

# Journal Pre-proof



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

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

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

55 **Objective:** We aimed to investigate whether Dexmedetomidine, an  $\alpha$ 2-  
56 adrenergic receptor agonist, is superior to propofol.

57 **Methods:** We randomized 160 consecutive patients undergoing first AF ablation to  
58 ODNA sedation by dexmedetomidine (DEX group) versus propofol (PRO group),  
59 according to a standardized protocol. Patients were unaware of treatment allocation.  
60 The primary endpoint was a composite of inefficient sedation, termination/change of  
61 sedation protocol or procedure abortion, hypercapnia (transcutaneous CO<sub>2</sub> >55  
62 mmHg), hypoxemia (SpO<sub>2</sub> <90%) or intubation, prolonged hypotension (systolic blood  
63 pressure <80 mmHg), and sustained bradycardia necessitating cardiac pacing.  
64 Secondary endpoints were the components of the primary endpoint and patient  
65 satisfaction with procedural sedation, as assessed by a standardized questionnaire the  
66 day following ablation.

67 **Results:** The primary endpoint occurred in 15 DEX group and 25 PRO group patients  
68 (19% vs. 31%; p=0.068). Hypercapnia was significantly more frequent in PRO group  
69 patients (29% vs. 10%; p=0.003). There was no significant difference among the other  
70 components of the primary endpoint, no procedure was aborted. Patient satisfaction  
71 was significantly better in PRO group patients (visual analog scale 0-100; median 100  
72 in PRO group vs. median 93 in DEX group; p<0.001).

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

78

79 **Keywords**

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

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## 82 **Introduction**

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

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

108

**109 Methods**

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

**116 Trial participants and randomization**

117 We enrolled 160 patients undergoing first pulmonary vein isolation for atrial fibrillation  
118 by cryoballoon ablation or by radiofrequency ablation. All patients were randomized  
119 1:1 to procedural sedation with dexmedetomidine or propofol. Randomization was  
120 stratified by the method of pulmonary vein isolation (cryoballoon and radiofrequency  
121 ablation), with the aim to include 80 patients each treated by cryoballoon or  
122 radiofrequency ablation. To be included in the study, patients had to be  $\geq 18$  years of  
123 age and undergo first pulmonary vein isolation. Patients were excluded if they were  
124 unsuited for ODNA sedation, had a contraindication to propofol or dexmedetomidine  
125 sedation, severe heart failure, body mass index  $>35$  kg/m<sup>2</sup> or American Society of  
126 Anesthesiology (ASA) classification  $>III$ . Inclusion and exclusion criteria are detailed in  
127 the Supplementary Table 1. Patients were unaware of treatment allocation.

**128 Sedation during ablation**

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

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

149

#### 150 Ablation procedure

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



160 >350 seconds. After the procedure, patients were monitored on an intermediate care  
161 unit or a cardiology ward with measurements of blood pressure and heart rate every  
162 15 minutes for the first 2 hours, every 30 minutes for another 2 hours and hourly for  
163 another 2 hours.

164

### 165 Endpoints

166 The primary study outcome was a composite endpoint of inefficient sedation,  
167 respiratory depression and hemodynamic changes. Inefficient sedation was defined as  
168 the inability to achieve a target score of  $\leq 3$  on the “Modified Observer’s Assessment of  
169 Alertness/Sedation” (MOAA/S) scale, termination or violation of sedation protocol and  
170 procedure abortion due to sedation issues. Respiratory depression included  
171 hypercapnia ( $\text{tcCO}_2$  rise  $>20$  mmHg or  $\text{tcCO}_2 >55$  mmHg), hypoxemia ( $\text{SpO}_2 <90\%$ )  
172 despite airway management (chin lift and oropharyngeal airway), and tracheal  
173 intubation. Hemodynamic changes were prolonged hypotension with a systolic blood  
174 pressure of  $<80$  mmHg and sustained bradycardia necessitating cardiac pacing.  
175 Pacing because of bradycardia or asystole during or shortly after pulmonary vein  
176 isolation was not considered a primary endpoint. A more detailed definition of the  
177 components of the primary endpoint is provided in the Appendix 3. Secondary  
178 endpoints included all single components of the primary endpoint, and patient  
179 satisfaction with sedation. Primary endpoints were registered at the end of the  
180 procedure by the treating electrophysiologist and by the nurse that monitored the  
181 patient. Two electrophysiologists (HS and LR) later analyzed all procedural and  
182 monitoring data and adjudicated all endpoints.

### 183 Follow-up

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

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

190

### 191 **Statistical analyses**

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

206

## 207 **Results**

### 208 Patient and procedural characteristics

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

### 216 Procedural sedation

217 DEX group patients received a mean of  $231 \pm 111$  mcg dexmedetomidine during the  
218 procedure. In PRO group patients, a mean of  $657 \pm 356$  mg of propofol was  
219 administered. At the beginning of the ablation procedure, ondansetron was given to 74  
220 DEX group patients (93%) and no PRO group patients. Cumulative dose of fentanyl  
221 administered was lower in DEX group compared to PRO group patients ( $134 \pm 52$   $\mu$ g  
222 versus  $151 \pm 53$   $\mu$ g;  $p=0.044$ ). Both DEX and PRO group patients received a median of  
223 1 mg of midazolam (range 1-3 mg for both groups;  $p=0.890$ ). Electrical cardioversion  
224 was performed during the procedure in 37 DEX group patients (46%) and 33 PRO  
225 group patients (41%;  $p=0.524$ ). For electrical cardioversion 25 DEX group patients  
226 (68%) received an additional dose of 20 mg (interquartile range [IQR] 20-40) of  
227 propofol. Median mean and minimal MOAA/S score attained during the procedure was  
228 3 and 2, respectively, and not different among groups (Table 2; Figure 1).  
229 Anesthesiology support was not needed for any procedure, nor was any procedure  
230 aborted. Adverse events are summarized in the Supplementary Table 2. During  
231 procedures using an electroanatomical mapping system we found no difference in the

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

#### 234 Endpoints

235 The combined primary endpoint occurred in 40 patients (25%), 15 patients (19%) in  
236 the DEX group, and 25 patients (31%) in the PRO group ( $p=0.068$ ; Table 3). The  
237 sedation protocol was changed in 3 DEX group patients (3%; details see  
238 Supplementary Table 3). In one DEX group patient (1%) we were unable to achieve a  
239 MOAA/S score  $\leq 3$  but completed the procedure without changing the sedation protocol  
240 (1%). In the PRO group, sedation protocol was never changed and was efficient in all  
241 patients. Hypercapnia was significantly less frequent in DEX group compared to PRO  
242 group patients (10% versus 29%;  $p=0.003$ ). Episodes of prolonged hypotension  $<80$   
243 mmHg were not different among groups (DEX group 8% versus PRO group 3%;  
244  $p=0.147$ ). Figure 2 shows the evolution of heart rate, SpO<sub>2</sub>, systolic blood pressure  
245 and tcCO<sub>2</sub> for DEX and PRO group patients during the first two hours of the procedure.  
246 Blood pressure was significantly lower and heart rate significantly slower in DEX group  
247 patients up to 4 hours after the procedure (Supplementary Table 4). In a post-hoc  
248 subgroup analysis (Figure 3), patients with a NT-proBNP level  $<327$  pg/mL were  
249 significantly less likely to achieve a primary endpoint when randomized to DEX group  
250 compared to PRO group ( $p=0.014$ ).

#### 251 Patient satisfaction with procedural sedation

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

## 258 Discussion

259 This single-center, randomized-controlled clinical trial was the first to compare  
260 dexmedetomidine with propofol for operator-directed, nurse-administered sedation in  
261 adult patients undergoing catheter ablation of atrial fibrillation. The main findings of our  
262 study are as follows: 1) there was no difference regarding efficacy of sedation with  
263 dexmedetomidine compared to propofol; 2) hypercapnia occurred less frequently with  
264 dexmedetomidine; and 3) patient satisfaction was better with propofol sedation (Figure  
265 4).

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

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

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

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

301 Severe hypoxemia during ODNA sedation is reported in the range of 1-2% of cases.<sup>2</sup>  
302 <sup>3</sup> We monitored tcCO<sub>2</sub> levels to assess respiration during all procedures and set an  
303 upper limit of tcCO<sub>2</sub> level of 55 mmHg. TcCO<sub>2</sub> monitoring allows to recognize  
304 respiratory depression at an earlier stage than with monitoring of SpO<sub>2</sub>.<sup>22</sup> Accordingly,  
305 the endpoint of hypercapnia was observed frequently in both groups, whereas we did  
306 not observe severe hypoxemia in any patient. Dexmedetomidine is known to cause  
307 less respiratory depression than propofol,<sup>23, 24</sup> and hypercapnia was significantly more  
308 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.

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

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

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352 **References**

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

- 377 **9.** Alizadehasl A, Sadeghpour A, Totonchi Z, Azarfarin R, Rahimi S, Hendiani A.  
378 Comparison of sedation between dexmedetomidine and propofol during  
379 transesophageal echocardiography: A randomized controlled trial. *Ann Card*  
380 *Anaesth* 2019;22:285-290.
- 381 **10.** Chen YT, Sun CK, Wu KY, et al. The Use of Propofol versus  
382 Dexmedetomidine for Patients Receiving Drug-Induced Sleep Endoscopy: A  
383 Meta-Analysis of Randomized Controlled Trials. *J Clin Med* 2021;10.
- 384 **11.** Constantin JM, Momon A, Mantz J, et al. Efficacy and safety of sedation with  
385 dexmedetomidine in critical care patients: a meta-analysis of randomized  
386 controlled trials. *Anaesth Crit Care Pain Med* 2016;35:7-15.
- 387 **12.** Goettel N, Bharadwaj S, Venkatraghavan L, Mehta J, Bernstein M, Manninen  
388 PH. Dexmedetomidine vs propofol-remifentanil conscious sedation for awake  
389 craniotomy: a prospective randomized controlled trial. *Br J Anaesth*  
390 2016;116:811-821.
- 391 **13.** Hughes CG, Mailloux PT, Devlin JW, et al. Dexmedetomidine or Propofol for  
392 Sedation in Mechanically Ventilated Adults with Sepsis. *N Engl J Med*  
393 2021;384:1424-1436.
- 394 **14.** Shehabi Y, Howe BD, Bellomo R, et al. Early Sedation with Dexmedetomidine  
395 in Critically Ill Patients. *N Engl J Med* 2019;380:2506-2517.
- 396 **15.** Ter Brugge F, Ceuppens C, Leliveld L, Stronks DL, Huygen F.  
397 Dexmedetomidine vs propofol as sedation for implantation of  
398 neurostimulators: A single-center single-blinded randomized controlled trial.  
399 *Acta Anaesthesiol Scand* 2019;63:1321-1329.
- 400 **16.** Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or Radiofrequency  
401 Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med* 2016;374:2235-2245.

- 402 **17.** Daverio M, Sperotto F, Zanetto L, et al. Dexmedetomidine for Prolonged  
403 Sedation in the PICU: A Systematic Review and Meta-Analysis. *Pediatr Crit*  
404 *Care Med* 2020;21:e467-e474.
- 405 **18.** Erickson SJ, Millar J, Anderson BJ, et al. Dexmedetomidine Sedation in  
406 Mechanically Ventilated Critically Ill Children: A Pilot Randomized Controlled  
407 Trial. *Pediatr Crit Care Med* 2020;21:e731-e739.
- 408 **19.** Cho JS, Shim JK, Na S, Park I, Kwak YL. Improved sedation with  
409 dexmedetomidine-remifentanil compared with midazolam-remifentanil during  
410 catheter ablation of atrial fibrillation: a randomized, controlled trial. *Europace*  
411 2014;16:1000-1006.
- 412 **20.** Sairaku A, Yoshida Y, Hirayama H, Nakano Y, Ando M, Kihara Y. Procedural  
413 sedation with dexmedetomidine during ablation of atrial fibrillation: a  
414 randomized controlled trial. *Europace* 2014;16:994-999.
- 415 **21.** Absalom AR, Glen JI, Zwart GJ, Schnider TW, Struys MM. Target-Controlled  
416 Infusion: A Mature Technology. *Anesth Analg* 2016;122:70-78.
- 417 **22.** Waugh JB, Epps CA, Khodneva YA. Capnography enhances surveillance of  
418 respiratory events during procedural sedation: a meta-analysis. *J Clin Anesth*  
419 2011;23:189-196.
- 420 **23.** Nolan PJ, Delgadillo JA, Youssef JM, Freeman K, Jones JL, Chehrehsa A.  
421 Dexmedetomidine Provides Fewer Respiratory Events Compared With  
422 Propofol and Fentanyl During Third Molar Surgery: A Randomized Clinical  
423 Trial. *J Oral Maxillofac Surg* 2020;78:1704-1716.
- 424 **24.** Shin HJ, Kim EY, Hwang JW, Do SH, Na HS. Comparison of upper airway  
425 patency in patients with mild obstructive sleep apnea during dexmedetomidine  
426 or propofol sedation: a prospective, randomized, controlled trial. *BMC*  
427 *Anesthesiol* 2018;18:120.

428 **Figure legends**

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

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

436

437 **Figure 2. Vital parameters during the ablation procedure.**

438 Graphs showing A) heart rate, B) SpO<sub>2</sub>, C) systolic blood pressure, and D) tcCO<sub>2</sub> and  
439 95% confidence intervals for the first 120 minutes of the ablation procedure. SpO<sub>2</sub>:  
440 saturation of peripheral oxygen; TcCO<sub>2</sub>: transcutaneous carbon dioxide level.

441

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

444

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

448

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

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

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

458

459

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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 <sup>2</sup>	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 <sub>2</sub> DS <sub>2</sub> Vasc 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 <sup>2</sup>	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 (1<sup>st</sup>; 3<sup>rd</sup>) 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<sup>st</sup>; 3<sup>rd</sup>) 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



478

479 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
<b>Secondary endpoints (components of the primary endpoint)</b>				
Termination or change of sedation protocol	3 (4%)	-	4% (-0%; 8%)	0.080
Inability to achieve MOAA/S score $\leq 3$	1 (1%)	-	1% (-1%; 4%)	0.316
Aborted procedure due to sedation issues	-	-	-	-
Hypercapnia (tcCO <sub>2</sub> rise >20 mmHg OR tcCO <sub>2</sub> >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

480 Data are provided as median with interquartile range (1<sup>st</sup>; 3<sup>rd</sup>) or frequencies with

481 percentages. MOAA/S: Modified Observer's Assessment of Alertness/Sedation

482 Scale; tcCO<sub>2</sub>: transcutaneous carbon dioxide level.

483

484 Table 4. Patient satisfaction with sedation.

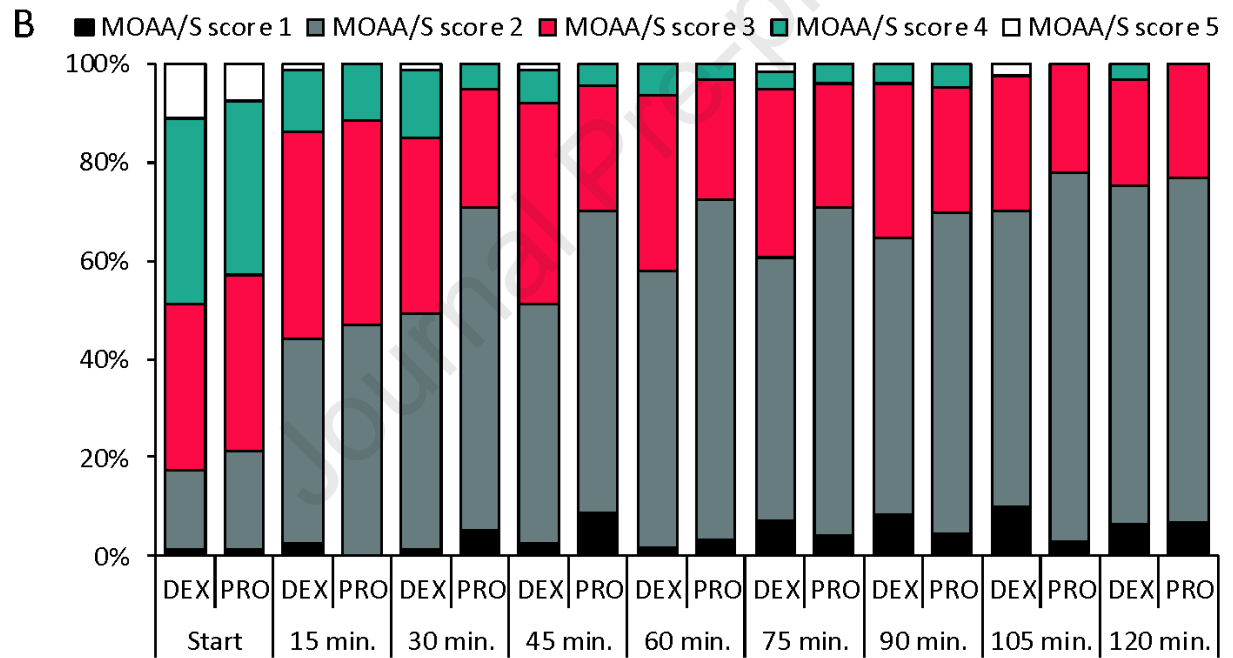
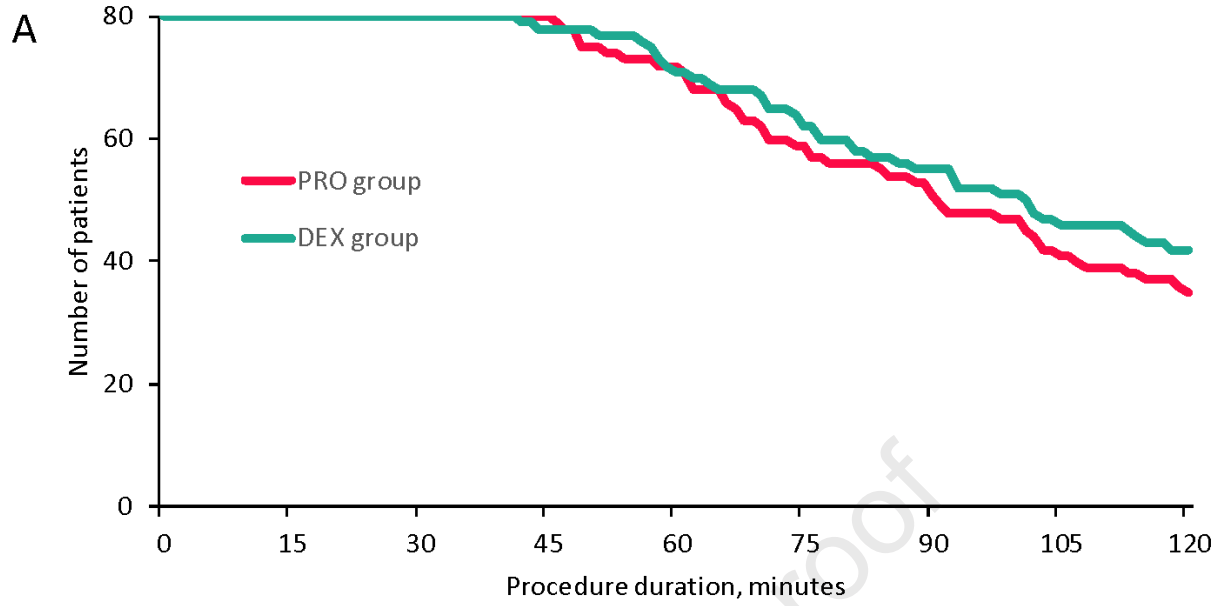
	All N=160	DEX group N=80	PRO group N=80	P Value
<b>General satisfaction with sedation</b>				
How satisfied were you with the sedation?	100 (90; 100)	93 (80; 100)	100 (100; 100)	<0.001
How well have you recovered from sedation?	90 (75; 100)	80 (70; 100)	90 (80; 100)	0.028
Would you choose the same type 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%)	
<b>During the procedure, in the electrophysiology lab</b>				
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
<b>When waking up in the electrophysiology lab</b>				
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
<b>After the procedure, on the ward</b>				
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

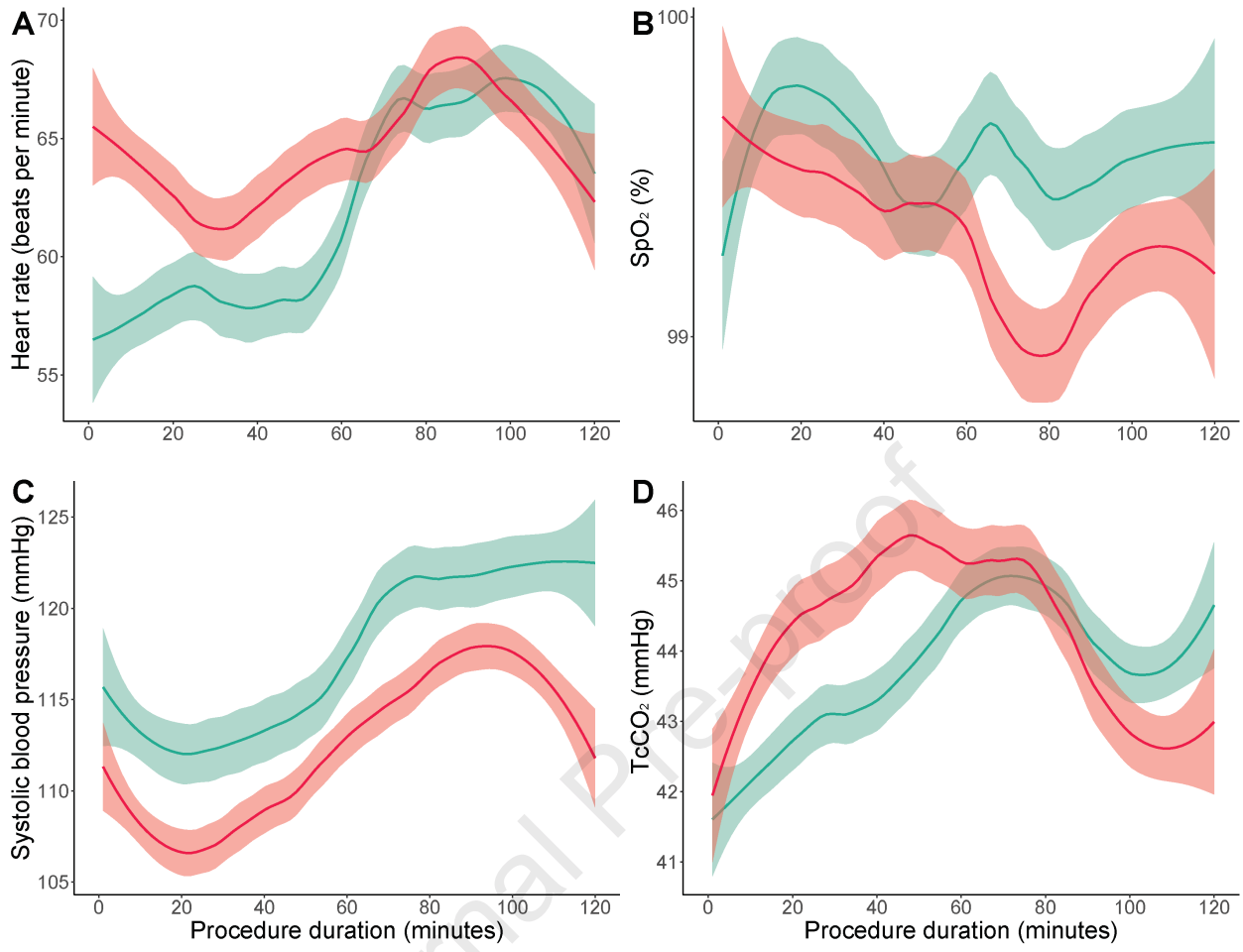
485 Data are provided as median with interquartile range (1<sup>st</sup>; 3<sup>rd</sup>) or frequencies with

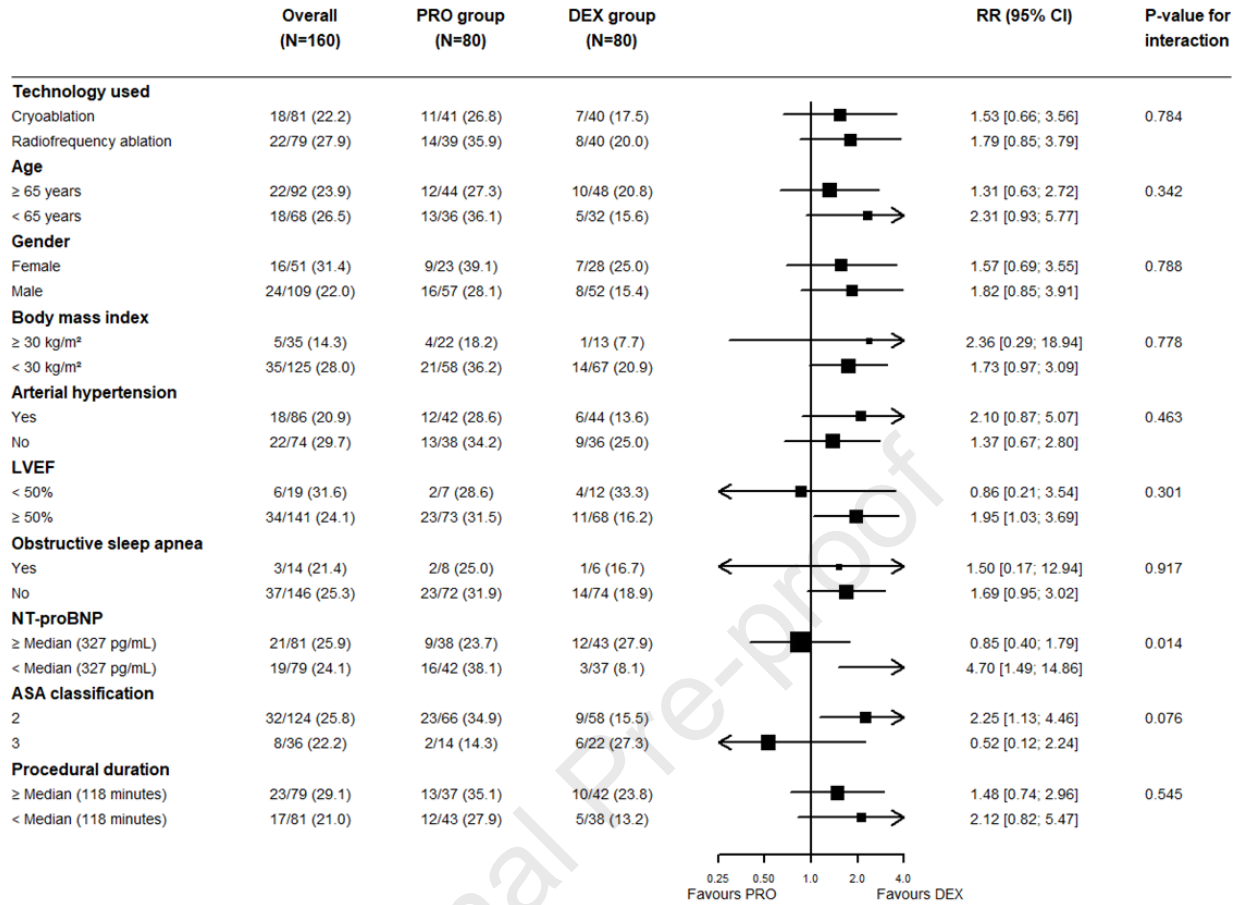
486 percentages in parentheses of patient responses on a visual analogue scale (Range

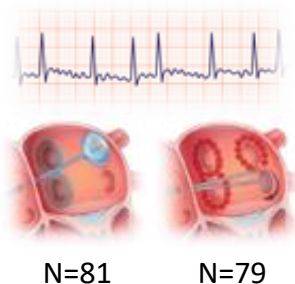
487 0-100), or frequencies with percentages in parentheses, as appropriate. DEX:

488 dexmedetomidine; PRO: propofol.







**A**

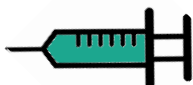
N=81

N=79

Operator-directed  
nurse-administered

Dexmedetomidin

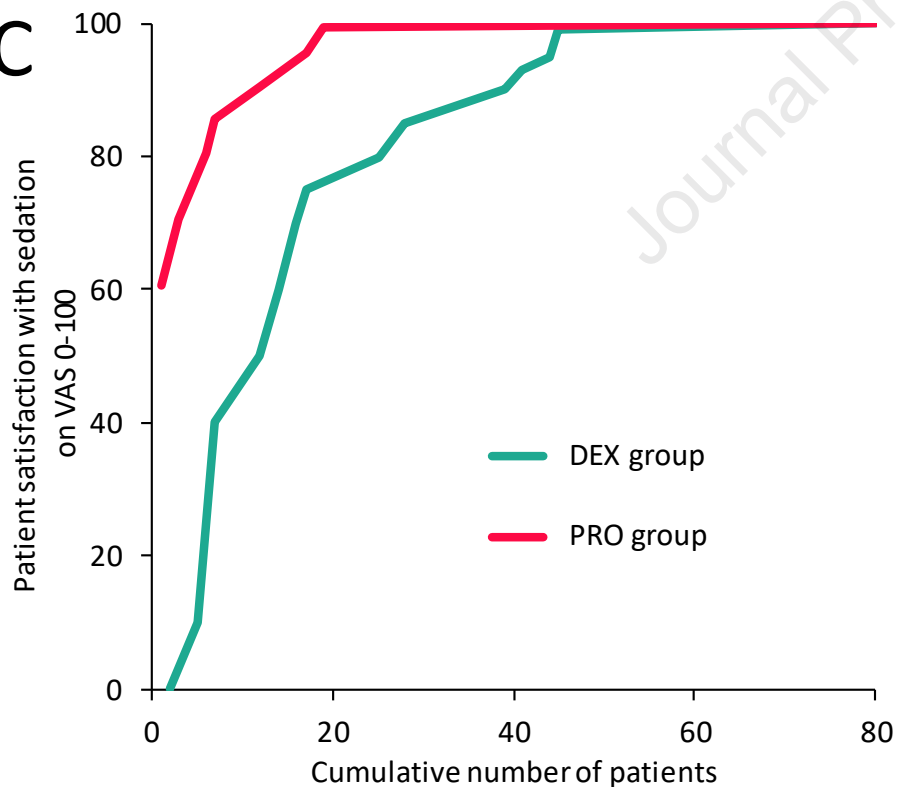
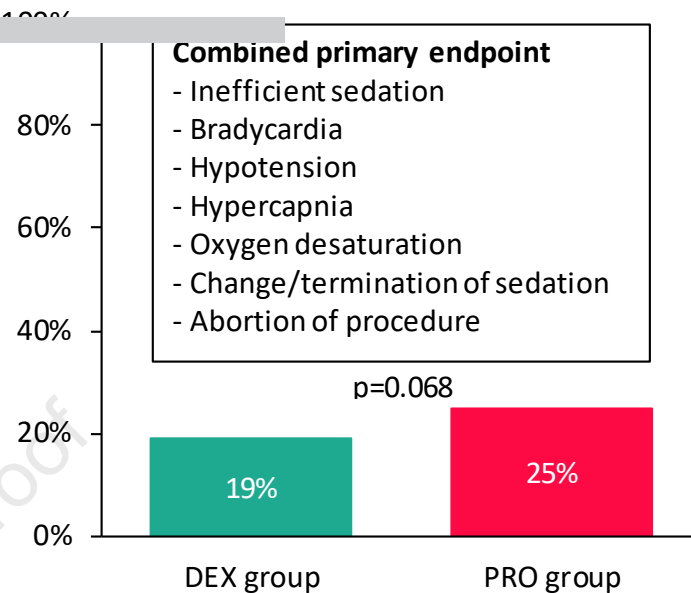
N=80



Randomized

Propofol

N=80

**C****D****D**

Patient questionnaire:  
Would you choose the same sedation method again?

■ Yes ■ Unsure ■ No

