Central venous-arterial $pCO_2$ difference as a tool in resuscitation of septic patients

Abstract Purpose: To investigate the interchangeability of mixed and central venous-arterial carbon dioxide differences and the relation between the central difference ($pCO_2$ gap) and cardiac index (CI). We also investigated the value of the $pCO_2$ gap in outcome prediction.

Methods: We performed a post hoc analysis of a well-defined population of 53 patients with severe sepsis or septic shock. Mixed and central venous $pCO_2$ were determined earlier at a 6 h interval ($T = 0$ to $T = 4$) during the first 24 h after intensive care unit (ICU) admittance. The population was divided into two groups based on $pCO_2$ gap (cut off value 0.8 kPa).

Results: The mixed $pCO_2$ difference underestimated the central $pCO_2$ difference by a mean bias of $0.03 \pm 0.32$ kPa (95% limits of agreement: $-0.62$–$0.58$ kPa). We observed a weak relation between $pCO_2$ gap and CI. The in hospital mortality rate was 21% (6/29) for the low gap group and 29% (7/24) for the high gap group; the odds ratio was 1.6 (95% CI 0.5–5.5), $p = 0.53$. At $T = 4$ the odds ratio was 5.3 (95% CI 0.9–30.7); $p = 0.08$.

Conclusions: From a practical perspective, the clinical utility of central venous $pCO_2$ values is of potential interest in determining the venous-arterial $pCO_2$ difference. The likelihood of a bad outcome seems to be enhanced when a high $pCO_2$ gap persists after 24 h of therapy.

Keywords Central venous-arterial $pCO_2$ difference · Cardiac index · Septic shock · Hemodynamics

Introduction

Shock is defined as global tissue hypoxia secondary to an imbalance between systemic oxygen delivery ($DO_2$) and oxygen demand ($VO_2$). Global tissue hypoxia as a result of systemic inflammatory response or circulatory failure is an important indicator of serious illness preceding multiple organ failure. The development of organ failure predicts the outcome of the septic patient [1]. Unrecognized and untreated global tissue hypoxia increases morbidity and mortality: decreased mixed venous oxygen saturation ($SvO_2$) values or central venous oxygen saturation ($ScvO_2$) values predict poor prognosis in septic shock [2, 3]. However, in the majority of patients with severe sepsis or septic shock who are acutely admitted to the intensive care unit (ICU) $ScvO_2$ values are >70 %
[4, 5]. Hence, normal ScvO₂ values do not guarantee adequate tissue oxygenation and other circulatory parameters are needed to evaluate resuscitation efforts.

A variable that has been described in this context is the central venous-arterial carbon dioxide difference (pCO₂ gap) [6]. Under physiological conditions, venous-arterial carbon dioxide difference usually does not exceed 0.8 kPa (6 mmHg) [7] and reflects adequacy of venous blood flow, i.e., cardiac output (CO) [8, 9]. At the macrocirculatory level, an inverse relationship between pCO₂ gap and cardiac index (CI) has been described in critically ill patients [10, 11]. Indeed, in patients who fulfilled resuscitation endpoints according to international guidelines [1] a cutoff value for pCO₂ gap of 0.8 kPa discriminated between high and low lactate clearance and CI [6]. Thus, combining ScvO₂ values as a surrogate for global tissue hypoxia and the pCO₂ gap as a surrogate for CI may be useful during resuscitation of critically ill patients. However, in patients with severe sepsis, on the microcirculatory level distributive changes may be independent of CO [12, 13]. This means that, on a regional level, in accordance with the possibility of persistent tissue hypoxia despite normal ScvO₂ levels, the accumulation of carbon dioxide (CO₂) may occur in sepsis despite adequate CO. In line with investigations on the agreement between SvO₂ and ScvO₂, it seems useful to determine whether an agreement between the mixed and central venous-arterial carbon dioxide difference exists in septic patients [5, 11]. In other words, are mixed and central venous-arterial carbon dioxide differences interchangeable?

We examined the relationship between central venous-arterial carbon dioxide difference and CI and addressed the question of whether central venous-arterial carbon dioxide differences are of additional value in outcome prediction. Additionally, we investigated the agreement between mixed and central venous-arterial carbon dioxide differences in a well-defined population of patients with severe sepsis or septic shock [5].

**Patients and data collection**

This post hoc analysis of data from a prospective observational study included a population of patients we have described before [5]. All patients were 18 years or older, with sepsis or septic shock according to international criteria as the principal reason for ICU admittance [14]. Patients were included in case of a clinical indication for additional hemodynamic monitoring using a pulmonary artery catheter (PAC) [Criticath SP 5507H TD, Becton–Dickinson, Singapore] or a Continuous Cardiac Output (CCO) catheter [Arrow Deutschland GmbH, Erding, Germany]. The catheter was inserted into an internal jugular or subclavian vein according to standard procedure. Position was confirmed by the presence of pulmonary artery pressure tracings and chest radiography. Primary data, including hemodynamic variables, were collected at 6-hour intervals (T₀, T₁, T₂, T₃, T₄) during the first 24 h after acute ICU admittance. Standard blood samples of 2 ml were drawn simultaneously from an arterial line, distal (pulmonary artery; PA) and proximal/side portals (superior caval vein; SCV) from PAC or CCO catheter. To avoid false high readings due to aspiration of pulmonary capillary blood, aspiration was done gently to avoid high negative pressure when blood samples were taken. Blood was sampled from the proximal port of the catheter as representative of central venous blood [15, 16]. All blood samples were analyzed by a point-of-care co-oximeter (Radiometer ABL800 flex, Copenhagen, Denmark) available in both ICU's which ensured rapid assessment to avoid poor quality measurements. The Acute Physiology, Age and Chronic Health Evaluation (APACHE) II-score after 24 h of ICU admittance was calculated [17].

**Statistical analysis**

For analysis the population was divided into two groups: patients with a low pCO₂ gap (<0.8 kPa) vs. patients with a high pCO₂ gap (>0.8 kPa) at ICU admission (T = 0). Statistical tests were two-tailed and performed by the statistical package for the social sciences (IBM SPSS 19 for Windows, Chicago, IL, USA). GraphPad software (Prism 5.0, La Jolla, CA, USA) was used for graphics. Measurements were not independent but clustered within each patient. All data were tested for normal distribution with the D’Agostino-Pearson omnibus normality test before further statistical analysis. Differences between both groups were assessed using Student’s t test in case of normal distribution. For categorical data, the Chi Square test or Fisher’s exact test was used. For each time point (T₀–T₄) the difference between arterial CO₂ partial pressure (paCO₂) and central venous (pvCO₂), i.e. pCO₂ gap was calculated. Also, for each time point the average CI, mean arterial pressure (MAP), ScvO₂.

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**Methods**

**Setting**

We studied ICU populations in two teaching hospitals: the Martini Hospital [Groningen, The Netherlands] (MH) with a 14-bed “closed format” mixed medical/surgical ICU department and the Medical Center Leeuwarden [Leeuwarden, The Netherlands] (MCL) with a 16-bed “closed format” mixed medical/surgical ICU, including cardiothoracic patients. Previously, written informed consent was obtained in all cases from the patient or from the patient’s legal representative. The use of earlier obtained data [5] was approved by both local ethics committees.

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For analysis the population was divided into two groups: patients with a low pCO₂ gap (<0.8 kPa) vs. patients with a high pCO₂ gap (>0.8 kPa) at ICU admission (T = 0). Statistical tests were two-tailed and performed by the statistical package for the social sciences (IBM SPSS 19 for Windows, Chicago, IL, USA). GraphPad software (Prism 5.0, La Jolla, CA, USA) was used for graphics. Measurements were not independent but clustered within each patient. All data were tested for normal distribution with the D’Agostino-Pearson omnibus normality test before further statistical analysis. Differences between both groups were assessed using Student’s t test in case of normal distribution. For categorical data, the Chi Square test or Fisher’s exact test was used. For each time point (T₀–T₄) the difference between arterial CO₂ partial pressure (paCO₂) and central venous (pvCO₂), i.e. pCO₂ gap was calculated. Also, for each time point the average CI, mean arterial pressure (MAP), ScvO₂.
lactate, and infusion rate of both norepinephrine and dopamine was calculated. The agreement between CI and $pCO_2$ gap was assessed by the mean bias and 95% limits of agreement (mean bias ± 1.96 × standard deviation) as described by Bland and Altman (BA) [18]. Spearman correlation coefficient between mixed and central venous-arterial $pCO_2$ differences was determined. Finally, the odds ratio for mortality between patients with a high $pCO_2$ gap and patients with a low $pCO_2$ gap at both $T = 0$ and $T = 4$ were calculated. Data are displayed as mean ± SD. Statistical significance was assumed at $p < 0.05$.

### Results

We enrolled 56 patients, of whom three patients were excluded due to lack of data (technical problems). We evaluated data from 53 patients with sepsis. Thirty patients were enrolled at MCL and 23 patients were enrolled at MH. No complications other than transient arrhythmias were observed during the insertion of any catheter. Altogether 245 paired blood samples were obtained. At $T = 0$, 29 patients had a central $pCO_2$ difference of less than 0.8 kPa (low gap group), and 24 patients had a central $pCO_2$ difference larger than 0.8 kPa (high gap group). Baseline characteristics and outcome of the total population and both groups are shown in Table 1. Length of stay at the ICU (LOSICU) was 12 ± 10 days and length of stay at the hospital (LOSHOSP) was 25 ± 18 days.

### Agreement mixed and central $pCO_2$ difference

The mixed venous-arterial $pCO_2$ difference underestimated the central venous-arterial $pCO_2$ difference by a mean bias (or absolute difference) of 0.03 ± 0.32 kPa in all paired measurements. The 95% limits of agreement ranged from −0.62 kPa to 0.58 kPa (Fig. 1a). Correlation was significant ($p < 0.01$) with Spearman correlation coefficient $r_s$ of 0.54, 95% CI 0.43–0.63 (Fig. 1b). The mean delta was not significantly different from 0 ($p = 0.11$): both values tend to be equal. This was confirmed by an intraclass coefficient between the mixed and central $pCO_2$ differences of 0.70 ($p < 0.001$).

The results at various time points were similar with those at $T = 0$, with a mean bias of −0.13 ± 0.40 kPa and 95% limits of agreement of −1.0–0.8 kPa.

When the CI was plotted against the central $pCO_2$ difference for all paired measurements, there was an inverse logarithmic relationship with increasing central $pCO_2$ difference as CI decreased (regression equation: $CO_2$gap = $10^{0.90 \times CI + 0.07}$; $R^2 = 0.07$ $p < 0.0001$; Fig. 2).

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total population ($n = 53$)</th>
<th>Low gap ($n = 29$)</th>
<th>High gap ($n = 24$)</th>
<th>$P$ value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>66 ± 12</td>
<td>67 ± 13</td>
<td>66 ± 11</td>
<td>0.83</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>28/25</td>
<td>17/12</td>
<td>11/13</td>
<td>0.41$^a$</td>
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<tr>
<td>APACHE II</td>
<td>27 ± 8</td>
<td>26 ± 7</td>
<td>27 ± 9</td>
<td>0.70</td>
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<tr>
<td>Diagnosis</td>
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<td>25</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>16</td>
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<td>7</td>
</tr>
<tr>
<td></td>
<td>Urological</td>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>7</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Therapy</td>
<td>Mechanical ventilation</td>
<td>52/53</td>
<td>28/29</td>
<td>24/24</td>
</tr>
<tr>
<td></td>
<td>RRT</td>
<td>15/53</td>
<td>5/29</td>
<td>10/24</td>
</tr>
<tr>
<td></td>
<td>Dopamine (µg/kg/min)</td>
<td>4.1 ± 3.9</td>
<td>3.6 ± 3.5</td>
<td>4.8 ± 2.7</td>
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<tr>
<td></td>
<td>Norepinephrine (µg/kg/min)</td>
<td>0.20 ± 0.18</td>
<td>0.23 ± 0.23</td>
<td>0.16 ± 0.19</td>
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<td></td>
<td>MAP (mmHg)</td>
<td>66 ± 10</td>
<td>68 ± 9</td>
<td>63 ± 11</td>
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<tr>
<td></td>
<td>CVP (mmHg)</td>
<td>12 ± 5</td>
<td>12 ± 5</td>
<td>13 ± 6</td>
</tr>
<tr>
<td></td>
<td>CI (L/min/m²)</td>
<td>3.7 ± 1.2</td>
<td>4.1 ± 1.1</td>
<td>3.3 ± 1.1</td>
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<tr>
<td></td>
<td>Lactate (mmol/L)</td>
<td>3.3 ± 3.0</td>
<td>2.8 ± 3.1</td>
<td>3.9 ± 2.9</td>
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<tr>
<td></td>
<td>ScvO₂ (%)</td>
<td>71.8 ± 10.1</td>
<td>74.5 ± 9.3</td>
<td>71.1 ± 7.1</td>
</tr>
<tr>
<td></td>
<td>SvO₂ (%)</td>
<td>71.9 ± 10.7</td>
<td>73.2 ± 9.1</td>
<td>70.3 ± 6.6</td>
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<tr>
<td></td>
<td>$pCO_2$ difference (kPa)</td>
<td>0.70 ± 0.52</td>
<td>0.38 ± 0.42</td>
<td>1.10 ± 0.33</td>
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<tr>
<td></td>
<td>Hematocrit (%)</td>
<td>31 ± 1</td>
<td>30 ± 5</td>
<td>31 ± 6</td>
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<tr>
<td></td>
<td>SaO₂ (%)</td>
<td>96 ± 2</td>
<td>97 ± 2</td>
<td>96 ± 3</td>
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<tr>
<td></td>
<td>pH</td>
<td>7.30 ± 0.10</td>
<td>7.31 ± 0.09</td>
<td>7.29 ± 0.11</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or as numbers.

$^a$ statistically significant difference

$^b$ low gap vs. high gap group

* Fisher’s exact test

$\chi^2$ Square test

### Differences between low gap and high gap group

At $T = 0$, patients in the low gap group had a significantly lower $pCO_2$ gap than patients of the high gap group (0.38 ± 0.42 kPa vs 1.10 ± 0.33 kPa; $p < 0.001$). There was no significant difference between the two groups for age, gender, APACHE II, diagnosis and treatment received (Table 1). The groups did not differ in both arterial blood pressure with equivalent inotropic doses and degree of hyperlactaemia. CI was significantly lower in the high gap group ($p = 0.01$).

Figure 3 shows the evolution in time of the central $pCO_2$ difference and CI. During the first 24 h of treatment there was no significant difference in ScvO₂ (except for $T = 0$), MAP, and lactate. At all time points, there was no significant difference in either norepinephrine and dopamine infusion rate or the number of patients receiving these catecholamines.
Outcome

The hospital mortality rate for all patients was 24.5 % (13/53). The in hospital mortality rate was 21 % (6/29) for the low gap group and 29 % (7/24) for the high gap group; the odds ratio was 1.6 (95 % CI 0.5–5.5), \( p = 0.53 \). Patients with a central \( p\text{CO}_2 \) difference larger than 0.8 kPa at \( T = 4 \), which was already present at \( T = 1 \), had a higher mortality change (\( n = 8 \); in hospital mortality 38 %) compared to patients with a central \( p\text{CO}_2 \) difference smaller than 0.8 kPa at \( T = 4 \) (\( n = 39 \); in hospital mortality 10 %); this odds ratio was 5.3 (95 % CI 0.9–30.7); \( p = 0.08 \).

Discussion

We observed a strong agreement between the mixed venous \( p\text{CO}_2 \) and the central venous \( p\text{CO}_2 \) differences...
with seemingly relatively small limits of agreement in patients with severe sepsis or septic shock. From a practical perspective, the clinical utility of central $p$CO$_2$ values is of potential interest in determining the venous-arterial $p$CO$_2$ difference. The present BA analysis implacably demonstrates a strong agreement between mixed and central venous $p$CO$_2$ differences. This is in line with recent findings by Cuschieri et al [11]. They observed a minimal but significant difference with slightly higher mean mixed $p$CO$_2$ values compared to mean central $p$CO$_2$ values (difference 0.02 kPa). Similarly, we found a mean delta equal to zero. Despite the practical attractiveness of the abovementioned observations, we believe that the 95% limits of agreement (−0.62–0.58 kPa and −1.0–0.8 kPa at $T = 0$) are relatively wide compared to the clinical relevant cutoff value of 0.8 kPa. This means that both central venous $p$CO$_2$ values as well as mixed venous $p$CO$_2$ values may be used for the calculation of a venous-arterial $p$CO$_2$ difference, but based on our findings we recommend not interchanging these variables during treatment.

We observed a weak but significant inverse logarithmic relation between the $p$CO$_2$ gap and global blood flow, i.e. CI, in this specific sepsis population. Cuschieri et al. [11] found a stronger relation between $p$CO$_2$ gap and CI, but they described a mixed population of critically ill patients. About one-third of their population were patients with circulatory and cardiogenic shock. The relationship between CO and $p$CO$_2$ gap in those patients is best described by the steep part of the CO$_2$-production-isopleths [19]. Our findings are in line with physiological theory, which describes an inverse curvilinear relationship between cardiac output and $p$CO$_2$ difference, according to a modified Fick equation for a range of CO$_2$-production-isopleths [19]. Various studies described such an inverse relationship between mixed venous-arterial $p$CO$_2$ difference and CI in septic circulatory failure [20–22]. The increase in the venous-arterial $p$CO$_2$ gradient is explained by a inadequate washout of CO$_2$. Hence, a low-flow state is characterized by failure in oxygen delivery to the tissues and excesses of CO$_2$ in venous blood. In addition to this, in sepsis an increase in $p$CO$_2$ difference may persist in higher ranges of cardiac output. Due to the heterogeneity of microcirculatory blood flow, inadequate washout of CO$_2$ in microcirculatory weakunits, despite normal or even elevated cardiac output, has been observed during sepsis [12, 13]. Vallée et al. [6] tested this hypothesis in patients with septic shock, who were supposedly adequately resuscitated at the systemic level, with a ScvO$_2$ ≥70 % [1]. A central venous-arterial $p$CO$_2$ difference >6 mmHg at baseline was inversely correlated with lactate clearance and reduction in SOFA score after 24 h. This might be due to the observed significant lower cardiac index in the high gap group, but the normal ScvO$_2$ also points towards the possibility of distributive deficits of a normal or elevated systemic blood flow. As expected [4], in our population the mean ScvO$_2$ values were higher than 70 %. The far majority of patients with a high CO$_2$ gap at ICU admittance were in the horizontal part of the cardiac output—CO$_2$ gap curve, indicating the relative independence of the two variables in this particular range of systemic blood flow.

Finally, the predictive value of the $p$CO$_2$ difference for outcome is questionable. However, a modest time-dependent relationship between an increased $p$CO$_2$ difference and outcome was found. Although not significant, with the persistence of an increased $p$CO$_2$ difference the odds ratio for bad outcome increases. Whether the significantly higher CI and ScvO$_2$ in the low $p$CO$_2$-gap group is causatively related or is an epiphenomenon remains a topic of debate, since protocols that aim for supranormal values have been proven to be harmful in critically ill patients [23, 24].

This study has limitations. First, this was a multicenter, post hoc study, and its observational character, including the lack of power analysis, has clear constraints. On top of that, the primary study [5] was not designed to evaluate the relevance of the $p$CO$_2$ gap. Second, statements about any impact on therapeutic intervention are not possible. Third, data described are based on only five time points and not on continuous measurements which hinders a complete insight in the course of variables, including CO$_2$ values. Fourth, since all patients were septic, our findings may not be generalized to patients less critically ill or to those with other forms of shock. Fifth, due to the fact that 13 patients died within the first 24 h, not all data on the relationship between the $p$CO$_2$-gap and death were available. It is conceivable that this lead to underestimation of the predictive value of the $p$CO$_2$-gap. Finally, lack of clear insight of treatment prior to ICU admittance at the different EDs or wards was a limitation of our study as well. Nevertheless, since we focused on the usefulness of the central venous CO$_2$ difference after ICU admittance, we think these factors are not pertinent to the results.

**Conclusion**

From a practical perspective, i.e. easily obtained and satisfying data, the clinical utility of central $p$CO$_2$ values is of potentially great interest in determining the venous-arterial $p$CO$_2$ difference.

A priori, the predictive value for outcome of the central venous $p$CO$_2$ difference is questionable but persistence of an increased central venous $p$CO$_2$ difference after 24 h of therapy seems to enhance the likelihood of bad outcome.
References