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REPORTS OF ORIGINAL INVESTIGATIONS

Remimazolam to prevent hemodynamic instability during catheter ablation under general anesthesia: a randomized controlled trial

Le remimazolam pour prévenir l'instabilité hémodynamique lors de l'ablation par cathéter sous anesthésie générale : une étude randomisée contrôlée

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Abstract

Purpose *Maintaining hemodynamic stability during cardiac ablation under general anesthesia is challenging. Remimazolam, a novel ultrashort-acting benzodiazepine, is characterized by maintaining comparatively stable blood pressure and does not influence the cardiac conduction system, which renders it a reasonable choice for general anesthesia for cardiac ablation. We aimed to evaluate whether remimazolam is associated with a decreased incidence of intraoperative hypotension compared with desflurane.*

Methods *In this single-centre, parallel-group, prospective, single-blind, randomized clinical trial, we randomized patients (1:1) into a remimazolam group (remimazolam-based total intravenous anesthesia) or desflurane group (propofol-induced and desflurane-maintained inhalational anesthesia) during cardiac ablation procedures for arrhythmia. The primary outcome was the incidence of intraoperative hypotensive events, defined as mean arterial pressure of < 60 mm Hg at any period.*

Results *Overall, we enrolled 96 patients between 2 August 2022 and 19 May 2023 (47 and 49 patients in the remimazolam and desflurane groups, respectively). The remimazolam group showed a significantly lower incidence of hypotensive events (14/47, 30%) than the desflurane group (29/49, 59%; relative risk [RR], 0.5; 95% confidence interval [CI], 0.31 to 0.83; P = 0.004). Remimazolam was associated with a lower requirement for bolus or continuous vasopressor infusion than desflurane was (23/47, 49% vs 43/49, 88%; RR, 0.56; 95% CI, 0.41 to 0.76; P < 0.001). No between-group differences existed in the incidence of perioperative complications such as nausea, vomiting, oxygen desaturation, delayed emergence, or pain.*

Conclusions *Remimazolam was a viable option for general anesthesia for cardiac ablation. Remimazolam-based total intravenous anesthesia was associated with significantly fewer hypotensive events and vasopressor requirements than desflurane-based inhalational anesthesia was, without significantly more complications.*

Study registration *ClinicalTrials.gov (NCT05486377); first submitted 1 August 2022.*

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Résumé

Objectif *Le maintien de la stabilité hémodynamique lors d'une ablation cardiaque sous anesthésie générale est un défi. Le remimazolam, une nouvelle benzodiazépine à action ultra-courte, se caractérise par le maintien d'une tension artérielle relativement stable et son absence d'influence sur le système de conduction cardiaque, ce qui en fait un choix raisonnable pour l'anesthésie générale pour l'ablation cardiaque. Nous avons cherché à déterminer si le remimazolam est associé à une diminution de l'incidence d'hypotension peropératoire comparativement au desflurane.*

Méthode *Dans cette étude clinique randomisée, prospective, en simple aveugle, en groupes parallèles et monocentrique, nous avons randomisé des patient·es (1:1) dans un groupe remimazolam (anesthésie intraveineuse totale à base de remimazolam) et un groupe desflurane (anesthésie volatile induite par propofol et maintenue par desflurane) pendant des interventions d'ablation cardiaque pour arythmie. Le critère d'évaluation principal était l'incidence d'événements hypotensifs peropératoires, définis comme une tension artérielle moyenne de < 60 mm Hg à n'importe quelle période.*

Résultats *Au total, nous avons recruté 96 patient·es entre le 2 août 2022 et le 19 mai 2023 (47 et 49 personnes dans les groupes remimazolam et desflurane, respectivement). Le groupe remimazolam a montré une incidence significativement plus faible d'événements hypotensifs (14/47, 30 %) que le groupe desflurane (29/49, 59 %; risque relatif [RR], 0,5; intervalle de confiance [IC] à 95 %, 0,31 à 0,83; P = 0,004). Le remimazolam a été associé à des besoins plus faibles de bolus ou de perfusion continue de vasopresseurs que le desflurane (23/47, 49 % vs 43/49, 88 %; RR, 0,56; IC 95 %, 0,41 à 0,76; P < 0,001). Il n'y avait pas de différences entre les groupes dans l'incidence des complications périopératoires telles que les nausées, les vomissements, la désaturation en oxygène, l'émergence retardée ou la douleur.*

Conclusion *Le remimazolam a constitué une option viable pour l'anesthésie générale en vue d'une ablation cardiaque. L'anesthésie intraveineuse totale à base de remimazolam a été associée à un nombre significativement plus faible d'événements d'hypotension et de besoins en vasopresseurs que l'anesthésie par inhalation à base de desflurane, sans complications significativement plus nombreuses.*

Enregistrement de l'étude *ClinicalTrials.gov (NCT05486377); soumis pour la première fois le 1er août 2022.*

Keywords cardiac arrhythmia · cryoablation · general anesthesia · hemodynamics · remimazolam

Cardiac ablation is a painful procedure since it uses thermal energy to create a scar in the heart via intracardiac catheterization to block irregular electrical signals and restore normal heart rhythm.[1] General anesthesia with or without neuromuscular blocking agents is preferred over sedation because it renders patients motionless and unresponsive for safe and effective cardiac ablation.[2,3] Moreover, compared with sedation, general anesthesia is associated with a higher procedural success rate and lower recurrence rate of atrial fibrillation because it provides a patent airway and regular respiration throughout the procedure.[3,4] Nevertheless, selecting an anesthetic agent for cardiac ablation can be challenging because the ideal agent must preserve hemodynamic stability while exerting no electrophysiologic effects on the cardiac conduction system.[2]

Remimazolam, a new ultrashort-acting benzodiazepine, has a lower risk of intraoperative hypotension than propofol.[1,5–9] Unlike propofol and inhalational anesthetics, it does not affect the cardiac conduction system.[9] Remimazolam also exhibits quick onset/offset characteristics facilitated by flumazenil. Dose adjustments in older patients and those with renal or hepatic impairment are not necessary.[5,10–12] Thus, remimazolam has become an appealing anesthetic for use outside the operating room.

Nevertheless, remimazolam has only recently been approved for general anesthesia in a few countries (Japan in 2020, Republic of Korea and China in 2021, and the European Union/European Economic Area in 2023). To date, there is insufficient evidence regarding its effects compared to conventional anesthetics for cardiac ablation.[5,13] We hypothesized that total intravenous anesthesia (TIVA) with remimazolam would be more beneficial than desflurane-based inhalational anesthesia at lowering hypotensive events during cardiac ablation. Previously, we conducted a retrospective study using data of patients who underwent cardiac ablation for atrial fibrillation under general anesthesia, and the results were supportive of this hypothesis.[14] Accordingly, we aimed to conduct a randomized controlled trial (RCT) to confirm whether remimazolam-based TIVA is more beneficial than desflurane-based anesthesia induced by propofol in terms of stable blood pressure during cardiac ablation under general anesthesia.

Methods

Study design and ethics

This single-centre, parallel-group, single-blind prospective RCT was approved by the ethics committee of Seoul National University Bundang Hospital in the Republic of Korea (IRB number: B-2205-757-001). We conducted the study in accordance with the tenets of the Declaration of Helsinki. All patients provided written informed consent. We registered this study at ClinicalTrials.gov (NCT05486377; first submitted 1 August 2022; principal investigator, In-Ae Song) and report the results according to the Consolidated Standards of Reporting Trials guidelines.[15]

Study population

We enrolled adult patients (aged $\geq$ 20 yr) who underwent ablation for cardiac arrhythmia under general anesthesia. The exclusion criteria were inability to provide written informed consent, age $<$ 20 yr, history of severe adverse effects or hypersensitivity to benzodiazepines or their additives, acute alcohol intoxication, coma or shock state due to conditions other than heart problems, or acute narrow-angle glaucoma. We randomized the participants at a 1:1 ratio into randomly permutated blocks using programming code developed by an independent researcher to either receive remimazolam-based TIVA (intervention group) or desflurane-based inhalational anesthesia (control group) during catheter ablation for arrhythmias. A single researcher blinded to the group allocation process screened the patients based on predefined inclusion and exclusion criteria. The researchers blinded to the group allocation process obtained written consent from the patients who were also blinded to this process. Thereafter, one researcher opened a concealed random number table and assigned the participants to a group.

Because of differences in anesthetic methods, the anesthesiologists who managed the participants throughout procedures could not be blinded to the allocated group. Nevertheless, the participants remained unaware of the medication during consciousness at the time of anesthesia induction and were kept blinded to the group until the study ended.

The electronic medical record system automatically recorded perioperative vital signs. Additionally, anesthesiologists, who were not blinded to the group allocation, recorded perioperative parameters such as time from anesthetic administration to loss of consciousness and time until recovery from anesthesia, as well as complications such as injection pain during the induction of anesthesia.

Medical staff in the intensive care unit and ward, who were blinded to the group allocation, assessed, and managed the clinical outcomes, including postoperative pain, nausea, and vomiting; desaturation events; delayed emergence; and hypotensive events.

The recruitment period was between 2 August 2022 and 19 May 2023 (including follow-up).

Anesthetic management

Intervention group

The participants in the remimazolam group received TIVA with remimazolam and remifentanil for anesthesia. Anesthesia was induced by a continuous infusion of remimazolam (6 $mg \cdot kg^{-1} \cdot hr^{-1}$ *iv*) and target-controlled infusion (TCI) (Minto model) of remifentanil (3.0 $ng \cdot mL^{-1}$ *iv*) and rocuronium (0.6 $mg \cdot kg^{-1}$ *iv*). The anesthesiologists maintained Bispectral Index™ (BIS™; Covidien/Medtronic, Minneapolis, MN, USA) values within the range of 40–60 by administering a continuous infusion of remimazolam (1–2 $mg \cdot kg^{-1} \cdot hr^{-1}$ *iv*) throughout the procedure. Anesthesia and analgesia in both the remimazolam and desflurane groups were maintained using remifentanil.

At the end of the procedure, all patients received flumazenil (0.2 mg *iv*) as per institutional routine, except for those who were in a fully awake state before flumazenil administration. Moreover, the physicians administered additional doses of flumazenil if deemed necessary. The administration followed a pattern of repeating 0.1–0.2 mg of flumazenil at 60-sec intervals, with a maximum flumazenil dose of 1 mg.

We administered sugammadex based on the train-of-four monitoring results.

Control group

In the desflurane group, induction of anesthesia was achieved with propofol (1–2 $mg \cdot kg^{-1}$ *iv*) or (in one patient) etomidate (0.2 $mg \cdot kg^{-1}$ *iv*), desflurane (6–10 vol %), remifentanil TCI (3 $ng \cdot mL^{-1}$ *iv*), and rocuronium (0.6 $mg \cdot kg^{-1}$ *iv*). Desflurane was used to maintain BIS values of 40–60. Remifentanil was infused continuously to maintain anesthesia and analgesia during surgery, similar to the remimazolam group. At the end of the procedure, we administered sugammadex based on the neuromuscular monitoring results.

Clinical management

Monitoring indices during anesthesia included noninvasive blood pressure, arterial blood pressure, end-tidal carbon

dioxide ($EtCO_2$), temperature, heart activity (five-lead electrocardiogram [ECG]), oxygen saturation (pulse oximetry), and BIS (BIS monitor). For between-group comparisons, we recorded the perioperative mean arterial pressure (MAP) and heart rate (HR). Continuous monitoring of arterial blood pressures occurred through arterial cannulation after loss of consciousness till the end of anesthesia.

The medical team transferred the patients to the intensive care unit for postanesthesia care for four hours. Subsequently, internal medicine physicians and cardiologists cleared them for transfer to the general ward after physical examination and follow-up echocardiography. Cardiac telemetry was used to actively monitor vital signs and ECG status. An attending physician determined if the patients were stable and discharged them the next day after surgery, based on physical and laboratory examinations. Cardiologists specializing in echocardiography as well as certified sonographers routinely performed both pre- and postprocedural echocardiography. Using the Simpson biplane method, the medical team assessed the left ventricular ejection fraction.

Outcomes

The primary outcome of interest was the incidence of intraoperative hypotension, which was defined as a MAP of < 60 mm Hg at any period.

The secondary outcomes included the incidence of bolus or continuous infusion of intravenous vasopressors; incidence and duration of continuous infusion of vasoactive agents; maximum rate of vasopressor infusion; time from induction to loss of consciousness using Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores; recovery time; and postprocedural complications.

We administered a small dose of vasopressor bolus (50–100 μg of phenylephrine or 5–10 mg of ephedrine) to correct hypotension prolonged over five minutes. Prolonged hypotension lasting over 15 min was treated with a continuous infusion of vasopressor (phenylephrine or norepinephrine).

We recorded perioperative vital signs from admission to the ward until discharge and calculated the infusion rate of vasopressors to a norepinephrine-equivalent dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$). We converted phenylephrine to norepinephrine at a conversion ratio of 1:10.[16]

A score of zero on the MOAA/S scale defined loss of consciousness. Failure to regain consciousness within one hour after general anesthesia defined delayed emergence. The participants were determined to be in a full-awake state when exhibiting a score of 15 on the Glasgow Coma Scale or 0 on the Richmond Agitation–Sedation Scale after anesthesia.

Oxygen desaturation that could not be corrected with supplemental oxygen for > 20 min via a simple nasal cannula or facial mask defined a desaturation event. The provision of oxygen via a high-flow nasal cannula, manual positive-pressure ventilation using a bag-valve mask or a ventilator to maintain adequate oxygenation, and ventilation to correct desaturation or hypercapnia defined respiratory failure.

We defined injection pain during anesthesia induction as pain of any intensity including mild-to-severe pain, pain mentioned only when questioned, pain without or with any behavioural sign, pain reported spontaneously not as a result of questioning, or pain associated with grimacing, withdrawal movement of the forearm, or tears.[17] We defined postoperative pain as pain of any intensity following the procedure for 24 hr, and defined postoperative nausea and vomiting as nausea, retching, and vomiting of any intensity within 24 hr after anesthesia.

Sample size calculation

In a previous study, a sample size of 46 patients in each group provided 80% power to detect 27% reduced hypotensive events with a two-sided type 1 error of 5% in the remimazolam group compared with the conventional anesthesia group for cardiac surgery.[7] We planned to perform intention-to-treat analyses.

Statistical analyses

We used the Shapiro–Wilk test to determine the normality of distribution of continuous variables. Normally distributed continuous variables were presented as mean (standard deviation) and were compared using *t* tests. Additionally, nonnormally distributed continuous variables are presented as median [interquartile range (IQR)] and were compared using the Mann–Whitney *U* test. Categorical variables were presented as percentages (%) and were compared using Fisher's exact test. We performed all statistical analyses using R software version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ indicated statistical significance, except for the analysis of vital signs adjusted for multiple comparisons, in which $P < 0.0027$ and $0.0027 = 1 - (1 - 0.05)$ ^ (1/19) via Dunn–Šidák correction indicated statistical significance.[18]

Results

Patient characteristics

We enrolled 96 patients (47 in the remimazolam group and 49 in the desflurane group) (Fig. 1; Table 1). Since no protocol violations occurred in any of the patients, we included all patients in the analyses (Fig. 1). Patients in the desflurane group received propofol (median [IQR], 1.4 [1.3–1.5] $mg \cdot kg^{-1}$) for general anesthesia induction, except for one patient who received etomidate (0.2 $mg \cdot kg^{-1}$). The patients in the remimazolam group received a median [IQR] cumulative dose of 0.1 [0.1–0.1] $mg \cdot kg^{-1}$ until loss of consciousness after starting a continuous infusion of remimazolam (6 $mg \cdot kg^{-1} \cdot hr^{-1}$) for anesthesia induction. We infused 500 [500–850] μg of remifentanil in the remimazolam group and 250 [200–300] μg of remifentanil in the desflurane group from induction to the end of the procedure. The median [IQR] duration of surgery was 100 [84–133] min and 95 [75–128] min and the duration of anesthesia was 130 [115–161] and 122 [102–156] min in the remimazolam and desflurane groups, respectively.

Incidence of hypotension and vasopressor use

The incidence of hypotensive events (defined as MAP values $<$ 60 mm Hg) was significantly lower in the remimazolam group compared with the desflurane group. Using a definition of hypotension of MAP $<$ 65 mm Hg, a sensitivity analysis similarly showed that the incidence of hypotensive events was significantly lower in the remimazolam group than the desflurane group. The requirement for vasoactive agents to maintain blood pressure within the normal range was significantly lower

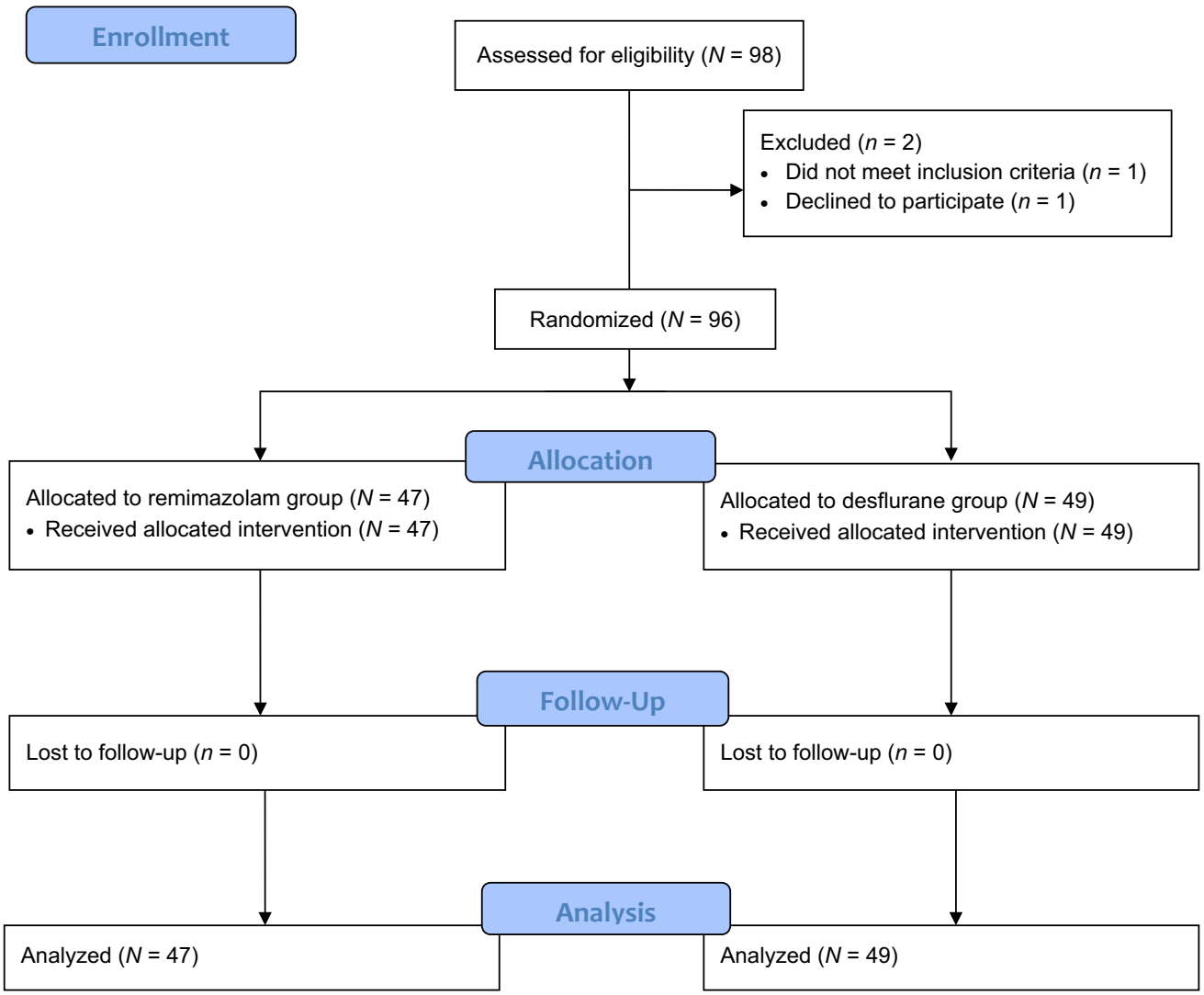

Fig. 1 CONSORT flow diagram

Table 1 Baseline characteristics and anesthetic data of the patients

Variable	Remimazolam $N = 47$	Desflurane $N = 49$
Age (yr), median [IQR]	62 [56–69]	59 [50–67]
Sex (male), *n*/total *N* (%)	37/47 (79%)	33/49 (67%)
BMI ($kg \cdot m^{-2}$), median [IQR]	26 [23–29]	27 [25–29]
Type of procedure, *n*/total *N* (%)		
Cryoablation	23/47 (49%)	27/49 (55%)
Radiofrequency ablation	24/47 (51%)	22/49 (45%)
Type of arrhythmia, *n*/total *N* (%)		
Atrial fibrillation	45/47 (96%)	45/49 (92%)
Atrial flutter	7/47 (15%)	8/49 (16%)
Others	2/47 (4%)	2/49 (4%)
ASA Physical Status, *n*/total *N* (%)		
III	39/47 (83%)	43/49 (88%)
IV	8/47 (17%)	6/49 (12%)
Comorbidities, *n*/total *N* (%)		
Hypertension	23/47 (49%)	21/49 (43%)
Diabetes mellitus	10/47 (21%)	10/49 (20%)
Cerebral stroke	3/47 (6%)	8/49 (16%)
Heart failure	10/47 (21%)	10/49 (20%)
Coronary arterial disease	3/47 (6%)	4/49 (8%)
Moderate to severe liver disease	1/47 (2%)	1/49 (2%)
End-stage renal disease	1/47 (2%)	1/49 (2%)
Preoperative echocardiography results		
Left ventricular ejection fraction (%), median [IQR]	59% [56–64]	58% [54–60]
Left ventricular ejection fraction < 50%, *n*/total *N* (%)	6/47 (13%)	5/49 (10%)
Valvular disease, *n*/total *N* (%)	19/47 (40%)	21/49 (43%)
Moderate to severe valvular disease, *n*/total *N* (%)	9/47 (19%)	9/49 (18%)
Anesthetic data, median [IQR]		
Remifentanil (μg)	500 [500–850]	250 [200–300]
Duration of procedure (min)	100 [84–133]	95 [75–128]
Duration of anesthesia (min)	130 [115–161]	122 [102–156]

ASA = American Society of Anesthesiologists; BMI = body mass index; IQR = interquartile range

in the remimazolam group than the desflurane group. The incidence of hypotension and rate of vasopressor use are presented in Table 2. As shown in Fig. 2, the MAP at 20 min after intubation during incision and at 15 min after incision was significantly lower in the desflurane group than the remimazolam group. Nevertheless, there was no significant between-group difference in HR.

Induction and recovery profile

As shown in Table 3, the time from induction agent administration to loss of consciousness was significantly longer in the remimazolam group than in the desflurane group. Anesthesia induction with propofol or etomidate caused loss of consciousness within two minutes in all patients, whereas induction with remimazolam caused loss of consciousness within two minutes in only 83% of patients. All patients showed loss of consciousness within three minutes after the induction of anesthesia.

In the remimazolam group, flumazenil (median [IQR], 0.3 [0.2–0.5] mg) was used in all patients, except for two patients who did not require flumazenil for recovery. Four patients required doses ranging between 0.7 mg and 1 mg for full awakening.

Postanesthesia complications

Postanesthesia complications such as postoperative pain, nausea and vomiting, desaturation, delayed emergence, or hypotension showed no significant between-group

Table 2 Comparison of intra- and postoperative hypotensive events and vasopressor use between the remimazolam and the desflurane groups

Variables	Remimazolam $N = 47$	Desflurane $N = 49$	RR/MD (95% CI)	P value
Hypotension, n/total N (%)	14/47 (30%)	29/49 (59%)	0.50 (0.31 to 0.83)	0.004[a]
Before incision	4/47 (9%)	11/49 (22%)	0.38 (0.13 to 1.1)	0.09[a]
After incision	13/47 (28%)	28/49 (57%)	0.48 (0.29 to 0.82)	0.004[a]
Incidence of bolus or continuous infusion of intravenous vasopressors, n/total N (%)	23/47 (49%)	43/49 (88%)	0.56 (0.41 to 0.76)	< 0.001[a]
Incidence of continuous infusion of intravenous vasopressors, n/total N (%)	9/47 (19%)	44/49 (90%)	0.21 (0.12 to 0.39)	< 0.001[a]
Duration of continuous infusion of vasopressors (min), median [IQR]	0 [0–0]	90 [70–115]	−0.41 (−0.52 to − 0.30)	< 0.001[b]
Maximal rate of continuous infusion of vasopressors ($\mu g \cdot min^{-1}$), median [IQR]	0 [0–0]	0.5 [0.3–0.6]	−72 (−92 to − 51)	< 0.001[b]

CI = confidence interval; IQR = interquartile range; MD = mean difference; RR = relative risk

[a]Fisher's exact test

[b]Mann–Whitney U test

differences (Table 4). None of the patients showed respiratory failure.

Discussion

Remimazolam-based TIVA was more beneficial than desflurane-based anesthesia induced with propofol regarding hypotensive events. Compared with the desflurane group, the remimazolam group showed a significantly lower incidence of hypotension, reduced requirement for vasopressor use, and decreased amount and duration of continuous infusion of vasopressors. Overall, our findings indicated that remimazolam did not increase postoperative complications. The present findings are consistent with the results of our previous retrospective study.[14]

Intraoperative hypotension is common; however, it has been associated with serious renal, neurologic, and cardiovascular complications, as well as death.[19–21] A systematic review found that end-organ injury may occur if the MAP is < 80 mm Hg for over ten minutes.[22] Only one minute of exposure to MAP < 55 mm Hg may be associated with perioperative complications.[19] Therefore, we selected the incidence of hypotensive events as the primary outcome.

Nevertheless, maintaining stable blood pressure for cardiac ablation is challenging. First, patients might have underlying cardiovascular disease. Second, cardiac injury could occur during the ablation procedures. Third, anesthetics or medications may cause hypotension or interfere with the procedure by blocking or promoting arrhythmia. Finally, there may be a lack of personnel and equipment for handling serious perioperative situations because cardiac ablation is performed outside the operating room.[1] Remimazolam may be a suitable alternative anesthetic for cardiac ablation because it involves fewer hypotension events and does not exert electrophysiologic effects on the cardiac conduction system.[23–28] There is no evidence that remimazolam was associated with QT interval prolongation or blocking of supraventricular arrhythmias during cardiac procedures.[2,3,29,30]

Several studies have compared the efficacy of remimazolam with that of other induction agents during heart surgery.[5,31,32] Remimazolam as an induction agent for general anesthesia during valve replacement surgery showed more stable hemodynamics compared with propofol.[7] Low-dose remimazolam (0.2 $mg \cdot kg^{-1}$) and etomidate (0.3 $mg \cdot kg^{-1}$) showed similar hemodynamics. Nevertheless, remimazolam (0.3 $mg \cdot kg^{-1}$) showed worse hemodynamics during cardiac valve surgeries.[28] Another study that compared the hemodynamics between remimazolam (0.3 $mg \cdot kg^{-1}$) and propofol (1.5 $mg \cdot kg^{-1}$) during valve surgery found lower hemodynamic fluctuations in the remimazolam group than in the propofol group.[31]

Remifentanil may cause hypotensive events and can induce hypotension to reduce bleeding during surgeries.[33,34] A higher remifentanil dose was used in the remimazolam group than in the desflurane group, possibly to achieve balanced anesthesia. Alternatively, the attending anesthesiologists may have reduced the remifentanil doses because of hypotensive events in the desflurane group. Despite the higher doses of remifentanil, the remimazolam group showed higher blood pressures than the desflurane group did.

Previous studies have reported a delayed induction time using remimazolam, as observed in this study.[23] As

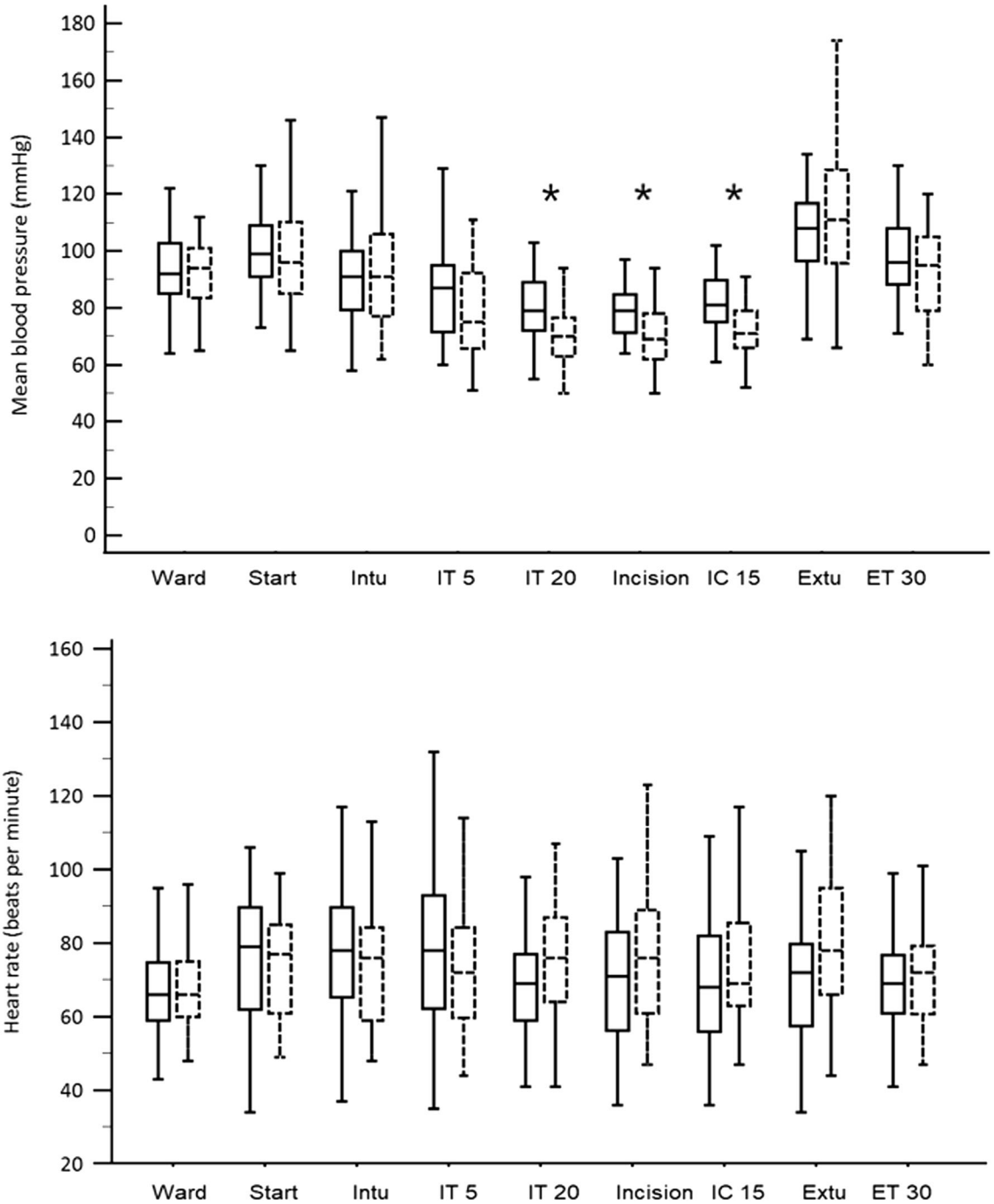

Fig. 2 Between-group comparison of cardiac parameters. Upper panel: mean arterial pressure (MAP); lower panel: heart rate (HR). The median and interquartile range of perioperative MAP and HR on the ward, before induction, from loss of consciousness to tracheal intubation, 5 min after tracheal intubation, 20 min after tracheal intubation, during skin incision, 15 min after skin incision, at the time of tracheal extubation, and 30 min after tracheal extubation are illustrated as boxes and whiskers, respectively. Remimazolam group, solid lines; desflurane group, dotted lines.

*$P < 0.0027$

ET 30 = 30 min after extubation; Extu = extubation; IC 15 = 15 min after incision; Intu = intubation; IT 20 = 20 min after intubation; IT 5 = 5 min after intubation; Start = start of induction

Table 3 Comparison of induction and recovery profile between the remimazolam and the desflurane groups

	Remimazolam $N = 47$	Desflurane $N = 49$	MD (95% CI)	P value[a]
Time from induction to loss of consciousness (min), median [IQR]	1.0 [1.0–1.0]	1.0 [1.0–1.0]	0.35 (0.19 to 0.52)	< 0.001
Emergence time (min), median [IQR]	7.0 [5.0–10.0]	7.0 [5.0–10.0]	0.21 (−1.1 to 1.57)	0.83

[a]Mann–Whitney U test

Table 4 Comparison of perioperative complications between the remimazolam and the desflurane groups

	Remimazolam group $N = 47$	Desflurane group $N = 49$	RR (95% CI)	P value
Injection pain during administration of induction dose, *n*/total *N* (%)	0/47 (0%)	4/49 (8%)	0.12 (0.01 to 2.1)	0.14[a]
Postoperative pain, *n*/total *N* (%)	9/47 (19%)	16/49 (33%)	0.59 (0.29 to 1.2)	0.2[a]
Postoperative pain requiring rescue medication	9/47 (19%)	14/49 (29%)	0.67 (0.32 to 1.4)	0.4[a]
Location of pain, *n*/total *N* (%)				
Chest	2/47 (4%)	8/49 (16%)	0.26 (0.06 to 1.2)	0.11[a]
Operation site	2/47 (4%)	1/49 (2%)	2.1 (0.20 to 22)	0.97[a]
Postoperative desaturation event, *n*/total *N* (%)	2/47 (4%)	1/49 (2%)	2.1 (0.20 to 22)	0.97[a]
Postoperative nausea and vomiting, *n*/total *N* (%)	1/47 (2%)	5/49 (10%)	0.21 (0.03 to 1.7)	0.2[a]
Postoperative nausea and vomiting requiring rescue medication, *n*/total *N* (%)	1/47 (2%)	3/49 (6%)	0.35 (0.37 to 3.2)	0.62[a]
Delayed emergence, *n*/total *N* (%)	2/47 (4%)	0/49 (0%)	5.2 (0.26 to 110)	0.46[a]
Postoperative hypotension event, *n*/total *N* (%)	1/47 (2%)	2/49 (4%)	0.52 (0.05 to 5.6)	1.0[a]

Values denote the number (proportion)

CI = confidence interval; RR = relative risk

[a]Fisher's exact test

mentioned previously, propofol induction was faster than remimazolam induction despite lower doses, which could be attributed to cardiac problems and other comorbidities in older patients.[35]

There was no between-group difference in the emergence time. In this study, the medical team routinely administered flumazenil at the end of surgery because it was difficult to taper remimazolam before the procedure as predicting the cardiac ablation end point is difficult. General anesthesia with remimazolam could cause decreases in the quality of recovery compared with general anesthesia with propofol when recovering without flumazenil.[37] Regarding remimazolam-based general anesthesia, extubation could be delayed over 15 min without routine flumazenil administration.[25,36]

In a meta-analysis of patients with benzodiazepine intoxication, agitation and gastrointestinal symptoms were the most common adverse events in the flumazenil group, while supraventricular arrhythmia and convulsions were the most common severe adverse events.[37] Nevertheless, there may be a bias because flumazenil was used mainly in the emergency room to manage patients with benzodiazepine intoxication before using it to reverse remimazolam-induced anesthesia. Patients with benzodiazepines overdose are suspected of either multidrug intoxication, alcohol abuse, or long-term drug abuse, different from the general population undergoing elective surgery and anesthesia. Seizures are not thought to be caused by a direct toxic impact of flumazenil, but rather by reversal of the benzodiazepine's anticonvulsant effect in the presence of proconvulsive medications or other seizure predispositions.[37]

The present study has some limitations. First, this was a single-centre study. Global multicentre trials are thus required to validate our findings. Second, given the obvious differences between inhalation anesthesia and TIVA, the anesthetic staff were not blinded during the perioperative period. Nevertheless, to avoid bias, we selected the incidence of hypotensive events as the primary outcome, which could be calculated based on data mostly recorded automatically in electronic medical record systems to avoid the subjective judgement of the researcher as recommended by the International Council for Harmonization harmonized tripartite guidelines. Third,

this study did not evaluate long-term outcomes such as the success rate or recurrence rate of cardiac procedures. Fourth, we could not determine whether hypotension was directly attributed to the ablation procedure itself or the anesthetic agent used. Nevertheless, the participants in this study were randomly assigned to two groups and had equal chances of receiving any specific step of the procedure. Both groups did not differ in type of ablation or arrhythmia. Finally, this study was based on the controversial assumption that hypotension is associated with worse clinical outcomes.[38] There remain no definite thresholds for intraoperative hypotension, with the reported range varying widely.[39]

In conclusion, remimazolam-based TIVA may be a favourable option for cardiac ablation procedures given its reduced incidence of hypotensive events and vasopressor requirements combined with a low incidence of complications. We advocate for future multicentre RCTs to investigate the comparative effects of remimazolam-based anesthesia on long-term outcomes after cardiac ablation.

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