Prognostic significance of central venous-to-arterial carbon dioxide difference during the first 24 hours of septic shock in patients with and without impaired cardiac function

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Abstract

Objective: To investigate the prognostic significance of central venous-to-arterial carbon dioxide difference (cv-art CO₂ gap) during septic shock in patients with and without impaired cardiac function.

Methods: We performed a prospective cohort study in 10 French intensive care units. Patients suffering from septic shock were assigned to the impaired cardiac function group (‘cardiac group’, n=123) if they had atrial fibrillation (AF) and/or left ventricular ejection fraction (LVEF) <50% at study entry and to the non-cardiac group (n=240) otherwise.

Results: Central venous and arterial blood gases were sampled every 6 h during the first 24 h to calculate cv-art CO₂ gap. Patients in the cardiac group had a higher cv-art CO₂ gap [at study entry and 6 and 12 h (all P<0.02)] than the non-cardiac group. Patients in the cardiac group with a cv-art CO₂ gap >0.9 kPa at 12 h had a higher risk of day 28 mortality (hazard ratio=3.18; P=0.0049). Among the 59 patients in the cardiac group with mean arterial pressure (MAP) >65 mm Hg, central venous pressure (CVP) ≥8 mm Hg and central venous oxygen saturation (ScvO₂) ≥70% at 12 h, those with a high cv-art CO₂
gap (>0.9 kPa; n = 19) had a higher day 28 mortality (37% vs. 13%; P = 0.042). In the non-cardiac group, a high cv-art CO₂ gap was not linked to a higher risk of day 28 death, whatever the threshold value of the cv-art CO₂ gap.

**Conclusion:** Patients with septic shock and with AF and/or low LVEF were more prone to a persistent high cv-art CO₂ gap, even when initial resuscitation succeeded in normalizing MAP, CVP, and ScvO₂. In these patients, a persistent high cv-art CO₂ gap at 12 h was significantly associated with higher day 28 mortality.

**Key words:** blood gas analysis; septic shock; central venous-arterial CO₂ difference

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**Editor’s key points**

- The difference between venous and arterial pCO₂ can reflect the adequacy of cardiac output and tissue perfusion and has been associated with worse outcomes in sepsis, but the influence of co-existing cardiac dysfunction is unknown.
- In this study of patients with sepsis, the veno-arterial pCO₂ difference was higher in those with cardiac dysfunction and persisted despite resuscitation.
- Despite restoration of other cardiovascular variables, a high veno-arterial pCO₂ difference at 12 h was associated with increased mortality.
- In contrast, the veno-arterial pCO₂ difference was lower in patients without overt cardiac dysfunction and there was no relationship to outcome.
- The prognostic significance of a high veno-arterial pCO₂ difference may depend on cardiac function.

The veno-arterial difference in partial pressure of carbon dioxide (pCO₂), either calculated using mixed (mv-art CO₂ gap) or central venous blood (cv-art CO₂ gap), grossly reflects the veno-arterial difference in CO₂ content (v-art CO₂ gap). This difference is inversely related to cardiac output (CO) and with tissue oxygen delivery and perfusion in case of normal or high CO. Interestingly, in the context of septic shock and its accompanying microcirculatory shunts, a high v-art CO₂ gap (or mv-art CO₂ gap or cv-art CO₂ gap) may unmask tissue hypoperfusion. High values of mv-art CO₂ gap or cv-art CO₂ gap seem associated with poor outcome in septic shock. However, this is not yet definitely established, perhaps because these variables are imperfect surrogates for v-art CO₂ gap and/or are worse performing than the ratio of mv-art CO₂ gap to anteriovenous difference in oxygen content [C(a-v)O₂] in detecting anaerobic metabolism.

An alternative explanation may lie in the well-known inverse relationship between mv-art CO₂ gap or cv-art CO₂ gap and CO: patients with impaired cardiac function are logically more prone to exhibit increased mv- or cv-art CO₂ gap values in stressful situations such as septic shock. However, studies that have investigated the mv- or cv-art CO₂ gap outcome relationship in septic shock patients rarely report the patients’ cardiac status (e.g. a history of chronic cardiac failure).

Accordingly, our aim was to compare the temporal course and relationship to outcome of the cv-art CO₂ gap during the first 24 h of septic shock in cardiac and non-cardiac subsets of patients.

**Methods**

This prospective, multicentre study was a planned companion study of a previously published cohort analysis focused on central venous oxygen saturation (ScvO₂) in septic shock carried out in 10 French medical-surgical intensive care units (ICUs). The Ethics Committee of the teaching hospital of Limoges, France, approved the protocol for all involved hospitals (agreement number 65-2011-11) and waived the need for prior informed consent.

Consecutive adult patients with circulatory failure of septic origin (i.e. with either severe sepsis plus hypotension, or septic shock) were included within 12 h after ICU admission as soon as they had an intra-arterial and superior vena cava (internal jugular or subclavian) catheter [see Supplementary Table S1 (available at British Journal of Anaesthesia online) for detailed inclusion criteria].

**Measurements and data collection**

Blood gas and lactate measurements were performed as soon as possible (time defined as H0) by sampling blood simultaneously from the superior vena cava through the central venous catheter and then every 6 h during a 24-h period (i.e. at H6, H12, H18 and H24) and from arterial blood at each time point.

Besides underlying chronic diseases, severity scores, and survival status at day 28, a number of clinical and laboratory variables were recorded at each time point (see the complete list in Supplementary Table S2). In addition, we collected the patient’s left ventricular ejection fraction (LVEF) if measured by ultrasonography during the first 24 h of the study. No study-specific instructions were given to the clinicians regarding when to perform echocardiographic examination or how to measure LVEF.

**Patients’ management**

Patients were managed following international and national guidelines. None of the participating ICUs had implemented systematic treatment algorithms based on ScvO₂ monitoring.

**Definitions**

Septic shock and severe sepsis were defined according to the definitions available at the time of the study.11 To classify the patients into cardiac and non-cardiac groups we took into account only objective variables: a patient was considered as belonging to the cardiac group (i.e. as having a suspected or known impaired systolic function) if he/she had atrial fibrillation (AF) at study entry and/or a decreased LVEF ≤50% either previously known or as observed on echocardiography (if performed) during the first 24 h of admission.

We calculated the cv-art CO₂ gap as the difference between the central venous and arterial CO₂ partial pressures measured on blood samples drawn simultaneously.

We calculated the cv-art CO₂ gap:C(a-cv)O₂ ratio in patients with available blood haemoglobin measurement and used it as
a surrogate for the mv-art CO2 gap:C(a-v)O2 ratio reflecting the contribution of non-aerobic metabolism to global CO2 production. We also assessed the contribution of non-aerobic metabolism by calculating the ratio between the cv-art CO2 gap and the oxygen extraction ratio (cv-art CO2 gap:EO2), which was available for nearly all patients at each time point, where EO2 was calculated as (SaO2–ScvO2)/SaO2.

Data analysis
The temporal course of the cv-art CO2 gap, its relationship to day 28 death, and potential differences between cardiac and non-cardiac groups were analysed in the framework of a linear mixed-effects model, with patients and centres as variables with random effect. The value of the cv-art CO2 gap was compared at each time point between levels of variables with fixed effects (cardiac/non-cardiac group, day 28 survival status, and time point at which blood samples were taken) using least square means comparisons.

In case of a significant difference in the cv-art CO2 gap at a given time point between day 28 survivors and non-survivors, we defined the cv-art CO2 gap threshold that best discriminates survivors from non-survivors as the one provided by locally weighted scatterplot smoothing (LOWESS) analysis. We compared survival over time between patients showing cv-art CO2 gaps below or above this best threshold and also between CO2 gap $\leq 0.8$ or $>0.8$ kPa (6mmHg), as used in previous studies, using a Cox proportional hazards model with mixed effects and adjusting hazard ratios (HRs) for the patients’ Simplified Acute Physiology Score II (SAPS II), ScvO2, and lactate level (i.e. the three most powerful predictors of death identified in our previous analysis). Between-subgroup comparisons of temporal courses of lactate level, dosages of vasoressors, ScvO2, and cumulative amount of fluid administered for volume expansion were also performed.

Continuous variables are reported as mean (sd). Proportions were compared by chi-square test or Fisher exact test. HRs are given with their 95% confidence interval (CI). A two-tailed P-value $<0.05$ was considered statistically significant. We did not input missing values. Linear mixed-effects and Cox proportional hazards models were used for icu survival over time between patients showing cv-art CO2 gap differences between non-survivors as the one provided by locally weighted scatterplot smoothing (LOWESS) analysis. We compared survival over time between patients showing cv-art CO2 gaps below or above this best threshold and also between CO2 gap $\leq 0.8$ or $>0.8$ kPa (6mmHg), as used in previous studies, using a Cox proportional hazards model with mixed effects and adjusting hazard ratios (HRs) for the patients’ Simplified Acute Physiology Score II (SAPS II), ScvO2, and lactate level (i.e. the three most powerful predictors of death identified in our previous analysis). Between-subgroup comparisons of temporal courses of lactate level, dosages of vasoressors, ScvO2, and cumulative amount of fluid administered for volume expansion were also performed.

Sample size
The study was primarily planned to enrol at least 350 patients, including at least 100 non-survivors. Because of the lack of published estimates of cv-art CO2 gap differences between cardiac and non-cardiac subsets of patients with septic shock, we considered this sample size sufficient for the exploratory purpose of the present study.

Results
We included 363 patients (Table 1), 240 in the non-cardiac group and 123 in the cardiac group (Fig. 1). Among the 1815 theoretically expected cv-art CO2 gap measurements, 49 (2.7%) were missing, with a monotonous missing pattern due to early dropouts (early death or early withdrawal of arterial catheter due to rapid improvement of the patient’s condition).

In the whole population of 363 patients, belonging or not to the cardiac group ($P=0.044$) and time of blood sampling ($P=0.031$) had a significant influence on the cv-art CO2 gap value. Although the cv-art CO2 gap appeared to be higher in non-survivors at H0 ($P=0.037$) using bivariate analysis (Supplementary Fig. S1), linear mixed model analysis showed that cv-art CO2 gap evolution was not significantly different ($P=0.083$) between day 28 survivors and non-survivors in the whole study population.

In the non-cardiac group, the cv-art CO2 gap was higher in day 28 non-survivors than in survivors only at H0 ($0.9 \pm 0.6$ vs. $0.7 \pm 0.5$ kPa; $P=0.002$), H6 ($P=0.005$), and H12 ($P=0.023$) and showed a more pronounced decline in the cv-art CO2 gap over the first 24 h (Fig. 2).

Importantly, similar differences in the cv-art CO2 gap were consistently observed whatever the criteria used to categorize the patients into the cardiac and non-cardiac groups (Supplementary Fig. S2).

Temporal course of the cv-art CO2 gap in subgroups of patients
In the non-cardiac group, the cv-art CO2 gap was higher in day 28 non-survivors than in survivors only at H0 ($0.9 \pm 0.6$ vs. $0.7 \pm 0.5$ kPa; $P=0.027$) (Fig. 3). In the cardiac group, the initial cv-art CO2 gap was not significantly different between day 28 non-survivors and survivors ($1.0 \pm 0.6$ vs. $0.9 \pm 0.5$ kPa, respectively; $P>0.05$) but showed a less pronounced decline with time in non-survivors, resulting in a higher cv-art CO2 gap at H12 ($0.9 \pm 0.5$ vs. $0.8 \pm 0.4$ kPa; $P=0.043$) (Fig. 3).

Relationship to day 28 survival
Non-cardiac group
The LOWESS analysis identified the cv-art CO2 gap value of $<0.7$ or $>0.7$ kPa (5mmHg) at H0 as a potential discriminative threshold (Supplementary Fig. S4). However, patients with a cv-art CO2 gap below or above this threshold had similar ICU and day 28 mortality ($31/118$ (26%) vs. $33/118$ (28%); $P=0.8$ and $30/118$ (25%) vs. $40/118$ (34%); $P=0.15$, respectively). They also had a similar adjusted risk of day 28 mortality [$HR 1.39 (95\% CI 0.82–2.38)$; $P=0.23$]. The threshold of 0.8 kPa (6mmHg) for the cv-art CO2 gap did not perform better [$HR 1.33 (95\% CI 0.75–2.31)$; $P=0.31$], nor did other thresholds (cv-art CO2 gap of 0.4, 0.5, 0.9 or 1.1 kPa).

Cardiac group
We identified the cv-art CO2 gap value of 0.9 kPa (7mmHg) at H12 as a potential discriminative threshold (Supplementary Fig. S3). The ICU mortality was higher in patients with a cv-art CO2 gap $>0.9$ kPa than in patients with a cv-art CO2 gap $\leq 0.9$ kPa at H12 [$15/38$ (39%) vs. $15/76$ (20%); $P=0.024$], but the difference did not reach statistical significance [$15/38$ (39%) vs. $18/76$ (24%); $P=0.08$] at day 28. However, the patients with a cv-art CO2 gap $>0.9$ kPa at H12 had a higher adjusted risk of day 28 death [$HR 3.18 (95\% CI 1.42–7.14)$; $P=0.0049$] (Fig. 4), even in subgroups of patients with high ($\geq 2$ mmol L$^{-1}$) or low ($<2$ mmol L$^{-1}$) blood lactate levels at H12 [$HR 2.71 (95\% CI 1.04–7.04)$; $P=0.041$ and 5.28 (95\% CI 1.05–26.6); $P=0.044$], respectively (Supplementary Fig. S4). Once again, the threshold of 0.8 kPa (6mmHg) did not significantly discriminate non-survivors from survivors [$HR 2.02 (95\% CI 0.93–4.37)$; $P=0.075$].

The patients with a cv-art CO2 gap $>0.9$ kPa at H12 significantly distinguished themselves from the other patients only from this time point in terms of the cv-art CO2 gap value (Supplementary Fig. S6) and non-survivors showed a significant
increase in lactate after H12 ($P=0.039$) (Fig. 5). In contrast, in patients with a cv-art CO$_2$ gap $\lesssim0.9$ kPa at H12, the lactate level showed parallel evolution between non-survivors and survivors (Fig. 5).

Patients with a cv-art CO$_2$ gap $\lesssim0.9$ or $>0.9$ kPa at H12 were similar regarding their clinical characteristics and treatments received before H12 (Supplementary Table S3), with two notable exceptions: ScvO$_2$ was significantly lower ($P=0.008$) (Supplementary Table S3 and Fig. S6) and the cumulative amount of fluid administered for volume expansion at H12 tended ($P=0.05$) to be lower in patients with a cv-art CO$_2$ gap $>0.9$ kPa at H12 (Supplementary Fig. S7).

Table 1 Clinical characteristics, treatments, and outcomes of the studied patients. Values are expressed as n (%) unless stated otherwise.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-cardiac group (n=240)</th>
<th>Cardiac group (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>155 (64.6)</td>
<td>76 (61.8)</td>
</tr>
<tr>
<td>Age (years), mean (so) (range)</td>
<td>64.5 (14.1) (18–87)</td>
<td>68.5 (13.7) (30–92)</td>
</tr>
<tr>
<td>Severe sepsisa at inclusion</td>
<td>19 (7.9)</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Septic shockb at inclusion</td>
<td>221 (92.1)</td>
<td>117 (95.1)</td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>68 (28.3)</td>
<td>30 (24.4)</td>
</tr>
<tr>
<td>Source of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung/pleura</td>
<td>102 (42.7)</td>
<td>63 (51.6)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>54 (22.6)</td>
<td>29 (23.8)</td>
</tr>
<tr>
<td>Urine</td>
<td>36 (15.1)</td>
<td>9 (7.4)</td>
</tr>
<tr>
<td>Skin, bones, joints</td>
<td>20 (8.4)</td>
<td>10 (8.2)</td>
</tr>
<tr>
<td>Other</td>
<td>21 (8.8)</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>Source not identified</td>
<td>7 (2.9)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Underlying diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>34 (14.2)</td>
<td>29 (23.6)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>130 (54.2)</td>
<td>68 (55.3)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>19 (7.9)</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>66 (27.5)</td>
<td>34 (27.7)</td>
</tr>
<tr>
<td>Chronic haemodialysis</td>
<td>2 (0.8)</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Immunocompromised stateb</td>
<td>68 (28.3)</td>
<td>42 (34.1)</td>
</tr>
<tr>
<td>Cardiac status at study entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic heart failurec</td>
<td>16 (6.7)</td>
<td>20 (16.3)</td>
</tr>
<tr>
<td>Atrial fibrillation at study entry (H0)</td>
<td>—</td>
<td>60 (48.8)</td>
</tr>
<tr>
<td>Known LVEF $\leq50%$</td>
<td>—</td>
<td>57 (46.3)</td>
</tr>
<tr>
<td>LVEF $\leq50%$ on echocardiography between H0 and H24d</td>
<td>—</td>
<td>86 (69.9)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation on admission</td>
<td>89 (37.1)</td>
<td>39 (31.7)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation during ICU stay</td>
<td>201 (83.8)</td>
<td>104 (84.6)</td>
</tr>
<tr>
<td>Norepinephrine on admission</td>
<td>94 (39.2)</td>
<td>42 (34.1)</td>
</tr>
<tr>
<td>Continuous i.v. norepinephrine or epinephrine from admission to H24</td>
<td>235 (97.9)</td>
<td>121 (98.4)</td>
</tr>
<tr>
<td>Dobutamine on admission</td>
<td>6 (2.5)</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Dobutamine between admission and H24</td>
<td>10 (4.2)</td>
<td>29 (23.6)</td>
</tr>
<tr>
<td>Transfusion of blood products between admission and H24</td>
<td>38 (15.8)</td>
<td>20 (16.3)</td>
</tr>
<tr>
<td>Renal replacement therapy during ICU stay</td>
<td>46 (19.2%)</td>
<td>38 (30.9)</td>
</tr>
<tr>
<td>Initial (H0) arterial blood lactate concentration (mmol L$^{-1}$)e</td>
<td>3.3 (3.2)</td>
<td>3.3 (2.6)</td>
</tr>
<tr>
<td>Initial (H0) ScvO$_2$ (%)</td>
<td>74.6 (10.6)</td>
<td>73.1 (11.6)</td>
</tr>
<tr>
<td>Initial (H0) cv-art CO$_2$ gap (kPa)</td>
<td>0.8 (0.5)</td>
<td>1.0 (0.5)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>55.8 (19.7)</td>
<td>58.6 (20.4)</td>
</tr>
<tr>
<td>SOFA score (highest value from H0 to H24)</td>
<td>10.3 (3.4)</td>
<td>10.5 (3.4)</td>
</tr>
<tr>
<td>ICU death</td>
<td>65 (27.3)</td>
<td>37 (30.1)</td>
</tr>
<tr>
<td>Day 28 deathf</td>
<td>71 (29.6)</td>
<td>40 (32.5)</td>
</tr>
</tbody>
</table>
Finally, among the 59 patients [out of 114 (52%)] with MAP ≥65mmHg and central venous pressure (CVP) ≥8mmHg and ScvO2 ≥70% at H12, 32% (19/59) still had a cv-art CO2 gap >0.9 kPa. In this subgroup of “apparently” resuscitated patients, the day 28 mortality was higher in patients with a cv-art CO2 gap >0.9 kPa at H12 [7/19 (37%) vs. 5/40 (13%); P=0.042].

**Ratio of cv-art CO2 gap to arteriovenous difference in oxygen content**
Neither threshold values of cv-art CO2 gap:C(a-cv)O2 nor threshold values of cv-art CO2 gap:EO2 could discriminate patients with high lactate levels or poor lactate clearance from patients with low lactate levels or good lactate clearance, whether in patients of the cardiac or non-cardiac group (pages 14–16, Supplementary data, available at British Journal of Anaesthesia online).

**Discussion**
Our main findings are that patients in septic shock with AF and/or low LVEF, i.e. with supposedly impaired cardiac function, showed higher cv-art CO2 gap values than patients with supposed normal cardiac function, and that the persistence of a high cv-art CO2 gap at 12 h in patients in the cardiac group was associated with increased mortality at day 28, even in patients with apparently well-conducted early resuscitation with regard to MAP, CVP, and ScvO2.

We hypothesized that the cardiac status of the studied populations, i.e. their preserved or impaired capacity of adequately increased CO in stressful situations, could be a key determinant of the statistical link between cv-art CO2 gap and mortality reported in the literature. Indeed, as observed in clinical cohorts of septic shock patients15 or mathematically modelled,18 CO is

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**Fig 1 CONSORT diagram.**

5955 patients were admitted in ICUs
852 had sepsis and circulatory failure on admission or during the first 24 h
182 patients with sepsis and circulatory failure were missed for screening for logistic reasons
670 patients screened
Femoral venous access (n=91)
Central venous access not needed (n=82)
Late and/or failed insertion of central venous and/or arterial catheters (n=52)
Patients with shock considered to have started too long before admission (n=6)
Moribund patients on admission (n=2)
Patients previously enrolled (n=1)

436 eligible patients
73 non included patients
Logistic issues (missed or workload too high or study staff unavailable)

363 patients enrolled and analyzed
240 patients in the non-cardiac group
123 patients in the cardiac group
the major determinant of the cv-art CO₂ gap.19 In low-flow states, the prolonged transit time of blood through the microvasculature and the high diffusion coefficient of CO₂ through the tissues lead to CO₂ enrichment of venous blood.14 15 20 21 As we expected, patients in the cardiac group had higher cv-art CO₂ gap values than patients in the non-cardiac group. Importantly, due to the predominant role of CO in the cv-art CO₂ gap, and considering that ScvO₂ was significantly lower in patients with a high cv-art CO₂ gap, our results strongly suggest that patients in the cardiac group more frequently suffered from insufficient organ perfusion flow, even if we did not measure CO. Although a causal relationship cannot be definitively affirmed, the persistence of a high cv-art CO₂ gap at H12 was associated with increased day 28 mortality. Importantly, the finding that such an association was not observed in our non-cardiac group does not deny that the cv-art CO₂ gap may be used to detect insufficient CO in this population, but simply reflects that patients of the non-cardiac group less frequently suffered from insufficient organ perfusion flow than patients in the cardiac group. Indeed, as in the cardiac group, patients in the non-cardiac group showed significantly lower ScvO₂ values with a high (>0.9 kPa) compared with a low (≤0.9 kPa) cv-art CO₂ gap at H12 (Supplementary Fig. S8).

Of note, the two criteria we chose to categorize the patients into cardiac and non-cardiac groups may be questioned, as they are not universally used. However, compared with the different stages of the New York Heart Association functional classification, which are often difficult to ascertain with objectivity after patient, practitioner, and family interviews,22 23 they offer a pragmatic and objective classification tool. Indeed, LVEF, rapidly assessed by echocardiography, is a strong criterion for heart failure when <50%,24 and AF, associated with decreased diastolic filling interval and loss of atrial systole, leads to a decrease in CO or in worsening of pre-existing heart failure.25

The prognostic significance of the cv-art CO₂ gap in septic shock has been examined in four recent studies. A retrospective study of 35 patients8 showed no link between the initial cv-art CO₂ gap and ICU mortality. In a prospective study of 50 septic shock patients with ScvO₂ >70%, a 20% difference in day 28 mortality was observed between patients with a high (>0.8 kPa) or low (≤0.8 kPa) initial cv-art CO₂ gap, but did not reach statistical significance (P = 0.16).3 In a single-centre study of 85 septic shock patients, sequential measurements over the first 24 h showed higher cv-art CO₂ gap values in non-survivors.7 In a two-centre cohort of 53 patients, a trend towards higher mortality in patients with a persistent high cv-art CO₂ gap was observed.6 Our results in 363 septic shock patients confirm the link between a persistent high cv-art CO₂ gap and mortality and strongly suggest that patients with impaired cardiac function are more prone to persistent insufficient organ perfusion flow, even when initial resuscitation succeeded in normalizing MAP, CVP, and ScvO₂.
The imperfect repeatability of the cv-art CO₂ gap (two consecutive measurements in the same patient at steady state may show a difference of ~0.27 kPa²⁶) may lead to some measurement errors. The impact of such errors may be heightened in high CO states where tiny cv-art CO₂ gaps are expected.⁹ Additionally, a slight difference between the upper and lower parts of the body in the O₂ delivery:demand ratio and CO₂ production may also exist.⁶ Therefore, in high CO states, such as resuscitated septic shock in patients with normal baseline cardiac function, the cv-art CO₂ gap probably poorly reflects the true veno-arterial difference in CO₂ content. This may explain why we did not find any cv-art CO₂ gap cut-off value that could discriminate survivors from non-survivors in patients in the non-cardiac group. In contrast, patients in our cardiac group had a higher baseline cv-art CO₂ gap that was less sensitive to measurement errors. Measurement errors and differences between the upper and lower parts of the body also probably explain why we found no correlations between the cv-art CO₂ gap:CaO₂ and the cv-art CO₂ gap:EVO₂ ratios, which are supposed to reflect CO₂ production of anaerobic origin, and the evolution of lactate levels in our patients.

We found that a persistent cv-art CO₂ gap value >0.9 kPa (7mmHg) was associated with poor outcome in patients in the cardiac group, whereas previous studies identified the 0.8 kPa (6mmHg) threshold as discriminative.¹⁵ Once again, the variability of cv-art CO₂ gap measurement, but also the proportion of patients with impaired cardiac function, which was not known in previous studies, may explain these different findings.

**Practical implications**

Today, CO measurement techniques are scarcely used in clinical practice.²⁷ ²⁸ In light of our results, in septic shock patients with suspected impaired cardiac function, a persistent high cv-art CO₂ gap should reasonably cause one to measure CO, investigate whether there are possibilities to increase it with inotropes and/or fluids, and determine whether such an increase translates into better lactate clearance.

Although the cv-art CO₂ gap poorly reflects organ blood flow in patients with supposed normal cardiac function (for reasons detailed above), a persistent high cv-art CO₂ gap may still constitute a warning sign in these patients.
A low signal:noise ratio in high CO states and possible differences in the O\textsubscript{2} delivery:consumption ratio between the upper and lower parts of the body prevent utilization of the cv-art CO\textsubscript{2} gap:C(a-cv)O\textsubscript{2} ratio to assess the anaerobic/aerobic balance in CO\textsubscript{2} production. This ratio would be best assessed using a pulmonary artery catheter to sample mixed venous blood,\textsuperscript{1} which allows eliminating the possible error due to differences between the upper and lower parts of the body.

Limitations

Our study has several limitations. First, we did not evaluate diastolic function, dysfunction of which in stressful conditions might also be associated with alteration of CO and increased mortality. The relationship between diastolic dysfunction and cv-art CO\textsubscript{2} gap in septic shock remains to be explored. Second, errors in LVEF estimation are possible and data were missing for 71 patients. However, even if echocardiographic assessment was incomplete, it remains no less true that our definition (cardiac patients defined by AF and/or low LVEF) actually separated patients with high and low cv-art CO\textsubscript{2} gaps. Third, we did not differentiate patients with new-onset or permanent AF, although this might alter patient outcome. This deserves further research. Fourth, we used the veno-arterial difference in P\textsubscript{CO\textsubscript{2}} instead of CO\textsubscript{2} content. The use of CO\textsubscript{2} content might have yielded more accurate findings. However, calculating CO\textsubscript{2} content requires knowledge of the haemoglobin concentration, is cumbersome, and is subject to several potential measurement errors.\textsuperscript{29} In addition, in clinical conditions, the cv-art CO\textsubscript{2} gap was shown to have a temporal course similar to that of CO\textsubscript{2} content difference.\textsuperscript{4} And finally, in our study the cv-art CO\textsubscript{2} gap successfully identified patients at high risk of death in the cardiac group.

Conclusion

Patients in septic shock and with impaired cardiac function as defined by AF and/or low LVEF were more prone to a persistent high cv-art CO\textsubscript{2} gap. In these patients, a persistent high cv-art CO\textsubscript{2} gap at 12 h was significantly associated with higher day 28 mortality, even when initial resuscitation succeeded in normalizing MAP, CVP, and ScvO\textsubscript{2}.

Authors’ contributions

G.M. and T.B. conceived the study design and performed data collection, statistical analysis, and draft writing. E.M., P.V., M.H.L., T.K., A.D., V.B., G.P., J.P.F., F.B., J.P.Q., and P.F.D. performed data collection and critical revision of the manuscript. All authors helped design the study and approved the final manuscript.

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.
Declaration of interest

The authors declare no potential conflict of interest relative to this submission.

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