Compensatory Hypoventilation in Metabolic Alkalosis*

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Although hyperventilation is a well-known compensatory mechanism in metabolic acidosis, compensatory hypoventilation has been inconsistent and controversial in metabolic alkalosis. Six healthy subjects were studied under baseline conditions and during steady-state metabolic acidosis (seven episodes) and alkalosis (14 episodes). Minute ventilation (Ve) fell in metabolic alkalosis and rose in metabolic acidosis. These changes in ventilation were entirely due to reduction and elevation of tidal volume (Vt) respectively, while respiratory frequency (f) remained unchanged. Alveolar ventilation fell during metabolic alkalosis and resulted in elevation of arterial PCO₂ in all subjects. The ventilatory response to CO₂ breathing was also diminished. There was a linear relationship between PaCO₂ and plasma [HCO₃⁻] in metabolic acidosis and alkalosis which was defined as PaCO₂ (mm Hg = 0.7 [HCO₃⁻] + 20 (± 2 SEM), r = 0.95. Although arterial Po₂ and plasma [K⁺] fell during metabolic alkalosis, minute ventilation did not change upon breathing oxygen and there was no correlation between changes in plasma [K⁺] and plasma H⁺ regulation.

Hyperventilation is a well-known compensatory mechanism in metabolic acidosis and the relationship between reduction in plasma [HCO₃⁻] and arterial PCO₂ (PaCO₂) in the steady state have been defined, indicating a consistent and highly predictable degree of respiratory compensation.¹ ² On the other hand, studies of ventilatory compensation in metabolic acidosis in man have been inconsistent and controversial. Some studies indicate that hyperventilation usually does not occur³ ⁴ while others suggest the opposite.⁵ ⁶ ⁷ Theory, however, predicts that the chemosensitive areas, ie, peripheral and central chemoreceptors which are stimulated by excess [H⁺] in metabolic acidosis and mediate the hyperventilation, should also be sensitive to reduced [H⁺] in metabolic alkalosis and induce compensatory hypoventilation. This theory would also be consistent with the studies of Pappenheimer et al⁷ ⁸ in unanesthetized goats that showed that alveolar ventilation is a single function of [H⁺] in the environment of the central chemosensitive areas in the brain both in metabolic acidosis and alkalosis.⁷ ⁸

Consistent hypoventilation might be difficult to demonstrate in patients with metabolic alkalosis because of commonly associated diseases such as congestive heart failure or acute hypovolemia⁹ which may induce hyperventilation¹⁰ ¹¹ and reduce PaCO₂ despite metabolic alkalosis.

In order to determine the respiratory response to metabolic alkalosis and metabolic acidosis in the same subjects, different levels of steady state metabolic acidosis (seven episodes) and alkalosis (14 episodes) were studied in six normal laboratory personnel. The data indicate that compensatory hyperventilation occurred consistently in all individuals during metabolic alkalosis and that there was a linear relationship between PaCO₂ and plasma [HCO₃⁻] in both metabolic acidosis and alkalosis. The respiratory compensation in metabolic alkalosis was independent of alterations in plasma [K⁺] and remained unchanged during oxygen breathing.

METHODS

Six normal healthy individuals (average age 23, four men and two women) were studied. All were familiar with the routine tests performed. Although the details of the procedures were explained to them, respiratory compensation of metabolic acid-base disorders was not discussed and they were not interested in the results. Informed consent was obtained from all individuals.

Procedures (Baseline Studies)

Spirometric pulmonary function tests were obtained initially. With subjects supine, either a radial or a brachial artery was cannulated under local anesthesia. A one-way, low resistance Hans-Budolph valve was used to collect the expired air into a Douglas bag for measurements of minute

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ventilation, CO$_2$ production, dead space and alveolar ventilation. Further details of the routine procedures performed in this laboratory have been previously published. These measurements were made at least ten minutes after arterial cannulation and application of mouth-piece and nose clip to eliminate changes due to anxiety because of the apparatus or arterial cannulation. Arterial blood was obtained anaerobically in heparinized syringes and measurements were made, in duplicate, of Po$_2$, PcO$_2$, and pH at 37°C using appropriate electrodes (models 123 and 125, Instrumentation Laboratory, Lexington, MA). Plasma [HCO$_3$] was calculated using appropriate pK' and a (solubility coefficient for CO$_2$ in plasma). Plasma [K$^+$] was determined by flame photometry. The ventilatory response to CO$_2$ breathing was obtained by the steady-state technique.

**Induction of Stable Metabolic Alkalosis and Acidosis**

Different levels (14 episodes) of steady state metabolic alkalosis were induced by administration of daily doses of NaHCO$_3$ (varying from 150 to 400 mEq) and ethacrynic acid (varying from 80 to 160 mg/day) in six subjects. All subjects were taking less than 500 mg of NaCl daily. Similarly, seven episodes of stable metabolic acidosis were induced in the same subjects by daily doses of ammonium chloride varying from 160 to 280 mEq. Each episode of metabolic acidosis or alkalosis was separated by at least two weeks in any given subject.

Steady-state metabolic acidosis and alkalosis were thought to have been achieved seven days after an acid-base perturbation had started. In addition, during the last two or three days of this period, the CO$_2$ content of three successive venous samples had to be within ±2 mEq of each other without directional trends. If consistent venous CO$_2$ content values were not obtained, the protocol was continued to achieve a steady state. Baseline studies were then repeated, which usually occurred on the seventh or eighth day of acidosis or alkalosis.

**Oxygen Breathing**

In order to assess the contribution of hypoxemia in pre-venting the appropriate degree of hypoventilation in patients with metabolic alkalosis, the subjects breathed 100 percent oxygen for 15 minutes through a closed system, at which time measurements of ventilation were repeated.

The data were analyzed by analysis of variance (one group with repeated measurements). In case of significance, further statistical comparisons were made by two-tailed paired t-test. P values less than 0.05 were considered significant.

**RESULTS**

Pulmonary function tests (vital capacity, peak expiratory flow rate and the 1st second vital capacity—FEV$_1$) were normal in all subjects. There was a linear relationship between PaCO$_2$ and plasma [HCO$_3$] (Fig 1) in metabolic acidosis and alkalosis defined as PaCO$_2$ (in mm Hg) = 0.70 [HCO$_3$] plasma + 20 ± 2.0 (SEM) with r = 0.95. Standard error of the slope of 0.70 was 0.052 and 95 percent confidence intervals of the slope from 0.60 to 0.81. The lowest and highest plasma [HCO$_3$] and PaCO$_2$ were respectively 14.5 and 41.2 mEq/L and 28 and 51 mm Hg.

When PaCO$_2$ was plotted against plasma [HCO$_3$] in metabolic alkalosis alone, the relationship was: PaCO$_2$ = 0.70 [HCO$_3$] + 21 ± 1.5 (SEM) (r = 0.91). In metabolic acidosis alone, the relationship between PaCO$_2$ and plasma [HCO$_3$] was PaCO$_2$ = 0.79 [HCO$_3$] + 19 ± 2.0 SEM (r = 0.84). These two slopes were not significantly different from each other by analysis of covariance.

In metabolic alkalosis, the mean PaCO$_2$ and plasma [HCO$_3$] were significantly higher and the arterial [H$^+$] lower than baseline values, whereas in metabolic acidosis the converse was true (Table I). In every individual the PaCO$_2$ rose in metabolic alkalosis and fell in metabolic acidosis. The mean plasma [K$^+$] of 4.5 ± 0.1 mEq/L fell to 3.6 ± 0.02 (P <

![Figure 1. Relationship between arterial plasma bicarbonate content and PaCO$_2$ in six healthy subjects prior to (normal) and during 14 episodes of steady-state metabolic alkalosis and seven episodes of metabolic acidosis. The solid black line is the mean regression line and the shaded area represents the 95 percent confidence interval.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21277/ on 06/25/2017)
Table 1—Changes in Plasma Acid-base Parameters, Oxygen Tension and Ventilation under Baseline, Acidotic, and Alkalotic Conditions in 6 Normal Subjects (Mean ± 1 SEM)

<table>
<thead>
<tr>
<th></th>
<th>[H+]a</th>
<th>PaCO₂</th>
<th>[HCO₃⁻]</th>
<th>PaO₂</th>
<th>VE</th>
<th>f</th>
<th>VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>37.8</td>
<td>37.6</td>
<td>24.2</td>
<td>94</td>
<td>5.7</td>
<td>12.2</td>
<td>522</td>
</tr>
<tr>
<td>±1.0</td>
<td>±1.1</td>
<td>±0.4</td>
<td>±3.7</td>
<td>±0.16</td>
<td>±2</td>
<td>±72</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>31.3*</td>
<td>43.6*</td>
<td>34.4*</td>
<td>85*</td>
<td>4.6</td>
<td>13.3</td>
<td>422 *</td>
</tr>
<tr>
<td>alkalosis</td>
<td>(14 episodes) ±0.70</td>
<td>±1.4</td>
<td>±1.5</td>
<td>±3.5</td>
<td>±0.14</td>
<td>±2</td>
<td>±55</td>
</tr>
<tr>
<td>Metabolic</td>
<td>45.7*</td>
<td>32.1*</td>
<td>17.1*</td>
<td>109*</td>
<td>6.7*</td>
<td>11.6</td>
<td>624 *</td>
</tr>
<tr>
<td>acidosis</td>
<td>(7 episodes) ±1.3</td>
<td>±1.2</td>
<td>±0.2</td>
<td>±4.2</td>
<td>±0.14</td>
<td>±2</td>
<td>±92</td>
</tr>
</tbody>
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*P < 0.05 as compared to baseline. [H+]a = plasma H+ concentration, nM/L; PaCO₂ = arterial PaCO₂ in mm Hg; [HCO₃⁻] = plasma HCO₃⁻ concentration in mEq/L; PaO₂ = arterial PaO₂ mm Hg; VE = minute ventilation (L/min); f = breathing frequency per min; VT = tidal volume (ml) All volumes are expressed in BTPS.

0.05) in ten episodes of metabolic alkalosis where K⁺ was measured. There was no correlation (r = 0.06) between changes in plasma [K⁺] and percent H⁺ regulation in metabolic alkalosis, when percent H⁺ regulation was calculated by the method of Siesjö17 during ten episodes of metabolic alkalosis (Fig 2). This method of calculation allows for quantification of H⁺ compensation in response to changes in PaCO₂. One hundred percent compensation implies restoration of pH back to normal and 0 percent compensation would be that which occurs in a solution devoid of any buffering at all. In the present study, no relationship was demonstrated between changes in serum K⁺ and H⁺ compensation.

Minute ventilation (VE) was significantly reduced in metabolic alkalosis, and increased in metabolic acidosis. These changes in ventilation were due to changes in tidal volume (VT), while respiratory frequency was unchanged (Table 1). In metabolic alkalosis, alveolar ventilation (VA) fell, but physiologic dead space and CO₂ production did not change (Table 2). The ventilatory response to CO₂ was reduced significantly as compared to baseline values in metabolic alkalosis (Fig 3).

The mean arterial PaO₂ (PaO₂) was lower in metabolic alkalosis than under normal conditions (Table 1). Breathing 100 percent O₂ for 15 minutes did not change the minute ventilation in metabolic alkalosis (4.6 ± 0.14 vs 4.7 ± 0.3 L/min) or under normal baseline conditions (5.7 ± 0.16 vs 5.6 ± 0.33 L/min) (Fig 3).

**DISCUSSION**

Metabolic acidosis elicits a consistent and highly predictable degree of respiratory compensation. In the steady-state, the stimulus to ventilation in metabolic acidosis is mediated by excess [H⁺]

![VENTILATORY RESPONSE](image)

**Figure 3.** Minute ventilation (VE) during room air breathing and after 15 minutes of 100 percent O₂ breathing in six subjects with normal acid-base conditions and during 14 episodes of steady state metabolic alkalosis (left panel). Ventilatory response to CO₂ (ΔVE/ΔPaCO₂) in the same subject was reduced during metabolic alkalosis (right panel) when compared to that during normal and acid-base conditions. Mean value ± SEM.
either in the environment of the central\textsuperscript{7,8,18-20} or peripheral chemoreceptors\textsuperscript{19} or both. Theoretically, therefore, reduced [H\textsuperscript{+}] as would occur in metabolic alkalosis ought to diminish the integrated central neural output and depress ventilation. Compensatory hypocapnia in metabolic acidosis and hypercapnia in metabolic alkalosis would then tend to restore the central and peripheral [H\textsuperscript{+}] towards normal. The present study supports this hypothesis. In addition, it indicates that in the same subjects appropriate ventilatory responses to metabolic acid-base disorders occur regularly (Fig 1) and a high degree of correlation is observed between changes in plasma [HCO\textsubscript{3}\textsuperscript{-} ] and arterial Pco\textsubscript{2}.

Rodriguez et al\textsuperscript{19} infused NaHCO\textsubscript{3} intravenously into three subjects and measured arterial blood gases (80 times) over four hours and obtained a similar regression equation with PaCO\textsubscript{2} = 0.75 [HCO\textsubscript{3}\textsuperscript{-}] + 19.2. Our regression equation is somewhat different from that reported by van Ypersele de Strihou and Frans\textsuperscript{6} in patients with renal failure undergoing hemodialysis in that for a given plasma [HCO\textsubscript{3}\textsuperscript{-}], the calculated PaCO\textsubscript{2} is slightly lower using the equation in the present study. However, patients with renal failure may have other factors affecting their ventilation in addition to changes in plasma [HCO\textsubscript{3}\textsuperscript{-}].

The change in minute ventilation in both metabolic acidosis and alkalosis occurred because of reduction in tidal volume in metabolic alkalosis and increased tidal volume in metabolic acidosis (Table 2). There was no appreciable change in respiratory frequency. This change in pattern of breathing was an efficient mechanism for reduction of alveolar ventilation during metabolic alkalosis since it resulted in elevation of the dead space to tidal volume ratio (Vd/Vt) and diminished alveolar ventilation (Table 2).

Compensatory hypoventilation in metabolic alkalosis has been inconsistent and controversial. The reason for the inconsistency of data, particularly not demonstrating an appropriate degree of hypoventilation for the plasma [HCO\textsubscript{3}\textsuperscript{-}] increase, might have been due to superimposed acute respiratory alkalosis from different causes, such as anxiety and other extraneous psychic stimuli which are commonly associated with arterial puncture, application of nose clip and mouthpiece and the environment of the laboratory.\textsuperscript{21} These factors were eliminated from the present study since our subjects were pulmonary function laboratory personnel who had worked in the laboratory for several months and were familiar with the techniques, including arterial cannulation. In the present study every subject had an increase in PaCO\textsubscript{2} in metabolic alkalosis and this occurred in relatively mild to moderate alkalosis. Several studies have defined “significant” compensation as being a PaCO\textsubscript{2} greater than 46 mm Hg\textsuperscript{22-24} or greater than 55 mm Hg.\textsuperscript{22,24} From the data in the present study, such degrees of CO\textsubscript{2} retention require increases in plasma [HCO\textsubscript{3}\textsuperscript{-}] to 36 and 49 mEq/L respectively. It is therefore not surprising that the respiratory compensation in metabolic alkalosis of mild-to-moderate degree may be missed completely.

More importantly, however, in patients in whom metabolic alkalosis has been studied, other commonly associated conditions such as hypovolemia,\textsuperscript{11} congestive heart failure,\textsuperscript{10} and postoperative pulmonary complications such as infection and sepsis\textsuperscript{25} can falsely lower an otherwise appropriately lowered PaCO\textsubscript{2}.\textsuperscript{5,4}

In eight patients with metabolic alkalosis but without associated causes of respiratory alkalosis, compensatory hypoventilation occurred uniformly.\textsuperscript{6} and few studies on normal human subjects, although isolated, do show evidence of hypoventilation in steady-state metabolic alkalosis.\textsuperscript{26,27} In contrast, studies of acute metabolic alkalosis induced in normal man by intravenous infusion of NaHCO\textsubscript{3} show that immediate hypoventilation may be minimal or absent.\textsuperscript{5,4,21} The initial absence of hypoventilation with acute infusion of sodium bicarbonate is not surprising because the infused HCO\textsubscript{3}\textsuperscript{-} combines with H\textsuperscript{+} in plasma and increases the plasma Pco\textsubscript{2} which rapidly equilibrates with brain tissue Pco\textsubscript{2} and causes a fall in brain interstitial fluid pH.\textsuperscript{28} Consequently, increased [H\textsuperscript{+}] within the environment of the central chemosensitive areas stimulates ventilation. The change in minute ventilation, then, become an interplay between the initial central stimulatory effect of increased Pco\textsubscript{2} and the inhibitory effect of the peripheral chemoreceptors due to an alkaline blood pH.

Two other reasons have been presented to suggest why hypoventilation may not occur in metabolic alkalosis—hypoxemia and hypokalemia.\textsuperscript{29,30} The ventilatory response to hypoxia becomes significant when PaO\textsubscript{2} is less than 60 mm Hg.\textsuperscript{31} These low levels of oxygen tension may occur only in severe forms of metabolic alkalosis and, based on calculations from our present data, when plasma [HCO\textsubscript{3}\textsuperscript{-}] is in excess of 55 mEq/L. In addition, the sensitivity of the peripheral chemoreceptors to hypoxia is diminished when the blood or CSF pH is alkaline.\textsuperscript{32,33} In the present study, 15 minutes of O\textsubscript{2} breathing had no significant effect on ventilation (Fig 3). The lowest PaO\textsubscript{2} in the metabolic alkalosis subjects, however, was 76 mm Hg.

Hypokalemia is frequently associated with meta-
bolic alkalosis and it has been suggested that as a consequence of intracellular potassium losses, H+ moves into cells34 which, if it occurred within the chemoreceptor cells in the brain, would cause intracellular acidosis and stimulate ventilation.30 In this context, severe hypokalemia in the rat is associated with increased rather than decreased [HCO3] in the cerebrospinal fluid35 which per se changes should augment hypoventilation. A similar trend of changes in CSF [HCO3] with hypokalemia has been shown in human subjects.36 In the present study, no relationship was apparent between falls in plasma K+ and the respiratory compensation for metabolic alkalosis as demonstrated by the degree of H+ compensation (Fig 2).

How is hypoventilation mediated in metabolic alkalosis? The present study was not designed to specifically answer this question and our data do not allow for definite conclusions as to mechanism of hypoventilation in metabolic alkalosis. We and others7,8,17,35 have suggested that in metabolic acidosis, hyperventilation is brought about by increased [H+] in brain interstitial fluid. Reduction in brain interstitial [H+] could account for hypoventilation in metabolic alkalosis and the diminished ventilatory response to inhaled CO2 (Fig 3). This suggestion does not rule out further reduction in ventilatory drive mediated by peripheral chemoreceptors due to the alkaline blood pH. A recently published report by Irsigler, Stafford and Severinghaus37 has suggested that the reduced ventilatory drive in metabolic alkalosis is because of diminished peripheral chemoreceptor drive to ventilation without a significant depressant effect because of an alkaline CSF pH since in their subjects’ lumbar CSF pH remained unchanged.

In summary, our studies in normal man show that compensatory hypoventilation in metabolic alkalosis occurs as regularly as hyperventilation in metabolic acidosis and that there is a linear response of PCO2 to changes in plasma [HCO3] between 14 and 42 mEq/L in both metabolic acidosis and alkalosis.

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Symposium on Heat Stress and Heat Disorders

The American Society of Safety Engineers will present this one-day symposium on April 17 at the Marcus Education Center, Wichita State University, Wichita, Kansas. For information, contact: ASSE/WAOHN Heat Stress Symposium, Attn Patsy Quint, R.N., PO Box 2079, Wichita, Kansas 67201 (316:946-2268)

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The American Heart Association will present this course in Myrtle Beach, South Carolina, April 30-May 2. For information, contact the Administrator, Postgraduate Programs, American Heart Association, 7320 Greenville Avenue, Dallas 75231 (214: 750-5541).

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