Extreme Hypocapnia in the Critically Ill Patient

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Respiratory alkalosis was the most common acid-base disturbance observed in a computer analysis of 8,607 consecutive arterial blood gas studies collected over an 18 month period in a large intensive care unit.

Through a retrospective review of the randomly selected hospital records of 114 patients, we defined four groups based upon arterial carbon dioxide tension ($PaCO_2$) and mode of ventilation. Group 1, with a $PaCO_2$ of 15 mm Hg or less, consisted of 25 patients with an over-all mortality of 88 per cent. Group II, with a $PaCO_2$ of 20 to 25 mm Hg, consisted of 35 patients with a mortality of 77 per cent. Group III, with a $PaCO_2$ of 25 to 30 mm Hg, consisted of 33 patients with a mortality of 73 per cent, and Group IV, with a $PaCO_2$ of 35 to 45 mm Hg, consisted of 21 patients with a mortality of 29 per cent ($p < 0.001$). Shock and sepsis were most common in group I patients.

These findings suggest that extreme hypocapnia in the critically ill patient has serious prognostic implications and is indicative of the severity of the underlying disease.

Experience in the care of critically ill patients has emphasized the lethal potential of hypoxemia and both respiratory and metabolic acidosis. Although respiratory alkalosis has been linked to the development of cardiac arrhythmias [1], the frequency and importance of hyperventilation with hypocapnia has not been adequately stressed. We recently found that 45 per cent of 8,607 consecutive arterial carbon dioxide tension ($PaCO_2$) measurements were below 35 mm Hg; respiratory alkalosis was more common than all other acid-base abnormalities taken together (Table I). These observations stimulated a retrospective clinical study of the significance of severe hypocapnia. We present biochemical and physiologic observations in 25 patients with carbon dioxide tensions below 15 mm Hg and compare these findings with observations in two other groups of patients with milder degrees of hypocapnia and in patients with eucapnia.

METHODS

Arterial blood, collected anaerobically in a heparinized syringe, was analyzed for oxygen and carbon dioxide tension and pH using an International Laboratories, Inc. 113 micro pH and gas analyzing system. Results of the analyses were punched on standard data cards and processed on an IBM 7074 digital computer. The program calculates oxyhemoglobin saturation and bicarbonate by appropriate equations. Hydrogen ion concentration was calculated by computer as the antilog of pH.

Respiratory alkalosis was defined when the pH was 7.45 or greater and the $PaCO_2$ was less than 35 mm Hg without metabolic acidosis as the primary acid-base disturbance. The hospital records of four randomly selected groups of patients with varying $PaCO_2$ levels were reviewed: Group I

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(25 patients with extreme hypocapnia) with a $PaCO_2$ of 15 mm Hg or less, group II (35 patients) with a $PaCO_2$ of 20 to 25 mm Hg, group III (33 patients) with a $PaCO_2$ of 25 to 30 mm Hg. A comparable group of patients, group IV (21 patients), with a normal $PaCO_2$ (35 to 45 mm Hg) were selected for comparison.

Each group was subdivided based upon the mode of ventilation at the time the index blood gas determination was made. Ventilation was either spontaneous or unassisted, assisted pressure-cycled or assisted volume-cycled. The total group consisted of 114 patients.

Shock was defined on the basis of a decrease in systemic pressure as well as by signs of inadequate peripheral blood flow with the following criteria: (1) systolic blood pressure less than 80 mm Hg; (2) absent or poorly palpable pulses; (3) clammy skin; (4) depressed sensorium; (5) urine flow less than 25 ml/hour. Sepsis was considered present when there was gross evidence of suppuration clinically or when positive cultures from blood, urine, sputum or exudate were associated with a septic febrile course.

The Chi-square test was used for statistical comparison of the groups. The t test was used to analyze paired data. With each test a "p" value of >0.05 was considered not significant.

RESULTS

Clinical Characteristics. Table II summarizes the clinical characteristics and the mortality in each of the four groups. Mean age was not significantly different in each group. Males predominated 3 to 1 in the group of patients with unassisted ventilation, whereas sex distribution was equal in the group with assisted ventilation.

TABLE I Incidence of Arterial Blood Gas Abnormalities

Abnormalities	No.	%
Hypoxemia		
Significant (PaO_2 50–70 mm Hg)	1,698	19.7
Extreme (PaO_2 below 50 mm Hg)	759	8.8
Alkalosis		
Respiratory	3,849	44.7
Metabolic	1,916	22.2
Acidosis		
Respiratory	1,152	13.4
Metabolic	669	7.7
Within normal limits	703	8.2
Total individual determinations	8,607	

The incidence of shock and sepsis was significantly higher in patients with spontaneous extreme hypocapnia ($PaCO_2$ of 15 mm Hg or less). Mortality correlated inversely with the $PaCO_2$ level. When mortality between groups was compared, combining the patients in groups II and III ($PaCO_2$ 20 to 30 mm Hg), the differences were significant ($p < 0.05$). In patients with hypocapnia while maintained on a respirator mortality rates were also increased and were significantly different from the control group ($p < 0.001$). The median survival time for group I patients with

TABLE II Clinical Characteristics and Mortality in 114 Patients with Varying $PaCO_2$

Data	Group I 15 mm Hg or less	Group II 20–25 mm Hg	Group III 25–30 mm Hg	Group IV 35–45 mm Hg	P Value
			Unassisted Ventilation		
No. of patients	15	12	10	11	
Age (yr)					
Mean	55	61	59	55	NS
Range	20–84	25–77	29–71	23–74	
Sex					
Male	13	7	7	9	
Female	2	5	3	2	
Shock	11	2	2	5	<0.01
Sepsis	9	3	0	0	<0.01
Mortality	12	7	5	3	0.1 > p > 0.05*
			Assisted Ventilation		
No. of patients	10 (6 PC, 4 VC)†	23 (16 PC, 7 VC)	23 (13 PC, 10 VC)	10 (6 PC, 4 VC)	
Age (yr)					
Mean	65	61	61	54	NS
Range	25–86	3–86	21–83	25–82	
Sex					
Male	5	10	10	7	
Female	5	13	13	3	
Shock	8	8	10	2	<0.05
Sepsis	0	1	3	1	NS
Mortality	10	20	19	3	<0.001

* When groups II and III are combined, differences are statistically significant ($P < 0.05$).
† PC = pressure-cycled; VC = volume-cycled.

TABLE III Primary Diagnosis in 15 Patients with Spontaneous Extreme Hypocapnia*

Diagnosis	No. of Patients	Outcome	No. of Deaths Due to Septic Shock
Cerebrovascular accident	3	2 died	
		1 discharged	2
Hepatic coma	3	3 died	0
Bronchopneumonia	2	2 died	2
Acute myocardial infarction	2	1 died	1
		1 discharged	
Sepsis without antecedent cause	2	2 died	2
Rheumatic heart disease-mesenteric embolus	1	Died	1
Methyl salicylate overdose	1	Died	0
Heroin addiction with septic emboli	1	Discharged	0

* $PaCO_2$ 15 mm Hg or less.

spontaneous ventilation was 1 day, with a range of less than 24 hours to 44 days. Survival time was estimated from the moment the index arterial blood gas was drawn to the time of death.

The primary diagnosis for the group with extreme hypocapnia and unassisted ventilation is listed in Table III. Cerebrovascular disease, hepatic coma, bronchopneumonia, atherosclerotic heart disease and the major disease entities were also common entities in each of the other groups.

Laboratory Characteristics. Table IV summarizes a comparison of the laboratory characteristics of all groups of patients. All variables except arterial oxygen tension (PaO_2) were significantly different in each group (unassisted ventilation and assisted ventilation). The significant differences between the variables in both groups are shown in the table. The pH range in the group with extreme hypocapnia and spontaneous ventilation was 7.48 to 7.83; $PaCO_2$ ranged from 10.0 to 15.0 mm Hg. In the group with assisted ventilation the pH ranged from 7.48 to 7.99; $PaCO_2$ ranged from 12.6 to 15.0 mm Hg. Serum electrolytes, reported as mean ± standard deviation (SD) only for group I with unassisted ventilation, were sodium 131.9 ± 7.1 meq/liter, potassium 4.0 ± 0.9 meq/liter, chloride 96.4 ± 6.0 meq/liter and bicarbonate 19.3 ± 6.0 meq/liter. Undetermined anions calculated by subtracting the sum of chloride and bicarbonate ion concentrations from that of sodium and potassium were 26.8 ± 6.4 meq/liter, well above the normal of 15 meq/liter. The most important component of this parameter is lactate, which was not measured directly in this series of patients.

Figure 1 illustrates the mixed acid-base disturbances in each of the groups described. The regression line from the study of Arbus et al. [2] represents acute uncomplicated respiratory alkalosis. The shaded area encloses the 95 per cent confidence limits of that study. Since our group of patients with extreme hypocapnia falls below the lower limit of a $PaCO_2$ of 15 mm Hg from that study, the regression line and confidence limits have been extended for purposes of comparison. Seventeen of the 25 patients (68 per cent) in the groups with extreme hypocapnia had excess hydrogen ion concentrations and an element of acidosis exceeding what one would expect solely as compensation. In only three of these patients did the values fall within the significance band.

In contrast, all but one of the patients with a normal $PaCO_2$ had hydrogen ion concentrations lower than expected from the study of Arbus et al. The mild metabolic alkalosis observed in this group (Table IV)

TABLE IV Laboratory Characteristics in Patients with Varying $PaCO_2$

Variable	Group I 15 mg or less	Group II 20–25 mm Hg	Group III 25–30 mm Hg	Group IV 35–45 mm Hg	P Value
		Unassisted Ventilation			
pH (units)	7.59 ± 0.10*	7.59 ± 0.10	7.57 ± 0.02†	7.51 ± 0.04	<0.05
$PaCO_2$ (mm Hg)	13 ± 2	23 ± 2	27 ± 1	39 ± 3	<0.001
H^+ (nmol/liter)	26.6 ± 5.4	25.8 ± 2.9	26.6 ± 1.1‡	30.7 ± 2.7	<0.01
HCO_3^- (meq/liter)	12.9 ± 3.1	21.8 ± 1.8	24.4 ± 0.8§	30.4 ± 2.6	<0.001
PaO_2 (mm Hg)	106 ± 48¶	174 ± 129	148 ± 104	153 ± 68	NS
		Assisted Ventilation			
pH (units)	7.67 ± 0.16	7.60 ± 0.04	7.60 ± 0.02†	7.50 ± 0.05	<0.001
$PaCO_2$ (mm Hg)	14 ± 1	23 ± 1	27 ± 2	40 ± 3	<0.001
H^+ (nmol/liter)	23.0 ± 7.4	25.1 ± 2.1	25.3 ± 1.4‡	32.0 ± 4.0	<0.001
HCO_3^- (meq/liter)	17.0 ± 7.4	22.1 ± 1.5	25.7 ± 1.6§	30.1 ± 5.0	<0.001
PaO_2 (mm Hg)	232 ± 140¶	199 ± 135	208 ± 135	138 ± 102	NS

NOTE: Statistical comparison of variables in unassisted and assisted ventilation patients: † $P < 0.001$, ‡ $P < 0.01$, § $P < 0.001$. ¶ $P < 0.05$. nmol/liter = 10^{-9} moles per liter.

* Mean ± 1 SD.

may be due to potassium depletion, dehydration or mineralocorticoid activity. There were no major differences of these mixed acid-base abnormalities in the patients with unassisted ventilation from those supported with respirators.

Mortality. Figure 2 emphasizes the relationship between $PaCO_2$ and mortality. In each case mortality increases significantly as hypocapnia becomes more extreme. Mortality rates were comparable regardless of the mode of ventilation.

COMMENTS

The frequency of abnormal PaO_2 and $PaCO_2$ in critically ill patients was not appreciated until rapid membrane technics replaced laborious bubble equillibration technics for their analysis. Only 8 per cent of 8,607 separate analyses in our continuous series were completely normal. Hypoxemia was observed in 20 per cent of the studies and respiratory alkalosis in 45 per cent. Respiratory acidosis was seen in 13 per cent of the studies, suggesting that hyperventilation is considerably more common than hypoventilation in the critically ill patient.

Although early studies in respiratory failure emphasized the pattern of pure alveolar hypoventilation with hypoxemia and hypercapnia [3,4], continuing experience has demonstrated that hypoxemia may be associated with hypercapnia, eucapnia or hypocapnia. McFadden and Lyons [5], for example, observed that PaO_2 and airway obstruction, as measured by spirometry, were linearly related in patients with asthma, whereas $PaCO_2$ had a biphasic relationship. $PaCO_2$ was low in patients with mild to moderate airway obstruction, became normal with increasing airway obstruction and was elevated in patients with severe obstruction. Stated differently, hyperventilation was observed with mild to moderate obstruction, and hypoventilation with severe obstruction. Their data emphasize the importance of considering both PaO_2 and $PaCO_2$ in evaluating the adequacy of alveolar gas exchange.

The variable behavior of oxygen and carbon dioxide is explained by consideration of the factors regulating their arterial concentrations. Although alveolar ventilation, inequality of ventilation and perfusion, diffusion limitations and true venoarterial shunting all determine PaO_2, hypoxemia in the critically ill patient is generally due to the progressive development of diffuse atelectasis and is relatively independent of total alveolar ventilation. In contrast, $PaCO_2$ is primarily determined by the rate of alveolar ventilation although the amount of carbon dioxide produced by the body, mixed venous carbon dioxide tension and ventilation to perfusion relationships also influence its concentration in arterial blood.

Alterations in $PaCO_2$ are due to a rate of alveolar

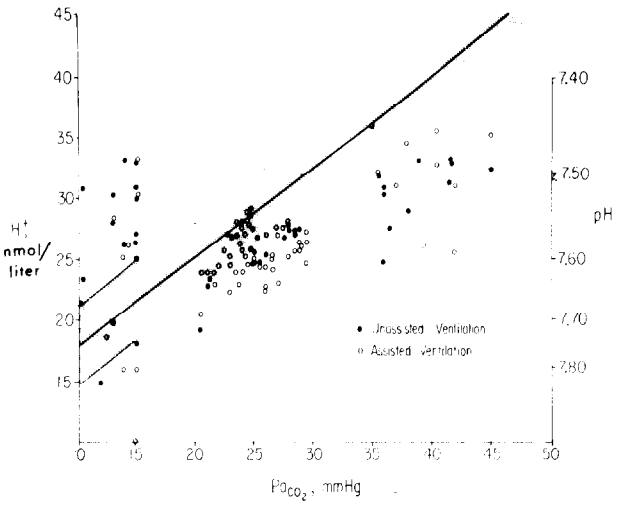

Figure 1. *Relationship between hydrogen ion concentration and $PaCO_2$ in critically ill patients illustrating mixed acid-base disturbances. The regression line represents acute uncomplicated respiratory alkalosis with 95 per cent confidence limits. Regression equation from Arbus et al. [2]: $H^+ = 0.74\ pCO_2 + 10.4$ (nmol/liter = nanomoles/liter = 10^{-9} moles/liter.)*

ventilation that is inappropriate to the patients' metabolic needs. That is, alveolar pCO_2 is inversely related to alveolar ventilation and directly related to the quantity of carbon dioxide produced by the tissues. In the normal person ventilation is adjusted to metabolic requirements so that $PaCO_2$ is maintained within close limits. $PaCO_2$ is normally slightly higher than alveolar pCO_2.

Respiratory alkalosis may be functional or organic. Important organic causes include central nervous system disorders, hypoxemia, fever, drugs, mechanical ventilation, cardiopulmonary disease and shock [6,7].

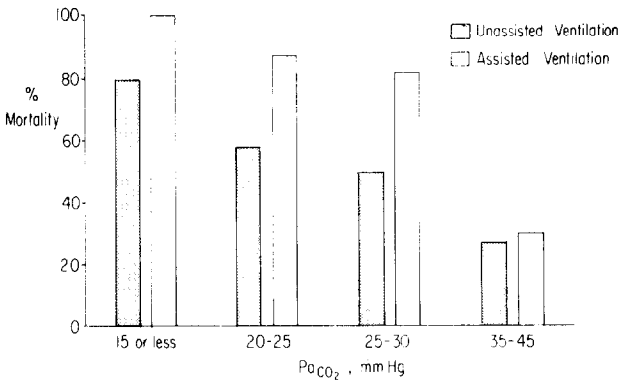

Figure 2. *Mortality related to mode of ventilation and level of $PaCO_2$. The inverse relationship is significant for the entire group ($p < 0.001$) and for the assisted ventilation group ($p < 0.001$). When groups II and III were combined in the unassisted ventilation group, the relationship was significant ($p < 0.05$).*

Although hypoxemia is generally regarded as a major stimulus to hyperventilation, the observation that hyperventilation persists after PaO_2 is restored to normal indicates that other factors may be instrumental. The studies of Pappenheimer [8] have emphasized the role of interstitial hydrogen ion concentration in regulating ventilation and have stressed the bicarbonate gradient which exists between cerebrospinal fluid and arterial blood.

Hypoxemia produces stimulation of ventilation via the carotid and aortic body chemoreceptors, and the glossopharyngeal and vagus nerves with transmission of impulses to the respiratory center in the medulla. The fall in pCO_2 reduces cerebrospinal fluid hydrogen ion concentration which decreases the neural activity arising in the medullary respiratory hydrogen ion receptors [9,10]. The reduced hydrogen ion concentration stimulates the choroid plexus and glia to actively restore cerebrospinal fluid hydrogen ion concentration toward normal [9].

Another mechanism for hyperventilation in the critically ill patient is the increase in mixed venous and jugular pCO_2 which accompanies a fall in cardiac output and cerebral blood flow.

Hyperventilation and respiratory alkalosis as frequent findings in septic shock and acute cerebrovascular disorders have been previously documented. MacLean et al. [11], and Simmons, Nicoloff and Guze [12], in their evaluation of patients with septic shock, found hyperventilation a valuable early sign of that syndrome. Respiratory alkalosis, elevated cardiac index and hypotension without peripheral vasoconstriction were findings in early sepsis. In a recent review of the hemodynamics of bacteremic shock, Winslow et al. [13] found that 17 of their 50 patients (34 per cent) had a $PaCO_2$ of less than 30 mm Hg. The precise explanation for this development of hyperventilation in sepsis has not been defined. The high incidence of septic shock in our patients with spontaneous extreme hypocapnia conforms to these previous observations.

Rout, Lane and Wallner [14], evaluating 41 patients with acute cerebrovascular accidents, found that hyperventilation with respiratory alkalosis was associated with a poor prognosis. None of their seven patients admitted with severe hyperventilation survived. Patients with a $PaCO_2$ of less than 35 mm Hg carried a 70 per cent mortality. Lane and colleagues [15], in their study of the mechanism of hyperventilation in acute cerebrovascular accidents, found that a nonchemical ventilatory drive such as central neurologic damage was responsible for the hyperventilation. These findings have been emphasized by Plum [16].

Hyperventilation and respiratory alkalosis is also found in patients with cirrhosis of the liver and particularly in patients with hepatic coma [17,18]. The blood levels of serum ammonia have occasionally been well correlated with the degree of hyperventilation, although not consistently. Vanamee et al. [19], in their study, had 25 of 29 patients with hepatic coma, coexistent respiratory alkalosis and elevated serum ammonia levels. The cause of hyperventilation and hypocapnia in hepatic disease is unknown. A rise in serum ammonia or hypoxemia has been considered and discounted. Eight of our patients were in hepatic coma and all died. In each case the $PaCO_2$ was less than 30 mm Hg.

Bronchopulmonary disease and pulmonary congestion may cause hyperventilation with respiratory alkalosis. Diminished pulmonary compliance, uneven ventilation perfusion ratios and venoarterial shunting are significant causes of hypoxemia and hyperventilation in acutely ill patients [20]. The use of pressure-cycled ventilators in such patients can compound the existing disturbance [21]. Ventilatory adjustment is essential with such respirators as pulmonary compliance increases.

The physiologic alterations produced by hyperventilation are many and varied [22]. Acid-base equilibrium is disturbed, cardiorespiratory changes are produced, and the oxygen carrying capacity of the blood is altered.

The effects of alkalemia are as profound as those of hypoxemia. Marked electrolyte shifts between intracellular and extracellular compartments lower serum potassium levels and raise serum lactate concentration, presumably in an effort to decrease total extracellular buffer capacity. The total amount of calcium may be unchanged, but the ionized fraction decreases. Although acidosis has traditionally been considered extremely harmful to cellular integrity, studies of intracellular hydrogen ion concentration indicate that the cell is actually less able to compensate for alkalosis than it is for acidosis [23].

The acid-base relationships of blood plasma are expressed in the Henderson-Hasselbalch equation in which hydrogen ion is seen to be a function of the ratio of bicarbonate concentration and carbonic acid concentration. Overbreathing will result in an increase in blood pH unless bicarbonate concentration falls proportionately to the decrease in pCO_2. Renal compensation for respiratory alkalosis involves suppression of both hydrogen ion formation and ammonia formation in renal tubular cells, with the excretion of sodium as bicarbonate, disodium phosphate as monosodium phosphate with the conservation of hydrogen ion. Lactatemia and intracellular bicarbonate shifts are also important in compensation [7].

Most of the patients with severe hypocapnia in this

study had hydrogen ion in excess of that expected with compensation for respiratory alkalosis (Figure 2). Albert et al. [24], who studied the ventilatory response to metabolic acidosis, were able to predict with reasonable certainty the degree of respiratory compensation for metabolic acidosis. These comparisons emphasize that mixed rather than uncomplicated acid-base disturbances are found in critically ill patients.

Increased blood lactate is found consistently during hyperventilation, with absolute levels of lactate during hyperventilation ranging from 2 to 10 mmol/liter [25]. Elevated blood lactate levels attributed directly to intracellular hypocapnia are perhaps due to inhibition of pyruvate carboxylase, to the accompanying intracellular alkalosis, to a shift of the oxyhemoglobin dissociation curve to the left, to an enhanced rate of glycolysis by red blood cells and to a decrease in lactate uptake by the liver due to reduced hepatic perfusion [26–29]. Whatever the mechanism of its production, lactate accumulation serves, together with renal excretion of bicarbonate, as a metabolic compensation process during respiratory alkalosis. During acute hypoxemia, a moderate increase in lactate occurs; however, chronic hypoxemia is not a cause of lactic acidosis.

Alkalosis, by shifting the oxyhemoglobin dissociation curve to the left with a decrease in 2,3-diphosphoglycerate, causes an increase in hemoglobin affinity for oxygen and a resultant increase in tissue hypoxia [30,31].

The arrhythmogenic properties of hypoxemia and inappropriate ventilation have been previously observed [1]. Alterations in membrane responsiveness leading to change in automaticity and to production of reentry circuits serve as the basis for the genesis of arrhythmias [32]. One third of our patients with extreme hypocapnia had recurrent tachyarrhythmias. However, these were not refractory to the usual modalities of therapy.

Hypocapnia has been shown to cause hypotension, a decrease in stroke volume, reduced cardiac output and an increase in peripheral vascular resistance in dogs [33]. The heart rate response has been variable. Studies in man have shown an increase in cardiac output, an increase in heart rate and a fall in peripheral vascular resistance. Rowe et al. [34] found an increase in arteriovenous oxygen (AVO_2) difference and a mean reduction of coronary blood flow with hyperventilation, using the nitrous oxide method of measurement.

There is little agreement on the mechanism responsible for the hypotension seen with hyperventilation. Interference with venous return due to the mechanical effect of increased respiration, and generalized reflex arteriolar dilatation due to hypocapnia have been postulated. Burnum, Hickam and McIntosh [35] found that hypocapnia produced vasodilatation and hypotension directly and is not mediated through the vasomotor centers. Recent studies of regional circulatory response to changes in blood pCO_2 suggest that not all areas of the vascular system respond in the same manner. Hypocapnia causes cerebral and cutaneous vasoconstriction but vasodilatation of skeletal muscle. Thus, total vascular resistance may not change significantly [36]. Monroe and co-workers [37] found no evidence of depressed ventricular function in dogs during hypocapnia.

Cerebral blood flow is decreased during hypocapnia. These changes in blood flow are accompanied by an elevation of lactate in the brain on the basis of increased anaerobic glycolysis.

Although hypocapnia cannot be incriminated conclusively for any increase in mortality or morbidity, it may be inferred that lactate production, impairment of tissue oxygenation due to a shift of the oxyhemoglobin dissociation curve and decreased cerebral perfusion all represent potential undesirable side effects of hypocapnia.

Controlled ventilation is obviously indicated in patients with hypercapnia or hypoxemia unresponsive to oxygen delivery by mask. Less obvious is the need to intubate and ventilate patients who have relatively normal oxygen tensions with respiratory alkalosis. Volume cycle respirators are more desirable in such situations with ventilation controlled by respiratory depressants such as morphine sulfate. An alternative approach is the addition of mechanical dead space during artificial ventilation [38]. Breivik et al. [39] demonstrated that the addition of carbon dioxide to inspired air is a more predictable method for normalizing $PaCO_2$ than the use of mechanical dead space. We believe that controlled ventilation is an acceptable mode of therapy for respiratory alkalosis and extreme hypocapnia although our data do not document decreased mortality using this modality. That the majority of our patients were being ventilated with pressure-cycle ventilators suggests that this type of ventilator may potentiate hypocapnia and respiratory alkalosis. Correction of the metabolic defect with bicarbonate administration is recommended before control of ventilation to prevent precipitous decreases in pH.

Cady et al. [40], evaluating a prognostic index of survival in 410 critically ill patients, found the plasma lactate level to be the most significant parameter relating to survival. $PaCO_2$ was not included in their discriminant function analysis. Wilson and co-workers [41], evaluating severe alkalosis in critically ill patients, found a strong correlation between the se-

verity of alkalosis and mortality. In their study, pH rather than $PaCO_2$ correlated with mortality.

Mortality in critically ill patients is related to the severity of the underlying disease. In our study, the presence of severe hypocapnia and respiratory alkalosis in such patients provided objective laboratory measurements to estimate survival since mortality correlated with the degree of hypocapnia. These results point to the potential usefulness of such objective measurements for determining the effectiveness with which intensive care is rendered.

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