Mixed Metabolic and Respiratory Acid-Base Disturbances: Diagnosis and Treatment

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Patients with primary ventilatory disturbances often have associated with their respiratory alkalosis or acidosis complicating metabolic acid-base disorders which profoundly affect their response to the respiratory disturbance. Physicians caring for them must be able to recognize these mixed disturbances if treatment is to be successful. Some day, computer terminals for diagnosis of acid-base problems will be standard equipment in most hospitals,1 but until such electronic consultation is readily available, clinicians must rely on their own ability to analyze acid-base data correctly. Basic to correct analysis of mixed acid-base disturbances is an understanding of normal compensatory processes in the four simple acid-base disorders. Elsewhere in this issue, Rastegar and Thier have reviewed the normal physiologic responses to acute and chronic hyper- and hypopcapnia. This paper reviews the compensatory changes which occur in metabolic acid-base disturbances and tries to show how these disorders affect the diagnosis and management of patients with ventilatory abnormalities.

**General Patterns of Compensatory Processes**

The Henderson-Hasselbalch equation states:

\[ \text{pH} = pK + \log \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3} \text{ or } \text{pH} = pK + \log \frac{\text{HCO}_3^-}{2\times P_{\text{CO}_2}} \]

Since pK is a constant, what the equation really says is that pH is determined not by the total amount of HCO₃⁻ or H₂CO₃ present, but the ratio of bicarbonate to carbonic acid. In a simple acid-base disturbance, the initial insult changes the normal concentration of either the numerator (the metabolic component) or the denominator (the respiratory component) of this ratio. Compensatory processes are secondary reactions by buffers, lungs and kidneys which return this ratio (and therefore pH) back toward normal. As discussed by Rastegar and Thier, in respiratory acidosis, renal and buffer mechanisms secondarily raise bicarbonate concentration, and in respiratory alkalosis they lower bicarbonate concentration. But since patients with metabolic acid-base disturbances have by definition a primary defect in the regulation of bicarbonate concentration, how can they compensate normally for a complicating primary respiratory disturbance? Similarly, hyperventilation is a major compensatory mechanism in metabolic acidosis, and hyperventilation occurs in metabolic alkalosis. Respiratory disturbances, therefore, prevent normal compensation for metabolic disturbances. And so begin the problems for the patient with combined respiratory and metabolic acid-base disorders.

We currently believe that the stimulus for compensation in a simple acid-base disturbance is the change in pH produced by the initial shift in PCO₂ or HCO₃⁻. If abnormal pH is the stimulus, normal compensation should not "over-correct" pH. It should not even return pH completely to control values.2 That does not mean that patients with a simple acid-base disturbance cannot have a normal pH. Since normal pH values occur over the range of 7.35-7.45, a mild disturbance, once compensated, might return pH to the range of normal. In chronic respiratory acidosis, for example, the likelihood of compensation returning pH to normal is inversely proportional to the level of PCO₂. At a PCO₂ of 50 mm Hg, 75 percent of patients might still have pH values in the normal range. At a PCO₂ of 80 mm Hg, that likelihood would drop to 15 percent, and at a PCO₂ of 70 mm Hg, fewer than 1 percent of patients would be expected to compensate well enough to return arterial pH even to low normal.3

From this, we can make two important generalizations which are helpful in recognizing whether or
not a given patient has a mixed acid-base disturbance. First, the more significant the stress of a primary acid base disorder, the less likely that pH will be normal and the more likely that a normal pH indicates the presence of a mixed acid-base disturbance. Second, a pH opposite to that predicted by the initial disturbance at a time when acid-base status is fairly stable makes a diagnosis of mixed disturbance mandatory.

Goldberg and colleagues, in developing a computer program for diagnosis of clinical acid-base disorders, have compiled the published information on normal compensation in simple acid-base disorders and depicted them graphically in the acid-base map shown in Figure 1. Shaded areas encompass with 95 percent confidence the range of PCO₂, pH and HCO₃⁻ you would expect to find in patients who have only one acid-base disturbance. If a patient's values fall outside these shaded areas, it is very unlikely that the patient has just one acid-base disturbance. If values fall inside the confidence bands for a simple acid-base disturbance, that fact alone does not prove a simple disturbance but just

![Acid-Base Map](image)
METABOLIC AND RESPIRATORY ACID-BASE DISTURBANCES

Table 2—Common Causes of Simple Acid-Base Disturbances

<table>
<thead>
<tr>
<th>Metabolic Acidosis</th>
<th>Metabolic Alkalosis</th>
<th>Respiratory Alkalosis</th>
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<tbody>
<tr>
<td>Hyperchloremic diarrhea</td>
<td>vomiting</td>
<td>psychogenic hyperventilation</td>
</tr>
<tr>
<td>acetazolamide</td>
<td>NG suction</td>
<td>primary CNS disease</td>
</tr>
<tr>
<td>NRC3, Arginine HC3</td>
<td>chlorotic diuresis</td>
<td>Gram negative sepsis</td>
</tr>
<tr>
<td>ureterosigmoidostomy</td>
<td>alkali Rx</td>
<td>atelectasis</td>
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<tr>
<td>intestinal renal disease</td>
<td>glucoseortetial Rx</td>
<td>respiratory acidosis</td>
</tr>
<tr>
<td>renal tubular acidosis</td>
<td>mineralocorticoid excesse</td>
<td>restrictive lung disease</td>
</tr>
<tr>
<td>Increased undetermined anion</td>
<td>severe K depletion</td>
<td>mechanical overventilation</td>
</tr>
<tr>
<td>generalized renal failure</td>
<td>in a Na depleted patient</td>
<td>pneumonia</td>
</tr>
<tr>
<td>diabetic ketonuria</td>
<td>respiratory acidosis</td>
<td>hepatic failure</td>
</tr>
<tr>
<td>lactic acidosis</td>
<td>metabolic acidosis</td>
<td>high altitude</td>
</tr>
<tr>
<td>methanol intoxication</td>
<td>metabolic acidosis</td>
<td>severe anemia</td>
</tr>
<tr>
<td>salicylate intoxication</td>
<td>metabolic acidosis</td>
<td>respiratory acidosis</td>
</tr>
<tr>
<td>ethylene glycol</td>
<td>respiratory acidosis</td>
<td>respiratory acidosis</td>
</tr>
<tr>
<td>intoxication</td>
<td>respiratory acidosis</td>
<td>respiratory acidosis</td>
</tr>
</tbody>
</table>

Respiratory Acidosis
obstructive lung disease
chest wall disease
mechanical underventilation
CNS depression
severe pulmonary edema
status asthmaticus
primary hyperventilation
pneumothorax
abdominal distension

are abnormal.
Next, calculate the undetermined anions by subtracting the sum of CO2 and chloride from the serum sodium concentration. This undetermined anion fraction (or anion gap or delta) is normally less than 12-14 mEq/L. It comprises anionic proteins, phosphates, sulfates and anions of various organic acids. Minor elevations in undetermined anion to 15 or 16 mEq/L are occasionally seen in respiratory alkalosis, and of course, erroneous elevation may occur if one of the three determinations used to calculate it are in error. A true elevation in undetermined anion, however, always indicates metabolic acidosis. (The converse is not true since some causes of metabolic acidosis are hyperchloremic with no increase in delta, Table 2). The higher the delta, the more one should suspect increased production of some organic acid. Deltas above 25 mEq/L are usually seen only in diabetic ketonacidosis, methanol or ethylene glycol poisoning, salicylate intoxication and lactic acidosis.

The third point to note in the routine electrolytes is the level of the serum potassium. Since important buffer systems exist inside cells, H+ shifts intracellularly in acidosis and moves from intracellular to extracellular fluid in alkalosis. These shifts of H+ across cells are in exchange for sodium and potassium. Since serum sodium concentration is high relative to the magnitude of the shift, pH changes in arterial blood have little noticeable effect on serum sodium concentration. For potassium, however, arterial pH is even more important than total body potassium in determining serum potassium concentration. The pH effects on potassium levels in blood are less obvious in respiratory than in metabolic acid-base disturbances, and there are exceptions to the rule. Nevertheless, serum potassium level can be a very useful indicator of arterial pH, particularly in a mixed acid-base disturbance. Acidemia usually begets hyperkalemia unless acidosis developed in an already potassium depleted patient or the acidosis itself was due to the loss of KCl. This occurs in diarrhoea, acetazolamide (Diamox) therapy and renal tubular acidosis. Alkalosis is usually associated with hypokalemia, but occasionally potassium loading either by increased intake or increased tissue breakdown can overwhelm the tendency for the rise in pH to lower serum potassium concentrations.

The fourth step in the systematic approach to acid-base diagnosis is to check other laboratory data for clues. These might include elevated blood sugar, ammonia or urea nitrogen, positive blood culture, abnormal spirogram, marked polycythemia, and so on. Other abnormal laboratory tests are easily
suggested by looking over the causes of the primary acid-base disturbances shown in Table 2.

One of the most common questions we are asked is, "Do you really need to get blood gases on every patient?" The answer is no. If, after going through steps 1 through 4, no acid-base diagnosis is apparent, then you don't need a pH. If the steps suggest a single disturbance of mild degree and nothing in the routine electrolytes or other laboratory studies contradicts the diagnosis, then again there is probably no need to get a pH. But if you suspect a mixed disturbance, or if any one of the steps so far turns up a surprise, then blood gases are in order. When you get them, explain them. Are they what you expected? If not, did you overemphasize a potential process in the history which turns out not to be clinically significant, or did you miss something? Most important, make sure that the changes in Pco2, pH and HCO3- which you are attributing to "compensation" are physiologically possible. Plotting data on the acid-base map may help answer the question.

**Pure Metabolic Acidosis**

The disease processes listed in Table 2 which produce metabolic acidosis do so either through loss of HCO3- from the body or retention of non-volatile acids, that is, acids other than carbonic acid which is "blown off" by the lungs. As pH falls and H+ concentration rises, the excess H+ is buffered immediately by extracellular fluid HCO3- in the following reaction:

\[ \text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2 \]

The CO2 formed is blown off by the lungs, allowing the reaction to move to the right and prevent accumulation of H+ in body fluids, but unfortunately HCO3- is consumed in the process. Were there no means for regenerating that HCO3- (and other body buffers), man would have very little tolerance to an acid load. Quantitatively, total extracellular fluid HCO3- amounts to about 450 mEq. If one considers bicarbonate buffer systems of hemoglobin, plasma proteins and intracellular fluid proteins, total body buffering capacity is only twofold that contributed by HCO3- or about 12-15 mEq/kg body weight acutely. In chronic acid loading, the value is somewhat higher due apparently to the slow titration of less readily available buffers stores in bone.6

Although total buffering capacity is limited, if you remember that the extremes of free H+ concentration which man can survive are only between .001 and .001 mEq/L, the importance of the immediate response of buffers to the slightest increase in H+ concentration is quite apparent.

Protection of body buffer stores is the province of the kidney. HCO3- consumed and excreted by the lungs in the reaction above must be regenerated by the renal secretion of H+. A more detailed discussion of both this and the chemistry of body buffers appears in the paper by Bastegar and Thier (thin issue). Briefly, renal regeneration of bicarbonate stores depends upon three processes: the complete reabsorption of filtered bicarbonate, the secretion of H+ onto urinary buffers resulting in a lowering of urinary pH, and the excretion of H+ by ionic trapping of NH3 as NH4+ in the acid tubular urine.7 By these mechanisms, the kidney is able to excrete several hundred milliequivalents of H+ a day and regenerate an equivalent amount of HCO3- and return it to the body buffer pool.

An important compensatory mechanism defending body pH in metabolic acidosis is hyperventilation which lowers the denominator of the HCO3-/H2CO3 ratio. Change in minute ventilation begins almost immediately after induction of metabolic acidosis. If acidosis develops slowly, full compensatory hyperventilation develops simultaneously and can lower Pco2 to as low as 10 mm Hg in severe acidaemia, thereby allowing virtually complete titration of body buffer stores before fatal acidemia ensues.8

Of all the normal compensatory mechanisms in simple acid-base disturbances, the ventilatory response to metabolic acidosis is probably the most predictable. Albert, Dell and Winter9 studied the relationship between Pco2 and HCO3- in 60 patients with simple metabolic acidosis. Their studies showed that the degree of compensatory hyperventilation that could be expected at any level of HCO3- in pure metabolic acidosis could be calculated by the following formula:

\[ \text{Pco}_2 = 1.54 \times \text{HCO}_3^- + 8.36 \pm 1.1 \]

This is simply a mathematical expression of the confidence band for metabolic acidosis shown in Figure 1. Given the values for pH, Pco2 and HCO3- in any patient with metabolic acidosis, if measured Pco2 is significantly higher than Pco2 predicted by the formula, then he has a complicating respiratory acidosis. Conversely, if his Pco2 is significantly lower than that predicted by the formula, hyperventilation is out of proportion to the acidosis and indicates a primary respiratory alkalosis.

A word of caution is in order in using either the acid-base map or Winter's formula. When metabolic acidosis develops rapidly, there may be a variable lag phase before maximum ventilatory response occurs. If there is rapid correction of metabolic
acidity with bicarbonate therapy, there may be a similar lag phase of 24 hours or more before hyperventilation stops.6 That means don’t jump to conclusions about a second primary disturbance if the acid-base picture is changing rapidly.

The primary mechanism which stimulates respiration in metabolic acidosis involves chemoreceptors in the aortic arch which sense a fall in arterial pH. There also appear to be central receptors sensitive to a change in pH of cerebrospinal fluid (CSF) and perhaps also medullary intracellular pH and pH of blood perfusing that region of the brain.11,12 The lag phase in turning off hyperventilation following rapid correction of metabolic acidosis may be due to differential permeability of Pco2 and HCO3 across the blood brain barrier, Pco2 equilibrating freely between blood and cerebrospinal fluid while HCO3 is transiently excluded.

**Pure Metabolic Alkalosis**

The primary defect in metabolic alkalosis is, by definition, an increase in serum HCO3 concentration. Since serum HCO3 levels are normally controlled by the kidney, you have to understand something about those mechanisms to know why factors listed in Table 2 produce metabolic alkalosis. Some of the processes affecting renal HCO3 reabsorption are shown in Figure 2.

Sodium is actively reabsorbed as sodium bicarbonate. How much sodium is reabsorbed is a function of effective arterial blood volume, filtration fraction, aldosterone and all the factors that regulate sodium balance. How much sodium is reabsorbed as NaCl and how much is reabsorbed in exchange for H+ or K+ depends in large measure on the availability of chloride, the only permeant anion in glomerular filtrate and therefore the only anion as such that can be reabsorbed with sodium. When chloride is not available for reabsorption, either because of chloride depletion or dilution of available chloride by infusion of impermeant anions such as sulfate or phosphate the percentage of sodium reabsorbed in exchange for H+ and K+ increases. Every mEq of H+ secreted into urine adds a mEq of HCO3 to blood, either by the somewhat indirect reabsorption of HCO3 (Fig 2) or through generation of a new HCO3 ion in the tubular cell. If abnormal volume regulation obligates complete sodium reabsorption, then associated chloride depletion will obligate excessive Na:H+ and Na:K+ exchange and lead to hypokalemic metabolic alkalosis.

In the absence of stimuli for excessive sodium reabsorption, the kidney will selectively reject sodium bicarbonate and correct the alkalosis. These mechanisms are so efficient that it is almost impossible to make a normal man alkalotic by feeding him HCO3 unless you add stimuli for increased sodium reabsorption such as preceding sodium depletion or mineralocorticoid therapy.

In clinical disease, any potential cause of metabolic alkalosis will have more profound effects on acid-base balance if they occur in a patient who is sodium depleted, has a sodium retaining state and generalized edema or who has excessive mineralocorticism.

Potassium depletion in metabolic alkalosis is common and results from increased renal Na:K exchange. Of itself, potassium depletion is usually not the cause of the alkalosis, although severe depletion may contribute to metabolic alkalosis by causing a renal chloride leak. The predominant mechanism underlying alkalosis in a given patient can be determined by measuring urinary chloride concentration off diuretic therapy.14 If chloride depletion is the problem, virtually no chloride appears in the urine. Urinary chloride concentrations above 10 mEq/L suggest that potassium depletion is also contributing to the alkalosis. Logistic therapy in either case is potassium chloride.

Since pH is determined by the ratio of
HCO3-/H2CO3 and the primary insult in metabolic alkalosis is a rise in HCO3- concentration, one would expect hyperventilation to be a normal compensatory mechanism and it is. But if you look at the width and shape of the normal range of compensation in metabolic alkalosis and compare it with other simple acid-base disorders in Figure 1, you will see that the band for metabolic alkalosis is both wider and less linear than any other. Graphically, this tells you that it is hard to predict the degree of hyperventilation for any given level of alkalosis. It also says that, beyond a certain point, no further ventilatory compensation can be expected no matter how high the serum HCO3- rises. It is probably hypoxia that limits any further respiratory compensation since hyperventilation to a Pco2 of 65 mm Hg, for example, would lower Po2 to 60 mm Hg, a level of hypoxia which in itself would stimulate respiration. That means that Pco2 values above 65 mm Hg must indicate primary respiratory acidosis.

Studies in which metabolic alkalosis has been induced in normal volunteers have not shown respiratory compensation to produce Pco2 values above 55 mm Hg.18 Although clinical studies suggest some patients can raise Pco2 to the mid 60's by compensatory hyperventilation.17 Given a patient with no history of pulmonary disease and no apparent cause of primary hyperventilation, who has a high HCO3-, an alkaline pH and a Pco2 in the gray zone of 55-65 mm Hg, how can you tell if the hypercapnia represents compensation for metabolic alkalosis or primary respiratory acidosis in a patient who also has metabolic alkalosis? Two maneuvers have been suggested to differentiate between the two possibilities. One is to examine the patient's response to breathing 100 percent oxygen for 12 minutes.19 Patients with primary respiratory acidosis develop increasing hypercapnia and frank acidosis on oxygen, while those with compensatory hyperventilation and pure metabolic alkalosis do not. It is interesting that in the series in which this test was originally proposed, six of seven patients with initial Pco2 values above 54 mm Hg developed respiratory acidosis while breathing oxygen, sug-

gesting that patients with pure metabolic alkalosis rarely compensate to Pco2 levels above 55 mm Hg.

A second maneuver which is theoretically reasonable but still needs to be proved clinically is to calculate the alveolar-arterial (Aa) oxygen gradient using Campbell's simplified gas equation. This estimates alveolar Po2 as equal to the partial pressure of oxygen in inspired air minus 1.25 × Pco2 of arterial blood. At normal atmospheric pressure, while breathing room air, this formula can be simplified to

\[
\text{alveolar Po2} = 150 - 1.25 \times \text{Pco2}
\]

To get the Aa gradient, simply subtract measured arterial Po2 from calculated alveolar Po2. The normal Aa gradient is 10 mm Hg or less. Values above 15 mm Hg indicate either a ventilation/perfusion defect or significant shunting of blood through the lungs. Findings you would hope should not occur in normal compensatory hyperventilation. Using this formula, you will find that some of the reported patients thought to have compensatory hyperventilation with Pco2 values above 60 mm Hg in supposed pure metabolic alkalosis have high Aa gradients and may actually have had a mixed disturbance.

Obviously, more study is required before we understand fully the limits of respiratory compensation in metabolic alkalosis. Until we do, it seems reasonable to suspect a complicating respiratory acidosis if the Pco2 is much above 55 mm Hg, particularly if the Aa gradient is above 15. One might also suspect that no rise in Pco2 might indicate primary respiratory alkalosis. While that may occur, potassium depleted patients characteristically do not develop hypercapnia, apparently because of paradox intracellular acidosis which prevents hyperventilation.18

RECOGNITION OF MIXED METABOLIC AND RESPIRATORY DISORDERS

There are two pitfalls in correctly assessing the clinical significance of a mixed metabolic and respiratory acid-base disturbance. One is to assume

<table>
<thead>
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<th>Table 3—Mixed Respiratory and Metabolic Acid-Base Disturbances</th>
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<td><strong>Additive Effect on pH</strong></td>
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<tr>
<td>Resp alkalosis</td>
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<td>pH</td>
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<tr>
<td>CO₂ content</td>
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<td>Combined Blood</td>
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<td>CO₂ content</td>
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that a normal CO₂ content means there is no acid-base emergency. The other is to assume a grossly abnormal CO₂ is an indication for immediate therapy. Neither is the case. As a matter of fact, the exact opposite is true. Table 3 gives the possible combinations of double acid-base disturbances involving a metabolic and a respiratory disorder. Notice that when two disturbances move pH in the same direction, they move HCO₃⁻ (and therefore CO₂ content) in opposite directions. That means patients with severe acidemia or alkalemia can be expected to have relatively normal CO₂ contents. If two disturbances move pH in opposite directions and therefore cancel out the separate effects, they move HCO₃⁻ in the same direction. That means patients with extremely high or low serum CO₂ values characteristically do not have a widely aberrant pH. These are just a few of the reasons why we urge a systematic approach to acid-base diagnosis such as the one outlined in Table 1. The following example demonstrates how such an approach avoids the pitfalls in evaluating clinical situations.

A patient with known chronic obstructive lung disease and stable chronic hypercapnia was admitted because of a urinary tract infection. Except for fever and flank pain, physical examination was unchanged from his last office visit. Admission blood studies showed Na 135, K 4.2, Cl 90, CO₂ 36, BUN 20, FBS 78, pH 7.30, PCO₂ 68, HCO₃⁻ 35. Treatment included his usual regimen of bronchodilators and IPPB and also a potentially nephrotoxic antibiotic. Fever subsided but he became increasingly restless and on the fifth day complained of nausea. Routine blood studies that morning were Na 135, K 6.3, Cl 96, CO₂ 25. At this point you are asked to evaluate the situation.

A quick review of the history certainly would show the potential for chronic respiratory acidosis. You might also recognize the additional potential for nephrotoxic antibiotics to produce unsuspected polyuric acute renal failure and metabolic acidosis. Physical examination is disturbing in that you cannot explain his restlessness on apparent worsening of his pulmonary disease. The routine electrolytes tell you what has happened. His now normal CO₂ is, HCO₃⁻ is clearly inappropriate to pure compensated respiratory acidosis. The increased undetermined anion, now 19 versus 9 on admission, indicates a complicating metabolic acidosis, although proof of the cause (acute renal failure) must await a repeat BUN (which was 75.) The hyperkalemia alerts you to increased acidemia since the history eliminated potassium-blocking diuretics, mineralocorticoid deficiency or potassium loading.

Blood gases only confirm what you know must have happened. They showed pH 7.06, PCO₂ 89, HCO₃⁻ 22. Notice that the complete analysis of the electrolyte pattern picked up the new problem even before you recognized the development of acute renal failure.

**COMMON CLINICAL SETTINGS OF MIXED DISTURBANCES**

If you look over the causes of simple acid-base disorders listed in Table 2, you will see that several clinical situations must commonly be associated with mixed metabolic and respiratory acid-base disturbances, for example: cardiac arrest (respiratory and metabolic acidosis), septic shock, salicylate intoxication, and hepatorenal syndrome (respiratory alkalosis and metabolic acidosis). Of all the possible mixed acid-base disturbances, however, the association of metabolic alkalosis and respiratory acidosis is so common that it deserves special comment.

Renal compensation for respiratory acidosis is increased reabsorption of HCO₃⁻ and renal chloride wasting, producing the typical blood picture of hypochloremia and an increase in CO₂ content. While both PCO₂ and HCO₃⁻ are elevated, the HCO₃⁻/PCO₂ ratio is not quite back to the normal 20/1. When treatment of the ventilatory disturbance lowers PCO₂, a transient alkalemia will develop until previously retained bicarbonate is excreted. Prolonged alkalemia, however, commonly occurs in patients with apparently stable chronic respiratory acidosis. In some series, as high as 5% of patients with chronic respiratory acidosis have had a complicating metabolic alkalosis. The cause may be therapy which of itself could cause metabolic alkalosis such as antacid or alkali ingestion for associated peptic ulcer disease or diuretics for cor pulmonale. A more important factor in most patients, however, is the chloride depletion incurred during the phase of compensation bicarbonate retention. As long as the patient has a stimulus to reabsorb sodium, and chloride depletion is perpetuated by a low sodium diet without chloride supplements, obligate renal bicarbonate reabsorption will maintain high serum bicarbonate levels even when arterial pH is frankly alkaline.

**TREATMENT OF MIXED ACID-BASE DISTURBANCES**

Obviously, one cannot discuss or even imagine all possible combinations of clinical diseases which could give rise to mixed acid-base disturbances. Rather, the purpose of this section is to go over the general principles upon which rational therapy is based in the four possible combinations of mixed...
metabolic and respiratory acid-base disorders.

**Respiratory Acidosis and Metabolic Alkalosis**

The clinical settings which give rise to this mixed disturbance have been reviewed above. The typical electrolyte pattern is one of hypochloremia, hyperkalemia, high CO₂ content and a near normal or moderately elevated pH. Since both the numerator and denominator of the HCO₃/H₂CO₃ ratio are increased, therapy must be directed at lowering both Pco₂ and HCO₃⁻ levels simultaneously. If only the ventilatory abnormality is treated, previously retained HCO₃⁻ can result in severe alkalemia and hypokalemia, clearly a hazard in patients receiving digitalis. This sudden alkalemia may be dangerous for another reason. The high blood pH may depress respiration and lead to a secondary rise in Pco₂. Since HCO₃⁻ moves slowly into the brain while Pco₂ equilibrates quickly, one may create the paradox of a falling CSF pH in the presence of frank alkalemia in blood. Whichever mechanism predominates, the danger of rapidly inducing alkalosis in respiratory failure is clear from the data of Asmundson and Kilburn who attributed 12 deaths among 146 patients to this therapeutic error.

Both hypokalemia and alkalosis can be avoided if chloride deficits are repaired at the same time therapy attempts to improve ventilation. This may be given as NaCl if the patient is sodium depleted, KCl in hypokalemic patients and those with edema, and arginine HCl in patients with both sodium excess and initially elevated levels of serum potassium. The appropriate treatment of respiratory acidosis is reviewed elsewhere in this symposium.

**Respiratory Acidosis and Metabolic Acidosis**

This combination represents an acid-base emergency. In terms of the HCO₃⁻/H₂CO₃ ratio, the numerator is falling while the denominator is rising. In terms of compensatory mechanisms, metabolic acidosis prevents both buffer and renal compensation for respiratory acidosis which in turn blocks ventilatory compensation for the metabolic disorder. The result is rapidly progressive acidemia. Serum CO₂ content may be normal if metabolic acidosis develops in a patient with previously compensated respiratory acidosis. If respiratory acidosis develops in a patient with pre-existing metabolic acidosis, CO₂ content will be low. The level of undetermined anion depends on the cause of the metabolic disturbance, but the potassium is almost always high.

Treatment must be aggressive and directed at both problems simultaneously. Precise management of the respiratory disturbance, of course, depends upon its cause. If the patient is hypotensive or the Pco₂ is less than 50 mm Hg, tissue hypoxia and increased lactate production may well be contributing to metabolic acidosis, and every effort must be expended to reverse the hypoxic hyperperfused state. Since hypoxic hypercapnic patients often increase arterial Pco₂ when given oxygen, and patients with mixed respiratory and metabolic acidosis can ill afford increasing hypercapnia, oxygen should probably be given only with intubation and artificial ventilatory support. If Pco₂ is 60 mm Hg or higher and the patient is not hypotensive, then it usually is safe to assume that tissue oxygen delivery is adequate enough to prevent excess lactate production. Whatever the cause of the metabolic acidosis, NaHCO₃ should be administered while the above measures are instituted to improve oxygenation and lower Pco₂. Remember that the aim of therapy is to return pH (not CO₂ content) to a safe range. An approximation of immediate HCO₃⁻ requirements can be made by plotting blood gas values on the acid-base map (Fig 1). Lay a ruler perpendicular to the Pco₂ scale to give you the isopleth for any given level of Pco₂. Find the HCO₃⁻ isopleth that intersects with the patient's current Pco₂. Then move down the Pco₂ isopleth until you reach a HCO₃⁻ value where pH is in a safer range. Multiply this increment in HCO₃⁻ (mEq/L) by the extracellular fluid (ECF) volume, i.e., 30 percent of body weight in kilograms to get the dose of HCO₃⁻. For example, if initial values are pH 7.02, Pco₂ 80, and HCO₃⁻ 21 in a 70 kg man, raising the HCO₃⁻ level acutely to 30 would raise pH to 7.2. Thus 9 mEq/L × 14L or 126 mEq of HCO₃⁻ would be a reasonable dose to give acutely. Appreciate that the alkali dose calculated is an underestimation since intracellular buffer stores must also be regenerated. Nevertheless, it gives you a "ball park" figure for acute ECF distribution and buys time for ventilatory therapy to begin lowering Pco₂.

Alkali is also the emergency treatment for hyperkalemia. Oral and rectal ion exchange resins should be started as well if hyperkalemia is associated with ECG changes and the patient is in renal failure. If large amounts of alkali are required as normally occurs in lactic acidosis, and the patient is unable to handle the sodium load either because of congestive heart failure or renal failure, dialysis may be required to allow continued administration of alkali by providing a port of exit for the sodium load.

**Respiratory Alkalosis and Metabolic Acidosis**

As noted previously, this combination of disturbances is not rare in seriously ill patients. It occurs most commonly in combined hepatic and renal failure and in septic shock and consequently de-
METABOLIC AND RESPIRATORY ACID-BASE DISTURBANCES

velops in a patient who already has a serious, complex disease. Of all of the mixed disturbances, this is the easiest one to miss. Usually metabolic acidosis is recognized because of the apparent renal failure. Then without systematically reviewing the acid-base data each time, a common error is to ignore a falling serum potassium concentration and attribute a low Pco2 to compensatory hyperventilation unless the patient is clearly alkalemic. This is a situation when calculating the appropriate Pco2 or plotting data on the nomogram can tell you if hyperventilation is excessive even before pH becomes frankly alkalenic. In seeing a great many patients with renal failure, we have noticed that patients will often begin to show a complicating respiratory alkalosis a day or so before they develop fever, hypotension and the full blown picture of septic shock. The reason for this is not clear, but the clinical value of advance warning in impending septic shock is obvious.

The typical blood picture in mixed respiratory alkalosis and metabolic acidosis is moderate hypokalemia, a pH near normal or slightly alkaline, and a severe depression of CO2 content. The danger of misinterpreting the situation as simple metabolic acidosis and treating the "CO2" by giving HCO3 is obvious. Since pH is usually almost normal, no immediate acid-base therapy is required. Therapy instead should be directed at primary disease states producing the acid-base disturbances.

Respiratory Alkalosis and Metabolic Alkalosis

Of all the possible mixed disturbances, this is the rarest, usually occurring only when a fortuitous (or not so fortuitous) association of primary diseases makes it possible. There is one clinical situation, however, in which one might predict this mixed disorder. This is in the wake of aggressive and successful correction of respiratory acidosis in a patient who had previously undergone renal compensation by increasing plasma bicarbonate concentration. The over-correction of Pco2 retention by too successful ventilatory assistance coupled with high serum bicarbonate concentration before the kidneys have had a chance to excrete it can produce severe alkalemia and hypokalemia, the major hazard of this disturbance. Treatment is to cut back on ventilatory assistance and allow Pco2 to rise at least to normal, and treat both the metabolic alkalosis and hypokalemia by giving potassium chloride.

In patients in whom the respiratory alkalosis is not due to mechanical over-ventilation, it is much more difficult to return Pco2 safely to normal. Usual management must depend on treatment of the disease process leading to primary hyperventilation. If pH reaches dangerously high levels in this mixed disturbance, it is usually safer to give arginine HCI intravenously to reduce the metabolic component, than to increase the concentration of Pco2 in inspired air and directly treat the respiratory disturbance.

SUMMARY

Acid-base disturbances are disease processes which, if otherwise unopposed, affect blood levels of Pco2, HCO3 and pH in characteristic ways. Anything that affects a patient's ability to defend body fluid pH is a significant clinical problem and must be recognized by the physicians treating him. That is why it is no more "roundmanship" to diagnose a triple acid-base disturbance than it is to recognize a simple acid-base disorder. For example, consider the patient with acute renal failure (metabolic acidosis), nasogastric suction (metabolic alkalosis) and bilateral pleural effusions (respiratory acidosis).

Because a mixed disturbance is the result of several primary and compensatory processes all affecting the same blood gas values, it is necessary to be able to recognize the limits of normal compensation to a given acid-base stress. Nomograms are helpful, but they cannot be used alone. Somehow, the clinician must be able to organize what he knows about acid-base balance and put it together with what he knows about the patient. The following system for diagnosing clinical acid-base disorders is easy to use and avoids most of the pitfalls of quick decisions based only on blood gas values and nomograms. The system has five steps: 1) scan the history for potential processes which lead to simple acid-base disorders; 2) note findings on physical examination which suggest an acid-base disturbance; 3) check the routine electrolytes for a) serum CO2 content (which tells you HCO3 concentration), b) undetermined anion (values significantly higher than 14 mean metabolic acidosis) and c) serum potassium (which usually moves opposite to arterial pH); 4) scan other lab data for disease processes associated with acid-base disturbances; 5) when you get blood gas values, explain them. In particular, be sure that a change in Pco2 or HCO3 which you are attributing to compensation is in the physiologically possible range.

REFERENCES

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