Central venous-to-arterial CO_2 difference is a poor tool to predict adverse outcomes after cardiac surgery: a retrospective study

La différence entre le CO2 veineux central et artériel est un outil médiocre pour prédire les devenirs défavorables après une chirurgie cardiaque : une étude rétrospective

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Abstract

Purpose *The venous-to-arterial carbon dioxide partial pressure difference (CO_2 gap) has been reported to be a sensitive indicator of cardiac output adequacy. We aimed to assess whether the CO_2 gap can predict postoperative adverse outcomes after cardiac surgery.*

Methods *A retrospective study was conducted of 5,151 patients from our departmental database who underwent cardiac surgery from 1 January 2008 to 31 December 2018. Lactate level ($mmol \cdot L^{-1}$), central venous oxygen saturation ($ScVO_2$) (%), and the venous-to-arterial carbon dioxide difference (CO_2 gap) were measured at intensive care unit (ICU) admission and on days 1 and 2 after cardiac surgery. The following postoperative adverse outcomes were collected: ICU mortality, hemopericardium or tamponade, resuscitated cardiac arrest, acute kidney injury, major bleeding, acute hepatic failure, mesenteric ischemia, and pneumonia. The primary outcome was the presence of at least one postoperative adverse outcome. Logistic regression was used to assess the association between $ScVO_2$, lactate, and the CO_2 gap with adverse outcomes. Their diagnostic performance was compared using a receiver operating characteristic (ROC) curve.*

Results *There were 1,933 patients (38%) with an adverse outcome. Cardiopulmonary bypass (CPB) parameters were similar between groups. The CO_2 gap was slightly higher for the "adverse outcomes" group than for the "no adverse outcomes" group. Arterial lactate at admission, day 1, and day 2 was also slightly higher in patients with adverse outcomes. Central venous oxygen saturation was not significantly different between patients with and without adverse outcomes. The area under the ROC curve to predict outcomes after CPB for the CO_2 gap at admission, day 1, and day 2 were 0.52, 0.55, and 0.53, respectively.*

Conclusion *After cardiac surgery with CPB, the CO_2 gap at ICU admission, day 1, and day 2 was associated with postoperative adverse outcomes but showed poor diagnostic performance.*

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Résumé

Objectif *La différence de pression partielle de dioxyde de carbone veineux versus artériel (gradient de CO_2) a été*

rapportée comme étant un indicateur sensible d'un débit cardiaque adéquat. Nous avons tenté d'évaluer si le gradient de CO_2 pouvait prédire les devenirs postopératoires défavorables après une chirurgie cardiaque.

Méthode *Une étude rétrospective a été réalisée en se basant sur les dossiers de 5151 patients issus de notre base de données départementale ayant subi une chirurgie cardiaque entre le 1er janvier 2008 et le 31 décembre 2018. Les taux de lactate ($mmol \cdot L^{-1}$), la saturation en oxygène veineux central ($ScVO_2$) (%), et la différence de dioxyde de carbone veineux versus artériel (gradient de CO_2) ont été mesurés lors de l'admission en réanimation (ICU) et aux jours 1 et 2 après la chirurgie cardiaque. Les complications postopératoires suivantes ont été colligées : mortalité en réanimation, hémopéricarde ou tamponnade, arrêt cardiaque récupéré, insuffisance rénale aiguë, saignements majeurs, insuffisance hépatique aiguë, ischémie mésentérique et pneumonie. Le critère d'évaluation principal était la présence d'au moins une complication postopératoire. La régression logistique a été utilisée pour évaluer l'association entre $ScVO_2$, taux de lactate et gradient de CO_2 et les complications. Leur performance diagnostique a été comparée à l'aide d'une courbe ROC (receiver operating characteristic).*

Résultats *Des complications sont survenues chez 1933 patients (38 %). Les paramètres de circulation extracorporelle (CEC) étaient semblables entre les groupes. Le gradient de CO_2 était légèrement plus élevé dans le groupe « complications » que dans le groupe « pas de complication ». Les taux de lactate artériels à l'admission, au jour 1 et au jour 2 étaient également légèrement plus élevés chez les patients ayant subi des complications. La différence de saturation en oxygène veineux central n'était pas significative entre les patients avec ou sans complications. L'aire sous la courbe ROC pour prédire les devenirs après la CEC pour le gradient de CO_2 à l'admission, au jour 1 et au jour 2 était de 0,52, 0,55 et 0,53, respectivement.*

Conclusion *Après une chirurgie cardiaque avec CEC, le gradient de CO_2 à l'admission en réanimation, au jour 1 et au jour 2 était associé aux complications postopératoires, mais sa performance diagnostique était médiocre.*

Over the last decades, cardiac surgery techniques have significantly improved, allowing increasingly complex procedures to be performed.[1] Multimodal management is key to improving outcomes after surgery.[2] Hemodynamic goal-directed therapy, including various treatments, relies on protocols that increase oxygen delivery by controlling blood pressure, the cardiac index, and central venous oxygen saturation. Individualized goal-directed hemodynamic optimization during high-risk surgery has been proven to improve morbidity and mortality.[3] This approach aims to adapt oxygen delivery to oxygen consumption to avoid tissue hypoperfusion during surgery.[4] Markers of adequate tissue perfusion (lactate, $ScVO_2$, and CO_2 gap) have their limitations. Hyperlactatemia does not always reflect tissue dysoxia or anaerobic metabolism and can be aspecific.[5] Central venous oxygen saturation ($ScVO_2$), used as a marker of dysoxia, can be normal despite microcirculatory impairment.[6]

Hence, the central venous-to-arterial CO_2 partial pressure difference (CO_2 gap) has been described as a parameter that reflects tissue hypoperfusion in insufficiently resuscitated critically ill patients.[7] Strong data support the necessity to monitor the CO_2 gap during the early phase of septic shock. Indeed, in patients with septic shock, a CO_2 gap > 6 mmHg and a normal $ScVO_2 > 70\%$ indicates a dependency on oxygen delivery with the need to pursue resuscitation.[8,9] In the latest guidelines on the monitoring of microcirculation, the CO_2 gap was recommended to manage septic shock in the early phase.[10]

In the perioperative settings of cardiac surgery, data are sparse and contradictory on CO_2 gap monitoring. The limits concern the small sample size, the very early postoperative time point of gap CO_2 assessment and the contradictory findings. Previous studies that evaluated the association between the CO_2 gap and outcomes of cardiac surgery patients showed poor diagnostic performance.[11,12] Thus, there is currently no clear position on the use of CO_2 gap monitoring in the postoperative period of cardiac surgery.

Thus, we aimed to investigate the association between the CO_2 gap and postoperative adverse outcomes in in a large retrospective cohort of patients who underwent cardiac surgery with cardiopulmonary bypass (CPB). Associations were measured at different times of the intensive care unit (ICU) stay.

Methods

Study population

All patients who underwent cardiac surgery from 1 January 2008 to 31 December 2018 in Amiens University hospital were included. The study was approved by the appropriate institutional review board, who waived the requirement for

written informed consent. The present report was drafted in line with the STROBE statement for observational studies in epidemiology.[13]

Data collection

We identified retrospectively all patients who underwent cardiac surgery at Amiens University hospital. Since 2007, the cardiothoracic unit of Amiens has had a computerized system (Centricity Critical Care Clinisoft®, GE Healthcare, Chicago, IL, USA) that collects all patient characteristics, surgery characteristics, and postoperative outcomes.

We extracted the following data from the Clinisoft database for each patient: age, sex, height (m), weight (kg), Simplified Acute Physiology Score (SAPS II), ICU stay (days), medical history (diabetes, hypertension, coronary disease characterized by the presence of a stent, peripheral vascular disease defined by the presence of a stent of bypass graft surgery in the lower limbs, chronic kidney disease defined as a glomerular filtration rate of < 60 mL·min^{-1}, and chronic obstructive pulmonary disease).

The following postoperative data for the first 48 hr were obtained from the same database: cumulative crystalloid infusion (mL), cumulative colloid infusion (mL), cumulative norepinephrine dose (mg), cumulative dobutamine dose (mg), and cumulative diuresis (mL).

Lactate, ScVO₂, and the CO₂ gap were measured at ICU admission and on days 1 and 2. Venous-to-arterial carbon dioxide difference on day 1 and day 2 was measured at the same time point in all patients.

Definitions of the postoperative outcomes

We collected the following data from our institutional database using the French classification for medical procedures "Classification Commune des Actes Médicaux" (CCAM). Each diagnosis (outcome) is associated with a unique diagnostic code number. Medical acts and diagnoses were coded in our database by the same physician. Each outcome was defined according to standard guidelines. For each diagnosis, computed extraction was performed by a request for the diagnosis code. Cardiac arrest was defined as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation. Acute kidney injury was defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine over 27 μmol·L^{-1} within 48 hr or urine output lower than 0.5 mL·kg^{-1}·hr^{-1} (KDIGO 1).[14] Mesenteric ischemia was defined by surgical abdomen exploration. Hemopericardium was defined in case of requirement for surgical/mediastinal revision. Major bleeding was defined

as requirement of more than four units of red blood cell transfusion. According to French guidelines, acute hepatic failure was defined as a prothrombin ratio under 50%.[15] Ventilator-acquired pneumonia was defined by the prescription of antibiotic therapy for a low respiratory infection.[16]

Outcome

The primary outcome was the presence of at least one postoperative adverse outcome during the hospital stay.

Statistical analysis

Data were collected on 5,928 patients during the study period. The present analysis was restricted to patients with cardiac surgery under CPB ($n = 5{,}151$). The demographic and clinical characteristics of the study participants of both groups were compared using the t-test for continuous variables and the χ2 test for discrete variables, as appropriate. A logistic regression model was used to evaluate the association between CO₂ gap/lactate and the outcome. We adjusted the model on differences in variables between "no outcome" and "adverse outcome" groups when the P value < 0.05. We built a receiver operating characteristic (ROC) curve to assess the diagnostic performance of arterial lactate, ScVO₂, and the CO₂ gap. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA). A $P < 0.05$ was considered significant.

Results

Study population

Between January 2008 and December 2018, 5,928 eligible patients were recorded in the database. Among them, 505 patients were excluded from analysis because of heart beating surgery, 165 because of minimal extracorporeal circulation, 25 because of CPB weaning requiring extracorporeal life support, and 82 because of a non-cardiac procedure under CPB. Five thousand one hundred and fifty-one patients were enrolled: 1,933 experienced adverse outcomes (38%) and 3,218 had no adverse outcomes (62%). The study flowchart is summarized in Fig. 1.

Baseline characteristics and surgical procedures for both groups are shown in Table 1. There were no difference in duration of CPB or aortic cross clamp between the two groups. In the "adverse outcomes" group, there were more cases of chronic kidney disease (8% vs 5%; $P < 0.0001$) and the mean (standard deviation) SAPS II were higher [41

Fig. 1 Flow chart. CPB = cardiopulmonary bypass; ECLS = extracorporeal live support; MECC = minimal extracorporeal circulation
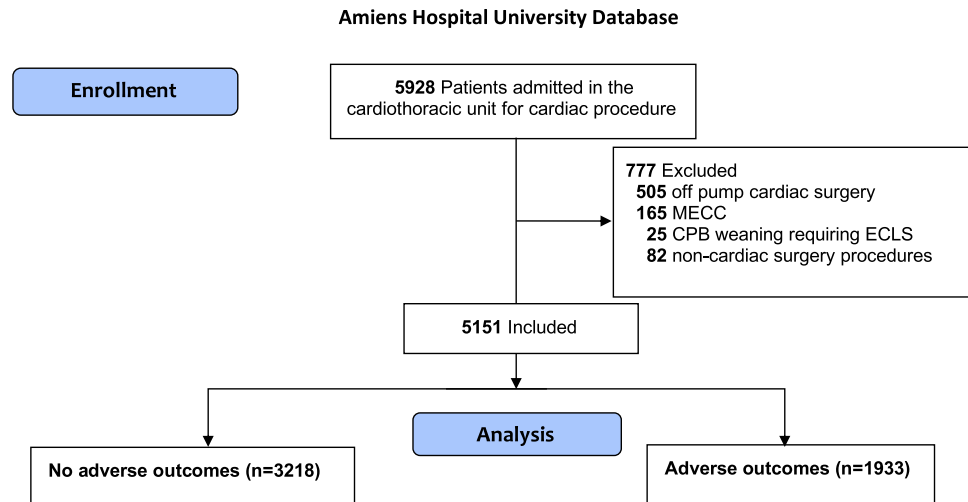
Amiens Hospital University Database

Enrollment

5928 Patients admitted in the cardiothoracic unit for cardiac procedure

777 Excluded
505 off pump cardiac surgery
165 MECC
25 CPB weaning requiring ECLS
82 non-cardiac surgery procedures

5151 Included

Analysis

No adverse outcomes (n=3218)

Adverse outcomes (n=1933)

TABLE 1 Demographics and intraoperative characteristics of the study population

Variables	No adverse outcomes (n = 3218)	Adverse outcomes (n = 1933)	P value
Age (yr)	66 (12)	68 (12)	0.21
BMI (kg·m^{-2})	28.8 (0.3)	28.2 (0.4)	0.25
Male, n (%)	2259 (70)	1289 (67)	0.01
Medical history, n (%)			
Diabetes	644 (20)	356 (18)	0.16
Hypertension	1772 (55)	1103 (57)	0.16
Coronary disease	367 (11)	− 12	0.35
Chronic kidney disease	84 (3)	151 (8)	< 0.001
Obesity	119 (4)	71 (4)	0.96
Vascular peripheral disease	149 (52)	121 (45)	0.01
Surgical type, n (%)			
CABG	1214 (38)	804 (42)	0.006
Valve surgery	1529 (47)	951 (49)	0.25
Combined surgery	475 (15)	178 (9)	0.002
SAPS II	34 (9)	41 (12)	< 0.001
Duration of CPB (min)	88 [62–119]	108 [73–145]	1
Duration of aortic clamp (min)	61 [42–86]	68 [45–99]	0.32

Data are expressed as mean (standard deviation), median [interquartile range], or numbers (percentages). BMI = body mass index, CABG = coronary artery bypass graft, CPB = cardiopulmonary bypass, SAPS = Simplified Acute Physiology Score

(12) *vs* 34 (9); $P < 0.001$]. Also, there were fewer males (67% *vs* 70%; $P = 0.01$), fewer cases of peripheral vascular disease (45% *vs* 52%; $P = 0.011$), and fewer cases of combined surgery (9% *vs* 15%; $P = 0.002$) in the "adverse outcome" group.

Association between ScVO$_2$, arterial lactate, and the CO$_2$ gap with adverse outcomes (Table 2, Fig. 3)

The CO$_2$ gap was slightly higher for the "adverse outcomes" group than the "no adverse outcomes" group. Arterial lactate at admission, day 1, and day 2 was also slightly higher in patients with adverse outcomes. Central venous oxygen saturation was not significantly different between patients with and without adverse outcomes. The area under the curve (AUC) to predict outcomes after CPB

TABLE 2 Association between perfusion parameters and adverse outcomes

Variables	No adverse outcomes (n = 3,218)	Adverse outcomes (n = 1,933)	P value
Arterial lactate (mmol·L^{-1})			
ICU	1.3 [1.1–1.7]	1.6 [1.2–2.2]	< 0.001
Day 1	1.7 [1.3–2.1]	2.1 [1.6–2.9]	< 0.001
Day 2	1.4 [1.1–1.7]	1.7 [1.3–2.2]	< 0.001
CO$_2$ gap (mmHg)			
ICU	7 [3–12]	7 [3–12]	0.01
Day 1	6 [3–10]	7 [3–10]	< 0.001
Day 2	8 [4–12]	9 [4–13]	< 0.001
ScVO$_2$ (%)			
ICU	65 [55–75]	65 [54–75]	0.26
Day 1	65 [57–72]	64 [57–72]	0.35
Day 2	65 [57–72]	64 [57–72]	0.35
Endpoints, n (%)			
Tamponade	–	316 (16)	–
Major bleeding	–	1270 (65)	–
Resuscitate cardiac arrest	–	141 (7)	–
Pneumonia	–	498 (25)	–
Mesenteric ischemia	–	100 (5)	–
Acute hepatic failure	–	285 (15)	–
AKI	–	628 (32)	–
Death	–	272 (14)	–
ICU stay (days)	2 (1)	10 (17)	< 0.001

Data are expressed as median [interquartile range IQR], mean (standard deviation), or numbers (percentages). AKI = acute kidney injury; CO$_2$ gap = venous-to-arterial carbon dioxide difference; ICU = intensive care unit. ScVO$_2$ = central venous oxygen saturation

for the CO$_2$ gap at admission, day 1, and day 2 were 0.52, 0.55, and 0.53, respectively.

Diagnostic performance of the CO$_2$ gap to predict adverse outcomes

The CO$_2$ gap was associated with postoperative adverse outcomes at ICU admission, on day 1, and on day 2. Odds ratios with 95% confidence intervals and AUCs are presented in Table 3. Receiver operating characteristic (ROC) curves for the CO$_2$ gap's diagnostic performance are presented in Fig. 2.

Diagnostic performance of arterial lactate and ScVO$_2$ to predict adverse outcomes

Arterial lactate was associated with postoperative adverse outcomes at ICU admission, on day 1, and on day 2. Central venous oxygen saturation was not associated with any major adverse outcomes after cardiac surgery. Odds ratios with 95% confidence intervals and AUCs are presented in Table 3. Receiver operating characteristic

curves showing the diagnostic performance of lactate and ScVO$_2$ are presented in Fig. 2.

Discussion

Our main finding was that the CO$_2$ gap has poor predictive characteristics for postoperative adverse outcomes in cardiac surgery. Arterial lactate showed better diagnostic performance. Microcirculatory dysfunction is known to be linked to organ failure, despite adequate macro-hemodynamic stability.[17] Markers of adequate tissue perfusion (lactate, ScvO$_2$, and the CO$_2$ gap) have their limitations.

Carbon dioxide production (oxygen consumption [VCO$_2$]) is proportional to O$_2$ consumption (VO$_2$): VCO$_2$ = R × VO$_2$, with R as the respiratory quotient. Thus, when aerobic metabolism increases, VCO$_2$ should increase to the same extent. The CO$_2$ content (CCO$_2$) cannot be easily calculated and in clinical practice, partial pressure of carbon dioxide (PCO$_2$) is expressed as PCO$_2$ = k x CCO$_2$, where k is a correction factor related to temperature,
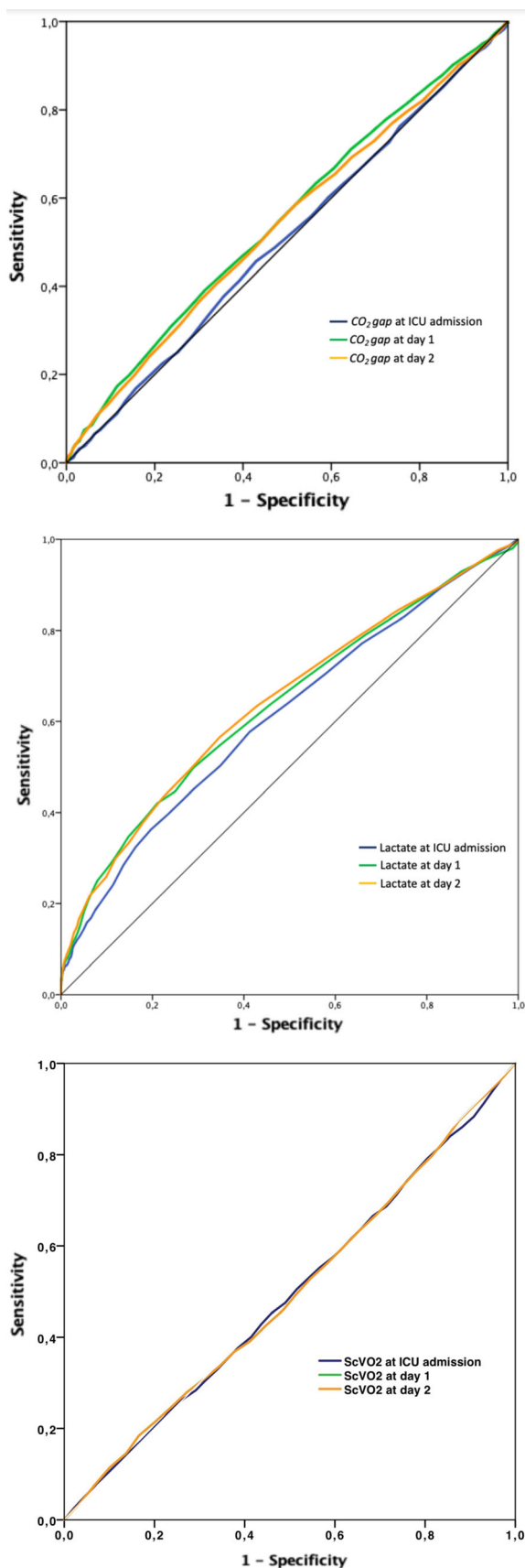
anemia, hypoxia, and other metabolic factors. Derived from the Fick equation, VCO_2 can be expressed as $VCO_2 = CO \times CO_2$ gap and thus the CO_2 gap as $(k \times VCO_2)/CO$.[18] The CO_2 gap is not a good marker of global anaerobic metabolism as in hypoxia, VCO_2 can decrease as a result of the decrease in VO_2 and increase in the k factor.[19] The CO_2 gap is rather a marker of CO than a marker of tissue hypoxia.[20] The variables involved in calculating the CO_2 gap can vary depending on the clinical situation, resulting in divergence between non-cardiac surgery, cardiac surgery, and critically ill septic patients.[21]

In septic shock, the CO_2 gap has been shown to be a reliable marker of the cardiac index and has been proposed to guide early resuscitation.[8,9] Numerous studies have suggested a role for the CO_2 gap in identifying patients with a $ScVO_2 > 70\%$ who are still inadequately resuscitated.[18,22,23] Thus, European guidelines on septic shock management propose using the CO_2 gap to guide hemodynamic management during septic shock.[10] The CO_2 gap increases during ischemic hypoxia (decrease in blood flow) but not under hypoxic hypoxia conditions (normal or high blood flow),[8,24] and the use of the CO_2 gap to assess microcirculatory flow and the hypoxic state is still a matter of debate.[25] Non-cardiac surgery studies have reported similar findings as for septic shock, showing that the CO_2 gap can predict the occurrence of adverse postoperative outcomes.[26,27]

Clinical studies on the CO_2 gap in cardiac surgery have shown contradictory results. First, interpretations of results depend on the author. Moussa et al. concluded a positive result of the CO_2 gap with an AUC of 0.64 whereas Guinot et al. concluded a negative result with a similar AUC.[11,12] In contrast, recent studies reported good performance of the CO_2 gap in predicting adverse outcomes after cardiac surgery. Mukai et al. found an AUC of 0.80, with a cut-off of 5.2 mmHg[29] and Chen et al. found an AUC of 0.84 with a cut-off of 7.1.[29]

Several factors can explain the discrepancy between positive and negative studies. First, authors' interpretations differ from one publication to another. Biomarkers are considered to have good discriminative properties when the AUC is higher than 0.75. Therefore, an AUC under 0.75 should be considered to have low clinical relevance and not a positive result.[30] Secondly, selected outcomes vary from one study to the other, making the external validity more

TABLE 3 Association of the CO_2 gap, arterial lactate, and $ScVO_2$ with major outcomes and area under the curve for diagnostic to predict major adverse outcomes after cardiac surgery

Variables	OR (95% CI)	P	AUC
CO₂ gap			
ICU admission	1.01 (1.00 to 1.02)	0.01	0.52
Day 1	1.04 (1.03 to 1.05)	< 0.001	0.55
Day 2	1.03 (1.02 to 1.04)	< 0.001	0.53
Arterial lactate			
ICU admission	1.85 (1.70 to 2.11)	< 0.001	0.63
Day 1	1.84 (1.70 to 2.00)	< 0.001	0.65
Day 2	2.26 (2.02 to 2.53)	< 0.001	0.65
ScVO₂			
ICU admission	1.00 (0.998 to 1.00)	0.26	0.49
Day 1	1.00 (0.997 to 1.01)	0.36	0.49
Day 2	1.01 (0.996 to 1.02)	0.36	0.49

Multiple regression was used and adjustment was performed on male sex, chronic renal disease, SAPS II, and surgical intervention type. Data were expressed as odds ratios with 95% confidence intervals. Areas under the curve (AUCs) are expressed as proportions. Commonly-used diagnostic AUCs are: greater than 0.9 indicates high accuracy, 0.7–0.9 indicates moderate accuracy, 0.5–0.7 indicates low accuracy, and 0.5 indicates a chance result

AUC = area under the curve; CI = confidence interval; CO_2 gap = venous-to-arterial carbon dioxide difference; ICU = intensive care unit; OR = odds ratio; SAPS = simplified acute physiology score;. $ScVO_2$ = central venous oxygen saturation

complicated. Finally, time point measurements may differ and this may account for these differences.

The heterogeneity of the findings between cardiac surgery and sepsis can be explained by possible changes in the relationship between PCO_2 and CO_2 content over time during cardiac surgery with CPB, thus altering the interpretation of the CO_2 gap.[31,32] The k factor (which defines the relationship between PCO_2 and CCO_2) depends on the state of hypoxia, hematocrit, temperature, and anemia.[33–35] These factors are all in play during cardiac surgery, so the CO_2 gap may not reflect the CCO_2. For example, the k factor increases in tissue hypoxia, increasing the CO_2 gap, even if the veno-arterial difference in CCO_2 does not change. According to Ruokonen *et al.*, an increase in the CO_2 gap is frequent after cardiac surgery and better reflects alterations in systemic and regional perfusion than tissue hypoxia.[36] Hemodilution was investigated by Dubin *et al.* and changes in the CO_2 gap were explained by a rightward shift of the relationship between PCO_2 and CCO_2.[37] Thus, the CO_2 gap increases as the cardiac index decreases or as CO_2 production increases. This explanation requires that homogeneous perfusion reflect total CO_2 production, which is only partially true during cardiac surgery. It has been shown that CPB induces capillary shunting, resulting in heterogeneous organ perfusion.[31,38] Disturbances in organ perfusion and metabolic changes induced by CPB likely interfere with the ability of the CO_2 gap to detect tissue hypoxia.

Our study had several major limitations. Data on the cardiac index would have been valuable to confirm that it was not low and to provide a more complete interpretation of our results, particularly regarding the significant association with the CO_2 gap but not with the $ScVO_2$. Data on the parameters that influence PCO_2 would also have helped us better interpret the CO_2 gap. Moreover, several studies have focused on the CO_2 gap/Ca-vO₂ ratio.[39,40] Unfortunately, we do not have this data. Another limitation was the retrospective design and that we collected data from 2008 to 2018. A lot has change during this time, including CPB management and hemodynamic management.

One of the characteristics of the CO_2 gap is its rapid reversibility.[41,42] Thus, taking measurements at a standardized time point represents measurement bias as outcome could not occur just after the measurement. Furthermore, the complication itself may lead to an increased CO_2 gap and, according to the time of measurement, the arrow of causation could be reversed. This bias is present in most cardiac surgery studies and makes it a limit to the use of the CO_2 gap to predict postoperative outcomes in cardiac surgery.

We believe that our database is reliable, as the data were recorded using the CCAM, and that these outcomes are robust, as they were easy to identify using generic keywords in the database. The strength of our study is that it is the largest sample yet focusing on this topic. External validation would be suitable, but previous studies
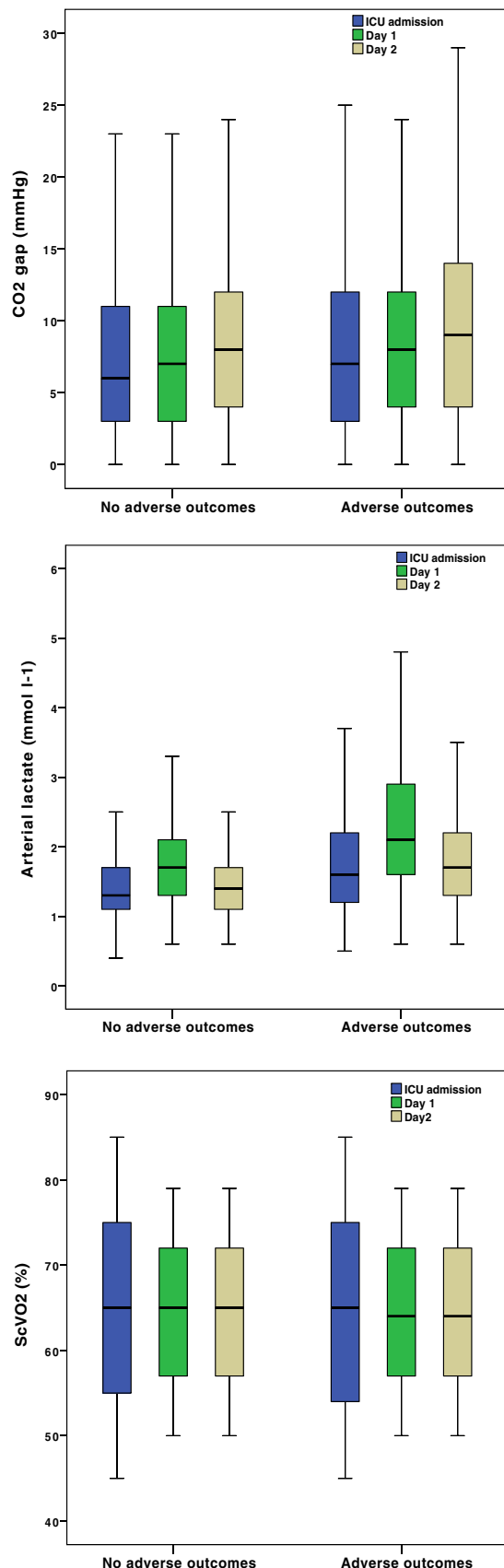
◀**Fig. 3** CO_2 gap, arterial lactate, and $ScVO_2$ at ICU admission and on days 1 and 2 after admission according to the occurrence of adverse outcomes. CO_2 gap = venous-to-arterial carbon dioxide difference; ICU = intensive care unit; $ScVO_2$ = central venous oxygen saturation

have obtained similar results.[29] Based on our study and on published data, the CO_2 gap should not be considered as a predictive marker of postoperative complications following cardiac surgery under CPB. Arterial lactate appears to show better sensitivity.

Conclusion

After cardiac surgery with CPB, the CO_2 gap at ICU admission and on days 1 and 2 after ICU admission was associated with postoperative adverse outcomes but with poor diagnostic performance. The CO_2 gap should not be used as a prognostic marker after cardiac surgery with CPB to identify patients who are insufficiently resuscitated.

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