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Isoflurane Sedation in Patients Undergoing Venoarterial Extracorporeal Membrane Oxygenation Treatment for Cardiogenic Shock—An Observational Propensity-Matched Study

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Objectives: The feasibility and hemodynamic effects of isoflurane sedation in cardiogenic shock in the presence of venoarterial extracorporeal membrane oxygenation treatment are currently unknown.

Design: Retrospective single-center study.

Setting: Cardiac ICU of Munich university hospital.

Patients/Subjects: Cardiogenic shock patients with venoarterial extracorporeal membrane oxygenation treatment under sedation with volatile isoflurane between November 2018 and October 2019 have been enrolled in this study and were matched by propensity score in a 1:1 ratio with IV sedated patients treated between January 2013 and November 2018 from the cardiogenic shock registry of the university hospital of Munich.

Measurements and Main Results: Isoflurane sedation was used in 32 patients with cardiogenic shock and venoarterial extracorporeal membrane oxygenation treatment. The mean age of conventionally sedated patients was 58.4 ± 13.8 years and 56.3 ± 11.5 years for patients with isoflurane sedation ($p = 0.51$). Administration of isoflurane was associated with lower IV sedative drug use during venoarterial extracorporeal membrane oxygenation treatment (86% vs 32%; $p = 0.01$). Mean systolic arterial pressure was similar (94.3 ± 12.6 vs 92.9 ± 10.5 mm Hg; $p = 0.65$), but mean heart rate was significantly higher in the conventional sedation group, when compared with the isoflurane group (85.2 ± 20.5 vs 74.7 ± 15.0 beats/min; $p = 0.02$). Catecholamine doses, venoarterial extracorporeal membrane oxygenation blood and gas flow, ventilation time (304 ± 143 vs 398 ± 272 hr; $p = 0.16$), bleeding complications bleeding academic research consortium 3a or higher (59.3% vs 65.3%; $p = 0.76$), and 30-day mortality (59.2% vs 63.4%, $p = 0.80$) were similar in both groups. The overall sedation costs per patient were significantly lower in the conventional group, when compared with the isoflurane group (537 ± 624 vs 1280 ± 837 €; $p < 0.001$).

Conclusions: Volatile sedation with isoflurane is feasible—albeit at higher costs—in patients with cardiogenic shock and venoarterial extracorporeal membrane oxygenation treatment and was not associated with higher catecholamine dosage or extracorporeal membrane oxygenation flow rate compared with IV sedation.

Key Words: cardiac arrest; cardiogenic shock; extracorporeal membrane oxygenation; hypnotics and sedatives; isoflurane; resuscitation

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Crit Care Expl 2020; 2:e0086

DOI: 10.1097/CCE.0000000000000086

Cardiogenic shock (CS) is a life-threatening disorder due to reduced cardiac output and frequently results in multiple organ failure and death. The outcome of CS

patients remains poor, and a 30-day mortality of 40–52% has been described in the large-scale randomized trials (IABP II [1], CULPRIT-SHOCK trial [2]). Some comprehensive contemporary registries reported even higher mortality rates ranging from 45% to 70% (3). In our registry including patients with CS of all-cause, we observed a 30-day mortality of ~ 55% and a 1-year mortality of ~69% (unpublished data).

A significant proportion of CS patients cannot be stabilized by medical treatment alone, and the utilization of mechanical cardiac support systems such as venoarterial extracorporeal membrane oxygenation (VA-ECMO) is required. In addition, VA-ECMO may also be implanted in the setting of ongoing resuscitation as a rescue therapy (4). The majority of these patients require sedative treatment in these clinical situations. However, there is no common strategy regarding the choice of anesthetic drugs in CS with VA-ECMO treatment to date. VA-ECMO treatment can alter pharmacokinetics and pharmacodynamics of anesthetic drugs due to increased volume of distribution for lipophilic drugs, abnormal protein binding, and other alterations related to pump speed, thereby complicating proper dosing (5, 6). Ex vivo studies with utilization of VA-ECMO demonstrated significant losses of midazolam and propofol warranting close-interval neurologic evaluations (7). According to current guidelines, caution should be taken with IV anesthetic drugs such as propofol that may induce hypotension and have cardiodepressive effects (8).

In addition to propofol and midazolam, volatile anesthetics such as isoflurane have been implemented as a safe and efficient long-term sedation technique in the ICU in recent years, as they lack accumulation and tolerance development (9). Several trials demonstrated that utilization of volatile anesthetics reduces the time to extubation (10), the return of consciousness (11), and the duration of the overall ICU stay (12). Furthermore, the use of inhaled sedatives for patients after out-of-hospital cardiac arrest (OHCA) was associated with reduced ventilation time, duration of ICU stay, and thus enabled early neurologic evaluation (12). In contrast, other trials demonstrated no effect of volatile sedatives on the reduction of ventilation time but were associated with higher norepinephrine dosages (13). Importantly, patients undergoing VA-ECMO treatment were excluded from the latter trials. Nevertheless, isoflurane is known as a potent coronary vasodilator, which may cause a hemodynamic steal effect by favoring the perfusion of health coronary arteries while limiting blood flow in stenotic segments, thereby abrogating its potential beneficial effect (14).

Since the vast majority of patients suffering from severe CS and undergoing VA-ECMO treatment are unconscious and mechanically ventilated, the question arises to what extent a volatile sedation strategy with the utilization of isoflurane 1) is feasible in these patients, 2) impacts the duration of ventilation and ICU stay, 3) influences catecholamine dosing and VA-ECMO flow support, and 4) impacts treatment costs. We hypothesized that patients with VA-ECMO and isoflurane sedation require higher doses of catecholamines and VA-ECMO flow compared with patients with VA-ECMO and conventional IV sedation due to the vasodilatory effects of isoflurane. Here, we analyzed these variables in patients with CS requiring VA-ECMO treatment at the cardiac ICU of Munich University Hospital.

METHODS

Study Population

CS patients treated between January 2013 and October 2019 in the cardiac ICU of the Munich university hospital were included in a CS registry in compliance with the Declaration of Helsinki and German data protection laws. The registry was approved by the local ethics committee (Institutional Review Board number: 18-001) and is registered at the World Health Organization International Clinical Trials Registry Platform (DRKS00015860). CS was defined in accordance with the IABP-SHOCK II trial (1). For this study, all ventilated patients with VA-ECMO treatment and a minimal survival time of at least 24 hours were retrospectively selected. Isoflurane sedation is available in this ICU since November 2018. To adjust for confounders, 32 patients with isoflurane treatment were matched by propensity score with patients without isoflurane treatment in a 1:1 ratio treated between January 2013 and November 2018. Following patient consent, phone calls were performed in order to collect postdischarge clinical endpoints.

Implantation of VA-ECMO

VA-ECMO implantation was performed in the catheterization laboratory under fluoroscopic control or directly at the ICU using sonographic guidance. Peripheral cannulation was achieved by using 21–25°F venous cannula and 15–19°F arterial cannula depending on patient body surface area. An antegrade 7°F catheter was distally inserted into the femoral artery to prevent leg ischemia. For mechanical circulatory support, the Stöckert Centrifugal Pump System (SCP; LivaNova, Munich, Germany) was used. Extracorporeal membrane oxygenation (ECMO) blood flow and gas flow were titrated based on clinical assessment and arterial blood gas analysis. In general, we run VA-ECMO at lowest possible flow rates to minimize left ventricular afterload. In case of pulmonary congestion, unloading the left ventricle was achieved by inotropes, that is, dobutamine or implantation of an Impella CP system (Abiomed, Danvers, MA). Unfractionated heparin was IV administered in order to achieve an activated partial thromboplastin time above 60 seconds in the absence of bleeding complications. All patients were weaned at the discretion of the attending physician. VA-ECMO decannulation was routinely performed at bedside with compression of the arterial access site using a compression system or by a closure device (15).

Sedation and Ventilation

After admission to the ICU, patients either received IV sedation with midazolam ± ketamine and/or propofol in the control group or volatile gas sedation with isoflurane. For analgesia, all patients received sufentanil. Isoflurane was administered by using the vaporizer system AnaConDa (Sedana Medical, Danderyd, Sweden, for detailed information see https://www.sedanamedical.com) as previously described by Sackey et al

(11) in combination with Phillips IntelliVue G7^{m} (Philips, Amsterdam, Netherland) anesthesia gas modules and EVITA ventilators (Dräger, Lübeck, Germany) via orotracheal tube or tracheotomy (16). Three Phillips IntelliVue G7^{m} (Philips) anesthesia gas modules were available in our cardiac ICU. Concerning environmental contamination, most of the exhaled isoflurane is adsorbed and reflected back to the patient upon inspiration. The residual gas exits through the exhaust of the ventilator and is captured by a filter system. In the VA-ECMO oxygenator, we use a solid air-tight membrane, which was shown to almost completely restrict diffusion of isoflurane (17). Isoflurane sedation was used in an all-comers strategy in patients with CS or cardiac arrest and was solely limited by the availability of gas modules. Patients with significant pulmonary edema have been excluded due to the assumed reduced absorption of isoflurane in the lungs. Isoflurane concentration was constantly monitored to achieve a mean end-tidal isoflurane concentration (end-tidal gas fraction) of 0.5–1.5%. All patients were initially ventilated in controlled biphasic positive airway pressure mode (target tidal volume 6–8 mL/kg of predicted body weight), and respirator settings were adjusted according to arterial blood gas analyses.

Study Endpoints

Study endpoints included the ventilation time, the duration of the ICU stay, VA-ECMO variables, occurrence of acute kidney injury, and requirement of dialysis. Catecholamine doses per hour were calculated by using the following formula: dobutamine (mg/hr) + 100 × epinephrine (mg/hr) + 100 × norepinephrine (mg/hr) as previously described (18). Lactate clearance was defined as the time interval from the admission to the ICU to the repetitive measurement of a serum lactate below 2.5 mmol/L. Cumulative IV sedation dose during VA-ECMO was calculated by determining mean percentage of maximum recommended ICU dose of propofol and midazolam. For example, if a patient was eligible for up to 200 mg/hr of propofol but was actually receiving 150 mg/hr of propofol, he or she would have received 75% of the maximum recommended sedation. Death and bleedings classified as 3a according to the bleeding academic research consortium (BARC) (19) during the first month were obtained and analyzed. To evaluate the neurologic outcome, neuron-specific enolase (NSE) serum concentration was measured between day 1–3 after ICU admission, and Pittsburgh Cerebral Performance Category (CPC) at ICU discharge was determined.

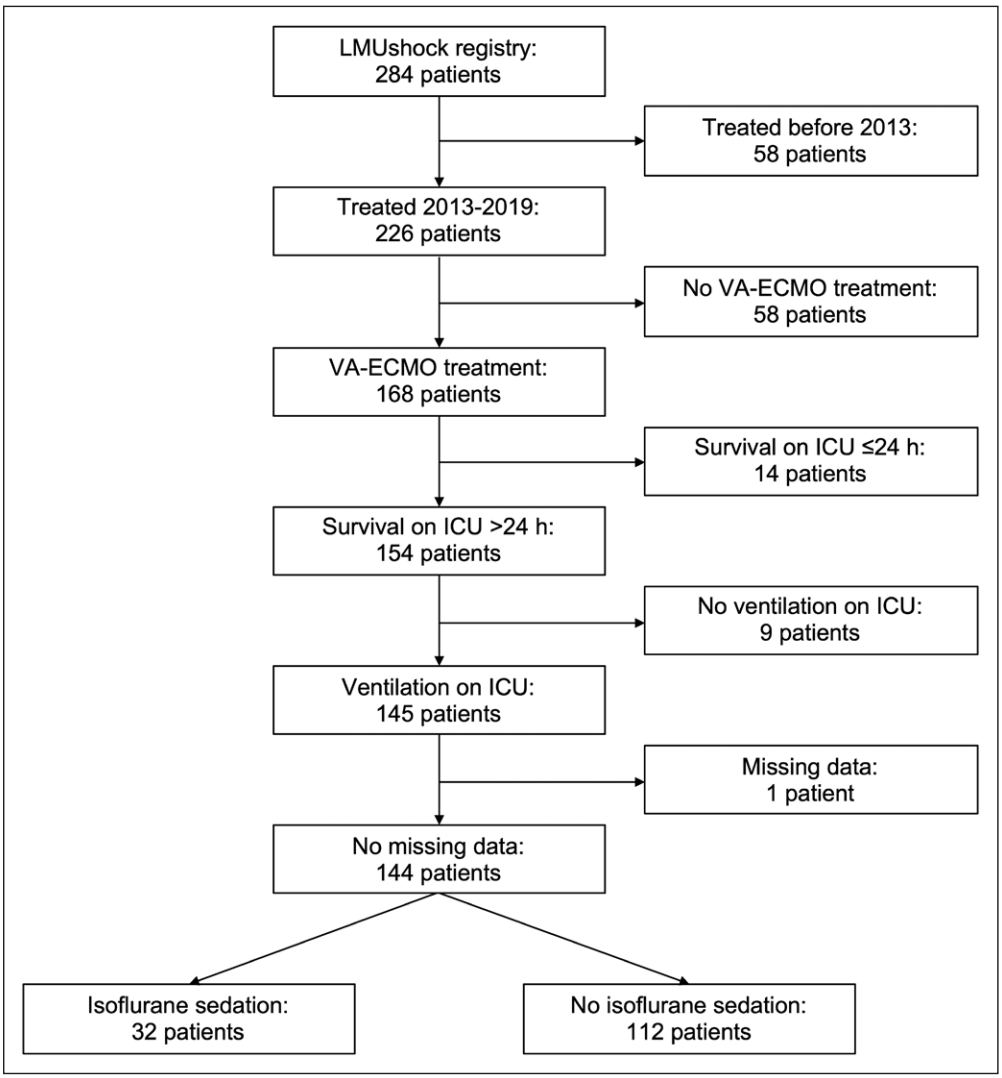

Figure 1. Flow diagram depicting patient selection. LMUshock = cardiogenic shock registry of the LMU Munich University Hospital, VA-ECMO = venoarterial extracorporeal membrane oxygenation.

Cost Analysis

Based on the purchase price of our pharmacy, we calculated the costs for sedation during the ICU stay. The following prices were used: 0.023 € per milligram propofol, 0.146 € per milligram midazolam, and 0.550 € per milliliter isoflurane. Patients treated with isoflurane caused daily costs of 70 € and additional 60 € per ICU (added based on our average expenses for the AnaConDa [Sedana Medical] equipment).

Statistical Analysis

Statistical analysis was performed using R (version 3.6.0, The R Foundation, Vienna, Austria) and Prism 8 (GraphPad Software, San Diego, CA). Normalized continuous variables were reported as mean with SD and nonnormalized continuous variables as median with interquartile ranges (25–75th percentile). To compare groups, one-way analysis of variance and Kruskal–Wallis rank sum test were used, respectively. Categorical variables were reported as absolute numbers and percentages.

To compare groups, Fisher exact test was used. All tests were two-tailed, and *p* values less than 0.05 were considered as significant. Mortality, bleeding rates, and VA-ECMO extraction rate were calculated using the Kaplan–Meier method, and comparisons were made by using log-rank tests.

For propensity score matching, the R package "Matching" version 4.9-6 (20) was used with a 1:1 nearest neighbor algorithm, no replacement, Mahalanobis distance measure, and a caliper of 0.25. The following baseline variables, which are known to impact ICU mortality in CS (5, 21), were used for matching: age, gender, first measured lactate in ICU, myocardial infarction, cardiac arrest, and catecholamine dose at admission. The propensity score was estimated by logistic regression. After matching, standard difference of mean was below 0.2 for all variables. One patient was excluded because of missing data.

RESULTS

Study Population and Baseline Characteristics

Registry data of 284 patients treated in cardiologic ICU with CS were available. After exclusion of patients who died within 24

TABLE 1. Baseline Characteristics of Patients

Variables	Conventional (*n* = 32)	Isoflurane (*n* = 32)	*p*
Age, yr (SD)	58.4 (13.8)	56.3 (11.5)	0.51
Male gender, *n* (%)	24 (75.0)	24 (75.0)	1.00
Body mass index (SD)	27.5 (4.6)	27.4 (3.8)	0.40
Past myocardial infarction, *n* (%)	6 (25.0)	9 (32.1)	0.80
Past stroke, *n* (%)	3 (9.4)	4 (12.5)	1.00
Peripheral artery disease, *n* (%)	3 (9.4)	1 (3.1)	0.61
Smoker, *n* (%)			0.62
Active smoker	15 (46.9)	14 (46.7)	
Former smoker	2 (6.2)	4 (13.3)	
Never smoked	15 (46.9)	12 (40.0)	
Hypertension, *n* (%)	22 (68.8)	19 (59.4)	0.60
High cholesterol, *n* (%)	15 (48.4)	15 (48.4)	1.00
Diabetes, *n* (%)			0.06
Diet	1 (3.1)	1 (3.1)	
Insulin	6 (18.8)	0 (0.0)	
Medication	4 (12.5)	8 (25.0)	
No	21 (65.6)	23 (71.9)	
Positive cardiovascular family history, *n* (%)	7 (22.6)	5 (16.7)	0.80
Cardiopulmonary resuscitation duration, min, median (IQR)	65.0 (19.3–100.0)	60.0 (17.0–100.0)	0.98
Cardiac arrest, *n* (%)	27 (84.4)	27 (84.4)	1.00
Out-of-hospital cardiac arrest, *n* (%)	11 (34.4)	13 (40.6)	0.80
Cause of cardiogenic shock, *n* (%)			0.49
Primary arrhythmia	2 (6.2)	1 (3.1)	
Cardiomyopathy	2 (6.2)	5 (15.6)	
Intoxication	0 (0.0)	1 (3.1)	
Pulmonary embolism	1 (3.1)	1 (3.1)	
Myocarditis	2 (6.2)	3 (9.4)	
Non-STEMI	6 (18.8)	8 (25.0)	
STEMI	16 (50.0)	13 (40.6)	
Other	3 (9.4)	0 (0.0)	

IQR = interquartile range, STEMI = ST elevation myocardial infarction.

hours and those were treated before 2013, 32 patients with isoflurane sedation and VA-ECMO treatment were considered eligible for analysis (**Fig. 1**). In order to adjust for confounding variables and reduce selection bias, we matched the conventional sedation and isoflurane treatment group as described above achieving a standard difference of mean below 0.2 for all variables.

The mean age at time of CS was 58.4 ± 13.8 years for conventional sedation and 56.3 ± 11.5 years for isoflurane sedation (p = 0.51) with 75% male patients in both groups (p = 1.00). Cardiovascular diseases and cardiovascular risk factors before the index event were distributed evenly (**Table 1**). There was no significant difference in OHCA (34% vs 40%; p = 0.80), Simplified Acute Physiology Score-II scores (69.2 ± 16.0 vs 72.0. ± 13.7; p = 0.49), and Survival after Veno-Arterial ECMO scores (–7.9 ± 4.9 vs -8.9 ± 4.4; p = 0.44) between both groups, respectively (**Table 2**). The dose of conventional IV sedation during VA-ECMO treatment was significantly higher in the conventional group in comparison with the isoflurane group (86% vs 32% of maximal recommended dose, p = 0.01). All baseline characteristics of the study groups are shown in Table 1.

ICU and VA-ECMO Variables

The median length of ICU stay was 8.6 days (2.3–13.4 d) in the conventional versus 12.5 days (6.0–21.0 d) in the isoflurane group (p = 0.15) (**Fig. 2*A***). Systolic (94.3 ± 12.6 vs 92.9 ± 10.5 mm Hg; p = 0.65) (Table 2) and diastolic blood pressure (64.3 ± 8.2 vs 63.4 ± 7.9 mm Hg; p = 0.65) (Table 2) were similar, but patients in the control group had a significant higher mean heart rate in comparison with patients sedated with isoflurane (85.2 ± 20.5 vs 74.7 ± 15.0 beats/min; p = 0.02) (Table 2). The ventilation time (**Fig. 2**, ***B*** and ***C***) and catecholamine dose per day (**Fig. 2*D***) were not statistically different in both groups. We could not detect any differences in acute kidney failure and dialysis treatment (Table 2). Although fewer patients accomplished lactate clearance in the conventional (n = 20) than in the isoflurane (n = 27) group (p = 0.09), patients in the isoflurane group reached this clearance at a later time point (median time span of 17.3 hr [7.4–23.0 hr] in control vs 40.8 hr [23.1–72.7 hr] in isoflurane group; p < 0.01) (**Fig. 2**, ***E*** and ***F***).

Patients sedated with isoflurane received longer median VA-ECMO treatment compared with conventional treatment group (p < 0.01) (**Fig. 3*A*** and Table 2). However, VA-ECMO flow and gas flow during the first 5 days were not statistically different (**Fig. 3**, ***B*** and ***C***).

Mortality, Bleeding Rate and Neurologic Outcome

A total of 59.2% of patients in the conventional treatment group and 63.4% of patients with isoflurane sedation died during the first

TABLE 2. ICU Variables and Clinical Endpoints

Variables	Conventional (n = 32)	Isoflurane (n = 32)	p
Simplified Acute Physiology Score-II score (SD)	69.2 (16.00)	72.0 (13.67)	0.49
Survival after Veno-Arterial ECMO score (SD)	−7.9 (4.9)	−8.9 (4.4)	0.44
VA-ECMO duration, d, median (IQR)	2.84 (1.84–4.07)	4.33 (2.52–7.60)	0.02
Average systolic blood pressure (SD)	94.3 (12.6)	92.9 (10.5)	0.65
Average diastolic blood pressure (SD)	64.3 (8.2)	63.4 (7.9)	0.65
Average heart rate (SD)	85.2 (20.5)	74.7 (15.0)	0.02
First lactate measured on ICU, median (IQR)	8.7 (5.9–12.9)	9.6 (4.2–13.0)	0.84
First glomerular filtration rate measured on ICU, median (IQR)	46.00 (39.50–57.50)	51.00 (38.00–62.50)	0.34
Dialysis during ICU stay, *n* (%)	14 (43.8)	17 (53.1)	0.62
Acute kidney injury during ICU stay, *n* (%)	32 (100.0)	27 (84.4)	0.06
Myocardial infarction during ICU stay, *n* (%)	1 (3.1)	1 (3.1)	1.00
Any bleeding event during ICU stay, *n* (%)	23 (71.9)	23 (71.9)	1.00
Cumulative IV sedation dose during VA-ECMO treatment in % (SD)	86.1 (84)	32.1 (62)	0.01
Cumulative cost of sedation during VA-ECMO treatment in € (SD)	539 (624)	1,280 (837)	<0.001
CPC on discharge, *n* (%)			0.91
CPC1	2 (6.2)	1 (3.1)	
CPC2	2 (6.2)	1 (3.1)	
CPC3	8 (25.0)	7 (21.9)	
CPC4	3 (9.4)	4 (12.5)	
CPC5	17 (53.1)	19 (59.4)	

CPC = Cerebral Performance Category, ECMO = extracorporeal membrane oxygenation, IQR = interquartile range, VA = venoarterial.

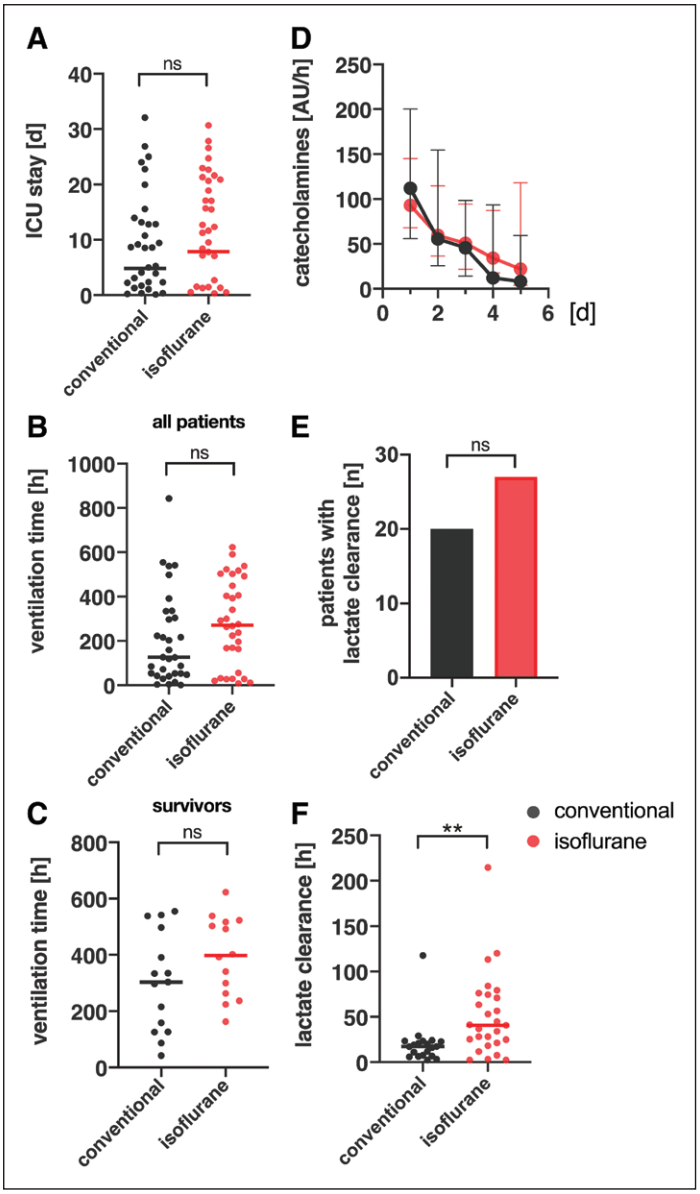

Figure 2. ICU outcome of patients with cardiogenic shock and venoarterial extracorporeal membrane oxygenation treated with conventional IV versus isoflurane sedation. **A**, Median length of the ICU stay in days for conventional (*black*) and isoflurane (*red*) treatment. **B**, Median ventilation time in hours for conventionally (*black*) and isoflurane (*red*) treated patients. **C**, Median ventilation time of surviving patients in hours for conventionally (*black*) and isoflurane (*red*) treated patients. **D**, Median cumulative catecholamine doses for conventionally (*black*) and isoflurane (*red*) treated patients. **E**, Absolute rates of patients with lactate clearance. **F**, Time in hours to lactate clearance. $^{*}p < 0.05$; $^{**}p < 0.01$. ns = not significant.

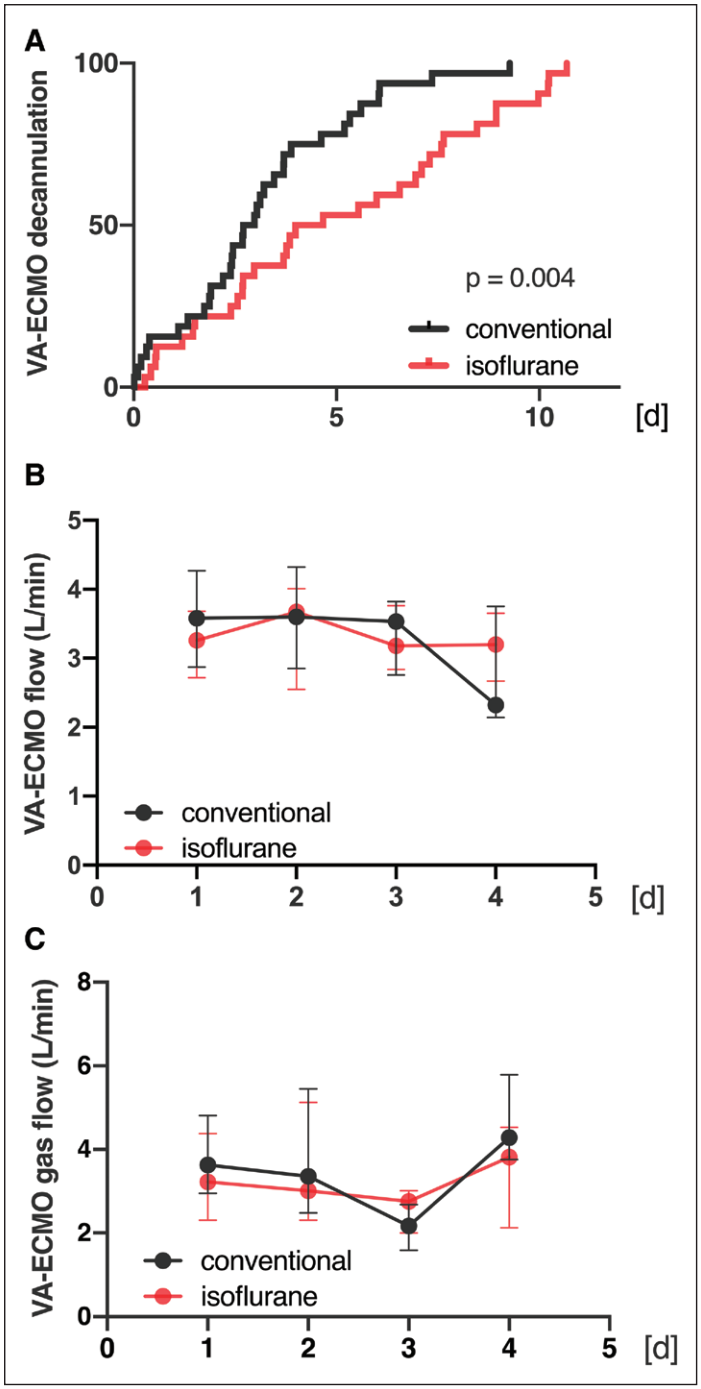

Figure 3. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) variables of patients with cardiogenic shock treated with conventional IV versus isoflurane sedation. **A**, VA-ECMO decannulation over time. **B**, Median VA-ECMO flow days 1–4. **C**, Median VA-ECMO gas flow days 1–4.

month (p = 0.80) (**Fig. 4*A***). Furthermore, bleeding events classified as BARC3a or higher (59.3% vs 65.3%; p = 0.76) (**Fig. 4*B***), and ischemic events (3.1% vs 3.1%; p = 1.00) (Table 2) were comparable in both groups. Among patients with isoflurane sedation, the hazard ratio for death was 0.92 (95% CI, 0.49–1.73) and 1.10 (95% CI, 0.58–2.10) for BARC3a or higher bleeding, compared with controls.

The neurologic outcome, measured as CPC score at discharge from ICU, was not significantly different in both groups (p = 0.91) (**Fig. 5*A*** and Table 2). Furthermore, NSE levels at day 1–3 among patients with OHCA were indistinguishable between the conventional and isoflurane treatment group (**Fig. 5*B***).

Cost Analysis

In our institution, the overall sedation cost per patient was significantly lower in the conventional group in comparison with the isoflurane group (537 ± 624 vs 1,280 ± 837 €; $p < 0.001$) (Table 2).

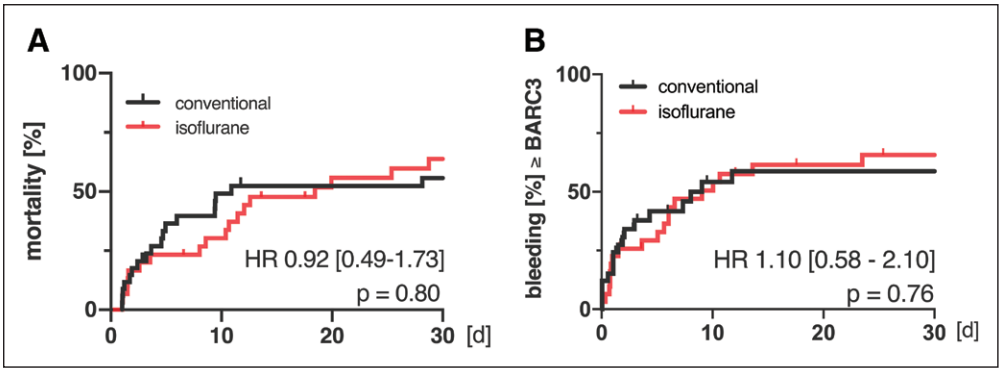

Figure 4. Mortality and bleeding of patients with cardiogenic shock and venoarterial extracorporeal membrane oxygenation treated with conventional IV versus isoflurane sedation. **A**, Cumulative incidence curves of deaths in conventionally (*black*) versus isoflurane (*red*) treated patients are shown for 30 d after the index event. **B**, Cumulative incidence curves of bleedings classified as bleeding academic research consortium 3a or higher in conventionally (*black*) versus isoflurane (*red*) treated patients are shown for 30 d after the index event. HR = hazards ratio.

DISCUSSION

In this retrospective analysis in CS patients treated with VA-ECMO, sedation with isoflurane was feasible, and no safety issue was detected compared with traditional, IV sedation. There was no significant difference in duration of ventilation, ICU stay, and catecholamine dosing. Regarding safety, we could not detect a difference of ischemic events, death, bleeding, and neurologic outcome.

To the best of our knowledge, no dedicated study so far has investigated the effect of isoflurane sedation in patients undergoing VA-ECMO treatment for CS. A study of OHCA patients without VA-ECMO showed that isoflurane sedation reduced ventilator time and the length of ICU stay (12). However, midazolam was used for sedation in the control group, which is known to significantly prolong ventilation time compared with propofol treatment (22). In contrast, other groups were unable to detect a difference in ventilator time and length of ICU stay in patients treated with isoflurane or propofol (13). In our study, there was no significant difference in ventilation time and duration of ICU stay between groups which also might be attributable to the possibility of propofol treatment in the control group. Nevertheless, the numerically longer duration of ICU stay in the isoflurane group might be explained by longer VA-ECMO treatment duration in this group. Although lactate clearance time was higher, numerically more patients achieved a lactate clearance in the isoflurane group which might be due to the higher mortality during the second week in the control group as demonstrated by Kaplan–Meier curve in Figure 3*A*. This could explain the difference in VA-ECMO treatment duration between both groups as well.

It is known that volatile anesthetics cause a dose-dependent decrease in blood pressure, presumably by decreasing systemic vascular resistance, myocardial contractility, and sympathetic function (23). Thus, administration of higher vasopressor doses was required in patients undergoing isoflurane sedation. In agreement with this finding, isoflurane sedation is associated with an increased IV noradrenalin use in patients (13). In contrast to prior studies (12, 22, 24), we could not detect any difference in catecholamine doses between isoflurane and conventional IV sedation in patients with VA-ECMO. In the aforementioned study, heart rate was increased in patients with volatile sedation presumably to compensate for a reduced blood pressure. In contrast, in VA-ECMO treated patients in our study, sedation with isoflurane on the contrary resulted in a significantly lower heart rate compared with conventional IV sedation. This is in line with an experimental study revealing a direct negative chronotropic effect of isoflurane on sinoatrial node pacemaker cells affecting a slow calcium current (25). There was no statistical difference between the two groups concerning ketamine use, which is known to cause tachycardia. A lower heart rate during VA-ECMO treatment might be beneficial for restoring cardiac function during severe CS as it was not associated with increased ECMO flow and catecholamine dosing in our study. However, this finding needs further investigation in the future.

Finally, we calculated higher costs for isoflurane sedation in our study which is caused by the expensive intensive daily exchange of a modified heat and moisture exchanger.

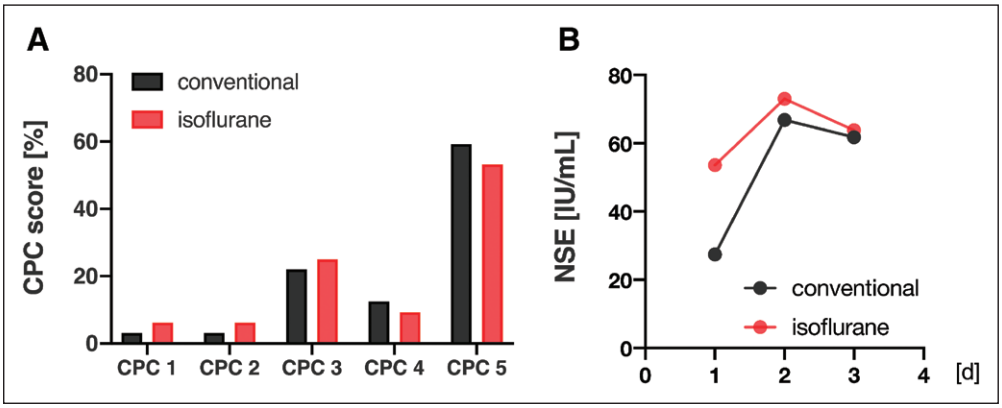

Figure 5. Neurologic outcome of patients with cardiogenic shock and venoarterial extracorporeal membrane oxygenation treated with conventional versus isoflurane sedation. **A**, Cerebral Performance Category (CPC) scores at discharge of patients with conventional (*black*) and isoflurane treatment (*red*). **B**, Median neuron-specific enolase (NSE) levels of conventionally and isoflurane treated patients 1–3 d after the index event.

This retrospective, observational, single-center analysis investigates volatile sedation with isoflurane in a small patient cohort, but it is the first analysis of this sedation approach in CS patients undergoing VA-ECMO treatment. We acknowledge that matching of groups from different treatment periods comes along with limitations inherent to such analysis. Differences between the two groups may not have been detectable due to the small sample size and the inherent heterogeneity of patients treated with VA-ECMO. Furthermore, matching of patients

can only decrease but not abrogate confounding factors, which may bias the results of this study.

CONCLUSIONS

Sedation in patients with CS remains an unresolved clinical issue with no available high-quality data on efficacy and safety of different sedation regimens including isoflurane treatment. Thus, randomized studies with sufficient patient numbers are needed to give high-level recommendations in future guidelines for acute heart failure. Based on the findings of our study, volatile sedation is feasible but more expensive in patients with CS and VA-ECMO treatment. However, differences between the isoflurane and the control group might not be detectable due to the small cohort size.

ACKNOWLEDGMENTS

We thank our nursing stuff for serving the critical ill patients every day.

Drs. Scherer, Kupka, and Stocker contributed equally to this article.

Dr. Orban received speaker honoraria from SedanaMedical and AstraZeneca, outside the submitted work; he received personal fees from Edward Life Sciences, outside the submitted work. Dr. Hausleiter received speaker honoraria and research support from Abbott Vascular and Edwards Lifesciences, outside the submitted work. The remaining authors declare no conflict of interests.

All ethical standards were met in writing and submitting this correspondence.

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