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

ANDREJ PERNAT,1 MAX HARRY WEIL,1 WANCHUN TANG,1,2 HITOSHI YAMAGUCHI,1 ANDREJA MARN PERNAT,1 SHIJIE SUN,1,2 AND JOE BISERA1,2

1Institute of Critical Care Medicine, Palm Springs 92262; and 2University of Southern California School of Medicine, Los Angeles, California 90033

Pernat, Andrej, Max Harry Weil, Wanchun Tang, Hitoshi Yamaguchi, Andreja Marn Pernat, Shijie Sun, and Joe Bisera. Effects of hyper- and hypoventilation on gastric and sublingual P\(\text{CO}_2\). J. Appl. Physiol. 87(3): 933–937, 1999.—We investigated the effects of hyper- and hypoventilation on gastric (\(P_{\text{gCO}_2}\)) and sublingual (\(P_{\text{sCO}_2}\)) tissue \(\text{CO}_2\) before, during, and after reversal of hemorrhagic shock. \(P_{\text{gCO}_2}\) was measured with ion-sensitive field-effect transistor sensor and \(P_{\text{sCO}_2}\) with a \(\text{CO}_2\) microelectrode. Under physiological conditions and during hemorrhagic shock, decreases in arterial (\(P_{\text{aCO}_2}\)) and end-tidal (\(P_{\text{ETCO}_2}\)) \(\text{CO}_2\) induced by hyperventilation produced corresponding decreases in \(P_{\text{gCO}_2}\) and \(P_{\text{sCO}_2}\). Hypoventilation produced corresponding increases in \(P_{\text{gCO}_2}\), \(P_{\text{ETCO}_2}\), \(P_{\text{PGCO}_2}\), and \(P_{\text{sCO}_2}\). Accordingly, acute decreases and increases in \(P_{\text{aCO}_2}\) and \(P_{\text{ETCO}_2}\) produced statistically similar decreases and increases in \(P_{\text{gCO}_2}\) and \(P_{\text{sCO}_2}\). No significant changes in the tissue \(P_{\text{CO}_2}\):\(P_{\text{aCO}_2}\) gradients were observed during hemorrhagic shock in the absence or in the presence of hyper- or hypoventilation. Acute changes in \(P_{\text{gCO}_2}\) and \(P_{\text{sCO}_2}\) should, therefore, be interpreted in relationship with concurrent changes in \(P_{\text{aCO}_2}\) and/or \(P_{\text{ETCO}_2}\). Mean arterial blood pressure fell from 80 to 35 and 40 Torr.

Recent reports indicated that, under physiological conditions, increases in arterial \(P_{\text{CO}_2}\) (\(P_{\text{aCO}_2}\)) are associated with increases in \(P_{\text{gCO}_2}\) and intestinal tissue \(P_{\text{CO}_2}\) (3, 22, 26). The effects of decreases in \(P_{\text{aCO}_2}\), under physiological conditions are as yet less well identified (22). Moreover, it is not as yet apparent how acute changes in \(P_{\text{aCO}_2}\) affect \(P_{\text{gCO}_2}\) and \(P_{\text{sCO}_2}\), as quantitative indicators of organ perfusion during the low-flow states of circulatory shock. In the present study, our intent was to extend earlier observations under physiological conditions to those under conditions of hemorrhagic shock. Our hypothesis was that, during hemorrhagic shock, acute increases or decreases in \(P_{\text{aCO}_2}\) induced by changes in the frequency of mechanical ventilation in anesthetized animals would alter the \(P_{\text{gCO}_2}\) and \(P_{\text{sCO}_2}\) measurements and thereby moderate the quantitative interpretation of these measurements as indicators of impaired tissue perfusion.

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 (Abbocath-T, Abbott Hospital, North Chicago, IL) was advanced into the trachea for a distance of 2 cm. End-tidal \(\text{CO}_2\) (\(P_{\text{ETCO}_2}\)) 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 \(\mu\)g·kg\(^{-1}\)·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 \(P_{\text{ETCO}_2}\) 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 were placed.
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.

PsICO₂ was measured with a CO₂ microelectrode (MI-720 CO₂ 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 PgCO₂ 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, PaCO₂ and PETCO₂ 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. PaCO₂ and PETCO₂ were then increased during hypoventilation, 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 PsICO₂, PsICO₂, PaCO₂, and end-tidal PCO₂ (PETCO₂) during hyperventilation (stippled area) superimposed on hemorrhagic shock in 5 animals. Hemodynamic data include mean arterial pressure (MAP), cardiac index, arterial blood lactate acid (lactate), and volume of blood removed before reinfusion (shed blood; shaded area). BL, baseline.
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 values within groups were analyzed by repeated-measures ANOVA. Differences in time-based values were analyzed 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 hyperventilation under physiological conditions

<table>
<thead>
<tr>
<th>Baseline 1 (30 min)</th>
<th>Hyperventilation (60 min)</th>
<th>Baseline 2 (90 min)</th>
<th>Hyperventilation (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>
</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>
</tr>
<tr>
<td>PETCO2, Torr</td>
<td>39 ± 3</td>
<td>24 ± 3</td>
<td>37 ± 2</td>
<td>71 ± 8</td>
</tr>
<tr>
<td>PgCO2–PaCO2, Torr</td>
<td>16 ± 6</td>
<td>13 ± 5</td>
<td>17 ± 7</td>
<td>20 ± 9</td>
</tr>
<tr>
<td>PslCO2–PaCO2, Torr</td>
<td>14 ± 2</td>
<td>10 ± 4</td>
<td>14 ± 6</td>
<td>19 ± 7</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.

When the frequency of ventilation was increased under physiological conditions in anesthetized animals, PaCO2 decreased from a baseline value of 36 ± 2 to 23 ± 2 Torr (P < 0.01). PETCO2 decreased corresponding (Table 1). These changes were accompanied by simultaneous decreases in both PgCO2 and PslCO2 by quantitatively similar amounts (Table 2, Fig. 1). When the frequency of ventilation was returned to baseline values, PaCO2, PETCO2, and tissue PCO2 values were restored to approximately baseline values. Changes in tissue PCO2 corresponded closely to those of PaCO2.

When the frequency of ventilation was decreased, PaCO2 increased from 34 ± 4 to 62 ± 10 Torr (P < 0.01), and there were comparable increases in PETCO2. Increases in tissue PCO2 exceeded those of PaCO2 by ~20%, but these differences were not statistically significant (Table 2).

The time series cross correlation between PaCO2 and PslCO2 was 0.93, and between PaCO2 and PgCO2 it was 0.91. The hemodynamic data, together with numerical gradients between PgCO2 and PaCO2, and the gradients between PslCO2 and PaCO2, are shown in Table 1. Except for decreases in mean arterial pressure during hyperventilation, there were no significant hemodynamic changes or differences in the PCO2 gradients.

After onset of bleeding, arterial pressure, PaCO2, and PETCO2 declined, and arterial blood lactate increased as expected (19). The PgCO2 increased from 50 ± 3 to 69 ± 11 Torr (P < 0.01), and PslCO2 increased from 47 ± 5 to 71 ± 8 Torr (P < 0.01) (Fig. 2). When the frequency of ventilation was increased after maximal decline in arterial pressure and cardiac index, PaCO2 decreased further from 26 ± 4 to 16 ± 2 Torr (P < 0.05), and PETCO2 decreased from 25 ± 5 to 14 ± 3 Torr (P < 0.05). PgCO2 decreased from 69 ± 11 to 52 ± 10 Torr (P < 0.05), and PslCO2 decreased from 71 ± 8 to 50 ± 5 Torr (P < 0.01). Accordingly, we observed directionally concordant reductions in PaCO2, PETCO2, PgCO2, and PslCO2 during hemorrhagic shock. All PCO2 values returned to those before hypocapnia after ventilation was restored to baseline levels. Decreases in tissue PCO2 and especially PslCO2 induced by hyperventilation during hemorrhagic shock were numerically larger, but numerical differences were not statistically different from those of PaCO2 (Table 3).

When the frequency of ventilation was decreased during hemorrhagic shock, PaCO2 increased from 25 ± 3...
and 4).

However, the onset of shock is associated with increases in PaCO₂ and PslCO₂ of between 15 and 25 Torr. As in the present experiments, circulatory shock and as quantitators of its severity (14, 16, 18, 19, 25). As in the present experiments, these experiments confirmed that acute increases or decreases in PaCO₂ produced comparable changes in tissue PCO₂ under physiological conditions in murine models as they did in pigs and in one reported human patient (3, 22, 26). During hemorrhagic shock, acute increases and decreases in PaCO₂ induced directional and quantitatively proportional changes in tissue PCO₂. PgCO₂, and, more recently, PslCO₂ serve as early indicators of the presence of perfusion failure and, therefore, circulatory shock and as quantitators of its severity (14, 16, 18, 19, 25). As in the present experiments, the onset of shock is associated with increases in PgCO₂ and PslCO₂ of between 15 and 25 Torr. However, increases in PaCO₂ of 24 Torr produced by hyperventilation would also account for these numerical increases in PgCO₂ and PslCO₂ under physiological conditions. The converse is also true. Increases in tissue PCO₂ due to shock would be neutralized by hyperventilation in which the PaCO₂ is decreased to 16 Torr, PgCO₂ from 69 to 52 Torr, and PslCO₂ from 71 to 50 Torr. Accordingly, we are alerted to the importance of taking acute changes of PgCO₂ and PslCO₂ into account under conditions when abnormal values of PaCO₂ accompany increases (or decreases) in PgCO₂ and PslCO₂.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>ΔPaCO₂</th>
<th>ΔPgCO₂</th>
<th>ΔPslCO₂</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. Δ, 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 levels, these effects were reversed (Fig. 3). As in the instance of hyperventilation, there were no significant differences in the magnitude of individual changes in PaCO₂, PgCO₂, and PslCO₂ or in the numerical gradients between PgCO₂ and PaCO₂ or PslCO₂ and PaCO₂ (Tables 3 and 4).

DISCUSSION

These experiments confirmed that acute increases or decreases in PaCO₂ produced comparable changes in tissue PCO₂ under physiological conditions in murine models as they did in pigs and in one reported human patient (3, 22, 26). During hemorrhagic shock, acute increases and decreases in PaCO₂ induced directional and quantitatively proportional changes in tissue PCO₂. PaCO₂ in the PCO₂ gap and a potential underestimate 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. 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.

Table 3. Absolute increases and decreases in PaCO₂ and tissue PCO₂ after increases or decreases in ventilation during hemorrhagic shock

<table>
<thead>
<tr>
<th>Condition</th>
<th>ΔPaCO₂</th>
<th>ΔPgCO₂</th>
<th>ΔPslCO₂</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>10 ± 4</td>
<td>17 ± 4</td>
<td>21 ± 7</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>24 ± 7</td>
<td>29 ± 12</td>
<td>22 ± 6</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Values are means ± SD in Torr.

Table 4. Tissue Pco₂-to-PaCO₂ gradients during hyperventilation and hypoventilation superimposed on hemorrhagic shock

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control, Prebleeding (BL)</th>
<th>Hyperventilation, Hemorrhagic Shock (60 min)</th>
<th>Hypoventilation, Hemorrhagic Shock (80 min)</th>
<th>Control, Hemorrhagic Shock (100 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PslCO₂-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>

Values are means ± SD in Torr; n = 5 animals each for hyperventilation, 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 as 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.

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 hyperventilation 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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Address for reprint requests and other correspondence: M. H. Weil, Institute of Critical Care Medicine, 1695 North Sunrise Way, Bldg. #B, Palm Springs, CA 92262-5309 (E-mail: WeilM@aol.com).

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