THE VENTILATORY RESPONSE IN DIABETIC KETOACIDOSIS

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SUMMARY

1. Previous studies of the ventilatory response to metabolic acidosis have usually
considered only patients with arterial blood pH above 7.10. To define the response
during more severe acidaemia, arterial CO₂ tension and pH were measured in
fifty-three episodes of diabetic ketoacidosis, including twenty-four with pH below
7.10, and ten with pH below 7.00.

2. The relation between arterial CO₂ tension, and both blood pH and plasma bi-
carbonate concentration, in these cases with generally severe metabolic acidaemia
(mean pH 7.12 ± SD 0.13), was very similar to the relations between those variables
found by others in patients with less severe acidaemia, such as that due to renal failure.

3. As arterial blood hydrogen ion activity increased, arterial CO₂ tension decreased
inversely, reflecting well-sustained hyperventilation, even during profound acidaemia.

4. The inverse relation between arterial CO₂ tension and hydrogen ion activity
suggests that during metabolic acidosis, alveolar ventilation increases in direct
proportion to the increased blood hydrogen ion activity.

Key words: acidosis, diabetic acidosis, ketosis, respiration, ventilation.

Metabolic acidosis causes hyperventilation which lowers alveolar carbon dioxide tension. The resulting decrease of arterial carbon dioxide tension (PaₐCO₂) mitigates the severity of acidaemia and reflects the magnitude of hyperventilation. Previous studies of the ventilatory response to metabolic acidosis have usually been limited to individuals with blood pH > 7.10 (Gray, 1946; Cowie, Lambie & Robson, 1962; Pauli, Riedwil, Reubi & Wegmüller, 1963; Pauli & Reubi, 1963; Lambie, Anderton, Cowie, Tothill & Robson, 1965; Pierce, Fedson, Brigham, Mitra, Sack & Mondal, 1970; van Ypersele de Strihou & Frans, 1970). There is little information about the ventilatory response in patients with more severe metabolic acidosis, except for a suggestion by Kety, Polis, Nadler & Schmidt (1948) that hyperventilation might actually lessen in such patients. We have studied the PaₐCO₂ levels during severe meta-

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bolic acidaemia by measuring the initial arterial blood gas tensions and pH in fifty-three episodes of diabetic ketoacidosis, including twenty-four with arterial pH (pHₐ) < 7·10.

METHODS

Patients

Arterial blood specimens were obtained before treatment in fifty-three episodes of diabetic ketoacidosis in thirty-nine patients hospitalized on this Medical Service during a 1-year period. Symptoms developed at least 24 h before admission, all the patients having uncontrolled diabetes mellitus, with a positive serum test for acetone, and arterial pH < 7·37. Patients with severe hyperglycaemia and dehydration, but little or no ketonaemia, were excluded. The twenty-five women and fourteen men averaged 40 years of age (range 15–80 years).

Methods

Arterial blood was obtained by puncture and taken anaerobically into a lightly heparinized syringe, with care that the patient's breathing pattern did not change. The blood in the sealed syringe was kept at 4°C until pH and gas tensions were measured within 30 min with a pH–blood gas analyser 313 (Instrumentation Laboratory Inc., Boston, Massachusetts, U.S.A.), oxygen saturation being measured with an oximeter (model 10800, American Optical Co., Buffalo, New York, U.S.A.) (Fulop, Horowitz, Aberman & Jaffé, 1973). Rectal temperatures lay between 36° and 38°C in most but small temperature corrections were made to pH and Pco₂ values. Plasma bicarbonate concentrations ([HCO₃⁻]) were calculated from the Henderson–Hasselbalch equation using these corrected values, and the appropriate values for pK' and CO₂ solubility (Severinghaus, Stupfel & Bradley, 1956; Severinghaus, 1965). Regression equations were calculated for the best-fit straight lines, after appropriate transformation of the data when warranted (Snedecor & Cochran, 1967).

RESULTS

Clinical features

The cases were divided into two groups, based on the presence or absence of possible complications. The twenty-nine cases in Group I had uncomplicated ketoacidosis, with no other abnormality that might affect acid–base balance or pulmonary ventilation; all had systolic blood pressure of at least 100 mmHg and arterial oxygen saturation of at least 90%; none had a serum Na⁺ concentration above 144 mmol/l or a serum K⁺ concentration below 3·4 mmol/l. The twenty-four cases in Group II had various complications that could have altered acid–base balance or pulmonary ventilation, such as pulmonary, liver and cerebral disorders, therapy with diuretics, narcotics or glucocorticosteroids, or they were agitated.

Arterial blood values

The mean pre-treatment arterial blood values in the twenty-nine uncomplicated cases were: pHₐ 7·11 (SD 0·12); Pa,co₂ 2·27 (SD 0·67) kPa (17·0 (SD 5·0) mmHg); plasma [HCO₃⁻] 5·7 (SD 3·1) mmol/l. In the twenty-four 'complicated' cases the mean values were: pH 7·14 (SD 0·14); Pa,co₂ 2·77 (SD 1·11) kPa (20·8 (SD 8·3) mmHg); plasma [HCO₃⁻] 7·7 (SD 5·0) mmol/l.

Individual values of arterial pH, Pco₂ and derived [HCO₃⁻] are given in a table (Clinical Science and Molecular Medicine, Table 73/30), which is deposited with the Librarian, Royal
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Society of Medicine, from whom copies may be obtained on request.

The relation between $P_{a,CO_2}$ and $pH_a$ in the twenty-nine uncomplicated cases was $P_{a,CO_2} = 3.89 \times pH - 25.40$; $r = 0.73$, SEM 0.46 kPa. However, the relation between $\log P_{a,CO_2}$ and $pH_a$ fitted the data equally well ($r = 0.71$), in addition to providing a better fit to data reported by others in patients with metabolic acidosis (see below).

Fig. 1 shows such a logarithmic plot of the data in our twenty-nine uncomplicated cases, with the regression equation and 95% confidence limits. Fig. 2 shows the results in the other twenty-four cases, including the 95% confidence band from Fig. 1. Four of these complicated cases had $P_{a,CO_2}$ values higher than the 95% confidence limits of Fig. 1; two had obstructive lung disease, another (with $pH_a 7.29$) had been a long-time heroin addict, and the fourth (with $pH_a 7.14$) had an acute gastrointestinal haemorrhage. Two of the complicated cases had $P_{a,CO_2}$ values appreciably below the 95% limits: one had acute viral hepatitis, and the other was agitated.

The regression equation relating $P_{a,CO_2}$ and plasma $[HCO_3^-]$ in our twenty-nine uncomplicated cases was $P_{a,CO_2} = 0.20 \times [HCO_3^-] + 1.13$ ($r = 0.93$, SEM 0.25 kPa). The regression equation for all fifty-three cases was not significantly different ($P_{a,CO_2} = 0.20 \times [HCO_3^-] + 1.35$ ($r = 0.91$, SEM 0.39 kPa)).

**DISCUSSION**

In previous studies of the ventilatory response to metabolic acidosis only patients having $pH_a > 7.10$ have been included; the present study extends this to patients with more severe metabolic acidosis. We have assumed $P_{a,CO_2}$ to be an inverse index of alveolar ventilation.
FIG. 2. Relation between $P_{A,CO_2}$ and pH, in twenty-four complicated cases of diabetic ketoacidosis. $P_{A,CO_2}$ is plotted on a logarithmic scale, and the shaded area shows the 95% confidence limits calculated from the data in the twenty-nine uncomplicated cases shown in Fig. 1. □, Two cases with bronchitis and hypoxaemia; ○, four cases with agitation and possibly unstable hyperventilation; △, eighteen cases with various other complications (see text).

$(\dot{V}A)$ (Comroe, Forster, Dubois, Briscoe & Carlsen, 1962), which depends upon steady-state conditions, with equilibrium between the metabolic production and the pulmonary excretion of $CO_2 (\dot{V}CO_2)$, and equality of alveolar and arterial $CO_2$ tensions. These assumptions can probably be sustained in uncomplicated, gradually evolving, diabetic ketoacidosis, during which $VCO_2$ has been found to be normal, Fisher & Kleinerman (1952) reporting a mean $VCO_2$ of 207 ml/min (SEM 11) in eleven patients with ketoacidosis, a value which was not significantly different from that found (185 ml/min (SEM 28)) in seven convalescent non-diabetics.

Such assumptions may not be valid, however, if acidosis is of very short duration, if it changes rapidly, or if $CO_2$ production increases abruptly, as during intense lactic acidosis (Peters & Van Slyke, 1946). In the latter event, the increased $CO_2$ production might be associated with at least a transient rise of $P_{A,CO_2}$, even if $\dot{V}A$ is well maintained. There is a delay in the development of the full hyperventilatory response to a metabolic acidosis, for dogs given intravenous HCl required up to 8–12 h to reach their lowest $P_{A,CO_2}$ (Asch, Dell, Williams, Cohen & Winters, 1969). In man, comparable information is limited, but $P_{A,CO_2}$ stabilized within 24 h in patients with acidosis secondary to cholera (Pierce et al., 1970). Our patients had symptoms, often including deep or laboured breathing, for at least 24 h before our studies, but this does not guarantee that their $\dot{V}A$ and $P_{A,CO_2}$ had become stable in all. In any event, the confidence limits shown here, and elsewhere (Elkinton, 1966; Albert, Dell & Winters, 1967; Pierce et al., 1970; van Ypersele de Strihou & Frans, 1970), may not apply to patients with rapidly increasing intense metabolic acidosis, such as the lactic acidosis associated with cardio-circulatory failure.
### Table 1. Regression relations between arterial $CO_2$ tension and plasma bicarbonate concentration in several series of cases of metabolic acidosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Predominant types of case</th>
<th>Duration of acidosis</th>
<th>No. of observations</th>
<th>Range of plasma $[HC03^-]$ (mmol/l)</th>
<th>Regression equation</th>
<th>Correlation coefficient</th>
<th>SEM$^{(1)}$</th>
<th>SEM$^{(2)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>Adults with diabetic ketoacidosis$^{(2)}$</td>
<td>Acute</td>
<td>29</td>
<td>2–14</td>
<td>$Y = 0.20X + 1.13$</td>
<td>0.93</td>
<td>0.25</td>
<td>(1.9)</td>
</tr>
<tr>
<td></td>
<td>Adults with diabetic ketoacidosis$^{(3)}$</td>
<td>Acute</td>
<td>53</td>
<td>2–19</td>
<td>$Y = 0.20X + 1.35$</td>
<td>0.95</td>
<td>0.39</td>
<td>(2.2)</td>
</tr>
<tr>
<td>Elkinton (1966)</td>
<td>Adults with renal failure</td>
<td>Chronic</td>
<td>27</td>
<td>3–19</td>
<td>$Y = 0.20X + 1.17$</td>
<td>0.95</td>
<td>0.53</td>
<td>(4.0)</td>
</tr>
<tr>
<td>Albert et al. (1967)</td>
<td>Infants and children with diarrhoea or renal failure</td>
<td>Acute to subacute</td>
<td>60</td>
<td>4–16</td>
<td>$Y = 0.21X + 1.11$</td>
<td>0.97</td>
<td>0.15</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Pierce et al. (1970)</td>
<td>Adults with cholera</td>
<td>Acute</td>
<td>20$^{(4)}$</td>
<td>8–13</td>
<td>$Y = 0.15X + 1.65$</td>
<td>0.98</td>
<td>0.20</td>
<td>(1.5)</td>
</tr>
<tr>
<td>van Ypersele de Strihou &amp; Frans (1970)</td>
<td>Adults with renal failure</td>
<td>Chronic</td>
<td>145</td>
<td>11–21</td>
<td>$Y = 0.16X + 1.45$</td>
<td>0.98</td>
<td>0.28</td>
<td>(2.1)</td>
</tr>
</tbody>
</table>

$^{(1)} Y = Pa_{CO2}$ in kPa and $X = \text{plasma } [HC03^-]$ in mmol/l. The regression equations and SEM values in parentheses give the corresponding $Pa_{CO2}$ values in mmHg.

$^{(2)}$ The uncomplicated cases of Group I.

$^{(3)}$ All the cases in the present series.

$^{(4)}$ Twelve cases of cholera with $[HC03^-]$ $8–13$ mmol/l, and eight controls.
Kety et al. (1948) reporting on fourteen adults with diabetic ketoacidosis, noted that the patients with blood pH between 7.0 and 7.1 had the highest total minute ventilation (Ve). Four of their more acidaemic patients had somewhat lower Ve and a slightly higher Pa,CO₂ (2.40–3.20 kPa; 18–14 mmHg), so they suggested that severe acidaemia may depress the respiratory centre. Our findings do not support that idea, for among our ten patients with pH <7.00, only the two with bronchitis had Pa,CO₂ >2.00 kPa (15 mmHg). Of the four patients of Kety et al. (1948) with ‘inappropriately high’ Pa,CO₂, three were hypotensive, and so may have had superimposed rapidly evolving lactic acidosis.

The relation between Pa,CO₂ and plasma [HCO₃⁻] in our cases was very similar to that described by others in patients with less severe acidaemia (Table 1) (Elkinton, 1966; Albert et al., 1967; Pierce et al., 1970; van Ypersele de Strihou & Frans, 1970). This is noteworthy because these series differed in several important respects: the cause and the duration of acidosis, the patients’ ages, and the range of plasma [HCO₃⁻] values. The close correlation between Pa,CO₂ and plasma [HCO₃⁻] should not be overinterpreted, for although some authors have suggested that pK' varies predictably with blood pH (Cowie et al., 1962; Siggaard Andersen, 1962; Severinghaus, 1965), others have reported that the blood pK' values may vary unpredictably in patients with acute acid–base disturbances (Trenchard, Noble & Guz, 1967). Furthermore, the correlation between Pa,CO₂ and [HCO₃⁻] results in part from the derivation of [HCO₃⁻] values from Pa,CO₂ and pH (Albert et al., 1967). It follows that the close correlation between log Pa,CO₂ and pH in our cases (Fig. 1 and Fig. 2) is of more relevance, and this relationship also fits data from other studies.
The data from five recent studies of patients with stable chronic renal failure are shown in Fig. 3 with the 95% confidence limits derived from our twenty-nine uncomplicated cases. There is generally an excellent correspondence between the results in these renal cases with moderate chronic acidaemia (mean pH 7.30), and our cases of subacute ketoacidosis with more severe acidaemia (mean pH 7.11).

Similarly, Fig. 4 shows the data from three other reports of forty-four cases of diabetic ketoacidosis. Although some of these patients had complicating disorders, here, too, most of the data lie within our confidence band. Several of Møller's (1959) cases with pH > 7.25, and one with pH 6.80, had Pa,CO₂ values slightly higher than our uncomplicated cases. This may just reflect our limited data in milder cases with pH > 7.25, or the presence of complications in Møller's unselected series. His one case that deviated prominently, with pH 7.02 and Pa,CO₂ 43 mmHg, had pulmonary oedema, a well-recognized cause of hypercapnia (Aberman & Fulop, 1972; Fulop et al., 1973).

Our results suggest that patients with uncomplicated metabolic acidosis and pHₐ below 7.10 should be expected to have Pa,CO₂ < 3.33–3.47 kPa (25–26 mmHg), and with pH below 7.00 should be expected to have Pa,CO₂ < 2.80–2.93 kPa (21–22 mmHg) (Fig. 2). The lowest Pa,CO₂ values observed were ~1.33 kPa (10 mmHg), as also noted by others (Elkinton, 1966; Zimmet, Taft, Ennis & Sheath, 1970; Clements, Blumenthal, Morrison & Winegrad, 1971).

The mechanism by which metabolic acidosis causes hyperventilation has evoked much interest and study, particularly with regard to the nature and site of action of the stimulus (Cunningham & Lloyd, 1963; Kellogg, 1964; Brooks, Kao & Lloyd, 1965). Fencl, Miller & Pappenheimer (1966) believe that the hyperventilatory response is mediated exclusively by central neural receptors that sense the acidity of cerebral interstitial fluid (ISF) (Fencl, Vale & Broch, 1969). In the steady state, pH in cerebral ISF is presumed to equal that in cisternal or ventricular fluid (Fencl et al., 1966, 1969), which decreases far less than pHₐ during metabolic...
acidaemia (Fencl et al., 1966, 1969; Bradley & Semple, 1962; Pauli & Reubi, 1963; Mitchell, Carman, Severinghaus, Richardson, Singer & Shneider, 1965; Posner & Plum, 1967; Ohman, Marliis, Aoki, Munichoodapppa, Khanna & Kozak, 1971). Therefore Mitchell et al. (1965) suggested that the peripheral chemoreceptors also participate in the ventilatory response to metabolic acidosis. Do the clinical data shed any light on this problem?

Some authors have suggested that blood acidity be expressed as hydrogen ion activity (a\textsubscript{H+}) rather than pH values (Arbus, Hebert, Levesque, Etsten & Schwartz, 1969; Flenley, 1971). Because we are concerned with the relation between VA and a\textsubscript{H+}, and Pa\textsubscript{CO\textsubscript{2}} is related inversely to VA, we have examined the inverse relation between a\textsubscript{H+} (nmol/l) and Pa\textsubscript{CO\textsubscript{2}} in data pooled from our own studies, and those of others. Fig. 5 shows the data from our twenty-nine uncomplicated ketoacidosis cases (Fig. 1), and the forty-four individual renal cases with generally

![Graph](image_url)

Fig. 5. Relation between Pa\textsubscript{CO\textsubscript{2}} and (1/a\textsubscript{H+}) in seventy-three cases of metabolic acidosis, our twenty-nine uncomplicated cases of diabetic ketoacidosis, and the forty-four cases of renal acidosis shown as solid circles in Fig. 3. The diagonal line shows the regression equation, Pa\textsubscript{CO\textsubscript{2}} = (173-746/a\textsubscript{H+}) + 0.075, r = 0.79, SEM 0.644 kPa.

less severe acidaemia (Fig. 3). The high correlation coefficient for these pooled data (n = 73, r = 0.79), and the random distribution of the Pa\textsubscript{CO\textsubscript{2}} deviations throughout the range, suggest that the relation between Pa\textsubscript{CO\textsubscript{2}} and 1/[a\textsubscript{H+}] is well described by the straight line shown. This, in turn, implies an inverse relation between Pa\textsubscript{CO\textsubscript{2}} and a\textsubscript{H+}, and the dashed line in Fig. 6 shows the corresponding hyperbola defined by these seventy-three cases. The relation between Pa\textsubscript{CO\textsubscript{2}} and a\textsubscript{H+} for the 149 cases shown in Figs. 1-4, excluding Möller’s two moribund patients, is very similar.

The inverse correlation between Pa\textsubscript{CO\textsubscript{2}} and a\textsubscript{H+} in the pooled clinical data suggests that VA could be related to arterial a\textsubscript{H+} in a linear fashion during metabolic acidosis. A theoretical hyperbolic relationship between Pa\textsubscript{CO\textsubscript{2}} and a\textsubscript{H+} can be constructed by making it pass through
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the mean normal values ($a_{H^+} = 40 \text{ nmol/l}$ and $P_{a,CO_2} = 55.3 \text{ kPa}$); this relationship is given by $P_{a,CO_2} \times a_{H^+} = 213.3 \text{ kPa nmol}^{-1} \text{l}^{-1}$. This concept neglects Gray's (1946) suggestion that the hypocapnia caused by compensatory hyperventilation might, in turn, mitigate the hyperventilatory response. If $a_{H^+}$ is limited to 40–160 nmol/l, the solid line in Fig. 6 shows the hyperbola defined by the theoretical equation. The modest discrepancy between the ‘actual’ and ‘theoretical’ curves in the mild acidaemia range ($a_{H^+} = 40–80 \text{ nmol/l}$) may simply reflect the state of mild compensated metabolic acidosis, with subnormal $P_{a,CO_2}$ and ‘normal’ $pH_a$. Robson, Bone & Lambie (1972) have also recently reported finding an inverse relation between $P_{a,CO_2}$ and arterial $a_{H^+}$ in a group of cases with ‘metabolic’ acid–base disturbances, that included some with alkalosis.

Fig. 6. Relationship between $P_{a,CO_2}$ and $a_{H^+}$ (in nmol/l). Solid line: calculated from the theoretical equation $P_{a,CO_2} = 213.3 \times a_{H^+}$. The dashed hyperbola was obtained by transforming the straight-line regression relation between $P_{a,CO_2}$ and $(1/a_{H^+})$ in the seventy-three cases shown in Fig. 5.

The close similarity of the two curves in Fig. 6 does not of course prove that arterial $a_{H^+}$ is the proximate stimulus to hyperventilation. Spinal fluid pH was not measured in our patients, and the actual stimulus to hyperventilation could be the $a_{H^+}$ of cerebral ISF, or even that of cerebral intracellular fluids (Robin, Whaley, Crump, Bickelmann & Travis, 1958). If so, Fig. 6 implies that such a ‘critical’ $a_{H^+}$ would be closely and linearly related to the $a_{H^+}$ of arterial blood over this range. A final decision about the predominance of peripheral or central chemoreceptors in the hyperventilatory response must await studies in more severely acidaemic animals, with intact and denervated peripheral chemoreceptors, with measurements of $CO_2$ excretion as well as $P_{a,CO_2}$, and with measurements of spinal fluid as well as arterial $a_{H^+}$. Nevertheless, it may be concluded that, during metabolic acidosis, $V_A$ increases as if arterial $a_{H^+}$ is the stimulus responsible.
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