD	ENROLMENT		INTERVENTIONS			FOLLOW-UP	
	Screening	Pre-procedure[a]	During procedure	Recovery	Discharge	30 days (±7 days)	90 days (±14 days)
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Demographics		X					
INTERVENTIONS							
HFNC or LFNC (as allocated)			X				
ASSESSMENTS							
Medical history		X					
Baseline vital signs[b]		X					
Procedural data			X				
Primary outcome (hypoxemic events)			X				
Secondary outcomes[c]			X	X	X		
Adverse events			X	X	X	X	X
Readmissions						X	X

[a] Within 24 hours before the procedure.
[b] Including respiratory rate, SpO_2 and blood pressure.
[c] Including airway interventions, conversion to general anesthesia, lowest SpO_2, duration of lowest SpO_2.

Fig. 2 SPIRIT study schedule of enrolment, interventions and assessments

Sample size

The sample size in this prospective study was calculated according to a similar study with the mean lowest SpO2 95.2% (LFNC) and 99.3% (HFNC), with a standard deviation of 0.1 respectively in two different oxygen therapies.[9] Please note that this sample size is, although based on a similar study which compared the HFNC vs LFNC, also based on a different indication and with use of shorter (<75 min) duration of treatment.[9] To achieve 80% statistical power with α error rate of 0.05, the number of patients was calculated to be 94 for each group. An online statistical calculator, Statulator, was used to calculate the sample size for comparing two independent means.

Recruitment

The patient will be informed by the cardiologist about the indication for a RFCA treatment during an outpatient clinic visit at the cardiology department. The patient is also informed that treatment will be under deep sedation or general anesthesia. During this consultation, the patient is asked whether he/she may be approached about current studies. Each patient who indicates to be open to participate in current studies will receive a patient information letter and will be informed by phone about the study aims and risks.

Assignment of interventions: allocation

Sequence generation

The allocation of participants to groups will be randomized using computer-randomized allocations (data management system used: Castor). Sequence generation will be performed in blocks of 2,4,6 stratified by gender.

Concealment mechanism

Allocation concealment will be guaranteed with sealed opaque envelopes.

Implementation

The allocation sequence will be generated by 2 members of the research team. After screening for eligibility, the patients can be allocated. The patients will be allocated on the day of treatment. The assigned allocation by the enrolling will be communicated to the physician assistant (PA)/nurse anesthetist (NA) using sealed envelopes. The PA/NA performs the treatment which is assigned to the participant.

Assignment of interventions: Blinding

Who will be blinded

Patients or personnel involved in the trial cannot be blinded to the treatment conditions due to the nature of the intervention. The outcome measurements are objective and are online registered in an automatic patient data management system, PDMS. Only data analysts will be blinded.

Procedure for unblinding if needed

The design is open label with only data analysts being blinded therefore unblinding will not occur.

Data collection and management

Plans for assessment and collection of outcomes

Baseline characteristics of the participants will be collected. Data such as age, gender, height, weight, medical history and ASA classification, will be obtained from the medical record. Data from during sedation such as heart rate, blood pressure, bispectral index (BIS), duration of PSA, duration of procedure, will be obtained from the anesthesia record (online automatic patient data management system, PDMS). The ISAS questionnaires is a validated questionnaire that measures patient experience with monitored anesthesia care. Patients respond to eleven statements (e.g. I felt pain) by placing a six-choice vertical response column (e.g. "disagree, moderate").

Plans to promote participant retention and complete follow-up

Patients will receive an email after a week if they did not respond to the questionnaire invitation. All other data are recorded during admission.

Data management

Data management system Castor will be used for data storage and the eCRFs. All research data is stored encrypted in the database so the privacy of the participants is ensured. Members of the research team will have access to the source documents with personally identifiable information. All patients will receive a Castor ID. This Castor ID is composed of any numbers of figures, not based on age, date of birth, name or gender (e.g. 000001, 000002, 000003). The key to the code is safeguarded by the research team in the source document. A monitor and national supervisory authorities e.g. IGJ can access the data to control the research team. The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet AVG, UAVG).

Confidentiality

The key to the code is safeguarded by the research team in the source document. Without authorization one cannot access the source document. Only the research team has authorization to access the source document with personally identifiable information.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

Not applicable because there are no biological specimens in this study.

Statistical methods

Statistical methods for primary and secondary outcomes

Primary outcome

The primary outcome parameter is the lowest SpO2. SpO2 is a continuous variable and will be presented as mean and standard deviation (SD). Univariable between-group analysis using the independent-samples t-test will be performed. To adjust for potentially confounding variables we will perform multiple linear regression analysis. Covariates will be age, gender, BMI, ASA classification, duration of RFCA procedure, hypotension and BIS. We will impute missing data using multiple imputation with fully conditional specification. The number of imputations will be set to the percentage of incomplete records. All analyses will be performed according to the intention-to-treat principle. All participants who are randomized are included in the statistical analysis and analyzed according to the group originally assigned to, regardless of the treatment received.

Secondary outcome

Cross over of therapy is a binary categorical variable. We will compare the difference in cross-over between groups using Pearson's chi-squared test. The analysis of the incidence of hypoxemia is performed either with logistic or Poisson regression depending on the distribution. All continuous variables like area under the curve SpO2, ISAS score, mean TcCO2 and peak TcCo2, will be presented as group mean and SD. Univariable analysis using the independent-samples t-test will be performed. Further analysis will be done using multiple linear regression. Covariates will be specified as age, gender, BMI, ASA classification, duration of RFCA procedure, hypotension and BIS. The occurrence of adverse events will be presented as count and percentage per group. Analysis will be performed using a logistic regression model. Likert type questions will be reported as percentage of patients that scored each of the options, stratified by group. The median for central tendency and frequencies for variability are calculated for analyzing this descriptive statistics. The response on the Likert type questions will be analyzed separately for each question using the Mann-Whitney U test.

Interim analyses

After inclusion of 50 participants in each group we will perform a blinded sample size control with the SpO2 data of the participants. The sample size is based on a similar study which compared the HFNC vs LFNC.[9] However, this study was based on a different indication and conscious sedation instead of prolonged deep sedation.

Methods for additional analyses (e.g. subgroup analyses)

Additional analyses are not planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

All analyses will be performed according to the intention-to-treat principle. We will impute missing data using multiple imputation with fully conditional specification. The number of imputations will be set to the percentage of incomplete records.

Plans to give access to the full protocol, participant level-data and statistical code

In case of audits of health authorities and funder or other researchers needing to access data for scientific purposes, we will give access to the full protocol, participant level-data, and statistical code.

Oversight and monitoring

Composition of the coordinating center and trial steering committee

All researchers will be a part of the trial management committee. Study coordination will be performed by the Department of Anesthesiology MUMC+. Data acquisition will be performed by 2 members of the research team. Statistical analysis will be performed by the independent statistician

Composition of the data monitoring committee, its role and reporting structure

Clinical Trial Center Maastricht (CTCM) designed a data monitoring plan for this study. This study has been classified into the '*Negligible* risk category. The monitoring tasks are General and Source Data Verification/Review (SDV/R) related tasks. The monitoring intensity can be adapted during the trial. CTCM is independent from the funder and sponsor.

Adverse event reporting and harms

Adverse events

All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. For example, an adverse event can also be related to a diagnostic procedure (e.g. contrast allergy during the pre-procedure computed tomography) or to an already existing condition (e.g. cardiac decompensation due to atrial fibrillation).

Serious adverse events

A SAE is any untoward medical occurrence or effect that results in death, is life threatening (at the time of the event), tamponade, requires prolongation of existing inpatients' hospitalization, results in persistent or significant disability or incapacity or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a SAE because the participant is admitted for the treatment. Most SAE's are related to the RFCA procedure not to PSA. Considering the severity of the SAE's they should be reported. The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs: short-term hypoxemia (SpO_2 <90% <180 seconds), hypoxemia (SpO_2 <90% >180 seconds) responding to protocol deviation, unexpected extended recovery time > 8 hours, unexpected admission on ICU or CCU, the procedure is terminated. These SAEs will be reported within a period of maximum 30 days. The period of maximum 15 days may be exceeded. All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported until the end of the study within the Netherlands.

Frequency and plans for auditing trial conduct

Plans for auditing trial conduct are not included. The independent data safety and monitoring committee will provide an assessment of the patient safety and recommendation to the principal investigator and the researchers about the continuation of this trial. The assessment of the data safety and monitoring committee will be communicated to Clinical Trial Center Maastricht. The Ethical Committee of the MUMC+ will be informed via an annual progress report.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

In case of protocol modifications (e.g., changes to outcomes, analyses), we will communicate it to the Ethical Committee and trial registry. Protocol amendments will be reported and documented in the Trial Master File.

Dissemination plans

The sponsor and the investigator agreed to publish the results. This is independent of the results of the study. Publication will take place in accordance with the CCMO guideline regarding publication.

DISCUSSION

Procedural sedation and analgesia has become a common practice given the increasing demand to relieve anxiety, discomfort and pain during invasive diagnostic and therapeutic procedures. In 2018 the Department of Anesthesiology at MUMC+ performed 2040 PSA procedures. The majority (n=888) of PSA procedures were performed during RFCA and cardiac electrophysiology testing. Our experience is that as the procedure and PSA time increase, saturation more often shows a gradual decrease and desaturations occur more frequently. The aim is to prevent patients from desaturation and hypoxemia. BMI as selection criteria was therefore decreased to 32 kg m^{-2} instead of 35 kg m^{-2}. And the PSA (and procedure) time is limited to a maximum of 4 hours.

To our knowledge, this is the first study to investigate the effects of HFNC during prolonged deep sedation in patients undergoing RFCA. HFNC is increasingly used as a technique for oxygen delivery in procedural sedation and analgesia. The effect of HFNC vs LFNC during sedation has been investigated in several small studies. No difference in primary outcomes of oxygen desaturation was reported. The explanation could be the small sample-sizes and the level of sedation. The intervention could have a positive effect in this study because deep sedation is performed in supine position for a prolonged time up to 4 hours.

The sample size in this prospective study was calculated and adjusted using a similar study which compared HFNC vs LFNC in a different population.[9] In this study participants underwent dental surgery. However the duration of sedation and treatment were shorter (<75 minutes), which will affect primary outcome.[9] Therefore, we decided to perform a sample size control.

The secondary outcomes include ratings of experiences of participants and staff using 5-point Likert scales. Validated questionnaires were preferred, but unfortunately these are not available.

To ensure that all colleagues work according to the study protocol and follow GCP guidelines education and training is provided. The AC are trained to obtain informed consent. The AC are instructed and trained in the use of the Optiflow and Vsign. They are also trained to provide PSA according to this study protocol during sedation. The group of PA's and AC consists of 7 colleagues.

Trial status

Trial recruitment is started on 15 November 2022. Recruitment will take approximately two years. This is the first protocol version registered on 21 November 2020. We plan to start recruitment by 1 September 2021 and to complete recruitment by 31 August 2023.

ABBREVIATIONS

AF	Atrial Fibrillation
CTCM	Clinical Trial Center Maastricht
HFNC	High Flow Nasal Cannula
LFNC	Low Flow Nasal Cannula
MUMC+	Maastricht University Medical Center+
NA	Nurse Anesthetist
PA	Physician Assistant
PDMS	Patient Data Management System
RFCA	Radiofrequency catheter ablation

DECLARATIONS

Acknowledgements

Not applicable.

Authors' contributions

MCH conceived of the study. MCH, EAB, BAJ and WFB initiated the study design. SMK designed the statistical methods. DL helped with the implementation. MCH, EAB and DL will recruit patients. MCH and SMK are conducting the primary statistical analysis. MCH is the coordinating researcher. WFB is the principal investigator. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Availability of data and materials

Data can be obtained by contacting the coordinating researcher. Data will be available by contacting by email the coordinating researcher using details on trial published articles. Email for requests: marloes.homberg@mumc.nl.

Ethics approval and consent to participate

Ethics approval is obtained from the METC (NL72859.068.20) of the MUMC Maastricht. Patients will only be included in the study after written informed consent is obtained.

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Effects of high-flow nasal oxygen on oxygenation and the incidence of hypoxemic events during procedural sedation for atrial fibrillation catheter ablation

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Effects of high-flow nasal oxygen on oxygenation and the incidence of hypoxemic events during procedural sedation for atrial fibrillation catheter ablation
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ABSTRACT

Background High flow nasal oxygen (HFNO) may improve oxygenation and reduce the incidence of hypoxemia during procedural sedation.

Objective The objective of this study was to investigate the effects of high flow nasal oxygen in comparison to low flow nasal oxygen (LFNO) on oxygenation during atrial fibrillation (AF) catheter ablation performed with procedural sedation and analgesia (PSA).

Design Randomized controlled trial.

Setting This single-center study conducted at an academic hospital in the Netherlands, was terminated prematurely for futility.

Participants Adults undergoing AF catheter ablation with sedation administered by an anesthesia care provider, under anesthesiologist supervision from December 2021 to November 2024.

Interventions Participants were randomized 1:1 to HFNO (50L/min and a 50:50 oxygen–air ratio) or LFNO (5L/min).

Main outcome The primary outcome was the average lowest oxygen saturation (SpO_2) and the duration of the lowest saturation. Statistical analysis of the outcomes was performed using the independent samples *t*-test.

Results A total of 101 participants were randomized and had the primary outcome measured. Mean lowest SpO_2 was 89.6% (± 6.6) with HFNO and 87.7% (± 5.9) with LFNO ($p = 0.127$). Duration of desaturation was longer with HFNO (55.7 ± 99.4 s) than LFNO (41.3 ± 54.2 s; $p = 0.002$). Oxygen delivery crossover occurred in 13.7% of HFNO and 6.0% of LFNO cases ($p = 0.205$). One hypoxemic event occurred in the LFNO group (AUCDESAT 240 s·%).

Conclusions HFNO did not improve oxygenation in selected patients during PSA for AF ablation, nor was it associated with increased complications. Routine use of HFNO in this setting cannot be recommended.

Trial registration ClinicalTrials.gov identifier: NCT04842253

INTRODUCTION

Catheter ablation (CA) has become a cornerstone intervention in the management of atrial fibrillation (AF), particularly in patients with symptomatic or drug-refractory disease.[1] AF ablation is typically performed under either procedural sedation and analgesia (PSA) or general anesthesia (GA), both aim to ensure patient comfort and minimize movement to facilitate catheter stability and lesion formation. Deep sedation often approximates the physiological depth of GA and necessitates the presence of an anesthesiologist, a second physician, or a specially trained nurse in most electrophysiology laboratories.[2, 3, 4, 5] While the clinical significance of short-term desaturation events remains debated, such episodes may serve as sentinel markers for compromised airway patency or ventilation, particularly in the setting of deep sedation and prolonged procedural times[6].

High-flow nasal oxygen (HFNO) has emerged as a promising non-invasive strategy to mitigate respiratory compromise during sedation. By delivering heated, humidified oxygen at flow rates up to 70 L/min, HFNO offers several physiological advantages over conventional low-flow nasal oxygen (LFNO).[7] These include increased pharyngeal pressure to reduce upper-airway collapse,[8] enhanced functional residual capacity to optimize ventilation-perfusion matching,[9] and improved mucociliary clearance, which may reduce respiratory workload.[10] Consequently, it is possible to expect that these effects may result in a lower incidence of hypoxemia and respiratory sedation-related complications during AF ablation. This study therefore aims to evaluate whether HFNO, compared with LFNO, improves oxygenation during sedation. We tested this hypothesis in patients undergoing point-by-point catheter ablation for AF under deep sedation.

METHODS

Study design and participants

This single-center randomized controlled trial (RCT) was conducted at Maastricht University Medical Centre $^{+}$ in adults (aged > 18 years) undergoing PSA for elective point-by-point AF catheter ablation. Patients were randomized 1:1 to HFNO or LFNO. Because blinding was not feasible, participants and staff were aware of treatment allocation. Patients were excluded from the study if they were ≤ 18 years, incapacitated, had a Body Mass Index (BMI) above 32 kg/m^2, were diagnosed with sleep-disordered breathing (SDB), had chronic obstructive pulmonary disease (COPD) gold IV or COPD gold III with frequent or recent exacerbation, were diagnosed with pulmonary or cardiac condition requiring chronic oxygen therapy, had complete nasal obstruction, active nose bleeding, untreated pneumothorax (pre-existing), recent upper airway surgery, recent base of skull fracture, expected difficult airway, COVID-19 infection or previous participation. Ethical approval for this RCT (registration number METC20-072) was provided by the Medical Ethics Re-

view Committee, Maastricht, the Netherlands on 23-12-2020. The trial was prospectively registered (NCT04842253). The study protocol conforms to the 1975 Declaration of Helsinki. Informed consent was obtained.

PSA was conducted following the recommendations from the European Society of Anesthesiology and Intensive Care and the national guideline on procedural sedation and analgesia for adults.[11, 12] PSA was administered by a physician assistant (PA) or nurse anesthetist (NA) under supervision of an anesthesiologist in line with Dutch standard of care. They managed sedation, monitored patients continuously, and alerted the supervising anesthesiologist in case of any clinical concerns. No restrictions were placed on concomitant care**.** The anesthesia team employed standard physiological monitoring devices and titrated sedation according to their routine clinical practice. Capnography was used in all cases. In participants randomized to HFNO, CO_2 monitoring was performed using a sampling adaptor integrated into the latest-generation Optiflow® nasal cannula system. PSA regimen included continuous infusion of propofol in combination with a short-acting opioid (remifentanil or alfentanil), and in some cases, supplementation with esketamine. To prevent post-procedural pain, intravenous (i.v.) acetylaminophen was administered, optionally in combination with i.v. piritramide or i.v. morphine, based on clinical judgment. No additional restrictions were imposed on type or dose of sedatives used by the PA or NA. The cardiological intervention—point-by-point catheter ablation for AF—requires deep sedation and is frequently associated with hemodynamic fluctuations due to heart rate variability. Low-dose norepinephrine was administered when needed to stabilize blood pressure. All medications and dosages administered during the procedure were documented.

Interventions

Intervention: High flow nasal oxygen

HFNO was applied with the Optiflow™ device (Fisher & Paykel Healthcare, Auckland, New Zealand). The Optiflow™ device included a heated breathing tube and chamber, along with a nasal cannula for oxygen delivery. Temperature was set to 37 °C and adjusted for comfort. Gas flow started at 10 L/min before PSA and increased during induction to a maximum of 50 L/min. The inspired oxygen fraction (FiO_2) was set at 40% and adjusted to maintain adequate SpO_2.

Standard care: Low flow nasal oxygen

LFNO was administered via Microstream® Smart CapnoLine® O_2 at 5 L/min, titrated according to SpO_2. In cases of airway obstruction, a nasal or oral airway was added.

Protocol deviation

Protocol deviations were possible in specific well-defined situations. Crossover from LFNO to HFNO was considered if ongoing desaturation (SpO_2 < 90% for > 180 seconds) occurred. Desaturation did not improve following interventions such as airway repositioning, tactile stimulation, increasing supplemental oxygen, or the use of an oral (Intersurgical Guedel®) or nasopharyngeal airway. Crossover from HFNO to LFNO, in combination with an oral (Intersurgical Guedel®) or nasopharyngeal airway, was implemented in cases of airway obstruction caused by upper airway collapse. Additionally, crossover from HFNO to LFNO occurred if the participant was unable to tolerate HFNO due to discomfort.

Outcomes and data collection

Primary outcomes for this study were the difference in the lowest SpO_2 observed during procedural sedation for point-by-point AF ablation between LFNO and HFNO and the difference in duration of the lowest SpO_2 between LFNO and HFNO. Secondary outcomes included hypoxemic events (SpO_2 <90% for >180 s); the area under the curve for desaturation (AUC_{DESAT}), calculated as the difference between the 90% threshold and actual SpO_2 summed per minute below this value; the occurrence of sedation-related adverse events; and adverse effects related to the oxygen delivery system. Further outcomes included patient-reported experience with sedation; minimal, mean and peak transcutaneous carbon dioxide ($TcCO_2$); experienced comfort with the oxygen delivery device; anesthesia assistants' ratings of difficulty in maintaining oxygenation and oxygen delivery device handling; and electrophysiologists' satisfaction with catheter stability.

Peripheral oxygen saturation (SpO_2) was measured in percentages (%) and was continuously monitored using a Masimo® SpO_2 sensor at a frequency of one measurement per 15 seconds. The recorded SpO_2 values were extracted from the Philips Medical Systems Intellivue MX800 1&2 and automatically stored in a patient data management system (PDMS). Adverse sedation events were measured using the tracking and reporting outcomes of procedural sedation (TROOPS) research tool.[13] Adverse effects of oxygen delivery system were noted on the TROOPS form. Patient experience with sedation was measured using the Iowa Satisfaction with Anesthesia Scale (ISAS).[14] Patients respond to eleven statements (e.g., "I felt pain") by placing a mark along a six-choice vertical response column (e.g., "Disagree moderately") below each statement. The mean of their responses to each of the 11 statements gives a single number, which is a quantitative measure of a patient's satisfaction with their MAC. The range of possible values is 0-33.[14] $TcCO_2$ was continuously measured in kilopascal (kPa) using the Sentec Digital Monitoring system with VSign™ 2 sensor. Participants were asked to rate comfort with the oxygen delivery device and PA/NA were asked to rate their perceived level of difficulty in maintaining oxygenation and perceived level of difficulty in using the oxygen delivery device, using a five-point Likert scale. Electrophysiologists (EPs) were asked to rate their satisfaction with catheter

stability in relation to sedation, using a five-point Likert scale. All questionnaires were administered through the Castor® electronic data capture system.

Adverse events (AEs) were defined as any undesirable medical occurrence, regardless the relationship with the intervention. Short-term mild desaturation (SpO_2 < 90% for >15 seconds), transient severe desaturation (SpO_2 ≤ 85% for >15 seconds), hypoxemia (SpO_2 < 90% for >180 seconds) that responded to protocol deviation, and unexpected recovery room stays exceeding 8 hours were recorded as AEs. Serious adverse events (SAEs) were defined as any medical occurrence that resulted in death, was life-threatening at the time of the event, required prolongation of existing inpatient hospitalization, or resulted in persistent or significant disability or incapacity. In this study, the following events were additionally classified as SAEs: hypoxemia (SpO_2 < 90% for >180 seconds) not responding to protocol deviation and resulting in invasive ventilation or procedure termination; termination of the procedure due to sedation failure; cardiac tamponade; and unexpected admission to the intensive care unit (ICU) or coronary care unit (CCU). After the first 10 participants, the classification of short-term desaturation was amended from SAE to AE.

Sample size determination

The sample size for this study was calculated based on previous data reporting lowest mean SpO_2 95.2% with LFNO and 99.3% with HFNO (SD ± 0.1).[8] To achieve 80% power at $\alpha = 0.05$, 94 participants per group were required. After 50 per group were enrolled, a blinded interim sample size reassessment was conducted by an independent researcher. According to the sample size re-evaluation a substantially larger number of participants would have been required. Furthermore, recruitment declined because single-shot pulsed field ablation gradually replaced many point-by-point AF ablation. In addition, increasing numbers of patients were newly diagnosed with SDB between pre-assessment and treatment, making them ineligible. As a result, completion within a reasonable timeframe was unlikely, and the trial was discontinued.

Allocation

Block-randomized sequence stratified by gender was generated via Castor® prior to each procedure.

Statistical analyses

Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) depending on the distribution of the data. Dichotomous outcomes were presented with absolute numbers (n) and percentages (%). Univariable between-group analyses were performed using the independent-samples *t*-test. Continuous outcomes were further analyzed using univariate linear regression models. Poisson regression was used when the assumption of normality was violated. For dichotomous outcomes univariate logistic regression analyses was performed. As sensitivity analysis, multivariable analyses were conducted, adjusted for age, gender, BMI, and ASA classification (supplemental Table 1 see page 99). Duration of PSA, hypotension and BIS were considered potential colliders due to the potential effect of the outcome on these measures and were excluded as covariates. Responses to Likert-type questions were reported as the percentage of selecting each response option, stratified by treatment group. Median values were used to describe central tendency, and frequencies were reported to assess variability of Likert scales. Responses to individual Likert-type questions were analyzed separately using the Mann–Whitney U test. All analyses will be performed according to the intention-to-treat principle. Complete case analysis was conducted for all participants for whom a primary outcome was available, due to the limited amount of missing data. As a result one case out of 102 (0.98%) was excluded from analysis. Statistical analysis was performed using R version 4.1.3.

RESULTS

Participants

From December 2021 to November 2024, 554 patients were screened for eligibility (Fig. 1). A total of 104 participants were randomized. The intervention group (HFNO) included 54 patients, while the control group (LFNO) included 50 patients. Three patients were excluded: two due to rescheduling, and one diagnosed SDB between inclusion and the procedure.

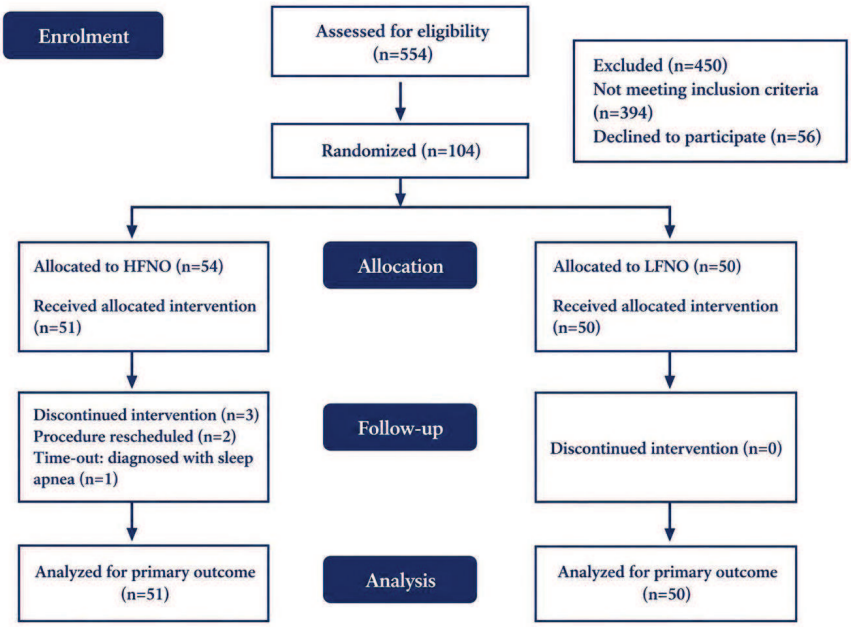


Fig.1 CONSORT flow diagram

Baseline characteristics are presented in Table 1. Most participants were male, aged >50 years, and ASA physical classification status II. The activity level was ≥4 METS in 98% of the participants. Duration of sedation was 175 minutes ± 51 minutes. There were no substantial imbalances of baseline characteristics between the two treatment groups.

Table 1 Baseline characteristics of all procedures, LFNO group and HFNO group.

		Total n = 101		HFNO n = 51		LFNO n = 50		Missing
		n	%	n	%	n	%	%
Sex	Men	80	79.2	40	78.4	40	80.0	
	Women	21	20.8	11	21.6	10	20.0	
Age – mean (SD)		65.53	9.29	66.0	7.3	65.0	11.0	
BMI – mean (SD)		26.31	2.72	26.11	2.57	26.5	2.9	
Activity level	<4 METS	1	1.0	1	2.0	-		
	≥4 METS	100	99.0	50	98.0	50	100.0	
ASA classification	ASA 2	78	77.2	41	80.4	37	74.0	
	ASA 3	23	22.8	10	19.6	13	26.0	
	ASA 4	-	-	-	-	-	-	
Cardio vascular disease		30	29.7	12	23.5	18	36.0	
Congestive heart failure		4	4.0	1	2.0	3	6.0	
Hypertension		56	55.4	26	51.0	30	60.0	

		Total n = 101		HFNO n = 51		LFNO n = 50		Missing
Dyslipidaemia		35	34.7	14	27.5	21	42.0	
Diabetes Mellitus		7	6.9	3	5.9	4	8.0	
Decreased kidney function		19	8.8	8	15.7	11	22.0	
COPD		2	2.0	1	2.0	1	2.0	
Smoking	Actively	13	12.9	7	13.7	6	12.0	1.0
	Previously	33	32.7	18	35.3	15	30.0	
	Never	54	53.5	26	51.0	28	56.0	
Alcohol consumption	None	22	21.8	10	19.6	12	24.0	
	< 7 units/week	55	54.4	29	56.9	26	52.0	
	≥ 7 units/week	24	24.8	12	23.5	12	24.0	
STOP-BANG (reported by patients)	Snoring	16	15.8	11	21.6	5	10.0	2.0
	Tiredness	17	16.8	9	17.6	8	16.0	2.0
	Observed apneas	2	2.0	2	3.9	0	0.0	2.0
	High blood pressure	56	55.4	26	51.0	30	60.0	0.0
	BMI>35kg/m2	-	-	-	-	-	-	0.0
	Age>50years	94	93.1	50	98.0	44	88.0	0.0
	Neck circumference >40cm	-	-	-	-	-	-	100.0
	Male	80	79.2	40	78.4	40	80.0	
Duration PSA (mean SD)	minutes	175	51	180	47	171	55	
Duration procedure (mean SD)	minutes	155	47	160	44	151	51	

BMI: body mass index; METS: Metabolic Equivalent of Task Score; ASA-classification: American Society of Anesthesiologists physical status classification; PVI: pulmonary vein isolation; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; SD: standard deviation.

Primary outcome

The average lowest measured SpO_2 was 89.6% (± 6.6) in the HFNO group and 87.7% (± 5.9) in the LFNO group (p = 0.127) (Table 2). The duration of SpO_2 desaturation was significantly longer (55.7 (± 99.4) seconds) in the HFNO group, compared to the LFNO group (41.3 (± 54.2) seconds) (p = 0.002).

Secondary outcomes

Crossover of oxygen modality occurred in 13.7% of HFNO versus 6.0% of LFNO cases (p = 0.205). A single hypoxemic event was recorded in the LFNO group, with an area under

the curve for desaturation (AUC_{DESAT}) of 240 seconds·%. Minimal $TcCO_2$ levels were unaffected across groups. Mean $TcCO_2$ was 6.8 ± 0.8 kPa in the HFNO group and 6.4 ± 0.7 kPa in the LFNO group (p = 0.036). However, maximum $TcCO_2$ was significantly higher in the HFNO group compared to the LFNO group (7.8 ± 1.0 kPa vs 7.4 ± 0.9 kPa; p = 0.032). The duration of procedural sedation and analgesia (PSA), as well as the total procedure time, did not differ significantly between groups. ISAS scores were also comparable. Response rates for Likert questionnaires were 64.4% for patients, 63.4% for ACPs (user-friendliness and oxygenation maintenance), and 43.6% for EPs. Although distributions across the Likert scales varied (Table 2), there were no statistically significant differences in median scores or IQRs between the groups.

Table 2 Primary and secondary outcomes

	HFNO N=51			***LFNO N=50***			***p-value***
	n	%	Mean ± SD	n	%	Mean ± SD	Univariate
Primary outcome							
Lowest SpO_2 % (mean ± SD)			89.6% (± 6.6)			87.7% (± 5.9)	0.127
Duration lowest SpO_2 seconds (mean ± SD)			55.7 (± 99.4)			41.3 (± 54.2)	<0.001[a]
Duration lowest sp02 Quartile							
Q1-Q3	39	76.5		46	93.9		
Q4	12	23.5		3	6.1		0.023
Secondary outcome							
Cross over therapy	7	13.7		3	6.0		0.205
Hypoxemic events	0	0.0		1	1.0		n.a.
AUC incidence	0	0.0		1	1.0		n.a.
AUC (mean ± SD)		n.a.			240		n.a.
Min TcCO2 (mean ± SD)			4.9 (± 0.7)			4.9 (± 0.8)	0.824
Max TcCO2 (mean ± SD)			7.8 (± 1.0)			7.4 (± 0.9)	0.017
Mean TcCO2 (mean ± SD)			6.8 (± 0.8)			6.4 (± 0.7)	0.036
DURATion PSA minutes *(mean ± SD)*			179.9 (± 47.1)			171.4 (± 54.8)	0.404
DURATION PSA Quartile							
Q1-3	36	75.2		40	80.0		
Q4	15	24.7		10	20.0		0.276
Duration procedure minutes *(mean ± SD)*			160.2 (± 43.9)			151.0 (± 50.7)	0.334
DURATION PROCEDURE Quartile							
Q1-3	38	77.2		40	80.0		
Q4	13	23.8		10	20.0		0.511

	HFNO N=51		*LFNO N=50*		*p-value*
ISAS *(mean ± SD)*	25.1 (± 5.9)		27.3 (± 5.9)		0.081[a]
Patients comfort with oxYgen delivery device *(mean ± SD)*	4.00 (± 0.8)[b]		4.00 (± 0.8)[b]		0.396[c]
LIKERT scale 1	1	2.9	1	3.3	
LIKERT scale 2	n.a.	n.a.	1	3.3	
LIKERT scale 3	16	45.7	7	23.3	
LIKERT scale 4	13	37.1	18	60.0	
LIKERT scale 5	5	14.3	3	10.0	
ACP user-friendliness oxygen delivery device *(mean ± SD)*	4.0 (± 0.8)[b]		4.0 (± 1.0)[b]		0.169[c]
LIKERT scale 1	n.a	n.a	n.a	n.a	
LIKERT scale 2	6	19.4	n.a	n.a	
LIKERT scale 3	1	3.2	4	12.1	
LIKERT scale 4	19	61.3	21	63.6	
LIKERT scale 5	5	16.1	8	24.3	
ACP Difficulty maintaining oxygenation status *(mean ± SD)*	4.0 (± 1.1)[b]		4.0 (± 1.0)[b]		0.150[c]
LIKERT scale 1	1	3.2	1	3.0	
LIKERT scale 2	3	9.7	3	9.1	
LIKERT scale 3	5	16.1	8	24.2	
LIKERT scale 4	10	32.3	16	48.5	
LIKERT scale 5	12	38.7	5	15.2	
EP satisfaction with catheter stabilisation *(mean ± SD)*	5.0 (± 1.2)[b]		4.0 (± 1.2)[b]		0.124[c]
LIKERT scale 1	1	4.0	1	5.3	
LIKERT scale 2	1	4.0	2	10.5	
LIKERT scale 3	2	8.0	3	15.8	
LIKERT scale 4	6	24.0	6	31.6	
LIKERT scale 5	15	60.0	7	36.8	

[a]Poisson regression; [b]median (±IQR); [c]Mann–Whitney U; n.a.: not applicable; ISAS: Iowa Satisfaction with Anesthesia Scale

Adverse events

In the HFNO group, four AE's and four SAE's were reported. In the LFNO group, there were seven AE's and five SAE's, including two cases that required conversion to general anesthesia. AE's were categorized as short-term mild desaturation (n = 1) and transient severe desaturation (n = 10). An overview of all AE's is presented in Table 3.

Table 3 Adverse Events

	HFNO		LFNO		p-value
	n	%	n	%	
Adverse events	4	7.8	7	14.0	0.33
Serious adverse events	4	7.8	5	10.0	0.70
Reported Adverse event PSA	26	39.2	24	48.0	0.37
Conversion to general anesthesia	0	0.0	2	8.3	
POst procedural stay recovery Room 0-2 hours	44	86.3	43	86.00	0.97
POst procedural stay recovery Room 2-6 hours	7	13.7	5	10.0	0.56
POst procedural stay recovery Room overnight	0	0.0	1	2.0	
Post procedural HDCU	0	0.0	1	2.0	
POST procedural ICU	0	0.0	0	0.0	
unexpected extended hospital admission	2	3.9	2	4.0	
extended hospital stay CAtheter ablation related	2	3.9	2	4.0	

No tests were performed in case of ≤ 3 events

In total, nine SAE's occurred across both groups (see Table 4). Sedation-related complications were observed in 39.2% of HFNO and 48.0% of LFNO cases. Most patients experienced a post-procedural recovery room stay of 0 to 2 hours. There were four cases of unexpected, prolonged hospital stay, evenly distributed between both groups. All were attributable to complications related to the catheter ablation procedure rather than the sedation or oxygen delivery modality.

Table 4 Summary of Serious Adverse Events (SAEs)

SAE#	Description
1	Short-term mild desaturation*
2	Transient oropharyngeal bleeding following transesophageal echocardiography (TEE), requiring intubation, prolonged post-anesthesia care unit stay (>8 hours), and extended hospitalization.
3	Protocol deviation: patient was unable to tolerate high-flow nasal cannula (HFNO) due to hyper salivation.
4	Short-term mild desaturation* and transient severe desaturation
5	Short-term mild desaturation*
6	Post procedural event with prolonged hospitalization. In the post-ablation ward, telemetry documented an in-hospital cardiac arrest (IHCA) due to sinus bradycardia with complete atrioventricular (AV) block. Spontaneous return of AV conduction occurred after approximately 60 seconds. The event was attributed to a probable extreme vagal response involving stimulation of the left atrial ganglionated plexus. The patient was admitted to the cardiac care unit (CCU) and received a temporary pacemaker. Discharged after 5 days without residual symptoms.
7	Conversion to general anesthesia due to long-term mild desaturation unresponsive to protocolized interventions.
8	Procedure related complication with prolonged hospitalization. Post-procedural transthoracic echocardiogram (TTE) revealed a pericardial effusion, necessitating pericardiocentesis and CCU admission. The patient was discharged 3 days later without physical complaints.
9	Conversion to general anesthesia and extended hospital stay. Upper airway obstruction occurred after induction of sedation; oral airway placement was ineffective. Additionally, a groin hematoma developed, requiring prolonged monitoring on the ward.

*short-term mild desaturation was classified as an SAE, at the onset of the study. Following a protocol amendment, this type of desaturation was subsequently recorded as an AE.

DISCUSSION

This was a negative study, as HFNO did not result in a measurable improvement in oxygenation compared with LFNO during procedural sedation for atrial fibrillation ablation. This is consistent with results from previous studies.[15, 16, 17, 18] The lack of benefit may be explained by several factors. First, the inspired oxygen fraction in the HFNO group may have been insufficient to enhance oxygen levels under these procedural conditions. In addition, the depth of sedation and the frequently undiagnosed presence of sleep-disordered breathing in the AF population could have contributed to inadequate ventilation. Despite the negative findings, this trial provides valuable evidence regarding the role of HFNO in this setting.

Deep sedation often approximates the physiological depth of general anesthesia, during which airway interventions may be required and spontaneous ventilation may become inadequate. One commonly proposed physiological effect of HFNO is an increase in upper airway pressure, which may help maintain airway patency. However, recent data from apneic patients under general anesthesia demonstrated minimal airway pressure increase during HFNO when the mouth remained open.[19, 20] In our study, no specific

instructions were provided regarding mouth positioning during HFNO administration. Therefore, the impact of mouth position on oxygenation remains unclear.

We excluded patients with a clinical diagnosis of sleep-disordered breathing (SDB) or those considered high risk based on the STOP-BANG questionnaire during pre-anesthesia assessment. While such screening strategies may be effective in the general population, they may have limitations in patients with AF. Studies have shown the STOP-BANG questionnaire has limited accuracy for detecting SDB in patients with AF.[21, 22] Furthermore, the VIRTUAL-SAFARI study demonstrated that SDB is largely underdiagnosed in patients scheduled for AF ablation.[23, 24] Therefore, some of our participants likely had undiagnosed SDB, which may have affected oxygenation. SDB includes conditions in which the upper airway narrows or collapses during sleep, leading to impaired breathing. HFNO may be less effective in such cases. In 13.7% of HFNO cases, crossover to LFNO was required. In all cases, the reason for the crossover was upper airway obstruction, which was resolved using an oral airway. The study protocol prohibited simultaneous HFNO and oral airway use to avoid pressure loss through the airway.

As described in a previous study on HFNO during PSA for cardiac implantable electronic device procedures, the oxygen–air blend (50:50) may not be equivalent to the oxygen supplementation received compared to LFNO (5 L/min of 100% oxygen).[17] This highlights the potential need to determine the optimal oxygen-to-air ratio for HFNO during sedation. Another plausible explanation is that HFNO may impair the reliable monitoring of capnography waveforms. CO_2 sampling via an unsealed nasal cannula at high flow can dilute exhaled gases and degrade waveform quality. This challenge is particularly relevant in the event of upper airway obstruction—a common occurrence during deep sedation—where airflow is restricted, and effective exhalation through the upper airway is impaired. In such cases, capnographic waveforms may be absent or inaccurate, increasing the risk of undetected and prolonged hypoventilation.[25] In our study, HFNO cannulas with an integrated CO_2 sampling line were employed. Despite this, higher mean and maximum transcutaneous carbon dioxide ($TcCO_2$) concentrations were observed in the HFNO group, suggesting that such episodes may have occurred more frequently in this cohort. However, no hypoxemic events occurred in the HFNO group. The single hypoxemic event was in the LFNO group.

Patient satisfaction with sedation was comparable between groups. The likelihood that patients would rate the comfort of the oxygen supplementation device positively was slightly higher in the HFNO group (68.6%) compared to the LFNO group (60.0%). Although there was no statistically significant difference in comfort related to oxygen administration, a greater variation in responses was observed within the HFNO group.

Prior to the study, all PA/NA had limited experience with the HFNO device, and received on-the-job training. During the study period, most PA/NA used the device between two and ten times. In six cases, two PA/NA rated HFNO as user-unfriendly. Limited experience may have influenced these perceptions. PA/NA reported difficulty maintaining oxygenation in six cases—five due to airway obstruction and one due to excessive salivation. The PA/NA questionnaire response rate was 64.3%. Electrophysiologists rated satisfaction with catheter stability at the highest level (Likert scale 5) in 60.0% of HFNO cases, compared to 36.8% in the LFNO group. The overall response rate among EPs was 49.1% (49.0% in the HFNO group vs. 38.0% in the LFNO group). Both PA/NA and EPs may have been more inclined to report negative experiences than positive ones.

During study design, considerable effort was made to select the most appropriate variable for sample size calculation. Most previous trials focused on oxygenation. Another study on HFNO during PSA cardiac implantable electronic device procedures based its sample size on $TcCO_2$, but noted in their discussion that future sample size calculations should be based on the incidence of hypoxemia. In our study the incidence on hypoxemia was 1 in 50. This implies a very large sample size would be required to demonstrate a difference. Conducting such a large single-center RCT within a limited timeframe is unlikely feasible, particularly in a PSA population where the intervention itself remains unchanged.

Strengths and limitations

A key strength of this study is its randomized, prospective design. Randomization minimized baseline confounding and helped to reduce bias, thereby enhancing the internal validity of the results. The findings from this trial can be generalized to other clinical settings where patients undergo prolonged deep sedation in the supine position.

However, several limitations should be noted. First, when recruitment declined, the protocol was amended to include all point-by-point AF ablations rather than radiofrequency procedures only. Including single-shot ablations such as pulsed field ablation was considered but rejected to avoid greater heterogeneity as these procedures tend to deliver a more intense stimulus. Second, an increasing number of patients who were diagnosed with SDB between the pre-assessment and treatment, rendering them ineligible. In addition, many RFCA procedures for first-time AF ablations were gradually replaced by single-shot pulse field ablations, further reducing the pool of eligible participants. Only 101 of 554 screened patients were ultimately included. Consequently, the study was unlikely to be completed within a reasonable timeframe. Third, the study protocol did not mandate use of a validated sedation scale at set intervals. According to the local sedation protocol, the Ramsey Sedation Scale (RSS) should be used to assess sedation depth. However, in this study, RSS scores were not recorded at predetermined time points, and thus were not systematically reflected in the data. Depth of sedation was continuously monitored us-

ing the Bispectral Index (BIS), and the duration of the procedures was sufficient to allow for reliable BIS measurements. These measurements revealed no significant differences between the groups. Nonetheless, although unlikely, the possibility remains that undetected differences in sedation depth could have influenced the study outcomes. Finally, relatively low response rates from ACPs and EPs on questionnaires may have introduced response bias, potentially distorting the results.

CONCLUSION AND RECOMMENDATIONS

High-flow nasal oxygen does not improve oxygenation compared to LFNO, nor is it associated with a higher rate of complications. The safety of HFNO is well established. Based on the findings of this study, HFNO appears to offer no added value during PSA for AF ablation. Given the additional costs and environmental impact associated with HFNO, routine use for this indication cannot be justified. Conducting a large single-center RCT within a limited timeframe is not feasible, particularly in a PSA population where the intervention remains unchanged. Future research should focus on alternative study designs, such as multicenter collaborations or adaptive trial methods, to more effectively and efficiently evaluate the potential benefits of HFNO.

SUPPLEMENTAL TABLES

Supplemental Table 1 Multivariate analysis

Primary outcome	p-value
Lowest SpO_2 % (mean±SD)	0.167
Duration lowest SpO_2 seconds (mean±SD)	0.002[a]
Duration lowest sp02 Quartile	
Q1-Q3	
Q4	0.024
Secondary outcome	
Cross over therapy	0.158
Hypoxemic events	n.a.
AUC incidence	n.a.
AUC (mean±SD)	n.a.
Min TcCO2 (mean±SD)	0.923
Max TcCO2 (mean± SD)	0.032
Mean TcCO2 (mean±SD)	0.058
Duration PSA minutes *(mean±SD)*	0.322
Duration PSA Quartile	
Q1-3	
Q4	0.222
DURATION procedure minutes *(mean ±SD)*	0.242
DURATION PSA Quartile	
Q1-3	
Q4	0.365
ISAS *(mean±SD)*	0.093[a]

[a]Poisson regression; [b]median (±IQR); [c]Mann–Whitney U; n.a.: not applicable; ISAS: Iowa Satisfaction with Anesthesia Scale; Covariates multivariate analyses: age, gender, BMI and ASA-classification.

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6

Post-procedural pain following percutaneous thermal liver tumor ablation under procedural sedation and analgesia

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ABSTRACT

Background and Objectives: The incidence of post-procedural pain following percutaneous thermal liver ablation under procedural sedation and analgesia (PSA) is yet largely unknown. Only a few small studies investigated tumor and ablation factors on pain, whereas psychological or PSA factors as possible predictors for pain were not investigated. The primary aim of the current study is to measure the prevalence and severity of post-procedural pain based on maximal NRS. Secondary aim of this study is to identify predictors for post-procedural pain after liver ablation under PSA.

Methods: This single-center retrospective cohort study was conducted in a tertiary teaching hospital in The Netherlands from November 2018 until May 2023. It involved adult patients (18 years or older) treated with thermal liver ablation under PSA. Prevalence of pain was based on percentage of patients with post-procedural pain (defined as numeric rating scale (NRS) score ≥4).

Results: In total, 170 records of 117 patients were included in the analysis of this study. The prevalence of post-procedural pain after thermal liver ablation was 42.7%. Predictors of post-ablation pain were psychological factors e.g. depression, anxiety disorder or the use of psychopharmacological drugs (β 2.58, 95%CI: 1.44-4.07, p-value < 0.001). A background of chronic pain (β 1.23, 95%CI: 0.11-2.36, p-value 0.03), female gender (β 1.09, 95%CI: 0.17-2.01, p-value 0.02) and age (β -0.04 per calendar year, 95%CI: -0.091 to -0.006, p-value 0.05) were shown to predict acute ablation pain. Tumor location, distinction between primary and secondary tumors and number of tumors did not predict post-ablation pain.

Conclusion: The incidence of post-procedural pain after thermal liver ablation is 42.7%. Predictive factors of post-procedural pain after thermal liver ablation under PSA are psychological factors like depression and anxiety as well as the use of psychopharmacological drugs. Tumor characteristics did not predict post-procedural pain after ablation.

INTRODUCTION

Liver cancer is one of the most common types of cancer. In 2020 an estimated 905,700 people were diagnosed with, and 830,200 people died, from liver cancer globally.[1] Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer with 65% of all cases.[2] Secondary liver cancer is most commonly due to metastasis from colon cancer, breast cancer or melanoma.[2] The principal treatment for both primary and secondary liver tumors is surgical resection, for which not all patients are suitable[3]. This may be due to the location of the tumor, prior surgery, (severe) comorbidities, poor hepatic reserve, or advanced cancer stage or the patient's age.[3] In many of these cases, thermal liver ablation can be a good alternative.[3, 4]

Thermal ablation in patients with liver tumors is generally performed by an interventional radiologist (IR) under computed tomography scan or ultrasound guidance and procedural sedation and analgesia (PSA) or general anaesthesia (GA). PSA is monitored by anesthesia care providers (ACP) and aimed to minimize per- and post-procedural discomfort including pain. In recent years, the number of treatments performed with thermal ablations has risen considerably.[5] The subjective perception of anesthesia care providers and interventional radiologists is that some patients suffer from severe post-procedural pain after PSA and local infiltration and others do not. The varying and unpredictable occurrence of unacceptable pain during PSA in patients after thermal liver ablation is not completely understood.

Several studies have been conducted to study minimizing pain during PSA in thermal liver ablation patients.[3, 6, 7, 8] Based on these studies, an optimal combination of intravenous (i.v.) medication for PSA during percutaneous radiofrequency ablation (PRFA) induced pain cannot be recommended and remains controversial.[6, 7, 9, 10] Most frequently used and recommended drugs for PSA during thermal ablation are sedatives (e.g., propofol, midazolam) in combination with an opioid (e.g., fentanyl, remifentanil, morphine or piritramide). Optimizing peri- and post-procedural analgesia is of major importance also in view of the prevention of possible complications including the development of acute and/or post-procedural pain.[11] In order to minimize procedural pain during and after PSA, opioids are first choice of treatment. However, as the use of large doses of opioids is associated with opioid dependence and hyperalgesia, multimodal PSA based on relatively low concentrations of opioids in combination with i.v.-medication, is nowadays used.[8, 11] Esketamine is an NMDA receptor antagonist, and directly involved in modulating central sensitization, a process known to be pivotal in the development and chronification of pain.[12] Esketamine is increasingly used as an adjuvant for postoperative pain control in major surgery where severe postoperative pain is expected to occur and where opioid analgesia has been shown to be inadequate.[8, 11, 13, 14, 15] Metamizole is a non-selective NSAID with a strong analgesic effect. The analgesic effect occurs within 30 minutes

after intravenous administration and lasts approximately 4 hours.[16] In the Netherlands metamizole has rarely been used since the 1970s because of what was thought to be an unacceptable risk of agranulocytosis.[15] The incidence of metamizole-induced agranulocytosis is controversial, but the risk is likely to be limited with short-term postoperative use in patients with increased risk for stomach or renal problems.[17]

The prevalence of post-procedural pain after percutaneous tumor ablation under PSA is yet unknown. Therefore, the primary aim of this study was to determine the prevalence and severity of post-procedural pain after percutaneous thermal liver ablation in patients under PSA. Only a few studies on pain post percutaneous thermal liver tumor ablation investigated tumor and ablation factors on pain. However, these studies do not include psychological and PSA factors. Therefore, the secondary aim of this study was to identify predictive factors for the development of post-procedural pain following transcutaneous tumor ablation under PSA.

METHODS

Study Design & ethical approval

This retrospective single-center cohort study was performed at the Maastricht University Medical Centre (MUMC$^+$) in The Netherlands. Ethical approval for this study (METC 2020-2222) was provided by the ethics committee of MUMC$^+$ on 25 August 2020, Maastricht, The Netherlands. This study was conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Participants

Patients with primary and secondary liver tumors receiving PSA for a percutaneous thermal liver tumor ablation from November 2018 until May 2023 were included in this study. For characteristics of patients included (Table 1). Pre-, per-, and post-procedural anesthesiologic and radiologic data were required. Exclusion criteria were: age < 18 years, patients who received GA, sedated patients who did not receive an ablation.

Interventions & outcome measures

All patients were treated under moderate to deep sedation. PSA treatment always included an opioid and propofol. The short-acting opioids remifentanil or alfentanil were administered during PSA. Piritramide or morphine in combination with acetaminophen were administered during PSA to prevent post-procedural pain. Based on the clinician's experience and preference esketamine and/or metamizole was administered for multimodal treatment. All patients received supplementary local anaesthesia before PRFA started. In some cases loco-regional anaesthesia like spinal or epidural was combined with PSA.

Post-procedural pain (based on the numeric rating scale (NRS)) was assessed at a minimum of 2 time-points: 1. upon arrival in the recovery room, 2. at departure of the recovery room. In cases when NRS maximum was not equal to NRS arrival or departure a third time-point during the recovery stay is included for assessment of NRS.

Transcutaneous thermal liver tumor ablation

A pre-ablation ultrasound was performed in all patients. All thermal ablations were microwave ablations and performed transcutaneous with ultrasound or CT-guidance. The procedure was performed by an experienced interventional radiologist (CvdL and SdB). The NeuWave Microwave ablation system (Ethicon; Johnson & Johnson) or the HS Amica generator (HS; Hospital Service) was used for the thermal ablation. The duration of the ablation procedure and the energy level (wattage) were determined by the IR.

Clinical assessments

The NRS was questioned by the recovery room staff and documented in the patient data management system (PDMS). The length of stay in the recovery room was automatically recorded in PDMS. During PSA and stay in the recovery room the vital parameters were continuously monitored using the Philips Medical Systems IntelliVue MX800 1&2 and automatically stored in PDMS. Administered medication during PSA and recovery stay was entered in real time into PDMS. Anesthesiology data were collected from PDMS and the pre-operative anaesthesia evaluation form. Risk factors for pain were registered on available data from the electronic patient file and medication overview. Psychological factors were defined as patients who were known to have experienced an episode of depression, anxiety or sleep disorders. Radiological images and reports were assessed using SECTRA IDS7 software (version 23.2.0.2452). Assessment of the images was performed by a trained master medical student and a researcher (K.J. and R.K.) with routine checking by an IR (CvdL). All data required for this study were extracted from the hospital electronic health systems and incorporated in an online database (Castor EDC v2022.5.4.0).

Statistical methods

All analyses were performed using SPSS statistics software version 25.0. A P-value < 0.05 was considered significant. Patient characteristics were described using standard descriptive statistics. The prevalence of pain was tested by using standard descriptive statistics. Linear mixed-effects models were used to accommodate clustering of multiple procedures within patients. Univariable and multivariable models were used to identify baseline characteristics that are associated with the development of having postoperative pain. An NRS difference of 1.4 on the 11-point numeric rating scale was considered clinically relevant.[18, 19] Subsequently, maximum pain intensity (NRS max) was categorized and analyzed using univariable and multivariable linear mixed-effects models. The NRS 11-point numeric rating scale was categorized into: acceptable pain (NRS 0-3) and moderate to severe pain (NRS 4-10).[20] Multivariable models were performed to correct

for potential confounding factors i.e., age, sex, history of chronic pain and psychological factors. These were based on expert opinion and previous literature.[21, 22, 23, 24, 25]

RESULTS

Patient characteristics

From November 2018 until May 2023, 170 thermal liver ablations were performed in 117 patients under PSA. Most procedures were performed in male patients (66.5%), the mean age was 68±10 (mean ± SD), most frequent ASA classification was 3 (60%) and in most procedures 1 liver lesion was treated (67.6%). The median tumor diameter was 18.8 ± 7.0 mm (median ± IQR), (range 5-47 mm). Most frequently ablated tumors were HCC (50.5%) and colorectal metastases (46.5%). Patient characteristics at baseline are summarized in Table 1. The mean length of stay on the recovery room was 103 ± 45 minutes (mean ± SD; range 37-281 min).

Table 1 Baseline characteristics of all procedures, NRS 0-3 group and NRS 4-10 group. Values are number (percentages) unless stated otherwise.

		Total (n = 170)		**NRS 0-3 (n = 98)**		**NRS 4-10 (n = 72)**	
Sex N (%)	Men	113	66.5	73	74.5	40	55.6
Age – mean (SD)		68	10	69	8	66	11
BMI – mean (SD)		26.9	4.1	26.8	3.9	27.0	4.3
Intoxications	Smoking	36	21.6	18	18.8	18	25.4
	Alcohol	72	43.1	33	33.7	30	41.7
	Drugs	4	2.4	1	1.0	3	4.2
ASA classification	ASA 2	63	37.1	36	36.7	27	37.5
	ASA 3	102	60.0	60	61.2	42	58.3
	ASA 4	5	2.9	2	2.0	3	4.2
History of chronic pain		27	15.9	12	12.2	15	20.8
Psychological factors		17	10.0	3	3.1	14	19.4
Thermal ablation last year		53	31.2	29	29.5	24	33.3
Surgery last year		68	40.0	35	35.7	33	45.8
Prognosis	Curative	153	90.0	90	91.8	63	87.5
Received chemotherapy		54	31.8	32	32.7	22	30.9
Tumor type	Primary	91	53.5	52	53.1	39	54.2
	Secondary	79	46.5	46	46.9	33	45.8

		Total (n = 170)		NRS 0-3 (n = 98)		NRS 4-10 (n = 72)	
Liver cirrhosis		73	42.9	33	41.8	9	34.6
Number of lesions	1	115	67.6	68	69.4	47	65.3
	2	40	23.5	21	21.4	19	26.4
	>2	15	8.9	9	9.2	6	8.3
Tumor location	Subcapsular	84	49.4	45	45.9	39	54.2
	Deep	85	50.0	52	53.1	33	45.8
Maximum tumor diameter – mean (SD)	Mm	19.8	7.0	19.2	6.7	20.5	7.5
Vascular involvement	No	97	57.4	59	60.2	38	53.5
	<5mm	31	18.3	20	20.4	11	15.5
	Against vessel	41	24.3	19	19.4	22	31.0

BMI: body mass index; ASA-classification: American Society of Anesthesiologists physical status classification; physiological factors was defined as patients were known to have an episode of depression, anxiety or sleep disorders; SD: standard deviation.

NRS outcomes and predictive factors

The prevalence of having a maximal NRS score ≥4.0 was 42.4%. In the recovery the mean maximal NRS score was 3.1 ± 2.8, 95% confidence interval (CI) 2.69 to 3.50. Details of the distribution per NRS score are summarized in Table 1 of the supplemental data (see page 113). The presence of psychological factors, i.e. depression, anxiety disorder or the use of psychopharmacological drugs (regression coefficient (β) 2.58, 95%CI: 1.44-4.07, p-value < 0.001) was associated with higher NRS scores (Table 2). Also, a background of chronic pain (β 1.23, 95%CI: 0.11-2.36, p-value 0.03), female gender (β 1.09, 95%CI: 0.17-2.01,p-value 0.02) and age (β -0.04 per year, 95%CI:-0.091 to -0.006, p-value 0.05) resulted in a significant increase of the NRS-score. Location (aβ -0.40, 95%CI:-1.21-0.33), size (aβ 0.02, 95%CI:-0.03-0.08) or type (aβ -0.27, 95%CI:-0.90-0.36) of the tumor did not have a significant effect on the maximum NRS score (supplemental data Table 2 page 113). Neither the number of lesions (aβ 0.21, 95%CI:-0.24-0.65) ablated nor the duration of anesthesia (aβ 0.00, 95%CI:-0.09-0.11) or duration of procedure (aβ 0.00, 95%CI:-0.1-0.01) did affect the maximum NRS score. Esketamine was administered during PSA and tended to reduce the maximum NRS score in 33.5% of the procedures (aβ -0.74, 95%CI:-1.53-0.04, p-value 0.06). Mean dosage of esketamine was 0.17 mg/kg SD ± 0.11 (range 0.05-0.55 mg/kg). It is not possible to reliably estimate the effect of metamizole on post-procedural pain as this drug was administered in only 6.5% of the cases.

An average higher NRS score at arrival in the recovery (aβ 0.79, 95%CI:0.69-0.88, p-value < 0.001) was shown to be associated with a higher maximum NRS score. Patients with

a NRS score ≥ 4.0 required more analgesics in the recovery room (piritramide aOR 18.4, 95%CI: 7.78-43.45 or morphine aOR 10.64, 95%CI:2.71-41.74).

Table 2 maximum NRS in univariable linear mixed-effects model

	β	95% CI	P-value
Gender	1.09	0.17-2.01	0.02
Age*	-0.04	-0.09-0.00	0.05
BMI	0.00	-0.11-0.11	0.99
ASA	-0.06	-0.83-0.72	0.89
Chronic pain	1.23	0.11-2.36	0.03
Psychological factors	2.58	1.44-4.07	<0.001
Smoking	-0.39	-0.98-0.19	0.19
Alcohol	-0.42	-0.85-0.02	0.06
Drugs	-0.83	-1.90-0.24	0.13
Cirrhosis	-0.19	-1.07-0.70	0.68
Chemotherapy**	-0.28	-1.18-0.62	0.55
Surgery**	-0.25	-1.07-0.57	0.55
Thermal ablation**	0.01	-0.83-0.84	0.98
Duration anesthesia	-0.00	-0.01-0.01	0.98
Duration procedure	0.00	-0.01-0.01	0.75
Maximum tumor diameter	0.02	-0.04-0.07	0.56
Tumor location	-0.30	-1.07-0.47	0.44
Vascular involvement	0.03	-0.45-0.51	0.90
Number of lesions	0.12	-0.36-0.59	0.63

β:regression coefficient; CI: confidence interval. * per calendar year;** < 1 year prior to treatment.

DISCUSSION

The incidence of postoperative pain based on maximal NRS score ≥4 was 42.4% after thermal liver ablation. This is slightly lower than reported after upper abdomen surgery.[26] A prevalence of 41% of moderate or severe pain (based on a visual analogue scale (VAS) score of >40) on day 0 after surgery was noted in a group of 1490 surgical inpatients.[26] On day 0, but 1 hour after surgery, when patients were in the recovery room 55% of the patients after intermediate upper abdomen surgery i.e., cholecystectomy and 47% major abdomen surgery i.e. hepatectomy suffered from postoperative pain based on a visual analogue scale (VAS) score of >40.[26] Hence, our results in patients after thermal liver ablation, a percutaneous minimal invasive procedure, are in the same range as those reported after upper abdomen surgery.[26] Nevertheless liver ablation is characterized by three moments which are known to be painful: skin puncture, liver capsule puncture, as well as the moment of the thermal energy transfer.[3] This then may underlie the fact that

this relatively minimal invasive procedure results in a prevalence of postoperative pain similar to that noted after more invasive surgeries like upper abdomen surgery.[26]

Previous studies have demonstrated that tumor characteristics such as location, type or size are known risk factors for the occurrence of peri-procedural pain.[6, 7, 9, 10, 27] In our study, tumor characteristics did not predict post-ablation pain. A study by Andreano et al. reported an association between the volume of the ablation zone on CT and presence of post-procedural pain (NRS ≥ 4.0).[28] The latter association is also not noted in our study, suggesting a limited effect of tumor type on post-procedural pain intensity. One explanation might be that PSA strategies differ between the studies.[6, 7, 9, 10] The depth of sedation varied from light to moderate and moderate to deep. In the groups with light to moderate sedation the patients were able to indicate whether they experienced pain during ablation and if so then the dosage of pain medication was increased. In general patients experience a moment of intense acute pain during ablation which subsequently faded away post-ablation. During moderate to deep sedation, as in our study, patients did not consciously experience pain during ablation. The first notable pain the patients in our study experienced was the pain when they recover and became conscious. Of those patients which reported NRS ≥ 4 the dosage of analgesics was increased during PSA if there were any signs of discomfort or pain during e.g., face expressions, increasing ventilation rate, tachycardia, hypertension or movement. In all studies[6, 7, 9, 10] reported up till now different combinations of medication were administered. This may vary from midazolam, dexmedetomidine or propofol as sedatives and a range of opioids e.g., pethidine, fentanyl, oxycodone, remifentanil, piritramide or morphine. During PSA there is a limitation on the dosage of opiates due to dose-related complications like respiratory depression sometimes resulting in oxygen desaturation and apnea. Esketamine has been reported not to result in these side-effects and therefore is increasingly used as an adjuvant for postoperative pain.[8, 11, 13, 14, 15] Although esketamine does not significantly reduce pain based on the NRS score, it still may prevent patients from reaching clinically relevant levels of NRS score ≥4. In our study it is not possible to reliably estimate the effect of using metamizole due to a small group size. It is thus worth considering a prospective study on the effect of metamizole on post-procedural pain after thermal liver ablation.

This retrospective single-center study has several limitations. Due to the retrospective observational nature of the study we were not able to adjust the analyses for unmeasured potential confounders. Biases might have occurred such as: 1. pre-operative pain, 2. psychological factors and 3. sedation strategy. Due to the retrospective design we had to work with the available data from the electronic patient file and medication overview. In 31.8% of the cases there were missing data of NRS score pre-procedural. The effect of pre-procedural pain on the maximum NRS might therefore be underestimated. Psychological factors were defined as patients who were known to have experienced an episode of depression, anxiety or sleep disorders. The incidence might be underreported as we used

the available data of the electronic patient file. Ideally registration was based on prospective data such as validated questionnaires (e.g. Hospital Anxiety and Depression Scale). It has been documented that preoperative high expectations of postoperative pain by the patient is also a predictor for postoperative pain. Unfortunately this information was not documented. Finally, sedation practitioners in our study were free to choose their sedation strategy for the individual patient.[24, 29] Although the retrospective design might also affected the generalizability of the study, the results suggest that predictors for thermal liver ablation are similar to predictors for acute postoperative pain. For a follow-up study, a prospective design is preferred.

CONCLUSIONS

First, the incidence of post-procedural pain (NRS score $\geq$4) after thermal liver ablation is 42.7%. Second, predictive factors of post-procedural pain after thermal liver ablation under PSA are psychological factors such as depression and anxiety as well as the use of psychopharmacological drugs, and a background of chronic pain, female gender and age.

SUPPLEMENTAL TABLES

Supplemental Table 1. Distribution per NRS score

NRS	N	%	Cumulative %
0	37	21.8	21.8
1	25	14.7	36.5
2	27	15.9	52.4
3	9	5.3	57.6
4	17	10.0	67.6
5	19	11.2	78.8
6	12	7.1	85.9
7	13	7.6	93.5
8	7	4.1	97.6
9	2	1.2	98.8
10	2	1.2	100.0
Total	170	100	

N: frequency; %: percentage

Supplemental Table 2 maximum NRS in univariable linear mixed-effects model

	aβ	95% CI	P-value
BMI	0.03	-0.06-0.13	0.50
ASA	0.05	-0.67-0.77	0.90
Smoking	-0.26	-0.79-0.26	0.32
Alcohol	-0.32	-0.71-0.07	0.10
Drugs	-0.49	-1.50-0.52	0.34
Cirrhosis	0.06	-0.77-0.88	0.89
Chemotherapy*	-0.53	-1.38-0.32	0.22
Surgery*	0.15	-0.64-0.94	0.72
Thermal ablation*	0.04	-0.77-0.85	0.92
Duration anesthesia	0.00	-0.09-0.11	0.83
Duration procedure	0.00	-0.01-0.01	0.73
Maximum tumor diameter	0.02	-0.03-0.08	0.40
Tumor location	-0.40	-1.21-0.03	0.29
Vascular involvement	-0.03	-0.48-0.42	0.90
Number of lesions	0.21	-0.24-0.65	0.36
Esketamine**	-0.74	-1.53-0.04	0.06
Metamizole**	-0.46	-2.24-1.32	0.62

aβ:regression coefficient adjusted for psychological factors, gender, chronic pain and age; CI: confidence interval; * < 1 year prior to treatment; ** administrated during PSA.

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7

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DISCUSSION

The aim of this thesis is to study and evaluate the safety and quality of procedural sedation and analgesia (PSA), with particular attention to complications and clinical outcomes in non-operating room anesthesia (NORA) settings. Furthermore, the opportunities to improve procedural quality and patient care are identified. In the following sections findings related to the research questions (RQ) as formulated in the Introduction of this thesis (Chapter 1 page 10-11) are summarized and discussed in a broader context. The role of sedation in the context of the rising numbers of minimal invasive procedures is addressed. Potential directions for future research are proposed.

RQ 1. What is the status on optimization of practices of procedural sedation and analgesia during atrial fibrillation ablation?

In Chapter 2 the current status on optimization of PSA during atrial fibrillation (AF) ablation is presented. This review concludes that no single optimal sedation strategy exists for all AF ablation patients. Sedation should be individualized based on patient characteristics, the required depth of sedation, the type and duration of the procedure, and the experience of the anesthesia care provider to ensure safety and effectiveness.[1] Patients with AF often are presented with other comorbidities like hypertension, diabetes, heart failure and sleep-disordered breathing (SDB) which all may affect the response to sedation. These comorbidities should be monitored and taken into account when selecting the optimal sedation strategy and technique for patients undergoing AF ablation. SDB, which is highly prevalent among AF patients, is an important factor influencing sedation management. The commonly used STOP-BANG questionnaire demonstrates limited validity in this specific population, underscoring the need for more accurate screening tools.[2] Looking forward, data-driven approaches, including artificial intelligence–based prediction models, may further enhance pre-procedural assessment by integrating multidimensional patient characteristics, comorbidities, and procedural factors to estimate individualized sedation risk.[3] Additionally, the use of high-flow nasal oxygen (HFNO) has been shown to reduce the risk of desaturation during procedural sedation in general populations, suggesting its potential value in AF ablation settings.[2] Meanwhile, evidence from our study in the AF ablation population showed no benefit of HFNO in reducing the incidence of hypoxemia (see Chapter 5). Overall, these findings support a trend towards more personalized sedation strategies that integrate patient-specific factors and procedural requirements. Such an approach may contribute to improved safety, efficiency, and patient satisfaction during AF ablation.

Procedural success depends on selecting a sedation strategy that enables the procedure to be completed safely, smoothly, and without unnecessary interruptions. Patient comfort should be ensured by providing an appropriate level of sedation and analgesia, tailored

to the patient's needs and the anticipated procedural stimuli. Time efficiency is improved when the chosen sedation regimen, covering drug regimen and sedation depth, allows for predictable onset, stable conditions during the procedure, and a swift and uncomplicated recovery.[4] For these reasons, we focus on the drug regimen, the depth of sedation and monitoring.

The choice of a sedative or opioid (see Chapter 1 Introduction page 7) is influenced by the type of procedure, local availability, and the preference and experience of the anesthesia care provider. When medication is used occasionally for specific indications, it is more difficult to achieve well-balanced PSA. The anesthesia care provider's experience may be insufficient to rapidly reach the desired level of sedation without respiratory or hemodynamic fluctuations. This may compromise the intended effect for both patient and clinician. In general, propofol is the sedative of first choice for prolonged deep sedation. For painful procedures, propofol should be combined with an opioid. Alfentanil is an appropriate analgesic for short interventions, whereas remifentanil is more suitable for longer procedures or situations in which the degree of analgesia needs to be adjusted during the treatment. For very painful procedures, esketamine can be added to provide additional analgesia. The preference and experience of the anesthesia care provider and local institutional practices are more decisive than the agent that may theoretically be the better pharmacological choice.[5, 6] Therefore, the implementation for tailored pharmacological regimens in common practice remains limited.[7]

Sedation depth exists along a continuum (see levels of sedation: Chapter 1 Introduction page 5-6), and it is not always possible to predict how an individual patient will respond. Clinical assessment and systematic documentation of sedation depth are therefore essential to ensure both the quality and safety of sedation.[8] Continuous evaluation is required to determine whether the patient is unintentionally over- or under-sedated. The value of bispectral index (BIS) monitoring in procedural sedation is still controversial.[8] BIS monitoring allows an objective assessment of the sedation depth and has been suggested to reduce complications.[9] However, studies also show that BIS monitoring does not improve oxygenation, reduce cardiopulmonary events, or provide clear clinical benefit during endoscopic sedation.[10, 11] Although BIS monitoring during propofol sedation has been associated with higher patient and clinician satisfaction, as well as more efficient titration and shorter procedures, the overall evidence remains inconsistent.[10, 11] In general, sedation depth should thus be carefully tailored, avoiding unnecessarily deep levels when possible and limiting exposure time. At present, it remains unclear whether there is a correlation between sedation depth and adverse effects on cognitive domains. Evidence from general anesthesia research suggests caution: prolonged exposure to surgery under general anesthesia has been independently associated with negative effects on executive functioning, selective attention and mental speed, and information-processing speed.[12] Cumulative exposure to general anesthesia may contribute to long-term cognitive de-

cline, although age and education remain more influential factors.[12] The findings in this report, however, cannot be directly applied to sedation depth or procedural sedation, as the study examined overall lifetime exposure to general anesthesia.[12] Nevertheless, the observed association between anesthetic exposure and cognitive decline may suggest that deeper, frequent or more prolonged sedation may carry increased long-term risks.[13] In the context of AF ablation, a continuously deep level of sedation is typically required, as patients must remain immobile. In addition, the duration of the procedure is frequently prolonged and potentially contributing to greater cumulative anesthetic exposure.

During PSA continuous and systematic physiological monitoring is essential to ensure patient safety and to facilitate the early detection of adverse events. Standard monitoring for PSA typically during moderate to deep sedation includes non-invasive blood pressure measurement (NIBP), pulse oximetry, cardiac rhythm monitoring, and end-expiratory capnography ($EtCO_2$).[8, 14] Pulse oximetry provides continuous assessment of oxygen saturation and heart rate. Capnography is valuable for monitoring ventilation during PSA. As a real-time measure of end-expiratory CO_2, capnography enables earlier identification of respiratory depression and apnea compared with pulse oximetry.[8] This earlier detection allows prompt intervention and may reduce the incidence and severity of hypoxic events. The incidence of apnea itself is not reduced, apnea can be detected earlier with capnography, enabling timely intervention and potentially preventing further respiratory compromise.[15] Consequently, the incorporation of $EtCO_2$ monitoring is recommended, especially in settings involving moderate to deep sedation or in patients at increased risk of respiratory complications. When reliable $EtCO_2$ monitoring is technically not feasible, transcutaneous CO_2 monitoring ($TcCO_2$) can serve as an alternative.[16] $TcCO_2$ is a non-invasive method that can be used during PSA as a substitute for laboratory-based blood CO_2 measurements.[16] While standard monitoring is generally sufficient for most patients undergoing PSA, invasive arterial blood pressure or central venous pressure monitoring may be indicated in selected high-risk patients or during more complex procedures. As the majority of AF patients receiving PSA are classified as ASA II, standard monitoring should be sufficient for this group. For more complex patients, $TcCO_2$ monitoring may provide an early warning signal for respiratory complications such as apnea, by enabling continuous trend assessment.

RQ 2. Is it possible to determine the incidence and severity of respiratory complications during procedural sedation and analgesia in atrial fibrillation ablation, and to identify predictive factors for their occurrence?

In order to answer this RQ, a retrospective cohort study of 232 patients undergoing PSA for atrial fibrillation (AF) ablation is performed (Chapter 3). The main outcome of our retrospective study was a relatively high incidence of respiratory complications during AF ablation with PSA of 42.2%. Which occurred as follows: 0.4% minor**,** 35.0% intermediate,

and 15.1% severe**.** In 3 cases (1.3%)**,** there was a conversion to general anesthesia. While age over 50 years is typically linked to an increased risk of respiratory complications, this threshold showed limited ability to differentiate risk in the present cohort, as most patients undergoing AF ablation were above this age. A key predictive factor related to the procedure is the duration of PSA.

Our study presents a number of important strengths. The collaboration between the Departments of Anesthesiology and Cardiology at MUMC$^+$ facilitates an integrated clinical perspective, thereby strengthening the impact of the study's findings. The use of a large, systematically collected dataset from the ISOLATION cohort enhances both the reliability and validity of the findings. ISOLATION is a two-center prospective cohort study including patients undergoing AF ablation. The ISOLATION cohort study collects clinical characteristics and routine clinical test results, as well as results from the following additional diagnostics: determination of body composition, pre-procedural rhythm monitoring, extended surface electrocardiogram, biomarker testing, genetic analysis, and questionnaires.[17] For the present analysis, only patients from the ISOLATION cohort who were enrolled at Maastricht University Medical Center$^+$ (MUMC$^+$) were included. A key contribution of this cohort study is the identification of novel, easily measurable patient characteristics, such as neck circumference or visceral fat percentage, that may serve as practical indicators for pre-procedural risk stratification in patients undergoing PSA. Besides these strengths, several limitations should also be acknowledged. For instance, the application of strict exclusion criteria, including the exclusion of patients with a high body mass index or known obstructive sleep apnea, may have introduced selection bias and consequently limits the generalizability of the results to the broader AF-patient population. In addition, the single-center and retrospective nature of the study introduces a potential risk of missing or incomplete data, especially regarding dose–response relationships. Documentation of the type and dosage of sedative and analgesic agents administered was not performed in a systematic manner.

Findings of our cohort study (see results Chapter 3) provide valuable opportunities for future follow-up research and clinical application. The results obtained underscore the potential to refine pre-anesthesia assessment procedures by integrating more objective and systematic screening methods, such as routine sleep studies or automated prediction tools based on identified risk factors.[2] The BOSS-GAP score may serve as a pre-selection tool to identify patients with atrial fibrillation who are likely to benefit from further evaluation for sleep-disordered breathing (e.g., sleep studies).[2] Excluding patients with low scores may improve both the efficiency and cost-effectiveness of screening pathways. The BOSS-GAP score has been derived from a single cohort of limited size, and external validation remains insufficient.[2] The score does not replace gold-standard sleep studies but is intended to serve as a supportive tool within the clinical workflow. These insights may further contribute to the development of standardized protocols for

patient selection for PSA in AF ablation, ultimately improving patient safety and procedural efficiency. Furthermore, the results of our study may provide information for future investigations into novel ablation technologies, including pulsed field ablation, in which deeper sedation introduces further respiratory challenges. The use of PSA in novel AF ablation techniques requires careful assessment of sedation strategies and intraoperative risk management.[18] Physiological responses and sedation needs may differ from those in conventional procedures such as cryoballoon or radiofrequency ablation. Nevertheless, several factors may limit the implementation of these findings into clinical practice. The growing demand for anesthesia support during AF ablations places additional strain on anesthesia resources. Furthermore, considerable heterogeneity in sedation practices across institutions continues to hinder the development of standardized operating protocols.

Non-operating room anesthesia (NORA), including PSA, offers a safe way to manage patient comfort and safety while performing procedures like AF ablation. The demand for NORA has increased substantially in recent years, driven by the growing number of minimally invasive and diagnostic procedures performed outside the operating room.[19] This includes interventional radiology procedures such as embolization and tumor ablations, cardiology procedures such as device implantation and catheter ablation, and a wide range of endoscopic interventions, many of which require deeper levels of sedation or general anesthesia. The expansion of these procedures is largely attributable to the advantages of minimally invasive techniques, which are associated with shorter recovery times, fewer complications, and lower costs compared with traditional surgical approaches.[19] Consequently, both patients and healthcare providers are increasingly opting for such procedures, thereby reinforcing the essential role of NORA in ensuring patient comfort and safety.[20]

In this context, maintaining patient safety during procedural sedation remains a key priority, particularly in NORA settings. In NORA settings, including PSA, respiratory depression remains a major patient safety concern. Contributing factors include the absence of standardized protocols, the increasing age and comorbidity burden of the patient population, the physical separation from the operating room, and the limited familiarity among NORA team members.[21] Collectively, these elements contribute to the relatively high incidence of respiratory complications observed in NORA. The updated Helsinki Declaration on Patient Safety in Anaesthesiology 2.0 provides an enhanced framework emphasizing evidence-based protocols, monitoring standards, and quality improvement measures that support safe anesthetic practice across all care settings, including procedural sedation and non-operating room anesthesia.[22] In line with this, the 2022 Anesthesia Patient Safety Foundation (APSF) Stoelting Conference released consensus recommendations from a multidisciplinary group of experts on the safe practice of NORA, which include patient selection.[23] The recommendations address many areas that are cited as contribu-

tory to safety problems in NORA: facility and location, access to equipment and supplies, teamwork issues, peri-procedural care, and quality improvement.[23] With the growing number of unique patient populations, including geriatric, obese, and medically complex individuals with multiple comorbidities, the NORA-team must remain acutely aware of the heightened susceptibility of these patients to respiratory events. Providers involved in their care should be prepared to manage these complex situations effectively in order to maximize safety and optimize patient outcomes.

Safety may be compromised by the absence of internationally standardized requirements for training, competencies, and credentialing in PSA which results in substantial variation in clinical practice.[4] To improve safety recent expert consensus outlines a minimum set of knowledge, skills, and attitudes essential for the safe and effective delivery of sedation care.[4] Structuring these competencies within a Competency-Based Medical Education framework, supported by Entrustable Professional Activities (EPAs), clarifies the responsibilities of sedation practitioners and provides a systematic approach for assessing competence.[4, 24] Continuous quality improvement, including systematic auditing of sedation practice, monitoring of adverse events, adherence to established protocols, and engagement in ongoing professional development, is essential for maintaining safe and effective sedation care.[4] Collectively, these recommendations form a foundation for the standardization of sedation practice and support further discussion on harmonizing training, defining professional roles, and optimizing the delivery of safe sedation care. This approach applies to all professionals performing PSA, regardless of whether they have a background in anesthesiology, another medical specialty, or practice as a nurse sedation provider. Nurse-led sedation can be safe and effective when practitioners have undergone specialized training and operate within a robust safety framework.[4, 25, 26, 27] Although one may aim for international consensus on standardized requirements for training, competencies, and credentialing in procedural sedation, local agreements ultimately remain crucial. These should define which procedures and patients are suitable or unsuitable for nurse-led sedation, specify the required skill level of the sedation provider, and ensure adequate backup arrangements for emergency situations. This is particularly important because the composition of the anesthesia team, as well as the education and scope of practice of anesthesia nurses or other non-medical anesthesia team members, differ considerably from country to country.[4, 8]

In sedation practice, it is fundamental to establish clear agreements with collaborating departments. In centers performing AF ablations where sedation is provided by the anesthesia department, explicit expectations must be defined. This requires formalized working arrangements between the departments of anesthesiology and cardiology, to which all team members are expected to adhere. The sedation practitioner frequently operates as a guest within a team from another department. It is important that the sedation practitioner does not act like a guest, but functions as a fully integrated member

of the team.[4] It is therefore crucial that the sedation practitioner has a clearly defined role within the multidisciplinary team, in which effective collaboration is essential and arguably even more so than in the operating theatre. Close collaboration between care providers, supported by clear and consistent communication, is fundamental to a safe and efficient sedation practice.

RQ 3. Does high-flow nasal oxygen affect oxygenation and the incidence of hypoxemia during procedural sedation for atrial fibrillation catheter ablation?

The study protocol underlying our study on HFNO and the incidence of hypoxemia during PSA for AF catheter ablation was published and outlined in Chapter 4, and this then provided the methodological foundation for the study as reported in Chapter 5. The results presented in Chapter 5 show that HFNO does not improve oxygenation compared with LFNO and is not associated with an increased risk of complications. Although the safety and use of HFNO is well established, our study demonstrates that HFNO provides no additional benefits during PSA for CA in selected patients with AF. Considering the associated costs and environmental impact, routine use of HFNO for this indication can thus not be justified.

It should be taken into account that the prospective and randomized design of our study (see Chapter 5) enhanced the internal validity and minimized bias, thereby strengthening the robustness of the findings. The results of our study are generalizable to other clinical settings in which AF patients undergo prolonged deep sedation in a supine position. PSA is also performed in patients without AF or in AF patients positioned laterally or prone, particularly during gastrointestinal procedures such as gastroscopy or colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP).[28, 29] The results of our study cannot be generalized to these situations. Furthermore, the safety profile of HFNO during PSA for AF catheter ablation was confirmed in our study as no increase in complications was observed compared with LFNO (see Chapter 5).[30, 31, 32]

The current available evidence on the use of HFNO during PSA presents a mixed picture, highly dependent on the clinical setting and procedures selected.[30, 31, 32, 33, 34, 35, 36] Meta-analyses and randomized trials in procedures such as gastrointestinal endoscopy and bronchoscopy consistently demonstrate that the use of HFNO does reduce the incidence of hypoxemia, increase nadir SpO_2, and lower the need for airway interventions as compared to conventional low-flow oxygen (LFNO).[31, 32, 33, 34, 36, 37] These benefits of HFNO are related to procedures involving the upper airway, where transient desaturation is both common and clinically significant. However, the depth of sedation, often light to moderate and not always recorded in these studies, is not comparable to the deep sedation as applied in our study in cardiologic patients with CA for AF ablation. Moreover, while HFNO has demonstrated benefits in non-obese and obese patients, its effects are less evi-

dent in those with morbid obesity.[31] Given the increased risk of upper airway obstruction, atelectasis, hypoxemia, and hypercapnia in this population, clinicians should be cautious when considering HFNO during sedation or anesthesia, as its advantages may be limited or even absent in these patients with morbid obesity.[31] Furthermore, the largest systematic review and meta-analysis reported in literature concluded that the evidence supporting the benefits of HFNO—specifically improved oxygenation, reduced need for airway interventions, and fewer procedure interruptions during endoscopic procedures—is of low to moderate quality, indicating that these findings should be interpreted with caution.[32] Many systematic reviews and meta-analyses are based on an identical set of core randomized controlled trials, resulting in considerable overlap and limited inclusion of unique participants.[31, 32, 33, 34, 36] As a result, the apparent strength of evidence in this field (and benefits of HFNO) may overstate the degree of independent validation.

In contrast to procedures in gastrointestinal endoscopy and bronchoscopy, evidence from cardiology-related procedures supporting the use of HFNO during PSA to reduce the incidence of hypoxemia is less favorable. In a study on patients undergoing transcatheter aortic valve replacement with conscious sedation, HFNO did not provide superior arterial oxygenation compared with standard oxygen therapy.[35] Conway et al. investigated HFNO during cardiac implantable electronic device procedures and found the therapy to be safe but without measurable improvement in oxygenation or CO_2 clearance compared with LFNO, findings that are in line with the results of our study.[30] This raises a critical paradox: despite the fact that the cardiac study populations as for instance CA in AF patients are known with a relatively high incidence of hypoxemia [38], use of HFNO does not result in additional benefits. These findings suggest that the effectiveness of HFNO may not simply depend on baseline hypoxemic risk, but rather on specific procedural and physiological factors. The combination of supine positioning and upper airway obstruction due to the depth of sedation, along with a higher chance of sleep-disordered breathing (SDB) as noted in our study population of CA in AF patients may explain why we did not observe benefits of HFNO. In our study protocol as well as that used by Conway et al., it is stipulated that HFNO should not be used in combination with a nasal or oral airway.[30] Given the fact that HFNO has been shown to be more effective than LFNO, particularly in studies involving a shared airway [31, 33, 34, 37] it is therefore reasonable to suggest that use of HFNO in combination with a nasal/oral airway might be more effective than LFNO during sedation in device implantations and CA in AF patients.

Table 1. HFNO during PSA in various procedures

Study	Year	Setting	Sample Size	Comparator	Primary Outcome	Key Findings
RCTs Cardiology						
Conway et al. [30], randomized controlled trial	2022	Cardiac device implantation with PSA	126	LFNO (5 L/min, 100% O_2)	$TcCO_2$, hypoxemia incidence, safety	HFNO safe; no significant improvement in oxygenation compared to LFNO.
Scheuermann et al. [35], randomized controlled trial	2022	Transcatheter aortic valve replacement (TAVR) with conscious sedation	80	Standard oxygen therapy	Hypoxemia, hypercapnia, safety	HFNO did not significantly improve oxygenation or CO_2 clearance but was safe
Homberg et al., randomized controlled trial	2025	Catheter ablation for AF with PSA	101	LFNO (5 L/min, 100% O_2)	Lowest SpO_2, duration Lowest SpO_2	HFNO did not improve oxygenation; no added value over LFNO, but safety confirmed.
Systematic reviews / Meta-analysis						
Su et al. [34], systematic review & meta-analysis	2021	Bronchoscopy with sedation	257 (5 RCTs)	LFNO / conventional oxygen	Incidence of hypoxemic events, lowest SpO_2	HFNO reduced hypoxemia and improved nadir SpO_2.
Carron et al. [31], systematic review & meta-analysis	2022	Gastrointestinal endoscopy with deep sedation	2,867 (6 RCTs)	LFNO / standard oxygen	Hypoxemic events, min SpO_2, airway interventions, procedure interruption	HFNO reduced hypoxemia, airway interventions, and procedure interruptions.
Zhang et al. [36], systematic review & meta-analysis	2022	Digestive endoscopy with sedation	2,998 (7 studies)	Standard nasal cannula (LFNO)	Hypoxemia incidence, airway interventions	HFNO lowered hypoxemia rates and reduced need for interventions.
Tao et al. [33], systematic review & meta-analysis	2022	Endoscopic procedures with sedation	4093	LFNO / conventional oxygen	Oxygenation, desaturation, procedure interruption	HFNO improved oxygenation, reduced desaturation and interruptions.
Thiruvenkatarajan et al. [32] systematic review & meta-analysis	2023	Procedural sedation (across specialties)	4121 (15 RCTs)	Standard O_2	Incidence of hypoxemia, airway events	HFNO reduced risk of hypoxemia across procedures but with moderate heterogeneity.

Several limitations of our study must, however, be acknowledged. The most notable limitation was the reduced sample size, as only 101 participants were included instead of the originally planned 188 based on power analysis. Recruitment challenges were compounded by the exclusion of patients diagnosed with SDB and/or by a shift in clinical practice toward single-shot pulse field ablations, which reduced the eligible study population. PFA induces diaphragmatic stimulation, and is therefore not directly comparable to RF ablation techniques. As a result, our study was terminated prematurely for futility. In our study (see Chapter 5) the sedation depth was continuously monitored using BIS [39, 40], and the procedure duration allowed for reliable BIS assessment. In retrospect, the protocol would likely have benefited from correlating BIS with the systematic application of a validated clinical sedation scale, such as the Ramsay Sedation Scale (RSS).[41] The RSS was unfortunately not included into the protocol as it was thought that it may potentially influence the interpretation of sedation depth given the potential for inter-observer variability.

RQ 4. What is the prevalence and severity of acute post-procedural pain following percutaneous thermal liver tumor ablation under procedural sedation and analgesia?

Our retrospective cohort study (see Chapter 6) in patients following percutaneous liver tumor ablation demonstrates that acute post-procedural pain in the recovery room following PSA frequently occurs, with a prevalence of 42.7%, if pain is defined as a maximum Numeric Rating Scale (NRS) score of ≥4. The mean maximum pain intensity on the NRS in the recovery unit was 3.1 ± 2.8 (mean + SD). Psychological factors, including depression and anxiety, and the use of psychopharmacological medication, were shown to be significant predictors of higher pain scores. A history of chronic pain, female gender, and younger age was also associated with increased post-procedural pain in the patients with percutaneous tumor ablation following PSA. In contrast [42, 43, 44], tumor-related characteristics such as lesion size, location, and number of tumors showed no association with pain severity post-ablation. These findings underscore the importance of patient-specific psychological and physiological factors to be related to pain perception, rather than tumor characteristics. Notably, the observed prevalence and pain severity are comparable to those reported following upper abdominal surgery, despite the minimally invasive nature of percutaneous ablation.[45, 46] This emphasizes the need for individualized, multimodal analgesic approaches that incorporate both biological and psychological determinants of pain and allows to optimize peri-procedural management and patient recovery.

Post-procedural pain, although often associated with surgical procedures, can also occur following minimally invasive interventions. New models are being developed to identify patients at increased risk of adverse postoperative pain outcomes. During the preoperative assessment, it is essential to recognize patients who are at risk of experiencing long-

term but also severe acute postoperative pain (APOP). This requires a broad approach that considers physical complaints as well as psychological and social factors, health literacy, and expectations regarding APOP.[47] Perioperative medicine will therefore need to move toward tailored, early-onset pain management strategies.[48, 49] Preoperative interventions for patients at highest risk of poor pain control and opioid use disorder continue to evolve.[47] Preoperative opioid use remains an important concern, as it is associated with increased postoperative morbidity, greater pain, and higher opioid consumption.[47] Although current strategies focus primarily on preventing withdrawal and applying multimodal analgesia, for patients using high-dose opioids a regional technique combined with PSA or general anesthesia is an appropriate option for percutaneous thermal liver tumor ablation.

Predictive models using questionnaires, as well as machine-learning algorithms based on routinely available electronic health record data may help identify patients at highest risk of APOP, though further validation is needed.[50] Psychological preparation, such as procedural information, cognitive techniques, and relaxation, may have positive effects on APOP, with the strongest evidence supporting cognitive behavioral therapy (CBT) and mindfulness-based interventions.[47] However, CBT requires 6–8 weeks of preparation, which is not feasible for all oncology patients, including those undergoing liver tumor ablation. The AMAZONE study may provide valuable insights into whether shorter, scalable online education programs offering surgical information and healthy lifestyle guidance can improve APOP.[51] In this multicenter randomized trial, high-risk breast cancer patients are assigned to either e-CBT or online education.[51]

Non-pharmacological approaches, such as communication strategies like Skills4Comfort and Comfort Talk®, or medical hypnosis, may play a relevant role in reducing procedural anxiety and the anticipation of acute pain.[52, 53, 54, 55, 56, 57] Anxiety is known to amplify the subjective perception of pain, increase sympathetic activation, and negatively affect cooperation during procedures performed with PSA. Targeted comfort communication techniques aim to foster a sense of trust, safety and control, thereby reducing emotional distress and anticipated pain, and improving the patient's overall procedural experience.[55, 58] In addition, improved patient reassurance and engagement may decrease the need for higher sedative or opioid doses.[58] Although robust evidence in the context of acute post-procedural pain following percutaneous thermal liver tumor ablation is not available, the broader literature suggests that structured communication techniques can meaningfully contribute to patient comfort. Integrating such approaches alongside PSA may therefore be advisable.

Minimal invasive procedures, NORA including PSA

This section discusses the minimally invasive procedures of AF ablation and percutaneous thermal liver tumor ablation and their relationship to NORA and PSA, as well as their implications for clinical and scientific research. PSA is applied across a wide range of procedures, each with its own clinical implications, duration, and required depth of sedation although core monitoring requirements and fundamental safety considerations remain universal. As a result, sedation strategies cannot be uniformly extrapolated across all indications and procedures.

Both atrial fibrillation (AF) ablation and percutaneous thermal liver tumor ablation are minimally invasive procedures performed in patients undergoing PSA.[59, 60, 61] In both procedures PSA aims to optimize patient comfort, minimize procedural stress, and maintain immobility, thus contributing to the success of the intervention. The anesthetic objectives are comparable, focusing on achieving adequate sedation depth, preserving spontaneous ventilation, and maintaining stable hemodynamic conditions throughout the procedure. Additionally, both procedures require careful titration of sedatives and analgesics, as their relatively long duration and potential for respiratory compromise require careful and continuous monitoring and dose adjustment. The monitoring requirements in both procedures are comparable, involving continuous assessment of respiratory and cardiovascular parameters, including the use of capnography, and regular evaluation of sedation depth.[8, 14] Individual patient characteristics, including age, body composition, and comorbid conditions such as sleep apnea or cardiopulmonary disease, are important determinants of sedation safety and post-procedural recovery.[8, 62] Both AF and percutaneous liver tumor ablation are typically performed in the supine position and under deep sedation. Patient movement, particularly respiratory motion, can directly affect procedural accuracy. Episodes of hypoventilation or exaggerated respiratory excursions may compromise catheter stability during AF ablation or interfere with the ultrasound or CT-guided visualization of the ablation needle tip during liver tumor ablation.[61, 63, 64, 65, 66] Procedure-related discomfort represents a further similarity, underscoring the importance of tailored analgesic strategies. Both procedures involve extended periods without painful stimulation, interrupted by sudden episodes of nociceptive input during the ablation phase.[43, 67] Interdisciplinary collaboration plays a crucial role in ensuring procedural safety and optimal sedation management.[19] This collaboration contributes to consistent procedural standards and contributes to improve clinical outcomes.

Despite these similarities, several important differences exist between the two procedures. AF ablation takes place in an electrophysiology laboratory with continuous cardiac monitoring, while liver tumor ablation is performed under ultrasound and CT guidance. Both settings are classified as NORA environments, which are associated with a higher incidence of anesthesia-related complications compared to procedures performed in the operating room.[68] The most notable distinction relates to the nature and intensity of

nociceptive stimulation. The acute pain provoked by thermal injury during liver tumor ablation tends to be considerably more severe than that observed during AF ablation. Discomfort during AF ablation is generally transient and primarily related to vascular access, transesophageal echocardiography probe placement, and transient myocardial stimulation during ablation. In contrast, tumor ablation induces pain through direct tissue destruction, which is often abrupt and severe.[43] As a result, the analgesic requirements during liver tumor ablation are typically increased, and maintaining adequate sedation depth while preserving spontaneous ventilation presents a greater challenge. Furthermore, post-procedural pain also differs between the two procedures: patients undergoing liver tumor ablation frequently experience moderate to severe post-ablation pain [45], whereas post-procedural discomfort after AF ablation is typically minimal and brief. These procedural and physiological differences necessitate tailored sedation strategies and close interdisciplinary communication to ensure both patient safety and procedural efficacy.

In recent years NORA, and particularly PSA in general have undergone remarkable growth, paralleling the rapid advancement of non-operative and minimally invasive techniques.[69] Driven by ongoing technological innovation, PSA has become an essential part of NORA as image-guided interventions evolve in complexity, precision and clinical impact.[69] In the field of electrophysiology, the management of AF has undergone rapid evolution with the introduction of advanced catheter technologies such as pulsed-field ablation and hybrid surgical–catheter strategies, which collectively enhance procedural precision, safety and efficacy.[59] Similarly, with interventional radiology, minimally invasive treatment of liver tumors has transformed profoundly, progressing from conventional percutaneous radiofrequency or microwave ablation to stereotactic and robot-assisted image-guided techniques, supported by sophisticated navigation and multimodal fusion imaging systems.[70, 71] These technological advancements may have important implications for anesthetic management. Procedures that were previously feasible with PSA may no longer be suitable as technical demands increase. In particular, interventions requiring extremely stable respiratory conditions, such as controlled respiratory frequency, minimal diaphragmatic excursion, or periods of apnea, exceed the practical limits of PSA and necessitate general anesthesia.

In addition, these rapid technological advancements have not only substantially improved therapeutic outcomes but have also introduced major methodological challenges for clinical research. The continuous evolution of procedural standards, diversification of techniques, and increasing heterogeneity among patient populations have made it progressively more difficult to design prospective studies that maintain both statistical robustness and procedural consistency. In rapidly developing fields such as electrophysiology and interventional radiology, the ongoing technological progress further complicates trial design, as new technologies and techniques often emerge before

ongoing studies are completed. Consequently, achieving sufficient statistical power without compromising the homogeneity of the study population has become increasingly challenging. This dynamic environment underscores the importance of adopting adaptive, pragmatic, and flexible trial designs that can accommodate technological progress while preserving scientific validity and clinical relevance. Therefore, the findings of these studies provide relevant insights into universal safety principles in PSA, while also highlighting the fact that sedation strategies must be tailored to the specific physiological demands and risk profiles of each clinical indication. This balance between generalizable safety principles and procedure-specific considerations frames the clinical implications. It furthermore reinforces the need for future research that embraces the heterogeneity of PSA practice, while building an evidence-based foundation strong enough to support standardization where appropriate.

Future research

Research should serve as the foundation for providing safe and effective care during procedures conducted outside the operating room. Many aspects of NORA remain insufficiently studied, partly because it initially involved a relatively small patient population. However, the expansion of NORA procedures, including PSA, requires continuous advancement of knowledge. This thesis focuses on optimizing sedation care. As PSA is increasingly applied to more complex and newly developed interventions, the need for evidence-based guidelines and standardized quality indicators becomes increasingly important. Establishing a uniform complication registry is essential to accurately capture the frequency and severity of adverse events and to support ongoing quality improvement.

Future research in PSA should focus on patient- and procedure-related risk factors and reducing complications, particularly those that are frequent or associated with severe outcomes such as respiratory events and aspiration. Optimizing patient comfort and overall experience, through both pharmacological and non-pharmacological management of anxiety and pain, should also be a key objective, guided by evidence-based approach to ensure interventions are both effective and safe. Innovative technologies, including advanced respiratory monitoring, decision-support systems, and predictive algorithms (e.g. for respiratory depression or acute pain) offer opportunities to identify risks early and improve patient outcomes. Further work is needed to develop and validate prediction models, evaluating these innovative monitoring technologies and the impact of sedation depth on cognitive function and quality of life. Conducting research across integrated care pathways will further strengthen multidisciplinary collaboration between anesthesiology and other specialties.

Given the rapid technological advances occurring in NORA environments, multicenter studies will be crucial to achieve adequate statistical power without compromising clinical relevance. Importantly, implementation should be guided by robust data and clinical feasibility, rather than the practice-based approaches that have too often driven PSA.

Based on the findings and retrospective studies presented in this thesis, future research should preferably be conducted through prospective, multicenter observational cohort designs. This will allow validation of the current findings and help overcome the methodological limitations inherent to retrospective analyses, particularly given that existing evidence (as in Chapters 3,4 and 5) is largely derived from single-center cohort studies. Future research should furthermore focus on the development and external validation of a data-driven prediction model to support identification of patients at risk for respiratory complications during AF ablation. Additionally, a prospective study on post-procedural pain incorporating prediction modeling will be essential to identify patients at increased risk and to enable more targeted and effective peri-procedural analgesic strategies, including non-pharmacological approaches to anxiety and pain.

Future research on use and implementation of HFNO should prioritize multicenter and innovative study designs, such as adaptive trials or large prospective registries with standardized HFNO/LFNO protocols. This approach will help to overcome low event rates and the limitations of single-center studies. Future studies should explicitly compare HFNO plus airway adjuncts (oral/nasal airway, jaw thrust) versus LFNO plus airway adjuncts and evaluate broader respiratory outcomes (including hypoxemia, airway interventions, procedure interruption) rather than focusing on hypoxemia. Systematic pre-procedural screening for SDB (e.g. STOP-BANG or BOSS-GAP in AF patients) should be incorporated, as unrecognized SDB may influence responsiveness to HFNO. If the overall, unselected PSA population has a low baseline risk of hypoxemia, it will be challenging to detect a meaningful difference between HFNO and LFNO. An alternative approach would therefore be to investigate subgroups in whom the effectiveness of HFNO may be reduced, such as patients with a high risk of upper-airway obstruction, including those with SDB or obesity. Targeted studies in these subpopulations could help determine whether HFNO is, or is not, effective in particular risk groups or during specific types of procedures.

Conclusions

Procedural sedation and analgesia administered by anesthesia care providers in NORA settings is generally considered safe and effective, although further optimization is required. PSA strategies should be tailored to individual patient characteristics and specific procedural needs. Further refinement is necessary to minimize complications, particularly respiratory events, and to improve patient experience by reducing post-procedural pain. The present findings provide new knowledge that supports safer, more refined sedation practices and lay the groundwork for future prospective research to advance peri-procedural patient care. Moreover, this thesis demonstrates that before meaningful progress toward truly personalized sedation care can be achieved, further evidence based findings focused on effects of PSA and its implementation in clinical practice is needed.

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SUMMARY

Procedural sedation and analgesia (PSA) provided by anesthesia care providers is commonly applied in non–operating room settings. The primary objective of PSA is to ensure patient comfort by minimizing anxiety and pain during diagnostic or therapeutic interventions. Adequate patient tolerance—achieved through anxiolysis, amnesia, and/or analgesia—is essential for the safe and successful completion of such interventions.

The primary aim of this thesis was to evaluate the safety and quality of PSA administered by anesthesia care providers, with particular attention to complications and clinical outcomes in non–operating room anesthesia (NORA) settings. It seeks to identify opportunities to improve the quality of PSA and thereby optimize patient care. The studies included in this thesis focus on two common clinical indications: (1) catheter ablation for atrial fibrillation (AF) and (2) percutaneous thermal ablation of liver tumors. While deep sedation is applied in both procedures, the associated clinical challenges differ. During catheter ablation for AF, respiratory complications constitute the primary concern, whereas during percutaneous thermal liver tumor ablation, pain management represents the predominant challenge.

Chapter 1 introduces the background on various aspects of procedural sedation and analgesia. This chapter provides a concise description of procedural sedation and analgesia and the role of the anesthesia care provider, as well as the pharmacological agents used for sedation and analgesia and the associated side effects. The introductory Chapter concludes with the presentation of the research questions (RQs) that guide this thesis.

Chapter 2 reviews current evidence on the optimization of PSA during AF catheter ablation in non–operating room settings. The review demonstrates that no single optimal sedation strategy exists and emphasizes the need for individualized sedation based on patient characteristics, comorbidities, procedural complexity, required sedation depth, and provider experience. AF patients frequently present with comorbidities such as obesity and sleep-disordered breathing (SDB), which significantly increase the risk of respiratory complications and complicate the sedation management. Common screening tools for SDB show limited validity in this population, highlighting the need for improved preprocedural risk stratification. Key determinants of clinical success include the selection of sedative and analgesic agents, appropriate sedation depth, and adequate monitoring strategies.

Chapter 3 studies the incidence and predictors of respiratory complications during PSA for AF catheter ablation through a retrospective cohort study including 232 patients. Respiratory complications occurred frequently (42.2%). Severe respiratory complications occurred in 15.1% of cases, including prolonged hypoxemic events and conversion to

general anesthesia in 1.3% of patients. Several predictive factors for respiratory complications during PSA were identified. Key patient-related predictors included increased neck circumference, higher visceral fat percentage, self-reported tiredness, and the presence of comorbidities such as obstructive sleep apnea and chronic obstructive pulmonary disease. Due to the age distribution of the cohort (predominantly >50 years) the factor age showed limited discriminative value. A major procedure-related predictor was the duration of procedural sedation and analgesia, with longer sedation times associated with a higher risk of respiratory complications.

Chapters 4 and 5 examine the role of high-flow nasal oxygen (HFNO) during PSA for AF catheter ablation. The study protocol, described in Chapter 4, formed the methodological basis for the prospective, randomized controlled trial (RCT) reported in Chapter 5. The results of this RCT demonstrate that HFNO does not improve oxygenation compared with low-flow nasal oxygen (LFNO) in selected AF patients undergoing prolonged deep sedation, nor does it reduce the incidence of hypoxemia or sedation-related complications. Although HFNO was shown to be safe, it provided no additional clinical benefit in this setting. Given the associated costs and environmental impact, routine use of HFNO during PSA for AF ablation cannot be justified. These findings support a more selective and context-specific application of HFNO in cardiology-related PSA.

Chapter 6 investigates, based on a retrospective cohort study, the prevalence, severity, and predictors of acute post-procedural pain following percutaneous thermal liver tumor ablation with PSA. Acute pain in the recovery room occurred frequently, with a prevalence of 42.7% when defined as a Numeric Rating Scale (NRS) score ≥4 and a mean maximum NRS of 3.1 ± 2.8. Psychological factors—including depression, anxiety, and the use of psychopharmacological medication—were the strongest predictors of higher pain scores. In addition, female sex, younger age, and a history of chronic pain were associated with increased post-procedural pain, whereas tumor-related characteristics such as size, location, and number of lesions showed no association with pain severity. These findings underscore the importance of patient-specific psychological and physiological factors in pain perception and support a shift toward individualized, multimodal peri-procedural analgesic strategies. Early identification of patients at risk, combined with tailored pharmacological and non-pharmacological interventions, may improve pain control, recovery, and overall patient experience following percutaneous liver tumor ablation.

Chapter 7 provides an overview and a general discussion of the results of the studies included in this thesis. A dedicated section of the general discussion focuses on minimally invasive procedures and NORA, including PSA, in the context of the two clinical indications (1) catheter ablation for atrial fibrillation (AF) and (2) percutaneous thermal ablation of liver tumors. Methodological considerations are addressed, and directions for future research are proposed. Future research should focus on identifying patient- and

procedure-related risk factors for complications and on optimizing patient comfort through individualized pharmacological and non-pharmacological strategies. Multidisciplinary collaboration between experts from different departments and specialties will be essential to translate these insights into clinical practice.

SAMENVATTING

Het belangrijkste doel van dit proefschrift was om te onderzoeken hoe veilig en goed sedatie (een roesje) is wanneer die wordt gegeven door anesthesiezorgverleners op plekken in het ziekenhuis buiten de operatiekamer. Daarbij is vooral gekeken naar veiligheid, mogelijke complicaties en factoren die het risico op een complicatie kunnen vergroten. Het doel van procedurele sedatie en pijnstilling (PSA) is om ervoor te zorgen dat patiënten zo min mogelijk angst en pijn hebben tijdens een onderzoek of behandeling. Bij PSA krijgt de patiënt medicijnen waardoor hij of zij rustiger wordt, minder pijn voelt en zich de behandeling soms niet goed herinnert. Hierdoor voelt de patiënt zich comfortabel en kan de arts het onderzoek of de behandeling veilig en goed uitvoeren. De studies in dit proefschrift richten zich op twee medische behandelingen. De eerste is ablatie bij boezemfibrilleren. Dit is een behandeling waarbij een cardioloog via dunne slangetjes in het hart kleine stukjes weefsel uitschakelt, zodat het hartritme weer normaal kan worden. De tweede behandeling is percutane leverablatie. Hierbij wordt een tumor in de lever kapotgemaakt door via de huid een naald in de lever te plaatsen en de tumor weg te branden. Bij beide behandelingen krijgt de patiënt een diepe sedatie. De uitdagingen tijdens deze behandelingen zijn verschillend. Bij de behandeling van boezemfibrilleren gaat het vooral om problemen met de ademhaling die kunnen optreden tijdens de sedatie. Bij de behandeling van levertumoren is het goed onder controle houden van pijn de grootste uitdaging.

Hoofdstuk 1 is de inleiding van dit proefschrift en geeft achtergrondinformatie over procedurele sedatie en analgesie (PSA). In dit hoofdstuk wordt eerst kort uitgelegd wat PSA is en wat de rol is van de anesthesiezorgverlener. Daarna worden de verschillende niveaus van sedatie besproken. Ook wordt uitgelegd welke medicijnen worden gebruikt om patiënten te laten ontspannen en om pijn te verminderen. Verder wordt een overzicht gegeven van mogelijke bijwerkingen die kunnen optreden bij sedatie. Tot slot worden de onderzoeksvragen beschreven die de basis vormen voor de studies in dit proefschrift.

Hoofdstuk 2 beschrijft wat er in de literatuur bekend is en de ideeën over het verbeteren van PSA tijdens ablatie bij boezemfibrilleren. Uit het literatuuronderzoek blijkt dat er geen één beste manier van sedatie bestaat die voor alle patiënten geschikt is. Daarom is het belangrijk dat de sedatie wordt aangepast aan de individuele patiënt**.** Daarbij spelen verschillende factoren een rol, zoals kenmerken van de patiënt, andere ziekten die iemand heeft, de moeilijkheid van de behandeling, hoe diep de sedatie moet zijn en de ervaring van de zorgverlener. Veel patiënten met boezemfibrilleren hebben ook andere gezondheidsproblemen, zoals overgewicht of ademhalingsproblemen tijdens de slaap. Deze aandoeningen vergroten de kans op ademhalingsproblemen tijdens de sedatie en maken het geven van sedatie ingewikkelder. Veel gebruikte vragenlijsten om slaap gerelateerde ademhalingsstoornissen op te sporen blijken bij deze patiëntengroep niet

altijd betrouwbaar. Dit laat zien dat een betere inschatting van risico's vóór de behandeling nodig is. Belangrijke factoren voor een succesvolle behandeling zijn onder andere de keuze van de medicijnen voor sedatie en pijnstilling, een passende diepte van sedatie en goede bewaking van de patiënt tijdens de procedure.

Hoofdstuk 3 onderzoekt hoe vaak ademhalingsproblemen voorkomen tijdens procedurele sedatie en pijnstilling (PSA) bij katheterablatie voor boezemfibrilleren, en welke factoren het risico hierop vergroten. Hiervoor werd een retrospectieve studie uitgevoerd bij 232 patiënten. Bij een retrospectieve studie kijken onderzoekers achteraf naar medische dossiers of bestaande gegevens van patiënten om te onderzoeken wat er is gebeurd. Uit de resultaten bleek dat ademhalingsproblemen regelmatig voorkwamen. Bij 42,2% van de patiënten trad een probleem met de ademhaling op. Ernstige ademhalingsproblemen kwamen voor bij 15,1% van de patiënten, bijvoorbeeld periodes waarin het zuurstofgehalte in het bloed langere tijd te laag was. Bij 1,3% van de patiënten moest de sedatie worden omgezet naar algehele anesthesie (narcose). De studie liet ook zien welke factoren het risico op ademhalingsproblemen vergroten. Belangrijke patiëntgebonden factoren waren onder andere een grotere nekomvang, meer buikvet, vermoeidheidsklachten die door de patiënt gemeld worden en andere ziekten, zoals obstructief slaapapneusyndroom en chronisch obstructieve longziekte (COPD). Omdat bijna alle patiënten in deze studie ouder waren dan 50 jaar, bleek leeftijd minder geschikt om verschillen in risico tussen patiënten te voorspellen. Daarnaast speelde ook een factor van de behandeling zelf een rol. Hoe langer de sedatie duurde, hoe groter de kans op ademhalingsproblemen tijdens de procedure.

Hoofdstuk 4 en 5 onderzoeken of nasale high-flow zuurstof (HFNO) nuttig is tijdens procedurele sedatie en pijnstilling (PSA) bij ablatie voor boezemfibrilleren. HFNO is een methode waarbij via een neusbril verwarmde en bevochtigde zuurstof met een hoge snelheid wordt toegediend om de ademhaling te ondersteunen. In **hoofdstuk 4** wordt het studieprotocol beschreven. Dit protocol vormde de basis voor een prospectieve, gerandomiseerde studie. Dit betekent dat patiënten vanaf het begin van het onderzoek werden gevolgd en dat gegevens tijdens het onderzoek werden verzameld. Daarnaast werden de deelnemers door loting in verschillende groepen verdeeld, zodat de behandelingen eerlijk met elkaar konden worden vergeleken. De resultaten worden in **hoofdstuk 5** gepresenteerd. De resultaten van deze studie laten zien dat HFNO de zuurstofvoorziening van patiënten niet verbetert in vergelijking met gewone zuurstof via een neusbril met lage flow (LFNO) bij patiënten met boezemfibrilleren die langdurige diepe sedatie krijgen tijdens een ablatie. Ook zorgde HFNO niet voor minder momenten waarop het zuurstofgehalte in het bloed te laag werd (hypoxemie) en niet voor minder sedatie gerelateerde complicaties. Hoewel HFNO veilig was, gaf het geen extra voordeel voor de patiënt in deze situatie. Omdat HFNO bovendien duurder is en meer belasting van het milieu veroorzaakt, is het niet nodig om deze methode standaard te gebruiken tijdens

PSA bij ablatie voor boezemfibrilleren. Deze resultaten wijzen erop dat HFNO beter alleen gebruikt kan worden bij specifieke patiënten.

Hoofdstuk 6 beschrijft de resultaten van een retrospectieve studie naar pijn na een behandeling waarbij levertumoren worden weggebrand (percutane thermische leverablatie) onder sedatie. In de studie werd gekeken hoe vaak pijn voorkomt na de behandeling, hoe ernstig de pijn is en welke factoren het risico op pijn vergroten. Uit de resultaten blijkt dat pijn na de behandeling regelmatig voorkomt op de uitslaapkamer. Bij 42,7% van de patiënten was er sprake van matige tot ernstige pijn, gemeten met de Numeric Rating Scale (NRS**)**, een pijnschaal van 0 tot 10. Een score van 4 of hoger betekent dat iemand matige pijn heeft. Bij een pijnscore van 7 of hoger heeft een patiënt ernstige pijn. De gemiddelde hoogste pijnscore na de behandeling was 3,1 ± 2,8 op 10. De studie liet ook zien welke factoren samenhangen met het ervaren van meer pijn. Vooral psychologische factoren speelden een belangrijke rol. Patiënten met depressie, angstklachten of die psychofarmacologische medicijnen gebruiken hadden vaker hogere pijnscores na de behandeling. Daarnaast bleek dat vrouwen, jongere patiënten en patiënten met chronische pijn in de voorgeschiedenis vaker meer pijn hadden na de behandeling. Kenmerken van de tumor, zoals de grootte, de plaats in de lever en het aantal tumoren**,** hadden geen duidelijk verband met de mate van pijn. Door patiënten met een verhoogd risico op pijn al vóór de behandeling te herkennen, kan de zorg beter worden aangepast. Een combinatie van medicijnen en andere maatregelen om pijn te verminderen kan helpen om de pijn beter onder controle te houden, het herstel te verbeteren en de ervaring van patiënten na de behandeling te verbeteren.

Hoofdstuk 7 geeft een overzicht van de belangrijkste resultaten uit de studies die in de eerdere hoofdstukken zijn beschreven. In de algemene discussie wordt ook aandacht besteed aan minimaal invasieve behandelingen en zorg buiten de operatiekamer (NORA), waaronder procedurele sedatie en pijnstilling (PSA). Minimaal invasieve behandelingen zijn behandelingen waarbij artsen via kleine openingen in het lichaam werken, waardoor de ingreep minder zwaar is voor de patiënt. Dit wordt besproken aan de hand van twee behandelingen: 1. ablatie bij boezemfibrilleren en 2. Percutane thermische ablatie van levertumoren. Daarnaast wordt besproken hoe de onderzoeken zijn uitgevoerd en welke sterke en minder sterke punten daarbij een rol spelen. Ook worden mogelijkheden voor toekomstig onderzoek beschreven. Verder is het belangrijk om te onderzoeken hoe het comfort van patiënten verder kan worden verbeterd, bijvoorbeeld door behandelingen en pijnstilling beter af te stemmen op de individuele patiënt. Goede samenwerking tussen verschillende afdelingen en specialisten is daarbij belangrijk om deze kennis in de dagelijkse zorg voor patiënten te delen en toe te passen.

VALORISATION

Clinical academic research should extend beyond scientific contribution alone. It should generate demonstrable benefits for patients, healthcare professionals, and healthcare organizations. The research presented in this thesis is therefore considered within the broader context of societal relevance, also referred to as valorisation. Valorisation is defined as "the process of creating value from knowledge, by making knowledge suitable and/or available for social and/or economic use and by making knowledge suitable for translation into competitive products, services, processes and new commercial activities."[1] The findings of this thesis contribute to societal, economic, and ecological value.

The increasing demand for minimally invasive procedures performed outside the operating room highlights the vital role of safe and effective procedural sedation and analgesia (PSA) in non-operating room anesthesia (NORA) settings. This development is clearly reflected in the growth of the sedation practice at Maastricht UMC$^+$. When PSA was first introduced under the responsibility of the Department of Anesthesiology and Pain Medicine at MUMC$^+$ in 2014, anesthesia care providers supported 183 procedures during the first year. By 2024, this number had increased to 2288 procedures per year. This growth demonstrates that PSA is no longer a supplementary service. Instead, it has become an essential component of high-quality and safe patient care in NORA environments, at least within MUMC$^+$ Maastricht.[2] This local development reflects broader national and international trends. Across Europe and the United States, demand for NORA continues to rise, together with a marked shift towards performing a larger proportion of interventional procedures under monitored anesthesia care and PSA.[3, 4, 5] These developments highlight the necessity of structured risk stratification and standardized sedation pathways. Addressing these needs is crucial for maintaining patient safety and ensuring sustainable workforce deployment. In addition, this rapid growth illustrates not only increasing clinical demand but also the growing reliance on PSA within modern healthcare systems.[6, 7]

Societal value

From a social perspective, improved PSA practices enhance patient safety, comfort, and the overall procedural experience.[2, 3, 6] A large proportion of elective procedures performed with PSA take place in an outpatient or day-care setting, where efficient recovery and rapid discharge are essential.[8] Among these procedures, specifically patients undergoing PSA for atrial fibrillation (AF) or percutaneous liver tumor ablation are common target groups. Reducing the incidence of respiratory complications and acute post-procedural pain leads to faster recovery and potentially shorter hospital stays, which can positively influence patient satisfaction and trust in healthcare services. Optimization of sedation strategies and the identification of high-risk patients before their procedure can further reduce unplanned interventions, procedure interruptions, prolonged recovery times, and escalation to general anesthesia or even rescheduling of procedures. Better

risk stratification supports more efficient patient selection and monitoring, contributing to fewer complications and preserving high-quality care. Shorter procedure and recovery times, fewer interruptions, and a reduced need for conversion to general anesthesia all translate into meaningful social value by improving patient experience and continuity of care.

However, it is important to acknowledge that the increasing demand for PSA cannot always be matched by current and future workforce capacity. This insight is directly relevant for hospital management and policymakers when designing future PSA service models and training pathways. A growing discrepancy exists between the rising clinical demand for PSA and the current workforce capacity of trained anesthesia care providers. This mismatch between demand and supply highlights the need for strategic resource planning. It also underlines the importance of expanded training pathways and innovative care models to ensure sustainable access to safe PSA services in the future. PSA by anesthesia care providers is frequently selected because general anesthesia capacity is limited; therefore, improved prediction of respiratory risk allows more efficient allocation of anesthesiology resources. Reducing complications not only improves patient safety but also contributes to a more positive procedural experience, reinforcing patient confidence and acceptance of repeated interventions when necessary.

Our study on post-procedural pain following percutaneous thermal liver ablation identified clinically relevant pain and highlights key predictors such as psychological comorbidity, chronic pain history, younger age, and female sex. These findings have substantial social relevance. Post-procedural pain significantly influences patient comfort, recovery trajectories, and satisfaction. Pain is a highly prevalent health problem that causes significant discomfort and suffering. Previous research has demonstrated that pain severity is an important determinant of quality of life.[9, 10]

Early identification of high-risk patients enables tailored peri-procedural analgesic strategies, contributing to improved patient experience and reduced physical and psychological burden. Not all anxiety, distress, or pain requires a pharmacological solution. Greater emphasis should be placed on integrating non-pharmacological interventions within hospital care, consistent with biopsychosocial models of care. This approach supports the systematic integration of psychological expertise into procedural pathways. Approaches such as structured communication techniques, mindfulness, medical hypnosis, music, and the use of virtual reality may play an important role in reducing procedural anxiety and the anticipation of acute pain.[11, 12, 13] This is an area in which both patients and healthcare professionals still have much to learn and develop. If patients and healthcare providers invest time in learning, applying, and continuously refining these techniques, this can improve patients' experience and procedural satisfaction. In addition, investing time in learning, refining and applying the techniques may contribute significantly to the

joy and well-being of healthcare professionals in their daily work. Implementation of such interventions may be facilitated through targeted staff training and incorporation into existing PSA protocols.

Economic value

PSA services are increasingly delivered in a production-driven environment, where efficiency and workflow performance are central elements of daily practice. This is related to the nature of the procedures being supported. Staffing levels are determined by the patient's medical condition and the complexity of the procedure. When patient condition and procedural complexity permit, PSA may be safely delivered by a single anesthesia care provider, typically a nurse specialized in PSA. An anesthesiologist remains available to provide support if required. This approach allows a single anesthesiologist to supervise multiple procedures and locations simultaneously. It supports efficient resource utilization and improved cost-effectiveness.

However, due to the current shortage of anesthesia personnel in the Netherlands, the pool of professionals available to provide PSA services is already limited. In times of workforce shortages, the challenge is to maintain a healthy balance between productivity demands and professional quality and well-being of the anesthesia care provider. It is essential to prevent the limited human resources from being further strained as a result of over-demand on the individual anesthesia care provider, which may result in reduced job satisfaction and/or burnout.

Better prediction of respiratory complications, combined with improved patient selection, reduces procedure interruptions and the need for additional airway interventions. It also reduces prolonged recovery times and the need for conversion to general anesthesia. These improvements contribute to lower healthcare costs while sustaining high-quality care delivery. Furthermore, the findings regarding the limited added value of high-flow nasal oxygen (HFNO) in selected patient groups promote cost-conscious clinical decision-making. This reduces unnecessary use of equipment and avoids interventions that do not demonstrably improve outcomes. Optimized risk stratification for post-procedural pain after liver tumor ablation, combined with targeted analgesia, reduces prolonged recovery and additional medication requirements. This lowers healthcare costs while improving efficiency of care. Together, these findings as presented in Chapters 3, 5 and 6 provide evidence to balance patient safety, efficiency, and staff workload in high-volume NORA settings.

Ecological value

Evidence-based recommendations that discourage routine use of resource-intensive equipment, such as HFNO when not indicated, contribute to reducing the environmental footprint of sedation practices. As sustainability becomes increasingly important in

healthcare, evidence-based guidance supporting environmentally responsible choices gains societal relevance.[14, 15] Optimizing PSA practices can therefore reduce waste generation, energy consumption, and the broader ecological impact of anesthesia care. Therefore, the findings reported in this thesis contribute to institutional sustainability goals and align with broader healthcare initiatives aimed at reducing the environmental impact of clinical practice.

Future directions

Further development of a clinically applicable decision-making tool on peri-procedural respiratory complications is needed. A small pilot study should be conducted to clinically validate this, followed by the development of a digital risk tool implemented within the electronic health record. The findings in this thesis (Chapters 3-5) form the foundation for a further optimization of the preoperative pathway for AF ablation and thus may further support accurate risk assessment. Earlier and more comprehensive screening for sleep-disordered breathing plays an important role in this process. Implementation activities and presentations at conferences will help spread these findings and facilitate their integration into clinical practice. Local implementation of improved PSA risk assessment should be initiated.

The results in this thesis as presented in Chapter 6 support the further implementation of an enhanced pre-procedural screening process for post-procedural pain after tumor ablation that integrates psychological and chronic pain indicators and thereby may and will be able to further refine patient selection and peri-procedural planning. A predictive model offers a foundation for developing clinical decision-support tools to improve pain risk assessment. These insights may be translated into updated sedation protocols and digital risk tools embedded within the electronic health record. Knowledge sharing through conference presentations, interdisciplinary collaboration, and local implementation initiatives will support broader clinical adoption.

Finally, the findings in this thesis contribute to support policymaking, training, and the implementation of quality standards in PSA by providing practical insights.[2, 3, 16] The result of the studies in this thesis (Chapters 3-6) will guide the development of updated sedation protocols, risk-stratification tools, and interdisciplinary collaboration models. These outputs offer practical value for clinicians, hospital administrators, professional societies, and educational institutions aiming to standardize competence-based sedation care.[16]

At the same time, it is important to recognize that a highly production-driven work environment may promote a practice-driven rather than an evidence-based approach, particularly when workload and efficiency pressures limit adherence to clinical guidelines and best practices.[17] Continued investment in training, reflective practice, and structured evaluation is therefore critical to ensure that PSA services remain safe, evidence-based,

and responsive to future developments in healthcare. By combining clinical relevance with evidence-based risk stratification, the findings in this thesis contribute to the development of sustainable, high-quality PSA practice not only within Maastricht UMC^{+}, but may also support policy changes in other hospitals.

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DANKWOORD

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CURRICULUM VITAE

Marloes Homberg was born on January 4th, 1979 in Weert, and grew up in Eijsden (The Netherlands). She graduated high school in 1996 at Jeanne d' Arc College in Maastricht.

She started her nursing education at Atrium Medical Center in Heerlen. After completing her nursing training, she began her professional career as a registered nurse at the Academic Hospital Maastricht (azM) in 2000. In 2002, she started her training as a nurse anesthetist, which she successfully completed in 2004. From 2006 she combined her role as a nurse anesthetist with a position as a transplant coordinator.

In 2013, she began her training as a Physician Assistant at the Department of Anesthesiology at Maastricht University Medical Center+. She completed this program in 2016. Since then, her professional focus has been on procedural sedation and analgesia (PSA) and preoperative assessment. Her research focuses on PSA, with particular attention to patient safety and quality of care.

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- Homberg MC, Betz K, Linz D, Vernooy K, Buhre WFFA, Bouman EAC. Identifying patient-related factors for respiratory complications during deep sedation catheter ablations in patients with atrial fibrillation: a single-centre retrospective study. Presented at: European Society of Anaesthesiology and Intensive Care (ESAIC); 2025 May 25–27; Lisbon, Portugal.

Manuscripts under review

- Homberg MC, Linz D, Brandts L, Joosten EA, Buhre WFFA, Bouman EAC. High-flow versus low-flow nasal oxygen during procedural sedation for atrial fibrillation ablation: a randomized controlled trial. Submitted to: *Eur J Anaesthesiol Intensive Care*. 2026.

