Measurement of central and mixed venous-to-arterial carbon dioxide differences in cardiac surgery patients

H. Heinze¹, H. Paarmann¹, M. Heringlake¹, H. V. Groesdonk²

¹Department of Anesthesiology, University of Lübeck, Germany; ²Department of Thoracic and Cardiovascular Surgery, University of Saarland, Homburg, Germany

Abstract

Background: Measurement of central venous-to-arterial CO₂ difference (p(cv-a)CO₂) as an estimate of mixed venous-to-arterial CO₂ difference (p(v-a)CO₂) has been recommended as an supplementary parameter to identify the inadequacy of tissue oxygenation in septic and post-operative non-cardiac high risk surgery patients. This study investigates the agreement between p(cv-a)CO₂ and p(v-a)CO₂, and explores the relationship of p(v-a)CO₂ with parameters of global and regional tissue oxygenation.

Methods: Simultaneous measurements of p(cv-a)CO₂ and p(v-a)CO₂ were performed in post-operative cardiac surgery patients immediately before and after cardiopulmonary bypass (CPB), and up to 6 hours post CPB. In addition, parameters of global blood flow and tissue oxygenation, i.e. cardiac index, mixed venous oxygen saturation (SvO₂), arterial lactate, and regional blood flow, i.e. gastric tonometry were assessed. Pooled data were used for Bland-Altman and correlation analysis, as appropriate.

Results: Although significantly correlated, p(cv-a)CO₂ and p(v-a)CO₂ showed large limits of agreement (6.7 mmHg, percentage error of 115 %). Correlation analyses revealed no meaningful correlation between p(v-a)CO₂ and CI, SvO₂, arterial lactate, and p(g-a)CO₂ (R²: 0.013, 0.007, 0.000, 0.006, respectively, with p > 0.05 each).

Conclusions: In cardiac surgery patients p(cv-a)CO₂ cannot be used as an estimate of p(v-a)CO₂ with acceptable accuracy. There is no evidence that measurements of p(cv-a)CO₂ or p(v-a)CO₂ could help diagnose global or regional tissue hypoxia in this patient group.

Key words: central-venous-to-arterial carbon dioxide difference, gastric tonometry, mixed venous-to-arterial carbon dioxide difference, arterial lactate, cardiac surgery, mixed venous oxygen saturation, tissue oxygenation, hemodynamic

Introduction

Since the landmark study by Rivers et al. [1] measurement of central venous oxygen saturation (ScvO₂) has been extensively used in intensive care and perioperative medicine. ScvO₂ serves as an estimate of true mixed venous oxygen saturation (SvO₂) and therefore oxygen delivery/uptake relationship [2]. The physiological limitations of ScvO₂, usually measured in the superior venae cava, are well known, and in certain patients large differences between ScvO₂ and SvO₂ may occur [3]. Beside this and the fact that Rivers et al. studied severely septic patients during the first 6 hours after hospital admission, ScvO₂ meas-
urements have been recommended in perioperative elective cardiac surgery patients [4].

Recent studies in high risk major abdominal surgery and septic shock revealed that a ScvO₂ > 70% may not rule out the inadequacy of tissue oxygenation [5,6]. In this aspect the authors recommended the measurement of the central venous-to-arterial CO₂ difference (p(cv-a)CO₂) as a complementary target to identify persistent ischaemic hypoxia [5,6]. P(cv-a)CO₂ is an estimate of mixed venous-to-arterial CO₂ difference (p(v-a)CO₂) and may have the same limitations as the ScvO₂, e.g. the exact sampling site, the haemodynamic condition, and the level of sedation. Patients after cardiac surgery exhibit certain problems after hypothermic cardiopulmonary bypass (CPB), namely rewarming, reperfusion, inflammation, and are often haemodynamically compromised to a certain degree. This may have a profound effect on regional and global perfusion in the immediate postoperative period, influencing p(cv-a)CO₂. Thus, whether a widening of the p(cv-a)CO₂ in the face of a ScvO₂ > 70% could also serve as a complementary target to identify inadequate global or regional tissue oxygenation in cardiac surgery patients is yet unknown.

Therefore we re-analyzed a study published before [7] where simultaneous measurements of ScvO₂, SvO₂, pcvCO₂, pvCO₂, arterial carbon dioxide pressure (paCO₂), gastric luminal carbon dioxide pressure (pgCO₂), cardiac index (CI), and arterial lactate levels were performed.

The aim of this study was to study the agreement between p(cv-a)CO₂ and p(v-a)CO₂, and explore the relationship of p(v-a)CO₂ with parameters of regional blood flow, i.e. gastric tonometry and global tissue oxygenation, namely SvO₂, and arterial lactate levels.

Material and methods
This is a re-analysis of a prospective observational study in elective cardiac surgery patients, investigating intramyocardial oxygen monitoring [7].

Following approval by the local ethical committee of the University of Lübeck and written informed consent, 28 patients underwent standard CABG. The data of three patients experiencing perioperative complications have been excluded from this analysis and have been published before [8]. Therefore 25 remaining patients were analysed.

Anaesthesia and surgical technique
Anaesthesia was induced with etomidate (0.3-0.5 mg·kg⁻¹) and sufentanyl (0.5-1 µg·kg⁻¹) and maintained with continuous infusions of propofol (5-8 mg·kg⁻¹·h⁻¹) and sufentanil (0.5-1 µg·kg⁻¹·h⁻¹). Muscle relaxation was achieved with pancuronium bromid (0.1 mg·kg⁻¹). Patients were mechanically ventilated in a volume controlled mode with 100% oxygen throughout the surgical procedure; the respiratory rate was adjusted to achieve normocapnia. Intraoperative fluid management was adjusted to achieve and maintain a central venous pressure between 8 to 12 mmHg and a pulmonary artery capillary occlusion pressure (PAOP) between 15 to 18 mmHg. Volume replacement was performed with Ringer’s solution and gelatine polysuccinate, as appropriate. Naso-pharyngeal and rectal temperature was continuously measured during the whole observation time. Standard CABG was performed in moderate hypothermia (32°C naso-pharyngeal) with a membrane oxygenator (Hilite; Medos, Stolberg, Germany) and a roller pump (Stöckert, München, Germany). The pump was primed with 1.430 ml Ringer’s solution, 250 ml of 20% mannitol, and 20 ml 8.4% (1 M) natriumbicarbonate. After median sternotomy and harvesting of the bypass grafts, patients were fully heparinized according to body weight in a dose of 300 IE/kg body weight. Activated clotting time was kept greater than 450 seconds. Aortic and two stage venous cannulation was used and after cross-clamping the heart was arrested using antegrade
cold crystalloid cardioplegia which was repeated every 20 minutes. Mean arterial blood pressure (MAP) during CPB was maintained at 60 to 80 mmHg. Vasopressors (nor-epinephrine) were applied, if necessary.

**Measurements**

Intra- and postoperatively all parameters were taken before CPB and every hour up to 6 hours after CPB. All patients were mechanically ventilated as long as clinically appropriate and were sedated with continuous infusion of propofol.

Additionally to standard monitoring with a three lead electrocardiogram, a transcutaneous oxygen sensor, a radial arterial and a central venous line, all patients were equipped with a pulmonary artery catheter for continuous determination of pulmonary artery pressures, automated semicontinuous measurement of cardiac output (CO)/cardiac index (CI), and continuous measurement of mixed venous oxygen saturation (SvO₂) (Vigilance®; Edwards Lifescience, Irvine, USA). Arterial blood samples were drawn for determination of oxygen (paO₂) and carbon dioxide (PaCO₂) tension, base excess (BE), arterial bicarbonate, and arterial pH (ABL 505 blood gas analyzer, Radiometer, Copenhagen, Denmark), as well as haemoglobin concentration and arterial lactate concentration. Simultaneously, central venous and mixed venous blood samples were drawn for determination of pcvCO₂, ScvO₂, and pvCO₂. p(cv-a)CO₂ and p(v-a)CO₂ were calculated.

A nasogastric tonometry catheter (TRIP NGS catheter, Tonometric Division, Instrumentarium, Helsinki, Finland) was placed in the stomach. Correct positioning was verified by auscultation over the gastric region, aspiration of gastric contents and radiologically with the next routine chest X-ray. The tonometer was connected to a Tonocap® (Datex, Helsinki, Finland). The Tonocap® measures gastric luminal pCO₂ (pgCO₂) which is in equilibrium with gastric mucosal pCO₂ by automatic gas capnometry. Briefly, the tonometer balloon is automatically filled with approximately 6 mL air and pCO₂ is measured every 10 min in a recirculating mode [9]. The difference of arterial and gastric pCO₂ (p(g-a)CO₂) was calculated which has been shown to reflect gastro-intestinal stagnant hypoxia secondary to hypovolaemia [10,11]. Negative values of p(g-a)CO₂ were set to zero. There was no enteral feeding as long as the tonometric tube was in place. To rule out intra-gastric CO₂ generation following the buffering of acid with bicarbonate patients received 300 mg ranitidine [12].

**Statistics**

Agreement between p(cv-a)CO₂ and p(v-a)CO₂, and ScvO₂ and SvO₂ were analyzed using the method by Bland and Altman [13]. The percentage error was calculated as 1.96 * SD/mean of reference method [14]. Correlations were assessed by calculating Pearson’s coefficient (r) and the coefficient of determination (R²). All data are presented as mean (SD) unless stated otherwise. A p value less than 0.05 was regarded significant.

**Results**

The demographic and operative data of the studied 25 patients are listed in table 1. The perioperative course of p(v-a)CO₂ and p(cv-a)CO₂ is shown in fig.1. Pooled data of 127 simultaneous measurements could be analyzed. P(v-a)CO₂ and p(cv-a)CO₂ showed a significant correlation with a correlation index of r = 0.600. The Bland-Altman transformation revealed a bias of p(cv-a)CO₂ of 1.2 (3.4) mmHg, LOA of 6.7 mmHg with a percentage error of 152% (fig. 2). SvO₂ and ScvO₂ showed a significant correlation as well. Bias of ScvO₂ was -0.3 (7.8) % with LOA of 15.3 %. This resulted in a percentage error of 21.9 % (fig. 3).

Correlation analysis between p(v-a)CO₂ and CI, SvO₂, arterial lactate, and p(g-a)CO₂
revealed no meaningful significant correlations (see fig. 4).

**Discussion**

The main findings of this study are as follows:

- In cardiac surgery patients p(cv-a)CO$_2$ cannot be used as an estimate of p(v-a)CO$_2$ with acceptable accuracy.

- There is no reasonable association between p(v-a)CO$_2$ and Cl, SvO$_2$, or arterial lactate levels, as markers of the adequacy of global tissue oxygenation, and p(g-a)CO$_2$, as a marker of regional perfusion. Therefore neither p(v-a)CO$_2$, nor p(cv-a)CO$_2$ measurement can be recommended to rule out tissue hypoxia in postoperative cardiac surgery patients.

### Table 1: Demographic and perioperative data

<table>
<thead>
<tr>
<th>Gender [female / male]</th>
<th>7 / 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>69 (8)</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>171 (7)</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>77 (14)</td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>61 (13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of grafts performed</th>
<th>2-ACVG [n]</th>
<th>2-ACVG + IMA [n]</th>
<th>3-ACVG [n]</th>
<th>3-ACVG + IMA [n]</th>
<th>4-ACVG + IMA [n]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>8</td>
<td>5</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of surgery [min]</th>
<th>226 (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross clamp time [min]</td>
<td>45 (20)</td>
</tr>
<tr>
<td>Duration of cardiopulmonary bypass [min]</td>
<td>93 (17)</td>
</tr>
<tr>
<td>Duration of ventilation [hours]</td>
<td>13 (5)</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; ACVG, Aorto coronary venous graft; IMA, Internal mammaria artery graft

**Figure 1: Perioperative course of p(v-a)CO$_2$ and p(cv-a)CO$_2$**
These results are in contrast with some of the existing literature. In a heterogenous group of critically ill patients Cuschieri et al. showed a strong agreement between p(v-a)CO\(_2\) and p(cv-a)CO\(_2\) measurements [15]. In addition, they revealed a high correlation between p(cv-a)CO\(_2\) and CI. There are possible reasons for these different results. Unfortunately, p(cv-a)CO\(_2\) mostly represents venous carbon dioxide from the upper part of the body, even if the tip of the central venous catheter is located near the right atrium. Cerebral CO\(_2\)-production is very different between awake and sedated states, not necessarily reflecting different states of cardiac performance [2,16]. In addition, CO\(_2\)-production from the lower part of the body might increase very much during reperfusion after hypothermic CPB. This will result in false low CO\(_2\)-differences when p(cv-a)CO\(_2\) is measured to estimate p(v-a)CO\(_2\). In our opinion p(cv-a)CO\(_2\) should be used very cautiously, at least in cardiac surgery patients.

There is clear experimental evidence, that stagnant tissue hypoxia is associated with a widening of the venous-to-arterial pCO\(_2\)-difference, depending on the region of interest [17-19]. In the present study no clear relationship between p(v-a)CO\(_2\) and markers of global tissue oxygenation, as SvO\(_2\) and arterial lactate levels, or CI could be demonstrated. One reason could be the inevitable inaccuracy of blood gas analyzers, accounting for up to
10% bias. In contrast to laboratory studies in clinical investigations much less parameters effecting CO$_2$-production, eg. exact body temperature, level of sedation, and alveolar ventilation, can be controlled for. Especially body temperature is a very crucial point in postoperative cardiac surgery patients. There is a high interindividual variability in the rate of rewarming of peripheral tissue beds after hypothermic CPB, resulting in a varying degree of CO$_2$-production. These factors might even be worse in clincial routine, where eg. different blood gas analyzers are used, possibly increasing the inaccuracy.

Vallée et al. demonstrated in patients with septic shock that some degree of tissue hypoxia might be present even with ScvO$_2$ values $> 70\%$ [5]. In their study these patients could be identified by a p(cv-a)CO$_2$ of more than 6 mmHg [5]. Futier et al. reported on patients undergoing major abdominal high risk surgery [6]. 15% of the patients showed a ScvO$_2$ $> 71\%$, but developed major complications. A p(cv-a)CO$_2$ of more than 5mmHg had the most predictive threshold value in these patients [6]. That patients with a ScvO$_2$ $> 70\%$ still have an inadequacy of regional or global tissue oxygenation may be due to the inevitable limitations of the parameter [20-22]. For example, stagnant tissue hypoxia in the lower part of the body may be unrecognized. While ScvO$_2$ measurements are an established monitoring parameter in septic patients [1], many questions have not been answered for other patient groups [21,23,24]. Sander et al. studied cardiac surgery patients and revealed a reasonable correlation and bias between SvO$_2$ and ScvO$_2$ measurements, but large limits of agreement [23]. They conclude, that under certain conditions
these parameters may differ significantly. We confirmed these results with the present study showing a high, significant correlation, and a low bias, but large LOA between the two parameters. Perz et al. demonstrated that in elective cardiac surgery patients a low (< 60%) and a supranormal (> 77%) ScvO2 were associated with an unfavourable outcome, while patients with normal values (61-76%) showed no complications. Values for p(cv-a)CO2 were not reported [25].

Thus, up to now ScvO2 monitoring should be used very cautiously, especially in cardiac surgery patients.

In the present study no reasonable relationship between p(v-a)CO2 and lactate or p(g-a)CO2 could be demonstrated. While arterial lactate is a well accepted routine marker of global tissue oxygenation [26], gastric tonometry has been criticized of being unspecific to tissue hypoxia in critically ill patients [27]. In addition, interventional trials aimed at improving an abnormal gastric mucosal pH, showed no impact on outcome [28]. Therefore, routine use of gastric tonometry is not recommended [29]. Nevertheless, gastric tonometry has been proven to be an early warning sign of low regional oxygen delivery [27,30-32]. As neither lactate nor p(g-a)CO2 increased in parallel with widening of p(v-a)CO2, this parameter cannot be recommended for routine use in cardiac surgery patients, until further information about thresholds, sensitivity, and timing are elaborated.

There are limitations of the study.

The studied patients group is very small, and the study is a re-analysis of an older study. Although the data were prospectively collected, they were not intended to evaluate the relationship between p(v-a)CO2 and p(cv-a)CO2. Therefore no definite conclusions can be drawn.

No patients showed an unfavourable course. As can be seen in the Bland Altman diagram, a wide range of p(v-a)CO2 and SvO2 values were observed. But these did not seem to have an effect on outcome. We conclude that in cardiac surgery patients p(cv-a)CO2 cannot be used as an estimate of p(v-a)CO2 with acceptable accuracy. There is no evidence that measurements of p(cv-a)CO2 or p(v-a)CO2 could help diagnose global or regional tissue hypoxia in this patient group. Unless more information on the relationship between central-venous parameters with other parameters of tissue oxygenation and especially the therapeutic implications of pathological values of these parameters are known, p(cv-a)CO2 or p(v-a)CO2 and ScvO2 should be interpreted very cautiously.

Financial Support

This study was supported by institutional resources of the Department of Anesthesiology, University of Luebeck, Germany.

References


Correspondence address:
Hermann Heinze, M.D.
Department of Anesthesiology
University of Lübeck
Ratzeburger Allee 160
23538 Lübeck
Germany
hermann.heinze@uk-sh.de