The assessment of acid–base disturbance in man
by the use of carbon dioxide titration curves

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Summary

1. Carbon dioxide titration curves were determined in vivo in dog and man at various degrees of acute non-respiratory acidaemia and alkalaemia.

2. The slope of the CO₂ titration curve (\(\Delta \text{log } \text{PCO}_2/\Delta \text{pH}\)) was found to increase with the severity of the acute non-respiratory acidaemia. In states of acute non-respiratory alkalaemia the slope (\(\Delta \text{log } \text{PCO}_2/\Delta \text{pH}\)) tended towards unity.

3. A simple scheme based on the CO₂ titration curves determined in vivo has been proposed for the assessment of acute acid-base disturbances in man.

4. Carbon dioxide titration curves were also determined in vivo in patients with chronic respiratory and non-respiratory acidaemia and it was found that these curves were not significantly different from those obtained in states of acute acid-base disturbances. It is therefore suggested that the scheme described in this paper is applicable to all acid-base disturbances.

Key words: acid–base balance, carbon dioxide-titration curves, acidaemia.

Introduction

A method for the assessment of states of acute acidaemia in both dog and man, based on the CO₂ titration curves of blood in vivo, has been previously described (Kappagoda, Linden & Snow, 1970; Stoker, Kappagoda, Grimshaw & Linden, 1972). These authors introduced the use of the non-respiratory pH of arterial blood as the index of the non-respiratory component of an acute acidaemia. The non-respiratory pH is defined as the pH which would occur if the P\(\text{CO}_2\) of arterial blood (P\(\text{aCO}_2\)) were adjusted in vivo to 5.32 kPa (40 mmHg). It is well known that the CO₂ titration curve for blood in vivo differs significantly from that obtained for blood in vitro. This difference is one reason why the assessment of acid–base disturbances by methods based on the CO₂ titration curve of blood in vitro (e.g. Astrup, Jorgensen, Siggaard-Anderson & Engel, 1960) can lead to significant errors when applied to the whole body (Stoker et al., 1972). The method previously described (Kappagoda et al., 1970; Stoker et al., 1972) avoids these errors, but so far it has only been developed to allow assessment of acute states of acidaemia.

In this paper this method has been extended to be of use in the assessment of acute acid–base disturbances in patients with an alkalaemia and in patients with chronic respiratory and chronic renal disease. Results obtained in states of acute alkalaemia, and additional results from the normal state, have been considered along with previously published data (Kappagoda et al., 1970; Stoker et al., 1972; Kappagoda, Stoker, Snow & Linden, 1972) to provide a comprehensive account of all acute acid–base disorders, thus extending the application of this method to include states of acute alkalaemia. Data from both man and dog have been combined and analysed collectively, since it has been shown that there is no significant difference in the respective slopes of the CO₂ titration curves in vivo (e.g. Brackett, Cohen & Schwarz, 1965; Stoker et al., 1972). In addition CO₂ titration curves were obtained in patients with chronic acid–base disturbances.
secondary to both renal disease and chronic CO₂ retention. The nature of these CO₂ titration curves were compared with those obtained in patients with acute acid–base disturbances to show that the scheme proposed for acute acid–base disturbances can also be applied to these patients.

Methods

Carbon dioxide titration curves in acute acid–base disturbances

A series of CO₂ titration curves in vivo was obtained in twenty-two human subjects and twelve anaesthetized dogs.

Of the human subjects, eleven were studied during open heart surgery, when an acute non-respiratory acidaemia occurred spontaneously, two after a massive pulmonary embolus, one with a minor barbiturate overdose with alkalosis due to repeated gastric lavage and a further eight at routine pre-operative diagnostic cardiac catheterization. Clinical details and serial measurements of pH, Pco₂ and Po₂ are given in Clinical Science and Molecular Medicine Table 74/14, deposited with the Librarian, The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, from whom copies may be obtained on request.

The dogs were rendered acidaemic and alkalaemic by the intravenous infusions of 1 mol/l HCl and 1 mol/l NaHCO₃ respectively. The experimental details and protocol for obtaining CO₂ titration curves in vivo have been described previously (Kappagoda et al., 1970; Stoker et al., 1972; Kappagoda et al., 1972). Arterial blood was withdrawn into heparinized syringes and analysed for pH, Pco₂ and Po₂. After control samples were obtained the PaCO₂ was increased by the addition of CO₂ in concentrations of up to 10% to the inspired gas and decreased by hyperventilation. Blood samples were obtained 5–10 min after the start of each change in inspired air composition or ventilation. The procedure was completed by returning the ventilation to its initial value and final control samples were obtained. Only titration curves in which the initial and final control non-respiratory pH values differed by less than 0·02 pH unit were accepted for analysis.

Carbon dioxide titration curves in chronic acid–base disturbances

Carbon dioxide titration curves were obtained in seven patients with chronic renal disease and seven patients with chronic respiratory disease and CO₂ retention. The relevant clinical details of these patients are given in Clinical Science and Molecular Medicine Table 74/14, deposited with the Librarian, The Royal Society of Medicine. These studies were completed with the patients in a stable state with respect to their respiratory and renal function. The experimental protocol adopted for the determination of the CO₂ titration curves in these patients has been published previously (Kappagoda et al., 1972).

The aims of this study were explained to the patients and their consents obtained before commencement of the investigation. The ethics of the investigation were approved at Killingbeck Hospital.

Results

Carbon dioxide titration curves in acute acid–base disturbance

A total of forty-eight CO₂ titration curves in vivo were obtained, twenty-eight curves in twenty-two human subjects and twenty curves in twelve dogs, and regression lines calculated for each. Two parameters were obtained from each titration curve: the slope (Δlog Pco₂/ΔpH) and the pH at Paco₂ 5·32 kPa (40 mmHg), i.e. the non-respiratory pH.

The relationship between the slope (Δlog Pco₂/ ΔpH) and the non-respiratory pH was determined by curvilinear regression analysis (Snedecor & Cochran, 1967). The best fit to the data was obtained by using a third degree polynomial, represented by the following equation (higher degree polynomials did not significantly reduce the sum of the deviations from regression):

\[ y = 181·05 - 42·12x + 1·706x^2 + 0·095x^3 \]

where \( y \) = slope (Δlog Pco₂/ΔpH) and \( x \) = non-respiratory pH. This cubic equation fitted the data significantly better than linear \((P<0·01)\) or quadratic \((P<0·05)\) ones. The standard errors for the coefficients of the above equation were: 181-05 ± 54·8; 42·2 ± 17·4; 1·706 ± 2·172; 0·095 ± 0·12.

A plot of all the data obtained and the calculated regression curve are shown in Fig. 1. Also shown are the 95% confidence limits for the regression curve and the 95% tolerance limits for a single estimate of slope from a given value of the non-respiratory pH. From the above equation it is apparent (see Fig. 1) that the slope of the CO₂ titration curve in vivo becomes steeper with increasing non-respiratory acidaemia and decreases with non-respiratory alkalaemia and approaches –1. By the use of this relationship a family of CO₂ titration curves in vivo has been constructed (Fig. 2).
Fig. 1. Relationship between the slope of the CO₂ titration curves and the non-respiratory pH (pH at Pa CO₂ 5.32 kPa) in acute acid–base disturbances. The interrupted lines are the confidence limits (95%) for the curve and the bars represent the tolerance limits (95%) for individual points. O, Human; •, dog.

Fig. 2. Carbon dioxide titration curves in vivo constructed from the curvilinear relationship illustrated in Fig. 1. The non-respiratory pH during an acute acidemia can be obtained from the arterial pH and Pa CO₂ as follows: the relevant point is plotted on this diagram and the titration curve in vivo is drawn through it; the pH value on this curve, corresponding to Pa CO₂ 5.32 kPa is the non-respiratory pH. Below the curves a table provides a clinical record sheet for the maintenance of chronological details of the acid–base status of the subject.

Fig. 3. Examples of CO₂ titration curves in vivo in patients with chronic non-respiratory acidemia (•) and chronic respiratory acidemia (O).
Carbon dioxide titration curves in chronic acid–base disturbances

Fourteen CO₂ titration curves were obtained from patients with chronic acid–base disturbances; seven were from patients with chronic renal disease and seven from patients with chronic respiratory disease. Examples of titration curves from each group are shown in Fig. 3. For the purpose of statistical analysis regression lines were constructed and two parameters were considered for each curve; the slope (Δlog PₐCO₂/ΔpH) and the pH at PₐCO₂ 5·32 kPa (40 mmHg) (Table 74/14). The relationship between these two parameters in patients with chronic renal disease is represented by the equation

\[ y = -2·34x + 18·3 \]

where \( y = \Delta \log PₐCO₂/\Delta pH \) and \( x = \) non-respiratory pH. The corresponding relationship for the patients with chronic respiratory disease is represented by the equation

\[ y = -1·78x + 14·6 \]

where \( y = \Delta \log PₐCO₂/\Delta pH \) and \( x = \) non-respiratory pH.

Over the range of values of non-respiratory pH studied, both the above regression lines, which relate slope to non-respiratory pH, lie within the 95% confidence limits of the regression lines for the total population (Fig. 4).

Discussion

It has been shown previously that the slope of the CO₂ titration curve (i.e. \( \Delta \log PₐCO₂/\Delta pH \)) of blood in vivo becomes steeper as the non-respiratory pH decreases (Kappagoda et al., 1970; Stoker et al., 1972). Also the relationship between the non-respiratory pH and the slope of the CO₂ titration curve in states of acute non-respiratory acidaemia was described by a linear regression equation. The additional data, reported here, were obtained from subjects who were either within the normal range of pH and PₐCO₂ or were in a state of chronic non-respiratory acidaemia or alkalaemia. For instance, chronic CO₂ retention leads to a high plasma bicarbonate and a high non-respiratory pH. We have compared the slopes of the CO₂ titration curves in this situation (i.e. a chronically elevated non-respiratory pH) with the slopes of the CO₂ titration curves in states where the non-respiratory pH is acutely elevated. A comparable analysis was also made in patients with chronic non-respiratory acidaemia. In this way, it was possible to determine whether the relationship between the slope and the non-respiratory pH which was found in acute acid–base disturbances is applicable to the chronic situation.

Thus it is now possible to extend the range over which the relationship between the non-respiratory pH and the slope of the CO₂ titration curve may be defined. The results show that over this extended range the relationship is curvilinear (Fig. 1), and appears to be in agreement with the mathematical model proposed by Wolff (1967) and referred to by Russell, Illickal, Maloney, Rocher & Deland (1972). The slope of the CO₂ titration curve in vivo is dependent on the function of numerous buffering systems in the whole body (see Roos & Thomas, 1967) and not those in blood alone. Thus in diseases which result in chronic acid–base disturbances (e.g.
chronic renal disease) it is likely that in addition to
the obvious effects on the plasma proteins and
haemoglobin, other body proteins are also affected
by the underlying disease. Thus a change in the
buffering power of the whole body, as reflected in
the slope of the CO₂ titration curve in vivo, could be
expected in these chronic acid–base disturbances.
For instance, in patients with chronic renal disease,
the regression line relating the slope (Δlog PA,CO₂/
ΔpH) to the non-respiratory pH is below that in
states of acute acidaemia (Fig. 4). One could specu­
late, in these patients, that this results from a
reduction in buffering power brought about by
changes in body proteins similar to those observed
in the plasma proteins and haemoglobin. The
converse appears to be the case in the patients
with chronic respiratory disease, probably as a result
of the often concurrent polycythaemia. However,
the present study has indicated that these changes in
buffering power, with respect to CO₂, while remain­
ing an attractive hypothesis do not attain statistical
significance. Thus in practice it becomes unnecessary
to adopt a different system for the assessment of
these chronic acid–base disturbances.

The slope of the acute CO₂ titration curve in
subjects with chronic respiratory acidaemia has also
been described by Flenley, Franklin & Millar (1970),
Goldstein, Gennari & Schwartz (1971) and Ingram,
Millar & Tate (1973). Data from these publications
have been recalculated, in terms of Δlog PCO₂/ΔpH
and non-respiratory pH, and are compared with the
results obtained in this study (Fig. 5), where it will be
seen that these previously obtained results of other
authors all lie within the 95% confidence limits of
the regression line obtained in this study. However,
the values obtained by Goldstein et al. (1971) must
be treated with some caution since they did not
measure PCO₂ but calculated PCO₂ from measure­
ments of pH and CO₂ content with the Henderson–
Hasselbalch equation. The imprecision arising from
such a procedure has been described by Linden &
Norman (1971). For our purposes to insert points
on Fig. 5 it was therefore necessary to recalculate
the values for PCO₂ originally published by Goldstein
et al. (1971), the corrections to the pH' value of the
Henderson–Hasselbalch equation proposed by
Linden & Norman (1971) being used. Thus it may be
concluded that in the groups of subjects so far
studied, by us and other workers, the relationship
between the non-respiratory pH and the slope of the
CO₂ titration curve may be defined by a single
equation.

The derived titration curves (Fig. 2) could there­
fore provide a simple method of assessing all
disorders of acid–base balance as follows. The
existence of a respiratory acid–base disorder is
established by the determination of the PA,CO₂ and
its severity is assessed in the conventional manner
as the difference in the PA,CO₂ from the normal
value. The presence of a non-respiratory disturbance
is established by plotting the measured values (pH
and PA,CO₂) on the diagram shown in Fig. 2. The
placement of this point from the normal line, i.e. the
titration curve in vivo passing through pH 7.4 and
PA,CO₂ 5.32 kPa (40 mmHg), indicates the
existence of any non-respiratory disturbance. The
magnitude of the disturbance is indicated by the non-respiratory pH, i.e. the pH at $P_{a,CO_2}$ 5.32 kPa (40 mmHg), which is found by following the titration curve through the point.

Since the non-respiratory pH for any one individual is predicted from a slope derived from a curve which is deduced from all our studies (Fig. 1 and Fig. 4), this procedure will obviously incorporate a systematic error which accrues from the 95% tolerance limits for an individual value of this slope (see Fig. 1). For example, a patient with blood pH 7.245 and $P_{a,CO_2}$ 6.6 kPa (50 mmHg) will have a non-respiratory pH of 7.32 and the 95% tolerance limits for this value will be ±0.026. These tolerance limits for the non-respiratory pH value should not detract from its use in the diagnosis of the nature of the acid–base disturbances. Further, in the treatment of such disturbances in a given patient it is relatively unimportant, as it is recommended that the analyses be repeated after any therapeutic intervention, such as an infusion of sodium bicarbonate in states of acute acidaemia. Since one is then investigating a changing state in a given individual the systematic error mentioned above diminishes in importance.

Thus the system may be used in each of the three groups of acid–base disturbance as a practical tool with which to follow the patient back to the 'normal' state. However, there is another major reason for advocating the use of non-respiratory pH as yet another method for assessing acute acid–base disorders. No methods, so far advocated, are capable of estimating (a) the total stores of buffers within the body or (b) whether these stores have decreased or increased since the beginning of the disease. It is not possible to predict from such measurements as base deficit or total buffer anion concentration in blood the amount of bicarbonate required to correct a non-respiratory acidaemia, even in acute disturbance. Such a difficulty is obviously increased in the chronic disturbance because of the long duration of the illness and the probable resulting change in the body store of buffers. The use of non-respiratory pH as an index in these disturbances, although the above difficulties are recognized, leaves the clinician with the choice of 'titrating' the patient back to a value which meets his clinical assessments. It also recognizes that correction of the acid–base state to a rigidly stipulated value such as a base deficit of zero in blood, or a non-respiratory pH value of 7.40, is probably not the best course of therapy for a patient who has a chronic acid–base disturbance. Thus a flexible system which permits the titration of the patient's acidaemia to a non-respiratory pH value which is considered optimum for each individual remains the most rational form of therapy for acid–base disorders.

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References


