Anaesthesia and ICU sedation with sevoflurane do not reduce myocardial injury in patients undergoing cardiac surgery
A randomized prospective study

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Abstract
Background: To evaluate the effect of anaesthesia and ICU sedation with sevoflurane to protect the myocardium against ischemia-reperfusion injury associated to cardiac surgery assessed by troponin release.

Methods: We performed a prospective, open-label, randomized study in cardiac surgery with cardiopulmonary bypass. Patients were randomized to an algorithm-based intervention group and a control group. The main outcome was the perioperative kinetic of cardiac troponin I (cTnI). The secondary outcomes included composite endpoint, GDF-15 (macrophage inhibitory cytokine-1) value, arterial lactate levels, and the length of stay (LOS) in the ICU.

Results: Of 82 included patients, 81 were analyzed on an intention-to-treat basis (intervention group: n = 42; control group: n = 39). On inclusion, the intervention and control groups did not differ significantly in terms of demographic and surgical data. The postoperative kinetics of cTnI did not differ significantly between groups: the mean difference was 0.44 ± 1.09 μg/ml, P = .69. Incidence of composite endpoint and GDF-15 values were higher in the sevoflurane group than in propofol group. The intervention and control groups did not differ significantly in terms of ICU stay and hospital stay.

Conclusion: The use of an anaesthesia and ICU sedation with sevoflurane was not associated with a lower incidence of myocardial injury assessed by cTnI. Sevoflurane administration was associated with higher prevalence of acute renal failure and higher GDF-15 values.

Abbreviations: CABG = coronary artery bypass graft surgery, CPB = cardiopulmonary bypass, cTnI = cardiac troponin I, GDF-15 = Growth differentiation factor 15 or macrophage inhibitory cytokine-1, ICU = intensive care unit, MAC = minimum alveolar concentration, MAP = mean arterial blood pressure, RASS = Richmond Sedation-Agitation Scale.

Keywords: cardiac surgery, outcomes, post-conditioning, pre-conditioning, propofol, volatile anaesthetic
1. Introduction

Since a ground-breaking study in the 1980’s demonstrated the protective effects of ischaemic preconditioning,\[1\] doctors and researchers from varied horizons have attempted to apply the findings to cardiac surgery. There is extensive evidence of the efficacy of conditioning by volatile anaesthetics in both animal and human models.\[2–5\] Two protective windows have been described: the first is an early and transient maximum protective effect in the first 2 hours after the injury, and the second is a delayed lower-intensity phase that appears less than 12 hours after preconditioning and that persists for 72 hours. Volatile anaesthetics have been shown to have conditioning effects (pre-, per-, and post-conditioning) on the myocardium, the kidneys, the brain, the liver, and the muscles\[6–7\] though observational and randomized studies in adult patients have produced conflicting results.\[8\] De Hert et al reported the cardioprotective effect of sevoflurane when it was administrated throughout surgery,\[9\] and, later, Steurer et al demonstrated the effect of late post-conditioning on myocardial function, even with low-dose administration.\[10\] A recent pragmatic multicentric randomized study concluded that volatile anaesthetics used during coronary artery bypass do not have cardioprotective effect.\[10\] But few studies have assessed the effects of sevoflurane anaesthesia and sedation on myocardial injury or other postoperative complications. The existing studies were primarily interested in evaluating the cardioprotective effects during coronary artery bypass graft (CABG) surgery.\[11–12\] In addition, sevoflurane may have detrimental effects on other organs such as kidney with the effect of compound A or brain with seizure.\[13\] Data concerning potential organ dysfunction following the use of volatile anaesthetics during cardiac surgery are sparse despite the potential effects such as the direct effects of conditioning and the indirect effects of hemodynamic instability due to cardiac dysfunction.

Growth differentiation factor 15 or macrophage inhibitory cytokine-1 (GDF-15) is a cytokine that is weakly expressed under physiological conditions, but when the body is subjected to stressful conditions such as hypoxia, inflammation, oxidative stress and ischemia/reperfusion, GDF-15 expression increases.\[14\] Plasma GDF-15 levels are a proven marker of impaired renal function\[15\] and GDF-15 could potentially be used to identify patients at a high risk of other complications. In addition, elevated GDF-15 is closely associated with all-cause mortality and has been identified as an independent marker of mortality.\[15\]

The main objective of the present study was to determine whether, compared with propofol, anaesthesia and sedation with sevoflurane lowers postoperative levels of cardiac troponin I. The secondary objectives were to assess the effect of sevoflurane on postoperative complications using a composite criterion and GDF-15 values.

2. Material and methods

2.1. Patients

We performed a prospective, single-centre open-label, parallel, randomized controlled trial at University Hospital between October 2015 and August 2016. Ethical approval for this study (ref. 2015-000476-99) was provided by the Ethical Committee. The trial was registered at ClinicalTrials.gov (NCT02851433). The trial was designed to investigate the potential superiority of total anaesthesia and ICU sedation with sevoflurane. We used TENALEA online software for randomization (Paris, France). Patients were randomized in a 1:1 ratio to receive sevoflurane (intervention group) or propofol (control group) and were stratified by age, sex, and Euroscore II. Surgeons were blinded to treatment. Written, informed consent was obtained from all patients prior to surgery. The protocol is available as a supplementary file.

Inclusion criteria were: age $\geq$ 18 years, cardiac surgery with the use of cardiopulmonary bypass (CPB) for coronary artery bypass grafting (CABG), the surgical correction of aortic stenosis or combined surgery (CABG and valve disease). Exclusion criteria were: myocardial infarction less than 90 days prior to surgery, chronic renal failure, dialysis, pregnancy, and withdrawal of consent.

2.2. Anaesthesia protocol

Preoperative, operative and postoperative care was standardized for all the patients. Preoperative medications were maintained according to established guidelines. Anaesthesia and cardiopulmonary bypass procedures were standardized for all patients. Anaesthesia was induced with propofol (0.4–2mg/kg) and sufentanil (0.5mg/ml). Sufentanil was administrated continuously using the Schnider target-controlled infusions model. Tracheal intubation was facilitated with cisatracurium (0.15mg/kg). According to group allocation, anaesthesia was maintained with target-controlled infusions of propofol (started at 2–4mg/ml) or inhalation of sevoflurane (at 1 minimum alveolar concentration (MAC)). Sedation titration with propofol was based on the bispectral index (Covidien, Boulder, CO, USA) to obtain a value between 40 and 60.

Cardiopulmonary bypass was standardised and comprise a heart-lung machine (Stockert Sorin S5, Heart Lung, Milan, Italy) with a target blood flow of 2.4l/minutes per m\(^2\).\[16,17\] The mean arterial blood pressure (MAP) was maintained at more than 65 mm Hg by increasing the pump flow rate or, if required, by administering a bolus of phenylephrine (100 $\mu$g) or norepinephrine (5 $\mu$g). The pump primes for the CPB circuit contained 1500 ml of crystalloids (Plasma-Lyte; Baxter, Lessines, Belgium) and 5000 IU of heparin. After systemic heparinization (300 UI/kg) to obtain a hemocron level of 400 second, median sternotomy, aortic and right auricular cannulations were started. Myocardial protection was ensured with multidose intermittent antegrade cold blood cardioplegia (via the aortic root, every 15 minutes). During aortic cross clamping, moderate hypothermia (32–34°C) was maintained. At unclamping, we applied a low reperfusion pressure by decreasing blood flow rate to 1 l/minutes per m\(^2\), and then slowly increased the flow to 2.4 l/minutes per m\(^2\) over a period of 3 minutes. Normoglycemia (arterial blood glycaemia <10 mmol) was maintained with intravenous insulin (intravenous bolus of 5–10 UI) if necessary. Patients with a haemoglobin value below 8 g/dl received homologous red blood cell trans-fusions. During CPB, sevoflurane was administrated through the oxygenator at MAC = 1. Heparin was reversed with protamine. None of the study participants underwent intraoperative hemofiltration and none received corticosteroids or ketamine.

2.3. Post-surgical management

After surgery, sedation and mechanical ventilation were continued for all patients until haemodynamic stability, normothermia, and absence of significant active haemorrhage (less than 1 ml/kg
per hour) could be verified. Sedation was maintained between -2 and -3 on the Richmond Sedation-Agitation Scale (RASS). The patients were managed by a team of physicians specialized in the postoperative care of cardiac surgery patients, including a cardiologist. Circulatory support was guided by institutional protocols to achieve predefined endpoints: mean arterial pressure >65 mm Hg, cardiac index >2.25/min/m², and urine output >0.5 ml/kg/h. Analgesia was standardized and consisted of intravenous paracetamol and patient-controlled morphine. Patients were extubated as described in existing guidelines.

In the control group, patients were anaesthetized and then sedated with intravenous infusion of propofol. In the intervention group, patients were anaesthetized and sedated with inhaled sevoflurane. Post-surgical ICU sedation with sevoflurane was delivered with the MIRUS system (Pall medical, Pall Europe Limited, Portsmouth, England).

2.4. Preoperative data acquisition

All data were continuously recorded on an electronic case report form by a clinical data manager who was blinded to patient allocation. The following preoperative variables were recorded: age, gender, bodyweight, height, personal medical history, ASA score, EuroSCORE II, type of cardiac surgery, preoperative left ventricular ejection fraction, the duration of CPB, duration of aortic clamping, need for intraoperative blood transfusion, need for norepinephrine and dobutamine, time to extubation, any complications that occurred during the surgery and/or in the ICU, and the length of stay in the ICU.

Blood samples were collected on admission to the ICU, 6 hours after admission, and several times a day thereafter on request from the attending physician for assessment of arterial lactate, cardiac troponin I (cTnI), liver enzymes, creatinine and GDF-15. cTnI was measured using a sandwich immunoassay LOCI method with the Dimension Vista (Siemens Healthcare Diagnostics, Deerfield, Illinois, USA). Sensitivity of the assay is 0.03 μg/ml with a variation coefficient of <10%. Plasma GDF-15 levels were measured before induction and 24 hour after surgery. Blood samples were immediately centrifuged after collection, and levels were measured before induction and 24 hours after surgery.

2.5. Endpoints

The primary endpoint was the kinetics of cTnI in the 48 hours after surgery (measured at baseline, end of surgery, 6 hours, 12 hours, 24 hours and 48 hours after the end of the surgery). The secondary endpoints were: a composite endpoint based on occurrence of major cardiovascular events within 7 postoperative days (aortic fibrillation or flutter, second or third degree atrioventricular blockade requiring pacemaker implantation, ventricular tachycardia or fibrillation, myocardial infarction, stroke, and acute kidney injury (KDIGO)), vasoplegic syndrome, left ventricular ejection fraction (LVEF) <25%, estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m², cTnI, GDF-15, and length of hospital stay (days).

2.6. Statistical analysis

Using the procedures described by Cromheecke et al and de De Hert et al, we calculated that 41 patients per group would allow us to demonstrate a variation of 1.8 μg/ml of cTnI, with a power of 0.8 and an alpha risk of 0.05.

Table 1

| Variables                                      | Intervention group (n = 42) | Control group (n = 39) | P value |
|------------------------------------------------|-----------------------------|------------------------|--------|
| Age, (years)                                   | 69 (10)                     | 68 (11)                | .636   |
| Gender (M, n (%))                              | 28 (60)                     | 24 (67)                | .651   |
| Body mass index (kg/m²)                        | 28 (4)                      | 28 (5)                 | .923   |
| EuroSCORE II (%)                               | 1.4 [0.85–2.34]             | 1.2 [0.84–1.71]        | .441   |
| Medical history, n (%)                         |                             |                        |        |
| Myocardial infarction                          | 8 (19)                      | 8 (20)                 | 1.00   |
| Coronary disease                               | 11 (26)                     | 12 (30)                | .806   |
| Arrhythmia (atrial fibrillation)               | 8 (19)                      | 5 (14)                 | .551   |
| Dyslipidaemia                                  | 30 (71)                     | 31 (77)                | .620   |
| Active smoking                                 | 3 (7)                       | 7 (18)                 | .193   |
| Chronic arterial hypertension                  | 32 (76)                     | 32 (80)                | .793   |
| Diabetes (type 1 or 2)                         | 15 (36)                     | 15 (38)                | 1.00   |
| Chronic renal insufficiency                    | 7 (17)                      | 6 (15)                 | .835   |
| Stroke (ischemic)                              | 5 (12)                      | 2 (5)                  | .434   |
| Treatment, n (%)                               |                             |                        |        |
| Beta blocker                                   | 25 (60)                     | 23 (58)                | 1.00   |
| Calcium channel blocker                        | 10 (24)                     | 11 (28)                | .800   |
| Aspirin                                        | 25 (60)                     | 21 (54)                | .658   |
| Clopidogrel                                    | 7 (17)                      | 11 (28)                | .286   |
| Angiotensin converting enzyme inhibitor        | 30 (71)                     | 28 (70)                | 1.00   |
| Statins                                        | 27 (64)                     | 27 (69)                | .814   |
| Oral antidiabetic agent                        | 14 (32)                     | 10 (26)                | .476   |
| Cardiac Troponin I (ng/ml)                     | 0.02 [0.01–0.03]            | 0.02 [0.01–0.02]       | .437   |
| Left ventricular ejection fraction (%)         | 61 (11)                     | 62 (7)                 | .488   |
| Creatinine (mmol l⁻¹)                          | 81 (21)                     | 78 (17)                | .365   |
| Estimated glomerular filtration rate (ml/min/1.73 m²) | 82 (17)                     | 86 (17)                | .261   |
| GDF-15 (mangociceptor inhibitory cytokine-1)   | 1118 [773–1825]            | 1089 [675–1363]        | .438   |
years (males: 28), and the median EuroSCORE II was 1.27 (0.9–2.1). Baseline characteristics and operative data did not differ between groups (Tables 1 and 2, Flow chart diagram).

3.1. Primary endpoint

The postoperative kinetics of cTnI did not differ significantly between groups: the mean difference was 0.44 ± 1.09 μg/ml, \( P = .69 \) (Fig. 1, Tables 2 and 3). The mean difference remained non-significant after adjustment for preoperative variables (surgery type, lactate values, catecholamine use) (1.15 ± 1.24 μg/ml, \( P = .35 \)).

3.2. Secondary endpoints (Table 3)

The time to extubation was shorter in the sevoflurane group. The incidence of norepinephrine use and the arterial lactate value were higher in the sevoflurane group than in the propofol group. The incidence of the composite endpoint was higher in the intervention group as a result of the higher rate of acute kidney injury. GDF-15 levels were also higher in sevoflurane group than in propofol group. The groups did not differ in term of ICU stay.

4. Discussion

The present results demonstrate that total conditioning anesthe-sia and post-surgical sedation with sevoflurane were not associated with a decrease in myocardial injury, as assessed by cTnI. On the contrary, sevoflurane administration was associated with a higher rate of vasopressor use, higher levels of arterial lactate and GDF-15, and a higher incidence of complications such as acute kidney injury.

The conditioning effect of volatile anaesthetic agents in cardiac surgery has been addressed extensively in the literature. Studies have used varied protocol (pre, peri, post, continuous or intermittent administration) in both CABG surgery and non-CABG surgery. A recent multicentric study did not demonstrated that volatile agents have a positive clinical effect during CABG surgery.\(^{[10]}\) This study did not standardize the protocol of conditioning and have focused on the operative period. To date, few studies have assessed the effect of conditioning based on both peri and postoperative administration of volatile anaesthetic agents. Two studies found that sevoflurane use did not improve myocardial protection during CABG surgery.\(^{[12,13]}\) Though it has been documented in previous work, we were unable to demonstrate the clinical cardioprotective effect of sevoflurane even with a strict protocol of conditioning. Quite the opposite, we found that sevoflurane used at 1 MAC was associated vasoplegia and renal failure.

Several factors may explain our findings. First, a switch from crystalloid cardioplegia to iterative blood cardioplegia has improved cardioplegia techniques since the first studies on myocardial conditioning were published. Blood antegrade cardioplegia is associated with a lower release of cTnI and improved myocardial protection.\(^{[20]}\) Recent studies, including ours, have used antegrade blood cardioplegia.\(^{[12,13,21]}\) Moreover, different administration protocols (dosing, route, continuous or intermittent administration) were used, as in the study of Landoni et al.\(^{[11]}\) These types of changes can influence the positive or negative effects of sevoflurane or propofol.\(^{[3,6]}\) In our study, sevoflurane MAC was set to 1 to be sure to administer an effective cardioprotective dose.

Additional factors such as age, sex, lidocaine administration, sulphonylurea treatment, or blood glucose level can alter the protective effect of sevoflurane.\(^{[22,23]}\) In our study, patients were randomized according to sex, age and EuroSCORE II in order to avoid such biases. The prevalence of diabetic patients and treatment with sulphonylurea did not differ between the 2 groups. We did not administer lidocaine, and all patients had standardized blood glucose management. We can therefore exclude such effects.

We found that sevoflurane was positively associated with markers of vascular dysfunction such as arterial lactate values, vasopressor use, and GDF-15 values.\(^{[14,24,25]}\) The macro and micro-hemodynamic effects of sevoflurane have been demonstrated, and sevoflurane is known to have more pronounced effects on vasodilation during surgery and CPB than propofol. In addition, sevoflurane was shown to alter microcirculation with change of blood flow, oxygen consumption and alteration of cell respiration.\(^{[26,27]}\) All of these effects are dose dependant, explaining our finding with the use of MAC set to 1. Even so, our results and those of Wąsowicz et al demonstrated a higher use of vasopressor agents despite varying protocols for sedation. We also observed a higher value of GDF-15, which is known to increase in response to tissue injury and inflammation. In the

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**Table 2**

Operative characteristics. The \( P \) value always refers to comparisons between the intervention group and the control group.

| Variables | Intervention group (n = 42) | Control group (n = 39) | \( P \) value |
|-----------|---------------------------|-----------------------|-------------|
| Aortic valve surgery | 23 (55) | 19 (45) | .659 |
| Mean number of coronary artery bypass grafts per procedure | 4 (1) | 4 (1) | .932 |
| Surgery time (min) | 193 [162–238] | 193 [158–225] | .464 |
| Cardiopulmonary bypass time (min) | 88 [79–116] | 93 [61–111] | .567 |
| Aortic cross clamp time (min) | 64 [53–69] | 68 [54–80] | .751 |
| Heparin (UI) | 2400 [2100–2500] | 2400 [2100–2500] | .958 |
| Internal electrical defibrillation, n (%) | 8 (12) | 5 (13) | .551 |
| Vasopressor, n (%) | | | |
| Phenytoine | 32 (89) | 25 (64) | .330 |
| Norepinephrine | 21 (51) | 10 (26) | .039 |
| Dobutamine, n (%) | 3 (7) | 1 (3) | .617 |
| Total fluid administration (ml) | 1000 [500–1500] | 500 [0–1000] | .420 |
| Transfusion, n (%) | 2 (5) | 4 (10) | .427 |
| Arterial lactate at the start of CPB (mmol/l) | 1.9 [1.3–2.3] | 1.7 [1.3–2.2] | .589 |
| Arterial lactate at the end of CPB (mmol/l) | 2 [1.5–2.2] | 1.4 [1.3–2] | .002 |
Framingham cohort, Andersson et al. demonstrated an association between high levels of GDF-15 and vascular stiffness and endothelial dysfunction.\(^{[28]}\) This is in line with the results of Lind et al. who demonstrated that circulating GDF-15 levels in seniors were directly associated with endothelium-dependent vasodilation in resistance vessels.\(^{[29]}\)

The higher incidence of postoperative complications in our study was likely related to the higher incidence of acute kidney injury, but our results contradict a previous report of renal protective effects following the use of volatile agents.\(^{[30]}\) In non-cardiac surgery, anaesthesia with sevoflurane was associated with postoperative acute kidney injury.\(^{[31]}\) Acute kidney injury following CBP is a complex disease characterized by ischemia-reperfusion injury, renal perfusion alterations, and an imbalance between the delivery and consumption of oxygen.\(^{[32]}\) meaning that there are several potential mechanisms behind the increase in kidney disease seen in our study. Firstly, the higher use of norepinephrine in the sevoflurane group could alter renal perfusion through glomerular vasoconstriction.\(^{[33]}\) Secondly, endothelial dysfunction and changes in cell respiration may worsen the discrepancy in oxygen delivery and oxygen consumption. Thirdly, propofol can modulate the inflammatory response induced by ischemia reperfusion injury following aortic cross clamping.\(^{[34]}\) Wasowicz et al also observed a trend towards a lower glomerular filtration rate in their volatile anaesthetic group.\(^{[13]}\) The reported association between GDF-15 and acute
kidney injury following cardiac surgery also reinforces the validity of our results.\[15\]

In summary, surgical and anaesthesia techniques, myocardial protection and perioperative care have improved considerably since the early years of cardiac surgery. Because of the low clinical cardioprotective effect of volatile agents and the advances in care, it may be difficult to demonstrate any effect on cTnI kinetics. On the other hand, because of its negative influence on macro and microcirculation, sevoflurane can be associated with side effects limiting its usefulness.

The present study has several limitations. First, our use of the MIRUS system did not allow us to blind medical and paramedical staff. Nevertheless, the surgeon, cardiologist and clinical data manager were blind to group allocation. The relatively small number of patients might also limit our study's external validity. We calculated the study's sample size based on the kinetics of cTnI, and we were not able to demonstrate a significant difference with all the secondary outcomes. We did not measure other variable of cardiac damage such as myoglobin or CK-MB. Most of studies have focused on cardiac troponin that is recommended for myocardial injury diagnosis. The use of propofol for the induction of anaesthesia in all patients may have created a bias. However, given the pharmacokinetics and pharmacodynamics of propofol, it could be argued that a single dose used for the induction of general anaesthesia did not alter the protective effect on the myocardium. In addition, we attempted to minimise the potential pharmacological biases by controlling for cardioplegia, insulin, corticosteroids and ketamine. Lastly, we included a mixed cardiac surgical population (CABG and aortic valve repair). Though most positive studies investigated CABG surgery, the cardioprotective effect of volatile agent was also demonstrated in valve surgery.\[4\] We believe that such a bias would be negligible.

5. Conclusion

The use of anaesthesia and post-surgical sedation with sevoflurane was not associated with a lower incidence of myocardial injury, as indicated by cTnI. Sevoflurane administration was associated with vascular alteration (norepinephrine use, arterial lactate, GDF-15 values) and a worse postoperative course, even with shorter intubation times. Our results do not indicate that the use of sevoflurane during cardiac surgery with cardiopulmonary bypass delivers an additional cardioprotective effect.

### Table 3

Post-operative course. The \( P \) value always refers to comparisons between the intervention group and the control group.

| Variables                                      | Intervention group (\( n = 42 \)) | Control group (\( n = 39 \)) | \( P \) value |
|------------------------------------------------|----------------------------------|------------------------------|--------------|
| Arterial lactate (mmol/l)                       |                                  |                              |              |
| at admission to ICU                             | 1.7 [1–2.5]                      | 1.2 [0.9–1.4]                | .026         |
| on first postoperative day                      | 1.5 [1–2]                       | 1.6 [1.2–2.4]                | .135         |
| GDF-15 on first postoperative day (ng/l)        | 3299 [1962–5016]                | 2530 [1581–3471]             | .045         |
| Creatinine (mmol/l)                             |                                  |                              |              |
| at admission to ICU                             | 78 (20)                         | 72 (18)                      | .149         |
| on first postoperative day                      | 91 (38)                         | 78 (34)                      | .120         |
| Estimated glomerular filtration rate (ml/min/1.73 m\(^2\)) |                       |                              |              |
| at admission to ICU                             | 82 (17)                         | 86 (18)                      | .261         |
| on first postoperative day                      | 75 (25)                         | 84 (21)                      | .074         |
| Haemoglobin at admission to ICU (g/dl)          | 10.9 (1.5)                      | 11.1 (1.6)                   | .646         |
| Troponin Ic (ng/ml)                             |                                  |                              |              |
| at admission to ICU                             | 5 [2–8.2]                       | 4 [2.1–7.1]                  | .69          |
| 6 hours after surgery                           | 5.4 [2.8–10.5]                  | 6.4 [3.2–9.5]                |              |
| 12 hours after surgery                          | 3.2 [1.4–3.8]                   | 3.8 [2.6–8.4]                |              |
| 24 hours after surgery                          | 2.2 [1.4–3.8]                   | 2.2 [1.5–4.8]                |              |
| 48 hours after surgery                          | 1.3 [0.7–1.9]                   | 1.1 [0.7–1.9]                |              |
| Catecholamine use, n (%)                        |                                  |                              |              |
| Norepinephrine                                  | 26 (61)                         | 15 (38)                      | .046         |
| Dobutamine                                      | 3 (7)                           | 0 (0)                        | .242         |
| Left ventricular ejection fraction at ICU discharge | 60 (7.8)                    | 58 (9.2)                     | .399         |
| Endpoint composite score, n (%)                 | 27 (64)                         | 16 (41)                      |              |
| Stroke                                          | 1 (2)                           | 0 (0)                        | .046         |
| Atrial fibrillation                             | 10 (24)                         | 6 (15)                       |              |
| Myocardial infarction                           | 2 (5)                           | 2 (6)                        |              |
| Acute renal failure                             | 16 (38)                         | 9 (23)                       |              |
| KDIGO 1                                         | 11 (69)                         | 7 (78)                       |              |
| KDIGO 2                                         | 3 (19)                          | 2 (22)                       |              |
| KDIGO 3                                         | 2 (12)                          | 0                             |              |
| Atrioventricular block requiring pacemaker implantation | 1 (2)                   | 4 (10)                       |              |
| Death                                           | 1 (2)                           | 0                             | .001         |
| Time to extubation (minutes)                    | 36 [15–60]                      | 75 [44–170]                  |              |
| ICU stay (hours)                                | 41 [23–72]                      | 26 [23–58]                   | .381         |
| Hospital stay (days)                            | 9 (4)                           | 9 (3)                        | .860         |
| Death at Day 30                                 | 1 (2)                           | 0                             | 1.00         |

ICU = intensive care unit.
Author contributions

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