The relationship of CO2 metabolism to tissue perfusion, microcirculation, and treatment response in shock and sepsis
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CHAPTER 2

END-TIDAL CO\(_2\) PRESSURE DETERMINANTS DURING HEMORRHAGIC SHOCK
ABSTRACT

Objectives: To examine the relationship between end-tidal CO\(_2\) (PETCO\(_2\)) and its physiological determinants, pulmonary blood flow (cardiac output, CO) and CO\(_2\) production (VCO\(_2\)), in a model of hemorrhagic shock during fixed minute ventilation.

Design and setting: Prospective, observational study in a research laboratory at a university center.

Subjects and interventions: Six anesthetized, intubated, and mechanically ventilated mongrel dogs. Progressive stepwise bleeding.

Measurements and results: We continuously measured PETCO\(_2\) with a capnograph, pulmonary artery blood flow with an electromagnetic flow probe, arterial oxygen saturation (SaO\(_2\)) with a fiberoptic catheter, and oxygen consumption (VO\(_2\)) and VCO\(_2\) by expired gases analysis. Oxygen delivery (DO\(_2\)) was continuously calculated from pulmonary blood flow and SaO\(_2\). We studied the correlation of PETCO\(_2\) with CO and VCO\(_2\) in each individual experiment. We also calculated the critical point in the relationships PETCO\(_2\)/DO\(_2\) and VO\(_2\)/DO\(_2\) by the polynomial method. As expected, PETCO\(_2\) was correlated with CO. The best fit was logarithmic in all experiments (median \(r^2 = 0.90\)), showing that PETCO\(_2\) decrease is greater in lowest flow states. PETCO\(_2\) was correlated with VCO\(_2\), but the best fit was linear (median \(r^2 = 0.77\)). Critical DO\(_2\) for PETCO\(_2\) and VO\(_2\) was 8.0±3.3 and 6.3 ± 2.5 ml.min\(^{-1}\).kg\(^{-1}\), respectively (NS).

Conclusions: Our data reconfirm the relationship between PETCO\(_2\) and CO during hemorrhagic shock. The relatively greater decrease in PETCO\(_2\) at lowest CO levels could represent diminished CO\(_2\) production during the period of VO\(_2\) supply dependency.

Keywords. Capnography - End-tidal CO\(_2\) pressure - CO\(_2\) production - Cardiac output - Hemorrhagic shock

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INTRODUCTION

Alveolar CO₂ and end-tidal CO₂ are normally determined by CO₂ production (VCO₂), alveolar ventilation, pulmonary perfusion, and V/Q matching [1]. Despite this some investigators [2, 3, 4] suggest that in low-flow states end-tidal CO₂ pressure (PETCO₂) depends primarily on blood flow. In recent years there has been a growing experimental and clinical body of evidence demonstrating that PETCO₂ monitoring is a useful and simple method of tracking cardiac output (CO) during cardiopulmonary resuscitation [5, 6, 7, 8]. Additionally, investigators have confirmed that PETCO₂ can be used as a prognostic tool in cardiac arrest [2, 9, 10-12]. We have also shown its value in other low-flow states such as hemorrhagic shock [13]. To better characterize this relationship we studied PETCO₂ and its physiological determinants during fixed minute ventilation in a model of hemorrhagic shock. We hypothesized that during critical reductions in CO the fall in PETCO₂ could also be ascribed to decreased metabolic production of CO₂. In addition to, previous studies have measured CO by thermodilution, a method that lacks accuracy in low-flow conditions. We sought to improve this drawback by the use of an electromagnetic flow probe.

MATERIALS AND METHODS

This study was approved by the local Animal Care Committee. Care of the studied animals was in accordance with National Institutes of Health guidelines.

Animal preparation

Six mongrel dogs weighing 27.3 ± 5.9 kg were anesthetized with 30 mg/kg sodium pentobarbital, with supplemental doses as needed. They were intubated and ventilated in supine position, with a volume-cycled ventilator (Harvard Apparatus Dual Phase Control Respirator Pump Ventilator, model 613 A, Harvard Apparatus, Southnatick, Mass., USA), with a tidal volume of 15 ml/kg, FIO₂ of 0.21, a respiratory rate adjusted to an initial PETCO₂ of 30 torr, and I/E ratio of 0.3. This pattern was kept constant throughout the experiment. Neuromuscular blockade was provided with pancuronium bromide (0.06 mg/kg). Catheters (Oximetrix Flow-directed thermodilution fiberoptic pulmonary artery catheter model P 7110, Abbott Critical Care Systems, Mountain View, Calif., USA) were placed in the pulmonary artery through the right jugular vein and in the abdominal aorta through the right femoral artery to continuously measure oxygen saturations and to extract blood samples. We also cannulated the left femoral artery and vein to bleed the dogs and to measure mean arterial pressure and to administer fluids and drugs, respectively. After performing a medial sternotomy the main pulmonary artery was carefully dissected and a 14- or 16-mm electromagnetic
flow probe (Flo-probe Blood Flowmeter Transducer, Gould-Statham Instruments, Oxnard, Calif., USA) was placed around it.

Measurements and calculations
Pulmonary blood flow was continuously measured with an electromagnetic flow transducer (Spectramed Blood Flowmeter model SP 2202 B, Spectramed, Oxnard, Calif., USA). PETCO₂ was continuously measured at the tip of the endotracheal tube with a previously calibrated capnograph (Tonocap, Datex Instrumentarium, Helsinki, Finland). Minute-to-minute oxygen consumption (VO₂) and CO₂ elimination (VCO₂) were measured with a metabolic cart (Deltatrac, Datex Instrumentarium) [14]. Oxygen delivery (DO₂) was continuously calculated as the product of pulmonary blood flow and arterial oxygen content (CaO₂). CaO₂ was estimated as hemoglobin x arterial O₂ saturation x 1.34 + 0.0031 x arterial PO₂. The aortic fiberoptic catheter constantly displayed arterial oxygen saturation, and PaO₂ was calculated from it with the aid of the oxyhemoglobin dissociation curve. Fiberoptic catheter oxygen saturation was calibrated with a simultaneous blood sample measured in a co-oximeter (OSM 3, Radiometer, Copenhagen, Denmark). After each bleeding step arterial and mixed venous samples were extracted to measure gases (ABL 30, Radiometer), oxygen saturations, and hemoglobin. CaO₂ was corrected with each new hemoglobin value. Pulmonary blood flow, PETCO₂, and oxygen saturation were continuously acquired with a personal computer through a digital-analogical converter.

Experimental procedure
After basal hemodynamic and oxygen transport measurements we performed consecutive bleeding of 6 ml/kg with 10 min between them. The experiment continued until a circulatory crisis of rapidly falling arterial blood pressure occurred. Core temperature was monitored by the pulmonary catheter and was kept constant with a heating lamp throughout the experiment. At the end of the protocol dogs were killed with an intravenous KCl bolus.

Data analysis
Digitally acquired PETCO₂ and pulmonary blood flow values were averaged for 1-min periods, and correlations with simultaneously gathered VCO₂ values were examined. In each experiment, the relationships of PETCO₂ to CO and to VCO₂ were tested for linear as well as for logarithmic fit, using the method of least square regression. We chose the function that showed the best determination coefficient (the best r²). Additionally, we compared linear against logarithmic fits using a nonparametric test (Wilcoxon signed rank test). Critical DO₂ points for PETCO₂/DO₂ and VO₂/ DO₂ relationships were calculated by the polynomial method [15] and compared by a t test.
RESULTS
Table 1 displays hemodynamic and metabolic data at baseline and at each bleeding step. PETCO₂ was correlated with CO. In all experiments the logarithmic fit was better than the linear [median $r^2 = 0.90$ (range = 0.63-0.95) vs. 0.82 (range = 0.49-0.89), $p < 0.02$], which suggests that PETCO₂ decrease is accentuated with low flow values. PETCO₂ was also correlated with VCO₂, but the best fit was linear [median $r^2 = 0.77$ (range = 0.59-0.85) vs. 0.74 (range = 0.60-0.83), $p <0.05$]. Figure 1 shows the relationships of PETCO₂ with CO and VCO₂ in a typical experiment. Figure 2 shows changes in PETCO₂, VO₂, and VCO₂ related to changes in DO₂ during bleeding (mean ± SEM). Mean critical DO₂ for PETCO₂ and VO₂ were 8.0 ± 3.3 and 6.3 ± 2.5 ml • min⁻¹ • kg⁻¹, respectively (NS).

DISCUSSION
In steady-state conditions alveolar CO₂ elimination, and therefore PETCO₂, depend on CO₂ production and on alveolar ventilation and pulmonary perfusion, that is to say, CO. If any two of these variables are held constant, any change in PETCO₂ reflects an alteration in the third variable. Using this relationship, investigators have demonstrated that PETCO₂ effectively tracks hemodynamic changes in experimental and clinical settings of no-flow or low-flow conditions [2-13]. For example, during cardiac arrest PETCO₂ falls close to zero [5-12]. When cardiopulmonary resuscitation starts, PETCO₂ increases and is correlated to pulmonary blood flow [5-7]. Other investigators extended these findings to low-flow conditions such as hemorrhagic [13, 16], anesthetic [17], and obstructive shock [18].

The PETCO₂/CO relationship has been described as linear. Weil et al. [5] and Gazmuri et al. [7] have described a strong linear correlation between CO and PETCO₂ after the induction of ventricular fibrillation in minipigs. Isserles and Breen [18] induced an acute decrease in CO in dogs and found that the proportional decrease in PETCO₂ was directly correlated with the decrease in CO. Lastly, in anesthetized patients undergoing aortic aneurismal surgery with constant ventilation Shibutani et al. [17] described a linear correlation of both PETCO₂ and VCO₂ with CO; ratios between the proportional decrease in PETCO₂ and VCO₂ to the proportional decrease in CO were 1:3.

However, other investigators have reported other findings on the PETCO₂/CO relationship. Morimoto et al. [19] during cardiopulmonary resuscitation in dogs found a 37 % decrease in PETCO₂, corresponding to a 77% reduction in CO, which would result in a greater ratio (approximately 1:2). In a model of hemorrhagic shock in dogs we have previously shown that a logarithmic function better fits the PETCO₂/CO relationship; this implies that the greatest PETCO₂ decrements occur with the lowest blood flows [13]. Ornato et al. [16] obtained similar results to ours in a design of stepwise reductions in CO in sheep.
<table>
<thead>
<tr>
<th>Metric</th>
<th>Basal</th>
<th>Bleeding # 1</th>
<th>Bleeding # 2</th>
<th>Bleeding # 3</th>
<th>Bleeding # 4</th>
<th>Bleeding # 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH</td>
<td>7.36 ± .04</td>
<td>7.35 ± 0.05</td>
<td>7.33 ± 0.06</td>
<td>7.31 ± 0.06</td>
<td>7.27 ± 0.09*</td>
<td>7.18± 0.12*</td>
</tr>
<tr>
<td>Arterial PCO₂ (torr)</td>
<td>27 ± 1</td>
<td>30 ± 4</td>
<td>28 ± 4</td>
<td>27 ± 5</td>
<td>24 ± 5</td>
<td>24 ± 3</td>
</tr>
<tr>
<td>Arterial PO₂ (torr)</td>
<td>72 ± 15</td>
<td>70 ± 9</td>
<td>68 ± 11</td>
<td>72 ± 21</td>
<td>77 ± 26</td>
<td>74 ±2 5</td>
</tr>
<tr>
<td>End-tidal PCO₂ (torr)</td>
<td>23 ± 4</td>
<td>22 ± 4</td>
<td>21 ± 4</td>
<td>20 ± 5</td>
<td>16 ± 5</td>
<td>14 ± 5*</td>
</tr>
<tr>
<td>CO (l min⁻¹ kg⁻¹)</td>
<td>0.099 ± 0.015</td>
<td>0.077 ± 0.007*</td>
<td>0.060 ± 0.007**</td>
<td>0.045 ± 0.005*</td>
<td>0.032 ± 0.005*</td>
<td>0.028 ± 0.012**</td>
</tr>
<tr>
<td>DO₂ (l min⁻¹ kg⁻¹)</td>
<td>14.6 ± 4.2</td>
<td>11.6 ± 3.5</td>
<td>9.0 ± 2.8</td>
<td>6.6 ± 2.3**</td>
<td>4.3 ± 1.9**</td>
<td>3.5 ± 1.8**</td>
</tr>
<tr>
<td>VO₂ (l min⁻¹ kg⁻¹)</td>
<td>5.3 ± 0.6</td>
<td>4.8 ± 0.7</td>
<td>4.8 ± 0.7</td>
<td>4.3 ± 0.9</td>
<td>3.9 ± 0.9</td>
<td>2.6 ± 0.8**</td>
</tr>
<tr>
<td>VCO₂ (l min⁻¹ kg⁻¹)</td>
<td>4.4 ± 0.5</td>
<td>4.2 ± 0.6</td>
<td>4.0 ± 0.6</td>
<td>3.6 ± 0.7</td>
<td>3.3 ± 0.7</td>
<td>2.6 ± 0.7**</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>0.84 ± 0.07</td>
<td>0.88 ± 0.10</td>
<td>0.84 ± 0.06</td>
<td>0.86 ± 0.07</td>
<td>0.86 ± 0.06</td>
<td>1.02 ± 0.07*</td>
</tr>
<tr>
<td>Pa-ETCO₂ (torr)</td>
<td>3.0 ± 1.3</td>
<td>6.7 ± 3.7</td>
<td>6.5 ± 2.2*</td>
<td>8.3 ± 3.2*</td>
<td>9.2 ± 3.4**</td>
<td>10.5 ± 3.5**</td>
</tr>
<tr>
<td>Pv-aCO₂ (torr)</td>
<td>5.7 ± 3.7</td>
<td>5.0 ± 2.2</td>
<td>7.8 ± 0.8</td>
<td>11.2 ± 9.0</td>
<td>22.3 ± 10.7*</td>
<td>27.7 ± 13.7*</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001 vs. basal (by repeated measures of analysis of variance followed by t test with Bonferroni correction)
Our results could be explained at least by three factors. First, we studied not only the steep and plateau portions of the curve but its whole range, from mild decreases in CO, as Shibutani et al. [17] did, to deep shock. Next, we took a different approach to data analysis, comparing linear to logarithmic fit and choosing the best determination coefficient ($r^2$). Finally, continuous digitalized data might improve the description of a mathematical function. To our knowledge, this is the first shock study evaluating PETCO$_2$/CO relationship in which CO is measured with an electromagnetic flow probe. Accuracy in low CO ranges may certainly be greater than with the thermodilution method [20].

As expected, PETCO$_2$ and VCO$_2$ were linearly correlated. VCO$_2$ depends on two different factors: pulmonary excretion and metabolic production of CO$_2$. In low flow and constant ventilation conditions, VCO$_2$ falls secondary to decreased delivery of CO$_2$ to the lungs and to pulmonary blood flow heterogeneity, with subsequent increase in alveolar deadspace. Although precise patterns of perfusion can be defined only by the multiple inert gases technique, an increased arterial-end-tidal PCO$_2$ gradient (Pa-ETCO$_2$) might reflect high V/Q relationships frequently noted.

Fig. 1. Relationships of end-tidal CO$_2$ pressure (PETCO$_2$) with CO and CO$_2$ production (VCO$_2$) in a typical experiment.

Fig. 2. Relationship between end-tidal CO$_2$ pressure (PETCO$_2$), CO$_2$ production (VCO$_2$), and O$_2$ consumption (VO$_2$) with O$_2$ delivery. Data are shown as mean ± SEM.
in this setting [21]. Accordingly, in this study Pa-ETCO₂ rose significantly after the last bleeding period (from 3 ± 1 to 11 ± 4 torr). Determination of CO₂ production, the other variable that affects VCO₂ and PETCO₂, is more elusive. Metabolic carts do not report the extent to which the measured reduction in VCO₂ is due to a fall in excretion or in production. Some investigators have questioned whether reductions in CO₂ production in cardiac arrest and shock might affect VCO₂ [17, 18]. Weil et al. [22, 23] showed that VCO₂ nearly fell to zero after induction of ventricular fibrillation in pigs, and that it increased parallel to CO with the start of chest wall compression. When normal heart rhythm was restored, there was a great elevation in CO and an overshoot in VCO₂, in accordance with a fall in the venoarterial PCO₂ gradient. Relman [24] concludes that the findings of Weil et al. not only show a reduction in pulmonary CO₂ excretion but suggest a net reduction in CO₂ production as well, because VCO₂ overshoot after rhythm restoration was lower than cumulative reduction in CO₂ excretion during ventricular fibrillation. In cardiac arrest studies CO certainly decreases below the level that supports critical oxygen delivery to tissues (DO₂crit) [25], hence oxygen consumption falls and, accordingly, CO₂ production decreases, which leads to diminished PETCO₂ and VCO₂. In our study DO₂crit was also reached (6.3 ± 2.5). Interestingly, this value did not differ statistically from the DO₂ level below which PETCO₂ fell (8.0 ± 3.3). As in the study by Guzman et al. [3], PETCO₂ effectively indicated the onset of supply dependency.

The likelihood of changes in CO₂ stores after CO modifications further complicates the analysis [26]. An increase in CO increases CO₂ transport from the tissues to the lung, and tissue CO₂ stores therefore decrease. Conversely, a decrease in CO builds up CO₂ storage [26]. For example, in head-out immersion CO increases by 47 %, and CO₂ stores decrease by 148 ml. CO₂ elimination starts rapidly and recovers after a mean of 79.3 s [27]. Longer stabilization periods have been suggested, particularly during decreases in CO [28]. These calculations demand a breath-to-breath technique to measure VCO₂, and a limitation of this study is that the metabolic cart reports it on minute-to-minute basis. In our experimental design the relatively long periods of 10 min between each bleeding step should have allowed a steady state, at least in blood CO₂ stores.

In conclusion, with an improved methodology, our results reaffirm the logarithmic relationship between CO and PETCO₂. Although not confirmed in this study, the greatest reduction in PETCO₂ observed with a critical CO decrease might be attributed not only to a lessening of its excretion but also to a decrease in its production, during the phase of oxygen supply-dependent metabolism. Our data provide a better description of a physiological phenomenon and reinforce previous work on the clinical usefulness of PETCO₂ for tracking changes in pulmonary blood flow and for warning of ongoing anaerobic metabolism.
REFERENCES