RESPIRATORY ADAPTATION TO ACUTE METABOLIC ACIDOSIS IN GOATS WITH ETC(U)

JUN 82 R A STEINBROOK, S HAVHERI, R A GABEL

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**Respiratory Adaptation to Acute Metabolic Acidosis in Goats with Ablated Carotid Bodies**

In awake goats before and after ablation of carotid bodies (CBx) we studied the effect of acute metabolic acidosis (AMA) produced by intravenous infusion of HCl on resting pulmonary ventilation, on composition of arterial blood and CSF, and on ventilatory responsiveness to hyperoxic CO₂ rebreathing. AMA caused decrease in PaCO₂ (breathing air at rest) and shifted position of CO₂ response curves toward lower values of PCO₂. These changes were similar before and after CBx, though the levels of PCO₂ in arterial blood during air breathing, and in
expired gas at a given level of ventilation during CO₂ rebreathing were higher after CBx. We conclude that a respiratory adaptation to AMA does occur in goats deprived of peripheral chemoreceptors, and is probably mediated by the central chemoreceptors.
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RESPIRATORY ADAPTATION TO ACUTE METABOLIC ACIDOSIS
IN GOATS WITH ABLATED CAROTID BODIES.

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Abbreviated title: Metabolic acidosis and chemodenervation

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ABSTRACT

In awake goats before and after ablation of carotid bodies (CBx) we studied the effect of acute metabolic acidosis (AMA) produced by intravenous infusion of HCl on resting pulmonary ventilation, on composition of arterial blood and CSF, and on ventilatory responsiveness to hyperoxic CO₂ rebreathing. AMA caused decrease in PaCO₂ (breathing air at rest) and shifted the position of CO₂ response curves toward lower values of PCO₂. These changes were similar before and after CBx, though the levels of PCO₂ in arterial blood during air breathing, and in expired gas at a given level of ventilation during CO₂ rebreathing were higher after CBx. We conclude that a respiratory adaptation to AMA does occur in goats deprived of peripheral chemoreceptors, and is probably mediated by the central chemoreceptors.

Key words: CO₂ rebreathing, CSF, awake goats, CO₂ production
INTRODUCTION

Acid-base disturbances of primarily metabolic origin elicit respiratory compensation. In metabolic acidosis, $\text{PaCO}_2$ is lowered, which alleviates the acidemia. An opposite change in $\text{PaCO}_2$ occurs in primary metabolic alkalosis. Furthermore, the ventilatory responses to increase in $\text{PaCO}_2$ produced by $\text{CO}_2$ inhalation are shifted to lower values of $\text{PaCO}_2$ in metabolic acidosis, and to higher $\text{PaCO}_2$ values in metabolic alkalosis. The roles played by the carotid bodies (CB) and by the central chemoreceptors in these respiratory adaptations are disputed. A predominant role was ascribed to central chemoreceptors by Pappenheimer (20) and Fencl et al (7), while Mitchell (17) and Bainton (1) concluded from their studies in awake dogs that excision of CB (CBx) abolishes the respiratory response to primary metabolic acid-base disturbances. More recently, Javaheri et al (12) and Kaehny et al (13) reported that in dogs, metabolic acidosis does stimulate ventilation in the absence of CB.

In awake goats before and after CBx, we studied the effect of acute metabolic acidosis (AMA), on resting pulmonary ventilation, on composition of arterial blood and CSF, and on responsiveness to $\text{CO}_2$ rebreathing. Respiratory adaptation to AMA did occur in goats deprived of function of CB. It was manifested by decrease in the resting $\text{PaCO}_2$ and by a shift of the $\text{CO}_2$ response curves to lower $\text{PCO}_2$ values.

METHODS

General

The studies were performed in four awake goats weighing 36-44 kg (mean 40 kg), surgically prepared with carotid loops and with implanted
occipital guide tubes for sampling of cisternal CSF. The same animals were used in another study (26). On each experimental day we punctured the cistern through the guide tube, percutaneously inserted a plastic cannula into the carotid artery in the loop and inserted another into the superior vena cava through the contalateral external jugular vein. Carotid arterial blood pressure was continuously monitored with a transducer (Statham 23DB). We measured resting ventilation ($\dot{V}_E$) and CO$_2$ production ($\dot{V}_{CO_2}$), and sampled arterial blood and cisternal CSF while the goats inhaled room air. Next we measured the ventilatory response to hyperoxic CO$_2$ rebreathing. We then induced AMA by infusing 0.2 N HCl in isotonic saline into the superior vena cava. The total dose of HCl was 3 mM/kg of body weight, delivered over approximately one hour at a steady rate, unless there was indication for slowing the rate. Occasional extrasystoles and bradycardia were observed in some animals during the first minutes of infusion. The goats appeared calm during the infusion. Fifteen to twenty minutes after completion of the infusion, we repeated measurements of $\dot{V}_E$ and $\dot{V}_{CO_2}$, sampling of arterial blood and cisternal CSF, and testing by CO$_2$ rebreathing. Each animal was studied twice before and twice four to five weeks after CBx. Means of the two measurements in each condition were used for data analysis. Completeness of CBx was tested by measuring the ventilatory response to acute hypoxia and to injection of cyanide (1 $\mu$M/kg BW) as described and reported previously (26).

**Respiratory Measurements**

The techniques have previously been described in detail (26).
In brief, the goats wore latex rubber masks and breathed through a low resistance non-rebreathing valve (J-valve, Model P-307, dead space 92 ml, Warren E. Collins). Volume of expired gas was measured with a Wedge spirometer (Med-Science Electronics). Concentrations of CO₂ and O₂ at the airway were measured with an infrared analyzer (Beckman LB-2) and a mass spectrometer (Perkin Elmer, MGA 1100A). All measured variables were recorded on a strip chart (Gould Brush Model 200), and on a magnetic tape (Hewlett Packard Model 3968). Ventilation was calculated breath-by-breath with a computer. Alveolar ventilation ($V_A$) was calculated using Enghoff's modification of Bohr's formula for respiratory dead space. All ventilatory data were normalized to body weight 40 kg.

For hyperoxic CO₂ rebreathing, a modification (26) of Read's technique (23) was used. Linear regressions were derived for minute ventilation (on a breath-by-breath basis) as a function of the simultaneously measured end-tidal PCO₂ ($PE_{TCO2}$). Ventilatory responsiveness to CO₂ was compared using slopes of these regressions and values of $VE$ at $PE_T = 60$ torr.

**Analytical Techniques**

Radiometer electrodes and electronics (BMS 2MK2) were used to measure PCO₂, PO₂ and pH in arterial blood and CSF at 37°C, with correction to rectal temperature (10, 18). CO₂ concentration (CCO₂) in CSF was measured with a Natelson microgasometer (Scientific Industries), and [Cl⁻] in anaerobically separated plasma and in CSF by potentiometric titration (Aminco-Cotlove, American Instruments). Bicarbonate in plasma and in CSF was calculated from measured pH and PCO₂ or
CCO₂, applying published values for pK' and CO₂ solubilities (18). Base excess (BE) was determined with a Blood Gas Calculator (25).

Statistical Analyses

Student's t-test, analysis of variance, or a non-parametric test of variance (4) was applied, as indicated.

RESULTS

CBx abolished the ventilatory response to acute hypoxia (PaO₂ 45-60 torr for 5-10 minutes) in these goats, as reported previously (26). When CB were intact, hypoxia increased V̇ₑ from its mean normoxic (PaO₂ 85-95 torr) value of 11.7 ± 1.9 to 14.3 ± 1.6 l/min BTPS (p < 0.05). After CBx, V̇ₑ was not statistically different during normoxia and acute hypoxia (10.8 ± 1.1 and 11.3 ± 0.9 l/min BTPS, respectively).

The effects of CBx and AMA on resting pulmonary ventilation, and on the composition of arterial blood and CSF, are shown in Table 1. CBx produced a decrease in V̇CO₂ and hypoventilation with a mild but statistically significant hypercapnia; in CSF, no significant changes occurred in the mean values of PCO₂ and pH. These findings are similar to those we have reported in a group of five awake goats (26).

The standard infusion of HCl produced an AMA of similar severity before and after CBx. The mean (± S.E.) change in BE during AMA was -9.1 ± 0.8 and -7.7 ± 0.9 mE/l in intact and chemodenervated goats, respectively (not different by t-test for paired samples or by ranking test of variance). Mean values of BE, [Cl⁻] and [HCO₃⁻] in arterial
blood plasma during AMA were similar before and after CBx (Table 1).

In spite of the resting hypercapnia observed after CBx during normal metabolic acid-base balance, PaCO$_2$ decreased in response to AMA after CBx, as it did before chemodenervation. When CB were intact, AMA caused reduction in mean PaCO$_2$ from 37.1 to 33.0 torr (p < 0.05); after CBx, mean PaCO$_2$ decreased with AMA from 39.7 to 35.7 torr (p < 0.05). Mean (± S.E.) change in PaCO$_2$ in response to AMA was -3.4 ± 0.7 and -4.0 ± 1.4 torr in intact and in chemodenervated goats, respectively. The mean (± S.E.) decrease in PaCO$_2$ per unit of acute base deficit (ΔPaCO$_2$/ΔBE) was 0.37 ± 0.07 (mE/l)$^{-1}$ before CBx, and 0.53 ± 0.17 torr (mE/l)$^{-1}$ after chemodenervation (p < 0.05, by ranking test of variance). Thus the hyperventilation elicited by AMA was not less after CBx, and it appeared even somewhat more pronounced with ablated CB, although this was not detected in our measurements of resting ventilation possibly owing to a small decrease in VCO$_2$ during AMA (Table 1).

In CSF, mean PCO$_2$ was the same before and after CBx when the goats were in normal metabolic acid-base balance (Table 1, [26]). AMA caused a decrease in CSF PCO$_2$ both before and after CBx, but the mean (± S.E.) change was smaller after CBx than before (-3.3 ± 0.7 and -5.0 ± 1.2 torr, respectively; p < 0.05, ranking test of variance). Thus, during AMA, mean CSF PCO$_2$ was higher after CBx than before (41.6 vs 38.8 torr). In both conditions, a small increase in mean [Cl$^-$/] was manifest during AMA, with reciprocal change in [HCO$_3$]$^-$(p < 0.05). CSF pH did not change with AMA before or after CBx.

During normal acid-base balance, the mean (± S.E.) difference between PCO$_2$ in CSF and in arterial blood (PcsfCO$_2$ - PaCO$_2$) was 7.0 ± 1.0 and
4.9 ± 0.3 torr (p < 0.05) before and after CBx, respectively (26). In response to AMA, this difference was reduced when CB were intact (Figure 1), on the average by -1.8 ± 0.8 torr. In contrast, with CB ablated, (PcsfCO₂ - PaCO₂) increased in response to AMA in 3 of 4 observations, on the average by +1.5 ± 0.9 torr. These changes in (PcsfCO₂ - PaCO₂) during AMA in intact and chemodenervated goats are statistically different (p < 0.05 by t-test for paired samples; p < 0.001 by ranking test of variance).

Data on hyperoxic CO₂ rebreathing are summarized in Table 2 and Figure 2. In the normal metabolic acid-base balance, CBx produced a statistically significant (p < 0.01) shift of the CO₂ response curves to higher PETCO₂ values, as indicated by a decrease in the value of VE at PETCO₂ = 60 torr. However, the slopes of the curves were not significantly different, as previously reported (26). AMA produced a change in the ventilatory response to CO₂ that was similar before and after CBx. Slopes of the curves did not change significantly with AMA either before or after CBx, but in both conditions, AMA caused a statistically significant increase in the mean values of VE at PETCO₂ = 60 torr, indicating that position of the CO₂ response curves was shifted to lower PETCO₂ values.

**DISCUSSION**

We have shown in a previous communication (26) that the goats used in the present study were deprived of peripheral chemoreception after CBx: the ventilatory response to hypoxia of 5-10 minutes duration was abolished, and during hyperoxia (PaO₂ > 300 torr for
5-10 minutes), pulmonary ventilation was increased; stimulation of ventilation by acute hyperoxia typically occurs in chemodenervated animals (5, 16).

Surprisingly, the resting $V_{CO_2}$ was decreased after CBx, by almost 20 percent. Data of Forster et al (9) also show a statistically significant decrease in $V_{CO_2}$ in chemodenervated goats. However, $V_A$ decreased more than did $V_{CO_2}$; therefore, $P_{CO_2}$ was elevated both in our observations and in those of Forster et al. Starting from these higher baseline $P_{CO_2}$ values, chemodenervated goats lowered their resting $P_{CO_2}$ in response to AMA, just as they did when the CB were intact. The degree of lowering of $P_{CO_2}$ in relation to base deficit in blood was even greater after CBx. Thus, a ventilatory response to AMA was manifest in the chemodenervated awake goats. This is in agreement with findings in anesthetized cats (14) and in anesthetized (12) and awake dogs (13); but these findings are at variance with those of Mitchell (17) and of Bainton (1) in awake dogs. We have no explanation for this discrepancy. In our results, $CO_2$ response curves were shifted to lower $PCO_2$ values by induction of AMA, both before and after CBx. Similar results were obtained in anesthetized cats by Katsaros (14). It appears that a respiratory adaptation to AMA, manifest in lowering the resting $P_{CO_2}$ and in shifting $CO_2$ response curves to lower $PCO_2$ values, does occur in goats with ablated CB.

The question arises whether the observed respiratory adaptation to AMA could be mediated by the central chemoreceptors, as postulated by Pappenheimer (20) and Fencl et al (7) for stable metabolic acidosis. The stimulus for the central chemoreceptors is believed to be increase
in \([H^+]\) in the cerebral interstitial fluid (cISF) that surrounds the receptors (7, 19). In stable metabolic acid-base disturbances of several days' duration, \([H^+]\) in cisternal CSF appears to approximate \([H^+]\) in cISF (7, 20). However, during acutely developing metabolic acidosis, a "paradoxical" alkaline shift in CSF pH can be seen in spontaneously breathing animals (24). This results from the high permeability of the blood-brain barrier for \(CO_2\) on one hand, and the low permeability of the blood-CSF barrier for ions on the other. As ventilation is stimulated by the metabolic acidosis, \(PCO_2\) in brain tissue and in cisternal CSF decreases before any change in CSF \([HCO_3^-]\) occurs.

We sampled CSF about 1 hour after termination of HCl infusion. \(PCO_2\) in CSF was lowered at that time, both before and after CBx, however, we did not observe an alkaline shift in CSF pH. There was an indication that \([HCO_3^-]\) had begun to decrease, and \([Cl^-]\) to increase in CSF at the time of sampling. In such transient states, large-cavity CSF does not reflect the composition of cISF (6, 11, 15). In experiments in which pH was measured by electrodes attached to brain surface, and cerebral-tissue \(PCO_2\) derived from measured \(PCO_2\) values in arterial and sagittal sinus blood (22) it was found that in the fluid underlying the pH electrode (which presumably approximates cISF), \([H^+]\) increased and \([HCO_3^-]\) decreased within minutes after induction of acute metabolic acidosis, before any change in \([HCO_3^-]\) in cisternal CSF was detected (6, 11). It is thus possible that stimulation of central chemoreceptors by increased \([H^+]\) in cISF plays a role in respiratory adaptations to AMA (12) similar to that proposed for stable acid-base
disturbances (7, 20).

In chemodenervated goats, the values of PCO$_2$ in arterial blood while breathing air, and PET$_{CO_2}$ values at a given V$_E$ during CO$_2$ re-breathing, were higher than before CBx, both before and during AMA. However, the changes in these PCO$_2$ values produced by AMA were similar before and after CBx. Perhaps in the regulation of these adaptations to AMA, the input from CB influences the set-point, while gain of the controller reflects input from the central chemoreceptors.

PCO$_2$ in cisternal CSF approximates the cerebral-tissue PCO$_2$ (22). The difference between cisternal CSF PCO$_2$ and PaCO$_2$ ($\Delta$PCO$_2$) is mainly a function of cerebral blood flow (in relation to cerebral CO$_2$ production). While CB were intact, this $\Delta$PCO$_2$ was reduced during AMA, suggesting a (relative) increase in cerebral blood flow. This was similar to findings in awake dogs (3) and in humans (8) in metabolic acidosis. However, after CBx, the mean $\Delta$PCO$_2$ increased with AMA. This may suggest that the regulation of cerebral blood flow in response to AMA was changed after CBx. Cerebral vasodilation in response to hypercapnia and hypoxia was found to be reduced in anesthetized animals after CBx (21); this was not confirmed in another study (2). It has been shown that cerebral vascular responses to stimulation of peripheral chemoreceptors and baroreceptors can be altered by general anesthesia (27). Measurements of cerebral blood flow in intact awake animals are needed to determine whether CB have any role in the regulation of cerebral blood flow (and of cerebral-tissue PCO$_2$) in response to acid-base disturbances.
Footnote (on front page)

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The views, opinions, and/or findings in this report are those of the authors and should not be construed as an official Department of Army position, policy, or decision, unless so designated by other official documentation.

Presented in part at the 65th Annual Meeting of the Federation of American Societies for Experimental Biology, 12-17 April 1981, Atlanta, GA.
References


### TABLE 1

Effects of ablation of the carotid bodies and of acute metabolic acidosis on pulmonary ventilation and on composition of arterial blood and CSF.

<table>
<thead>
<tr>
<th></th>
<th>Arterial Blood</th>
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<tbody>
<tr>
<td></td>
<td>VE (l/min BTPS)</td>
<td>VA (l/min BTPS)</td>
<td>VCO₂ (ml/min STPD)</td>
<td>pH</td>
<td>PCO₂ (torr)</td>
<td>PO₂ (torr)</td>
<td>BE (mEq/l)</td>
<td>[HCO₃⁻] (mEq/l)</td>
<td>[Cl⁻] (mEq/l)</td>
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<tr>
<td>CB intact</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>10.5±0.5</td>
<td>4.6±0.2</td>
<td>204±6</td>
<td>7.42±0.005</td>
<td>37.1±1.0</td>
<td>93±1</td>
<td>-0.3±0.5</td>
<td>23.7±0.5</td>
<td>112±2</td>
<td>7.306±0.013</td>
<td>44.4±1.2</td>
<td>23.7±0.4</td>
<td>132±3</td>
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<td>AMA</td>
<td>11.3±1.2</td>
<td>5.1±0.4</td>
<td>195±14</td>
<td>7.28±0.023</td>
<td>33.0±0.9</td>
<td>95±3</td>
<td>-10.1±1.4</td>
<td>15.4±1.2</td>
<td>123±2</td>
<td>7.308±0.004</td>
<td>38.8±1.0</td>
<td>22.8±0.3</td>
<td>134±3</td>
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<tr>
<td>CB ablated</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Control</td>
<td>8.0±0.4</td>
<td>3.7±0.3</td>
<td>165±7</td>
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<td>39.7±0.8</td>
<td>86±2</td>
<td>-0.7±0.7</td>
<td>23.6±0.6</td>
<td>112±1</td>
<td>7.307±0.011</td>
<td>44.6±0.6</td>
<td>24.8±0.5</td>
<td>130±1</td>
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<td>AMA</td>
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<td>157±6</td>
<td>7.28±0.013</td>
<td>35.7±1.3</td>
<td>91±2</td>
<td>-9.0±0.9</td>
<td>16.2±0.8</td>
<td>120±2</td>
<td>7.306±0.015</td>
<td>41.6±0.6</td>
<td>23.6±0.2</td>
<td>131±1</td>
<td></td>
</tr>
</tbody>
</table>

Analysis of variance:

Effect of CBx on variables during control periods:

| p | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | NS | NS | NS | NS | NS | NS | NS | NS | NS |

Effect of CBx on variables during AMA:

| p | <0.05 | <0.05 | NS | NS | NS | NS | NS | NS | NS | NS | <0.05 | NS | NS | NS |

AMA vs Control, CB intact:

| p | NS | NS | NS | <0.005 | <0.05 | NS | <0.005 | <0.001 | <0.01 | NS | <0.05 | <0.05 | NS |

AMA vs Control, CBx:

| p | NS | NS | NS | <0.005 | <0.05 | <0.05 | <0.005 | <0.001 | <0.01 | NS | <0.05 | <0.05 | NS |

Values are means ± S.E. of repeated measurements in 4 goats. CB: carotid bodies; CBx: ablated CB; Control: normal metabolic acid-base balance; AMA: acute metabolic acidosis.
TABLE 2

Ventilatory response to hyperoxic CO₂ rebreathing of awake goats.

<table>
<thead>
<tr>
<th></th>
<th>$\dot{V}_E$ at PETCO₂ = 60 torr (1/min, BTPS)</th>
<th>Slope of CO₂ response curves (1/(min x torr))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carotid bodies intact</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>29.5 ± 6.7</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>AMA</td>
<td>43.0 ± 7.3*</td>
<td>3.6 ± 0.1</td>
</tr>
<tr>
<td><strong>Carotid bodies ablated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>17.3 ± 2.6†</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>AMA</td>
<td>23.8 ± 3.6†</td>
<td>3.2 ± 0.3</td>
</tr>
</tbody>
</table>

Analysis of variance:
* AMA significantly different from control (p < 0.05).
† Significantly different from the value with carotid bodies intact (p < 0.05).

Values are means ± S.E. of repeated measurements in 4 goats (PaO₂ > 300 torr).
Control: normal metabolic acid-base balance; AMA: acute metabolic acidosis (base deficit -9 to -10 mEq/l).
LEGENDS TO FIGURES

Figure 1. Effect of acute metabolic acidosis (AMA) on the difference in PCO₂ between cisternal CSF and arterial blood in goats with intact and ablated carotid bodies. The points joined by a broken line indicate mean values. C: Control (normal metabolic acid-base balance).

Figure 2. Effect of ablation of carotid bodies and of acute metabolic acidosis (AMA) on ventilatory responses to hyperoxia (PaO₂ > 300 torr) CO₂ rebreathing. Constructed from mean values of ŶE at PETCO₂ = 60 torr, and from mean values of slopes of the plots ŶE vs PETCO₂. See Table 2 for numerical data. Open symbols: mean (± S.E.) values of ŶE at PETCO₂ = 60 torr in normal metabolic acid-base balance. Closed symbols apply to AMA.
The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official department of the Army position, policy, or decision, unless so designated by other official documentation.