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Research Article

EVALUATION OF RESPIRATORY COMPENSATION IN METABOLIC ALKALOSIS [1, 2]

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It has been postulated that a metabolic alkalosis could be partially compensated by a decrease in respiratory exchange consequent to inhibition of the respiratory center by an elevated blood pH (1–5). The extent to which compensation may occur has been predicted to be within the limits imposed by alterations in blood oxygen and pCO_2 (2, 5). The calculated respiratory exchange which has been predicted with alterations in blood pH has been challenged on a theoretical basis (6), and the actual occurrence of significant respiratory compensation in metabolic alkalosis has been denied on the basis that no overt decrease in respiratory exchange was noted acutely following the administration of $NaHCO_3$ (7–9). However, there are few data on actual respiratory exchange or plasma pCO_2 during acute metabolic alkalosis in unanesthetized animals or human subjects, and the published data are insufficient to permit an evaluation of respiratory compensation in chronic metabolic alkalosis. Accordingly, the studies reported here were carried out on patients and dogs to determine the extent of respiratory compensation in both acute and chronic metabolic alkalosis. The data suggest that respiratory compensation is minimal in the majority of patients and dogs with metabolic alkalosis as produced by bicarbonate infusion, gastric drainage of chloride or potassium deficiency.

METHODS

The data presented here include analyses of blood pH, plasma carbon dioxide content and calculated plasma pCO_2 as determined on 34 patients with metabolic alkalosis and 19 normal patients. Clinically, the types of metabolic alkalosis which were encountered in the patients included: 1) potassium deficiency alkalosis resulting from post-operative deficits, inadequate intake or hyperadrenocorticism, 2) hypochloremic alkalosis as instigated by gastric drainage or vomiting secondary to upper small bowel obstruction, and 3) alkalosis resulting from exogenous lactate or bicarbonate administration. In the patients presented, the calculated plasma pCO_2 and measured pH were used as an index to determine the extent of respiratory compensation. Carbon dioxide content and pH in these patients were analyzed either on arterialized venous blood drawn without stasis or directly on arterial blood.[3] In some of the patients, venous blood was drawn without stasis, but was not previously arterialized. The blood was drawn for analysis at a time when the patients had not received sedation. The data from reports in the literature which are incorporated represent analyses which were carried out on unanesthetized dogs or patients with no deducible evidence of pulmonary dysfunction.

The experimental studies were carried out, in the present study, on unanesthetized dogs, and included measurements of minute volume, respiratory rate, alveolar ventilation, plasma carbon dioxide content and blood pH previous to and during a period of metabolic alkalosis induced either by infusion of sodium bicarbonate or by gastric drainage of chloride.

The animals were trained to stand quietly in a loosely restraining dog sling during the period of metabolic alkalosis. Gastric contents were collected from dogs by an indwelling catheter inserted through a permanent fistula created by the insertion of a biflanged steel button extending from the stomach to the abdominal wall.

In nine alkalotic dogs Sodium Pentothal® was given and the animals were then artificially ventilated to induce a decrease in alveolar ventilation which was just sufficient to reduce the blood pH to normal, and thus "compensate" the metabolic alkalosis. In these animals

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[2] We are indebted to Dr. Rulon W. Rawson for his cooperation and helpful suggestions in carrying out these studies and to Dr. Robert F. Pitts for reviewing this work.

[3] The inherent error in utilizing venous blood for analysis of pH and carbon dioxide must be considered since it is well known that the pH of venous blood is lower than in arterial blood, whereas the carbon dioxide content is higher. This error was partly obviated by using arterial blood or arterializing venous blood in some of the patients. However, the finding that the pH and pCO_2 did not reflect significant respiratory compensation even with the use of venous blood strengthens the premise, since it would be expected that the error would be in the opposite direction from that reported here.

arterial oxygen content and oxygen capacity were analyzed.

Arterial blood samples were drawn from an indwelling arterial catheter, and the chemical analyses of carbon dioxide and pH carried out according to previously described methods (10). Blood oxygen content and capacity were determined in duplicate by the method of Van Slyke and Neill (11). The animals were breathing room air throughout and expired gases were collected in a Tissot Gasometer through a set of valves and a snugly fitted rubber face mask which had a dead space of approximately 35 cc. Gas analyses were carried out according to the method of Scholander (12). Physiological dead space was calculated from the Bohr equation as modified by Rahn (13). It was assumed in these calculations that arterial pCO_2 was equal to the effective alveolar pCO_2 (14). Effective alveolar ventilation was then calculated as follows: Alveolar ventilation = (Tidal volume − Dead space) × Respiratory rate.

RESULTS

Figure 1 summarizes the plasma pH and pCO_2 at varying levels of carbon dioxide content in 21 unanesthetized dogs during metabolic alkalosis produced either by alkali infusion or gastric drainage of chloride. The published data of Pitts and Lotspeich (15) are included for comparison. As indicated by this overall summary, the blood pH increased, whereas the plasma pCO_2 remained within the normal range despite elevations in total carbon dioxide.

Although the unchanged plasma pCO_2 suggests that pulmonary ventilation is not significantly decreased in metabolic alkalosis, this was further confirmed by direct measurements of minute volume in nine of the animals studied. The data from these nine dogs are summarized in Table I, and show that there was not a consistent decrease in minute volume during metabolic alkalosis. Similarly, the effective alveolar ventilation during metabolic alkalosis was not consistently changed. In some of the animals alveolar ventilation decreased and in others it increased during the pe-

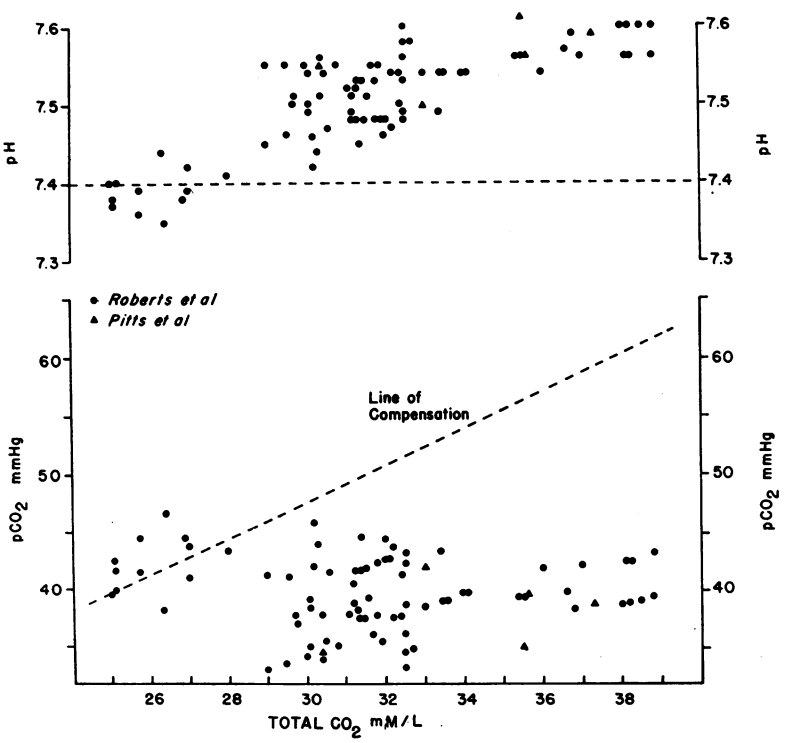

FIG. 1. BLOOD pH AND PLASMA pCO_2 IN RELATION TO TOTAL CARBON DIOXIDE CONTENT IN ALKALOTIC AND NORMAL DOGS

The line of compensation is calculated from a theoretical consideration of the change in plasma pCO_2 which would occur if the metabolic alkalosis were completely compensated, to produce a blood pH of 7.4. The data of Pitts and Lotspeich (15) are also plotted for comparison.

TABLE I

Average respiratory minute volume in dogs previous to and during metabolic alkalosis *

Type of metabolic alkalosis	Minute resp. volume *L./min.*	pH	Plasma CO_2 *mM/L.*	pCO_2 *mm. Hg*
1)				
Control	3.12	7.35	24.3	43
Alkalosis (Gastric drainage)	3.67	7.50	34.4	44
2)				
Control	2.89	7.39	27.06	44
Alkalosis (Gastric drainage)	2.9	7.47	30.58	41
3)				
Control	5.5	7.4	24.66	39
Alkalosis ($NaHCO_3$ infusion)	8.0	7.65	45.9	42
4)				
Control	5.62	7.25	19.7	43
Alkalosis ($NaHCO_3$ infusion)	5.60	7.56	37.2	41
5)				
Control	3.7	7.43	27.2	40
Alkalosis ($NaHCO_2$ infusion)	6.6	7.63	43.05	41
6)				
Control	5.6	7.37	24	41
Alkalosis ($NaHCO_3$ infusion)	6.0	7.51	31.63	39
7)				
Control	4.4	7.31	21.0	41
Alkalosis ($NaHCO_3$ infusion)	3.5	7.56	38.8	43
8)				
Control	4.6	7.40	23.14	37
Alkalosis ($NaHCO_3$ infusion)	4.9	7.57	38.6	42
9)				
Control	2.8	7.35	29.9	53
Alkalosis (Gastric drainage)	2.9	7.48	32.1	43

* The respiratory volume represents an average of two to three determinations in the control period and four to six determinations during the alkalotic interval. The plasma values represent single determinations in the control period and at the end of the alkalotic period.

riod of study. This is illustrated in Figure 2, which shows the alveolar ventilation ratio in six of the animals studied.[4]

Table II summarizes the maximal changes in arterial oxygen saturation during a period when alveolar ventilation was reduced sufficiently by anesthesia and artificial ventilation to completely compensate the metabolic alkalosis. In all of the animals arterial oxygen saturation decreased during the period of artificial compensation. In the five animals who were ventilated sufficiently to restore pH and pCO_2 to alkalotic levels it was noted that arterial oxygen saturation was restored toward control alkalotic values. We have interpreted this observation to indicate that the anesthesia *per se* had no effect on arterial oxygen saturation and that alterations noted during anesthesia were secondary to decreased pulmonary exchange.

Evaluation of respiratory compensation in patients with metabolic alkalosis

Figure 3 summarizes the plasma pCO_2 and blood pH in relation to total carbon dioxide content of the plasma in 34 patients studied by the authors. For comparative purposes published data of other authors (17–23) are included. The majority of patients shown demonstrated an elevation of blood pH, while pCO_2 was little changed from the normal range. This was true at all levels of plasma carbon dioxide content and regardless of the type of alkalosis encountered. Significant compensation was achieved by only five of the patients summarized from the literature. The remaining forty-five patients displayed minimal or no respiratory

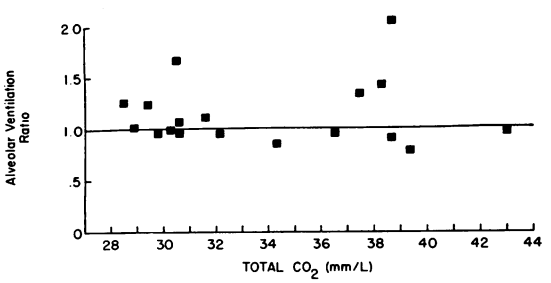

FIG. 2. ALVEOLAR VENTILATION RATIO IN DOGS DURING METABOLIC ALKALOSIS

The alveolar ventilation ratio was calculated as follows:

$$\frac{\text{Alveolar ventilation during metabolic alkalosis (L./min.)}}{\text{Control alveolar ventilation (L./min.)}}$$

Two measurements of alveolar ventilation were carried out on the animals during the control period and three measurements were carried out during the period of metabolic alkalosis at varying levels of plasma CO_2 content and at a time when the animals had been stabilized at the indicated levels for 30 to 40 minutes.

[4] The change in respiration necessary to compensate a metabolic alkalosis could be slight, and may not be detected by the usual methods of measurement. Since a knowledge of the plasma CO_2 tension can be utilized to give information regarding the overall ability of the lung to exchange CO_2 (16), this is probably a more reliable "index" of the degree to which respiratory compensation occurs in metabolic alkalosis.

TABLE II

Arterial oxygen saturation during the interval of metabolic alkalosis and following artificially induced respiratory compensation *

	Plasma			Arterial oxygen % saturation
	Carbon dioxide *mM/L.*	pH	pCO_2 *mm. Hg*	
1)				
Alkalosis	38.8	7.56	43	91
Anesthesia	Reduced ventilation			
	36.8	7.38	61	78
2)				
Alkalosis	38.8	7.63	37	97
Anesthesia	Reduced ventilation			
	49	7.38	81	73
Anesthesia	Increased ventilation			
	44.9	7.6	46	99
3)				
Alkalosis	38.6	7.57	42	94
Anesthesia	Reduced ventilation			
	52.3	7.41	81	50
Anesthesia	Increased ventilation			
	53.8	7.54	63	89
4)				
Alkalosis	32.4	7.6	33	95
Anesthesia	Reduced ventilation			
	36.7	7.4	58	84
Anesthesia	Increased ventilation			
	35.4	7.56	39	96
5)				
Alkalosis	30.1	7.54	35	98
Anesthesia	Reduced ventilation			
	31.6	7.41	49	87
6)				
Alkalosis	31.63	7.51	39	99
Anesthesia	Reduced ventilation			
	39.9	7.38	66	72
7)				
Alkalosis	31.3	7.52	38	96
Anesthesia	Reduced ventilation			
	37.8	7.40	60	82
Anesthesia	Increased ventilation			
	36.0	7.56	40	97
8)				
Alkalosis	31.58	7.51	39	93
Anesthesia	Reduced ventilation			
	33.6	7.41	52	86
Anesthesia	Increased ventilation			
	32.19	7.54	37	93.3
9)				
Alkalosis	44.4	7.61	44	97
Anesthesia	Reduced ventilation			
	46.8	7.42	71	47

* Arterial O_2 was studied in five of the animals who were breathed at a rate sufficient to return plasma pH and pCO_2 toward control alkalotic values. The values shown were determined at a time when the pH had remained constant for an interval of 20 to 40 minutes.

compensation as indicated by the failure of plasma pCO_2 to approach the "line of compensation."

DISCUSSION

The data presented cast doubt on the theoretical prediction that metabolic alkalosis is significantly compensated by an increase in plasma carbon dioxide resulting from a decrease in alveolar ventilation (1–5). In alkalotic dogs this failure was apparent directly from measurements of pulmonary ventilation and indirectly by calculations of plasma pCO_2. The finding that the pH was elevated and plasma pCO_2 was little changed from normal in the majority of patients presented, furnished indirect evidence that respiratory compensation is usually minimal in metabolic alkalosis. Conceivably, the interpretations of alveolar ventilation, plasma pH and pCO_2 during acute bicarbonate administration are subject to criticism on the basis that this circumstance does not represent a "steady state" (2). However, the similarity of the findings in the acute experiments, chronic potassium depletion alkalosis and hypochloremic alkalosis weakens this criticism.

The prediction that a decreased respiratory exchange occurs in metabolic alkalosis has presumably been based on the concept that extracellular pH is one factor which is instrumental in the chemical control of respiration. It is generally agreed that a decrease in plasma pH results in an increased alveolar ventilation and is partially responsible for compensating a metabolic acidosis (1–5, 24). For this reason, it has been assumed that an elevation of plasma pH would result in the opposite sequence of events. However, any speculation regarding the role of blood pH in the regulation of respiration must be tempered by a consideration of other factors which are also influential in the chemical control of respiration (1, 2, 4, 6, 9). The evidence indicating the role of blood oxygen and pCO_2 in this respect has led to the hypothesis that respiration is controlled by a variety of interrelated factors and that net alveolar exchange will be the resultant of these integrated forces (2, 5, 6). The studies reported here augment this thesis and suggest that significant respiratory compensation in metabolic alkalosis may be limited in part by the oxygen requirements of the organism. This consideration is strengthened

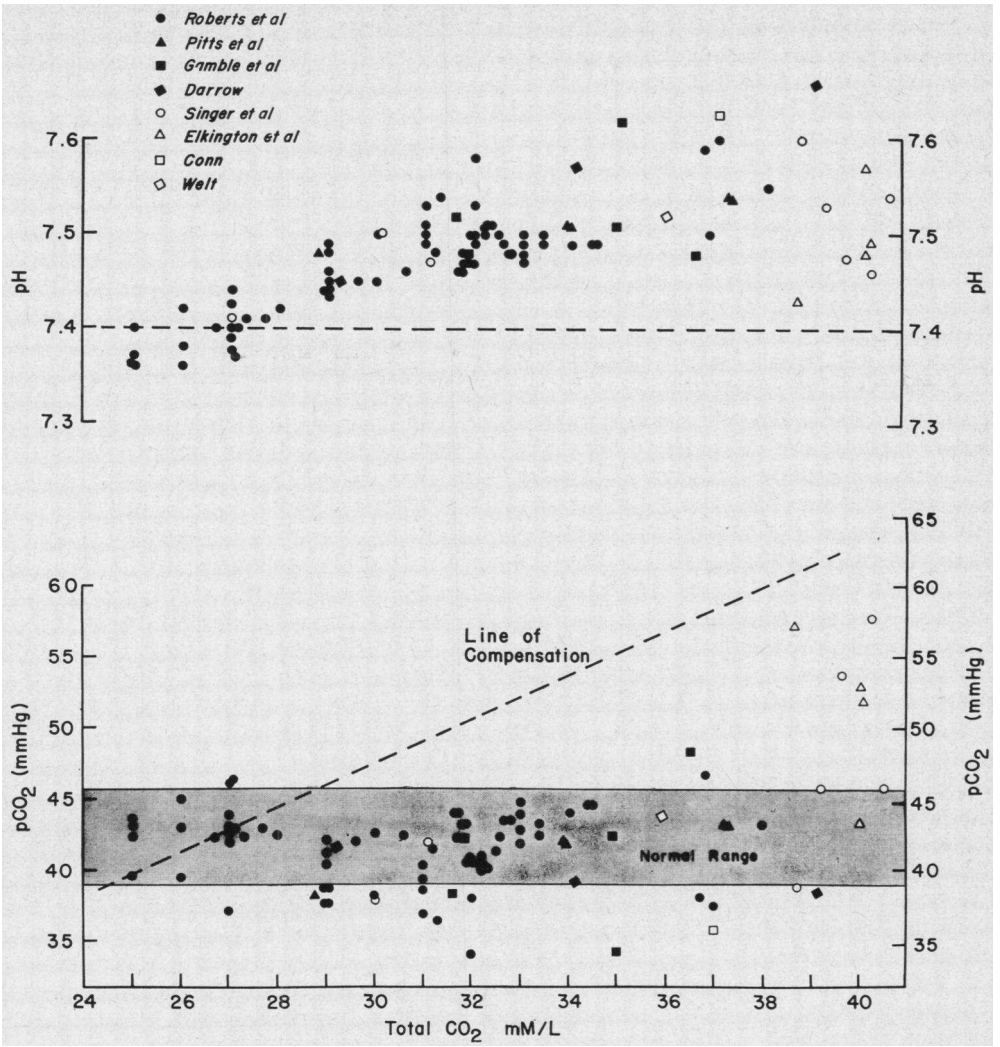

FIG. 3. BLOOD pH AND PLASMA pCO_2 IN RELATION TO TOTAL CARBON DIOXIDE CONTENT IN ALKALOTIC AND NORMAL PATIENTS

The plotted points represent from one to three separate determinations analyzed in duplicate on each patient. The data are also plotted from patients studied by Pitts (17), Elkinton, Squires, and Crosley (21), Conn (22), Welt (23), Darrow (19), and Gamble, Fahey, Appleton, and Maclachlan (20). The data of Singer, Clark, Barker, Crosley, and Elkinton (18) which have been plotted, represent one pCO_2 for each patient taken at the height of alkalosis (*i.e.*, highest total CO_2 content). Data from one patient reported by these authors have not been plotted since this patient had a pCO_2 which was already abnormally elevated in the central period (R. L.) (1). The stippled area indicates the range of normal values for plasma pCO_2 tension.

by the observation that a decrease in arterial oxygen saturation was found in the animals following a decrease in alveolar ventilation sufficient to completely compensate the metabolic alkalosis. However, the data do not permit an evaluation of the extent to which respiratory compensation could theoretically occur, without significant anoxia.

CONCLUSIONS

1. Respiratory compensation in metabolic alkalosis was found to be minimal in dogs and in the majority of patients shown.

2. In alkalotic dogs no consistent decrease in alveolar ventilation or minute volume was measured.

3. It has been suggested that changes in arterial oxygen saturation may limit respiratory compensation in metabolic alkalosis.

Addendum

Since this paper was submitted it has been reported, on the basis of changes in plasma pCO_2 that respiratory compensations occur in metabolic alkalosis (Bramlitt, E., and Hardy, J. D., Surgical Forum Program, p. 111, 41st Annual Clinical Congress, American College of Surgeons, 1955). Calculations utilizing either the Van Slyke nomogram or the Henderson-Hasselbalch equation and these authors published data of plasma carbon dioxide combining power (which closely approximates carbon dioxide content) and blood pH indicates that the average pCO_2 of these patients was 34.5 mm. Hg in the control period and 35.4 mm. Hg during the alkalotic period. This is a change of doubtful significance and well within the range of experimental error.

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