Renal Function in Respiratory Failure*

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ABSTRACT

Respiratory failure produces significant changes in many aspects of renal function. Whereas in response to acute hypercapnia, body buffering mechanisms are of primary importance in maintaining pH, in adaptation to chronic hypercapnia, increased renal excretion of acid is predominant. Augmented secretion of ammonia accounts solely for the net increase in renal acid excretion. During chronic hypercapnia, increased reabsorption of bicarbonate by the kidney serves to maintain elevated extra-cellular bicarbonate concentration.

In patients with chronic pulmonary disease, renal blood flow is usually reduced while glomerular filtration is less affected. Water and sodium excretion by the kidney is impaired when congestive failure is present. After recovery from heart failure, these parameters return towards normal levels. Renal blood flow and sodium excretion increase during moderate hypoxia but decrease significantly in response to severe hypoxia, hypercapnia, or to hyperoxia. Prolonged mechanical ventilation is often associated with renal water retention and congestive heart failure.

Respiratory failure is associated with profound alterations in the composition of body fluids. With ventilatory insufficiency, retention of carbon dioxide (hypercapnia), inadequate oxygenation (hypoxia) and respiratory acidosis ensue. These metabolic perturbations evoke multiple changes in renal function. As a compensatory mechanism, renal acid excretion increases in response to respiratory acidosis. In a less clearly adaptive reaction, renal hemodynamics and water and sodium excretion decrease from normal levels. The purpose of this account is to review alterations of renal function in acute and chronic respiratory failure, and to discuss the effects of several therapeutic measures, emphasizing primarily data gathered from studies performed in man.

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Renal Acid Excretion

The stimulus to increased acid excretion by the kidney in respiratory failure must be viewed in the perspective of the adaptive response of the total organism to carbon dioxide retention. Acute studies carried out in normal human subjects and investigations of patients with chronic pulmonary disease and respiratory failure have generated data which may be presented in the form of carbon dioxide titration curves. Representative results are shown in figure 1 where changes in plasma hydrogen ion concentration or pH on the ordinate are plotted as a function of changes in partial pressure of carbon dioxide on the abscissa.

Several facts are readily apparent. Increases in partial pressure of carbon dioxide are buffered; i.e. hydrogen ion concentration increases proportionately less than pCO₂. Buffering is more effective in patients with chronic lung diseases than in normal subjects exposed to increased concentrations of carbon dioxide in ambient air. For a given increment in pCO₂, hydrogen ion content of plasma increases less in chronic patients. Finally, compensation is imperfect and incomplete. Normal hydrogen ion concentration cannot be maintained in the face of progressive carbon dioxide retention.

The data may be presented in another way by plotting plasma bicarbonate level rather than hydrogen ion concentration against pCO₂ (figure 2). Bicarbonate content increases in response to hypercapnia, to a greater extent in patients with chronic respiratory failure than in normal subjects.

The increase in plasma bicarbonate concentration in chronic hypercapnia serves not only to restore pH towards normal, but also to buffer alterations in hydrogen ion concentration resulting from superimposed acute changes in pCO₂. Goldstein et al confirmed this fact when they demonstrated that dogs were better able to protect pH against acute increases in pCO₂ when adapted to chronic hypercapnia.

Buffering Mechanisms

In order to elucidate the difference in responses between acute and chronic hypercapnic states, body buffering mechanisms must be considered. The defense of extracellular pH against respiratory acidosis is mediated through buffers, primarily intracellular proteins, and compensatory renal excretion of acid. The contribution of these two mechanisms varies greatly in acute and chronic hypercapnia. In acute respiratory acidosis, Elkinton and co-workers
found that cellular buffering accounted for 90 percent or more of the increase in extracellular bicarbonate concentration. Giebisch et al. demonstrated, in nephrectomized animals, that buffering was accomplished by transcellular sodium and potassium exchange for hydrogen and by hydrogen-hemoglobin binding inside the red blood cell after diffusion of carbon dioxide with a shift of intracellular bicarbonate for extracellular chloride anion. By contrast, in chronic respiratory acidosis, renal buffering mechanisms are of primary importance.

**Review of Acid Secretion**

Before presenting the findings in respiratory failure, a brief review of acid excretion by the kidney is appropriate. The kidney secretes large amounts of hydrogen ion daily to effect reabsorption of bicarbonate, formation of titratable acid, and excretion of ammonium (figure 3). The great bulk of hydrogen ion, 3,000 to 4,000 mEq per day, is secreted to reclaim bicarbonate from the glomerular filtrate. This process of bicarbonate reabsorption involves the hydration of carbon dioxide in proximal and distal portions of the nephron through catalysis by carbonic anhydrase but results only in retention of bicarbonate already present in the body. In order to generate new bicarbonate requisite for buffering of acidosis, titratable acid must be formed or ammonium ions excreted. Thus, net renal acid excretion is represented by the sum of titratable acid plus ammonium ion excretion minus bicarbonate excretion. Under normal conditions, 60 to 80 mEq of hydrogen ion are excreted daily by the kidney with the generation of an equivalent number of bicarbonate ions for return to extracellular fluid.

In the formation of titratable acid, urinary buffers are acidified in distal parts of the nephron by the addition of hydrogen ions arising from the formation of carbonic acid within the renal tubular cell. The principle buffer in tubular fluid being phosphate, the net result is the transformation of disodium hydrogen phosphate (Na₂HPO₄) to monosodium dihydrogen phosphate (NaH₂PO₄).

Ammonia is produced by tubular cells in the distal nephron through the deamination of glutamine and various amino acids. Ammonia passively diffuses into the tubular lumen and may freely diffuse back into the renal tubular cell. However, the secretion of hydrogen ion from carbonic acid results in the trapping of ammonia through the formation of ammonium cation. For each ammonium cation excreted, a bicarbonate ion is returned to the blood.

The effects of acute hypercapnia on renal excretion of acid have been studied in normal human subjects. Titratable acid and ammonium ion excretion increases while bicarbonate excretion after previous bicarbonate loading decreases, and urine pH falls. As a result, net hydrogen ion excretion increases, but the increment accounts for only 5 to 10 percent of the estimated acid load resulting from the retention of carbon dioxide.
By contrast, the kidney plays a far greater role when carbon dioxide is retained on a chronic basis. Renal adaptation to chronic hypercapnia has been extensively studied in dogs by Schwartz and co-workers over periods of 7 to 11 days. During the first 24 hours, plasma bicarbonate increases without a change in urinary hydrogen ion excretion, the result primarily of cellular buffering. Thereafter, net renal acid excretion increases steadily. Secretion of ammonia is solely responsible for the increment as titratable acid excretion actually decreases and bicarbonate is incompletely reabsorbed from tubular fluid. In spite of bicarbonaturia, plasma bicarbonate concentration steadily increases. However, the observed increment in extracellular bicarbonate concentration is less than that predicted from cumulative net hydrogen ion excretion, some bicarbonate being required to buffer an increased production of organic acids and sulfate.

During recovery from chronic hypercapnia, extracellular alkalosis promptly develops as pCO₂ decreases more rapidly than bicarbonate. The return of plasma bicarbonate to normal values is not effected by renal excretion of bicarbonate, which actually declines. Net renal acid excretion also decreases, as ammonium excretion falls and titratable acid excretion rises to control levels. Chloride anion plays a critical role in the recovery phase. Animals depleted of chloride remain alkalotic with increased plasma bicarbonate levels in contrast to dogs maintained on an adequate chloride intake. The provision of extra chloride results in prompt correction of alkalosis with return of plasma bicarbonate to normal values.

Renal acid excretion during steady state chronic hypercapnia in man has been studied by Aber. Under these conditions, ammonium excretion accounts for 75 percent or more of net acid excretion and appears to be regulated by arterial pCO₂ and pH levels. The urine is essentially free of bicarbonate, in contrast to the finding of liberal bicarbonate excretion during the process of adaptation.

The absence of bicarbonate from the urine in the face of an elevated plasma bicarbonate level is characteristic of chronic respiratory acidosis and is indicative of increased tubular reabsorption of bicarbonate. Normally, the kidney acts to prevent plasma bicarbonate concentration from rising above 26 mEq per liter by dumping excess bicarbonate in the urine. The maintenance of bicarbonate at supranormal levels requires increased reabsorption of bicarbonate by the kidney. Renal bicarbonate reabsorption is related directly to plasma carbon dioxide tension and is also regulated by a number of other factors, including extracellular fluid volume, body potassium stores, plasma chloride content, and parathyroid hormone.

Renal Hemodynamics, Water and Sodium Excretion

In patients with chronic pulmonary disease, cardiac output is normal or decreased in the presence of congestive heart failure. The level of cardiac output is correlated with pulmonary artery pressure. Renal blood flow is more uniformly reduced, flow rates being related directly to arterial oxygen tension and inversely to pCO₂. Glomerular filtration rate is affected less than renal blood flow so that filtration fraction is increased. With signs of congestive failure, water and sodium excretion is impaired.

Following recovery from heart failure, renal blood flow increases but does not return to normal levels. Excretion of water and sodium improves but still remains abnormal. These changes in renal function occur in association with improvement of respiratory failure, as evidenced by increased arterial oxygenation and decreased retention of carbon dioxide.
The effects of acute changes in oxygenation in patients with chronic respiratory failure have been studied by Fishman and co-workers and Kilburn and associates. When moderately severe hypoxia is produced, renal blood flow and sodium excretion increase. With severe hypoxia, i.e., arterial PO₂ less than 35 mm Hg, renal blood flow, glomerular filtration rate, and water and sodium excretion decrease. Similar functional changes occur when hypercapnia is intensified to levels above 65 mm Hg.

Increased oxygenation has deleterious effects on renal function. During the breathing of oxygen mixtures containing 30 to 100 percent oxygen with resultant PO₂ levels between 60 and 650 mm Hg, renal blood flow decreases markedly while glomerular filtration rate, water and sodium excretion decrease to a lesser extent. Further data emphasizing the undesirable effects of prolonged mechanical ventilation in patients with chronic respiratory failure have been published. Sladen and associates reported the occurrence of positive water balance, pulmonary congestion with normal central venous pressure and decreased pulmonary compliance in 19 percent of patients undergoing prolonged ventilation. Possible mechanisms to account for water retention in these respirator patients include the hemodynamic alterations already mentioned, subclinical heart failure, hypoalbuminemia, increased airway and intrathoracic venous pressures and increased secretion of anti-diuretic hormone. Prevention of fluid overloading requires judicious water and sodium restriction and the use of diuretics.

Summary

The profound alterations in renal function which occur in acute and chronic respiratory failure and which develop from efforts to treat patients with these conditions have been reviewed. Understanding of acid excretion by the kidney and of abnormalities in renal hemodynamics and water and sodium handling are essential for the intelligent management of these seriously ill patients.

References


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"Mirth is like a flash of lightning that breaks through a gloom of clouds and glitters for a moment. Cheerfulness keeps up a daylight in the mind, filling it with a steady and perpetual serenity."

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Samuel Johnson