Metabolic Alkalosis Contributes to Acute Hypercapnic Respiratory Failure in Adult Cystic Fibrosis*

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Background and study objectives: Patients with end-stage cystic fibrosis (CF) develop respiratory failure and hypercapnia. In contrast to COPD patients, altered electrolyte transport and malnutrition in CF patients may predispose them to metabolic alkalosis and, therefore, may contribute to hypercapnia. The aim of this study was to determine the prevalence of metabolic alkalosis in adults with hypercapnic respiratory failure in the setting of acute exacerbations of CF compared with COPD.

Design: Levels of arterial blood gases, plasma electrolytes, and serum albumin from 14 consecutive hypercapnic CF patients who had been admitted to the hospital with a respiratory exacerbation were compared with 49 consecutive hypercapnic patients with exacerbations of COPD. Hypercapnia was defined as a PaCO₂ of ≥ 45 mm Hg.

Results: Despite similar PaCO₂ values, patients in the CF group were significantly more alkalotic than were those in the COPD group (mean [SD] pH, 7.43 ± 0.03 vs 7.37 ± 0.05, respectively; p < 0.01). A mixed respiratory acidosis and metabolic alkalosis was evident in 71% of CF patients and 22% of COPD patients (p < 0.01). The mean concentrations of plasma chloride (95.1 ± 4.9 vs 99.8 ± 5.2 mmol/L, respectively; p < 0.01) and sodium (136.5 ± 2.8 vs 140.4 ± 4.5 mmol/L, respectively; p < 0.01) were significantly lower in the CF group, and the levels of serum albumin were significantly reduced (27.4 ± 5.8 vs 33.7 ± 4.8 mmol/L, respectively; p < 0.01).

Conclusion: Metabolic alkalosis contributes to hypercapnic respiratory failure in adults with acute exacerbations of CF. This acid-base disturbance occurs in conjunction with reduced total body salt levels and hypoalbuminemia.

Key words: acid-base imbalance; COPD; cystic fibrosis; nutrition disorders; water-electrolyte imbalance

Abbreviations: ABG = arterial blood gas; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane regulator; CSF = cerebrospinal fluid

Metabolic alkalosis is a frequently reported initial presentation or complication of cystic fibrosis (CF) in infants and children. Predisposing factors include young age (ie, < 2 years of age), severe pulmonary involvement, and severe pancreatic insufficiency. The limited data suggest that metabolic alkalosis also may occur in adults with CF. Metabolic alkalosis is consistently associated with salt depletion and hypochloremia, indicating a likely association with defective epithelial cell chloride transport in CF. Malnutrition, a common feature of end-stage CF, also could contribute to metabolic alkalosis due to the role of albumin as a weak nonvolatile acid. The extent to which metabolic alkalosis occurs in CF patients with respiratory failure has not been evaluated.

Respiratory compensation for metabolic alkalosis results in hypoventilation and hypercapnia. The appearance of hypercapnia in patients with CF is considered significant, as it has been associated with poor prognosis. The extent to which metabolic alkalosis may contribute to hypercapnia in patients with advanced CF has not been examined. The aim of this study was to evaluate the acid-base and electrolyte balances in hypercapnic adult CF patients with acute exacerbations of respiratory disease, and to compare these with the balances in patients with hypercapnia due to an acute exacerbation of COPD.

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RESULTS

Of 210 patients attending the Adult CF Service during the study period, 124 required hospital admission. Of these patients, 14 satisfied the inclusion criteria.

The CF patients were significantly younger and more underweight than the patients with COPD, however, FEV₁ was not different (Table 1). The CF patients were significantly more alkalotic than patients in the COPD group, and only 1 of 14 CF patients had a pH < 7.40. This occurred despite similar levels of PaCO₂ and bicarbonate. However, the ratio of these values was altered in CF patients, indicating higher bicarbonate levels for any given level of PaCO₂ (p < 0.01). Levels of both plasma sodium and chloride were significantly lower in CF patients. Hypoalbuminemia also was evident in the CF group, with significantly lower values than those in the COPD group (p < 0.01). Plasma creatinine and urea levels were within the normal range for both groups.

The classification of patients according to their ABG values and the reference diagram of Stinebaugh and Austin³⁰ is shown in Figure 1. A simple respiratory acidosis was present in 29% of CF patients (4 of 14 patients) and 73% of COPD patients (36 of 49 patients). A mixed respiratory acidosis and metabolic alkalosis was present in 71% of CF patients (10 of 14 patients) but only 22% of COPD patients (11 of 49 patients) [p < 0.01].

A careful retrospective evaluation of medical records indicated that none of the patients with CF were being treated with alkalinizing agents, diuretics, or steroids. All CF patients had used pancreatic enzyme supplementation, but none had used salt supplements. No patient in either group had a short-term history that was consistent with heat exposure, vomiting, or diarrhea. In the COPD group, 14 patients (29%) were being treated with diuretics prior to hospital admission, and 7 patients (14%) had received therapy with oral corticosteroids. The two COPD patients who presented with a pure metabolic alkalosis had both taken diuretics prior to hospital admission. Of the 11 COPD patients who demonstrated a mixed disorder, 6 had received diuretics,
had received oral corticosteroids, and 1 had been treated with both oral corticosteroids and a diuretic. Five of the 10 cases of metabolic alkalosis in CF patients were recorded between November and March, while 3 of 13 of the COPD cases occurred during this time period.

**Discussion**

This study presents the novel finding that metabolic alkalosis contributes to hypercapnic respiratory failure in adults with acute exacerbations of CF. This has not previously been described. This acid-base disturbance occurs in conjunction with reduced plasma chloride and sodium levels and hypoalbuminemia.

There are two possible implications of metabolic alkalosis in CF. First, metabolic alkalosis causes a direct depression of respiratory drive in order to increase $\text{PaCO}_2$ and restore pH toward normal levels. This is a long-term central adaptation in which chloride plays a central role. Studies in which the plasma chloride level is lowered reveal a significant reduction of chloride in the cerebrospinal fluid (CSF). The analysis of acid-base balance by Stewart illustrates the fact that a reduction in CSF chloride concentration will result in an increased strong ion difference. As the CSF has no significant weak acids, bicarbonate levels will rise to equal the strong ion difference in order to preserve electroneutrality. The resulting reduction in central pH will result in hypoventilation. This hypoventilation may contribute to hypercapnia in patients with advanced lung disease.

Second, hypercapnia in CF patients is considered to be an indication for noninvasive ventilatory support, particularly in patients who are awaiting transplantation. It is likely that where there is a contribution from metabolic alkalosis, hypercapnia will respond with less alacrity to assisted ventilation. The restoration of normal electrolyte and fluid balances may be required to correct hypercapnia adequately in this group. A comprehensive analysis of acid-base balance may assist with these treatment decisions in patients with advanced CF.

This study did not aim to determine the cause of metabolic alkalosis in CF patients, however, several mechanisms previously have been proposed. Metabolic alkalosis is closely linked to chloride depletion, which leads to an increased reabsorption of bicarbonate in the distal renal tubule. CF is a disease that is characterized by altered epithelial cell chloride transport and increased chloride secretion, particularly through the sweat glands. High body temperature and weight loss have been associated with chloride-depletion and metabolic alkalosis in children with CF, features that are also characteristic of acute exacerbations in adults.

Local temperatures frequently exceed 30°C between November and March. Metabolic alkalosis associated with chloride loss and volume depletion might therefore be expected to occur with greater frequency in these months. However, this was not evident in our data, with half the cases of metabolic alkalosis in CF patients occurring outside of this 5-month period. This may reflect the greater importance of body temperature changes and fluid losses.
associated with acute exacerbations, or may simply reflect the small number of CF patients in the study.

Metabolic alkalosis may have renal or extrarenal causes. Urinary chloride excretion was not measured in this study; and thus defects in renal tubular function resulting in increased chloride excretion cannot be excluded. However, reduced urinary chloride excretion has been demonstrated in children with CF who have hypochloremic metabolic alkalosis, which is most likely secondary to volume depletion alkalosis, and because of this there is some controversy regarding their individual contributions to its maintenance. Other data also have suggested that renal electrolyte handling is normal in CF patients. Based on this literature, and in the absence of the use of diuretics and steroids in the CF group, it is likely that the observed hypochloremia resulted from sweat losses rather than from renal elimination.

Sodium deficits and extracellular volume contraction usually occur concurrently with chloride-depletion alkalosis, and because of this there is some controversy regarding their individual contributions to its maintenance. However, it seems likely that both volume and salt restoration may be necessary to correct metabolic alkalosis in CF patients. Mauri and colleagues treated five cases of acute severe metabolic alkalosis in infants who had CF with IV hypotonic saline solution and salt administration, and they reported a correction in ABG values within 2 to 5 days. Chronic malnutrition is a common feature of end-stage CF. The reduction in body mass index and the presence of hypoalbuminemia confirms the presence of this feature in our subjects with CF. Albumin plays a role in acid-base balance due to its action as a nonvolatile weak acid, and hypoalbuminemia has been shown to result in primary alkalosis in the serum of healthy persons. Therefore, it is likely that chronic malnutrition contributes to the observed metabolic alkalosis in CF patients.

Recent data have suggested that bicarbonate transport is also abnormal in CF patients. Mutations in the CF transmembrane regulator (CFTR) are known to cause abnormal chloride transport in CFTR-expressing cells. However, it has been confirmed that CFTR also alters the transport of bicarbonate. The presence of this defect appears to correlate well with pancreatic insufficiency in CF patients. As all the CF patients in this study required pancreatic enzyme supplementation, it is possible that bicarbonate abnormalities also played a role in the acid-base dysfunction.

In conclusion, metabolic alkalosis occurs commonly in patients with acute exacerbations of CF and hypercapnia. This is likely to be associated with chloride depletion, extracellular volume contraction, and malnutrition. The contribution of metabolic alkalosis should be considered when evaluating acid-base balance and ventilation requirements in hypercapnic CF patients.

References