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CLINICAL STUDY

Comparison of PCO_2gap, SvO_2 and plasmatic lactate in patients on venoarterial extracorporeal circulation support

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ABSTRACT

BACKGROUND: Clinical assessment and laboratory markers provide valuable information on tissue perfusion and enhance the optimalisation of management in the treatment of patients on extracorporeal membrane oxygenation (ECMO). The PCO_2 gap is a reliable marker of cardiac output (CO) and perfusion. The aim of this study was to evaluate the PCO_2 gap as a marker of tissue hypoperfusion and to compare it to lactate and SvO^2.

METHODS: A single-center retrospective study on 131 adult cardiac patients who underwent ECMO implantation in the period between 2010 and 2021. Baseline characteristics, laboratory markers and mortality were analyzed.

RESULTS: There was a statistically significant difference in the plasmatic levels of lactate, SvO_2 and PCO_2 gap between patients that survived and those who died post ECMO implantation (3.6±3.29 vs 7.15±7.38 mmol/l, $p<0.001$; 69.13±9 vs 67.38±10%, $p<0.001$; 7.65±2.93 vs 8.34±3.71, $p<0.001$ respectively). There was a statistically significant difference in PCO_2 gap in the first 5 arterial blood gas (ABG) samples post ECMO implantation between patients that survived and those who died (9.08±4.79 vs 10.37±5.35, $p<0.003$). For SvO_2, this difference was not statistically significant (69.82±11.91 vs 68.51±11.72, $p<0.104$). There was a statistically significant but low negative correlation between SvO_2 and PCO_2 gap post ECMO implantation ($r = –0.354$, $p<0.001$).

CONCLUSION: The PCO_2 gap is a valuable biomarker for monitoring tissue perfusion in patients on ECMO. It is associated with increased mortality and should be an integral part of clinical evaluation. *(Tab. 1, Fig. 5, Ref. 26)*. Text in PDF *www.elis.sk*

KEY WORDS: PCO_2 gap, VA-ECMO, lactate.

Introduction

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides rapid biventricular and respiratory support for patients in critical condition with cardiocirculatory failure (1). Despite significant technical and medical advances, the rate of complications and mortality remains very high (2). Although the basic principle of ECMO is simple it is a complex technique requiring continuous monitoring and precise, thorough, and constant management.

One of the key goals of ECMO therapy is to provide adequate tissue perfusion and oxygenation, ideally maintaining oxygen delivery at a level exceeding at least three times the oxygen consumption (3).

Even perfusion with adequate cardiac index (CI) might not be sufficient for patients with increased metabolic demands and vasodilation, as for example due to sepsis (4).

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Clinical assessment and laboratory markers provide valuable information on tissue perfusion and enhance the optimalisation of management. Plasmatic lactate and venous saturation (SvO_2, central and mixed) are established markers of tissue perfusion in critical patients including those with ECMO support (5). They are independent predictors of morbidity and mortality while the maintenance of normal SvO_2 and lactate clearance is part of a goal-oriented therapy (6, 7). However, despite these advantages, there are clinical situations when they are unreliable and do not adequately correspond to the actual state of tissue oxygenation. SvO_2 is known to be unreliable in states with reduced O_2 extraction and hyperdynamic circulation. Lactate has very slow clearance dependent on hepatic function and perfusion, limiting its ability to monitor more dynamic changes. Moreover, high lactatemia can be also caused by reduced clearance (e.g., in renal or hepatic failure) or from glycolysis activation due to high-dose adrenalin administration (8).

PCO_2 gap is the difference between the partial pressure levels of CO_2 in venous and arterial blood. It has been both experimentally and clinically proven to be a reliable marker of cardiac output (CO) and perfusion. Moreover, the PCO_2 gap can detect low CO in normal SvO_2 (8).

The aim of this study was to evaluate the PCO_2 gap as a marker of tissue hypoperfusion and to compare it to plasmatic lactate and SvO_2 in patients on VA-ECMO.

Materials and methods

Study population

We designed a single-center retrospective study. The population consisted of 131 adult cardiac patients who underwent ECMO implantation at the National Institute of Cardiovascular Diseases in Bratislava, Slovakia in the period between 2010 and 2021. Patients were indicated for ECMO therapy for refractory cardiogenic shock, post-cardiotomy cardiac failure, post-cardiac arrest syndrome or refractory cardiac arrest.

Data collection and biochemical analysis

Patient data were acquired from the National Cardiosurgical Registry of the National Health Information Centre (NCZI) (www.nczi.sk). Laboratory parameters and additional patient information were acquired manually from the electronic health system Doctus (www.doctus.sk) of the Institute of Expertise and Education. Patients´ consent form was obtained to present this study.

Blood was taken from the arterial line and central venous catheter as a part of standard laboratory monitoring for patients in the intensive care unit (ICU). Samples were analyzed at the Department of Laboratory Medicine of the National Institute of Cardiovascular Diseases in Bratislava, Slovakia according to standard laboratory protocol.

ECMO implantation

Both central and peripheral cannulations were used in the study population.

In peripheral cannulation, a Seldinger technique with an intravascular guide was used. A distal perfusion cannula was used when signs of limb ischemia were present. Limb perfusion was monitored by near-infrared spectroscopy (NIRS).

In central cannulation, the right atrium and ascending aorta were cannulated.

CARDIOHELP(MAQUET Cardiopulmonary AG, Germany) system with a magnetic levitation centrifugal pump, polymethylpentene oxygenator, and a heparin-coated tubing were used.

The VA ECMO circuit was primed with isotonic saline solution containing 5,000UI of heparin. In the absence of contraindications (e.g., coagulopathy or major bleeding) a second dose of unfractionated heparin was administered to achieve activated clotting time (ACT) above 180 s. After successful cannulation, the initial flow was gradually increased to ensure adequate CI. Patients were continuously monitored (clinical status, hemodynamic parameters, laboratory parameters, regular echocardiographic and x-ray examinations, etc.) while the ECMO flow, fraction of inspired oxygen, and sweep gas flow rate were adjusted accordingly.

PCO_2 gap calculation

The PCO_2 gap was calculated as the difference between the levels of venous partial pressure of CO_2 ($PvCO_2$) and arterial partial pressure of CO_2 ($PaCO_2$): PCO_2 gap = $PvCO_2 - PaCO_2$ (mmHg)

Statistical methods

Continuous variables are presented as means with standard deviation whereas categorical variables are presented as percentages. Normality of data was tested using a Shapiro–Wilk test. Unpaired Student t-test and Mann–Whitney test were used to compare continuous variables as appropriate. chi-squared and Fisher's exact test were used to compare categorical variables as appropriate. Receiver operating characteristic (ROC) curves together with respective values of sensitivity, specificity, and accuracy at various cut-off levels of the selected parameter were calculated to evaluate the diagnostic performance. $p < 0.05$ was considered statistically significant. Data were analysed using StatsDirect statistical software version 3.2.10 (http://www.statsdirect.com), JASP statistical software (Version 0.14.1, JASP Team 2020 (https://jasp-stats.org) and Python version 3.10 (https://www.python.org) with appropriate libraries.

Results

Our study population included 40 (30.53%) females and 91 males (69.47%) with mean age of 58.05 (SD±11.73). The in-hospital survival was 27.48%. Study population characteristics are presented in Table 1.

There was a statistically significant difference in the plasmatic levels of lactate, central venous saturation and PCO_2 gap between patients that survived and those who died post ECMO implantation (3.6±3.29 vs 7.15±7.38 mmol/l, p<0.001; 69.13±9 vs 67.38±10%, p<0.001; 7.65±2.93 vs 8.34±3.71, p<0.001 respectively) (Fig. 1)

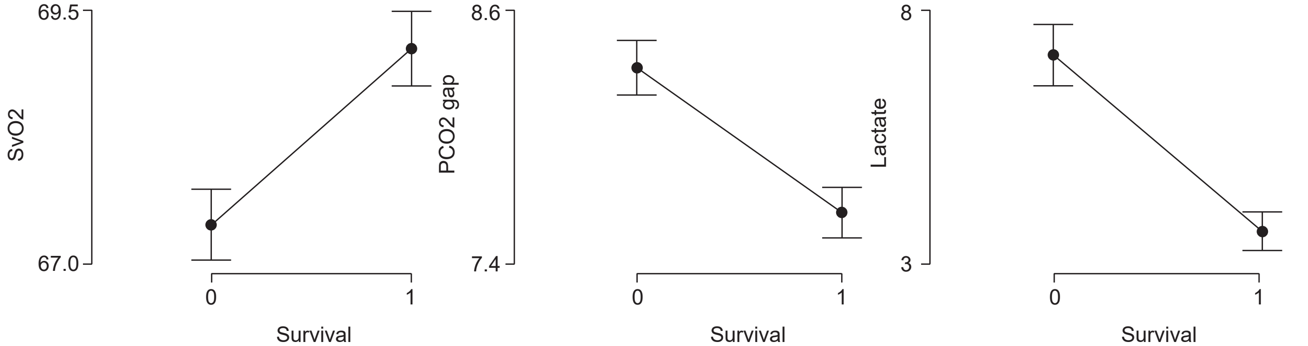

Fig. 1. Differences in SvO_2, lactate and PCO_2 gap in patients that survived and those who died on ECMO therapy.

There was a statistically significant difference in PCO_2 gap in the first 5 arterial blood gas (ABG) samples post ECMO implantation between patients that survived and those who died (9.08±4.79 vs 10.37±5.35, p<0.003) (Fig. 2). Mortality prediction based on PCO_2 gap from the first 5 arterial blood gas (ABG) samples post ECMO implantation showed very poor outcome prediction with receiver operating characteristic area under the curve (ROC ± AUC) of 0.58 (Fig. 3).

There was no statistically significant difference in SvO_2 in the first 5 ABG samples post ECMO implantation between patients that survived and those who died (69.82±11.91 vs 68.51±11.72, p<0.104) (Fig. 4).

There was a statistically significant but low negative correlation between SvO_2 and PCO_2 gap post ECMO implantation (r = –0.354, p<0.001) (Fig. 5).

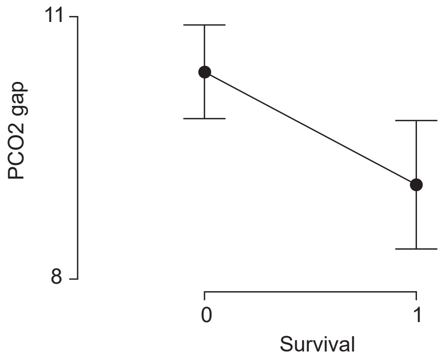

Fig. 2. Difference in PCO_2 gap between patients that survived and those who died in the first 5 ABG samples post ECMO implantation.

Tab. 1. Study population characteristics.

	Total (n=131)	Died during hospitalization (n=94)	Alive as at hospital discharge (n=37)	p
Age (years)	58.05±11.73	59.57±10.87	54.19±13.05	**0.025**
Male	91 (69.5%)	66 (70.2%)	25 (67.6%)	0.764
DM	26 (19.8%)	20 (21.3%)	6 (16.2%)	0.534
BMI	28.73±4.58	29.69±4.21	26.32±4.63	**<0.001**
Reoperation	22 (16.8%)	13 (13.8%)	9 (24.3%)	0.166
Hypertension	67 (51.1%)	51 (54.3%)	16 (43.2%)	0.265
Dyslipidaemia	57 (43.5%)	43 (45.7%)	14 (37.8%)	0.421
Hepatopathy	17 (12.9%)	15 (16.0%)	2 (5.4%)	0.106
Chronic dialysis	1 (0.7%)	1 (1.0%)	0	0.717
COPD	11 (8.4%)	9 (9.6%)	2 (5.4%)	0.477
Stroke	8 (6.1%)	6 (6.4%)	2 (5.4%)	0.880
PVD	6 (4.6%)	6 (6.4%)	0	0.130
Ejection fraction	38.38±16.54	38.62±16.24	37.78±17.48	0.850
Artificial respiration	21 (16.0%)	15 (16.0%)	6 (16.2%)	0.952
Pre-ECMO cardiac arrest	37 (28.2%)	29 (30.8%)	8 (21.6%)	0.301
Type of ECMO				
Veno-arterial (only)	93 (71.0%)	66 (70.2%)	27 (73.0%)	0.768
With LA/LV venting	20 (15.3%)	15 (16.0%)	5 (13.5%)	0.918
Mixed	18 (13.7%)	13 (13.8%)	5 (13.5%)	0.985
Indication for implantation				**0.003**
Acute myocardial infarction	19 (14.5%)	15 (16.0%)	4 (10.8%)	
Ventricular septal defect	4 (3.1%)	2 (2.1%)	2 (5.4%)	
Postcardiotomy syndrome	101 (77.1%)	76 (80.9%)	25 (67.6%)	
Acute HF/decompensation of CHF	7 (5.3%)	1 (1.0%)	6 (16.2%)	
Postoperative course				
Dialysis (%)	65 (49.6%)	51 (54.3%)	14 (37.8%)	0.096
Stroke (%)	15 (11.5%)	9 (9.6%)	6 (16.2%)	0.303
Sepsis (%)	8 (6.1%)	8 (8.5%)	0	0.064
Pneumonia (%)	9 (6.7%)	7 (7.4%)	2 (5.4%)	0.726
ECMO explantation (%)	70 (53.4%)	33 (35.1%)	37 (100%)	-
PRBC units per patient	15.43±13.77	15.09±13.18	16.29±15.30	0.945
FFP units per patients	6.85±7.85	6.90±8.04	6.70±7.44	0.631
PLT units per patient	3.15±4.16	3.35±4.31	2.64±3.79	0.200

IQ – interquartile range; DM – diabetes mellitus; BMI – body mass index; COPD – chronic obstructive pulmonary disease; PVD – peripheral vascular disease; ECMO – extracorporeal membrane oxygenation; LA – left atrium LV – left ventricle; HF – heart failure; CHF – chronic heart failure; PRBC – packed red blood cells; FFP – fresh frozen plasma; PLT – platelets

[a] Mixed – other mechanical circulatory support prior or post ECMO (LVAD, RVAD, BiVAD)

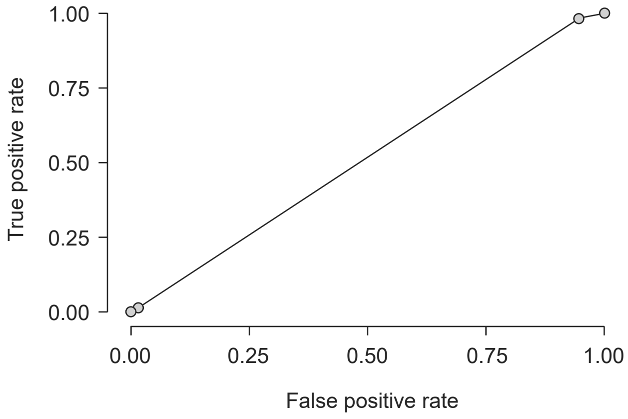

Fig. 3. ROC-AUC of PCO_2 gap from the first 5 ABG samples post ECMO implantation to predict survival.

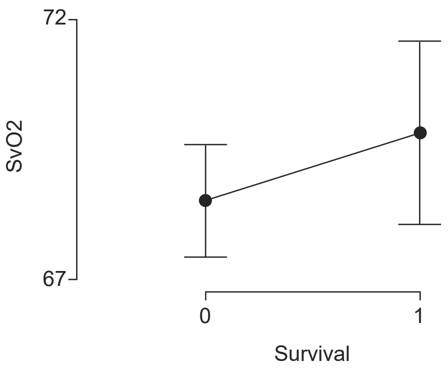

Fig. 4. Difference in SvO_2 gap between patients that survived and those who died in the first 5 ABG samples post ECMO implantation.

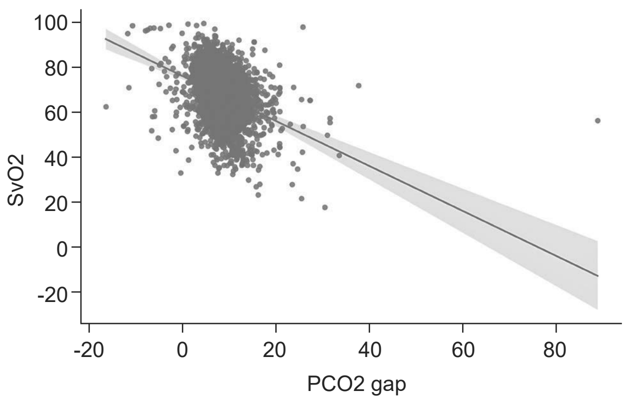

Fig. 5. Correlation between SvO_2 and PCO_2 gap.

Discussion

In our study population there was a statistically significant difference in the plasmatic levels of lactate, central venous saturation and PCO_2 gap post ECMO implantation between patients that survived and those who died. These results are in line with previously published research studies demonstrating a significant difference in these markers between patients who survived and those who died (9–11). Lactate is a metabolic product of anaerobic glycolysis formed by conversion of pyruvate by lactate dehydrogenase.

The plasmatic level of lactate is determined by the ratio of tissue production and hepatic clearance (12). Elevated lactate has been shown to correlate with increased risk of mortality in patients undergoing cardiac surgery as well as in patients on ECMO support (5, 6, 13). On the other hand, lactate clearance is relatively slow, which limits its utility to monitor rapid changes in tissue oxygenation. Moreover, elevated lactate levels can also be caused by reduced liver clearance, from glycolysis activation due to high dose adrenalin administration, and as a side-effect of cardiopulmonary bypass (type B hyperlactatemia) (6, 14). Venous oxygen saturation (SvO_2) measures the oxygen content of the venous blood returning to the right side of the heart. SvO_2 reflects inadequacy of systemic oxygenation when oxygen supply is insufficient to meet the metabolic demands of the tissues (15). Monitoring and maintaining optimal SvO_2 is a standard part of the treatment management in critically ill patients (16). Goal-oriented therapy in cases with cardiopulmonary bypass (CPB) targeting SvO_2 above 75% has been shown to improve short-term survival and decrease the risk of acute kidney injury (AKI) (7). However, SvO_2 is unreliable in hyperdynamic circulation, in conditions with reduced oxygen extraction in tissues, such as sepsis or in case of VV-ECMO due to recirculation (17). Moreover, several recent randomized trials have failed to show any survival benefit with early goal-oriented therapy based on SvO_2 monitoring (18). PCO_2 gap has been increasingly studied as a sensitive marker of tissue perfusion and poor outcome during circulatory shock. PCO_2 gap measures the difference between the levels of partial pressure of CO_2 in venous and arterial blood. It has been both experimentally and clinically proven to be a reliable marker of cardiac output (CO) and perfusion. Both central and mixed venous PCO_2 can be used for the calculation of the PCO_2 gap. Out of the three types of tissue dysoxia (stagnant, hypoxic or anemic, and cytopathic mechanism-based), the PCO_2 gap reflects only the stagnant type caused by inadequate cardiac output (8). Studies on animal models investigating the effects of either reduced blood flow or hypoxia demonstrated that PCO_2 gap changes only in stagnant and not in hypoxic conditions (19–22). Similarly, in an animal model and in a human case report with incidental poisoning, cytopathic dysoxia induced by high-dose metformin intoxication with mitochondrial defects comparable to cyanide poisoning showed no elevation in PCO_2 gap despite reduced VO_2 and severe lactate acidosis (23, 24).

In our study, the higher PCO_2 gap was associated with lower SvO_2 which is in line with the recent meta-analysis by Duhailib et al which included 21 studies with 2,155 patients hospitalized at ICU with shock and reported PCO_2 gap. On the other hand, the level of negative correlation was only low with r = –0.354. Although, both PCO_2 and SvO_2 reflect tissue hypoxia, each is results from a different pathophysiological pathway. Normal PCO_2 gap with low SvO_2 indicates anemic or hypoxic dysoxia, while elevated PCO_2 gap with low or normal SvO_2 indicates inadequate cardiac output with stagnant dysoxia, and normal PCO_2 gap with normal SvO_2 indicates cytopathic hypoxia (8).

Mortality prediction based on PCO_2 gap from the first 5 ABG samples post ECMO implantation showed very poor outcome prediction with AUC of 0.58. These results are in contradiction with a study conducted by Ellouze et al (11) which demonstrated relatively good predictive properties of PCO_2 gap measured early post-ECMO implantation with AUC of 0.76. However, besides a relatively small study population of 49 patients, the difference in PCO_2 gap was statistically significant only in one of the three investigated measurements. Moreover, this study investigated only a 72-hour survival post implantation. In our population, the survival rate was assessed for the entire duration of hospitalization period with an average of 27.34 days of follow-up ranging from 0 to 390 days. A similar study by McDonald et al (25) also demonstrated an increase in the risk of mortality with the increase in PCO_2 gap and anion gap. The prediction of 30-day mortality rate based on the PCO_2 gap scored AUC of 0.7, comparable to the results reported in the study conducted by Ellouze et al (11). On the other hand, a multivariate model based on PCO_2 gap and anion gap scored AUC of 0.89 (25). Although being also a relatively small retrospective study on 31 patients with cardiogenic shock, it indicates the potential of PCO_2 gap as a predictor of mortality for patients treated with ECMO, likely as a part of a multivariate scoring system. The SAVE-score is a tool to predict survival for patients receiving VA-ECMO for refractory cardiogenic shock. It is based on 16 clinical variables and was derived from a population of 3,846 patients with cardiogenic shock treated with ECMO. Although the external validation on an Australian population of 161 patients showed good AUC of 0.9, the original model scored only an AUC of 0.68 (26). An addition of PCO_2 gap to this scoring system could potentially further improve its diagnostic properties. The elevation in postoperative PCO_2 gap was associated with increased mortality and major complications after cardiac surgery, however, it showed only a limited diagnostic performance which is in line with the results of our study (8).

Study limitations

Our study had several limitations, notably being a single-center retrospective study, which may impact the generalizability of our findings. It is also difficult to extrapolate our results to the wider VA-ECMO population given the relatively low number of non-survivors and inclusion of both central and peripheral ECMO. Also, there were statistically significant differences in age, BMI and indication for implantation which could have affected the results since the pathophysiological mechanisms associated with shock caused by acute coronary syndrome, acute heart failure or post-cardiotomy syndrome differ.

Conclusion

PCO_2 gap is a valuable biomarker for monitoring tissue perfusion for patients on ECMO, it is associated with increased mortality, and should be a part of integrated clinical evaluation.

The role of PCO_2 gap as a predictor of mortality individually or preferably as a part of multivariate scoring system merits further research.

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