Effects of hyper- and hypoventilation on gastric and sublingual \( \text{PCO}_2 \)

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Pernat, Andrej, Max Harry Weil, Wanchun Tang, Hitoshi Yamaguchi, Andreja Marn Pernat, Shijie Sun, and Joe Bisera. Effects of hyper- and hypoventilation on gastric (\( \text{PgCO}_2 \)) and sublingual (\( \text{PslCO}_2 \)) tissue \( \text{PCO}_2 \) before, during, and after reversal of hemorrhagic shock. \( \text{PgCO}_2 \) was measured with ion-sensitive field-effect transistor sensor and \( \text{PslCO}_2 \) with a \( \text{CO}_2 \) microelectrode. Under physiological conditions and during hemorrhagic shock, decreases in arterial (\( \text{PaCO}_2 \)) and end-tidal (\( \text{PETCO}_2 \)) \( \text{PCO}_2 \) induced by hyperventilation produced corresponding decreases in \( \text{PgCO}_2 \) and \( \text{PslCO}_2 \). Hyperventilation produced corresponding increases in \( \text{PaCO}_2 \), \( \text{PETCO}_2 \), \( \text{PgCO}_2 \), and \( \text{PslCO}_2 \). Accordingly, acute decreases and increases in \( \text{PaCO}_2 \) and \( \text{PETCO}_2 \) produced statistically similar decreases and increases in \( \text{PgCO}_2 \) and \( \text{PslCO}_2 \). No significant changes in the tissue \( \text{PCO}_2 \)-\( \text{PaCO}_2 \) gradients were observed during hemorrhagic shock in the absence or in the presence of hyper- or hypoventilation. Acute changes in \( \text{PgCO}_2 \) and \( \text{PslCO}_2 \) should, therefore, be interpreted in relationship with concurrent changes in \( \text{PaCO}_2 \) and/or \( \text{PETCO}_2 \).

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MATERIALS AND METHODS

The study was approved by the Institute’s Animal Care Committee. All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research, and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health.

Animal preparation. Sprague-Dawley rats were fasted overnight, except for free access to water. Anesthesia was initiated by an intraperitoneal injection of 45 mg/kg pentobarbital sodium and supplemented with additional doses of 10 mg/kg at hourly intervals. Animals were positioned on a surgical board in a supine position with extremities immobilized in full abduction. The trachea was surgically exposed, and a 14-gauge cannula (Abboctath-T, Abbott Hospital, North Chicago, IL) was advanced into the trachea for a distance of 2 cm. End-tidal \( \text{PCO}_2 \) (\( \text{PETCO}_2 \)) was measured with a side-stream infrared \( \text{CO}_2 \) analyzer (End-Tid IL 200, Instrumentation Laboratory, Lexington, MA) adapted to the tracheal tube. The tracheal tube was connected to a volume-controlled mechanical ventilator (model 683, Harvard Apparatus, South Natick, MA). The inspired \( \text{O}_2 \) concentration was maintained at 60%. Neuromuscular blockade was induced with a bolus of 0.1 mg/kg vecuronium bromide injected intravenously followed by a continuous intravenous infusion of 1 \( \mu \text{g·kg}^{-1} \cdot \text{min}^{-1} \). Frequency of ventilation was initially established at 80 breaths/min and tidal volume at 0.65 ml/100 g body wt. Tidal volume was then adjusted to maintain \( \text{PETCO}_2 \) between 35 and 40 Torr.

From the surgically exposed right carotid artery, an 18-gauge polyethylene catheter (Intramedic PE50, Becton-Dickinson, Sparks, MD) was advanced into the thoracic aorta for aortic blood pressure measurements and blood sampling. Through the left jugular vein, another 18-gauge polyethylene catheter was advanced into the right atrium. This catheter allowed for injection of chilled saline at 10°C as a thermal tracer for cardiac output measurements. Through the surgically exposed left femoral artery and vein, 18-gauge catheters

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were advanced into the abdominal aorta and into the inferior vena cava. These catheters allowed for arterial blood shedding and for reinfusion of shed blood into the vena cava. Through the surgically exposed right femoral artery, a thermocouple microprobe (model 9030-12-34, Columbus Instruments, Columbus, OH) was advanced into the thoracic aorta for measurements of cardiac output. The dead space of the catheters was filled with normal saline containing 5 IU/ml bovine heparin. The aortic catheter was connected to the barrel of a 20-ml plastic syringe, which served as a reservoir for shed blood.

\( P_{slCO_2} \) was measured with a CO\(_2\) microelectrode (MI-720 CO\(_2\) electrode, Microelectrodes, Londonderry, NH). The sensor was lodged between the tongue and sublingual mucosa and secured against the closed mouth with adhesive tape.

For placement of the \( P_{gCO_2} \) sensor, the stomach was exposed with a midline epigastric incision. An ion-sensitive field-effect transistor sensor (CO-1035, Nihon Kohden, Tokyo, Japan) was embedded into the submucosa of the anterior wall of the stomach to a depth of 1 mm and secured by a ligature. The abdomen was then closed in one layer.

Experimental procedures. After anesthesia, instrumentation, neuromuscular blockade, and mechanical ventilation had been established, baseline measurements were recorded. Rats weighing between 450 and 550 g were investigated. Under physiological conditions, \( P_{aCO_2} \) and \( P_{ETCO_2} \) in five animals were decreased during hyperventilation for an interval of 30 min. They were then restored to baseline levels of ventilation for a subsequent interval of 30 min. \( P_{aCO_2} \) and \( P_{ETCO_2} \) were then increased during hyperventilation, also for an interval of 30 min, and then returned to baseline levels of ventilation for a final interval of 60 min. The protocol is summarized in Fig. 1.

Ten animals were subjected to bleeding over an interval of 60 min and then randomized to a protocol of either hyperventilation in five animals or hypoventilation in five animals, as shown in Figs. 2 and 3, respectively. Bleeding was commenced 15 min after the baseline measurements had been completed. Blood was allowed to flow from the aortic catheter into the reservoir filled with 1 ml of saline containing 5 IU of porcine heparin/ml to prevent clotting of shed blood. As previously described (28), the rate of bleeding was regulated by fine adjustments of pressure within the reservoir utilizing a pressure regulator (model 10, Fairchild, Winston-Salem, NC) and a mercury manometer. The barrel was initially pressurized at 100 mmHg for 10 min, and thereafter decreased to 80 mmHg for 20 min and to 70 mmHg for another 20 min. Aortic pressure was then reduced to values ranging from 55 to 60 mmHg, and it was maintained at this level for an additional 50 min. After 60 min, the animals were randomized to either hypocapnia or hypercapnia by the sealed-envelope method. Hypocapnia or hypercapnia was induced by increasing ventilatory frequency to 140 breaths/min or decreasing it to 40 breaths/min, respectively. After 20 min, ventilatory frequency was restored to the baseline level of 80 breaths/min and maintained at that level until blood was reinfused, as shown in Figs. 2 and 3. Measurements were obtained for an additional interval of 30 min after completion of reinfusion.

At the end of the experiment, animals were euthanized by an intravenous injection of 100 mg/kg pentobarbital sodium. An autopsy was performed with gross inspection of thoracic and abdominal organs to identify potential adverse effects of the surgical interventions.

Measurements. A two-point calibration of electrodes for measurements of \( P_{slCO_2} \) and \( P_{gCO_2} \) preceded and followed each experiment, with tonometers maintained at 37°C and with gas mixtures of nitrogen and either 5% or 15% CO\(_2\).

Blood pH, \( P_{aCO_2} \), \( P_{O_2} \), and lactate were measured on 0.5-ml blood samples utilizing an automated blood-gas and electrolyte analyzer (Stat Profile Ultra, Nova Biomedical, Waltham, MA). Cardiac output was measured by an adaptation of the thermodilution technique in which a bolus of 200 µl of saline was injected into the right atrium, and blood temperatures were measured in the thoracic aorta. Cardiac index was computed with an adaptation of commercially available data.
acquisition system and software (National Instruments, Austin, TX). All electronic outputs were recorded on a PC-based data-acquisition system utilizing CODAS software (DATAQ Instruments, Akron, OH) at a sampling rate of 300/s. Data analyses. Means ± SD are reported. Time-based values within groups were analyzed by repeated-measures ANOVA. Differences in time-based values were analyzed by Tukey's procedures for post hoc tests. Relationships among PGCO2, PslCO2, and PaCO2 were analyzed with time series cross-correlation techniques. Proportional changes in PaCO2 and tissue PCO2 parameters after hypo- and hypercapnia were compared by Friedman's ANOVA and the Wilcoxon signed-rank pairs test. A P value of <0.05 was regarded as significant.

RESULTS

No abnormalities were observed on gross examination at autopsy, and no animals were excluded from data analyses.

Table 1. Hemodynamic parameters, PETCO2, and tissue PCO2-to-PaCO2 gradients during hyper- and hypoventilation under physiological conditions

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1 (30 min)</th>
<th>Hyperventilation (60 min)</th>
<th>Baseline 2 (90 min)</th>
<th>Hypoventilation (120 min)</th>
<th>Normoventilation (180 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>154 ± 7</td>
<td>156 ± 9</td>
<td>139 ± 9*</td>
<td>134 ± 10*</td>
<td>142 ± 15</td>
</tr>
<tr>
<td>Cardiac Index, ml·min⁻¹·kg⁻¹</td>
<td>297 ± 27</td>
<td>276 ± 45</td>
<td>263 ± 32</td>
<td>277 ± 24</td>
<td>267 ± 33</td>
</tr>
<tr>
<td>PETCO2, Torr</td>
<td>39 ± 3</td>
<td>24 ± 3</td>
<td>37 ± 2</td>
<td>71 ± 8</td>
<td>36 ± 5</td>
</tr>
<tr>
<td>PGCO2-PaCO2, Torr</td>
<td>16 ± 6</td>
<td>13 ± 5</td>
<td>17 ± 7</td>
<td>20 ± 9</td>
<td>19 ± 6</td>
</tr>
<tr>
<td>PslCO2-PaCO2, Torr</td>
<td>14 ± 2</td>
<td>10 ± 4</td>
<td>14 ± 6</td>
<td>19 ± 7</td>
<td>16 ± 10</td>
</tr>
</tbody>
</table>

Values are means ± SD for n = 5 animals. MAP, mean arterial pressure; PETCO2, end-tidal PCO2; PGCO2-PaCO2, gradient between gastric and arterial PCO2; PslCO2-PaCO2, gradient between sublingual and arterial PCO2. *P < 0.01 vs. Baseline 1.
and 4).

...onset of shock is associated with increases in... As in the present experiments, indicators of the presence of perfusion failure and, there-

Table 2. Absolute increases and decreases in PaCO₂ and tissue PCO₂ after increases or decreases in ventilation under physiological conditions

<table>
<thead>
<tr>
<th></th>
<th>∆PaCO₂</th>
<th>∆PgCO₂</th>
<th>∆PslCO₂</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>12 ± 5</td>
<td>15 ± 1</td>
<td>16 ± 2</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>28 ± 8</td>
<td>33 ± 8</td>
<td>34 ± 8</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values are means ± SD in Torr. ∆, increase or decrease.

to 49 ± 5 Torr (P < 0.01), and PETCO₂ increased from 24 ± 4 to 54 ± 5 Torr (P < 0.01). These increases were associated with a time-coincident increase in PgCO₂ from 77 ± 11 to 106 ± 13 Torr (P < 0.05) and in PslCO₂ from 65 ± 6 to 87 ± 8 Torr (P < 0.01). After the frequency of ventilation was returned to baseline lev-

Table 4. Tissue PCO₂-to-PaCO₂ gradients during hyperventilation and hypoventilation superimposed on hemorrhagic shock

<table>
<thead>
<tr>
<th></th>
<th>Control, Prebleeding (BL)</th>
<th>Control, Hemorrhagic Shock (60 min)</th>
<th>Hyperventilation, Hemorrhagic Shock (80 min)</th>
<th>Control, Hemorrhagic Shock (100 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PgcO₂-PaCO₂</td>
<td>14 ± 3</td>
<td>43 ± 9*</td>
<td>36 ± 8*</td>
<td>40 ± 7*</td>
</tr>
<tr>
<td>PslCO₂-PaCO₂</td>
<td>13 ± 5</td>
<td>45 ± 12*</td>
<td>34 ± 6*</td>
<td>43 ± 6*</td>
</tr>
</tbody>
</table>

Hypoventilation

<table>
<thead>
<tr>
<th></th>
<th>Control, Prebleeding (BL)</th>
<th>Control, Hemorrhagic Shock (60 min)</th>
<th>Hyperventilation, Hemorrhagic Shock (80 min)</th>
<th>Control, Hemorrhagic Shock (100 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PgcO₂-PaCO₂</td>
<td>14 ± 6</td>
<td>52 ± 11*</td>
<td>57 ± 16*</td>
<td>52 ± 13*</td>
</tr>
<tr>
<td>PslCO₂-PaCO₂</td>
<td>13 ± 5</td>
<td>40 ± 6*</td>
<td>39 ± 7*</td>
<td>41 ± 10*</td>
</tr>
</tbody>
</table>

Values are means ± SD in Torr; n = 5 animals each for hyper- and hypoventilation, BL, baseline. *P < 0.01 vs. BL.

For practical purposes in clinical practice, acute increases or decreases in PgCO₂ or PslCO₂ may be adjusted by amounts that correspond to respective increases or decreases in PaCO₂, when these measurements are utilized for diagnosis and quantification of the severity of circulatory shock. As further demonstrated in our study, PETCO₂, of itself, is a close correlate of PaCO₂, and it may, therefore, serve as a noninvasive alternative for PaCO₂, for making such corrections. This is in accord with earlier proposals that differences between tissue PCO₂ and PaCO₂; the so-called tissue PCO₂-to-PaCO₂ gap, may be a more appropriate measurement than tissue PCO₂ alone (3, 5). The PCO₂ gap between tissues and arterial blood typically increases during shock. This reflects the effect of metabolic acidosis and especially lactic acidosis coincident with perfusion failure. Although the tissue PCO₂-to-PaCO₂ gap was not significantly different after the frequency of ventilation was increased or decreased in the present experiments, earlier studies provided evidence that the computation of such gradients increases precision. PgCO₂ and PslCO₂ were previously measured during hemorrhagic shock when mechanical ventilation remained constant (19). The PgCO₂-to-PaCO₂ gap increased from 43 ± 12 to 56 ± 8 Torr, and the PslCO₂-to-PaCO₂ gap increased from 52 ± 9 to 64 ± 6 Torr. Accordingly, measurement of the gap numerically amplified the changes. Yet, if hyperventilation is superimposed in the present study, there would be an apparent decrease in the PCO₂ gap and a potential underestimate of the severity of perfusion failure. Guzman et al. (15) have pointed to this dilemma. We also recognize the need for additional studies for the present experiments to pinpoint only acute changes in ventilation. Chronic effects of altered ventilation, the resulting respiratory acid-base changes, and how these may be related to measurements of PgCO₂ and PslCO₂ deserve additional studies. Such would best distinguish between compensated and decompensated states of acidosis (acidaemia) and alkalosis (alkalemia).

We further acknowledge that the present study is based on an experimental design that may not fully expose correction factors with which interpretation of tissue PCO₂ during circulatory shock states may be
improved. In selecting mechanical hypoventilation in anesthetized animals for inducing hypercarbia, rather than increases in inspired CO₂, we minimized hemodynamic effects. However, increases and decreases in ventilation were induced with mechanical ventilators in anesthetized animals. We, therefore, also recognize that both tissue measurements and gradients may be different during spontaneous hyper- or hypoventilation or in settings in which there are changes in the work of breathing.

In conclusion, quantitative values of tissue PCO₂ are moderated by acute changes in PaCO₂, both during normal circulation and in settings of hemorrhagic shock. Tissue PCO₂ as a marker of the severity of hypoperfusion must, therefore, be interpreted in relation to concurrent abnormalities in PaCO₂ and potentially in relationship to its noninvasive surrogate PETCO₂.

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