Comparing the hemodynamic effects of volume loading vs non-loading during induction of anesthesia in fluid responder patients with coronary artery disease undergoing elective coronary artery bypass graft surgery: a randomized controlled study

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Context
Postinduction hypotension is a modifiable risk that can be prevented by adjusting the technique for induction of anesthesia. Therefore, volume loading could prevent postinduction hypotension in fluid responder patients.
Aims
To compare the hemodynamic profile of patients who received volume loading before induction of general anesthesia in patients with CAD undergoing CABG.
Settings and design
A randomized, controlled, double-blinded trial.
Methods and material
Patients were randomly divided into two groups; control group were receive nothing before induction, while patients in volume loading group received volume loading of 8 ml/kg Ringer acetate over 10 min.
The primary outcome was the incidence of postinduction hypotension from start of induction of anesthesia till 15-minutes after intubation. The two groups were compared according to the following: Incidence of postinduction hypertension, bradycardia, and tachycardia in addition to mean arterial blood pressure, heart rate, stroke volume variation and cardiac index recordings.
Results
Fifty patient were included in this study. Patients in volume loading group received on average 771±289 ml of acetated ringer before induction of anesthesia to have their SVV below 13%. The incidence of postinduction hypotension was higher in the control group (13/25) compared to volume loading group (5/25) after induction of anesthesia ($P<001$).
Conclusions
Volume loading in fluid responder patients undergoing CABG effectively reduced the incidence of hypotension in the first 15 min postinduction period.

Keywords:
coronary artery disease, hemodynamics, hypotension

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Key Messages: Preoperative volume loading was effective in reducing the frequency of postinduction hypotension in fluid responder patients with coronary artery disease undergoing Coronary artery bypass graft.

Introduction

Patients with coronary artery disease (CAD) presenting for coronary artery bypass grafting (CABG) represent a high-risk group among the cardiac surgical population [1]. Anesthetic management of these patients is challenging due to increased risk of perioperative hypotension [2] and subsequently increased risk of postoperative morbidity and mortality [3]. Postinduction hypotension is a modifiable risk that can be largely prevented by adjusting the technique for anesthesia induction.

Thus, using predictors for postinduction hypotension would identify the high-risk patients, and allows modification of the conduct of anesthesia by decreasing the dose of induction agent, pre-anesthetic fluid loading, and even early administration of prophylactic vasopressors.

One of the main factors contributing for postinduction hypotension is the preoperative volume status. However, accurate assessment of volume status is sometimes challenging [4].

Pre-anesthetic Stroke Volume Variation [SVV] could predict incidence of decreased cardiac output [CO] and hypotension during induction of general anesthesia. Higher pre-anesthetic SVV (>13%) leads to higher incidence and faster onset of decreased CO during anesthesia induction. By measuring SVV before induction of general anesthesia, anesthesiologists can perform prophylactic volume expansion in patients at high-risk of decreased CO and hypotension [4,5].

The aim of this study is to compare the effect of volume loading before induction of anesthesia versus standard of care in patients with CAD undergoing CABG.

Subjects and methods

A randomized, controlled, double-blinded trial was conducted in University Hospital, after approval of the research ethics committee (MS-618–2021). The study was registered at **clinicaltrials.gov** registry system (NCT05462847). The study was conducted from May 2021 through May 2022. Written informed consent was obtained from the study participants.

Randomization was achieved by a statistician using an online random number generator. Patient codes were placed into sequentially numbered sealed opaque envelopes by a research assistant who was not involved in the study. An anesthesia resident not involved in patients' management was responsible for opening the envelope and giving the volume loading with no further involvement in the study. Before induction of anesthesia, another anesthesia resident blinded to the patients grouping was responsible for data collection.

Adult (>18 years) patients with CAD, scheduled for elective CABG surgery with SVV > 13% were included in the study. While patients with associated valvular heart disease, left ventricular systolic dysfunction <40%, persistent serious arrhythmias, congestive cardiac failure, on mechanical ventilation, intra-aortic balloon pump, emergency surgery, uncontrolled diabetes (HbA1C >8%) and those with known allergy to any of the study's drugs, severe systemic non-cardiac disease, other than controlled diabetes and hypertension, were excluded from the study.

All preoperative cardiac medications were continued till the morning of the surgery, except angiotensin converting enzyme inhibitors. Patients were pre-medicated with intramuscular morphine at 0.1 mg. kg−1 one hour before surgery. Upon arrival to the operating room, Initial monitoring included five lead electrocardiograms, non-invasive blood pressure, and pulse oximetry were applied. Intravenous midazolam (0.05 mg/kg) was administered for anxiolysis. Under local anesthesia an arterial line and central venous line were placed.

Before induction of anesthesia for all study patients, Electrical cardiometry device (ICON; Cardiotonic, Osypka; Berlin, Germany) was applied to the patient through 4 electrodes at the following sites: Below the left ear, above the midpoint of the left clavicle, Left mid-axillary line at level of the xiphoid process and 5 cm inferior to the third electrode. SVV was measured while patient maintaining deep breathing at 8 breath/minute for one-minute. Patients with SVV less than 13% were excluded from the study. Thus, all patients included were considered fluid responders [5]. The baseline data in the form of heart rate, systolic, and mean systemic arterial pressures, SVV was recorded during the study period in all the patients by an anesthesia resident responsible for the randomization.

Then, Patients were randomly divided into two groups; control group (n=25) received nothing before induction, and volume loading group (n=25) received volume loading of 8 ml/kg Ringer acetate over 10 min The volume loading was repeated until SVV would be below 13%.

The attending anesthetist induced general anesthesia to patients in both groups using 3 mcg/kg of fentanyl. Then in all patients, propofol was injected slowly in 0.25 mg/kg increments every 20 s till clinical loss of consciousness. Clinical loss of consciousness (defined as no response to auditory command) was assessed by asking the patients repeatedly every 20 s to open their eyes. After loss of consciousness, atracurium 0.5 mg/kg was administered to facilitate tracheal intubation. The stress response to laryngoscopy and tracheal intubation is secondary to marked increase in sympathetic activity and manifested in general as tachycardia and hypertension and was managed with increments 25 mcg fentanyl. Anesthesia was maintained by isoflurane (1-1.2%) in air-oxygen mixture. Patients were mechanically ventilated to have target of PO2 above 300 mmhg and PCO2 between 35-40 mmg.

Any episode of hypotension (defined as mean arterial pressure [MAP]<80% of the baseline reading and/or MAP <60 mmHg) was managed by 5 mcg norepinephrine while bradycardia (defined as heart

rate less than 50 bpm) was managed by IV atropine bolus (0.5 mg).

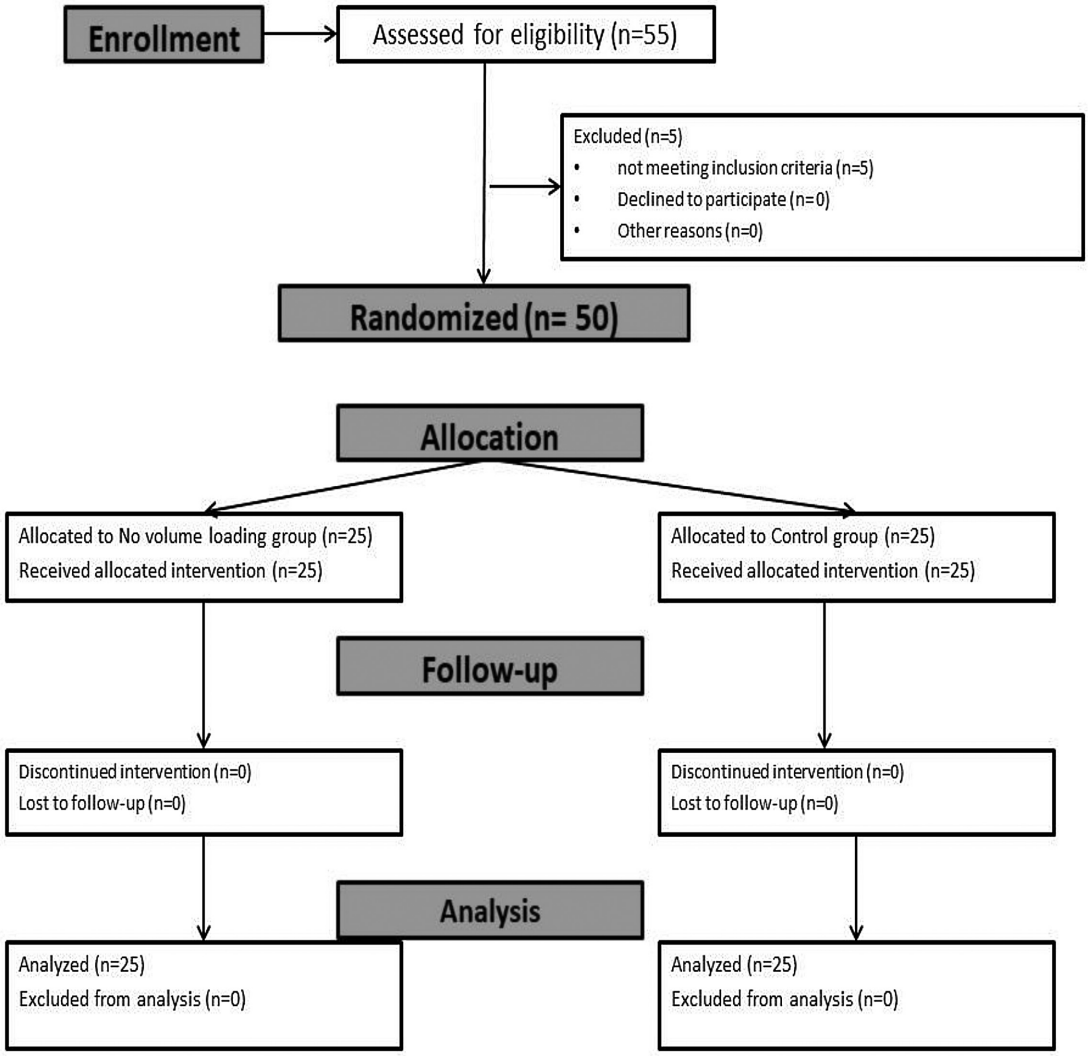
Heart rate and invasive blood pressure was continuously monitored during the study period (from induction of anesthesia until 15 min after intubation). SVV and CO measured by the electrical cardiometry were recorded 1-minte before the induction, 1-and 2-minutes after loss of consciousness, 1-minutes after intubation, and then every 2 min for 15-minutes after intubation, the endpoint of the present study.

Our primary outcome was the frequency of postinduction hypotension (defined as mean arterial blood pressure <80% from baseline and/or MAP <60 mmHg from the start of induction of anesthesia till 15-minutes after intubation). Secondary outcomes included hemodynamic data (SBP, heart rate, SVV and CO) at the baseline reading and 1 min before the induction, 1 and 2 min after loss of consciousness, 1 min after intubation, then every 2 min for 15 min after intubation, the frequency of postinduction hypertension, bradycardia, and tachycardia from the induction of anesthesia till 15-minutes after intubation.

In a pilot study on five patients, the incidence of postinduction hypotension in fluid responder patients receiving general anesthesia was 80%. At alpha error of 0.05, we calculated that 46 patients would give 80% power to detect 40% absolute reduction in the incidence of hypotension in the volume loading group. The number of prepared envelopes were be 50 (25 envelopes per group) to compensate for possible dropouts.

Statistical package for social science (SPSS) software, version 26 for Microsoft Windows (SPSS inc., Chicago, iL, USA) was used for data analysis. Categorical data were presented as frequency (%)

Figure 1



CONSORT chart.

Table 1 Demographics

	NO volume loading *N*=25	Volume loading *N*=25	*P* Value
Age	51±12	53±8	0.470
Weight	81±11	81±17	0.984
Height	167±8	169±6	0.191
Volume		771±289	
Male	11 (44.0%)	15 (60.0%)	0.256
ASA III	25 (100.0%)	22 (88.0%)	0.074
ASA IV	0 (0.0%)	3 (12.0%)	

Data are presented as mean ± standard deviation or number and (count%). * denotes statistically significant where *P* value less than 0.05. ASA, American society of anesthesia.

and were be analyzed by the chi square test. Continuous data were checked for normality using the Shapiro-Wilk test and were presented as mean (standard deviation) or median (interquartile range) as appropriate. Continuous data were analyzed using the unpaired t test or the Mann Whitney test according to normality of the data. Repeated measures were analyzed using the analysis of variance (ANOVA) for repeated measures with post-hoc pairwise comparisons using the Bonferroni tests. A *P* value less than 0.05 was considered statistically significant.

Results

Our study was conducted on 55 patients with CAD, scheduled for elective CABG surgery with SVV > 13% from May 2021 to May 2022. The consort chart is shown in Fig. 1. Briefly, five patients were excluded because they did not meet the inclusion criteria. Finally, fifty patients were randomized to volume loading group (*n*=25) or Control group (*n*=25). Patients in volume loading group received on average 771±289 ml of acetated ringer before of anesthesia to have their SVV below 13%. The American Society of Anesthesiologists' Physical Status classification was III (47/50), and IV (3/40) (as they had recent myocardial infarction in the past three months). The patient characteristics are summarized in (Table 1).

No statistical differences between the groups were found in the baseline hemodynamic data. Overall, in this study cohort (*n*=50), the baseline mean arterial blood pressure was 88±13 mmHg and the mean intraoperative mean arterial blood pressure during the first 15 min study period was 84±12 mmHg.

The incidence of postinduction hypotension was higher in the control group (13/25) compared to volume loading group (5/25) after induction of anesthesia (*P* <.001). During the induction period, the need for vasopressor drugs according to the study protocol was more frequent in the control. However, no differences were noted on other hemodynamics (hypertension, tachycardia or bradycardia) in both study groups as shown in (Table 2).

Table 2 Hemodynamics changes

	NO volume loading *N*=25	Volume loading *N*=25	*P* Value
Hypotension	13 (52.0%)	5 (20.0%)	0.018 *
Hypertension	10 (40.0%)	14 (56.0%)	0.258
Bradycradia	3 (12.0%)	0 (0.0%)	0.074
Tachycardia	8 (32.0%)	9 (36.0%)	0.765
Norepinephrine dose	13 (52.0%)	5 (20.0%)	0.018 *
Atropine dose	3 (12.0%)	0 (0.0%)	0.074

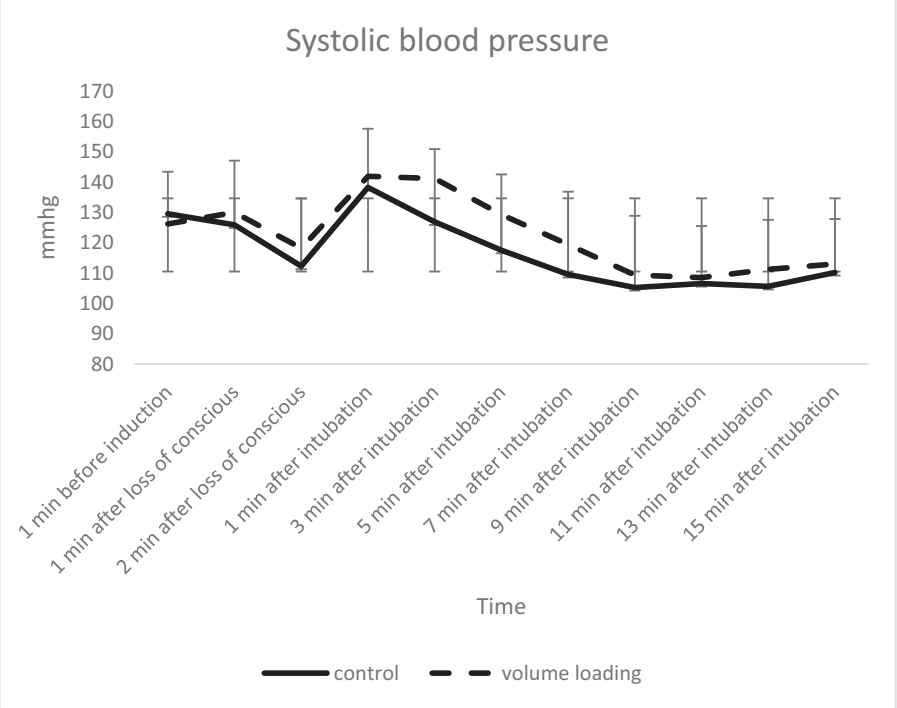
Data are presented as number and count%. *denotes statistically significant where *P* value less than 0.05.

In terms of hemodynamics monitoring throughout the first 15 min after induction, heart rate, MAP and SBP were comparable between both study groups, except for reading of blood pressure after 3 min of intubation and recordings of heart rate after 11 min of intubation as shown in (Figs. 1 and 2).

Cardiometry was applied to all patients before induction of anesthesia to guide for volume loading. All patients have their SVV > than 13%. In the control group, the mean SVV before induction of anesthesia was 17.3±3.7% versus 16.6±3.5% in volume loading group. SVV dropped to 10±1.5 in patients who received volume loading. In both study groups, the mean SVV throughout the study was 12.8±2.5. No statistically differences were noted between both groups in terms of SVV, stroke volume and cardiac output readings throughout the procedure.

To be mentioned, no correlations were found between the incidence of postinduction hypotension and increasing age (*P* value=0.081, r=0,249).

Figure 2



Systolic blood pressure.

Discussion

The results of this randomized study demonstrated that volume loading to target SVV below 13% could decrease the frequency of postinduction hypotension in patients with CAD undergoing CABG operations.

Hypotension after the induction of GA is a common occurrence. An arterial blood pressure decline below the lower limit of the vascular auto regulation curve could lead to vital organs (heart, brain, and kidney) ischemia.

In addition, a number of clinical studies have demonstrated that intraoperative hypotension and unfavorable effects on organ function and integrity (i.e. myocardial injury, stroke, and acute kidney injury) are highly connected in patients undergoing general [6], neurological [7], or cardiovascular surgery [8]. Moreover, intraoperative hypotension is linked with longer hospital length of stay, postoperative surgery related morbidity, and even mortality [9].

After induction of anesthesia, hypotension is primarily linked to vasoplegia (effect of anesthetic drugs) and the beginning of mechanical ventilation.

In patients undergoing cardiac surgery or with known cardiac diseases, cardiac dysfunction should be considered [10].

Blood pressure drop following induction of anesthesia can be compensated by two main methods; the use of vasoactive drugs and/or intravenous fluids [11].

Previous studies have documented benefits of fluid preloading in reducing the incidence of postinduction hypotension. A lower incidence (52 vs. 84%) of postinduction hypotension was observed with 20 mL/kg of Ringer's lactate preloading as compared with no preloading [12]. Another study also documented lower incidence (12.5 vs. 57.5%) of postinduction hypotension with 6 ml/kg crystalloid loading as compared with control [11]. Similarly, lower incidence (41.5 vs. 56.6%) of postinduction hemodynamic instability was seen with preinduction preloading of 8 ml/kg Ringer's acetate as compared with no preloading [13].

Theoretically, combining both preoperative fluids and vasoactive drugs may be a superior approach rather than using either method in terms of preventing postinduction hypotension. Moreover, the need for both fluids and vasopressors may be reduced that way. However, in the setting of hypovolemia, the solitary use of α1-agonists may cause abundant vasoconstriction and poor perfusion, so these should not be used as primary drugs before excluding or normalizing a low level of venous return with IV fluids [14].

An earlier study demonstrated preoperative volume loading with 8 ml/kg Ringer's lactate to be more effective than preinduction administration of ephedrine in maintaining hemodynamic stability during rapid-sequence induction with propofol without HR increase during intubation [15].

The scope of this study was mainly during the induction of anesthesia. However, there is no clear consensus on how to define the length of the induction period and no clear criteria for when a blood pressure drop is with clinical significance [16]. In this study, we defined the length of the period of anesthesia induction as the initial 15 min after intubation and postinduction hypotension as mean arterial blood pressure <80% from baseline and/or mean arterial blood pressure <60 mmHg. Other authors have defined a drop below MAP 65 mmHg as a profound physiological response [6,11] which we also have used as an endpoint in this study.

The 15-minute observation period was chosen based on recent evidence of a substantial impact on cardiovascular and renal complications within this time frame in the context of intraoperative hypotension [6].

At any time during a perioperative process, fluids loading should not be liberal to avoid hypervolemia [5]. Despite the fact that optimizing volume status is the challenging, most anesthesiologists use a very basic level of hemodynamic monitoring, with blood pressure and heart rate being their main measurements. A recent survey found that only 34% of anesthesiologists in America and Europe used cardiac output monitoring in high-risk surgery [17].

A meta analysis has concluded that SVV was well correlated with fluid responsiveness un mechanically ventilated patients; however the presence of spontaneous breathing compromises the predictive value of SVV [18]. Juri *et al.* have concluded in another study that pre-anesthetic SVV could predict incidence of hypotension during induction of general anesthesia. Higher SVV before induction of anesthesia leads to higher incidence and faster onset of decreased CO during anesthesia induction. By measuring pre-anesthetic SVV, anesthesiologists can perform prophylactic volume expansion in patients at high-risk of decreased CO and hypotension. In this study, targeted preoperative volume loading was applied primarily using electrical cardiometry. A stroke volume variation above 13% in patients breathing deeply denotes that these patients are fluid responder [4,5]. Based on the previous studies, by asking asked the patients to have deep breathing at 8 ml/kg, we may have missed some fluid responsive patients but at least the included patients were probably fluid responsive.

The results of this study suggest that crystalloid fluids can have specific advantages in anesthesia management compensating preoperative central hypovolemia and the drop of venous return due to general anesthesia induction. However, opposite views have been recently published and the need for preoperative fluid loading (especially colloids) has been questioned [19]. Indeed, liberal volume loading should be avoided. Even by this study protocol, there may be a possibility for transient hypervolemia; however, due to targeted total volume infused preoperatively using electrical cardiometry, this risk should be without pathological significance.

In this study, we primarily used the electrical cardiometry to measure SVV to aid volume loading before induction of anesthesia. The SVV (%) at baseline was high (17.3 vs. 16.6) in both the groups in our study as patients with low SVV were excluded. The SVV decreased significantly after fluid loading in the intervention group, while it did not change much in the control group. After induction of anesthesia, the SVV were comparable between both study groups.

We also used it to measure SV and CO after induction of anesthesia and we have not found any difference in these advanced cardiac indices between both study groups. Similarly,Paul *et al.* [20] have not found a significant difference in Cardiac index between volume loading and control group. In contrast, Tamilselvan *et al.* [21] found that cardiac output increase with both crystalloid and colloid preload. Our study was not powered enough to study these changes and this will need futures studies.

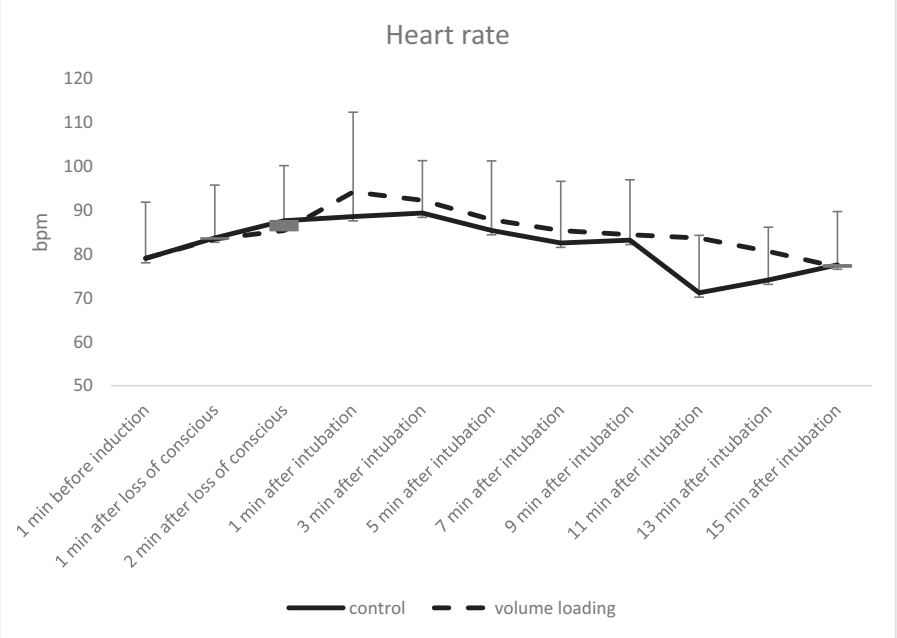
Limitation of the study

The study was made on patients with good systolic function. Patients with poor systolic function may respond negatively to volume loading and this should be further studied. In addition, this was a uni center study.

Conclusion

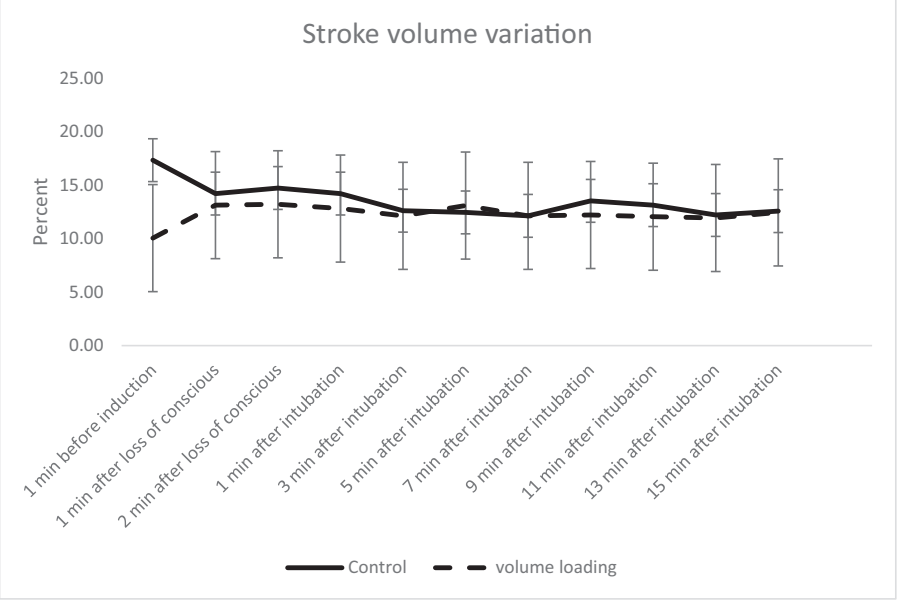
Preoperative volume loading was effective in reducing the frequency of postinduction hypotension in patients with CAD undergoing CABG. Volume loading was targeted using SVV measured by electrical cardiometry to prevent fluid overload and its adverse effects (Figs. 3 and 4).

Figure 3



Heart rate.

Figure 4



Stroke volume variation.

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Conflicts of interest
There are no conflicts of interest.

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