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Randomized comparison between dexmedetomidine–remifentanil and midazolam–fentanyl for deep sedation during catheter ablation of atrial fibrillation

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Abstract

Background and objectives: The efficacy of dexmedetomidine for radiofrequency catheter ablation (RFCA) of atrial fibrillation (AF) has not been well established. We evaluated the efficacy and safety of sedation using dexmedetomidine with remifentanil compared to conventional sedative agents during RFCA for AF.

Subjects and methods: A total of 240 patients undergoing RFCA for AF were randomized to either the dexmedetomidine (DEX) group (continuous infusion of dexmedetomidine and remifentanil) or the midazolam (MID) group (intermittent injections of midazolam and fentanyl) according to sedative agents. Non-invasive positive pressure ventilation was applied to all patients during the procedure. The primary outcome was patient movement during the procedure resulting in a 3D mapping system discordance, and the secondary outcome was adverse events including respiratory or hemodynamic compromise.

Results: During AF ablation, the incidence of the primary outcome was significantly reduced for the DEX group (18.2% vs. 39.5% in the DEX and the MID groups, respectively, $p < 0.001$). The frequency of a desaturation event (oxygen saturation < 90%) did not significantly differ between the two groups (6.6% vs. 1.7%, $p = 0.056$). However, the incidences of hypotension not owing to cardiac tamponade (systolic blood pressure < 80 mmHg, 19.8% vs. 8.4%, $p = 0.011$) and bradycardia (HR < 50 beats/min: 39.7% vs. 21.8%, $p = 0.003$) were higher in the DEX group. All efficacy and safety results were consistent within the predefined subgroups.

Conclusion: The combined use of dexmedetomidine and remifentanil provides higher stability sedation during AF ablation, but can lead to more frequent hemodynamic compromise compared to midazolam and fentanyl.

Keywords: Atrial fibrillation, Radiofrequency catheter ablation, Dexmedetomidine, Midazolam, Sedation

Introduction

The benefits of radiofrequency ablation (RFCA) in drug-refractory atrial fibrillation (AF) have been established in a number of randomized studies [1, 2]. RFCA for AF provides improved quality of life, decreased stroke risk, and decreased heart failure risk, as well as higher arrhythmia freedom [3–5]. Currently, RFCA is becoming an increasingly common procedure throughout the world. However, RFCA for AF requires a prolonged procedure time (2–4 h) and a large amount of ablation energy delivery, which can be painful for the patient. For both procedural success and prevention of complications, it is important to maintain an adequate level of sedation and to minimize the pain. Most centers use a three-dimensional (3D) mapping system during RFCA for AF, which allows precise electrophysiological, anatomic mapping, as well

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as the delivery of contiguous lesions around target anatomical structures [6]. Patient movement during the procedure can cause discordance of the 3D mapping system, which may limit the accuracy of ablation and lead to unintended damage to the intracardiac structure. For these reasons, RFCA for AF is often performed under deep sedation or general anesthesia [7]. However, general anesthesia requires a scheduled operating room and intensive monitoring with endotracheal intubation.

Deep sedation is a feasible and safe alternative that can achieve painless, stable analgesia for relatively long periods. For AF ablation, midazolam is commonly used as a sedative agent, combined with other analgesic agents such as fentanyl or remifentanil. However, the lack of analgesic effects of midazolam may lead to patient movement during the procedure or the use of unexpectedly higher doses of adjunctive opioids. Handling of adverse events, including hemodynamic or respiratory depression, during deep sedation might be difficult in an electrophysiology laboratory. Dexmedetomidine is a newer anesthetic agent having analgesic, sedative, and sympatholytic activity. It causes less respiratory depression [8, 9], and its efficacy and safety have been established in many previous studies for various clinical applications, including non-intubated invasive procedures [10–13]. However, its application to AF ablation has only been reported in relatively small randomized trials [14, 15].

We hypothesized that sedation by dexmedetomidine combined with remifentanil would provide better comfort for both physicians and patients compared to a conventional sedative regimen using midazolam and fentanyl. This study compared the frequency of significant patient movement and the safety profile during AF ablation between the two drug combinations.

Subjects and methods

Patients

Patients undergoing RFCA for AF at Seoul St. Mary's Hospital from April 2013 to July 2015 were prospectively enrolled. RFCA was indicated for patients with ECG-documented, drug-refractory AF (both paroxysmal and persistent) despite treatment with an antiarrhythmic agent for more than 6 weeks. Exclusion criteria were as follows: less than 18 years of age, prior adverse reaction to the sedatives or analgesics used in our study, American Society of Anesthesia (ASA) physical status class 4, or unwilling to enroll in the study. All included patients gave their written informed consent to participate. The study was approved by the institutional review board of Seoul St. Mary's Hospital (Study Number: KC12EISI0889).

Procedure

Eligible patients were randomly assigned in a 1:1 ratio to either the dexmedetomidine–remifentanil (DEX) group or the midazolam–fentanyl (MID) group before RFCA by simple randomization technique using a random number table. The target sedation level during RFCA was a Ramsay sedation score of 3–4 (3: patient responds to verbal commands only, 4: patient demonstrates a brisk response to a light glabellar tap or loud auditory stimulus) [16]. At the beginning of the procedure, patients in the DEX group received 0.8 μg/kg of intravenous dexmedetomidine over 10 min as a loading dose, followed by continuous infusion at a rate of 0.2–0.7 μg/kg/h to maintain adequate sedation [17]. Remifentanil was administered by continual infusion at a rate of 0.15 μg/kg/min initially and titrated every 5 min to a maximal dose of 0.5 μg/kg/min [18]. Patients in the MID group received an intravenous bolus of 0.05 mg/kg of midazolam and 1 μg/kg of fentanyl citrate at the beginning of the procedure, and a repeated dose was administered as required to maintain adequate sedation at a maximal interval of 30 min. The level of consciousness and patient movement were examined by two trained nurses every 5 min, and the infusion rate or administration interval of the sedative drugs was appropriately adjusted by the nurses according to sedation status.

Monitoring and recording of efficacy and safety outcomes

Appropriate equipment for emergency endotracheal intubation was prepared before the procedure. Non-invasive ventilation (NIV) was applied to all patients immediately after administration of the initial sedative agent dose. A full face NIV mask (ResMed®) was used and connected to a portable ventilator (LTV 1200, Carefusion Corporation, CA, USA). Bilevel positive airway pressure (BIPAP) was applied with the baseline setting of synchronized intermittent mechanical ventilation (SIMV), a fraction of inspired oxygen (FiO_2) of 60%, and a respiratory rate of 15 breaths/min. Inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), and FiO_2 were adjusted according to the tidal volume and monitored oxygen saturation. Vital signs, including peripheral blood pressure (BP), peripheral oxygen saturation (SpO_2), and heart rate (HR) on a 12-lead ECG, were monitored and recorded every 5 min.

The primary end point was patient movement resulting in discordance of the 3D mapping system and transient procedure interruption. Non-significant patient movement without error in the 3D mapping system was not regarded as the primary end point. If patient movement occurred, an additional dose of sedative agent was administered and the procedure was resumed after an adequate level of sedation was achieved. The secondary

end points were adverse events, including hypotension (systolic BP < 80 mmHg), bradycardia (HR < 50 beats/min), or hypoxia (SpO_2 < 90%). If any of the above adverse events occurred, the event was recorded and further infusion or injection of sedative agent was stopped until vital signs recovered to the normal range. In cases of severe (systolic BP < 70 mmHg) or refractory hypotension, an intravenous continuous infusion of dopamine was started. After the procedure was over, the sedation was stopped and patients were monitored in the procedure room until adequate motor and verbal responses to simple orders and normal vital signs were demonstrated.

Ablation procedure

All patients were anticoagulated before RFCA for at least 3 weeks and the absence of left atrial appendage thrombus was confirmed by transesophageal echocardiogram or cardiac computed tomography scan before RFCA. Ensite NavX (St. Jude Medical, St. Paul, MN, USA) 3D mapping system was used in 119/121 (98.3%) patients in the DEX group and 115/119 (96.6%) patients in the MID group. Reference catheter was positioned in the aortic sinus, and for a few cases in whom arterial line was inaccessible it was positioned in the coronary sinus. CARTO (Biosense Webster, Diamond Bar, CA, USA) 3D mapping system was used in the other six patients. After achieving an appropriate level of sedation, a vascular access site puncture was started. Once the vascular sheath was inserted, continuous or intermittent infusion of intravenous heparin was started. Infusion dose or interval was adjusted to maintain a blood activated coagulation time within 300–400 s throughout the procedure. A circular mapping catheter and an ablation catheter were advanced into the left atrium via double trans-septal accesses. The ablation procedure was performed using radiofrequency energy with an open irrigated catheter (Coolflex, St. Jude Medical, or Thermocool, Biosense Webster). Initially, circumferential ablation of all pulmonary vein antrum was performed. If AF persisted after successful pulmonary vein isolation (PVI), additional substrate modification, including linear ablation or complex fractionated atrial electrogram ablation, was performed.

Statistical analysis

An overall sample size of 240 was calculated to have 80% power when testing the superiority of the DEX group for the primary outcome. For this test, we used a two-tailed alpha of 0.05 and assumed a 5% study discontinuation rate. The expected procedure interruption rate was 16% in the DEX group and 30% in the MID group.

For baseline characteristics, study outcomes, and safety profiles, continuous variables are presented as the mean ± standard deviation and were compared using the Student's *t* test. Categorical variables are presented as the frequency with percentage (%) and were compared using the Chi square test or Fisher's exact test. After the main analysis, subgroup analyses were performed to assess the safety and efficacy of dexmedetomidine with remifentanil for different patient groups, defined according to age ≥ 65 years, ASA class ≥ 3, diabetes, and LVEF < 55%. All analyses were two-tailed, and a p value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS version 19 (SPSS Inc. Chicago, IL, USA).

Results

Baseline characteristics

A total of 240 patients were included in the current study. Of those, 121 patients were assigned to the DEX group and 119 patients were assigned to the MID group. The mean age was 61.3 years and 162 patients (67.5%) were male. There were no significant differences in age, gender, body surface area, underlying comorbidities, or the proportion of sinus rhythm at the beginning of the procedure between the two groups (Table 1). More than 60% of patients in both groups were in the ASA class ≤ 2. In terms of the initial vital signs at the procedure room, patients in the DEX group showed higher systolic BP (143 ± 21 vs. 137 ± 23 mmHg for DEX and MID group, respectively, $p = 0.015$) and lower HR (70 ± 21 vs. 76 ± 19 beats/min, $p = 0.017$). In the DEX group, the average dexmedetomidine dose was 0.86 ± 0.19 μg/kg/h and the average remifentanil dose was 3.40 ± 0.82 μg/kg/h. In the MID group, the average dose of midazolam was 95.6 ± 21.1 μg/kg/h and the average dose of fentanyl was 1.74 ± 0.40 μg/kg/h.

Procedure outcomes

Although initial BP before sedation was higher in the DEX group, BP response after sedation was similar in the two groups (Fig. 1a). Mean BP reached the lowest value at 30 min, then showed a gradual increase in both groups. Mean HR was lower in the DEX group at baseline (70.0 ± 20.7 vs. 76.2 ± 19.1 in the DEX and the MID groups, respectively, $p = 0.017$) and throughout the procedure (mean HR during procedure: 67.7 ± 14.6 vs. 74.6 ± 16.7, respectively, $p = 0.001$) (Fig. 1b). There was no significant difference in SpO_2 during the procedure (Fig. 1c). No patient showed allergic skin rash or airway spasm during RFCA.

The procedure was interrupted due to movement in significantly fewer patients in the DEX group (18.2% vs. 39.5%, $p < 0.001$) (Table 2). The average number of procedure interruptions per patient was also significantly lower in the DEX group (0.2 ± 0.4 vs. 0.5 ± 0.7, $p < 0.001$). The procedure interruption period was less than 5 min

Table 1 Baseline characteristics in the two groups

	Dexmedetomidine + remifentanil (*N* = 121)	Midazolam + fentanyl (*N* = 119)	*p* value
Age, years	62.0 ± 10.6	60.4 ± 11.0	0.265
Male, *n* (%)	78 (64.5%)	84 (70.6%)	0.311
Height, cm	164.6 ± 9.4	164.6 ± 8.3	0.943
Weight, kg	67.9 ± 11.2	68.8 ± 12.6	0.580
BMI, kg/m^2	25.0 ± 3.0	25.4 ± 3.7	0.321
BSA, m^2	1.76 ± 0.18	1.77 ± 0.19	0.626
SR at the beginning of the procedure	74 (61.2%)	73 (61.3%)	0.973
SBP, mmHg	143 ± 21	137 ± 23	0.015
DBP, mmHg	86 ± 13	81 ± 12	0.004
Heart rate, beats per min	70 ± 21	76 ± 19	0.017
ASA class ≤ 2	76 (62.8%)	73 (61.3%)	0.815
Hypertension, *n* (%)	67 (55.4%)	68 (57.1%)	0.782
Diabetes mellitus, *n* (%)	22 (18.2%)	23 (19.3%)	0.820
Stroke, *n* (%)	11 (9.1%)	14 (11.8%)	0.498
Heart failure, *n* (%)	15 (12.4%)	6 (5.0%)	0.066
Coronary artery, *n* (%) disease	7 (5.8%)	8 (6.7%)	0.764
Left ventricular ejection fraction, %	59.1 ± 6.8	60.4 ± 6.3	0.127
Procedure time, min	215 ± 55	215 ± 50	0.995
Dosage (midazolam or dexmedetomidine), μg/kg/h	Dexmedetomidine 0.86 ± 0.19	Midazolam 95.6 ± 21.1	
Dosage (fentanyl or remifentanil), μg/kg/h	Remifentanil 3.40 ± 0.82	Fentanyl 1.74 ± 0.40	

Categorical variables are presented as frequency with percentages (%) and continuous variables are presented as mean ± standard deviation. $p < 0.05$ is considered significant

BMI body mass index, *BSA* body surface area, *SR* sinus rhythm, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *ASA* American Society of Anesthesia

for all cases, with rapid sedation by additional drug dose and correction of the 3D mapping system. The incidence of desaturation events ($SpO_2 < 90\%$) during the procedure was not significantly different in the two groups (6.6% vs. 1.7% in the DEX and the MID groups, respectively, $p = 0.056$). No patient required emergent endotracheal intubation. Because dexmedetomidine has not been frequently used for electrophysiology procedures before this study, desaturation events were remarkably decreased with the accumulation of experience for dexmedetomidine. Among the 8 cases with a desaturation event in the DEX group, five occurred among the first 30 cases, two occurred among the next 30 cases of the DEX group, and only one event occurred among the subsequent 60 cases. The incidence of overall hypotensive event (SBP < 80 mmHg) was non-significantly higher in the DEX group (21.5% vs. 11.8%, $p = 0.056$). However, the incidence of hypotensive events not owing to echocardiographically documented cardiac tamponade (19.8% vs. 8.4%, $p = 0.011$) and hypotensive events requiring intravenous inotropic administration not owing to cardiac tamponade (13.2% vs. 2.5%, $p = 0.002$) was significantly higher in the DEX group. The DEX group also showed increased bradycardia events compared to the MID group (39.7% vs. 21.8%, $p = 0.003$). All adverse hemodynamic events except cardiac tamponade did not persist for longer than 20 min.

The benefit of dexmedetomidine on the primary end point was consistent in all subgroups defined according to age, ASA class, presence of diabetes, or left ventricular ejection fraction (Fig. 2a). For safety outcomes, only borderline interactions were observed in the two subgroups: patients with ASA class 3 or diabetes showed trends toward higher incidence of hypotension with the use of dexmedetomidine and remifentanil (Fig. 2b).

Discussion

In this study, continuous infusion of dexmedetomidine and remifentanil resulted in improved sedation stability compared to intermittent intravenous injection of midazolam and fentanyl without a significant increase in respiratory collapse. However, the incidence of hypotensive events except cardiac tamponade and the incidence of bradycardia were higher in patients receiving dexmedetomidine with remifentanil. Although there were some patients who required transient infusion of intravenous

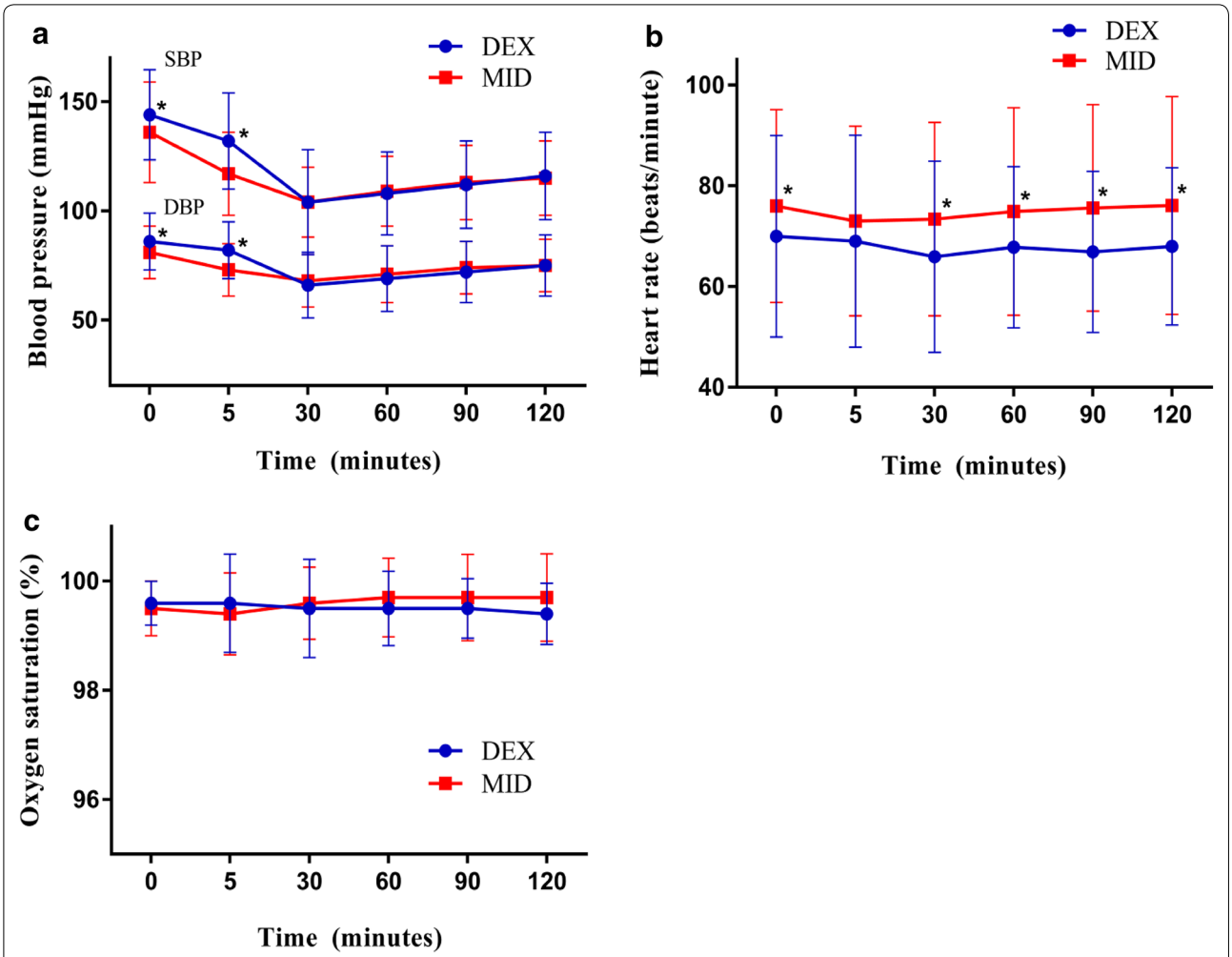

Fig. 1 Changes in the mean SBP and DBP (**a**), heart rate (**b**), and peripheral oxygen saturation (**c**) during radiofrequency catheter ablation for atrial fibrillation in the two groups. *$p < 0.05$ between the two groups at the time point. SBP: systolic blood pressure, DBP: diastolic blood pressure, DEX: dexmedetomidine + remifentanil, MID: midazolam + fentanyl

Table 2 Comparison of the primary and the secondary outcomes in the two groups

	Dexmedetomidine + remifentanil (*N* = 121)	Midazolam + fentanyl (*N* = 119)	*p* value
Procedure interruption due to patient movement, *n* (%)	22 (18.2%)	47 (39.5%)	< 0.001
Number of procedure interruption due to movement per patient	0.19 ± 0.42	0.53 ± 0.73	< 0.001
Desaturation[a], *n* (%)	8 (6.6%)	2 (1.7%)	0.056
Hypotension[b], *n* (%)	26 (21.5%)	14 (11.8%)	0.056
Hypotension not owing to cardiac tamponade, *n* (%)	24 (19.8%)	10 (8.4%)	0.011
Hypotension requiring IV inotropics (not owing to cardiac tamponade)	16 (13.2%)	3 (2.5%)	0.002
Bradycardia[c], *n* (%)	48 (39.7%)	26 (21.8%)	0.003

Categorical variables are presented as frequency with percentages (%) and continuous variables are presented as mean ± standard deviation. $p < 0.05$ is considered significant

[a] Event for peripheral oxygen saturation < 90%

[b] Event for systolic blood pressure < 80 mmHg

[c] Event for heart rate < 50 beats/min

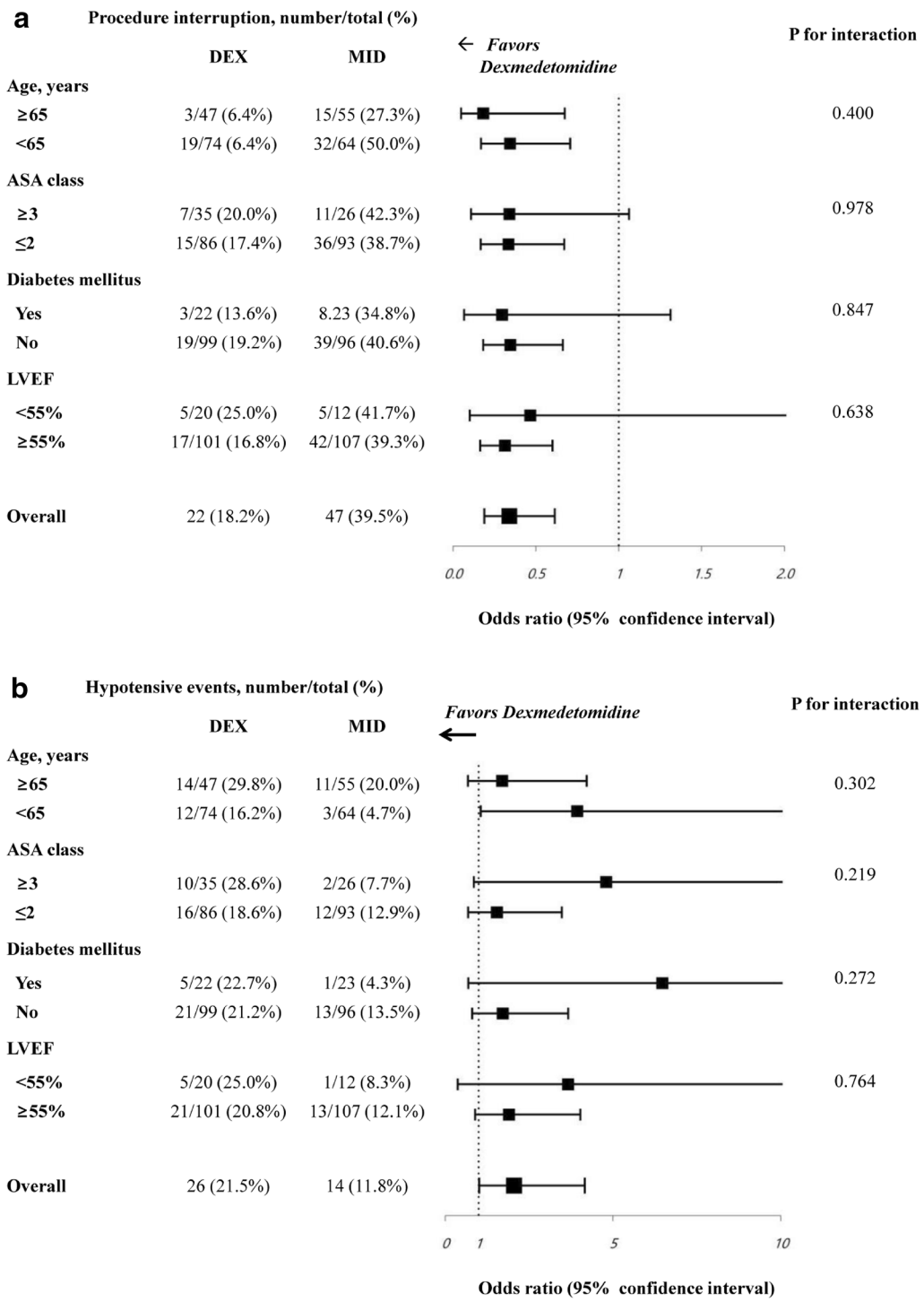

Fig. 2 Subgroup analyses in different predefined sub-populations for the primary end point (**a**) and the incidence of hypotension (systolic blood pressure < 80 mmHg) (**b**). DEX: dexmedetomidine with remifentanil, MID: midazolam with fentanyl, ASA: American Society of Anesthesia, LVEF: left ventricular ejection fraction

inotropics, all adverse events were resolved within several minutes of sedative agent dose reduction.

Midazolam is the most frequently used anesthetic agent for conscious sedation, but it can result in unwillingly prolonged sedation or respiratory depression. In previous studies, dexmedetomidine was associated with higher satisfaction and lower requirements for supplemental analgesia during various invasive procedures [19, 20]. Dere et al. compared the efficacy of midazolam and dexmedetomidine as a sedative agent during colonoscopy [21]. Dexmedetomidine provided significantly higher Ramsay sedation scale scores and satisfaction scores without a significant difference in hemodynamic stability. Accordingly, Huang et al. reported superior efficacy of dexmedetomidine compared to midazolam for the sedation of patients with non-invasive ventilation failure in the level of awakening from sedation and duration of mechanical ventilation [22].

For AF ablation, immobilization of the patient during the procedure is important for ablation outcome. Physicians may prefer anesthetic agents with higher sedation stability and dexmedetomidine can be more advantageous. Recently, two randomized trials demonstrated the utility of dexmedetomidine during AF ablation. Sairaku et al. compared the usability of dexmedetomidine to thiamylal in 87 patients undergoing AF ablation [15]. Dexmedetomidine was superior regarding respiratory stability and prevention of patient movement during the procedure. Incidence of hypotension events tended to be higher with dexmedetomidine (21% vs. 9%) without statistical significance. Cho et al. also reported superior efficacy and safety of dexmedetomidine and remifentanil compared to midazolam and remifentanil in a randomized study including 90 patients undergoing AF ablation [14]. In this study performed by anesthesiologists, the dexmedetomidine group showed a lower incidence of respiratory depression, a lower pain score, a higher satisfaction level of interventionists, and a non-significantly higher incidence of hypotension (mean arterial pressure < 60 mmHg: 11.1% vs. 0%, $p = 0.056$). In the current study, a large number of patients ($n = 240$) were included and dexmedetomidine with remifentanil was associated with better sedation stability and no significant difference in overall incidence of respiratory depression, which is consistent with previous studies. However, the incidences of bradycardia and hypotensive events not owing to cardiac tamponade were significantly higher with dexmedetomidine in our study. Furthermore, a significantly higher number of patients in the dexmedetomidine group needed intravenous inotropic agent administration due to adverse hypotensive events. Although direct comparison of the incidence of adverse hemodynamic events to previous studies is limited due to different definitions of adverse events, the trend of higher incidence of hypotension with dexmedetomidine in patients undergoing AF ablation has been consistently shown in previous studies [14, 15, 23].

Both hypotension and bradycardia are well-known adverse reactions during invasive procedures using dexmedetomidine. Among patients undergoing a variety of diagnostic or surgical procedures requiring monitored anesthesia care, the incidence of a bradycardia event was about 14% and the incidence of a hypotensive event was higher than 50% [17]. Because dexmedetomidine has a short half-life (2.1–3.1 h) [24], adverse hemodynamic effects are usually resolved without intervention and are generally well tolerated by patients. However, patients receiving RFCA for AF may have a more sensitive hemodynamic response to dexmedetomidine, since AF patients exhibit changed heart rhythms, have decreased left ventricular diastolic function, and usually receive multiple concomitant cardioinhibitory drugs [23]. Therefore, physicians have to pay more attention to hemodynamics in patients receiving dexmedetomidine during the procedure. The recommended dose of dexmedetomidine during procedural sedation is 1.0 μg/kg over 10 min as a loading dose, followed by 0.2–0.7 μg/kg/h titrated to achieve the required level of sedation [17]. The total dosage of dexmedetomidine in the current study was 0.86 ± 0.19 μg/kg/h and was seemingly higher than the recommended dose. In 23 patients who received less than 0.7 μg/kg/h of dexmedetomidine in our study, the incidence of hypotension was lower (4/23, 17.4%) with rare procedure interruption due to patient movement (1/23, 4.3%). There were no hypotensive events among patients who received less than 0.5 μg/kg/h of dexmedetomidine. Therefore, reduction of the dexmedetomidine infusion rate may be beneficial for patients who are likely to develop a hypotensive event during the procedure. In the subgroup analysis in our study, patients with diabetes or ASA class ≥ 3 tended to develop more hypotensive events with dexmedetomidine. In that population, the use of reduced dexmedetomidine dose or use of midazolam could be considered.

Our study has several limitations. First, an anesthesia specialist did not participate in our procedure, and the doctors and nurses who conducted the study had less experience with dexmedetomidine compared to midazolam, which may have confounded the study outcome. Second, there is a relative lack of significant obesity (body mass index > 30 kg/m^2, 6.3% among inclusion) in the included population, and the efficacy of dexmedetomidine in patients with severe obesity or sleep apnea cannot be clearly determined from our results. Third, although significant reduction in the patient movement was documented in the DEX group; this benefit did not lead to the

reduction in overall procedure time. Because we preferably used Ensite Navix 3D system, we could correct the map using the reference catheter and manual fusion without repeating the entire mapping procedure in the majority of cases when 3D map distortion occurred. Therefore, the procedure time may have been more affected by other factors, such as PVI time, the amount of extra-pulmonary vein ablation, or the type of ablation end point.

Conclusion

Continuous infusion of dexmedetomidine combined with remifentanil provided higher sedation stability for RFCA of AF compared to intermittent injection of midazolam with fentanyl. Although dexmedetomidine with remifentanil was associated with increased risk of transient hypotension or bradycardia events, adverse hemodynamic events did not lead to serious outcome or significant procedure disturbance. With careful drug dosing and patient monitoring, deep sedation using dexmedetomidine with remifentanil can be a preferable option for RFCA of AF.

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Authors' contributions
CY drafted the manuscript and analyzed the data. KSH, KJY, and OYS enrolled the subjects and acquired informed consents. HY, KTS, KJH, JSW, and LMY contributed to conceptualization of the study and conducting the study procedures. OYS substantially contributed to revising the article and researching data. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets analyzed during this study are not publicly available, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the institutional review board of the Seoul St. Mary's Hospital. All included patients gave their written informed consents.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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