Early veno arterial PCO_2 difference is associated with outcome in peripheral veno arterial extracorporeal membrane oxygenation

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Abstract

Background: Veno arterial membrane oxygenation (VA ECMO) is increasingly used for cardiogenic failure. However, hemodynamic targets for adequate resuscitation remain a challenge. The PCO 2 gap and the ratio between PCO 2 gap and the arteriovenous difference in oxygen (PCO 2 gap/Da–vO 2) are marker of peripheral hypoperfusion. We hypothesized that the PCO 2 gap and the PCO 2 gap/Da–vO 2 ratio might be useful parameters in VA ECMO patients. Methods: We conducted an observational prospective study between September 2015 and February 2017. All consecutive patients >18 years of age who had been treated with peripheral VA ECMO for cardiac failure were included. We compared 2 groups of patients: patients who died of any cause under VA ECMO or in the 72h following VA ECMO weaning (early death group) - and patients who survived VA ECMO weaning more than 72h (surviving group). Blood samples were drawn from arterial and venous VA ECMO cannulas at H0 and H6. The ability of PCO 2 gap and PCO 2 gap/Da–vO 2 to discriminate between early mortality and surviving was studied using ROC curves analysis. Results: We included 20 patients in surviving group and 29 in early death group. The PCO 2 gap was higher in the early death group at H6 (7.4 [5.7–10.1] vs. 5.9 [3.8–9.2], p < 0.01). AUC for PCO 2 gap at H6 was 0.76 (0.61–0.92), with a cut-off of 6.2 mmHg. The PCO 2 gap/Da–vO 2 was higher in the early death group at H0 (2.1 [1.5–2.6] vs. 1.2 [0.9–2.4], p < 0.01) and at H6 (2.1 [1.3–2.6] vs. 1.0 [0.8–1.7], p < 0.01). AUC for PCO 2 gap/Da–vO 2 at H0 and H6 were 0.79 and 0.73 respectively; the cut-off value was 1.4. Conclusions: The PCO 2 gap and the PCO 2 gap/Da–vO2 ratio are associated with early death in patients who undergo VA ECMO.

Background

The use of veno arterial extracorporeal membrane oxygenation (VA ECMO) to manage cardiocirculatory failure is becoming more common. The main indications of the process include cardiogenic shock, refractory cardiac arrest (RCA), post-cardiotomy cardiac failure, and post-cardiac arrest syndrome [1–4]. However, VA ECMO is a complex technique, and hemodynamic monitoring with targets for adequate resuscitation remains a challenge in the absence of clear recommendations [5]. Ensuring adequate oxygen (regulation of flow rate and oxygenation) and perfusion pressure to organs are usually the main goals; these parameters have to be personalized depending on the patient's need. However, systemic hemodynamic parameters and oxygen metabolism markers do not always reflect adequate resuscitation [6]. The use of lactate as a marker of anaerobic metabolism has been widely described [7–8]. Lactate is used to guide therapy; it is also a prognostic marker during shock states [9–10]. However, lactate does not always reflect anaerobic metabolism, and confounding conditions are frequent: high lactatemia might result from reduced clearance (during liver or renal failure) or from the activation of glycolysis when high doses of adrenaline are administered [11–12]. The partial pressure gradient in CO_2 between the venous and arterial level or the PCO_2 gap has been used as a marker of peripheral hypoperfusion, particularly in septic and cardiogenic shock [13–15]. Recently, the ratio of the PCO_2 gap to the arteriovenous difference in oxygen (PCO_2 gap/Da–vO_2) has been described as a marker of anaerobic

metabolism. A PCO_2 gap/$Da–vO_2$ > 1 as a target was found to be more relevant than the use of the PCO_2 gap alone [16–17].

This study hypothesized that the PCO_2 gap and the PCO_2 gap/$Da–vO_2$ ratio might serve as parameters of adequate resuscitation in VA ECMO patients. Hence, the aim of the study was to evaluate the usability of the PCO_2 gap, the PCO_2 gap/$Da–vO_2$ ratio, and lactatemia as prognostic markers of mortality occurring during peripheral VA ECMO support or early after VA ECMO withdrawal, highlighting inadequate resuscitation or incomplete organ recovery.

Methods

Study type

This study used an observational, prospective monocentric design in the Surgical Intensive Care and Circulatory Support Unit of the University Hospital of Dijon, France between September 2015 and February 2017. As the samples were realized systematically following the standard protocols of care for patients benefiting from VA ECMO, no oral or written consent was required. The study was submitted to the Ethics Committee of the French Society of Anaesthesia and Critical Care and was authorized and registered under the number IRB00010252018179. In order to utilize the patients' information, and in compliance with the law on personal data protection (*Loi informatique et libertés*, 6 January 1978; modified in 2004), the study was submitted to the National Commission for Data Protection (CNIL); it gained authorization and was registered under the number 1855426 v 0.

Patients and VA ECMO protocol

All patients over 18 years of age who were treated using peripheral VA ECMO for refractory cardiogenic shock, refractory cardiac arrest (RCA), post-cardiotomy cardiac failure, and/or post-cardiac arrest syndrome were included in the study. Exclusion criteria included patients with a central or pulmonary artery VA ECMO, and patients who already benefited from VA ECMO prior to the present episode. In the study institution, peripheral VA ECMO support initiation is standardized and follows the usual standard of care, as previously described [18]. Patients were initially intubated and sedated with continuous infusion of propofol. VA ECMO cannulas were systematically positioned using transoesophageal echocardiography guidance. Venous cannula was positioned in the right atrium in order to drain the venous return form superior and inferior vena cava. Arterial cannula guidewire was visualized in the descending thoracic aorta prior to cannulation.

For patients who were stabilized under VA ECMO and who did not have residual organ hypoperfusion, sedation and mechanical ventilation weaning were initiated as soon as possible. Vasopressors were introduced when needed to maintain a minimal mean arterial pressure of 60 mmHg. Left ventricular

unloading was set up in the absence of arterial pulsatility. Lower leg with arterial cannula was monitored twice daily by the nurse in charge, with Doppler examination.

VA ECMO weaning was initiated when left ventricular ejection fraction > 20%, subaortic velocity time integral > 10 cm, right ventricular tricuspid annular systolic excursion > 17 mm, right ventricular end diastolic basal diameter < 35 mm, and arterial lactate level < 2 $mmol.L^{-1}$ with a VA ECMO pump speed ≤ 1500 RPM.

Study protocol

Baseline (H0) was set when the desired VA ECMO flow rate was reached. Blood samples were drawn from arterial (after the oxygenator) and venous (before oxygenator) VA ECMO cannulas after purging 5 mL of blood to perform blood gas analyses and to measure lactate concentration on the VA ECMO at H0, H6, and H24. Arterial blood samples were drawn form VA ECMO arterial line due to variation of arterial catheter position (radial or femoral). The syringes were pneumatically sent to the laboratory (ABL800, Radiometer, Copenhagen, Denmark). For each series of samples, pH, CO_2 partial pressure (PCO_2), oxygen partial pressure (PO_2), oxygen saturation (SaO_2), bicarbonates, and lactate concentration were collected. The venous saturation of the VA ECMO was considered as the venous saturation (SvO_2) of the patient. The PCO_2 gap was calculated as the difference between the venous partial pressure in CO_2 ($PvCO_2$) and the arterial partial pressure in CO_2 ($PaCO_2$):

$$PCO_2 \text{ gap (mmHg)} = PvCO_2 - PaCO_2 \quad (1)$$

Arterial oxygen content (DaO_2), venous oxygen content (DvO_2), and arteriovenous difference in oxygen content ($Da–vO_2$) were calculated using the following equations:

$$DaO_2 = SaO_2 \times Hb \times 1.34 + 0.0031 \times PaO_2 \quad (2)$$

$$DvO_2 = SvO_2 \times Hb \times 1.34 + 0.0031 \times PvO_2 \quad (3)$$

$$Da\text{-}vO_2 = DaO_2 - DvO_2 \quad (4)$$

The $PCO_2/Da–vO_2$ ratio was calculated as follows:

$$PCO_2 \text{ gap}/Da–vO_2 \quad (6)$$

For each patient, demographic data, SOFA score, SAPS II score, hemodynamic and ventilatory parameters (heart rate, systolic, diastolic and mean arterial pressure, tidal volume, positive expiratory pressure, and respiratory rate), vasopressor, inotropic doses, and VA ECMO parameters at each time point (flow rate, sweep gas flow, inspired fraction of O_2 [FIO_2]) were collected. Duration of VA ECMO, duration of intensive care unit (ICU) stays, and 28-day mortality were collected as outcomes.

Definition

Early mortality was defined as any death occurring under VA ECMO or in the 72 hours following VA ECMO weaning secondary to multiple organ failure. This led to two groups of patients: patients who died under VA ECMO or in the 72 hours following VA ECMO weaning (i.e., early death), and patients who survived VA ECMO weaning and beyond 72 hours (i.e., survival).

Study endpoints

The primary endpoint was the ability to use the PCO_2 gap to determine early mortality. The secondary end-points were the PCO_2 gap/Da–vO_2 ratio, SvO_2, the SOFA score, and the IGS II score. Overall mortality was also evaluated at 28 days.

Statistical analysis

The quantitative data are presented as medians and interquartile ranges; the qualitative data are presented as numbers and percentages. Appropriate parametric or non-parametric tests were also performed. Normality was assessed using the Shapiro–Wilk test. Bonferroni correction was applied to interpret the p-values of repeated measures. Kaplan–Meier curves were drawn for censored data, and log rank tests were carried out using the reported cut-off values of 6 mmHg for the PCO_2 gap [13] and 1.4 for the PCO_2 gap/Da–vO_2 ratio [16]. Retrospectively, the power to assess the PCO_2 gap difference observed between the two groups at H6 was 77%. Correlation was assessed using Spearman's method. ROC curves were drawn to represent the ability of the PCO_2 gap, the PCO_2/Da–vO_2 ratio, and lactatemia to discriminate early death. AUC and optimal cut-off were determined using Youden's method. Statistical analysis was performed with R Studio Version 1.0.143 (© 2009–2016 R Studio, Inc. from R version 3.5.0 Patched; 2018-05-03 r74699).

Results

Population

During the study period, 51 adults were admitted to the ICU for VA ECMO. Two patients with metformin intoxication were excluded due to the inability to interpret lactate concentration; therefore, data from 49 patients were analyzed (Fig. 1). The baseline characteristics are shown in Table 1. The median age was 59 years (IQR 47–71). A total of 29 patients were classified in the early death group (59%), 25 (89%) died during VA ECMO, and 4 (11%) died within three days of VA ECMO weaning secondary to multiple organ failure. Three patient died 72 h after VA ECMO withdrawal due to limitation of life support. Higher initial SOFA and SAPS II were associated with early mortality. Duration of VA ECMO was 4 (IQR 4–8) and 3 (IQR

2–6) days, respectively, for survival and early death patients ($p > 0.05$). The overall 28-day survival rate was 35%.

Table 1

Baseline Characteristics

Characteristic	All (n = 49)	Survival (n = 20)	Early death (n = 29)	p-value
Age (years)	56 (51–69)	56 (52–70)	56 (51–69)	0.91
BMI ($kg.m^{-2}$)	27 (26–30)	28 (26–30)	27 (26–30)	0.80
Gender (male)	38 (78%)	17 (85%)	21 (72%)	0.49
SOFA	13 (12–14)	12 (11–14)	14 (12–15)	0.01
SAPS II	68 (52–89)	54 (30–71)	83 (64–91)	< 0.01
MAP (mmHg)	74 (67–81)	77 (72–80)	73 (60–82)	0.20
Haemoglobin ($g.dl^{-1}$)	10.6 (9.1–12.6)	11.3 (9.4–13.3)	10.1 (8.8–11.4)	0.16
SaO_2 (%)	100 (99–100)	100 (99–100)	100 (99–100)	0.87
PvO_2 (mmHg)	54 (43–65)	44 (42–54)	57 (51–72)	0.01
PaO_2 (mmHg)	324 (221–383)	235 (157–327)	346 (273–393)	0.03
Heart rate (bpm)	92 (75–109)	99 (91–112)	86 (69–105)	0.07
Norepinephrine (%)	30 (67%)	16 (84%)	14 (54%)	0.03
Norepinephrine ($ug.kg^{1}.min^{-1}$)	0.18 (0–0.52)	0.20 (0.10–0.52)	0.10 (0–0.66)	0.26
Epinephrine (%)	30 (67%)	12 (63%)	18 (69%)	0.67
Epinephrine ($ug.kg^{-1}.min^{-1}$)	0.07 (0–0.14)	0.06 (0–0.13)	0.07 (0–0.17)	0.67
Dobutamine (%)	13 (29%)	6 (32%)	7 (27%)	0.73
Dobutamine ($ug.kg^{-1}.min^{-1}$)	0 (0–2.6)	0 (0–7.1)	0 (0–0.1)	0.69
Indications for VA ECMO (%)				0.61
Cardiac arrest	20 (41%)	6 (30%)	14 (48%)	
Pulmonary embolism	3 (6%)	1 (5%)	2 (7%)	

Data are given as medians (IQR) or as n (%). SOFA: sequential organ failure assessment; SAPS II: simplified acute physiology score; MAP: mean arterial pressure; SaO_2: arterial oxygen saturation; PvO_2: venous oxygen pressure; PaO_2: arterial oxygen pressure; VA ECMO: veno arterial extracorporeal membrane oxygenation.

Characteristic	All (n = 49)	Survival (n = 20)	Early death (n = 29)	p-value
Postcardiotomy	16 (33%)	9 (45%)	7 (24%)	
Cardiogenic shock	7 (14%)	3 (15%)	4 (14%)	
Drug intoxication	3 (6%)	1 (5%)	3 (7%)	
VA ECMO flow rate ($L.min^{-1}$)	4.1 (3.6–4.7)	4.0 (3.6–4.2)	4.1 (3.6–4.9)	0.26
VA ECMO indexed flow rate ($L.min^{-1}.m^{-2}$)	1.3 (1.2–1.5)	1.3 (1.2–1.4)	1.4 (1.2–1.6)	0.19
28-day mortality	32 (65%)	3 (15%)	29 (100%)	
Cause of death Limitation of life support Multiple organ failure		3 (15%) 0	0 29 (100%)	

Data are given as medians (IQR) or as n (%). SOFA: sequential organ failure assessment; SAPS II: simplified acute physiology score; MAP: mean arterial pressure; SaO_2: arterial oxygen saturation; PvO_2: venous oxygen pressure; PaO_2: arterial oxygen pressure; VA ECMO: veno arterial extracorporeal membrane oxygenation.

PCO_2 gap

The PCO_2 gap was significantly higher in the early death group at H6 (7.4 [5.7–10.1] vs. 5.9 [3.8–9.2], $p < 0.01$) (Table 2). Applying the corrected p-value of 0.017 (0.05/3) for repeated measurement using Bonferroni's correction, early mortality was associated with a higher PCO_2 gap only when measured at H6. Regarding the determinants of arterial oxygen content: PaO_2, SaO_2, and hemoglobin did not significantly differ at H6 (Additional file – Table 1). Moreover, VA ECMO flow did not differ between the two groups at H6 (3.8 [3.5–4.1] vs. 3.9 [3.1–4.7] $p = 0.43$) (Additional file – Table 1). At baseline, the PCO_2 gap was the only metabolic variable correlated with VA ECMO flow rate (Additional file – Table 2); this correlation was weak. Neither lactatemia nor SVO_2 were significantly associated with VA ECMO flow rate (Additional file – Table 2). Area under the ROC curve, used to discriminate between early death and survival, was 0.76 (0.61–0.92), with an optimal cut-off of 6.2 (Table 3). Using a 6 mmHg threshold, a higher PCO_2 gap at H0 and H6 was associated with early death (Fig. 2).

Table 2

Metabolic variables at baseline, 6 hours and 24 hours

Metabolic variables		All (n = 49)	Survival (n = 20)	Early Death (n = 29)	p-value
SvO_2 (%)	H0	80 (73–86)	74 (61–83)	82 (75–89)	0.03
	H6	72 (65–80)	72 (64–80)	72 (67–83)	0.68
	H24	74 (64–78)	73 (65–77)	74 (64–78)	0.72
PCO_2 gap (mmHg)	H0	6.1 (4.8–9.2)	5.3 (3.4–7.1)	6.8 (5.2–10.3)	0.06
	H6	5.9 (3.8–9.2)	4.6 (3.1–5.9)	7.4 (5.7–10.1)	< 0.01
	H24	5.1 (2.9–7.6)	3.8 (2.8–6.9)	6.1 (3.1–7.9)	0.55
Lactatemia	H0	8.7 (4.6–12.4)	6.2 (3.7–8.4)	10.9 (8.0-13.7)	< 0.01
($mmol.L^{-1}$)	H6	5.5 (3.9–9.2)	4.4 (3.5–5.3)	7.3 (4.8–11.4)	< 0.01
	H24	3.1 (1.8–4.9)	2.4 (1.5–3.2)	4.5 (2.4–7.7)	< 0.01
PCO2 gap / $D_{a-v}O_2$	H0	1.5 (1.2–2.3)	1.2 (0.9–1.4)	2.1 (1.5–2.6)	< 0.01
($mmHgx100ml.ml^{-1}$)	H6	1.8 (0.9–2.4)	1.0 (0.8–1.7)	2.1 (1.3–2.6)	< 0.01
	H24	1.3 (0.7–1.9)	1.0 (0.7–1.7)	1.6 (1.1–2.1)	0.23

Data are expressed as median (IQR). PCO_2 gap = Difference between arterial and venous partial pressure in carbon dioxide; SvO_2: venous oxygen saturation; $D_{a-v}O_2$: arterio-venous oxygen content difference;

Table 3
Area and cut-off for discrimination between early death and survival

Variables		AUC	Optimal cut-off
PCO_2 gap (mmHg)	H0	0.67 (0.49–0.84)	-
	H6	0.76 (0.61–0.92)	6.2
Lactatemia	H0	0.77 (0.63–0.91)	8.5
($mmol.l^{-1}$)	H6	0.79 (0.59–0.89)	5.8
PCO_2 gap/Da–vO_2	H0	0.79 (0.65–0.93)	1.4
(mmHg x 100 $ml.ml^{-1}$)	H6	0.73 (0.57–0.89)	1.4

PCO_2 gap: difference between arterial and venous partial pressure in carbon dioxide; Da–vO_2: arteriovenous oxygen content difference.

PCO_2 gap/Da–vO_2

The PCO_2 gap/Da–vO_2 was also higher in the early death group at baseline (2.1 [1.5–2.6] vs. 1.2 [0.9–2.4], $p < 0.01$) and at H6 (2.1 [1.3–2.6] vs. 1.0 [0.8–1.7], $p < 0.01$) (Table 2 and Fig. 2). The PCO_2 gap/Da–vO_2 was neither associated with VA ECMO flow rate at baseline nor at H6 (Additional file – Table 2). Using an ROC curve analysis to discriminate between early death and survival at H0 and H6, the area was respectively 0.79 and 0.73; the best cut-off value was 1.4 (Table 3). Using a 1.4 threshold, a higher PCO_2 gap/Da–vO_2 ratio at H0 and H6 was associated with early death (Fig. 2).

Other metabolic variables

Arterial lactatemia was higher in the early death group at H0, H6, and H24 (Table 2). Lactatemia was not associated with VA ECMO flow rate. Using ROC curve analysis, the area for discrimination between early death and survival at H0 and H6 was 0.77 and 0.74, respectively (Table 3). SvO_2 was not associated with early death.

Discussion

The main findings of the current study are that the PCO_2 gap and the PCO_2 gap/Da–vO_2 ratio between venous entry and arterial exit of VA ECMO were higher at H6 in the early death group than in the control group. In addition, patients with a PCO_2 gap > 6 mmHg at H6 had a higher rate of early death. Finally, the early death group had higher lactatemia at all sample times when compared with the control group.

Venous circulation to the lung transports the accumulation of CO_2 produced by aerobic or anaerobic metabolism at the capillary level, where the CO_2 is then eliminated. When cardiac output is inadequate,

CO_2 accumulates, and the PCO_2 gap increases.(15) Several studies support this association between low cardiac output and a PCO_2 gap > 6 mmHg, whether in mixed or central venous blood [19-22]. Indeed, the central PCO_2 gap (PCO_2c) is correlated with the PCO_2 gap [19,21, 23-27]. This progressive increase in the PCO_2 gap, which occurs below the critical arterial oxygen transport, is secondary to an accumulation of CO_2 produced during ischemic hypoxemia (due to decreased cardiac output). This increase in the PCO_2 gap was revealed in the isolated hind limb model by lowering DO_2 via decreasing flow, whereas with the same production of CO_2, lowering DO_2 by decreasing blood oxygenation, did not affect the PCO_2 gap [15]. The same increase in the PCO_2 gap related to decreased cardiac output was observed in animal models of cardiac tamponade and hemorrhagic shock [22, 27].

Finally, the relationship between low cardiac output and a high PCO_2 gap was evaluated in septic shock patients [13, 25]. A significantly lower cardiac output was found in patients with a PCO_2 gap > 6 mmHg. Furthermore, their fluid responders had a decrease in the PCO_2 gap after fluid challenge [24]. In the early phase of septic shock, a correlation between PCO_2c gap and cardiac output was observed [26]. Moreover, a high PCO_2 gap, or a PCO_2 gap that remains high, are predictors of death. Patients with a PCO_2 gap that is constantly > 6 mmHg, and those with an increasing PCO_2 gap, have shown higher rates of organ dysfunction and lower survival rates [28]. In patients with low lactate clearance, a high PCO_2c was indicative of an impaired perfusion despite a high cardiac output [29]. Hemodynamic optimization based on PCO_2 gap normalization could be a resuscitation objective in patients with septic shock when initial hemodynamic objectives are achieved [29-31]. In septic shock, despite adequate arterial oxygen transport and macrocirculatory optimization, the development of microcirculatory abnormalities might lead to organ hypoperfusion and death [32].

Microcirculatory disorders might explain the CO_2 accumulation and a high PCO_2 gap despite optimized cardiac output. Indeed, a sublingual microscopy study reported a high PCO_2 gap in patients with low percentages of small perfused vessels (PPV). However, no correlation was found between cardiac output and percentages of small perfused vessels or a PCO_2 gap, suggesting a relationship between PCO_2 gap and microcirculatory abnormalities [33]. In one study, microcirculatory abnormalities using sublingual microscopy were documented in 48 patients undergoing VA ECMO for cardiogenic shock. Because neither macrocirculatory parameters at 12 hours nor lactate levels or inotropic scores were associated with mortality, the study results suggest that microcirculatory impairment affects prognosis regardless of macrocirculation [34]. In the present study, a PCO_2 gap > 6 mmHg at H6 was associated with early death in patients under VA ECMO. This increase in PCO_2 gap associated with early death cannot be explained by insufficient VA ECMO flow rate, as the VA ECMO flow rates were similar in both groups, and no significant correlation was found between VA ECMO flow rate and the PCO_2 gap.

Venous and arterial CO_2 content difference was not measured in order to overcome the Haldane effect, which has been described as a potential cause of an increased PCO_2 gap [35]. **Moreover, calculating veno arterial CO_2 content difference is complex and can lead to mistakes and negative values** [36].

However, in this study, there was no significant difference in SvO_2, PO_2, or SaO_2 at H6. Finally, a high PCO_2 gap in the early death group might reveal microcirculatory dysfunction.

The study observed that the PCO_2 gap/Da–vO_2 ratio was higher at H0 and H6 in the early death group. In cellular hypoxia, the aerobic production of CO_2 decreases, whereas anaerobic production increases. The concomitant decreases in oxygen consumption result in an increased VCO_2/VO_2 ratio. The PCO_2 gap/Da–vO_2 ratio > 1.4 and lactatemia > 2 $mmol.L^{-1}$ are correlated, suggesting that the PCO_2 gap/Da–vO_2 ratio reflects anaerobic metabolism [16]. Furthermore, patients with a PCO_2 gap/Da–vO_2 ratio > 1.4 had a lower 30-day survival rate. The optimal cut-off calculated in this study perfectly matched the 1.4 cut-off described for critically ill patients without VA ECMO [16].

To the best of the present authors' knowledge, this study is the first to evaluate the PCO_2 gap and the PCO_2 gap/Da–vO_2 ratio in VA ECMO patients. Interestingly, the cut-off values for the PCO_2 gap and the PCO_2 gap/Da–vO_2 ratio found in the patients were similar to those reported in other studies. We focused only on early mortality as defined previously, in order to avoid any brain death and life support limitation. Our aim was to assess if PCO_2 gap or PCO_2 gap/Da-vO_2 was an early marker of insufficient VA ECMO flow or patient resuscitation, in the early phase of circulatory shock or insufficient cardiac recovery. Indeed, lactate level or clearance, which is a usual used marker of organ hypoxia, can remain high in case of hepatic or renal failure, and optimizing VA ECMO flow in order to achieve adequate organ perfusion can be challenging.

Several limitations must be underlined. First, this is a monocentric study, and only 51 patients were included. One of the limits of using the PCO_2 gap is the Haldane effect; however, as mentioned above, there was no significant difference in SvO_2, SaO_2, or PaO_2 at H6 after implementation of VA ECMO. Other limitations include anemia and hemodilution, but there was no difference in hemoglobin levels at H6 [36, 37]. The final limitation of the study is the absence of a measurement of patients' own cardiac output and CO2 removed by mechanical verntilation or spontaneous breathing, which would have enabled better interpretation of the results. One can hypothesize that patients with a high PCO_2 gap and PCO_2 gap/Da–vO_2 ratio are patients for whom ECMO VA flow rate plus native cardiac output will be insufficient to ensure the required cardiac output.

Conclusion

In summary, the PCO_2 gap and the PCO_2 gap/Da–vO_2 ratio are associated with early death in patients under VA ECMO. However, the meaning of these parameters is complex, and whether the PCO_2 gap should be considered as a hemodynamic goal for therapy or as an additional marker of patient severity is unclear. Prospective studies are warranted to determine if targeting the PCO_2 gap and the PCO_2 gap/Da–vO_2 ratio normalizations can increase the survival rates of VA ECMO patients.

Declarations

Ethics approval and consent to participate: N/A

Consent for publication: N/A

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions:

Study design: OE

Data acquisition: OE, MN

Data analysis: OE, MN, PGG, BB

Data interpretation: OE, MN, AM, MR, VB, SA, OB, PGG, BB

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Figures

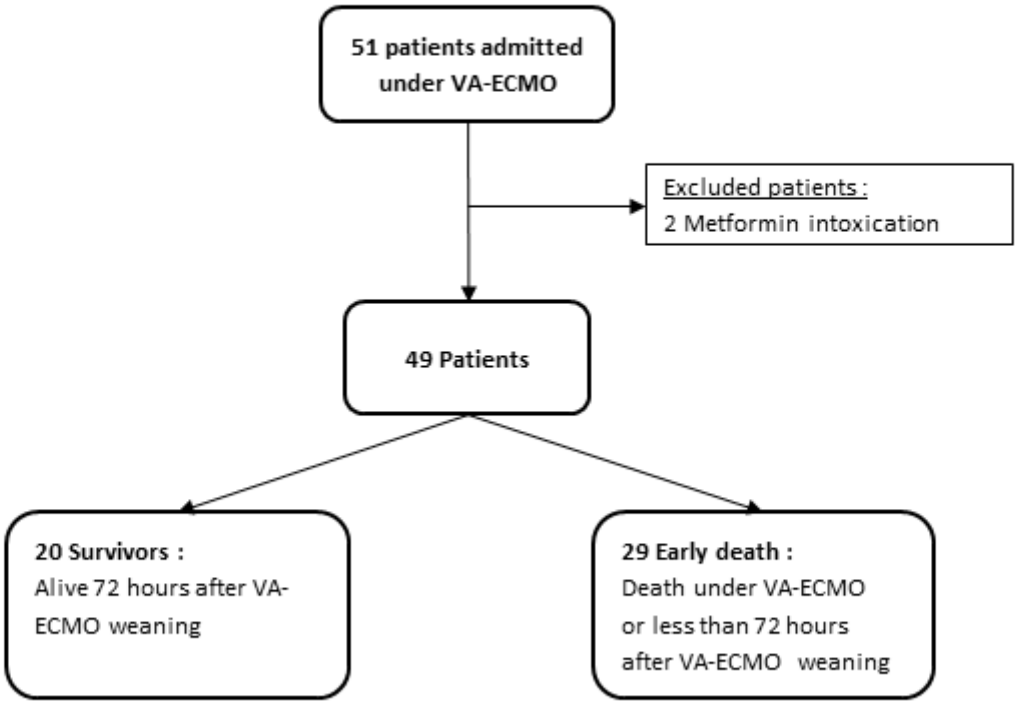

Figure 1

Flowchart of the study. VA ECMO: veno arterial extracorporeal membrane oxygenation

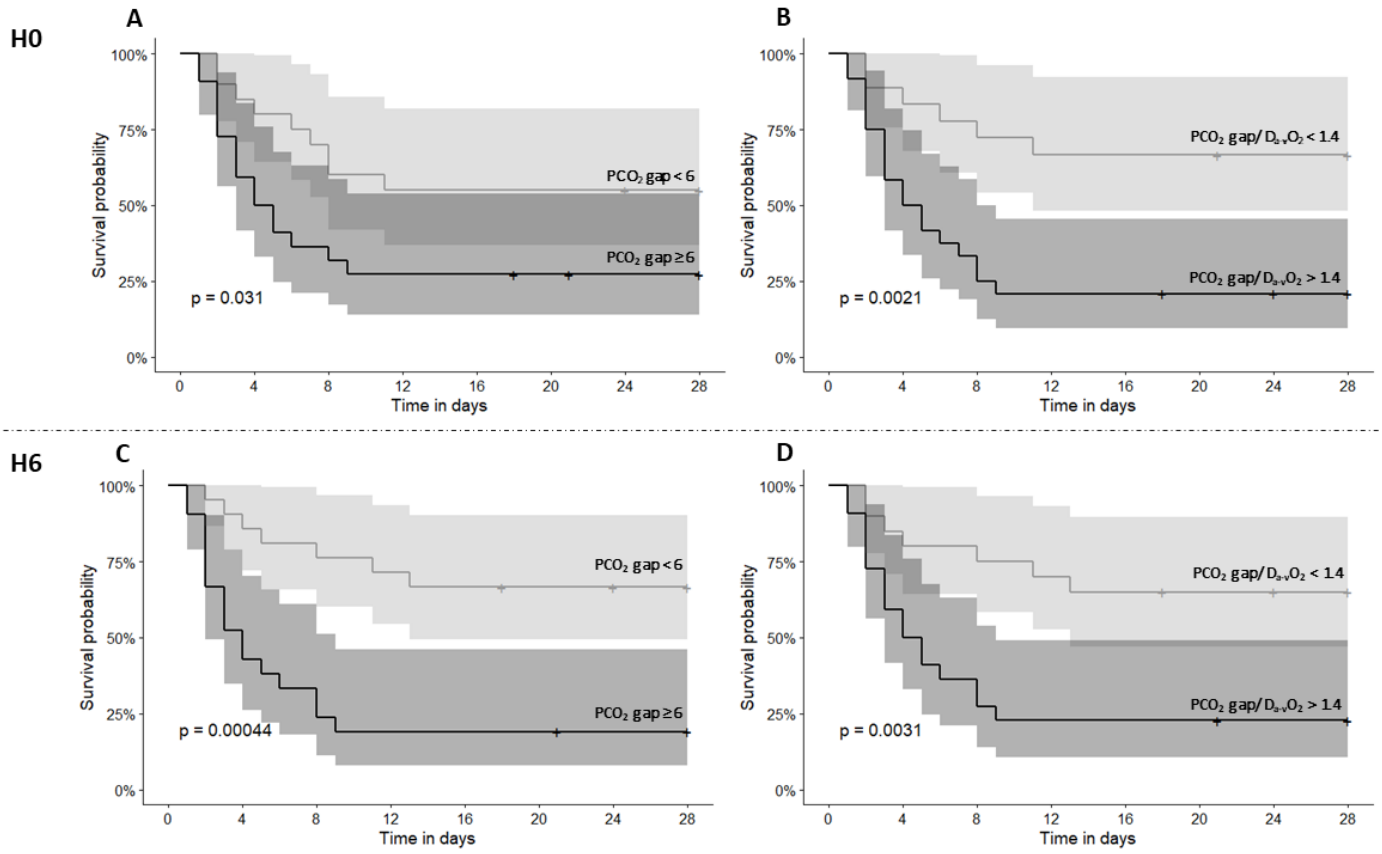

Figure 2

Kaplan–Meier curves for early mortality depending on PCO2 gap (6 mmHg threshold) and PCO2 gap/Da–vO2 ratio (1.4 mmHg x 100 ml/ml threshold) at H0 (A, B) and at H6 (C, D) PCO2 gap: difference between arterial and venous partial pressure in carbon dioxide; Da–vO2: arteriovenous difference in oxygen content.

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