



Differences in circulating blood volume changes during emergence from general anesthesia in transcatheter aortic valve implantation and MitraClip implantation

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Abstract

Purpose We aimed to compare changes in the circulating blood volume (CBV) during emergence from general anesthesia in patients undergoing transcatheter aortic valve implantation (TAVI) and MitraClip implantation.

Method We included 97 patients who underwent TAVI or MitraClip implantation. The primary outcome was the rate of change in the estimated CBV associated with emergence from general anesthesia. The secondary outcomes were hemoglobin and hematocrit values before and after emergence from anesthesia for each procedure. Additionally, the independent factors associated with changes in the estimated CBV were assessed using multiple regression analysis.

Results In the TAVI group, the hemoglobin concentration increased from 9.6 g/dL before emergence from anesthesia to 10.8 g/dL after emergence ($P < 0.001$; mean difference, 1.2 g/dL, 95% confidence interval [CI] 1.1–1.3 g/dL). Conversely, no statistically significant change was observed in the hemoglobin concentration before and after emergence from anesthesia in the MitraClip group. The mean rate of change in the estimated CBV was -15.4% (standard deviation [SD] 6.4%) in the TAVI group and -2.4% (SD, 4.7%) in the MitraClip group, indicating a significant decrease in the estimated CBV in the former than in the latter ($P < 0.001$; mean difference, 13.0%; 95% CI 9.9–16.1%).

Conclusion Emergence from general anesthesia increased the hemoglobin concentration and decreased the estimated CBV in patients undergoing TAVI but did not elicit significant changes in patients undergoing MitraClip implantation. These results may provide a rationale for minimizing blood transfusions during general anesthesia in patients undergoing these procedures.

Keywords Anesthesia · Circulating blood volume · Transcatheter aortic valve implantation · MitraClip · Starling equation

Introduction

Capillary hydrostatic pressure decreases due to the dilation of blood vessels caused by general anesthesia through either sympathetic inhibition or direct effects. The reduction in capillary hydrostatic pressure reportedly alters the Starling equation and causes reabsorption of the interstitial fluid, thus increasing the circulating blood volume (CBV) [1–3]. Similarly, the increased CBV associated with general anesthesia is considered to return to its original state due to increase

in the hydrostatic pressure associated with emergence from general anesthesia [1].

Sano et al. measured the anesthesia-induced changes in the CBV of patients without underlying diseases using various methods and showed that these changes corresponded to changes in blood pressure [1]. Damén et al. reported that in patients undergoing coronary artery bypass surgery, the increase in the CBV associated with anesthesia induction was reduced when the mean arterial pressure was maintained equal to that in the awake state using norepinephrine. These results indicate that change in blood pressure is a major factor affecting changes in the CBV associated with general anesthesia [2]. However, the effects of hemodynamic factors other than blood pressure on the CBV changes associated with anesthesia remain unclear.

Transcatheter aortic valve implantation (TAVI) and MitraClip implantation are transcatheter valvular heart disease treatments for severe aortic stenosis and severe

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mitral regurgitation, respectively. Heart valve disease is known to significantly affect systemic hemodynamics and is related to the CBV and hydrostatic pressure [4]. Furthermore, significant changes in hemodynamics occur during the procedure, especially in TAVI, with a significant increase in the cardiac output after valve implantation. Therefore, we hypothesized that patients undergoing these procedures would show different changes in the CBV in response to vasodilation associated with general anesthesia induction and vasoconstriction associated with emergence from general anesthesia. This phenomenon affecting hemoglobin concentration is clinically important because the threshold for transfusion is usually based on the hemoglobin concentration in many clinical guidelines. Hence, we retrospectively collected data from patients undergoing TAVI and MitraClip implantation to investigate the changes in the CBV before and after emergence from anesthesia.

Methods

Patients and ethics approval

This study enrolled patients who underwent TAVI or MitraClip implantation under general anesthesia between October 2020 and September 2022. Patients who were transferred to the intensive care unit without emergence from anesthesia from the operating room, those who received red blood cell transfusions upon emergence from anesthesia, and those with missing blood test data before or after emergence from anesthesia were excluded.

This retrospective study was approved by the Institutional Review Board of Sapporo Medical University (Approval number: 342-158) and conducted in accordance with the Declaration of Helsinki principles. The requirement for written informed consent was waived because of the retrospective and anonymous nature of the study. This trial is registered in the Japan Registry of Clinical Trials (jRCT1010220038).

Clinical management

General anesthesia was induced for all patients by a member of the cardiac anesthesia team at our hospital. First, a peripheral venous catheter was inserted in the forearm and an arterial catheter in the radial artery before induction of general anesthesia. Tracheal intubation was performed after inducing general anesthesia, and a central venous catheter was inserted in the right internal jugular vein in patients undergoing the MitraClip procedure and a 6-French gauge sheath and transient pacemaker in patients undergoing TAVI. Anesthesia was maintained by administering sevoflurane, desflurane, or remimazolam, at the discretion of the

anesthesiologist in charge. Similarly, norepinephrine was administered as needed at the discretion of the anesthesiologist. The need for red blood cell transfusion was determined by the anesthesiologist in charge according to hemoglobin levels and the degree of clinical bleeding. After the surgery, the muscle relaxation effect was antagonized using sugammadex, and the patient was transferred to the intensive care unit after extubation following emergence from anesthesia.

Samples and data collection

Blood tests, such as complete blood count and biochemistry, were performed at the end of the surgery as part of the routine medical care at the hospital, and in most cases, blood gas analysis was also performed at the same time. Additionally, blood gas analysis was performed again upon admission to the intensive care unit, as required by the institution's regulations. Blood samples were collected from the arterial line inserted into the radial artery into a safePICO aspirator (Radiometer Medical, Copenhagen, Denmark) on both occasions, and ABL-800 Flex (Radiometer Medical, Copenhagen, Denmark) was used for blood gas analysis. The ABL-800 Flex uses spectrophotometry to measure the hemoglobin content of blood that has been hemolyzed by ultrasound. An internal algorithm calculates the hematocrit value based on the measured hemoglobin content. Hematocrit values measured with the ABL-800 Flex have been reported in good agreement with hematocrit values measured with the central laboratory method [5]. The blood gas analysis conducted at the end of surgery was designated as “before emergence from anesthesia” and that conducted during the intensive care unit admission was designated as “after emergence from anesthesia.”

Information regarding patient age, sex, comorbidities, preoperative renal function, and intraoperative and postoperative blood pressure was obtained from electronic medical and anesthesia records. The blood pressure measurements before and after emergence from anesthesia were recorded during blood gas analysis.

The primary outcome was the rate of change in the estimated CBV associated with emergence from general anesthesia. The secondary outcomes were hemoglobin concentration and hematocrit values before and after emergence from anesthesia for each surgical procedure. The rate of change in the estimated CBV was calculated from the hematocrit values, as described previously [6]. The equations used are as follows:

$$\text{Rate of change in the estimated CBV} = 100 \times (\text{Hct}_{\text{pre}} / \text{Hct}_{\text{post}} - 1) / (1 - \text{Hct}_{\text{pre}}).$$

where Hct_{pre} is the hematocrit value before emergence from anesthesia and Hct_{post} is the hematocrit value after emergence from anesthesia.

Statistical analysis

Continuous variables were expressed as means (standard deviations [SD]) or median (interquartile range [IQR]) according to the distribution of the data. The normality was assessed using a histogram and the Shapiro–Wilk test. The student t-test, Mann–Whitney U test or chi-square test was used to compare the TAVI group (T group) and the MitraClip group (M group). The Mann–Whitney U test calculated the median difference and 95% confidence interval (CI) using the Hodges–Lehmann method. Paired t-tests were used for comparisons before and after emergence from anesthesia within the same group. Moreover, multiple regression analysis was used as a post-hoc analysis to adjust for confounding factors and investigate the independent effects of the type of procedure on the rate of change in the estimated CBV. The independent variables included the mean arterial pressure change rate before and after emergence from anesthesia according to previous studies [1–3] and the type of procedure, as well as age, sex, estimated glomerular filtration rate as renal function, and left ventricular ejection fraction as cardiac function. The type of procedure was converted to dummy variables, with MitraClip as 0 and TAVI as 1. Sex was also converted to dummy variables, with male as 0 and female as 1. All statistical analyses were performed using GraphPad Prism version 9 (GraphPad Software, La Jolla, CA, USA) and Statistical Product and Service Solutions version 25 (SPSS Inc., Chicago, IL, USA). P-values < 0.05 were considered statistically significant.

Results

During the study period, 120 patients were enrolled. After excluding patients fulfilling the exclusion criteria, data from 97 patients were analyzed, with 78 in the T group and 19 in the M group (Fig. 1). All patients in the T group received the transfemoral approach, including 52 with balloon-expandable and 26 with self-expandable devices. The mean number of clips for MitraClip was 1.3.

Table 1 shows the patient characteristics and perioperative variables. Patients undergoing chronic hemodialysis were not included. Considering the different patient populations undergoing each procedure, the number of patients who were old, short, and hypertensive was higher in the T group than in the M group. The M group included more patients receiving diuretics and beta-blockers than the T group, reflecting fluid overload due to severe mitral regurgitation and chronic heart failure. In addition, surgery and anesthesia times were longer in the M group, reflecting the differences between the two surgeries. The rate of change in the mean arterial pressure before and after emergence from anesthesia was significantly higher in the T group than in the

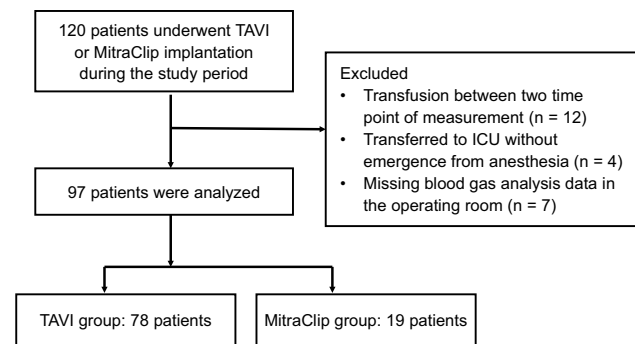


Fig. 1 Flow diagram of the study (TAVI: transcatheter aortic valve implantation, ICU: intensive care unit)

M group (Table 2). No significant difference was observed between the T and M groups in the proportion of patients receiving continuous norepinephrine injections at the time of blood sampling before emergence from anesthesia (34/78 [43.6%] vs. 11/19 [57.9%]; $P = 0.262$). No patient received a continuous injection of norepinephrine after emergence from anesthesia in either group.

The hemoglobin, hematocrit values, and rates of change in estimated CBV calculated by the hematocrit before and after emergence from anesthesia are shown in Fig. 2. After emergence from anesthesia, the hemoglobin and hematocrit values in the T group increased significantly ($P < 0.001$; mean difference, 1.2 mg/dL; 95% CI, 1.1–1.3 mg/dL and $P < 0.001$; mean difference, 3.6%; 95% CI 3.3–4.0%, respectively). On the other hand, the hemoglobin concentration did not change after emergence from anesthesia in the M group ($P = 0.053$; mean difference, 0.2 mg/dL; 95% CI 0.0–0.3 mg/dL), and the hematocrit levels increased only slightly ($P = 0.034$; mean difference, 0.5%; 95% CI 0.0–1.0%). The mean rate of change in the estimated CBV was -15.4% (SD, 6.4) in the T group and -2.4% (SD, 4.7) in the M group, indicating a significant decrease in the estimated CBV in the former than in the latter ($P < 0.001$; mean difference, 13.0%; 95% CI 9.9–16.1%).

Multiple regression analysis with the rate of change in the estimated CBV as the dependent variable revealed that the rate of change in the mean arterial pressure and type of procedure independently affected the rate of change in the estimated CBV (Table 3).

Discussion

This study examined the differences in the CBV changes after emergence from general anesthesia between patients who underwent TAVI and those who underwent MitraClip implantation. The T group showed a significantly greater decrease in the estimated CBV than the M group. Moreover,

Table 1 Patient characteristics and perioperative variables

	TAVI group (n = 78)	MitraClip group (n = 19)	P-value	Mean or median difference	95% CI	
Patient characteristics						
Male/female (n)	31/47 (40/60)	12/7 (63/37)	0.065			
Age (years)	84.8 (4.4)	76.7(7.1)	<0.001	−8.2	−10.8	−5.6
Height (cm)	152.3 (8.4)	158.2 (8.3)	0.007	5.9	1.6	10.2
Body weight (kg)	53.7 (10.0)	53.5 (10.9)	0.808	−0.6	−5.8	4.6
eGFR (mL/min/1.73 m ²)	54.5 (17.9)	40.3 (15.3)	0.002	−14.2	−23.1	−5.3
LVEF (%)	63.6 [57.9–65.7]	27.1 [23.1–39.9]	<0.001	−34.3	−37.9	−26.4
Comorbidity						
Hypertension	55 (70.5)	7 (36.8)	0.006			
Diabetes	23 (29.5)	5 (26.3)	0.784			
Medication						
Calcium channel blocker	37 (47.4)	7 (36.8)	0.406			
ACE-I or ARB	41 (52.6)	12 (63.2)	0.213			
Beta-blocker	20 (25.6)	14 (73.7)	<0.001			
Diuretic	35 (44.9)	18 (94.7)	<0.001			
Preoperative Hb (g/dL)	11.3 (1.5)	11.5 (2.2)	0.825	0.1	−1.0	1.2
Intraoperative variables						
Surgery time (min)	77.0 [64.0–90.0]	158.0 [142.0–197.0]	<0.001	84.5	71.0	100.0
Anesthesia time (min)	155.5 [136.8–172.5]	235.0 [209.0–311.0]	<0.001	86.0	67.0	109.0
Amount of crystalloid and colloid (mL)	1233.9 (361.0)	1333.3 (456.7)	0.437	87.2	−140.6	315.0
Amount of RBC (mL)	0 [0–0]	0 [0–0]	0.065	0.0	0.0	0.0
Estimated blood loss (mL)	23.5 [0–40]	50.0 [0–80.0]	0.038	20.0	0.0	40.0
Urine output (mL)	300.0 [115.0–500.0]	600 [250.0–1000.0]	0.009	220.0	50.0	450.0
Estimated in–out balance during anesthesia (mL)	927.7 (444.5)	617.6 (520.8)	0.029	−295.2	−527.7	−62.7
Amount of phenylephrine (mg)	0.3 [0–0.5]	0.2 [0–0.4]	0.434	0.0	−0.2	0.1
Amount of ephedrine (mg)	5.0 [0–10.0]	15.0 [5.0–25.0]	0.002	10.0	0.0	15.0
Amount of norepinephrine (μg)	159.0 [59.1–258.2]	291.8 [0–711.9]	0.343	56.4	−54.4	254.7
Amount of dobutamine (mg)	0 [0–0]	0 [0–25.8]	<0.001	0.0	0.0	8.8
Anesthetics						
Sevoflurane	62 (79.5)	13 (68.4)	0.431			
Desflurane	8 (10.2)	4 (21.1)				
Remimazolam	8 (10.2)	2 (10.5)				
Postoperative variable						
Postoperative 1-day Hb (g/dL)	10.6 (1.9)	10.1 (1.2)	0.42	0.4	−0.6	1.3

Data are presented as mean (standard deviations), median [interquartile range], or number (proportion). Median differences and their 95% confidence intervals were calculated with the Hodges-Lehmann method

(TAVI: transcatheter aortic valve implantation, CI: confidence interval, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, CCB: calcium channel blocker, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, Hb: hemoglobin, RBC: Red Blood Cell)

Table 2 Mean arterial pressure before and after emergence from general anesthesia

	TAVI group (n = 78)	MitraClip group (n = 19)	P-value	Mean difference	95% CI	
Before (mmHg)	63.8 (7.5)	66.8 (7.5)				
After (mmHg)	91.5 (12.4)	85.0 (11.8)				
Change rate (%)	144.9 (23.8)	129.0 (24.5)	0.011	−15.9	−28.1	−3.7

Data are presented as means (standard deviations). (TAVI: transcatheter aortic valve implantation, CI: confidence interval)

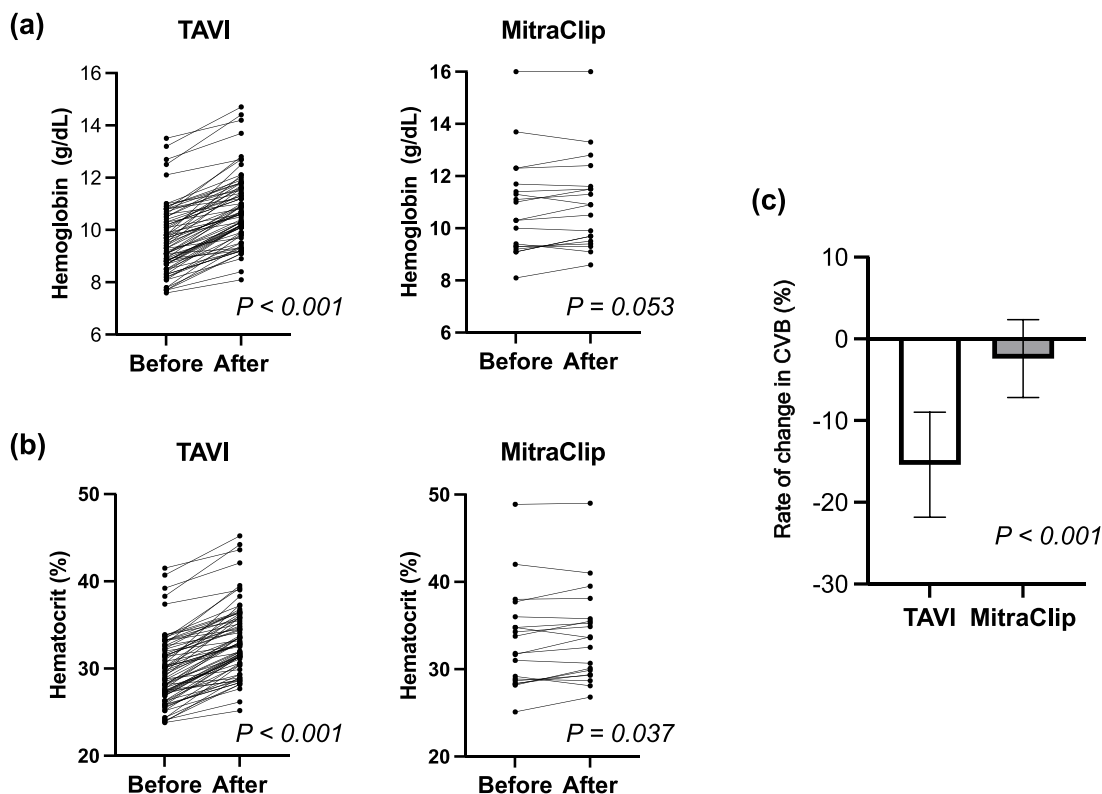


Fig. 2 Changes in the hematocrit, hemoglobin, and rate of change in circulating blood volume between the groups **a** Hemoglobin and **b** hematocrit changes before and after emergence from anesthesia in the TAVI and MitraClip groups (TAVI group: n=78, MitraClip group: n=19) Changes in each case are plotted and then analyzed using the

paired t-test. **c** Rate of change in the estimated CBV in the TAVI and MitraClip groups Data are presented as means and standard deviations and then analyzed using the student t-test. (TAVI: transcatheter aortic valve implantation, CBV: circulating blood volume)

Table 3 Multiple regression analysis with the rate of change in the circulating blood volume as the dependent variable

	B	SE	t	P	95% CI	
MAP change rate (%)	-0.101	0.024	-4.256	<0.001	-0.0148	-0.054
Type of procedure	-9.689	2.272	-4.264	<0.001	-14.153	-7.339
Age (years)	0.092	0.129	0.711	0.479	-0.164	0.348
Sex	-2.173	1.215	-0.135	0.077	-4.588	0.242
eGFR (mL/min/1.73 m ²)	-0.011	0.035	-0.299	0.765	-0.081	0.059
LVEF (%)	-0.054	0.070	-0.098	0.445	-0.192	0.085

Adjusted R²=0.545 (MAP: mean arterial pressure, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, SE: standard error, CI: confidence interval)

multiple regression analysis to correct for confounding by the mean arterial pressure change rate before and after emergence from anesthesia, age, sex, renal function and cardiac function confirmed that the difference in the type of procedure was an independent factor affecting the change in the estimated CBV.

The CBV reportedly increases with a decrease in blood pressure accompanied by vasodilatation [7]. This phenomenon is explained by fluid reabsorption associated with a decrease in the capillary hydrostatic pressure, according to

the Starling equation [8]. The Starling equation stipulates that transcapillary fluid exchange depends on the net balance between the hydrostatic and osmotic pressure gradients and that fluid is filtered in the arterioles and reabsorbed in the veins. Therefore, hypotension due to general anesthesia induction may decrease fluid filtration in the microarteries and promote capillary fluid reabsorption in the microvessels, causing an increase in the CBV. Conversely, upon emergence from anesthesia, vasoconstriction of blood vessels may increase the capillary hydrostatic pressure, resulting

in a decrease in the CBV. Recently, a revised Starling equation was proposed with the discovery of the endothelial glycocalyx layer, and the theory that fluid reabsorption is mediated by the lymphatic system has become dominant [9, 10]. However, the fact remains that changes in the capillary hydrostatic pressure can alter the intravascular volume.

During general anesthesia induction, an increase in the CBV can be prevented if the mean arterial pressure is maintained equal to the baseline value using noradrenaline [2, 3]. Similarly, in cases of vasodilatory shock, such as septic shock, elevated blood pressure with norepinephrine has been reported to decrease the CBV [7]. These studies indicate that change in blood pressure is a major factor affecting changes in the CBV. Our data also confirmed that the increase in blood pressure with the emergence from anesthesia is an independent factor contributing to the decrease in CBV. However, the influence of factors other than blood pressure on the CBV changes associated with anesthesia remains unclear.

TAVI and MitraClip implantation are transcatheter valvular heart disease treatment procedures performed for severe aortic stenosis and severe mitral regurgitation, respectively. Severe aortic stenosis often occurs in atherosclerosis and is characterized by afferent hypertrophy of the myocardium, often with coexisting hypertension [11, 12]. Severe mitral regurgitation is commonly associated with congestive heart failure, and the patient is considered to have a high CBV [4]. The mean arterial pressure changes affect the changes in the CBV. In this study, the mean arterial pressure change associated with emergence from anesthesia was greater in the T group than in the M group, which could be one of the reasons for the greater decrease in the estimated CBV in the former than in the latter. However, multiple regression analysis using the mean arterial pressure change rate and type of procedure as independent variables revealed that the type of procedure was also an independent factor contributing to changes in the estimated CBV. As mentioned earlier, severe mitral regurgitation is often associated with a high CBV and comorbid congestive heart failure, leading to high hydrostatic pressure in many cases. Therefore, even if the vessels dilate or constrict with anesthesia induction or emergence from anesthesia, the hydrostatic pressure may remain high, and the Starling equilibrium state may not change significantly. Additionally, the significant increase in the cardiac output with TAVI may have contributed to increased urine output and decreased estimated CBV in the T group.

The benefits of limited transfusion have been proposed recently, as patients who receive transfusions in the perioperative period of TAVI have been reported to have a nearly two-fold increase in 30-day mortality, regardless of the amount of blood loss or hemoglobin concentration [13]. The purpose of blood transfusion is to deliver oxygen to the systemic organs. Energy consumption and oxygen demand

are lower during general anesthesia than during wakefulness [14], resulting in a potentially acceptable decrease in hemoglobin levels during general anesthesia. This study showed that hemoglobin increased by 1.2 g/dL upon emergence from anesthesia in patients who underwent TAVI. This result may provide a rationale for limiting blood transfusions during general anesthesia in patients undergoing TAVI. In most cases, TAVI is performed under general anesthesia or monitored anesthetic care. Several studies have indicated that intraoperative and in-hospital blood transfusions are common with general anesthesia [15, 16]. This could be attributed to the hemodilution associated with general anesthesia, which modifies the hemoglobin concentration reduction during anesthesia.

This study has several limitations. Accurate data on infusion and urine volume before and after emergence from anesthesia were lacking. Similarly, blood data before and after anesthesia induction were lacking, and we were unable to determine the changes in the CBV associated with anesthesia induction. These are the limitations expected with a retrospective study design. Second, heterogeneity existed in the patient backgrounds between the T and M groups, including age, height, renal function, and hypertension. Therefore, the theory that the differences in valvular disease, severe aortic stenosis, and severe mitral regurgitation contributed to the present results is only one hypothesis. However, the fact remains that these background differences represent different patient populations undergoing TAVI versus the MitraClip procedure, with a greater reduction in the estimated CBV in the former than in the latter. Furthermore, the extent of estimated CBV changes may be overestimated, as it has been suggested that the hematocrit changes associated with general anesthesia may be contributed not only by CBV but also by splenic contraction and hyperemia [17–19]. In addition, the sample size was small, especially in the M group. Therefore, although the effects of some perioperative variables including baseline cardiac and renal functions were adjusted in the multiple regression analysis, the adjustment of other confounding factors might have been insufficient. Finally, as this was a single-center retrospective study, different results may have been obtained depending on the patient's preoperative fluid management status and anesthetic method. Therefore, future multicenter prospective studies including assessments before and after anesthesia induction and those before and after emergence from anesthesia are warranted.

In conclusion, emergence from general anesthesia increased the hemoglobin concentration and hematocrit value and decreased the CBV in patients who underwent TAVI. However, this phenomenon was very limited in patients who underwent MitraClip implantation. Hemodynamic differences due to valvular disease in the patients undergoing each procedure may have affected the results of

this study. Although these results may provide a rationale for minimizing blood transfusions during general anesthesia in patients undergoing TAVI, a prospective study is required to confirm these results.

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Author contributions Makishi Maeda: Conceptualization, Methodology, Investigation, Data curation, Writing—Original Draft, and Visualization; Yusuke Yoshikawa: Conceptualization, Methodology, and Writing—Review and Editing; Sho Ohno: Conceptualization, Methodology, and Writing—Review and Editing; Tomohiro Chaki: Conceptualization, Methodology, Formal analysis, and Writing—Review and Editing; Michiaki Yamakage: Conceptualization, Writing—Review and Editing, and Supervision.

Data availability Data will be shared in deidentified form upon reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

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