Early veno arterial PCO₂ 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–vO$_2$ ratio are associated with early death in patients who undergo VA ECMO.

Key words: ECMO; cardiogenic shock; Pressure of CO2 (PCO2) gap
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 CO₂ between the venous and arterial level or the PCO₂ gap has been used as a marker of peripheral hypoperfusion, particularly in septic and cardiogenic shock [13-15]. Recently, the ratio of the PCO₂ gap to the arteriovenous difference in oxygen (PCO₂ gap/Da–vO₂) has been described as a marker of anaerobic metabolism. A PCO₂
gap/Da–vO₂ > 1 as a target was found to be more relevant than the use of the PCO₂ gap alone [16-17].

This study hypothesized that the PCO₂ gap and the PCO₂ gap/Da–vO₂ 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 PCO₂ gap, the PCO₂ gap/Da–vO₂ 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 from 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 \(\leq 1500\) 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 from 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$_2$):

$$ \text{PCO}_2 \text{ gap (mmHg)} = \text{PvCO}_2 - \text{PaCO}_2 $$

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:

$$ \text{DaO}_2 = \text{SaO}_2 \times \text{Hb} \times 1.34 + 0.0031 \times \text{PaO}_2 $$

$$ \text{DvO}_2 = \text{SvO}_2 \times \text{Hb} \times 1.34 + 0.0031 \times \text{PvO}_2 $$

$$ \text{Da–vO}_2 = \text{DaO}_2 - \text{DvO}_2 $$

The PCO$_2$/Da–vO$_2$ ratio was calculated as follows:

$$ \text{PCO}_2 \text{ gap/Da–vO}_2 $$

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 PCO₂ 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 PCO₂ gap, the PCO₂/Da–vO₂ 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 72h 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%.

PCO₂ gap

The PCO₂ 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 PCO₂ gap only when measured at H6. Regarding the determinants of arterial oxygen content: PaO₂, SaO₂, 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 PCO₂ 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).

**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 PCO₂ gap and the PCO₂ gap/Da–vO₂ 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 PCO₂ 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 CO₂ produced by aerobic or anaerobic metabolism at the capillary level, where the CO₂ is then eliminated. When cardiac output is inadequate, CO₂ accumulates, and the PCO₂ gap increases.(15) Several studies support this association between low cardiac output and a PCO₂ gap > 6 mmHg, whether in mixed or central venous blood [19-22]. Indeed, the central PCO₂ gap (PCO₂c) is correlated with the PCO₂ gap [19,21, 23-27]. This progressive increase in the PCO₂ gap, which occurs below the critical arterial oxygen transport, is secondary to an accumulation of CO₂ produced during ischemic hypoxemia (due to decreased cardiac output). This increase in the PCO₂ gap was revealed in the isolated hind limb model by lowering DO₂ via decreasing flow, whereas with the same production of CO₂, lowering DO₂ by decreasing blood oxygenation, did not affect the PCO₂ gap [15]. The same increase in the PCO₂ 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 PCO₂ 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$_2$c 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$_2$c 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 CO$_2$ removed by mechanical ventilation 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 PCO₂ gap and the PCO₂ gap/Da–vO₂ ratio are associated with early death in patients under VA ECMO. However, the meaning of these parameters is complex, and whether the PCO₂ 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 PCO₂ gap and the PCO₂ gap/Da–vO₂ 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

Manuscript preparation: OE, MN, PGG, BB

Manuscript revision: all authors

Final approval: all authors
REFERENCES

1. Abrams D, Combes A, Brodie D. Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. J Am Coll Cardiol 2014;63(25 Pt A):2769-2778
2. Dangers L, Brechot N, Schmidt M, et al. Extracorporeal Membrane Oxygenation for Acute Decompensated Heart Failure. Crit Care Med 2017;45(8):1359-1366
3. Ellouze O, Vuillet M, Perrot J, et al. Comparable Outcome of Out-of-Hospital Cardiac Arrest and In-Hospital Cardiac Arrest Treated With Extracorporeal Life Support. Artif Organs 2018;42(1):15-21
4. Pineton de Chambrun M, Brechot N, Lebreton G, et al. Venoarterial extracorporeal membrane oxygenation for refractory cardiogenic shock post-cardiac arrest. Intensive Care Med 2016;42(12):1999-2007
5. Doufle G, Ferguson ND. Monitoring during extracorporeal membrane oxygenation. Curr Opin Crit Care 2016;22(3):230-238
6. Puskarich MA, Trzeciak S, Shapiro NI, et al. Outcomes of patients undergoing early sepsis resuscitation for cryptic shock compared with overt shock. Resuscitation 2011;82(10):1289-1293.
7. Meakins J, Long CN. Oxygen Consumption, Oxygen Debt and Lactic Acid in Circulatory Failure. J Clin Invest 1927;4(2):273-293
8. Mizock BA, Falk JL. Lactic acidosis in critical illness. Crit Care Med 1992;20(1):80-93
9. Jansen TC, van Bommel J, Woodward R, et al. Association between blood lactate levels, Sequential Organ Failure Assessment subscores, and 28-day mortality during early and late intensive care unit stay: a retrospective observational study. Crit Care Med 2009;37(8):2369-2374
10. Puskarich MA, Trzeciak S, Shapiro NI, et al. Whole blood lactate kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. Chest 2013;143(6):1548-1553
11. James JH, Luchette FA, McCarter FD, et al. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. Lancet 1999;354(9177):505-508
12. Levraut J, Ciebiera JP, Chave S, et al. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 1998;157(4 Pt 1):1021-1026
13. Bakker J, Vincent JL, Gris P, et al. Veno-arterial carbon dioxide gradient in human septic shock. Chest 1992;101(2):509-515
14. Teboul JL, Mercat A, Lenique F, et al. Value of the venous-arterial PCO2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. Crit Care Med 1998;26(6):1007-1010
15. Vallet B, Teboul JL, Cain S, et al. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. J Appl Physiol (1985) 2000;89(4):1317-1321
16. Mekontso-Dessap A, Castelain V, Anguel N, et al. Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. Intensive Care Med 2002;28(3):272-277
17. Ospina-Tascon GA, Umana M, Bermudez W, et al. Combination of arterial lactate levels and venous-arterial CO2 to arterial-venous O2 content difference ratio as markers of resuscitation in patients with septic shock. Intensive Care Med 2015;41(5):796-805
18. Ellouze O, Lamirel J, Perrot J, et al. Extubation of patients undergoing extracorporeal life support. A retrospective study. Perfusion 2019;34(1):50-57
19. Cuschieri J, Rivers EP, Donnino MW, et al. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. Intensive Care Med 2005;31(6):818-822
20. Durkin R, Gergits MA, Reed JF, 3rd, et al. The relationship between the arteriovenous carbon dioxide gradient and cardiac index. J Crit Care 1993;8(4):217-221
21. Tsaousi GG, Karakoulas KA, Amaniti EN, et al. Correlation of central venous-arterial and mixed venous-arterial carbon dioxide tension gradient with cardiac output during neurosurgical procedures in the sitting position. Eur J Anaesthesiol 2010;27(10):882-889
22. Zhang H, Vincent JL. Arteriovenous differences in PCO2 and pH are good indicators of critical hypoperfusion. Am Rev Respir Dis 1993;148(4 Pt 1):867-871

23. Mallat J, Pepy F, Lemyze M, et al. Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. Eur J Anaesthesiol 2014;31(7):371-380

24. Mecher CE, Rackow EC, Astiz ME, et al. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. Crit Care Med 1990;18(6):585-589

25. Rackow EC, Astiz ME, Mecher CE, et al. Increased venous-arterial carbon dioxide tension difference during severe sepsis in rats. Crit Care Med 1994;22(1):121-125

26. van Beest PA, Lont MC, Holman ND, et al. Central venous-arterial pCO2 difference as a tool in resuscitation of septic patients. Intensive Care Med 2013;39(6):1034-1039

27. Van der Linden P, Rausin I, Deltell A, et al. Detection of tissue hypoxia by arteriovenous gradient for PCO2 and pH in anesthetized dogs during progressive hemorrhage. Anesth Analg 1995;80(2):269-275

28. Ospina-Tascon GA, Bautista-Rincon DF, Umana M, et al. Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. Crit Care 2013;17(6):R294

29. Vallee F, Vallet B, Mathe O, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? Intensive Care Med 2008;34(12):2218-2225

30. Jakob SM, Groeneveld AB, Teboul JL. Venous-arterial CO2 to arterial-venous O2 difference ratio as a resuscitation target in shock states? Intensive Care Med 2015;41(5):936-938

31. Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please "mind the gap"! Intensive Care Med 2013;39(9):1653-1655

32. De Backer D, Creteur J, Preiser JC, et al. Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 2002;166(1):98-104
33. Ospina-Tascon GA, Umana M, Bermudez WF, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med 2016;42(2):211-221
34. Yeh YC, Lee CT, Wang CH, et al. Investigation of microcirculation in patients with venoarterial extracorporeal membrane oxygenation life support. Crit Care 2018;22(1):200.
35. Teboul JL, Scheeren T. Understanding the Haldane effect. Intensive Care Med 2017;43(1):91-93
36. Dubin A, Ferrara G, Kanoore Edul VS, et al. Venoarterial PCO2-to-arteriovenous oxygen content difference ratio is a poor surrogate for anaerobic metabolism in hemodilution: an experimental study. Ann Intensive Care 2017;7(1):65
37. Dubin A, Estenssoro E, Murias G, et al. Intramucosal-arterial Pco2 gradient does not reflect intestinal dysoxia in anemic hypoxia. J Trauma 2004;57(6):1211-1217
FIGURE LEGENDS

**Fig. 1.** Flowchart of the study. VA ECMO: veno arterial extracorporeal membrane oxygenation

**Fig. 2.** Kaplan–Meier curves for early mortality depending on PCO$_2$ gap (6 mmHg threshold) and PCO$_2$ gap/Da–vO$_2$ ratio (1.4 mmHg x 100 ml/ml threshold) at H0 (A, B) and at H6 (C, D)

PCO$_2$ gap: difference between arterial and venous partial pressure in carbon dioxide; Da–vO$_2$: arteriovenous difference in oxygen content.