

# The Respiratory Compensation of Metabolic Alkalosis. Influence of Blood Oxygen Tension on the Pattern of Adaptation

CHARLES van YPERSELE de STRIHOU and  
ALBERT FRANS

University of Louvain, Louvain, Belgium

Metabolic acidosis is a well known cause of hyperventilation. Conversely, metabolic alkalosis is widely assumed to have the opposite effect, namely to decrease ventilation and to elevate carbon dioxide tension. However, very few data have substantiated this contention. Metabolic alkalosis has been variously reported to be associated with elevated (Reeves & Brown, 1958; Stone, 1962) or with normal  $P_{CO_2}$  (Roberts et al, 1956; Popell et al, 1956; Austin, 1965). Furthermore, available data have up to now not allowed quantitation of the phenomenon.

In the present study an attempt is made to delineate the respiratory response to chronic metabolic alkalosis by reviewing the acid-base status of 30 uraemic patients treated by regular haemodialysis.

## MATERIAL AND METHODS

A total of 182 acid-base measurements was obtained over a 4 month period from 30 patients treated by regular haemodialysis for terminal renal failure. Dialysate solutions containing 32, 38 or 50 mEq/l acetate were used to produce a sustained elevation of plasma bicarbonate concentration. Observations were made only a week after the new dialysate had been used.

None of the patients had any evidence of impaired pulmonary function as evaluated by chest X-ray, or arterial  $P_{O_2}$  at normal plasma bicarbonate concentration. Arterial blood samples were drawn through the arterial cannula of the Scribner shunt prior to dialysis. The analytic methods and calculations have been described previously (van Ypersele & Frans, 1970). Blood  $P_{O_2}$  was determined in 180 samples at 37° C with a polarographic Clark electrode (Gerin-Portier et al, 1970).

## RESULTS

**Respiratory compensation for plasma bicarbonate levels ranging from 20 to 38 mEq/l**

Plasma bicarbonate concentration was equal to or higher than 20 mEq/l in

155 samples. Seventeen acid-base determinations obtained in a previous study with plasma bicarbonate concentrations higher than 20 mEq/l were pooled with the present data. Results were grouped according to increasing levels of bicarbonate, each group encompassing a 1 mEq/l interval.

Mean values of arterial  $P_{CO_2}$  observed in each group are presented in Figure 1 and Table I. It may be noted that  $P_{CO_2}$  increases in direct proportion with the elevation of plasma bicarbonate concentration. The calculated weighted regression line has a slope of 0.91, an intercept of 15.6 and a standard deviation of 2.9. The slope is shown by a 't' test to be different from zero ( $p < 0.001$ ). It was further demonstrated by an 'F' test that this relationship is linear.

A further analysis of individual response to metabolic alkalosis was carried out in 18 patients whose plasma bicarbonate concentration varied by at least 9 mEq/l and in whom a minimum of 7 determinations were available. The individual regression line ranged in slope from 0.76 to 1.27 and in intercept between 6.4 and 18.7. The correlation coefficient ranged from 0.80 to 0.98. The elevation of response lines, t. i. the value of  $P_{CO_2}$  adjusted to a mean bicarbonate concentration of 26.8 mEq/l, ranged from 36.8 to 43.6 mm Hg. Covariance analysis showed that there was no significant difference between the response lines with the steepest and the smallest slopes. This analysis was taken to indicate that there was no difference among the slopes of all response lines. The elevation of each response line was further compared with each of the seventeen others with a sequential test. Out of 155 comparisons, 24 showed a statistically significant ( $p < 0.05$ ) difference.

Mean hydrogen ion concentration is given for each bicarbonate group in Table I. Despite hypoventilation, hydrogen ion concentration falls in a curvilinear fashion as plasma bicarbonate concentration increases.

Arterial  $P_{O_2}$  decreases progressively with increasing levels of bicarbonate (Table I).

#### Confidence bands for the respiratory compensation for all metabolic acid-base disorders

The present data were pooled with observations made previously in patients with metabolic acidosis (van Ypersele & Frans, 1970). A total of 337 acid-base measurements in 48 patients were available.

Linearity of the  $P_{CO_2}$  bicarbonate relationship was demonstrated by an 'F' test over a range of plasma bicarbonate concentration going from 11 to 38 mEq/l. The calculated weighted regression line has the following equation:  $P_{CO_2} = 0.92 HCO_3^- + 15.4 (+ 2.6) -$  The linearity of the  $P_{CO_2}$  response line has provided a base for the calculation of a significance band that defines with an estimated 95% probability the changes in  $P_{CO_2}$  to be anticipated during uncomplicated metabolic acid-base disturbances. Figure 2 presents

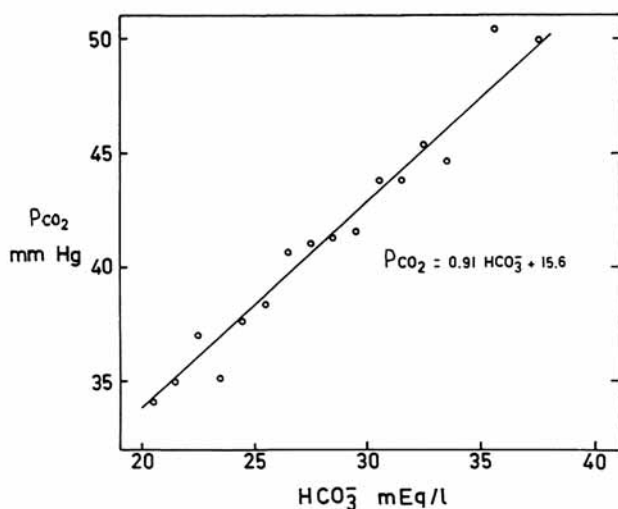


Figure 1. Relation between arterial  $P_{CO_2}$  and plasma bicarbonate concentration.  $P_{CO_2}$  values were grouped according to increasing levels of plasma bicarbonate, each group encompassing a 1 mEq/l interval. Each point represents the mean value for a given group. The solid line drawn through the points is the weighted regression calculated from individual values

Table I. Summary of arterial blood acid-base values and oxygen tensions in 30 uraemic patients made alkalotic by regular dialysis

Plasma Bicarbonate mEq/l	Number of observations	$P_{CO_2}$ mm Hg	Hydrogen ion concentration nM/l	$P_{O_2}$ mm Hg*
20.0 - 20.9	18	34.1 ± 2.3**	39.9 ± 2.6**	97.7 ± 7.5 (11)
21.0 - 21.9	14	34.9 ± 2.8	39.0 ± 3.0	89.5 ± 10.4 (9)
22.0 - 22.9	8	36.9 ± 2.0	39.6 ± 2.2	89.7 ± 7.9 (6)
23.0 - 23.9	6	35.1 ± 2.8	36.3 ± 2.8	83.8 ± 4.2 (3)
24.0 - 24.9	9	37.6 ± 1.8	36.9 ± 1.8	88.0 ± 6.8 (8)
25.0 - 25.9	6	38.3 ± 3.2	35.9 ± 3.4	84.9 ± 6.8 (6)
26.0 - 26.9	10	40.6 ± 2.5	36.2 ± 3.0	83.4 ± 8.5 (10)
27.0 - 27.9	13	41.0 ± 2.8	35.6 ± 2.6	82.8 ± 9.5 (12)
28.0 - 28.9	16	41.3 ± 3.0	34.7 ± 2.5	80.9 ± 7.5 (16)
29.0 - 29.9	21	41.6 ± 2.5	33.9 ± 2.1	76.7 ± 10.8 (21)
30.0 - 30.9	15	43.8 ± 3.2	34.4 ± 2.6	80.0 ± 6.9 (15)
31.0 - 31.9	10	43.8 ± 3.1	33.4 ± 2.0	79.7 ± 6.9 (10)
32.0 - 32.9	10	45.3 ± 2.8	33.3 ± 2.0	77.4 ± 5.8 (10)
33.0 - 33.9	8	44.6 ± 5.4	31.8 ± 3.8	78.5 ± 9.1 (9)
34.0 - 34.9	4	47.1 ± 2.0	33.0 ± 1.4	73.5 ± 8.4 (4)
35.0 - 35.9	3	50.4 ± 4.7	34.0 ± 2.8	70.6 ± 6.7 (3)
36.0 - 36.9	-	-	-	-
37.0 - 37.9	1	49.9	31.6	81.4 (1)

\* In parenthesis the number of observations  
 \*\* SD

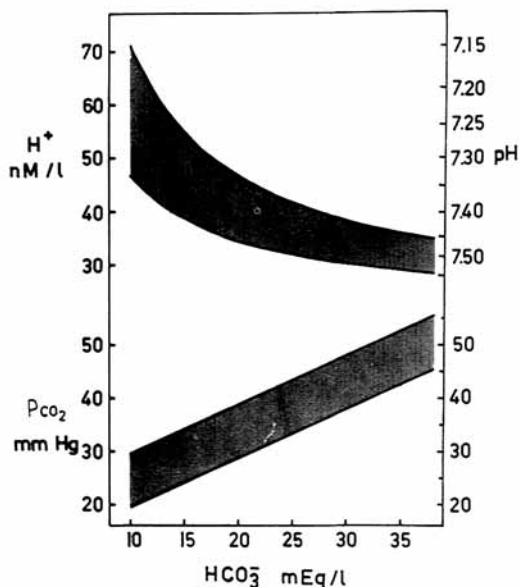


Figure 2. Significance bands for arterial blood pH and  $\text{Pco}_2$  in chronic metabolic acid-base disturbances. In uncomplicated cases, values for pH and  $\text{Pco}_2$  will fall within these limits with a probability of 95%

these bands as well as the corresponding bands for hydrogen ion concentration obtained by appropriate substitution in the Henderson-Hasselbalch equation.

#### DISCUSSION

The present data demonstrate clearly that chronic metabolic alkalosis induces a sustained elevation of arterial  $\text{Pco}_2$ . This response may be taken as representative of man's normal response to metabolic alkalosis: all the patients had a normal lung function as evidenced by chest X-ray and a normal arterial  $\text{Po}_2$  when bicarbonate concentration is normal. Furthermore, transient hyperventilation associated with arterial puncture was avoided by the use of permanently implanted arterial cannulae.

The relevance of the present data to the ventilatory response of normal man to metabolic alkalosis remains to be determined. The effect of uraemia on respiration remains a moot point. As we have previously pointed out (van Ypersele & Frans, 1970), there is at present no evidence that uraemic intoxication modifies the respiratory response to acid-base stimuli. In the present study no correlation was found between the level of blood urea or creatinine and the degree of respiratory compensation.

It was possible to evaluate individual  $\text{Pco}_2$  response lines in 18 patients whose bicarbonate concentration varied by at least 9 mEq/l. The response

lines had similar slopes but different elevations. A similar observation has already been reported during metabolic acidosis (van Ypersele & Frans, 1970). The maximal difference in the elevations of the response lines was virtually identical in both studies (6.8 and 6.9 mm Hg). This fact confirms our previous suggestion that the patients have a similar sensitivity, but a different threshold to acid-base stimuli.

The present data demonstrate that alkalotic hypoventilation is associated with a decreased arterial oxygen tension ( $P_{O_2}$ ). Within the limits of the bicarbonate range studied, it does not appear that the resultant hypoxaemia influences respiration. Indeed, for a given range of plasma bicarbonate concentrations,  $P_{CO_2}$  of subjects with a  $P_{O_2}$  of less than 70 mm Hg was not lower than that of subjects with a  $P_{O_2}$  above 80 mm Hg.

The progressive fall in arterial  $P_{O_2}$  is undoubtedly related to hypoventilation. Indeed,  $P_{O_2}$  is negatively correlated with  $P_{CO_2}$  ( $p < 0.001$ ). Furthermore, if alveolar oxygen tension is calculated, assuming a respiratory quotient of 0.85, it may be shown that arterial and alveolar oxygen tensions fall in a strictly parallel fashion. This observation suggests that the alveolo-arterial oxygen gradient remains constant despite the fall in alveolar oxygen tension, an unexpected finding as it is known that decrements in alveolar oxygen tension are associated with decreased alveolo-arterial gradients (Comroe, 1965).

Therefore it appears that other factors play a role in reducing arterial oxygen tension during metabolic alkalosis. One of them is clearly the shift of the oxyhaemoglobin dissociation curve produced by alkalosis (Comroe, 1965). Another factor might be a change in the so-called physiological shunt, that is the amount of blood perfusing the lung, but escaping close contact with alveolar air and thus remaining desaturated (Comroe, 1965). In order to evaluate this factor, the shunt has been calculated in 22 patients assuming that capillary and alveolar oxygen tensions are equal and that the oxygen arteriovenous difference is inversely related to the degree of anaemia. Results were grouped according to increasing hydrogen ion concentration. The mean shunt, expressed as percentage of cardiac output, for every group of hydrogen ion concentration, is presented in Figure 3. It may be noted that the amount of blood escaping full oxygenation increases progressively as hydrogen ion concentration decreases. These data should be taken with caution as their calculation rests on multiple assumptions. They suggest nevertheless that hypoxaemia results from alkalosis not only as a consequence of alveolar hypoventilation and of a shift of the oxyhaemoglobin dissociation curve, but also from changes in the ventilation perfusion ratio of the lungs. Arterial oxygen tension will thus fall faster than might be anticipated from the observed  $P_{CO_2}$ . Whether this fall curtails compensatory hypoventilation at bicarbonate concentrations higher than those observed in the present study remains to be determined.

The pooling of the present results with those obtained previously suggests

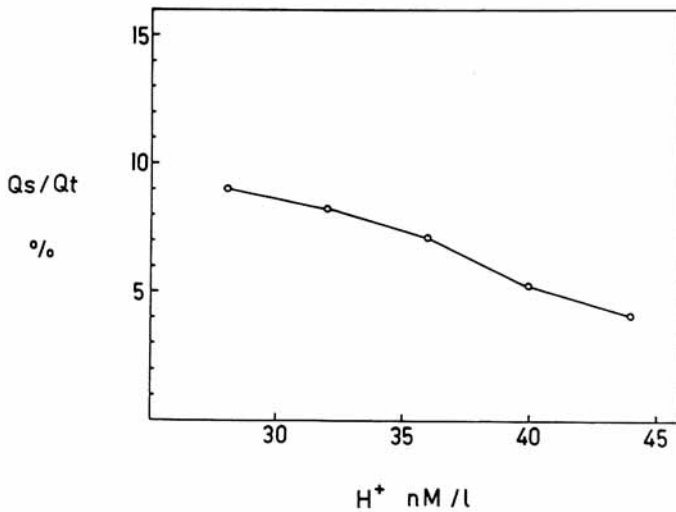


Figure 3. Relation between the percentage of cardiac output (Qt) escaping oxygenation in the lungs (shunt) and blood hydrogen ion concentration (see text)

that  $P_{CO_2}$  is linearly related to bicarbonate concentration over a large range of bicarbonate concentrations. The significance bands derived from these data define with an estimated 95% probability the changes in  $P_{CO_2}$  to be anticipated in chronic metabolic acid-base disturbances. The narrowness of these bands emphasises the precision of the ventilatory response: from a bicarbonate concentration of 10 mEq/l to a bicarbonate concentration 38 mEq/l,  $P_{CO_2}$  is expected to fall within a 10 mm Hg interval. Such confidence bands should allow the clinician to recognise and treat any superimposed respiratory acid-base disturbance by telling him what pH and what  $P_{CO_2}$  to expect for every level of bicarbonate.

#### SUMMARY

1. In chronic metabolic alkalosis, arterial  $P_{CO_2}$  is linearly related to plasma bicarbonate concentration.
2. Elevation of  $P_{CO_2}$  is associated with a fall in arterial  $P_{O_2}$ .
3. Indirect evidence suggests that hypoxaemia in alkalosis results not only from hypoventilation and a shift of the haemoglobin dissociation curve but also from changes in the ventilation/perfusion ratio of the lungs.
4. It is demonstrated that the overall  $P_{CO_2}/HCO_3^-$  relationship is linear for  $HCO_3^-$  levels ranging from 11 to 38 mEq/l.

## ACKNOWLEDGMENTS

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