

**Comparison of remimazolam-based and propofol-based total intravenous anesthesia on hemodynamics during anesthesia induction in patients undergoing transcatheter aortic valve replacement: a randomized controlled trial**

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## **Abstract**

**Purpose:** This study aimed to compare the hemodynamic effects of remimazolam- and propofol-based total intravenous anesthesia in patients who underwent transcatheter aortic valve replacement.

**Methods:** This was a single-center, single-blind, randomized controlled trial set at Nara Medical University, Kashihara, Japan. We included 36 patients aged  $\geq 20$  years scheduled to undergo elective transfemoral transcatheter aortic valve replacement (TAVR) under general anesthesia. The participants were randomly assigned to the remimazolam and propofol groups (n=18 each). Remimazolam- or propofol-based total intravenous anesthesia was initiated at 12 mg/kg/min or 2.5 mcg/mL via target-controlled infusion, respectively, along with remifentanyl. After confirming the loss of consciousness, the administration rate was adjusted using electroencephalographic monitoring. The primary outcome was the rate of arterial hypotension, defined as a mean arterial pressure  $<60$  mmHg, from anesthesia induction until the beginning of the surgical incision. The total doses of ephedrine and phenylephrine were also assessed.

**Results:** During anesthesia induction, the arterial hypotension rates were 11.9% and 21.6% in the remimazolam and propofol groups, respectively ( $P=0.01$ ). The total dose of ephedrine was higher in the propofol group (14.4 mg) than in the remimazolam group (1.6 mg) ( $P<0.001$ ); however, the total dose of phenylephrine was not significantly different between the two groups (propofol: 0.31 mg vs. remimazolam: 0.17 mg,  $P=0.10$ ).

**Conclusions:** Remimazolam-based total intravenous anesthesia resulted in a lower hypotension rate than propofol-based total intravenous anesthesia during induction in patients undergoing TAVR. Remimazolam-based total intravenous anesthesia can be used safely during anesthetic induction in patients with severe aortic stenosis.

## **Introduction**

Arterial hypotension, occurring from anesthetic induction to surgical incision, is highly prevalent and more likely to occur in older patients with a poorer preoperative physical status. [1-3] Patients with aortic stenosis (AS) also have an increased risk of developing arterial hypotension caused by vasodilation and bradycardia induced by anesthesia and require careful hemodynamic management. [4] Transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement are the current standard treatments for severe AS; however, TAVR is favored in older patients with high surgical risks. [5] Although both general anesthesia and monitored anesthesia care are feasible and safe for TAVR, general anesthesia has some advantages, such as the facilitated use of transesophageal echocardiography and easier management of surgical complications. [6] Propofol is widely used as an anesthetic agent for induction; however, it is associated with vasodilation and reduced cardiac output, resulting in arterial hypotension. [5,6] In contrast, remimazolam, a short-acting benzodiazepine that has recently become available for inducing general anesthesia, can provide hemodynamic stability even in patients with AS [7]; however, although some randomized controlled trials have evaluated the effects of remimazolam on hemodynamics during anesthesia [8-10], no randomized controlled trials on the use of remimazolam for inducing general anesthesia in patients with severe AS are available.

Based on the hypothesis that remimazolam-based total intravenous anesthesia contributes to lower hypotensive events in anesthesia induction than propofol-based total intravenous anesthesia, the present study aimed to compare the hemodynamic effects, particularly arterial hypotension occurring from the induction of anesthesia until the surgical incision, of remimazolam-based and propofol-based total intravenous anesthesia in patients with scheduled TAVR. We also assessed postoperative recovery,

postoperative delirium, length of hospital stay, and death within 30 days postoperatively.

## **Methods**

### ***Study design and population***

The current study was a single-center, single-blind, randomized controlled trial. Ethical approval for this study (approval number: 3043, chairperson: Prof. M. Yoshizumi) was provided by the local ethics committee on September 9, 2021. The study was registered at the UMIN Clinical Trials Registry (UMIN000045628). All included patients provided written informed consent. This study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [11]. Trial registration: UMIN000045628. (URL, [https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr\\_view.cgi?recptno=R000050360](https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000050360))

Patients aged  $\geq 20$  years scheduled to undergo elective transfemoral TAVR under general anesthesia were included. The exclusion criteria were as follows: lack of informed consent; chronic atrial fibrillation, which would disturb the use of a critical care monitor; hypersensitivity to the study medication; and pacemaker implantation.

The eligible patients were provided with an explanation regarding this study following routine pre-operative assessments at our institution. After obtaining written informed consent, 36 patients were enrolled on the day before the surgery between October 1, 2021, and April 7, 2023. The patients were randomized to receive general anesthesia with remimazolam- and propofol-based total intravenous anesthesia the day before the surgery using a random number generator by YN, who was not involved in collecting the perioperative clinical data. For randomization, we created our own randomization program for this research which runs on our server. It generates a random number each time the program is run. The generated number ranges from 0 to 1 as decimal.

Therefore, if the number was below 0.5, we assigned the case to remimazolam, and if it was above 0.5, we assigned the case to propofol. Rand() function used in the program is based on Mersenne Twister algorithm, which guarantees a high degree of randomness. Based on the results derived from the program, the attending anesthesiologist was informed of the group to which the patient was assigned just before entering the operating room.

At the pre-operative anesthesia clinic, patient demographics, comorbidities, serum albumin and creatinine levels, and medications were assessed routinely. In patients aged  $\geq 65$  years, grip-hand strength, cognitive function, and nutritional status were assessed using a digital Jamar hand dynamometer (MG-4800 MORITOH; Aichi, Japan), the Mini-Cog test, and the Mini Nutritional Assessment-Short Form (MNA-SF), respectively. [12] The Mini-Cog test, with a total score of 0–5, is recommended for cognitive screening by the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. [13,14] The MNA-SF score ranges from 0 to 14 points, with a higher score indicating a better nutritional status. [15] Pre-operative cardiac assessments, including echocardiography and cardiac computed tomography, provided the ejection fraction, aortic valve area, peak aortic flow velocity, and the presence of aortic regurgitation, mitral regurgitation, tricuspid regurgitation, and coronary artery disease.

### ***Outcomes***

The primary outcome in this study was the rate of arterial hypotension occurring from anesthesia induction until the beginning of surgical incision (frequency of arterial hypotension/number of measurements). [2] The secondary outcomes were the area under the curve of arterial hypotension, arterial hypertension with systolic blood

pressure >160 mmHg, cardiac index, stroke volume index, heart rate (HR), peripheral perfusion index (PPI), and total doses of ephedrine and phenylephrine administered from anesthesia induction until the beginning of the surgical incision. Cardiac index and stroke volume index were derived from Flo Trac sensors, which is one of the arterial pressure-based cardiac output and stroke volume. The area under the curve of mean arterial pressure < 60 mm Hg is calculated as the cumulative sum of the areas of mean arterial pressure < 60 mm Hg for a patient [16, 17]. PPI was obtained continuously from the patient monitor (Masimo, Irvine, CA, USA). Furthermore, the quality of recovery, postoperative delirium during the intensive care unit (ICU) stay, postoperative length of stay, and death within 30 days postoperatively were also evaluated. Surgical procedures, including rapid pacing and transesophageal echocardiography probe manipulation, affect hemodynamic variables; therefore, we focused on hemodynamic variables from anesthesia induction until the beginning of the surgical incision.

### ***Pre-operative and intraoperative management***

Daily oral medications used by the patients were continued, except for angiotensin receptor blockers and angiotensin-converting enzyme inhibitors; no medications were administered on the day of the surgery. After the attachment of standard anesthesia monitors, the arterial catheter was inserted and connected to a Flo Trac sensor (Edwards Lifesciences, Irvine, CA, USA) to record the hemodynamic parameters every 20 s. Anesthetic depth was adjusted using the SedLine® monitor (Masimo, Irvine, CA, USA) to achieve a patient sedation index (PSI) of 25–50. Fig. 1 shows a schematic representation of the drug adjustment and anesthetic procedures. Remimazolam or propofol administration was initiated at the dose of 12 mg/kg/min or 2.5 mcg/mL via target-controlled infusion (TCI) using Diprifusor with the Marsh model, respectively;

subsequently, rocuronium was administered to facilitate tracheal intubation after the confirmation of unconsciousness. Then, a transesophageal echocardiography probe was inserted, and a central venous catheter and transvenous lead for a temporary pacemaker were secured via the patient's right internal jugular vein; then, activation of temporary transvenous pacing was confirmed. After tracheal intubation, the remimazolam and propofol rates were adjusted using the following protocol. If  $PSI \leq 25$  persisted for more than 1 minute, remimazolam was decreased by 0.1 mg/kg/h or the propofol TCI setting was decreased by 0.1 mcg/ml. If  $PSI \geq 50$  persisted for more than 1 minute, remimazolam was increased by 0.2 mg/kg/h or the propofol TCI setting was increased by 0.2 mcg/ml. After the change, the PSI value was monitored for 5 minutes, and if it remained within appropriate levels, the patient was continued on the drug. However, if it was  $< 25$  or  $> 50$ , the same changes as above were repeated. If the mean blood pressure of 60 mmHg persisted for 20 s, 4 mg of ephedrine was administered if the HR was  $< 60$  bpm and 0.1 mg of phenylephrine was administered if the HR was  $\geq 60$  bpm. Subsequently, 10 mL of normal saline was administered following the administration of ephedrine or phenylephrine, and 1 min later, the mean blood pressure was assessed, and if necessary, ephedrine or phenylephrine was administered again. When the systolic blood pressure was  $> 160$  mmHg for 20 s, 5 mg of diltiazem was administered. During the induction, fluid therapy was performed using only 1% glucose containing acetic Ringer's solution.

Arterial hypotension was defined as a mean arterial pressure of  $< 60$  mmHg, in accordance with a recent review. [18] The percentage of total monitoring time owing to hypotension was calculated. As data could be stored every 20 s, if the time from anesthesia induction to the start of surgery was 40 min, there were 120 (40\*3) measurements, among which 30 occurrences of hypotension were observed, whereby

the percentage was calculated to be 25% (30/120). The HR and PPI were also recorded. The systematic vascular resistance index can be estimated using the cardiac index and central venous pressure; however, its real value cannot be measured. In contrast, PPI, which is derived from the photoelectric plethysmographic signal of a pulse oximeter, is a reliable indicator of vascular reactivity and peripheral vascular tone [19,20]; accordingly, PPI was selected as an alternative indicator of vascular resistance. Once the surgery was initiated, anesthetic management, including the management of blood pressure and fluid status, was at the discretion of each anesthesiologist. In the patients allocated to the remimazolam-based total intravenous anesthesia group, the use of flumazenil was dependent on the discretion of the attending anesthesiologist. Anesthesiologists were not involved in the collection of outcomes and the analysis of the patients' data.

### ***Postoperative management***

All patients were transferred to the ICU without tracheal tubes. Surgeons provided postoperative care according to the institutional protocols. Delirium was assessed using the confusion assessment method for the ICU (CAM-ICU) [21] thrice a day in the ICU; subsequently, we diagnosed delirium as at least one positive result during the ICU stay. The quality of recovery-15 (QoR-15) score was assessed on postoperative day (POD) 3.

### ***Sample size calculation***

Although one study presented a lower incidence of hypotension events (systolic blood pressure <80 mmHg) after intubation in patients who received remimazolam than in those who received propofol [22], there are no previous studies comparing the hypotension rates of remimazolam and propofol during anesthetic induction.



Accordingly, based on our unpublished preliminary data, assuming a mean hypotension rate of 15% in the propofol group, 16 patients were required to exhibit a difference of 5% ( $\alpha=0.05$ ,  $\beta=0.80$ , standard deviation=5). After considering the missing data to be 10%, we planned to enroll 18 patients in each group.

### ***Statistical analysis***

Continuous and categorical data were presented as means (standard deviations) and numbers (%), respectively. Statistical comparisons between the two groups were performed using the unpaired t-test or Fisher's exact test for continuous and categorical variables, respectively. Mixed-effects models that treated measurement time (a continuous variable) as a fixed effect with a random intercept were used to analyze repeated measures, including mean blood pressure, cardiac index, stroke volume index, HR, and PPI between the two groups at the following points: before anesthetic induction, immediately after tracheal intubation, and every 10 min after tracheal intubation until the completion of anesthetic induction. All data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set at  $P < 0.05$ .

We performed post-hoc analysis. One compared PSI and endo-tidal CO<sub>2</sub> between two groups using the unpaired t-test and the other compared only PPI measured after tracheal intubation (measurement points 3–7) using a mixed-effect model.

### **Results**

The date of enrolment of the first research participant was October 1, 2021. Overall, 36 patients consented to participate in the study and were randomly assigned to receive either the remimazolam- or propofol-based total intravenous anesthesia group. Among

the patients assigned to the propofol group, one patient had no data regarding grip strength due to physical problems, and two patients had no data regarding Mini-Cog due to visual loss. One patient assigned to the remimazolam group was excluded from the analysis of the primary outcome owing to monitoring device failure. One patient assigned to the propofol group was excluded from the secondary outcome analysis owing to the incidence of intraoperative ischemic stroke (Fig. 2). The pre-operative data are presented in Table 1. Flumazenil was administered to eight patients in the remimazolam group to facilitate recovery from anesthesia.

### ***Primary outcome***

During anesthetic induction, with a mean of 144 measurement points, the arterial hypotension rates were 11.9% and 21.6% in the remimazolam and propofol groups, respectively; the difference was statistically significant ( $P=0.01$ ) (Table 2).

### ***Secondary outcomes***

As shown in Table 2, the area under the curve of arterial hypotension (mmHg\*min) was larger in the propofol group than in the remimazolam group (propofol; 53.8 vs. remimazolam; 26.1,  $P=0.02$ ). The total dose of ephedrine was higher in the propofol group than that in the remimazolam group (propofol; 14.4 mg vs. remimazolam; 1.6 mg,  $P<0.001$ ); however, the total dose of phenylephrine was not different between the two groups (propofol; 0.31 mg vs. remimazolam; 0.17 mg,  $P=0.10$ ). The hypertension rate, fluid volume, and total dose of diltiazem during anesthesia induction did not differ between the two groups (Table 2).

Supplemental Digital Contents 1 and 2 present the changes in the mean blood pressure, cardiac index, stroke volume index, HR, and PPI during anesthetic induction

between the two groups. The cardiac index ( $P=0.001$ ) and HR ( $P<0.001$ ) were significantly higher in the remimazolam group than in the propofol group. Statistically significant differences were observed between the groups over time in the stroke volume index ( $P=0.01$ ) and PPI ( $P<0.001$ ). As shown in Table 3, no patient had myocardial or kidney injury, and no significant differences were noted in the postoperative outcomes. Other intraoperative and postoperative data are shown in Supplemental Digital Content 3 and 4.

## **Discussion**

This randomized controlled trial, which included patients undergoing elective transfemoral TAVR, demonstrated that the hypotension rate during anesthetic induction using remimazolam-based total intravenous anesthesia was lower than that during anesthetic induction using propofol-based total intravenous anesthesia, which required a higher average dose of ephedrine.

The effects of remimazolam on hemodynamics during anesthetic induction have been inconsistent among studies. Several factors, including the definition of hypotension, measurement period, and study design, may explain these differences. [7,22-24] In this study, hypotension was defined as ‘mean arterial pressure  $<60$  mmHg’ using a widely recognized consensus statement [18], and although our goal was to evaluate blood pressure for the entire duration of anesthesia induction, the measurement time was limited before the start of surgery in our evaluation to eliminate the influence of surgical manipulation. Our explanatory analyses, which should be interpreted with caution owing to the limited sample size and multiple comparisons of secondary outcomes, demonstrated a higher HR, which maintained the cardiac index, in the

remimazolam group than that in the propofol group. The patients' demographics were not compared because of a randomized controlled trial [25], but patients taking preoperative beta blockers tend to be more common in the remimazolam group (17.6% vs. 5.6%). Despite this fact, patients allocated in the remimazolam group demonstrated a higher HR. One post hoc analysis compared PSI between two groups, which showed that each PSI value was 37.3 (9.9) and 32.7 (9.7) in the remimazolam and propofol groups, respectively ( $p=0.009$ ). Another post hoc analysis using a mixed-effect model with only PPI measured after tracheal intubation (measurement points 3–7) revealed that the interaction between the anesthetics and elapsed time was significant ( $P=0.02$ ). This may reflect the fewer effects of remimazolam-based total intravenous anesthesia on the HR and vascular tone [19,20,26]; however, further studies are required to clarify the exact mechanisms contributing to the lower incidence of hypotension event.

Since calcification of the aortic valve serves as an indicator of atherosclerosis of the coronary arteries, candidates for aortic valve replacement are at a high risk of developing coronary artery disease. [27] Peripheral intravenous noradrenaline may be preferable to prevent hypotension during anesthesia in healthy patients; however, in patients with poor contractility and left ventricular systolic dysfunction, inotropes are preferable compared to vasopressors. [28] Moreover, the safety of the peripheral administration of noradrenaline was not confirmed at the beginning of this study [29]; therefore, we selected ephedrine and phenylephrine.

One patient with an intraoperative stroke was intentionally excluded from the analysis of secondary outcomes given the impact of intraoperative complications on the outcome assessment. The researcher approached the patient, who was able to answer the QoR-15 questionnaire. No significant secondary outcomes were observed in the remaining 34 patients. A post hoc paired t-test revealed no statistically significant

difference in the QoR-15 score before surgery (mean score, 132 points) or on POD 3 (mean score, 129 points) ( $P=0.13$ ). [30] Our previous study revealed that the QoR-15 score did not recover to the baseline value until POD 7 after abdominal cancer surgery [31], indicating that patients undergoing TAVR are at high risk; however, TAVR itself may be classified as a low-risk surgery. Accordingly, anesthetics may not make a difference with a limited sample size.

This study has some limitations. First, its generalizability was limited, as this was a single-center study including elective TAVR; however, this study would be a foothold for prospective multicenter trials. Second, although the initial infusion rates of both sedatives were determined based on the package insert and daily clinical dose [32], different initial infusion rates may have led to different results. However, despite a relative higher initial infusion rate of remimazolam, this study demonstrated lower hypotension rate in the remimazolam group. Third, the rate of administration of infusions during induction of anesthesia was not established. However, there was no difference in total fluid volume during induction of anesthesia. Forth, intraoperative management, including fluid therapy and vasoactive agent use, was at the discretion of each anesthesiologist; accordingly, the interpretation of secondary outcomes requires caution. In contrast, this study's strength was based on the fact that although this study was conducted on only patients undergoing TAVR, the results could be applied to anesthetic induction in patients with severe AS.

In conclusion, we demonstrated that remimazolam-based total intravenous anesthesia provided a lower hypotension rate and a lower ephedrine dose in anesthetic induction in patients who underwent elective TAVR. This results can contribute to hemodynamic stability for patients with severe AS.

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**Ethics committee approval:** Ethical approval for this study (approval number: 3043, Chairperson: Prof. M. Yoshizumi) was provided by the local ethics committee on 9 September 2021

**Informed consent:** All included patients provided written informed consent.

**Conflicts of interest:** None.

**Financial support and sponsorship:** None.

**Data availability**

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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**Tables legends**

Table 1. Preoperative data

Table 2. Outcomes during anesthesia induction

Table 3. Postoperative outcomes

**Figure Legends**

Fig. 1. Schema of drug adjustment and anesthetic procedures

Fig. 2. CONSORT flow diagram

## List of Supplemental Digital Content

Supplemental Digital Content 1.pdf

Supplemental Digital Content 2.docx

Supplemental Digital Content 3.docx

Supplemental Digital Content 4.docx

### Supplemental Digital Content 1. Supplementary Fig. 1.

Hemodynamic parameters

(A) Mean blood pressure; (B) Cardiac index; (C) Stroke volume index; (D) Heart rate; (E) Perfusion index

Data are presented as the mean values. Error bars indicate 95% confidence intervals

Measurement point 1 corresponds to before anesthetic induction, Measurement point 2 corresponds to immediately after tracheal intubation, Measurement point 3 corresponds to 10 min after tracheal intubation, Measurement point 4 corresponds to 20 min after tracheal intubation, Measurement point 5 corresponds to 30 min after tracheal intubation, Measurement point 6 corresponds to 40 min after tracheal intubation, Measurement point 7 corresponds to 50 min after tracheal intubation. Cardiac index and stroke volume index were derived from Flo Trac sencer.

Thirty-six patients had data at measurement points 1 to 6.



Twenty-nine patients (remimazolam group n=13 and propofol group n=16) at measurement point 6 and 19 patients (remimazolam group n=10 and propofol group n=9) at measurement point 7 had each data, respectively.

**Supplemental Digital Content 2.** Results of the mixed-effects models for hemodynamic parameters

Supplemental Digital Content 2A. Mean blood pressure

Supplemental Digital Content 2B. Cardiac index

Supplemental Digital Content 2C. Stroke volume index

Supplemental Digital Content 2D. Heart rate

Supplemental Digital Content 2E. Perfusion index

Cardiac index and stroke volume index were derived from Flo Trac sencer.

Supplemental Digital Content 3. Intraoperative and postoperative data

Supplemental Digital Content 4. The value of end-tidal CO<sub>2</sub> from tracheal intubation to the beginning of surgery

Table 1. Preoperative data

	Remimazolam (n=17)	Propofol (n=18)
Age (y)	82.7 (3.9)	84.7 (3.7)
Female	11 (64.7)	12 (66.7)
Height (cm)	152.1 (9.1)	151.7 (9.6)
Weight (kg)	53.3 (11.6)	57.3 (12.0)
Comorbidity		
Hypertension	14 (82.4)	14 (77.8)
Symptomatic cerebral vascular disease	7 (41.2)	4 (22.2)
Diabetes	6 (35.3)	4 (22.2)
Laboratory data		
Serum albumin (g/dL)	4.0 (0.2)	4.0 (0.3)
Serum creatinine (mg/dL)	1.06 (0.3)	0.89 (0.2)
Medication		
Beta blocker	3 (17.6)	1 (5.6)
Statin	7 (41.2)	5 (27.8)
Steroid	1 (5.9)	0 (0.0)

Grip-hand strength (kgf)	23.0 (8.9)	23.1 (8.9) (n=17)
Mini-Cog	3.2 (1.2)	3.8 (1.6) (n=16)
EuroSCORE2	4.8 (2.4)	5.1 (2.8)
Mini Nutritional Assessment Short-Form	11.5 (1.3)	11.6 (3.0)
Ejection fraction (%)	64.9 (9.7)	69.7 (5.5)
Aortic valve area (cm <sup>2</sup> )	0.80 (0.1)	0.79 (0.1)
Peak aortic flow velocity (m/s)	4.1 (0.5)	4.2 (0.4)
Aortic regurgitation	15 (88.2)	15 (83.3)
Mitral regurgitation	11 (64.7)	16 (88.8)
Tricuspid regurgitation	15(88.2)	14 (77.7)
Coronary artery disease	1 (5.9)	5 (27.8)
Quality of recovery-15 before surgery	131.2 (16.1)	134.7 (7.1)

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Mean (standard deviation) or number (%)

Table 2. Outcomes during anesthesia induction

	Remimazolam (n=17)	Propofol (n=18)	P value
Number of measurement point	143.3 (26.4)	144.7 (27.7)	0.88
Hypotension rate (%)	11.9 (10.1)	21.6 (10.7)	0.01
Hypertension rate (%)	3.2 (4.2)	2.9 (5.3)	0.81
Fluid volume (mL)	341 (97)	311 (65)	0.28
Ephedrine (mg)	1.6 (2.0)	14.4 (8.8)	<0.001
Phenylephrine (mg)	0.17 (0.12)	0.31 (0.31)	0.10
Diltiazem (mg)	0.7 (1.7)	0.6 (1.6)	0.82

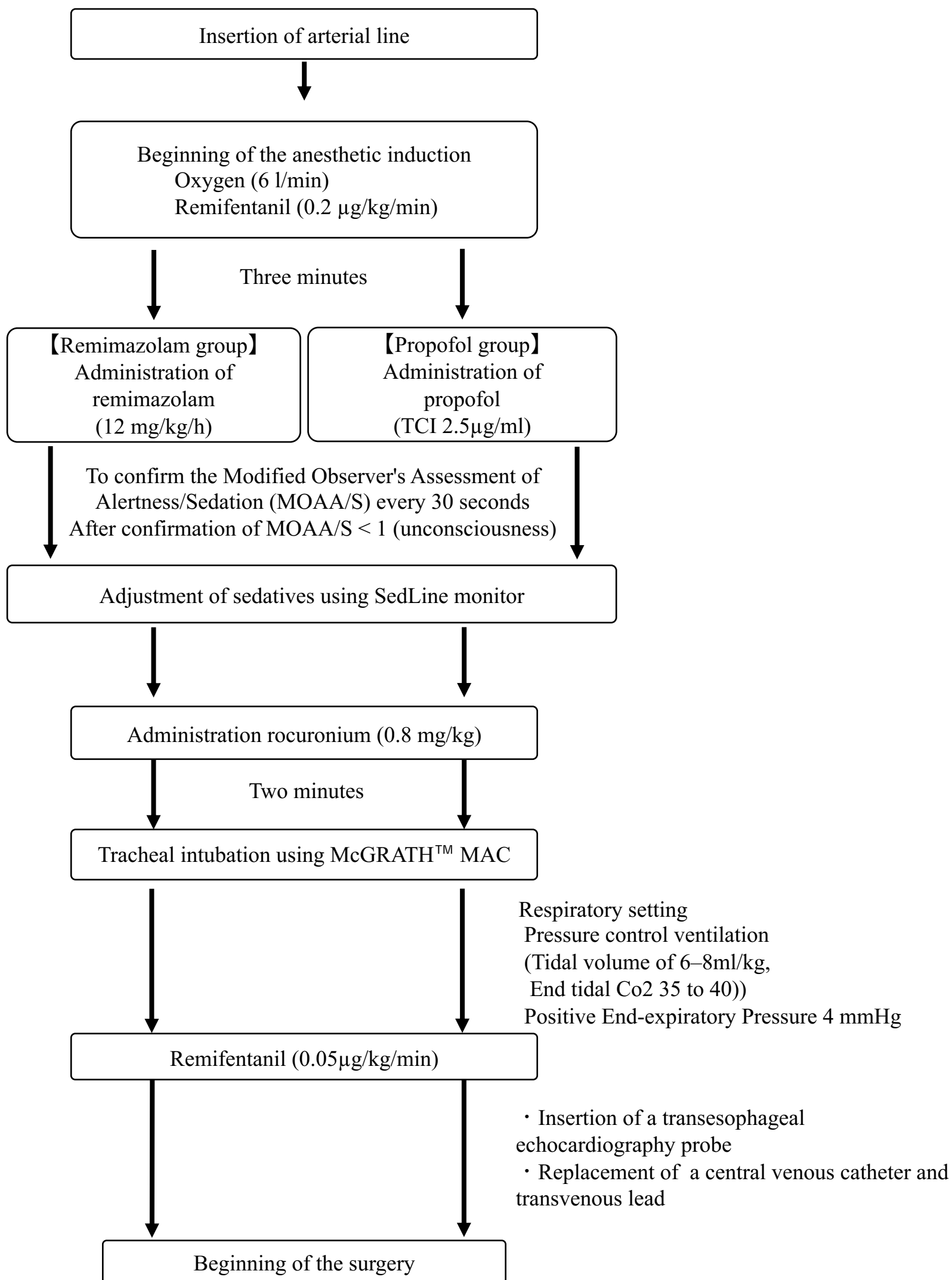
Mean (standard deviation)

Table 3. Postoperative outcomes

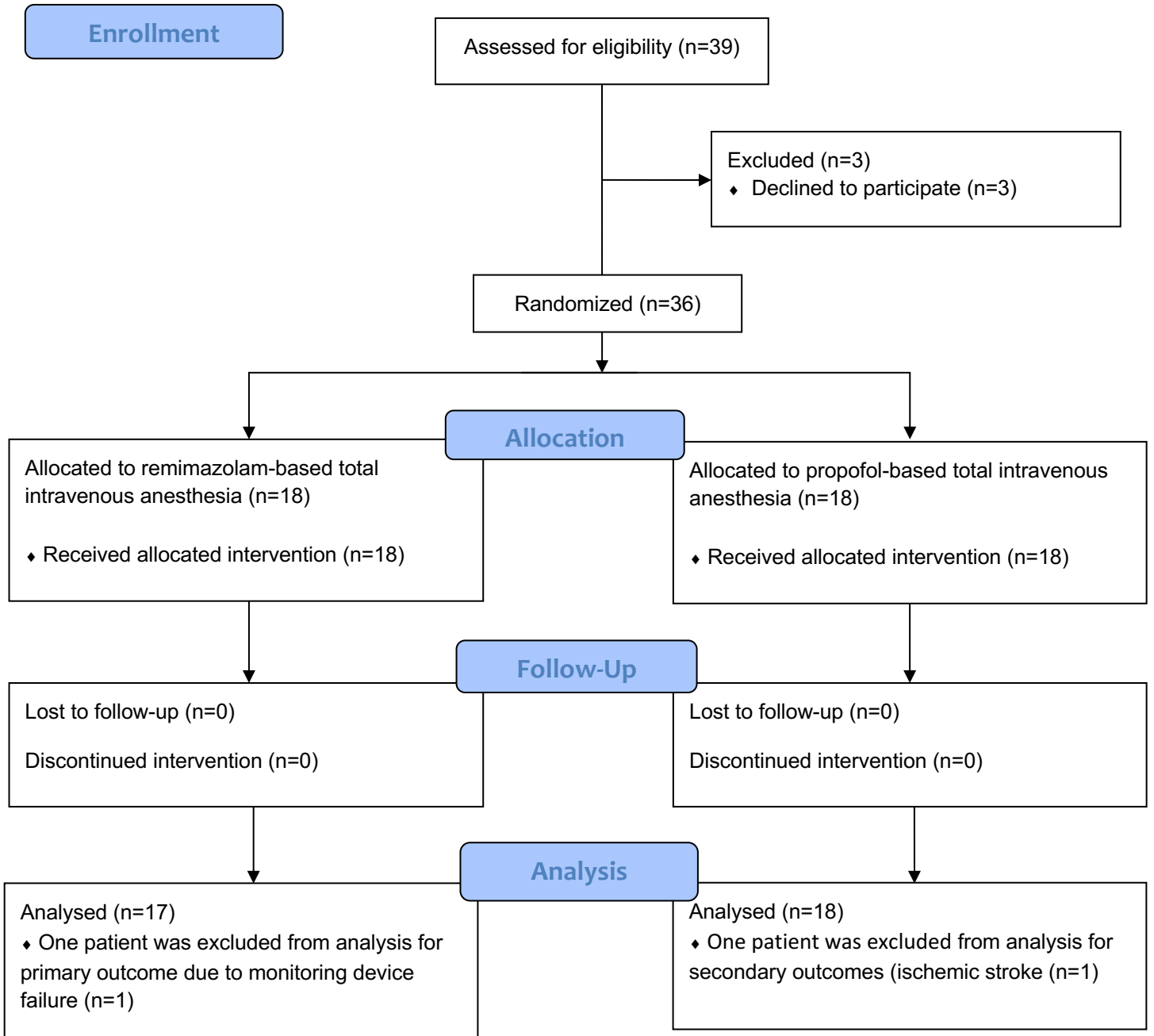
	Remimazolam (n=17)	Propofol (n=17)	<i>P</i> value
Quality of recovery-15 on POD 3	127 (18.7)	131 (12.7)	0.45
Delirium	3 (17.6)	3 (17.6)	1.00
Length of hospital stay (days)	8.5 (2.2)	8.3 (0.8)	0.63
Death within 30 days	0 (0.0)	0 (0.0)	Not available

Mean (standard deviation) or number (%); POD, postoperative day.

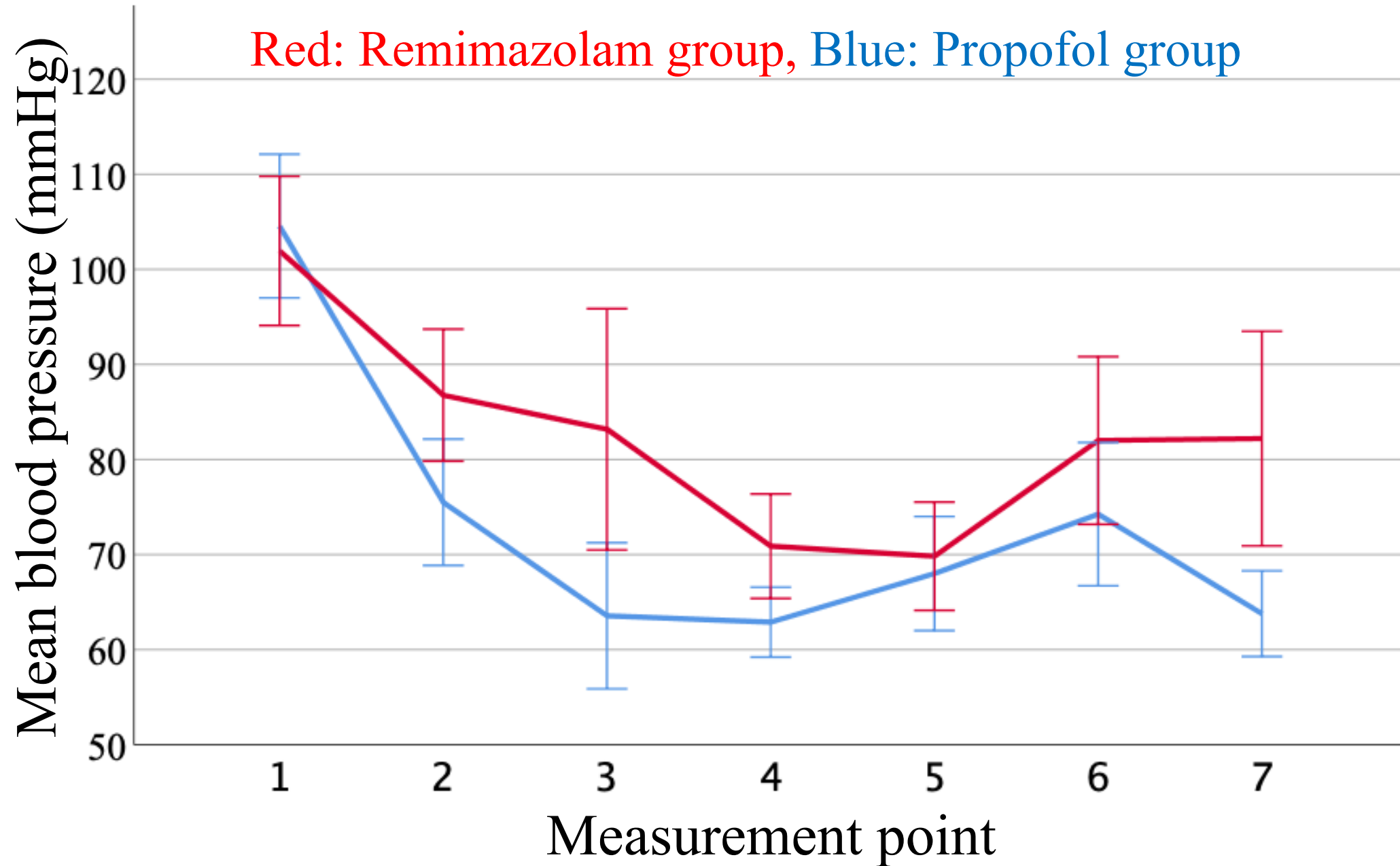
Figure 1 Schema of drug adjustment and anesthetic procedures



**Figure 2 CONSORT 2010 Flow Diagram**

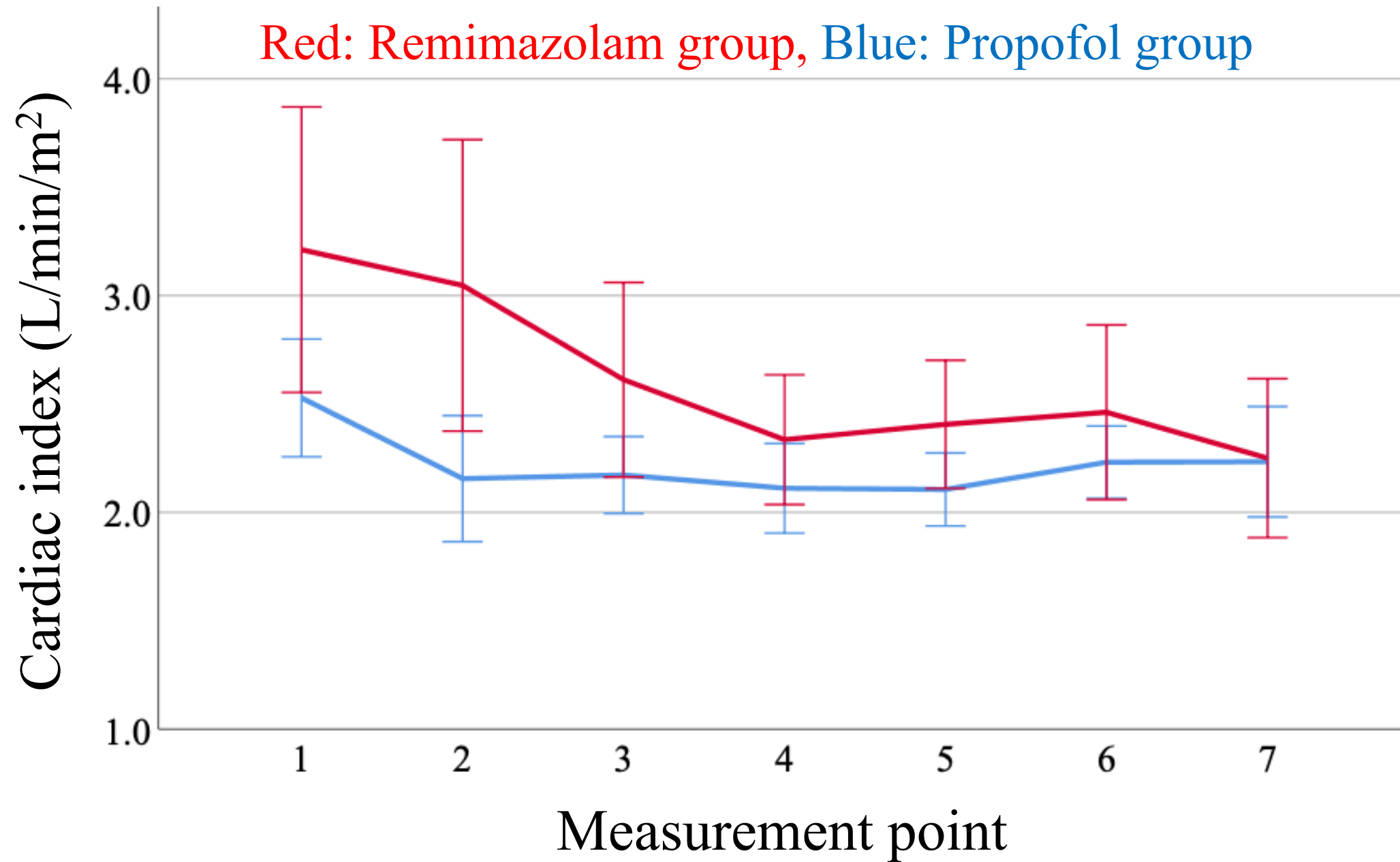


# Supplemental Digital Content 1A

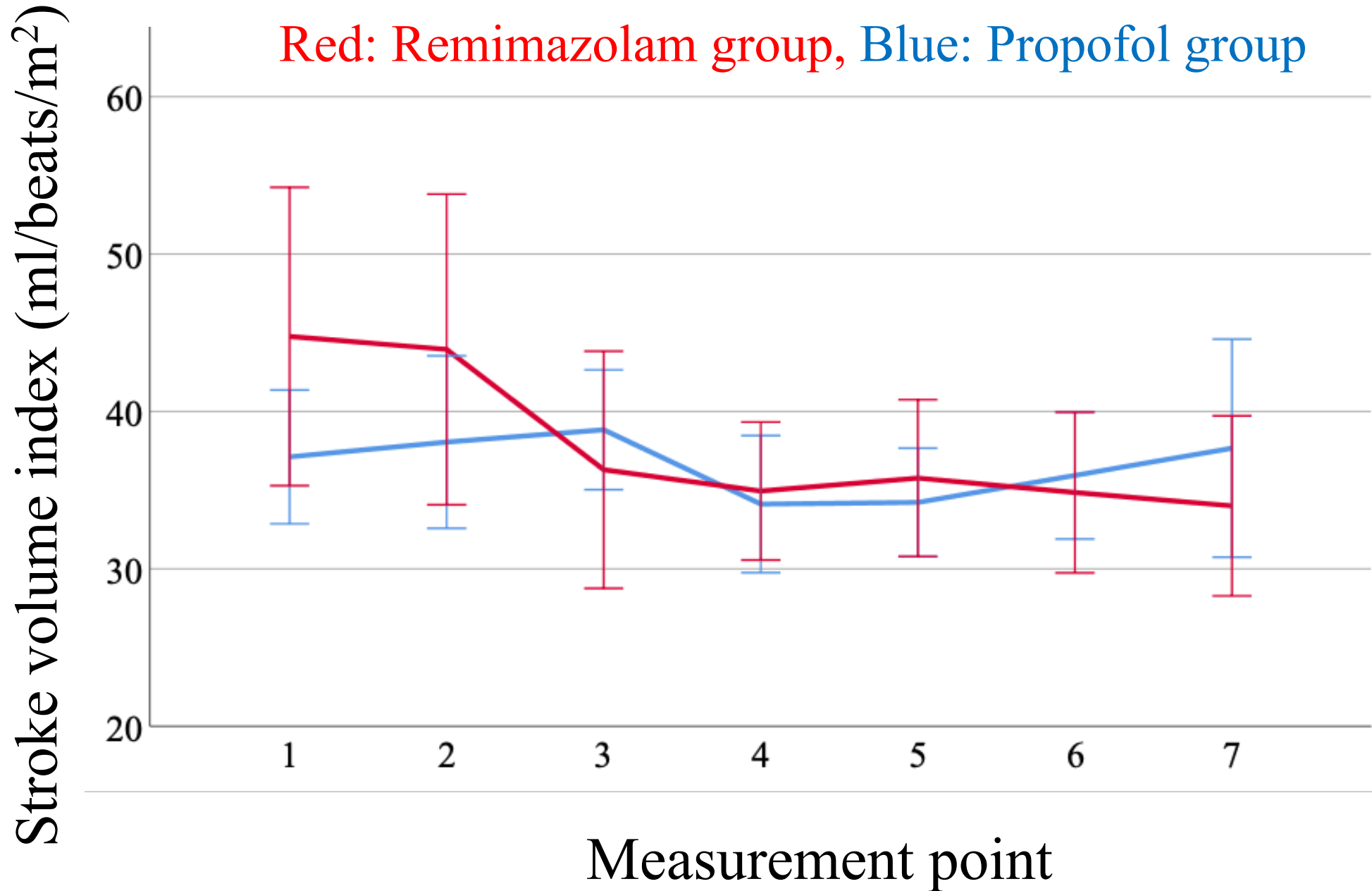




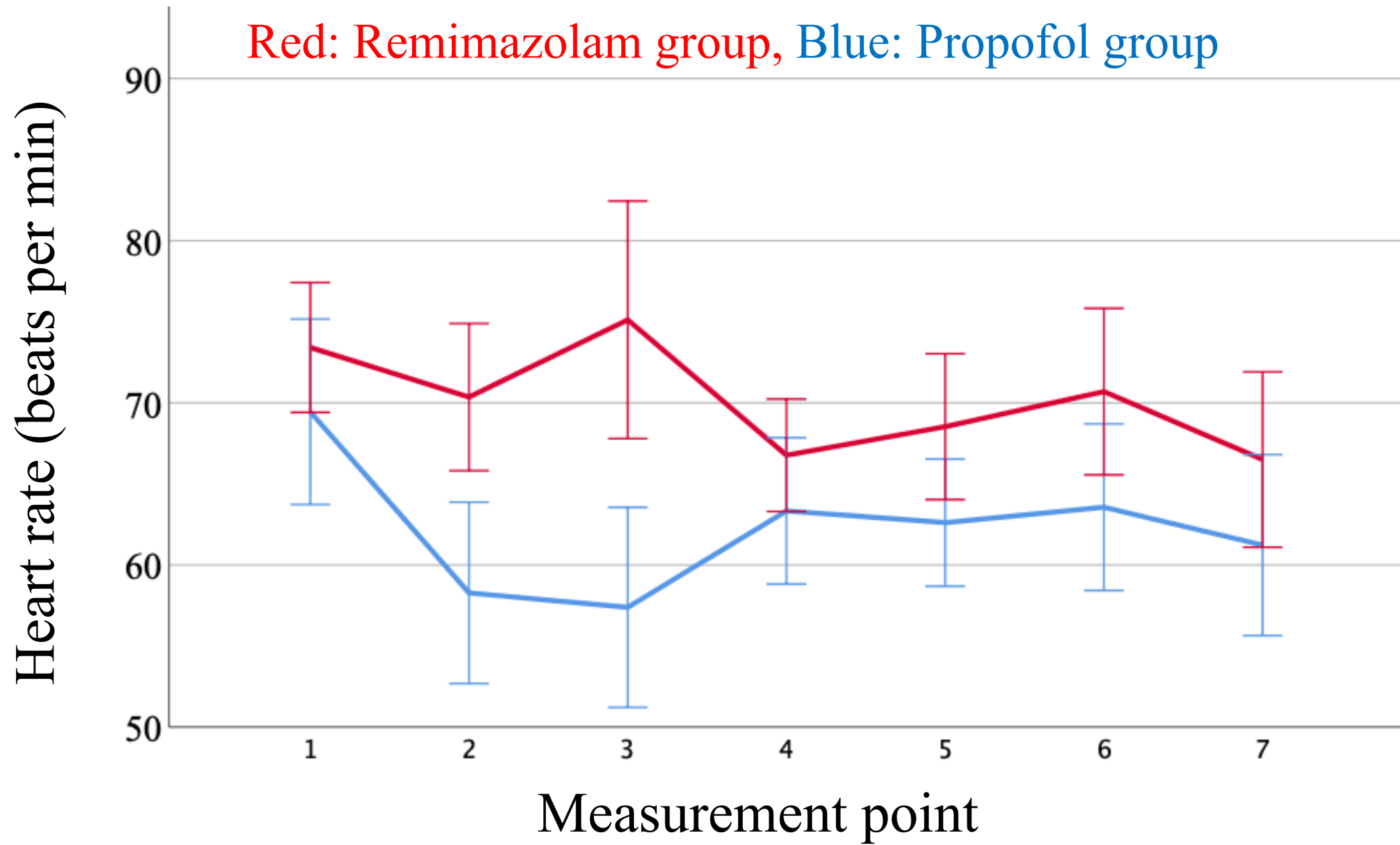
# Supplemental Digital Content 1B



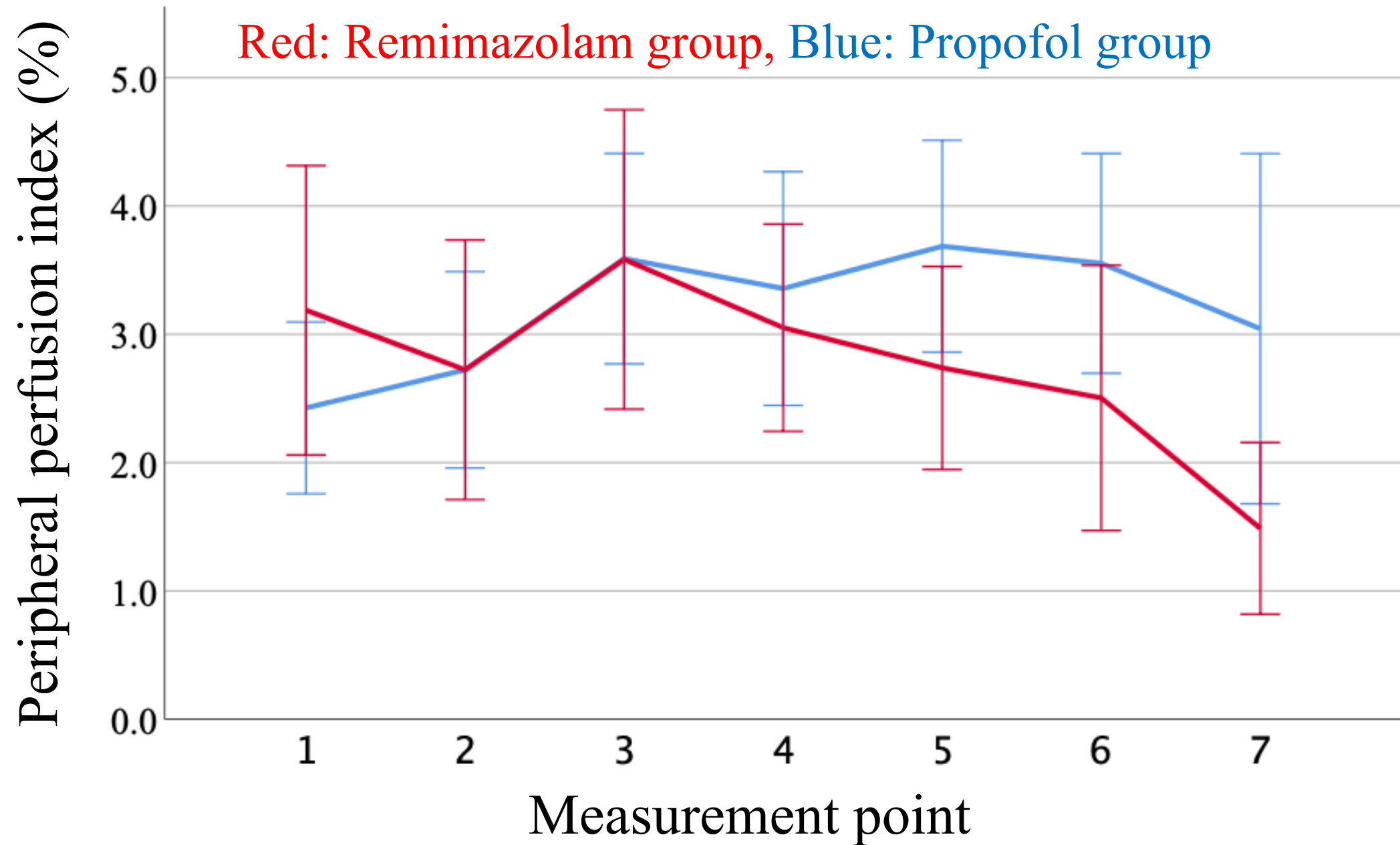
# Supplemental Digital Content 1C



# Supplemental Digital Content 1D



# Supplemental Digital Content 1E



Supplemental Digital Content 2. Results of the mixed-effects models for haemodynamic parameters

Supplemental Digital Content 2A. Mean blood pressure

	Estimate	Standard Error	<i>P</i> -value
Intercept	85.1	3.1	<0.001
Measurement point	-2.2	0.49	<0.001
Remimazolam	6.6	4.4	0.14
Interaction	0.32	0.71	0.64

Supplemental Digital Content 2B. Cardiac index

	Estimate	Standard Error	<i>P</i> value
Intercept	2.3	0.15	<0.001
Measurement point	-0.01	0.01	0.16
Remimazolam	0.75	0.22	0.001
Interaction	-0.06	0.01	<0.001

Supplemental Digital Content 2C. Stroke volume index

	Estimate	Standard Error	<i>P</i> value
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Intercept	37.6	2.5	<0.001
Measurement point	-0.24	0.17	0.16
Remimazolam	5.1	3.6	0.16
Interaction	-0.63	0.25	0.01

Supplemental Digital Content 2D. Heart rate

	Estimate	Standard Error	<i>P</i> value
Intercept	62.7	2	<0.001
Measurement point	-0.1	0.23	0.65
Remimazolam	10.5	2.9	<0.001
Interaction	-0.48	0.33	0.14

Supplemental Digital Content 2E. Perfusion index

	Estimate	Standard Error	<i>P</i> value
Intercept	2.8	0.38	<0.001
Measurement point	0.07	0.03	0.01
Remimazolam	0.54	0.55	0.33
Interaction	-0.16	0.04	<0.001

Supplemental Digital Content 3. Intra and postoperative data

	Remimazolam (n=17)	Propofol (n=18)	P value
Intraoperative data			
Fluid balance (mL)	865 (324)	766 (360)	0.40
Blood loss volume (mL)	0 (0)	13 (47)	0.24
Urinary output (mL)	322 (202)	330 (154)	0.9
Surgical duration (min)	98 (28)	103 (50)	0.69
Anesthetic duration (min)	168 (34)	180 (54)	0.44
Emergence time (min)	11 (3)	13 (5)	0.20
Postoperative data			
Length of intensive care unit stay (days)	1.1 (0.2)	1.1 (0.4)	0.68
Length of postoperative stay (days)	8.5 (2.2)	14.3 (25.6)	0.35

Mean (standard deviation)

Supplemental Digital Content 4. The value of end-tidal CO<sub>2</sub> from tracheal intubation to the beginning of surgery

	Remimazolam (n=17)	Propofol (n=18)	P value
Just after tracheal intubation	39.1 (3.8)	38.3 (3.3)	0.53
10 minutes after tracheal intubation	37.1 (3.2)	36.8 (2.3)	0.77
20 minutes after tracheal intubation	36.2 (2.9)	35.4 (2.3)	0.39
30 minutes after tracheal intubation	36.1 (2.0)	36.1 (1.69)	0.93
40 minutes after tracheal intubation	36.1 (1.9)	35.9 (1.9)	0.79
50 minutes after tracheal intubation	36.4 (1.6)	35.7 (2.5)	0.36

Mean (standard deviation)