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ORIGINAL RESEARCH ARTICLE

Epinephrine administration in venoarterial extracorporeal membrane oxygenation patients is associated with mortality: a retrospective cohort study

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Abstract

Aims Knowledge about the impact of epinephrine on the outcome in venoarterial (VA) extracorporeal membrane oxygenation (ECMO) patients is limited, and existing data are conflicting.

Methods and results We conducted a retrospective cohort study in a 1500 bed tertiary university hospital. Five hundred and eighty-nine VA-ECMO patients were analysed. The median age was 57 years [47–65], 68% of male. The major indications for ECMO were post-cardiotomy cardiogenic shock (CS) (38%) and medical CS (36%). Two hundred and sixty-two (44.5%) patients received epinephrine alone or associated with another catecholamine while on ECMO. Baseline factors significantly associated with epinephrine administration were younger age, higher sequential organ failure assessment score, cardiac arrest at implantation, and intra-aortic balloon pump support at implantation, whereas medical CS and dobutamine administration were significantly associated with a lower risk of epinephrine administration. Epinephrine administration was independently associated with death [hazard ratio = 1.68 (1.44–2.23); $P < 0.01$]. A sensitivity analysis with propensity score inverse probability weighting in complete cases confirmed a significant association of epinephrine administration with death [hazard ratio = 1.69 (1.43–2.00); $P < 0.001$].

Conclusions Among patients who required VA-ECMO, epinephrine administration was associated with an increased risk for death.

Keywords Extracorporeal life support; Vasopressors; Inotropes; Catecholamines; Cardiogenic shock; Outcome

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Introduction

The European and US guidelines support the use of vasopressors, such as norepinephrine or epinephrine, to increase blood pressure and vital organ perfusion in cardiogenic shock (CS).[1,2] However, several recent studies have highlighted potential negative effects of epinephrine on survival or organ failure in patients with medical causes of CS.[3–5] In contrast, a recent meta-analysis of randomized trials did not find any worse outcome associated with the continuous administration of epi. nephrine in critically ill patients, including CS patients.[6]

Data on the use of epinephrine in extracorporeal life support are limited.[4,7] The inflammatory response observed after extracorporeal membrane oxygenation (ECMO) implantation is similar to that seen in inflammatory shock, a state where efficacy and safety of epinephrine administration were found

similar to the association of dobutamine and norepinephrine.[8,9] Others advocated a less detrimental effect of epinephrine in hearts with reduced wall stress and better coronary perfusion.[4] Therefore, the main goal of our study was to determine the impact of epinephrine administration on survival in a large cohort of venoarterial (VA) ECMO patients.

Methods

Setting and patients

We conducted a retrospective analysis of prospectively collected data, in accordance with the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study took place in a 1500 bed tertiary university hospital. All patients who had ECMO during their stay from the 1 January 2005 to the 31 December 2019 were screened from our institutional ECMO database, and only patients with VA-ECMO were included. However, patients supported with VA-ECMO for primary graft failure following heart transplant were excluded. Indications for VA-ECMO therapy included medical and surgical causes of refractory CS in whom satisfactory systemic perfusion (systolic artery pressure $>$ 80 mmHg, left atrial pressure $<$ 20 mmHg, cardiac index higher than 1.8 L/min/m^2) could not be achieved despite optimal intravascular volume status, high-dose inotropic medication (epinephrine $>$ 0.2 μg/kg/min or dobutamine $>$ 15 μg/kg/min with or without norepinephrine $>$ 0.2 μg/kg/min), and/or other support. Our study complied with the Declaration of Helsinki. Our database was approved by the French data protection authority: Commission Nationale de l'Informatique et des Libertés (CNIL, Reference 1685088, 25 July 2013). The need for written consent was waived because of the observational design.

Surgical procedure

The standard protocol for VA-ECMO implantation in our institution has been previously published.[10] Briefly, the implanting team included two surgeons (senior and resident), a scrub nurse, and a perfusionist. All required material was available on a dedicated trolley to allow ECMO implantation to be performed wherever required, including in the operative theatre, intensive care units, and catheterization room. Peripheral implantation through the femoral access was used when possible. In all peripheral VA cases, a reperfusion catheter was introduced to prevent limb ischaemia. VA-ECMO implantation was performed within the cardiac surgery operating theatre if the patient could be safely transported, but in case of unstable haemodynamics or cardiac arrest, implantation was performed bedside. Removal of the VA-ECMO cannula was performed in the operating theatre (except in case of death under support) to allow optimal vessel repair.

Outcome

The primary outcome of the study was mortality within 30 days of ECMO implantation.

Statistical analysis

Statistical analysis was performed with the statistical software R 3.4.3 and the Statistical Package for Social Sciences Version 25 (SPSS Inc., IBM, Armonk, New York). Categorical variables were described as number (percentage), and continuous variables as median and interquartile range. The χ^2 test and Fisher's exact test were used to compare categorical variables as appropriate. The Mann–Whitney *U* test and the Kruskal–Wallis test were used to compare continuous variables. All univariate analyses were performed on complete cases. Multivariable logistic regression analysis was used to study variables associated with the use of epinephrine. The primary analysis of 30 days of mortality was performed using a multivariable Cox model.

Overall, 3.1% of data were missing (11.7% of patients had at least one missing value). For the purposes of the Cox multivariable analysis, missing data were assumed to be random and were handled by multiple imputation using chained equations. Ten imputed datasets were created, and the results were pooled according to Rubin's rule[11] and were reported as adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs). All variables with a univariate association with the primary outcome at a *P*-value $<$ 0.20 level were included in the multivariable analysis.

Finally, to evaluate the robustness of the primary analysis, a sensitivity analysis with propensity score (PS) inverse probability weighting (IPW) was performed in the entire population in order to generate a weighted cohort in which baseline characteristic distributions were independent of epinephrine exposure.[12,13] PS calculation was based on variables associated with epinephrine administration and/or death with a *P*-value $<$ 0.20 in the univariate analysis.

All tests were two-sided, and a *P*-value $<$ 0.05 was considered statistically significant.

Results

Population

During the study period, a total of 744 patients required ECMO support in our institution for other reasons than heart transplantation, including 589 patients who required

VA-ECMO (*Figure 1*). The median age was 57 years [47–65]. The major indications for ECMO were post-cardiotomy CS (38%) and medical CS (36%). The median sequential organ failure assessment (SOFA) score on the day of ECMO implantation was 11 [9–12] (*Table 1* and Supporting Information, *Table S1*). One-hundred and sixteen patients (20%) were intubated for more than 24 h before ECMO implantation, but the median duration of mechanical ventilation before implantation was 0 days [0–1]. In the majority of patients (94%), ECMO was implanted peripherally (*Table 1*).

Factors associated with epinephrine administration

Of 589 included patients, 262 (44.5%) received epinephrine alone or associated with another catecholamine while on ECMO. Baseline factors significantly associated with epinephrine administration are displayed on *Table 2*. A younger age was associated with epinephrine administration [adjusted odds ratio (OR) = 0.98 per each supplementary year, 95% CI (0.97–1.00); $P < 0.01$]. Patients with higher severity as suggested by higher SOFA score [adjusted OR = 1.33 per each supplementary point, 95% CI (1.21–1.45); $P < 0.01$] or cardiac arrest at ECMO implantation [adjusted OR = 2.14, 95% CI (1.26–3.65); $P < 0.01$] had a higher risk to receive epinephrine. Although medical CS and dobutamine administration were associated with a lower risk of epinephrine administration [adjusted OR = 0.22, 95% CI (0.13–0.38) and adjusted OR = 0.38, 95% CI (0.23–0.65); $P < 0.01$ for both], intra-aortic balloon pump support at implantation was associated with an increased risk of epinephrine administration [OR = 2.66, 95% CI (1.53–4.64); $P < 0.01$].

Outcomes

Factors associated with death after Cox model multivariable analysis are displayed on *Table 3*. Epinephrine administration was significantly associated with death [adjusted HR = 1.68, 95% CI (1.44–2.23); $P < 0.01$] (*Figure 2*). Additionally, a sensitivity analysis with PS IPW was performed in complete cases, which confirmed a significant association of epinephrine administration with death [HR = 1.69, 95% CI (1.43–2.00); $P < 0.001$].

Other outcomes are reported on *Table 4*. More patients of the epinephrine group died from persistent CS, although the difference was not statistically significant (16% vs. 10%, $P = 0.06$).

Figure 1 Flow chart of study population. ECMO, extracorporeal membrane oxygenation.

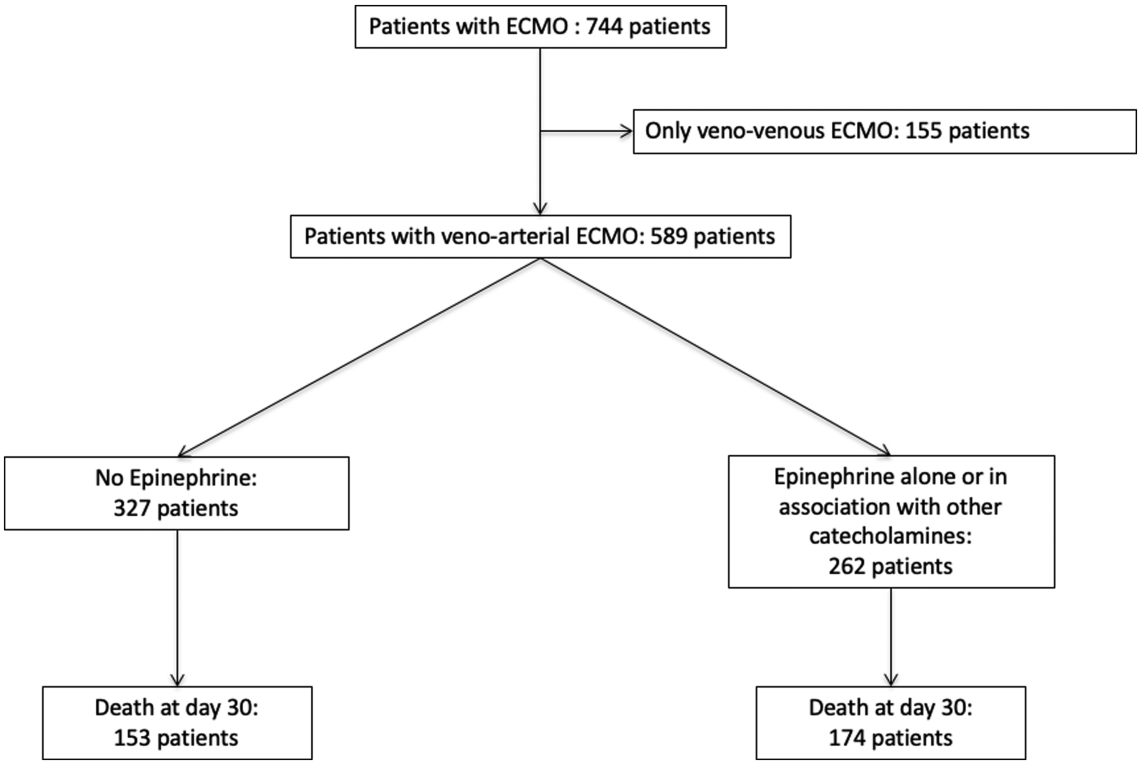

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Table 1 Baseline characteristics

Variables	All patients $n = 589$	Patients receiving epinephrine $n = 262$	Patients without epinephrine $n = 327$	*P*-value
Simplified acute physiology score II [IQR]	43 [33–59]	46 [35–63]	41 [31–53]	<0.01
Age, years [IQR]	57 [46–65]	55 [44–63]	58 [48–66]	<0.01
Male—no. (%)	402 (68)	178 (68)	224 (69)	0.95
Co-morbidities				
Diabetes—no. (%)	19 (3)	7 (3)	12 (4)	0.66
Arteriopathy—no. (%)	6 (1)	1 (0)	5 (2)	0.33
Hypertension—no. (%)	43 (7)	15 (6)	28 (9)	0.25
Reason for ECMO implantation				
Post-cardiotomy cardiogenic shock—no. (%)	221 (38)	98 (37)	123 (38)	1
Septic shock—no. (%)	3 (1)	1 (0)	2 (1)	1
Medical cardiogenic shock—no. (%)	212 (36)	79 (30)	133 (41)	0.01
Out of hospital cardiac arrest—no. (%)	80 (14)	47 (18)	33 (10)	<0.01
RV dysfunction during ARDS—no. (%)	16 (3)	7 (3)	9 (3)	1
Other support at ECMO implantation				
Intra-aortic balloon pump—no. (%)	102 (17)	53 (20)	49 (15)	0.12
Number of days with mechanical ventilation [IQR]	0 [0–1]	0 [0–1]	0 [0–1]	<0.01
Extra-renal epuration—no. (%)	35 (6)	23 (9)	12 (4)	0.02
Dobutamine—no. (%)	380 (66)	142 (55)	238 (74)	<0.01
Norepinephrine—no. (%)	377 (65)	163 (63)	214 (67)	0.37
Characteristics at ECMO implantation				
SOFA score [IQR]	11 [9–12]	11 [9–13]	10 [8–12]	<0.01
Cardiac arrest—no. (%)	151 (26)	90 (34)	61 (19)	<0.01
ECMO localization				
Central—no. (%)	36 (6)	16 (6)	20 (6)	1
Periphery—no. (%)	555 (94)	246 (95)	309 (95)	0.89
Central then periphery—no. (%)	4 (1)	1 (0)	3 (1)	0.63

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; RV, right ventricular; SOFA, sequential organ failure assessment.

Table 2 Baseline characteristics associated with epinephrine administration (logistic regression)

	Univariate			Multivariable		
Variables	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Simplified acute physiology score II	1.02	1.01–1.02	<0.01	1.00	0.99–1.02	0.42
Age	0.99	0.97–1	0.03	0.98	0.97–1.00	0.01
Male	0.9	0.62–1.3	0.57			
Co-morbidities						
Diabetes	0.85	0.32–2.27	0.75			
Arteriopathy	0.3	0.03–2.72	0.26			
Hypertension	0.75	0.38–1.46	0.39			
Other support at ECMO implantation						
Intra-aortic balloon pump	1.5	0.95–2.35	0.08	2.66	1.53–4.64	<0.01
Number of days with mechanical ventilation	0.99	0.94–1.04	0.65			
Extra-renal epuration	2.59	1.23–5.47	0.012	1.23	0.48–3.11	0.67
Dobutamine	0.36	0.25–0.53	<0.01	0.22	0.13–0.38	<0.01
Norepinephrine	0.75	0.52–1.07	0.11	0.43	0.26–0.70	0.12
Reason for ECMO implantation						
Post-cardiotomy	Ref	Ref	Ref	Ref	Ref	Ref
Septic shock	0.62	0.06–7.02	0.70	0.21	0.02–2.80	0.24
Cardiogenic shock	0.77	0.51–1.16	0.21	0.38	0.23–0.65	<0.01
Out of hospital cardiac arrest	1.93	1.09–3.40	0.02	0.52	0.23–1.19	0.12
RV dysfunction during ARDS	0.97	0.35–2.72	0.96	0.62	0.11–1.16	0.08
Characteristics at ECMO implantation						
SOFA score	1.13	1.06–1.21	<0.01	1.33	1.21–1.45	<0.01
Cardiac arrest	2.23	1.49–3.33	<0.01	2.14	1.26–3.65	<0.01
ECMO localization						
Central	0.78	0.36–1.7	0.53			
Periphery	1.12	0.51–2.49	0.78			
Central then periphery	0.4	0.04–3.92	0.43			

ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; OR, odds ratio; RV, right ventricular; SOFA, sequential organ failure assessment.

Table 3 Factors associated with death in full population (589 patients)

Variables	Number of patient with available data	Univariate analysis			Multivariable analysis		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Simplified acute physiology score II	527	1.02	1.01–1.03	<0.01	1.01	1.00–1.02	<0.01
Age	589	1.02	1.01–1.03	<0.01	1.02	1.01–1.03	<0.01
Male	589	0.96	0.76–1.21	0.72			
Co-morbidities							
Diabetes	589	1.15	0.63–2.10	0.65			
Peripheral artery disease	589	1.54	0.57–4.12	0.39			
Hypertension	589	1.41	0.97–2.05	0.07	0.98	0.66–1.47	0.93
Other support at ECMO implantation							
Intra-aortic balloon counter pulsation	589	0.89	0.67–1.19	0.44			
Number of days with mechanical ventilation	589	1.00	0.97–1.03	0.98			
Extra-renal epuration	589	1.64	1.09–2.47	0.02	1.15	0.70–1.88	0.59
Dobutamine	579	0.63	0.50–0.79	<0.01	0.78	0.59–1.02	0.07
Norepinephrine	579	1.13	0.89–1.43	0.30			
Reason for ECMO implantation							
Post-cardiotomy	532	Ref	Ref	Ref	Ref	Ref	Ref
Septic shock	532	1.09	0.53–2.22	0.82	1.45	0.38–5.61	0.58
Cardiogenic shock	532	3.44	0.91–12.99	0.07	0.98	0.74–1.30	0.89
Out of hospital cardiac arrest	532	1.01	0.49–2.07	0.98	0.98	0.64–1.49	0.93
RV dysfunction during ARDS	532	1.83	0.87–3.84	0.11	1.12	0.50–2.49	0.78
Characteristics at ECMO implantation							
SOFA score	589	1.01	0.97–1.05	0.63			
Cardiac arrest	589	2.19	1.74–2.76	<0.01	1.82	1.38–2.40	<0.01
ECMO localization							
Central	589	1.58	1.05–2.38	0.03	1.58	1.03–2.44	0.04
Catecholamine administration							
Epinephrine administration	589	1.79	1.44–2.23	<0.01	1.68	1.33–2.11	<0.01

ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; RV, right ventricular; SOFA, sequential organ failure assessment.

Discussion

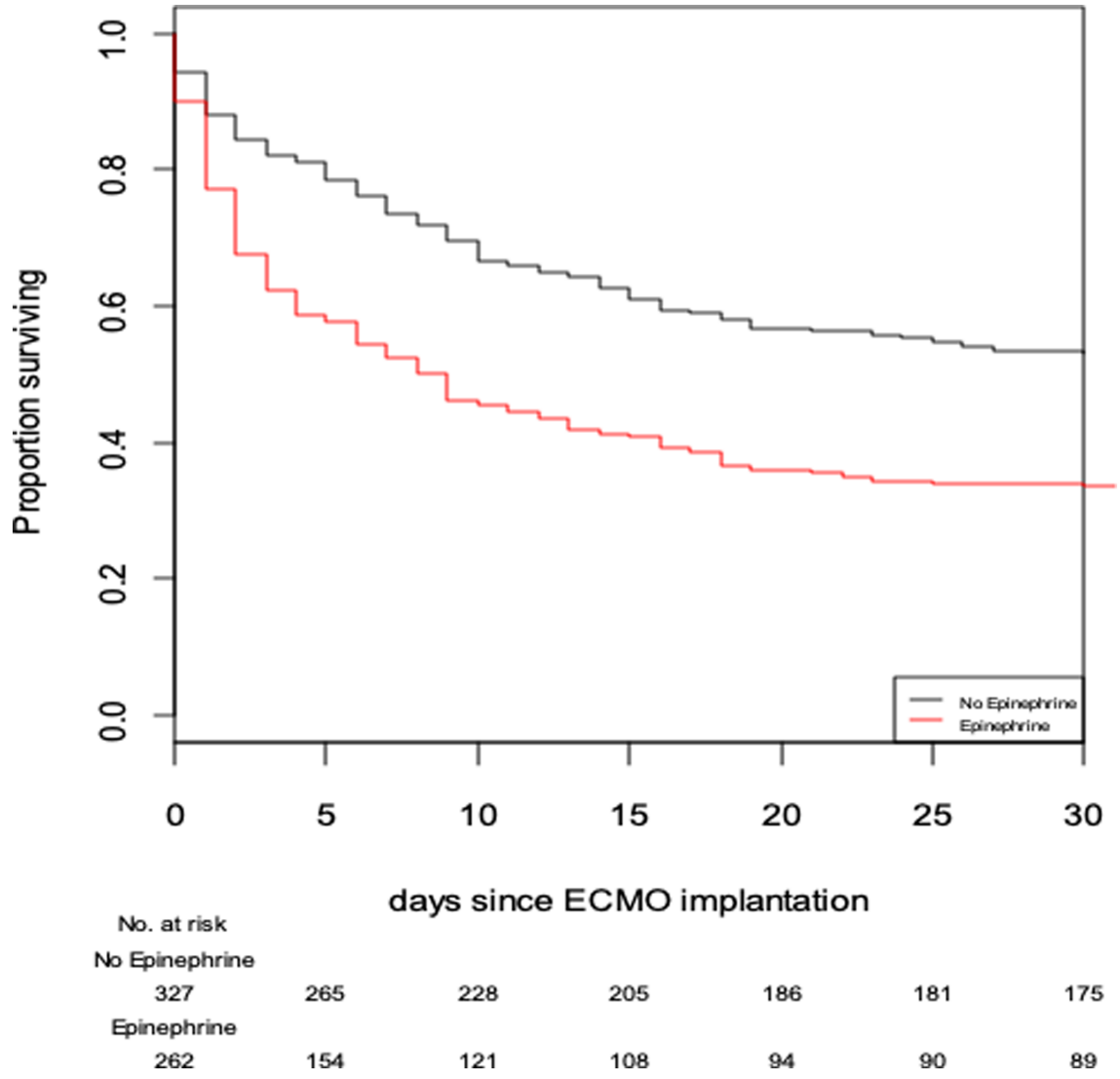
In this large single-centre observational study of 589 VA-ECMO patients, epinephrine administration was independently associated with an increased risk of death. A high proportion of VA-ECMO patients (44.5%) received epinephrine alone or associated with another catecholamine. Epinephrine use was associated with younger age, severity (higher SOFA score or cardiac arrest at implantation), and intra-aortic balloon pump support at implantation, whereas medical CS and dobutamine administration were associated with a lower risk of epinephrine administration.

The available data on epinephrine use in VA-ECMO are limited, and, to our knowledge only, one other study specifically compared the effects of epinephrine with other vasopressors in a VA-ECMO population. The authors compared the effect of epinephrine alone, epinephrine plus an inodilator (levosimendan and/or dobutamine), or no vasopressors, in 231 patients with VA-ECMO, implanted for CS or extracorporeal cardiopulmonary resuscitation.[7] As in our study, the authors found that the use of epinephrine with or without an inodilator was associated with increased 30 days of mortality. Of note, most of the patients received norepinephrine continuous infusion (90.5%).

The negative impact of epinephrine on survival has also been described in CS. The multinational CardShock study, which prospectively enrolled 219 patients with medical CS, demonstrated in several analyses using differing adjustment methods that epinephrine was independently associated with increased 90 days of mortality.[5] Moreover, an individual meta-analysis of 2583 CS patients found a significantly higher risk of short-term death in epinephrine-treated patients, and again this result was confirmed after adjustment on selected variables in a subset of 1227 patients and after PS matching of two sets of 338 patients.[4] Notably, in the same study, sensitivity analyses confirmed the association with a poor outcome in several subgroups, except in the small subgroup (n = 124) that benefited from extracorporeal life support therapy (defined as ECMO and left ventricular assist device in that study). The only double-blind multicentre randomized trial available compared the efficacy and safety of epinephrine versus norepinephrine for CS after acute myocardial infarction. When the vasopressor dose was adjusted to achieve equivalent cardiac index, epinephrine use was associated with a higher incidence of refractory CS. This preliminary finding led to early termination of the study, which included only 52 patients.[3] In contrast, a meta-analysis of randomized trials in critically ill patients, including the latter study, showed that continuous infusion of epinephrine was not associated with a worse outcome. However, most of the 1277 patients included in this study were septic shock patients (n = 677) with only 168 CS or cardiac surgery patients.[6]

Several mechanisms may explain the worse outcomes observed with the use of epinephrine in CS patients, supported

Figure 2 Survival curves for use of epinephrine with any catecholamine combination versus no epinephrine use (log-rank test). ECMO, extracorporeal membrane oxygenation.



by VA-ECMO or not. First, epinephrine infusion has been associated with an excess of myocardial work and myocardial oxygen consumption. Levy *et al*. found a significant increase of the double products (heart rate × systolic arterial pressure) and a higher heart rate during epinephrine infusion compared with the dobutamine–norepinephrine combination in CS from ischaemic aetiology or not.[3,14] Second, in the same studies, the authors found a transient increase in arterial lactate levels and tonometered PCO_2 gap (difference between gastric mucosal PCO_2 and arterial PCO_2), a surrogate of splanchnic perfusion adequacy. These results might reflect previously described epinephrine-related metabolic effects such as aerobic glycolysis or splanchnic thermogenic effects, but an excessive splanchnic vasoconstriction cannot be ruled out.[15,16] Moreover, epinephrine represses drug metabolism enzymes and induces a local inflammatory response via interleukin-6 production in human hepatocytes in primary culture and in the human HepaRG cell line, respectively.[17] Finally, epinephrine-related immune modulation might lead to immune paralysis with inhibition of tumour necrosis factor-α and an increase of interleukin-10 systemic productions,[18,19] as well as inhibition of nuclear factor-κB in monocytes[20] or down-regulation of toll-like receptors in macrophages.[21]

This study is, to date, the largest analysis evaluating the effects of epinephrine administration in VA-ECMO patients. The robustness of our results was challenged by the use of two differing adjustment methods, which produced comparable estimates of epinephrine treatment effect. However, our study does have several limitations. First, while the data were prospectively collected, this was a retrospective

Table 4 Outcomes

Variables	All patients $n = 589$	Patients receiving epinephrine $n = 262$	Patients without epinephrine $n = 327$	*P*-value
Length of ECMO support, days [IQR]	5 [2–9]	4 [1–8]	6 [3–10]	<0.001
Survivor at 30 days*	5 [2–9]	7 [4–10]	7 [4–10]	0.97
Length of vasopressor support, days [IQR]	6 [2–12]	5 [2–11]	7 [3–13]	0.006
Survivor at 30 days*	6 [2–12]	5 [8–15]	5 [8–13]	0.43
Length of stay in the ICU, days [IQR]	18 [11–33]	19 [12–35]	18 [10–31]	0.21
Thrombosis—no. (%)	316 (54)	146 (56)	170 (52)	0.25
Mesenteric ischaemia—no. (%)	23 (4)	12 (5)	11 (3)	0.59
Acute renal failure—no. (%)	244 (41)	115 (44)	129 (39)	0.32
Infection acquired during ECMO support—no. (%)	191 (32)	74 (28)	117 (36)	0.06
Death at Day 30—no. (%)	327 (55)	174 (66)	153 (47)	<0.001
Reason for death				
Persistent cardiogenic shock—no. (%)	74 (13)	41 (16)	33 (10)	0.06
Haemorrhage—no. (%)	12 (2)	3 (1)	9 (3)	0.28
Thrombosis—no. (%)	4 (1)	3 (1)	1 (0)	0.33
Mesenteric ischaemia—no. (%)	4 (1)	2 (1)	2 (1)	1
Neurologic complication—no. (%)	14 (2)	9 (3)	5 (2)	0.22
Infection acquired during ECMO support—no. (%)	10 (2)	4 (2)	6 (2)	1

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range.
*Among patients who survived at 30 days ($n = 269$, 174 patients without epinephrine and 88 receiving epinephrine).

observational analysis with its inherent limitations. Second, we acknowledge that sicker patients had higher chances to receive epinephrine, suggesting that this vasopressor could have been used as a rescue therapy in the most severely ill patients. However, a significant association between epinephrine administration and death was found after multivariable adjustment with a Cox model regression. The association held true after a second method of adjustment using PS with IPW. Although unmeasured confounding may persist despite statistical adjustment, our results suggest that the higher mortality observed among epinephrine recipients may not be solely explained by their more severe baseline profile. Third, some variables lacked granularity in the database such as 'medical CS', which included a wide range of ECMO indications. Finally, the single-centre design may also limit the generalizability of our findings.

In conclusion, epinephrine administration was associated with an increased risk of death in patients on VA-ECMO. These results support the findings of other recent studies that highlight possible detrimental effects of epinephrine in patients with CS. Together, these results support the need for a prospective randomized trial to address the optimum vasopressor strategy for patients on VA-ECMO.

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Conflict of interest

The authors declare that they have no competing interests.

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None.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Etiology of cardiogenic shock and association with death.

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