Journal Pre-proof

Dexmedetomidine versus Propofol for Operator-Directed Nurse-Administered Procedural Sedation during Catheter Ablation of Atrial Fibrillation: a Randomized Controlled Study

Helge Servatius, MD, Thomas Küffer, MSc, Samuel H. Baldinger, MD, Babken Asatryan, MD, PhD, Jens Seiler, MD, Hildegard Tanner, MD, Jan Novak, MD, Anna Lam, MD, Fabian Noti, MD, Andreas Haeberlin, MD, PhD, Antonio Madaffari, MD, Romy Sweda, MD, Aline Mühl, MSc, Mattia Branca, PhD, Sophie Dütschler, Gabor Erdoes, MD, Frank Stüber, MD, Lorenz Theiler, MD, Tobias Reichlin, MD, Laurent Roten, MD, MBA

PII: S1547-5271(21)02520-0

DOI: https://doi.org/10.1016/j.hrthm.2021.12.028

Reference: HRTHM 9092

To appear in: *Heart Rhythm*

Received Date: 27 October 2021

Revised Date: 2 December 2021

Accepted Date: 23 December 2021

Please cite this article as: Servatius H, Küffer T, Baldinger SH, Asatryan B, Seiler J, Tanner H, Novak J, Lam A, Noti F, Haeberlin A, Madaffari A, Sweda R, Mühl A, Branca M, Dütschler S, Erdoes G, Stüber F, Theiler L, Reichlin T, Roten L, Dexmedetomidine versus Propofol for Operator-Directed Nurse-Administered Procedural Sedation during Catheter Ablation of Atrial Fibrillation: a Randomized Controlled Study, *Heart Rhythm* (2022), doi: https://doi.org/10.1016/j.hrthm.2021.12.028.

Dexmedetomidine versus Propofol for Operator-Directed Nurse-Administered Procedural Sedation during Catheter Ablation of Atrial Fibrillation: a Randomized Controlled Study

Helge Servatius, MD[1]; Thomas Küffer, MSc[1]; Samuel H. Baldinger, MD[1]; Babken Asatryan, MD, PhD[1]; Jens Seiler, MD[1]; Hildegard Tanner, MD[1]; Jan Novak, MD[1]; Anna Lam, MD[1]; Fabian Noti, MD[1]; Andreas Haeberlin, MD, PhD[1]; Antonio Madaffari, MD[1]; Romy Sweda, MD[1]; Aline Mühl, MSc[1]; Mattia Branca, PhD[2]; Sophie Dütschler[1], Gabor Erdoes, MD[3]; Frank Stüber, MD[3]; Lorenz Theiler, MD[4]; Tobias Reichlin, MD[1]; Laurent Roten, MD, MBA[1]

1. Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
2. CTU Bern, University of Bern, Bern, Switzerland
3. Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
4. Department of Anaesthesiology, Kantonsspital Aarau, Aarau, Switzerland

Running title: DEX vs PRO Sedation for AF Ablation

ClinicalTrials.gov number: NCT03844841

Corresponding author

Laurent Roten, MD, MBA

Inselspital, Kardiologie, Freiburgstrasse, 3010 Bern, Switzerland

Email: laurent.roten@insel.ch

Conflict of interest:

Hildegard Tanner: Travel grant from Abbott, educational grant from Biosense Webster.

Andreas Haeberlin: Co-founder and head of Act-Inno, a cardiovascular device testing company. Travel/educational grants from Medtronic and Philips/Spectranetics. Research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the Swiss Heart Rhythm Foundation, the Hasler Foundation, the Velux Foundation, Novartis and the sitem-insel Support Funds, all for work outside the submitted study. Consultant/advisor for DiNAQOR and Biotronik for work outside the submitted study.

Mattia Branca: MB is employed by CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest, see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html.

Tobias Reichlin: Research grants from the Goldschmidt-Jacobson Foundation, the Swiss National Science Foundation, the Swiss Heart Foundation and the sitem-insel Support Funds, all for work outside the submitted study. Consulting, Advisory Boards, Speaker, Travel Support from Abbott/SJM, Astra Zeneca, Brahms, Bayer, Biosense-Webster, Biotronik, Boston-Scientific, Daiichi Sankyo, Medtronic, Pfizer-BMS and Roche, all for work outside the submitted study. Support for his institution's fellowship program from Abbott/SJM, Biosense-Webster, Biotronik, Boston-Scientific and Medtronic for work outside the submitted study.

Laurent Roten: Received speaker honoraria from Abbott/SJM and consulting honoraria from Medtronic.

Background: Operator-directed nurse-administered (ODNA) sedation with propofol is the preferred sedation technique for catheter ablation of atrial fibrillation (AF) in many centers.

Objective: We aimed to investigate whether Dexmedetomidine, an α2-adrenergic receptor agonist, is superior to propofol.

Methods: We randomized 160 consecutive patients undergoing first AF ablation to ODNA sedation by dexmedetomidine (DEX group) versus propofol (PRO group), according to a standardized protocol. Patients were unaware of treatment allocation. The primary endpoint was a composite of inefficient sedation, termination/change of sedation protocol or procedure abortion, hypercapnia (transcutaneous CO2 >55 mmHg), hypoxemia (SpO_2 <90%) or intubation, prolonged hypotension (systolic blood pressure <80 mmHg), and sustained bradycardia necessitating cardiac pacing. Secondary endpoints were the components of the primary endpoint and patient satisfaction with procedural sedation, as assessed by a standardized questionnaire the day following ablation.

Results: The primary endpoint occurred in 15 DEX group and 25 PRO group patients (19% vs. 31%; p=0.068). Hypercapnia was significantly more frequent in PRO group patients (29% vs. 10%; p=0.003). There was no significant difference among the other components of the primary endpoint, no procedure was aborted. Patient satisfaction was significantly better in PRO group patients (visual analog scale 0-100; median 100 in PRO group vs. median 93 in DEX group; p<0.001).

Conclusion: Efficacy of ODNA sedation with dexmedetomidine was not different to propofol. Hypercapnia occurs less frequent with dexmedetomidine, but patient satisfaction is better with propofol sedation. In selected patients, dexmedetomidine may be used as an alternative to propofol for ODNA sedation during AF ablation. (ClinicalTrials.gov number NCT03844841)

Keywords

Sedation; catheter ablation; atrial fibrillation; propofol; dexmedetomidine.

Introduction

The number of interventional procedures in cardiology increases steadily, particularly in electrophysiology. Catheter ablation of atrial fibrillation is the most frequently performed procedure. With growing demand, standard operating procedures allowing for efficient and safe procedural sedation are crucial for both the success and cost-efficiency of this intervention. Catheter ablation of atrial fibrillation typically lasts 1-3 hours, during which the patient is required to lie motionless. Patient movements can result in complications such as cardiac tamponade and may prolong the procedure if catheter stability is compromised or if a 3D mapping system is used and map shifts occur. Catheter ablation of atrial fibrillation is painful and administration of analgesics is required. Approaches for sedation during catheter ablation of atrial fibrillation include general anesthesia or sedation in an operator-directed nurse-administered (ODNA) model, according to individual patient characteristics, local policy and state law. Traditionally, benzodiazepines such as midazolam and opioids have been used for ODNA sedation. As an alternative, propofol has been investigated for ODNA sedation in several studies, and has been rated safe and efficient.[1-5] Today, ODNA sedation by appropriately trained staff is the standard of care in most centers and propofol the most widely used drug.[6] However, propofol can induce significant respiratory depression and hemodynamic instability, jeopardizing procedural efficacy and safety.

Dexmedetomidine, an alpha-2 adrenergic agonist with sedative and analgesic effects does not cause clinically significant respiratory depression compared to benzodiazepines or opioids.[7, 8] Dexmedetomidine is commonly used in intensive care units and for various interventional procedures.[9-15] It may also be advantageous for catheter ablation of atrial fibrillation. The aim of the present study was to compare ODNA sedation with dexmedetomidine to ODNA sedation with propofol for catheter ablation of atrial fibrillation.

Methods

In this investigator-initiated, single-center, single-blinded study we prospectively randomized patients with atrial fibrillation undergoing pulmonary vein isolation to ODNA sedation with propofol versus dexmedetomidine. The local ethics committee approved the study, and all patients provided written informed consent to participate. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Trial participants and randomization

We enrolled 160 patients undergoing first pulmonary vein isolation for atrial fibrillation by cryoballoon ablation or by radiofrequency ablation. All patients were randomized 1:1 to procedural sedation with dexmedetomidine or propofol. Randomization was stratified by the method of pulmonary vein isolation (cryoballoon and radiofrequency ablation), with the aim to include 80 patients each treated by cryoballoon or radiofrequency ablation. To be included in the study, patients had to be ≥18 years of age and undergo first pulmonary vein isolation. Patients were excluded if they were unsuited for ODNA sedation, had a contraindication to propofol or dexmedetomidine sedation, severe heart failure, body mass index >35 kg/m^2 or American Society of Anesthesiology (ASA) classification >III. Inclusion and exclusion criteria are detailed in the Supplementary Table 1. Patients were unaware of treatment allocation.

Sedation during ablation

Patients had to be fasting for at least 6 hours. Patients were continuously monitored during the ablation procedure by a trained and dedicated cardiology nurse, under the supervision of the treating electrophysiologist. This nurse was present in the electrophysiology lab at the head side of the patient throughout the procedure and exclusively responsible for sedation, monitoring of vital functions and drug

administration. Another nurse was available for assistance and other tasks, as needed. In-house on-call anesthesiology support was guaranteed at any time. Propofol was administered as target-controlled infusion and dexmedetomidine as continuous infusion after an initial loading dose. The exact protocol used for propofol and dexmedetomidine sedation is provided in the Appendix 1. Continuous oxygen was applied via a face mask. Heart rate, peripheral capillary oxygen saturation (SpO_2) and transcutaneous carbon dioxide level ($tcCO_2$) were continuously monitored during the procedure in all patients. Non-invasive blood pressure was measured every 5 minutes or in shorter intervals, as clinically indicated. All monitoring data were stored digitally for later analysis. Depth of sedation was assessed every 10-15 minutes according to the "Modified Observer's Assessment of Alertness/Sedation scale" (MOAA/S scale, Appendix 2) and communicated to the treating electrophysiologist. The target score on the MOAA/S scale for the ablation procedure was 3. If electrical cardioversion was necessary during the procedure, the target score on the MOAA/S scale was temporarily reduced to 2.

Ablation procedure

Prior to the procedure, a transesophageal echocardiography and a cardiac computed tomography were performed to exclude left atrial thrombus and to reconstruct left atrial anatomy for procedural planning. After obtaining femoral venous access, catheters were placed into the left atrium via either fluoroscopy-guided transseptal puncture or via a patent foramen ovale. Pulmonary vein isolation was carried out by either cryoballoon ablation (Arctic Front Advance Pro™, Medtronic, MN, US) or point-by-point radiofrequency ablation with 3D electroanatomic mapping (Thermocool Smarttouch SF® and Carto® 3 System, Biosense Webster, CA, US), as described previously.[16] Unfractionated heparin was administered to achieve a target activated clotting time of

>350 seconds. After the procedure, patients were monitored on an intermediate care unit or a cardiology ward with measurements of blood pressure and heart rate every 15 minutes for the first 2 hours, every 30 minutes for another 2 hours and hourly for another 2 hours.

Endpoints

The primary study outcome was a composite endpoint of inefficient sedation, respiratory depression and hemodynamic changes. Inefficient sedation was defined as the inability to achieve a target score of ≤3 on the "Modified Observer's Assessment of Alertness/Sedation" (MOAA/S) scale, termination or violation of sedation protocol and procedure abortion due to sedation issues. Respiratory depression included hypercapnia ($tcCO_2$ rise >20 mmHg or $tcCO_2$>55 mmHg), hypoxemia (SpO_2 <90%) despite airway management (chin lift and oropharyngeal airway), and tracheal intubation. Hemodynamic changes were prolonged hypotension with a systolic blood pressure of <80 mmHg and sustained bradycardia necessitating cardiac pacing. Pacing because of bradycardia or asystole during or shortly after pulmonary vein isolation was not considered a primary endpoint. A more detailed definition of the components of the primary endpoint is provided in the Appendix 3. Secondary endpoints included all single components of the primary endpoint, and patient satisfaction with sedation. Primary endpoints were registered at the end of the procedure by the treating electrophysiologist and by the nurse that monitored the patient. Two electrophysiologists (HS and LR) later analyzed all procedural and monitoring data and adjudicated all endpoints.

Follow-up

The day following the ablation procedure, patients were questioned by a study nurse (not involved in the sedation procedure) regarding their satisfaction with procedural

sedation using a detailed questionnaire. This questionnaire assessed several properties of procedural sedation with the use of a visual analog scale (VAS) ranging from zero (very dissatisfied or subject of question not present at all) to 100 (very satisfied or subject of question very present).

Statistical analyses

Continuous variables are expressed as means with standard deviations or medians with interquartile ranges (IQR), and categorical variables as frequencies with percentages. Continuous variables were compared using the Mann-Whitney U test or t-test in case of two-group comparison. Differences in proportions were tested with Pearson's $\chi 2$ test or Fisher's exact test, as appropriate. The trend over time is computed using the LOESS (locally weighted smoothing) to create smooth lines over time for both groups with time points summarized each minute. Relative risk are estimated by log-binomial regression, as well as the p-value for the interaction. All outcome analysis were done intention-to-treat and all tests were performed at a two-sided 5% significance level with 95% confidence intervals (CIs). All analyses were performed using Stata (StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) and R software (3.6.1 or newer), R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Results

Patient and procedural characteristics

Of 160 patients enrolled between September 2019 and October 2020, 80 patients received ODNA sedation with dexmedetomidine (DEX group), and 80 patients ODNA sedation with propofol (PRO group). Mean age of patients was 64.8 years and 32% were female. Baseline characteristics were not different between the two groups (Table 1). Cryoballoon ablation was performed in 81 patients and radiofrequency ablation in 79. Procedural details are shown in Table 2. All pulmonary veins were successfully isolated in all patients.

Procedural sedation

DEX group patients received a mean of 231±111 mcg dexmedetomidine during the procedure. In PRO group patients, a mean of 657±356 mg of propofol was administered. At the beginning of the ablation procedure, ondansetron was given to 74 DEX group patients (93%) and no PRO group patients. Cumulative dose of fentanyl administered was lower in DEX group compared to PRO group patients (134±52 µg versus 151±53 µg; p=0.044). Both DEX and PRO group patients received a median of 1 mg of midazolam (range 1-3 mg for both groups; p=0.890). Electrical cardioversion was performed during the procedure in 37 DEX group patients (46%) and 33 PRO group patients (41%; p=0.524). For electrical cardioversion 25 DEX group patients (68%) received an additional dose of 20 mg (interquartile range [IQR] 20-40) of propofol. Median mean and minimal MOAA/S score attained during the procedure was 3 and 2, respectively, and not different among groups (Table 2; Figure 1). Anesthesiology support was not needed for any procedure, nor was any procedure aborted. Adverse events are summarized in the Supplementary Table 2. During procedures using an electroanatomical mapping system we found no difference in the

number of patients with 3D map shifts that needed either recalculation or reconstruction of 3D maps (Table 2).

Endpoints

The combined primary endpoint occurred in 40 patients (25%), 15 patients (19%) in the DEX group, and 25 patients (31%) in the PRO group (p=0.068; Table 3). The sedation protocol was changed in 3 DEX group patients (3%; details see Supplementary Table 3). In one DEX group patient (1%) we were unable to achieve a MOAA/S score ≤3 but completed the procedure without changing the sedation protocol (1%). In the PRO group, sedation protocol was never changed and was efficient in all patients. Hypercapnia was significantly less frequent in DEX group compared to PRO group patients (10% versus 29%; p=0.003). Episodes of prolonged hypotension <80 mmHg were not different among groups (DEX group 8% versus PRO group 3%; p=0.147). Figure 2 shows the evolution of heart rate, SpO_2, systolic blood pressure and $tcCO_2$ for DEX and PRO group patients during the first two hours of the procedure. Blood pressure was significantly lower and heart rate significantly slower in DEX group patients up to 4 hours after the procedure (Supplementary Table 4). In a post-hoc subgroup analysis (Figure 3), patients with a NT-proBNP level <327 pg/mL were significantly less likely to achieve a primary endpoint when randomized to DEX group compared to PRO group (p=0.014).

Patient satisfaction with procedural sedation

Overall patient satisfaction with procedural sedation was significantly lower in DEX group patients (93 on VAS; IQR 80-100) compared to PRO group patients (100 on VAS; IQR 90-100; p for difference <0.001). Fifty-six DEX group patients (70%) and 76 PRO group patients (95%) indicated, that they would choose the same sedation approach in a future procedure (p for difference <0.001). Patient satisfaction with sedation is further detailed in Table 4.

Discussion

This single-center, randomized-controlled clinical trial was the first to compare dexmedetomidine with propofol for operator-directed, nurse-administered sedation in adult patients undergoing catheter ablation of atrial fibrillation. The main findings of our study are as follows: 1) there was no difference regarding efficacy of sedation with dexmedetomidine compared to propofol; 2) hypercapnia occured less frequently with dexmedetomidine; and 3) patient satisfaction was better with propofol sedation (Figure 4).

While there is abundant literature on the use of dexmedetomidine in intensive care units,[11, 13, 14] emergency departments, pediatric[17, 18] and adult procedures,[9, 10, 15] we found only two reports on dexmedetomidine use during catheter ablation of atrial fibrillation. In a small randomized controlled trial, Cho et al. compared sedation with dexmedetomidine and remifentanil versus sedation with midazolam and remifentanil.[19] Patients in the dexmedetomidine arm had significantly less respiratory depression, deeper sedation, better analgesia, and required a lower dose of remifentanil. Another study compared ODNA sedation with dexmedetomidine versus thiamylal, both combined with pentazocine.[20] Although most patients in the dexmedetomidine arm required additional thiamylal administration, sleep-disordered breathing and patient movements were significantly less frequent in the dexmedetomidine arm.

In our study, ODNA sedation with both propofol as well as dexmedetomidine achieved a level of sedation suitable for catheter ablation of atrial fibrillation. Overall, we found no difference among the two sedatives regarding mean and minimal MOAA/S score observed during the procedure. However, there were significantly more DEX group patients than PRO group patients in which we only achieved a mean MOAA/S score of 4 and in one DEX group patient we didn’t achieve the target MOAA/S score of ≤3 at any time during the procedure. One DEX group patient received additional propofol

because of inefficient sedation. The sedation protocol had to be changed in two additional DEX group patients because of drug side effects not directly associated with sedation. In PRO group patients on the other hand, we were always able to achieve a MOAA/S score of ≤3 and termination or change of the sedation protocol never occurred.

Previous reports described persistent hypotension during ODNA sedation with propofol in 10-13% of procedures, requiring propofol cessation.[2, 3] In our study, we observed persistent hypotension in only 3% of patients in the PRO group, and propofol sedation was successfully continued at lower doses until the end of the procedure in all patients. Importantly, we administered propofol by target-controlled infusion, which automatically calculates effect-site concentration, thereby reducing variation of propofol blood concentration and associated adverse events.[21] This probably explains the lower rate of hypotension in our study. Dexmedetomidine on the other hand also induces hypotension due to its alpha-2 adrenergic effect, and we observed prolonged hypotension in 8% of cases. However, overall systolic blood pressure during the ablation procedure was higher in DEX group patients compared to PRO group patients as shown in Figure 2c.

Severe hypoxemia during ODNA sedation is reported in the range of 1-2% of cases.[2, 3] We monitored $tcCO_2$ levels to assess respiration during all procedures and set an upper limit of $tcCO_2$ level of 55 mmHg. $TcCO_2$ monitoring allows to recognize respiratory depression at an earlier stage than with monitoring of SpO_2.[22] Accordingly, the endpoint of hypercapnia was observed frequently in both groups, whereas we did not observe severe hypoxemia in any patient. Dexmedetomidine is known to cause less respiratory depression than propofol,[23, 24] and hypercapnia was significantly more frequent in PRO group patients than DEX group patients in our study. Importantly,

309 respiratory depression did not result in intubation or change of sedation protocol in any
310 of our study patients.
311 If hypotension or hypercapnia occurs during ODNA sedation, the typical response is a
312 reduction or cessation of sedative dose, as ODNA sedation generally does not include
313 the administration of adrenergic drugs or intubation. Sedative dose reduction may
314 result in inefficient sedation and ultimately change of sedation protocol or even
315 procedure abortion. Therefore, sedative drugs which cause less respiratory depression
316 or hypotension are preferable for ODNA sedation. To this end, dexmedetomidine,
317 causing less hypercapnia, may be advantageous over propofol, at least in selected
318 patients in which significant respiratory depression is anticipated to occur with propofol
319 administration.
320 Patient satisfaction is another very important point to take into account. Procedural
321 sedation is among the few items, which patients can objectively evaluate. ODNA
322 sedation with propofol achieves impressive patient satisfaction, and sets the bar high
323 for any competing sedative. Although the majority of patients sedated with
324 dexmedetomidine would chose dexmedetomidine for a repeat procedure, propofol
325 clearly outperformed this rate. Some patients in the DEX group felt pain or remembered
326 part of the procedure. DEX group patients also felt significantly more tired after the
327 procedure, and hypotension and bradycardia were more common up to four hours after
328 the procedure compared to PRO group patients. This resulted in more
329 echocardiography examinations performed during post-interventional surveillance in
330 DEX group patients, to rule out cardiac effusion.
331 Limitations of our study include its single-blinded design, with both the operator and
332 the nurse administering anesthetics being aware of treatment allocation. Further, the
333 study was not powered to show any difference in serious adverse events, e.g.

intubation or hemodynamic collapse, as these are very rare events during ODNA sedation.

In conclusion, both propofol and dexmedetomidine are suitable anesthetics for ODNA sedation. Propofol achieves excellent patient satisfaction, whereas dexmedetomidine may be advantageous for patients in which respiratory depression during ODNA sedation is anticipated.

Acknowledgement

We would like to thank our study nurses Susanne Jenni, Helene Schenk, Lea Streich and Tu Hanh Zarrabi Saffari for their efforts to accomplish this study. Our thanks also goes to the entire staff of the electrophysiology lab for their patience and support of our study.

Funding

Dr. Helge Servatius was supported for this project from the Gottfried and Julia Bangerter-Rhyner-Stiftung and received a CTU-Grant from the Bern University Hospital, Switzerland.

References

1. Kottkamp H, Hindricks G, Eitel C, et al. Deep sedation for catheter ablation of atrial fibrillation: a prospective study in 650 consecutive patients. J Cardiovasc Electrophysiol 2011;22:1339-1343.
2. Salukhe TV, Willems S, Drewitz I, et al. Propofol sedation administered by cardiologists without assisted ventilation for long cardiac interventions: an assessment of 1000 consecutive patients undergoing atrial fibrillation ablation. Europace 2012;14:325-330.
3. Servatius H, Hofeler T, Hoffmann BA, et al. Propofol sedation administered by cardiologists for patients undergoing catheter ablation for ventricular tachycardia. Europace 2016;18:1245-1251.
4. Wutzler A, Rolf S, Huemer M, et al. Safety aspects of deep sedation during catheter ablation of atrial fibrillation. Pacing Clin Electrophysiol 2012;35:38-43.
5. Weinmann K, Heudorfer R, Lenz A, et al. Safety of conscious sedation in electroanatomical mapping procedures and cryoballoon pulmonary vein isolation. Heart Vessels 2021;36:561-567.
6. Garcia R, Waldmann V, Vanduynhoven P, et al. Worldwide sedation strategies for atrial fibrillation ablation: current status and evolution over the last decade. Europace 2021.
7. Dere K, Sucullu I, Budak ET, et al. A comparison of dexmedetomidine versus midazolam for sedation, pain and hemodynamic control, during colonoscopy under conscious sedation. Eur J Anaesthesiol 2010;27:648-652.
8. Venn RM, Bradshaw CJ, Spencer R, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 1999;54:1136-1142.

9. Alizadehasl A, Sadeghpour A, Totonchi Z, Azarfarin R, Rahimi S, Hendiani A. Comparison of sedation between dexmedetomidine and propofol during transesophageal echocardiography: A randomized controlled trial. Ann Card Anaesth 2019;22:285-290.

10. Chen YT, Sun CK, Wu KY, et al. The Use of Propofol versus Dexmedetomidine for Patients Receiving Drug-Induced Sleep Endoscopy: A Meta-Analysis of Randomized Controlled Trials. J Clin Med 2021;10.

11. Constantin JM, Momon A, Mantz J, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med 2016;35:7-15.

12. Goettel N, Bharadwaj S, Venkatraghavan L, Mehta J, Bernstein M, Manninen PH. Dexmedetomidine vs propofol-remifentanil conscious sedation for awake craniotomy: a prospective randomized controlled trial. Br J Anaesth 2016;116:811-821.

13. Hughes CG, Mailloux PT, Devlin JW, et al. Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. N Engl J Med 2021;384:1424-1436.

14. Shehabi Y, Howe BD, Bellomo R, et al. Early Sedation with Dexmedetomidine in Critically Ill Patients. N Engl J Med 2019;380:2506-2517.

15. Ter Bruggen F, Ceuppens C, Leliveld L, Stronks DL, Huygen F. Dexmedetomidine vs propofol as sedation for implantation of neurostimulators: A single-center single-blinded randomized controlled trial. Acta Anaesthesiol Scand 2019;63:1321-1329.

16. Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. N Engl J Med 2016;374:2235-2245.

17. Daverio M, Sperotto F, Zanetto L, et al. Dexmedetomidine for Prolonged Sedation in the PICU: A Systematic Review and Meta-Analysis. Pediatr Crit Care Med 2020;21:e467-e474.

18. Erickson SJ, Millar J, Anderson BJ, et al. Dexmedetomidine Sedation in Mechanically Ventilated Critically Ill Children: A Pilot Randomized Controlled Trial. Pediatr Crit Care Med 2020;21:e731-e739.

19. Cho JS, Shim JK, Na S, Park I, Kwak YL. Improved sedation with dexmedetomidine-remifentanil compared with midazolam-remifentanil during catheter ablation of atrial fibrillation: a randomized, controlled trial. Europace 2014;16:1000-1006.

20. Sairaku A, Yoshida Y, Hirayama H, Nakano Y, Ando M, Kihara Y. Procedural sedation with dexmedetomidine during ablation of atrial fibrillation: a randomized controlled trial. Europace 2014;16:994-999.

21. Absalom AR, Glen JI, Zwart GJ, Schnider TW, Struys MM. Target-Controlled Infusion: A Mature Technology. Anesth Analg 2016;122:70-78.

22. Waugh JB, Epps CA, Khodneva YA. Capnography enhances surveillance of respiratory events during procedural sedation: a meta-analysis. J Clin Anesth 2011;23:189-196.

23. Nolan PJ, Delgadillo JA, Youssef JM, Freeman K, Jones JL, Chehrehsa A. Dexmedetomidine Provides Fewer Respiratory Events Compared With Propofol and Fentanyl During Third Molar Surgery: A Randomized Clinical Trial. J Oral Maxillofac Surg 2020;78:1704-1716.

24. Shin HJ, Kim EY, Hwang JW, Do SH, Na HS. Comparison of upper airway patency in patients with mild obstructive sleep apnea during dexmedetomidine or propofol sedation: a prospective, randomized, controlled trial. BMC Anesthesiol 2018;18:120.

Figure legends

Figure 1. Procedure duration and distribution of the MOAA/S scores in the DEX and PRO groups.

A) Procedure duration curves for dexmedetomidine and propofol groups; y-axis: number of patients; x-axis: procedure duration in minutes (only the first 120 minutes are shown). B) Distribution of the MOAA/S score for dexmedetomidine and propofol groups during the ablation procedure. MOAA/S: Modified Observer's Assessment of Alertness/Sedation.

Figure 2. Vital parameters during the ablation procedure.

Graphs showing A) heart rate, B) SpO_2, C) systolic blood pressure, and D) $tcCO_2$ and 95% confidence intervals for the first 120 minutes of the ablation procedure. SpO_2: saturation of peripheral oxygen; $TcCO_2$: transcutaneous carbon dioxide level.

Figure 3. Forest plot displaying the effect of sedation with propofol or dexmedetomidine across subgroups.

Forest plot displaying the effect of sedation with dexmedetomidine or propofol across subgroups. ASA: American Society of Anesthesiology; DEX: dexmedetomidine; PRO: propofol. LVEF: left ventricular ejection fraction.

Figure 4. Graphical illustration of the study methodology and findings.

A) Study randomization flow chart. B) Percentage of patients meeting the combined primary endpoint in DEX and PRO group. C) Cumulative number of patients with accruing level of satisfaction with sedation on visual analogue scale (Range 0-100). The larger the area under the curves, the more satisfied patients were. D)

Percentage of patients in DEX and PRO group answering the question “Would you choose the same sedation method again?” with “yes”, “unsure”, and “no”. Cryo: cryoballoon ablation; DEX: dexmedetomidine; PRO: Propofol; RF: radiofrequency ablation.

460 **Tables**

461 Table 1. Patient characteristics.

	All N=160	DEX group N=80	PRO group N=80	P Value
Age, years	64.8±10.8	65.5±9.6	64.2±11.9	0.446
Gender, female	51 (32%)	28 (35%)	23 (29%)	0.396
Body mass index, kg/m^2	26.7±3.5	26.2 ±3.5	27.2 ±3.5	0.074
Arterial hypertension	86 (54%)	44 (55%)	42 (53%)	0.751
Diabetes mellitus	12 (8%)	5 (6%)	7 (9%)	0.548
Coronary artery disease	16 (10%)	10 (13%)	6 (8%)	0.292
History of stroke/embolism	14 (9%)	7 (9%)	7 (9%)	1.000
Peripheral artery disease	14 (9%)	6 (8%)	8 (10%)	0.576
History of congestive heart failure	19 (12%)	12 (15%)	7 (9%)	0.222
CHA_2DS_2Vasc score	2 (1; 3)	2 (1; 3)	2 (1; 3)	0.608
ASA* classification				
II	124 (78%)	58 (73%)	66 (83%)	0.130
III	36 (23%)	22 (28%)	14 (18%)	
Obstructive sleep apnea	14 (9%)	6 (8%)	8 (10%)	0.576
Pacemaker or ICD	5 (3%)	4 (5%)	1 (1%)	0.173
Paroxysmal atrial fibrillation	115 (72%)	59 (74%)	56 (70%)	0.598
Previous cardioversion	51 (32%)	27 (34%)	24 (30%)	0.611
Months since diagnosis of atrial fibrillation	11 (3; 44)	6 (3; 30.3)	19 (4; 70)	0.038
Previous use of class I/III antiarrhythmic drug	62 (39%)	33 (41%)	29 (36%)	0.516
Oral anticoagulation	142 (89%)	70 (88%)	72 (90%)	0.617
LVEF, %	58±8	57±9	59±7	0.140
LAVI ml/m^2	38.3 ±13	40±13.6	36.3 ±12.2	0.083
Systolic blood pressure, mmHg	147±26	144±26	150±25	0.160
Diastolic blood pressure, mmHg	83±17	80±18	85 ±16	0.071
NT-proBNP, pg/mL	538±654	612±755	465±529	0.156

462 Data are provided as mean ± standard deviation, as median with interquartile range
463 (1st; 3rd) or frequencies with percentages. *American Society of Anesthesiology (ASA)
464 classification – ASA I: A normal healthy patient; ASA II: A patient with mild systemic
465 disease; ASA III: A patient with severe systemic disease; ASA IV: A patient with
466 severe systemic disease that is a constant threat to life; ASA V: A moribund patient
467 who is not expected to survive without the operation. Abbreviations: ICD: internal
468 cardioverter defibrillator; LAVI: left atrial volume index; LVEF: left ventricular ejection
469 fraction.

470

471 Table 2. Procedural data

	All N=160	DEX group N=80	PRO group N=80	P Value
Radiofrequency ablation	79 (49%)	40 (50%)	39 (49%)	1.000
Cryoablation	81 (51%)	40 (50%)	41 (51%)	1.000
Procedure duration, min.	128±59	129±57	126±61	0.796
Fluoroscopy time, min.	14.9±9.8	15.3±9.9	14.4±9.7	0.581
Additional ablation sites				
Cavotricuspid isthmus	21(13%)	12 (15%)	9 (11%)	0.640
Roof line	3 (2%)	1 (1%)	2 (3%)	1.000
Mitral isthmus line	1 (1%)	1 (1%)	-	1.000
Focal atrial tachycardia	1 (1%)	-	1 (1%)	1.000
Mean MOAA/S score (median)	3 (2; 3)	3 (2; 3)	2 (2; 3)	0.155
1	2 (1%)	2 (3%)	-	0.497
2	76 (48%)	33 (42%)	43 (54%)	0.152
3	68 (43%)	34 (43%)	34 (43%)	1.000
4	12 (8%)	10 (13%)	2 (3%)	0.032
Minimal MOAA/S score (median)	2 (2; 2)	2 (2; 2)	2 (2; 2)	0.146
1	20 (13%)	8 (10%)	12 (15%)	0.474
2	120 (76%)	58 (73%)	62 (78%)	0.577
3	17 (11%)	12 (15%)	5 (6%)	0.121
4	1 (1%)	1 (1%)	-	1.000
Electrical cardioversion during procedure	70 (44%)	37 (46%)	33 (41%)	0.524
Number of electrical cardioversions	1 (1; 2)	1 (1; 2)	1 (1; 2)	0.329
3D Map shifts with map recalculation	9 (12%)	5 (13%)	4 (10%)	0.723
Number of recalculations	1 (1; 3.5)	1 (1; 4.5)	1 (1; 2.5)	0.540
3D Map shifts with map reconstruction	3 (33%)	1 (20%)	2 (50%)	0.343
Number of reconstructions	1 (1; 1)	1 (1; 1)	1 (1; 1)	1.000
Bradycardia during ablation	18 (11%)	10 (13%)	8 (10%)	0.617
Number of bradycardia episodes	1 (1; 2.5)	1 (1; 2.8)	1 (1; 3.3)	0.722
Ablation site causing bradycardia				
LSPV	13 (72%)	8 (80%)	5 (63%)	0.608
LIPV	8 (44%)	4 (40%)	4 (50%)	1.000
RSPV	4 (22%)	3 (30%)	1 (13%)	0.588
RIPV	1 (6%)	1 (10%)	-	1.000
Echocardiography during post-interventional surveillance	49 (31%)	36 (46%)	13 (16%)	<0.001

472 Data are provided as mean ± standard deviation, as median with interquartile range

473 (1^{st}; 3^{rd}) or frequencies with percentages. LIPV: left inferior pulmonary vein; LSPV:

474 left superior pulmonary vein; MOAA/S: Modified Observer's Assessment of

475 Alertness/Sedation Scale; PVI: pulmonary vein isolation; RIPV: right inferior

476 pulmonary vein; RSPV: right superior pulmonary vein.

477

Table 3. Primary and secondary endpoints

	DEX group (N=80)	PRO group (N=80)	Difference and 95% CI	P value
Combined primary endpoint	15 (19%)	25 (31%)	-13% (-26%; 1%)	0.068
Secondary endpoints (components of the primary endpoint)				
Termination or change of sedation protocol	3 (4%)	-	4% (-0%; 8%)	0.080
Inability to achieve MOAA/S score ≤3	1 (1%)	-	1% (-1%; 4%)	0.316
Aborted procedure due to sedation issues	-	-	-	-
Hypercapnia ($tcCO_2$ rise >20 mmHg OR $tcCO_2$ >55 mmHg)	8 (10%)	23 (29%)	-19% (-31%; -6%)	0.003
Oxygen desaturation <90% despite airway management	-	-	-	-
Prolonged hypotension (systolic blood pressure <80 mmHg)	6 (8%)	2 (3%)	5% (-2%; 12%)	0.147
Sustained hemodynamically relevant bradycardia necessitating pacing	1 (1%)	1 (1%)	-	1.0

Data are provided as median with interquartile range (1^{st}; 3^{rd}) or frequencies with percentages. MOAA/S: Modified Observer's Assessment of Alertness/Sedation Scale; $tcC0_2$: transcutaneous carbon dioxide level.

484 Table 4. Patient satisfaction with sedation.

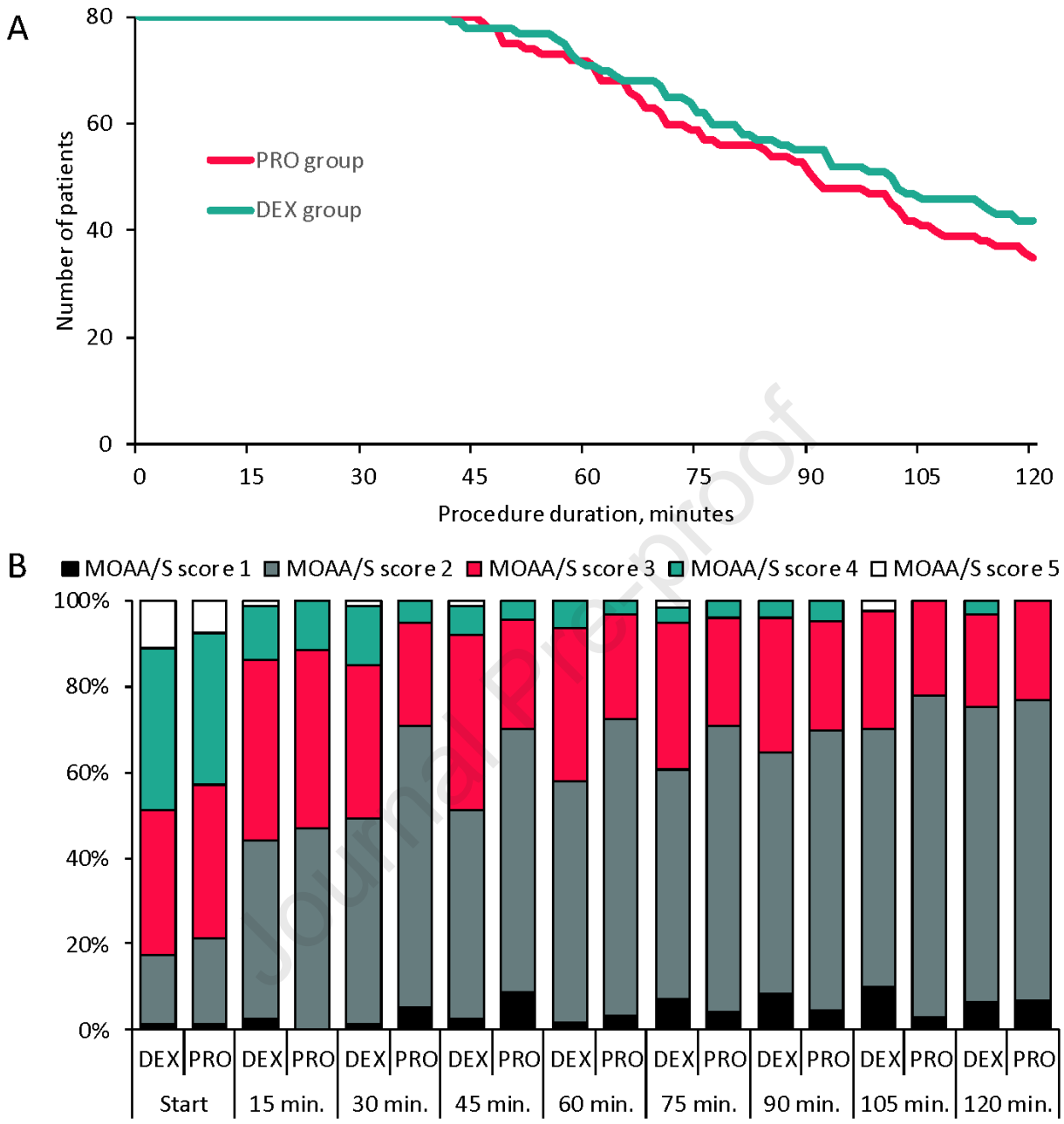
	All N=160	DEX group N=80	PRO group N=80	P Value
General satisfaction with sedation				
How satisfied were you with the sedation?	100 (90; 100)	93 (80; 100)	100 (100; 100)	<0.001
How well have you recovered from sedation?	90 (75; 100)	80 (70; 100)	90 (80; 100)	0.028
Would you choose the same type of sedation in the future?				
Yes	132 (83%)	56 (70%)	76 (95%)	<0.001
Uncertain	14 (9%)	11 (14%)	3 (4%)	
No	14 (9%)	13 (16%)	1 (1%)	
During the procedure, in the electrophysiology lab				
Did you feel pain?	0 (0; 0)	0 (0; 19)	0 (0; 0)	0.006
Were you scared?	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.919
Did you feel sick?	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.890
Can you remember when the procedure started?	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.300
Can you remember the procedure yourself?	0 (0; 0)	0 (0; 20)	0 (0; 0)	0.003
Do you remember the electric shock? (yes)	8 (13%)	5 (15%)	3 (10%)	0.604
When waking up in the electrophysiology lab				
Did you feel pain?	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.948
Were you scared?	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.278
Did you feel sick?	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.680
Do you remember waking up?	50 (0; 85)	30 (0; 80)	50 (0; 90)	0.760
Were you very tired?	70 (25; 90)	80 (50; 100)	55 (20; 90)	0.042
After the procedure, on the ward				
Did you feel pain?	0 (0; 14)	0 (0; 14)	0 (0; 14)	0.852
Were you scared?	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.507
Did you feel sick?	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.798
Were you very tired?	55 (30; 80)	70 (43; 90)	50 (13; 70)	<0.001

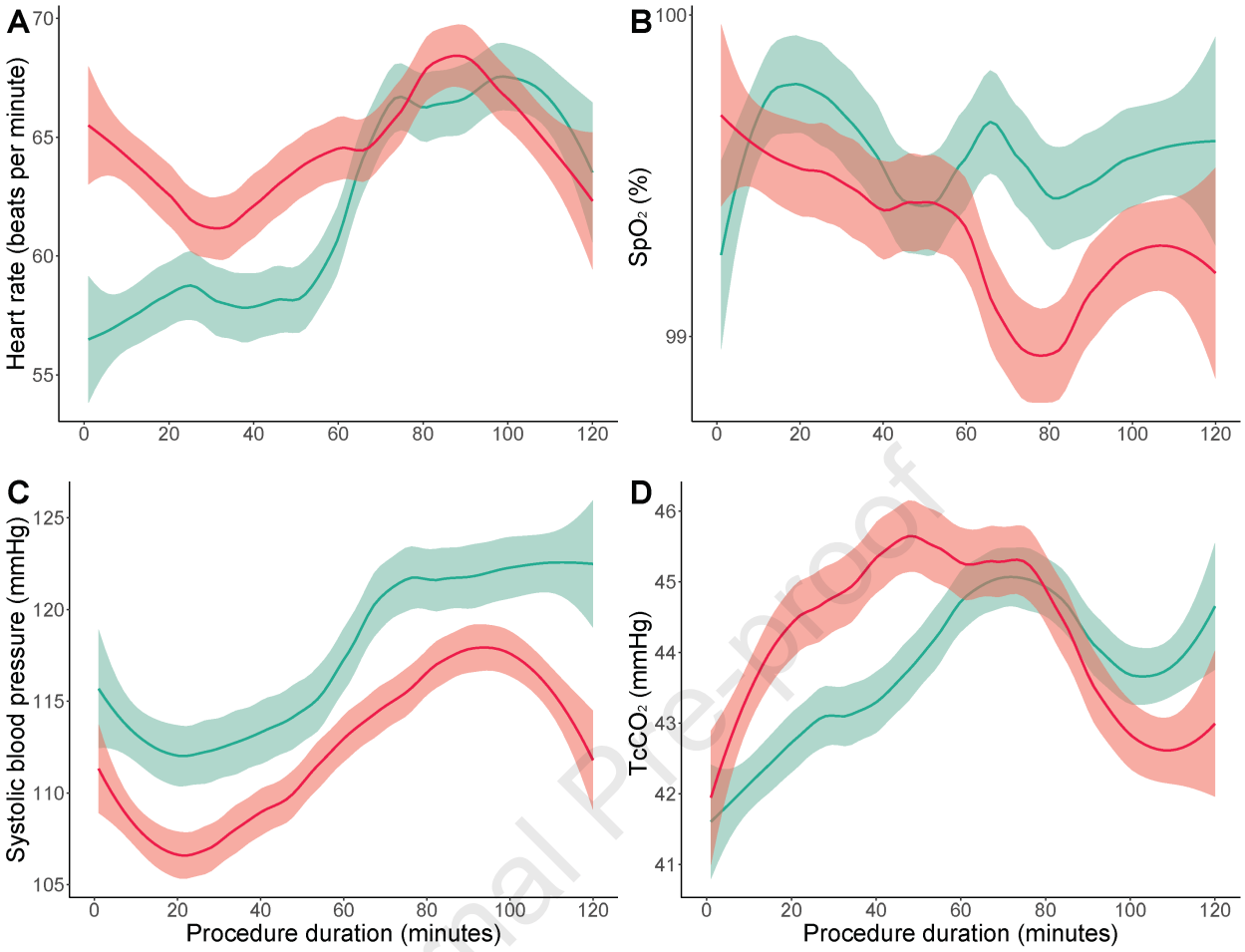
485 Data are provided as median with interquartile range (1st; 3rd) or frequencies with

486 percentages in parentheses of patient responses on a visual analogue scale (Range

487 0-100), or frequencies with percentages in parentheses, as appropriate. DEX:

488 dexmedetomidine; PRO: propofol.





	Overall (N=160)	PRO group (N=80)	DEX group (N=80)	RR (95% CI)	P-value for interaction
Technology used					
Cryoablation	18/81 (22.2)	11/41 (26.8)	7/40 (17.5)	1.53 [0.66; 3.56]	0.784
Radiofrequency ablation	22/79 (27.9)	14/39 (35.9)	8/40 (20.0)	1.79 [0.85; 3.79]	
Age					
≥ 65 years	22/92 (23.9)	12/44 (27.3)	10/48 (20.8)	1.31 [0.63; 2.72]	0.342
< 65 years	18/68 (26.5)	13/36 (36.1)	5/32 (15.6)	2.31 [0.93; 5.77]	
Gender					
Female	16/51 (31.4)	9/23 (39.1)	7/28 (25.0)	1.57 [0.69; 3.55]	0.788
Male	24/109 (22.0)	16/57 (28.1)	8/52 (15.4)	1.82 [0.85; 3.91]	
Body mass index					
≥ 30 kg/m²	5/35 (14.3)	4/22 (18.2)	1/13 (7.7)	2.36 [0.29; 18.94]	0.778
< 30 kg/m²	35/125 (28.0)	21/58 (36.2)	14/67 (20.9)	1.73 [0.97; 3.09]	
Arterial hypertension					
Yes	18/86 (20.9)	12/42 (28.6)	6/44 (13.6)	2.10 [0.87; 5.07]	0.463
No	22/74 (29.7)	13/38 (34.2)	9/36 (25.0)	1.37 [0.67; 2.80]	
LVEF					
< 50%	6/19 (31.6)	2/7 (28.6)	4/12 (33.3)	0.86 [0.21; 3.54]	0.301
≥ 50%	34/141 (24.1)	23/73 (31.5)	11/68 (16.2)	1.95 [1.03; 3.69]	
Obstructive sleep apnea					
Yes	3/14 (21.4)	2/8 (25.0)	1/6 (16.7)	1.50 [0.17; 12.94]	0.917
No	37/146 (25.3)	23/72 (31.9)	14/74 (18.9)	1.69 [0.95; 3.02]	
NT-proBNP					
≥ Median (327 pg/mL)	21/81 (25.9)	9/38 (23.7)	12/43 (27.9)	0.85 [0.40; 1.79]	0.014
< Median (327 pg/mL)	19/79 (24.1)	16/42 (38.1)	3/37 (8.1)	4.70 [1.49; 14.86]	
ASA classification					
2	32/124 (25.8)	23/66 (34.9)	9/58 (15.5)	2.25 [1.13; 4.46]	0.076
3	8/36 (22.2)	2/14 (14.3)	6/22 (27.3)	0.52 [0.12; 2.24]	
Procedural duration					
≥ Median (118 minutes)	23/79 (29.1)	13/37 (35.1)	10/42 (23.8)	1.48 [0.74; 2.96]	0.545
< Median (118 minutes)	17/81 (21.0)	12/43 (27.9)	5/38 (13.2)	2.12 [0.82; 5.47]