THE RELATIONSHIP BETWEEN ARTERIAL $P_{CO_2}$ AND HYDROGEN ION CONCENTRATION IN CHRONIC METABOLIC ACIDOSIS AND ALKALOSIS

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(Received 10 September 1973)

SUMMARY

1. An analysis was made of the relationship which exists between arterial $[H^+]$, $P_{CO_2}$ and $[HCO_3^-]$ in twenty-five patients with stable metabolic acidosis and alkalosis and in three normal subjects.

2. Contrary to previous reports, the relationship between $P_{CO_2}$ and $[H^+]$ was non-linear and could best be described in terms of a rectangular hyperbola ($P_{CO_2} = 962/([H^+] - 12)$).

3. The relationship between $P_{CO_2}$ and $[HCO_3^-]$ was curvilinear and best described by the quadratic function $23.8(P_{CO_2})^2 - 12P_{CO_2}[HCO_3^-] - 962[HCO_3^-] = 0$.

4. The small acute changes in $[H^+]$, $[HCO_3^-]$ and $P_{CO_2}$ produced by infusion of the weak organic acid 5,5-dimethyl 2,4-oxazolidinedione (DMO) could be predicted from the curvilinear regression.

Key words: $P_{CO_2}$, $[H^+]$, metabolic acidosis, metabolic alkalosis, ventilation.

In 1917 J. P. Peters first recognized that the ventilatory response to metabolic acidosis could be monitored by following the changes in the alveolar carbon dioxide partial pressure. In addition he showed that in stable states of acidosis there was a close relationship between alveolar $P_{CO_2}$ and the CO$_2$ combining power of the blood.

More recently technical refinements have facilitated measurements of pH and $P_{CO_2}$ in arterial blood and further attempts have been made to define the normal ventilatory response in patients with metabolic acidosis and alkalosis in terms of the relationship which exists, in arterial blood, between $P_{CO_2}$ and pH (or $[H^+]$) or between $P_{CO_2}$ and plasma bicarbonate concentration ($[HCO_3^-]$).

On the basis of such clinical studies linear relationships have been described between $P_{CO_2}$ and $[H^+]$ (Albert, Dell & Winters, 1967; Flenley, 1971a, b) and between $P_{CO_2}$ and $[HCO_3^-]$ (Elkington, 1966; Albert et al., 1967; Pierce, Fedson, Brigham, Mitra, Sack & Mondal, 1970; Van Ypersele de Strihou & Frans, 1970) and these have been generally accepted.

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The relationship of the three variables is given by equation (1).

\[
[H^+] = K' \frac{S \cdot PCO_2}{[HCO_3^-]} \tag{1}
\]

\(K'\) is the equilibrium constant for the first dissociation of carbonic acid and when \([H^+]\) is expressed in nmol/l, \([HCO_3^-]\) in mmol/l and \(PCO_2\) in mmHg, \(K'\) has a value of 794 in plasma at 38°C. The solubility factor \(S\) for carbon dioxide is 0.0301 mmol l\(^{-1}\)mmHg\(^{-1}\). In view of the form of this expression it is improbable that the relationship between any two of the three variables will take the form of a simple linear regression when all three are changing.

It follows from equation (1) that:

\[ PCO_2 = \frac{[H^+] [HCO_3^-]}{K' \cdot S} \tag{2} \]

When \([HCO_3^-]\) remains constant this can be re-written:

\[ PCO_2 = C[H^+] \]

where \(C\) is a constant incorporating \(K'\), \(S\) and \([HCO_3^-]\). In these circumstances the relationship between \(PCO_2\) and \([H^+]\) is linear, the slope of the line being proportional to \([HCO_3^-]\). In metabolic acidosis and alkalosis in which \([HCO_3^-]\) is not constant, the slope of the line varies and a curvilinear relationship between \(PCO_2\) and \([H^+]\) would be predicted. The equations for the linear regressions derived by Albert et al. (1967) and by Flenley (1971b) are given in Table 1. In the first of these studies the duration of the acidosis varied considerably and in some cases was as short as 24 h, so that doubt exists as to whether all the patients were in a steady state of acid-base balance. Moreover, half of the observations were made upon blood from children under 2 years of age, in whom it is likely that the relationship between \([H^+]\) and \(PCO_2\) differs from that found in adults (Albert & Winters, 1966). More important is the fact that the range of values for \([H^+]\) encountered in this series was limited to between 48 and 78 nmol/l, since this may have led to erroneous conclusions regarding the form of the relationship. The range of values analysed by Flenley (1971b) was much greater; in the data which he assembled \([H^+]\) varied from 30 to 80 nmol/l. Included in the analysis, however, are data from subjects studied by Møller (1959), Weller, Swan & Merrill (1953), Bergofsky, Lehr & Fishman (1962) and Chiesa, Stretton, Massond & Howell (1969), who were almost certainly not in a steady state, and this may have influenced the form of the calculated regression.

Inspection of equations (1) and (2) suggests that the relationship between \(PCO_2\) and \([HCO_3^-]\) in patients with disturbances of acid–base balance is also unlikely to be described by a simple linear regression. In most of the studies listed in Table 1, in which linear regressions were derived, the range of values for \([HCO_3^-]\) was limited and no cases of metabolic alkalosis were included. The widest range is found in the work of Van Ypersele de Strihou & Frans (1971), but these studies contain no examples of severe acidosis or alkalosis. In addition, the patients with cholera reported by Pierce et al. (1970), and some of the subjects of Albert et al. (1967), were almost certainly not in a steady state of acid–base balance. The older literature contains other, slightly less satisfactory studies (Lennon & Lemann, 1966; Møller, 1959), in which a linear relationship was reported to exist between \(PCO_2\) and \([HCO_3^-]\) in metabolic disorders of acid–base balance. Lennon & Lemann (1966) used venous blood and some of Møller’s patients appear to have had pulmonary disorders. In the present study we have analysed the values for
<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>No. of observations</th>
<th>Equation</th>
<th>Range of [HCO₃⁻] (mmol/l)</th>
<th>Range of [H⁺] (nmol/l)</th>
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</thead>
<tbody>
<tr>
<td>Albert et al. (1967)</td>
<td>Children and adults with acute and chronic metabolic acidosis (diarrhoea, renal disease)</td>
<td>60</td>
<td>$P_{CO_2} = 52.95 - 0.50[H^+] \pm 2.76^{(1)}$ (r = 0.83)</td>
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<td>Flenley (1971a, b)</td>
<td>Values taken from literature. Adults and children with metabolic acidosis (diarrhoea, ketoadidosis, renal disease). Normal subjects taking NaHCO₃, NH₄Cl or ethacrynic acid</td>
<td>143</td>
<td>$[H^+] = 86.8 + 1.17 PCO_2$</td>
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<td>Elkington (1966)</td>
<td>Adults with chronic metabolic acidosis (renal disease)</td>
<td>27</td>
<td>$P_{CO_2} = 8.8 + 1.51[HCO_3^-] \pm 4.0$</td>
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<tr>
<td>Albert et al. (1967)</td>
<td>Children and adults with acute and chronic metabolic acidosis (diarrhoea, renal disease)</td>
<td>60</td>
<td>$P_{CO_2} = 8.36 + 1.54[HCO_3^-] \pm 1.1$ (r = 0.97)</td>
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<td>Pierce et al. (1970)</td>
<td>Adults with acute metabolic acidosis (cholera)</td>
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<td>$P_{CO_2} = 12.38 + 1.11[HCO_3^-] \pm 1.45$ (r = 0.98)</td>
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<td>Van Ypersele de Strihou &amp; Frans (1970)</td>
<td>Normal subjects. Adults on chronic haemodialysis with metabolic acidosis and with metabolic alkalosis induced by high bath [acetate]</td>
<td>337</td>
<td>$P_{CO_2} = 15.4 + 0.92[HCO_3^-] \pm 2.6$</td>
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$^{(1)}$ 1 SE.
arterial pH, \( P_{CO_2} \) and \([HCO_3^-]\) obtained in twenty-five patients with stable disturbances of metabolic origin, comprising a wide range of acidosis and alkalosis. In the great majority of patients the arterial pH and \( P_{CO_2} \) were known to have been steady for at least 24 h. In the few patients in whom treatment could not be delayed there was good clinical evidence that the disturbance had developed gradually over the previous few days. Data from three normal healthy subjects have been included. In thirteen of the patients the effect of a small increase in blood \([H^+]\) produced by infusion of the weak organic acid 5,5-dimethyl 2,4-oxazolidinedione (DMO) was studied (obtained from L. Light and Co.).

### PATIENTS AND METHODS

Twenty patients had metabolic acidosis due to chronic renal failure and five had metabolic alkalosis arising from loss of acid or excessive intake of base. In no case was the metabolic alkalosis due to primary potassium depletion. No patient had airways obstruction, pulmonary oedema or parenchymal lung disease. In only one patient was the arterial pH less than 7.10.

Arterial blood was drawn directly into a heparinized syringe. In the three healthy subjects and two of the patients with metabolic acidosis, blood was obtained by direct puncture of the brachial artery with local anaesthesia; in all other cases blood was taken from an indwelling arterial cannula inserted before the beginning of the study. Blood pH was measured immediately with a Radiometer G 298A glass capillary electrode with a KCl liquid junction, at a temperature of 38°C, and a Radiometer pH meter, standardized with BDH standard buffers (7.380±0.005 pH units at 38°C; 6.840±0.005 pH units at 38°C). A factor of 0.01 was added to the observed blood pH to correct for alteration of the junction potential at the KCl junction by precipitated red cells (Andersen, 1961). The reproducibility of duplicate readings was within 0.005 pH unit. The \( P_{CO_2} \) was determined simultaneously by the Siggaard Andersen micro-equilibration technique with Radiometer BMS2 equipment (Siggaard Andersen, Engel, Jorgensen & Astrup, 1960). The plasma bicarbonate concentration was calculated by using the Henderson–Hasselbalch equation and the measured values for pH and \( P_{CO_2} \) with values for \( pK' \) determined in this laboratory (Cowie, Lambie & Robson, 1962).

Thirteen patients received an intravenous infusion of DMO. Approximately 0.8 mmol of DMO/kg body weight was dissolved in sterile 5% dextrose solution and infused over a period of 20–30 min. This provides about 0.8 mmol of \( H^+ \)/kg, i.e. a total of approximately 50 mmol of \( H^+ \). Arterial blood was taken before the DMO was given and 4 h after the beginning of the infusion. All patients who received DMO gave their consent for the procedure after it had been explained to them and for arterial cannulation. The procedure has been approved by the Advisory Ethical Committee of the hospital.

Regressions were calculated by using the method of least squares.

### RESULTS

The data from the twenty-five patients with stable metabolic acidosis and alkalosis and the three healthy subjects are shown in Table 2 together with the data obtained after infusion of DMO. Fig. 1 shows the relationship between arterial blood \( P_{CO_2} \) and \([H^+]\) in stable conditions of acid–base balance. As the arterial \([H^+]\) increases there is a reduction in \( P_{CO_2} \) resulting from an increase in ventilation; a fall in arterial \([H^+]\) is associated with a decrease in
PCO₂ in metabolic acidosis and alkalosis

TABLE 2. Arterial blood acid-base measurements

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>pH (nmol/l)</th>
<th>[H⁺] (mmol/l)</th>
<th>PCO₂ (mmHg)</th>
<th>[HCO₃⁻] (mmol/l)</th>
<th>pH (nmol/l)</th>
<th>[H⁺] (mmol/l)</th>
<th>PCO₂ (mmHg)</th>
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ventilation and an increase in PCO₂. In Fig. 1(a) a single linear regression, \( PCO₂ = 64.5 - 0.69 [H⁺] \), has been calculated to fit the data. Clearly this is inadequate since there is a preponderance of points above the line at either end of the range, and below the line in the middle. The sum of squares of deviations about the regression is 1226.

A much better description of the data is given by a single curvilinear regression in the form of a rectangular hyperbola, shown in Fig. 1(b), which is continuous over the whole range of values. The equation of the hyperbola, derived by the method of least squares, is

\[
PCO₂ = \frac{962}{[H⁺] - 12} \pm 5.4 \text{ (SE)}
\]
and there is a reduction in the sum of squares to 759. An almost identical hyperbolic curve can be derived by using the method of Hey & Hey (1960), in which the functional relationship between $[H^+]$ and $P_{CO_2}$ is defined by the equation

$$P_{CO_2} = \frac{926}{[H^+]-13} \quad \text{(sum of squares 353)}.$$ 

The changes that occur after infusion of approximately 50 mmol of the weak acid DMO are shown in Fig. 2. The small changes in $[H^+]$ and $P_{CO_2}$ might have been predicted from the curvilinear regression. In patients with metabolic alkalosis the change in $[H^+]$ is small but $P_{CO_2}$ falls by approximately 5 mmHg; in patients with metabolic acidosis the increase in $[H^+]$ is greater and the fall in $P_{CO_2}$ less. The curvilinear regression derived from all data, including those from patients who had received DMO 4 h previously, was not appreciably different from that shown in Fig. 1(b) and Fig. 2.

Once the equation of the rectangular hyperbola has been determined it is possible to obtain an expression relating $P_{CO_2}$ to $[HCO_3^-]$ using the Henderson equation (equation 1) and the equation of the hyperbola.

Thus

$$[H^+] = K' \frac{\alpha P_{CO_2}}{[HCO_3^-]}$$

Combining the constants $K' = 794$ and $\alpha = 0.03$

$$[H^+] = \frac{23.8 P_{CO_2}}{[HCO_3^-]}$$
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Substituting for [H⁺] in the equation for the hyperbola

\[ Pco₂ = \frac{962}{(23.8 Pco₂/[HCO₃^-]) - 12} \]

which, on rearranging, gives

\[ 23.8 (Pco₂)^2 - 12 Pco₂ [HCO₃^-] - 962 [HCO₃^-] = 0. \]

The curve represented by this quadratic function is shown in Fig. 3, together with the data from the individual patients and healthy subjects. The linear regression derived by Van Ypersele de Strihou & Frans (1970), for patients with mild acidosis and alkalosis, is also shown. Over the range covered by their investigations this regression agrees closely with the curve calculated from our data.

In Fig. 4 data derived from a number of published studies dealing with metabolic disturbances of acid–base balance are shown in relationship to the hyperbolic curve derived from analysis of our results (Cowie et al., 1962; Bradley & Semple, 1962; Stone, 1962; Bergofsky et al., 1962; Pauli, Riedwil, Reubi & Wegmuller, 1963; Lambie, Anderton, Cowie, Simpson, Tothill & Robson, 1965; Posner, Swanson & Plum, 1965; Falchuk, Lamb & Tenney, 1966; Goldring, Cannon, Heinemann & Fishman, 1968; Fencl, Vale & Broch, 1969; Chiesa et al., 1969; Zimmett, Taft, Ennis & Sheath, 1970). The subjects of these studies were patients with untreated metabolic acidosis, due to a variety of causes, or healthy volunteers taking sodium bicarbonate or diuretics. The criteria used for selection of subjects were similar to our own but,
Fig. 3. Arterial blood $[\text{HCO}_3^-]$ and $P\text{CO}_2$ in stable metabolic acidosis and alkalosis (○) and 4 h after infusion of approximately 50 mmol of DMO (●). ·····, Present data; ——, data from Van Ypersele de Strihou & Frans (1970). The parallel continuous curves indicate 1 SE.

in some cases, slightly less rigid. For this reason, in the studies on healthy volunteers reported by Bergofsky et al. (1962) and Chiesa et al. (1969) only the values obtained during control periods are shown in Fig. 4 or included in the analysis. Clearly there is no discrepancy between our own results and those of others. For the patients with extremely severe acidosis reported by Posner et al. (1965) and Zimmett et al. (1970) the extrapolated hyperbolic regression appears to describe the relationship between $P\text{CO}_2$ and $[\text{H}^+]$ satisfactorily. The hyperbolic curve computed from the data collected from the literature conforms to the equation $P\text{CO}_2 = 1169/(\text{[H}^+] - 8) \pm 6.2$ (SE) and does not differ appreciably from the curve that describes our own data and which is shown Fig. 4. There is also good agreement between a relatively small portion of our curve and the linear regression reported by Albert et al. (1967).

**DISCUSSION**

Analysis of a wide range of values for arterial $[\text{H}^+]$, $P\text{CO}_2$ and $[\text{HCO}_3^-]$, measured in patients with stable chronic metabolic acidosis or alkalosis, suggests that the relationship between $[\text{H}^+]$ and $P\text{CO}_2$ is best described by a rectangular hyperbola. The best description of the relationship between $[\text{HCO}_3^-]$ and $P\text{CO}_2$ is provided by a quadratic function. These findings are not unexpected since non-linear relationships between $[\text{H}^+]$ and $P\text{CO}_2$ and $[\text{HCO}_3^-]$ and $P\text{CO}_2$ might be predicted from the Henderson equation, but, in the past, linear regressions have been derived to describe the relationships between these pairs of variables and have been accepted. A linear regression often appears to be the most obvious way of defining the relationship.
between two variables and the existence of a curvilinear relationship is easily overlooked. This is particularly likely to happen when the ranges of values examined is limited, as it was in most reported studies. A curvilinear relationship may also be obscured when accumulated data from different laboratories are examined, because of variations in analytical methods and because of the variety of clinical and experimental material. In view of this it is of interest that analysis of published data obtained from selected studies upon subjects who were in a reasonably stable state of metabolic acidosis or alkalosis shows that the relationship between [H+] and PCO₂ can be described by a hyperbolic function similar to that derived from our own series of cases.

The linear regressions reported by Albert et al. (1967) and by Van Ypersele de Strihou & Frans (1970) correspond closely to the relevant sections of the curves described in this paper, differing from them only at the ends of the range of values for [H+]. They can therefore be used in clinical practice, in all but the most severe disturbances, to determine whether a particular value of PCO₂ is appropriate to the degree of acidosis or alkalosis. However, preoccupation with linear relationships has obscured the fact that arterial PCO₂ is inversely proportional to [H⁺]. In subjects in a steady state of acid–base balance PCO₂ is inversely proportional to
alveolar ventilation; although a discussion of the factors that control ventilation is outside the scope of this paper, the existence of a reciprocal relationship between $PCO_2$ and $[H^+]$ in patients with stable chronic metabolic acidosis and alkalosis supports the idea that the concentration of $H^+$ in arterial blood, or in some compartment of the body fluid in which proportionate changes in $[H^+]$ occur, is an important factor in regulating ventilation.

ACKNOWLEDGMENT

The authors are extremely grateful for the help of Dr D. A. Williams, Department of Statistics, University of Edinburgh.

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