

Respiratory Considerations in the Patient With Renal Failure

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Summary

Lung and kidney function are intimately related in both health and disease. Respiratory changes help to mitigate the systemic effects of renal acid-base disturbances, and the reverse is also true, although renal compensation occurs more slowly than its respiratory counterpart. A large number of diseases affect both the lungs and the kidneys, presenting most often with alveolar hemorrhage and glomerulonephritis. Most of these conditions are uncommon or rare, although three of them—Wegener's granulomatosis, systemic lupus erythematosus, and Goodpasture's syndrome—are not infrequently encountered by respiratory care clinicians. Respiratory complications of chronic renal failure include pulmonary edema, fibrinous pleuritis, pulmonary calcification, and a predisposition to tuberculosis. Urinothorax is a rare entity associated with obstructive uropathy. Sleep disturbances are extremely common in patients with end-stage renal disease, with sleep apnea occurring in 60% or more of such patients. The management of patients with acute renal failure is frequently complicated by pulmonary edema and the effects of both fluid overload and metabolic acidosis. These processes affect the management of mechanical ventilation in such patients and may interfere with weaning. Successful lung-protective ventilation in patients with acute lung injury and renal failure may require modification of hemodialysis in order to combat severe acidemia. Hemodialysis-related hypoxemia, which was once believed to be the result of pulmonary leukostasis and complement activation, is explained by diffusion of CO₂ into the dialysate, with concomitant alveolar hypoventilation in the process of maintaining a normal P_aCO₂. Like acute lung injury, renal failure is a common complication of critical illness. An increasing body of evidence also supports the notion that the kidneys, like the lungs, are susceptible to injury induced as a result of positive-pressure mechanical ventilation. *Key words: acute renal failure, chronic renal failure, hemodialysis, hypoxia,*

physiology, ventilatory drive, hypoventilation, pulmonary-renal syndrome, ventilator-induced renal injury. [Respir Care 2006;51(4):413–422. © 2006 Daedalus Enterprises]

Introduction

The relationships between the lungs and the kidneys are clinically important ones in both health and disease. This article first reviews the interactions between respiratory and renal function under normal conditions. It then provides a brief overview of the large group of diseases that affect both the lungs and the kidneys, and summarizes three of them in somewhat more detail. How chronic renal failure may affect respiratory function and the intrathoracic structures is then described, along with a brief review of the corresponding manifestations of acute renal failure and the ways in which respiratory care is affected by them. The phenomenon of dialysis-related hypoxemia is described and explained. Finally, the ways in which critical illness and its management may adversely impact kidney function are summarized.

Physiologic Connections Between the Lungs and the Kidneys

Under normal circumstances, the lungs and kidneys work together to maintain acid-base balance in the body, according to the relationship described by the Henderson-Hasselbalch^{1,2} equation:

$$\text{pH} = \text{pK} + \log (\text{base concentration/acid concentration})$$

According to this equation, the overall acidity or alkalinity of the blood, which we quantify by the negative logarithm of the hydrogen ion concentration (or pH), is determined by the relationship between the amount of base and the amount of acid present, also expressed logarithmically, as modified by a mathematical constant (pK) for the particular acid involved. The carbonic acid-bicarbonate system is the major buffering system of the extracellular fluid. Bicarbonate (HCO_3^-) dissociates into CO_2 and

water in the presence of the enzyme carbonic anhydrase, so that the acid-base quotient in the above equation can be thought of as the HCO_3^- concentration divided by the CO_2 concentration. The CO_2 concentration is related to the partial pressure of CO_2 in the arterial blood by the solubility constant 0.03, so the Henderson-Hasselbalch equation can be rewritten in terms of what clinicians typically measure:

$$\text{pH} = 6.1 + \log (\text{HCO}_3^- \text{ concentration}/(0.03 \times \text{P}_{\text{aCO}_2}))$$

Because the HCO_3^- concentration is normally regulated by the kidneys, and P_{aCO_2} is determined by alveolar ventilation, the relationship can also be rewritten conceptually as:

$$\text{pH} = \text{pK} + (\text{kidneys/lungs})$$

A decrease in HCO_3^- concentration (metabolic acidosis),³ whether from an increase in acid in the body or an overall loss of HCO_3^- , provokes an increase in alveolar ventilation (respiratory alkalosis),⁴ which tends to restore the balance between the two and thus bring the low arterial pH (acidemia) back toward normal. This may be thought of as respiratory compensation for metabolic acidosis. An increase in HCO_3^- concentration (metabolic alkalosis)⁵ causes an increase in arterial pH (alkalemia), which tends to decrease alveolar ventilation (respiratory acidosis).⁶ In this instance, however, respiratory compensation is usually less vigorous, because the respiratory stimulant effect of hypercapnia is much stronger than the respiratory depressant effect of alkalemia. In both instances, the respiratory changes are immediate (within a few minutes) because of the rapidity of equilibration between alveolar gas and pulmonary capillary blood.

The familiar clinical presentation of diabetic ketoacidosis is an example of respiratory compensation for severe metabolic acidosis. Patients with this disorder may hyperventilate to P_{aCO_2} levels of ≤ 10 mm Hg, which diminishes (but does not completely correct) their severe acidemia. On the other hand, in the less frequent circumstance of primary metabolic alkalosis, as is seen with protracted vomiting or the ingestion of excess alkali, patients typically present with only modest hypercapnia (eg, P_{aCO_2} 48–50 mm Hg) despite pH in excess of 7.60.

An increase in P_{aCO_2} stimulates the kidneys to hold on to HCO_3^- , producing metabolic alkalosis that tends to normalize arterial pH. Conversely, hypocapnia prompts an increased loss of HCO_3^- , causing a compensatory meta-

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Table 1. Renal Compensation for Respiratory Acidosis

	Normal	Acute Respiratory Acidosis (minutes to hours; no renal compensation)	Chronic Respiratory Acidosis (days to weeks; renal compensation present)
pH	7.40	7.24	7.38
P _a CO ₂ (mm Hg)	40	56	56
HCO ₃ ⁻ (mEq/L)	24	25	33

bolic acidosis that decreases arterial pH. The renal responses to respiratory acid-base disturbances occur much more slowly, however—over a few days—than do respiratory adjustments to metabolic disturbances. As a result, because carbonic-acid/HCO₃⁻ buffering acts immediately but is relatively weak, sudden alterations in respiratory acid-base status cause more sudden and severe changes in arterial pH than do their primary metabolic counterparts.

An example of the more gradual adjustment of metabolic status with changes in ventilatory status is respiratory acidosis in patients with chronic obstructive pulmonary disease. When such patients present in exacerbation they may be severely acidemic if hypercapnia has developed rapidly, whereas the same P_aCO₂ in a clinically stable patient tends to be associated with a much more normal pH (Table 1).

More comprehensive discussion of the different types of acid-base disturbance, their effects on respiratory and renal function, and their management is beyond the scope of this brief review. However, good recent reviews of these topics are available.³⁻⁸ The kidneys also regulate fluid balance in the body,¹ and derangements in overall volume status can affect pulmonary function, as discussed below.

Diseases That Affect Both Lungs and Kidneys

There are a number of “pulmonary renal syndromes” that affect both the lungs and the kidneys.⁹⁻¹¹ These disorders most commonly present with hemoptysis from diffuse alveolar hemorrhage, along with renal insufficiency associated with either acute glomerulonephritis or other vasculitis. However, patients may develop pulmonary hemorrhage without evidence of renal involvement, with the latter appearing only later in the clinical course. The reverse sequence may also occur.

Many of these diseases have overlapping and variable features, prompting investigators to classify them in various ways. Schwarz and colleagues have used the presence or absence of pulmonary capillaritis as a means of categorizing these diseases (Table 2).^{12,13} Another classification scheme uses the presence or absence of anti-glomerular basement membranes antibody, antineutrophil cytoplasmic antibody (ANCA), or prominent vasculitis,

Table 2. Diseases That Affect Both Lungs and Kidneys

Diseases that cause alveolar hemorrhage in the presence of pulmonary capillaritis
Wegener’s granulomatosis
Microscopic polyangiitis
Mixed cryoglobulinemia
Henoch-Schönlein purpura
Immune-complex-associated glomerulonephritis
Pauci-immune glomerulonephritis
Diseases that cause alveolar hemorrhage in which pulmonary capillaritis is variably present
Systemic lupus erythematosus
Other connective tissue diseases
Goodpasture’s syndrome
Diseases that cause alveolar hemorrhage without pulmonary capillaritis
Thrombotic thrombocytopenic purpura
Drug-induced (eg, penicillamine)
Diseases in which alveolar hemorrhage is not a typical feature
Allergic granulomatosis and angiitis (Churg-Strauss syndrome)

although here, again, overlapping features in different cases often makes clear distinction difficult. For example, in one series of 88 patients who presented with pulmonary hemorrhage and nephritis, 48 were positive for ANCA, 7 had both ANCA and anti-glomerular basement membranes antibodies, and 6 had only the latter, while the other 27 had a variety of other findings, including infection and pulmonary embolism.¹⁴

Three of the most familiar diseases with both pulmonary and renal manifestations are Wegener’s granulomatosis, systemic lupus erythematosus, and Goodpasture’s syndrome.

Wegener’s Granulomatosis

Wegener’s granulomatosis is a clinical syndrome consisting mainly of necrotizing granulomatous vasculitis of the upper and lower respiratory tract, along with glomerulonephritis.¹⁵ The eyes, ears, heart, skin, joints, and central nervous system may also be involved. It is the most common vasculitis involving the lungs, and most frequently affects middle-aged white men. Sinusitis is the most common clinical manifestation, followed by fever, arthralgias, cough, rhinitis, hemoptysis, otitis, and ocular inflammation.¹⁶ Although Wegener’s granulomatosis may be confined to the kidneys, the lungs are involved in more than four fifths of all patients with the disease. Likewise, some patients have pulmonary but not renal involvement. The pulmonary involvement is variable, but localized infiltrates and/or nodules, either bilateral or unilateral, are most common. Cavitation occurs in 10–20% of cases. The cause of the disease is unknown, but it is characterized by the presence of positive tests for ANCA in at least 90% of affected

patients. It was almost always fatal within a few months, prior to the advent of combination therapy with corticosteroids and cytotoxic agents, but today more than three quarters of all patients achieve complete remission, with long-term survival.¹⁵

Systemic Lupus Erythematosus

Systemic lupus erythematosus is a multisystem inflammatory disorder of unknown cause, which is most common in women, especially African-Americans.¹⁷ It is characterized by the presence of antinuclear antibodies. Among its many manifestations are a characteristic but highly variable malar rash, photosensitivity, arthritis, various neurologic problems, and hematologic and immune defects. Pulmonary and renal involvement are very common. Thoracic manifestations include pleuritis, acute lupus pneumonitis, interstitial pulmonary fibrosis, pulmonary vasculitis, diffuse alveolar hemorrhage, pulmonary hypertension, organizing pneumonia, and the "shrinking lung syndrome."¹⁵ Pleuritis, with pleuritic pain and effusions, is common, as is acute pneumonitis. Although these usually occur in patients with an established diagnosis of lupus, either of them, and any of the other intrathoracic processes listed, may be the initial manifestation of the disease. Lupus has a highly variable course, and both the response to treatment and the overall prognosis may be difficult to predict.

Goodpasture's Syndrome

Goodpasture's syndrome is a disorder of unknown etiology, manifested by diffuse alveolar hemorrhage and glomerulonephritis.¹⁰ It is also known as anti-glomerular basement membrane antibody disease, as the presence of such antibodies is characteristic and believed to account for at least some of its manifestations. It is most common in men, particularly in the third decade of life, and presents with cough, hemoptysis, and fatigue. Alveolar hemorrhage appears to be more common among patients who smoke. Although either pulmonary or renal involvement may be present in isolation, at least at the time of presentation, the majority of patients with Goodpasture's syndrome have both. The diagnosis is typically made with renal biopsy. The disease is treated with plasmapheresis, corticosteroids, and cytotoxic drugs, but the prognosis is guarded at best, and dialysis or renal transplantation are often necessary.

Respiratory Effects of Chronic Renal Failure

A number of complications related to the respiratory system occur in patients with chronic renal disease (Table 3).¹⁸⁻²⁰ Some of these are related to alterations in volume status, plasma oncotic pressure, bone and mineral metabolism, concomitant heart failure, and altered immune func-

Table 3. Complications of Chronic Renal Failure Related to the Respiratory System

Pulmonary edema
Fibrinous pleuritis
Pleuritic chest pain
Pleural effusion
Fibrothorax
Pericardial effusion
Tuberculosis and other infections
Pulmonary calcification
Urinothorax
Sleep apnea
Anemia
Dialysis-associated hypoxemia

tion in such patients, although in other instances the precise mechanisms are not well understood.

Pulmonary Edema

Pulmonary edema (Fig. 1) is a common complication in both acute and chronic renal failure. Its pathogenesis is controversial. Hypoalbuminemia, characteristic of chronic renal failure, decreases plasma oncotic pressure and thus fosters movement of fluid out of the pulmonary capillaries. Such movement is also promoted by the increased hydrostatic pressure that occurs in congestive heart failure, which is common in this condition. One would assume that the

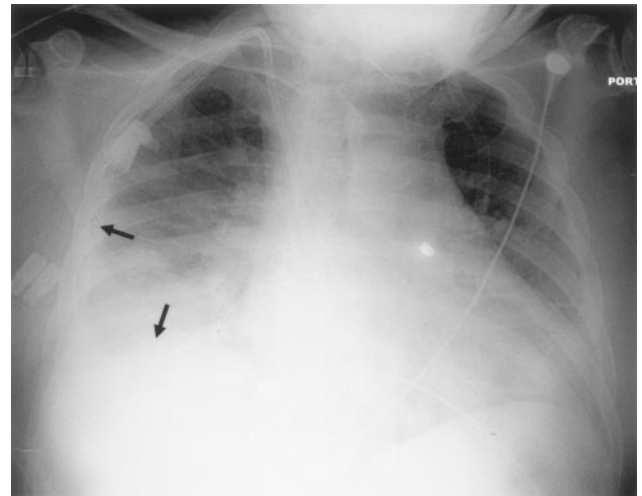


Fig. 1. A bedside chest radiograph of a patient with chronic renal failure who presented with shortness of breath. The cardiac silhouette is enlarged, suggesting congestive heart failure. The right hemidiaphragm is obscured, and the right lung is displaced laterally from the chest wall (black arrows), suggesting a large right-sided pleural effusion. Both lung fields have generally increased opacity and loss of the usual distinctness of the vascular markings, consistent with pulmonary edema. (Courtesy of Eric J Stern MD, University of Washington, Seattle, Washington.)

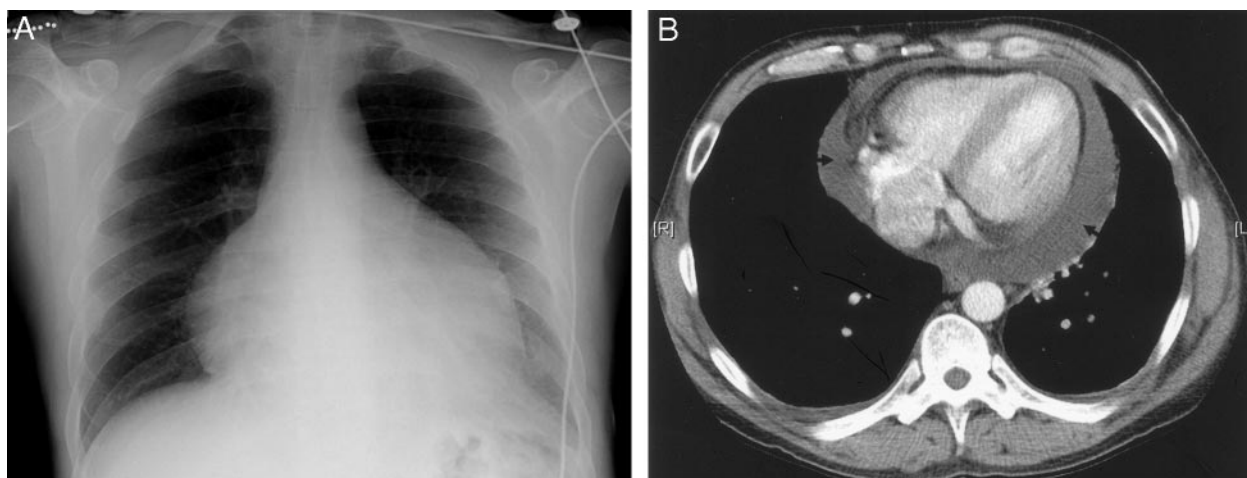


Fig. 2. Pericardial effusion in a patient with chronic renal failure. Left: On the plain chest radiograph, the markedly enlarged cardiac silhouette has a globular, “water-bag” appearance typical of a large chronic pericardial effusion. Right: Computed tomography confirms the presence of a large pericardial effusion (black arrowheads). (Courtesy of Eric J Stern MD, University of Washington, Seattle, Washington.)

edema fluid resulting from these processes would be low in protein, as is characteristic of “cardiac” or hydrostatic pulmonary edema. However, the finding of increased protein concentrations in the edema fluid of patients with renal failure²¹ suggests that capillary permeability is also altered. Such a suggestion is supported by the occurrence of pulmonary edema in patients who are clinically euvolemic and do not have other features of heart failure. However, other studies of the edema fluid in patients with chronic renal failure²² have found low protein levels, more consistent with those found in heart failure than in inflammatory conditions such as acute respiratory distress syndrome (ARDS). Left-ventricular failure and other cardiac diseases are common in chronic renal failure, further complicating attempts to clarify the nature of pulmonary edema in patients with this condition.

Pulmonary congestion in patients with chronic renal failure is associated with a restrictive pattern on pulmonary function testing, and reduced airflow can also be observed on spirometry. These abnormalities have been demonstrated to improve or resolve with hemodialysis.^{23–25} This observation would seem to strengthen the argument that increased lung water results primarily from overall hypervolemia in the presence of low serum albumen levels in this condition, and accounts for the symptoms and signs traditionally associated with “uremic lung.”¹⁹

Fibrinous Pleuritis

Pleural disease is common in chronic renal failure, being present in as many as 20–40% of autopsies on patients with this condition.^{26,27} The most common manifestation encountered clinically is pleural effusion (see Fig. 1), which was present in 3% of all patients with end-stage renal

disease in one series.²⁸ The effusion is typically an exudate, and may be hemorrhagic.^{27,29} They are typically unilateral, and can be quite large.

Most patients with fibrinous pleuritis are asymptomatic. Dyspnea is the most common symptom, but this condition can also be associated with fever and pleuritic chest pain, sometimes with an audible friction rub on auscultation. Fibrothorax can also occur.

Pericardial Effusion

Although the pathogenesis of fibrinous pleuritis is incompletely understood, it seems likely that a similar mechanism accounts for the occurrence of pericardial effusion³⁰ in patients with chronic renal failure. While the rapid development of even a small amount of pericardial fluid can cause hemodynamic compromise, gradual fluid accumulation allows the pericardium to stretch, and even large chronic effusions (Fig. 2) are usually asymptomatic. While acute uremic pericarditis may cause pain and systemic symptoms, requiring specific diagnostic and therapeutic procedures,³¹ pericardiocentesis is generally not required for chronic effusions, and the latter typically decrease with dialysis, renal transplantation, or other measures to control the underlying disease.

Tuberculosis and Other Infections

Although not so dramatically as those with acquired immune deficiency syndrome, malignancy, or treatment with immunosuppressive therapy, patients with chronic renal failure are immunocompromised. Compared to the general population, patients with chronic renal failure and those on chronic dialysis have at least a several-fold greater

risk of developing tuberculosis.³² Patients on chronic ambulatory peritoneal dialysis are particularly prone to development of tuberculous peritonitis,^{32,33} the symptoms and signs of which may be subtle in this population.

Pulmonary Calcification

Metastatic calcification occurs as a complication of chronic renal failure, and may be found in a wide variety of visceral organs and soft tissues. When it occurs in the lungs, it is usually asymptomatic. Although not typically apparent on chest radiography, pulmonary calcification can sometimes be detected with computed tomography, or, more specifically, by technitium-99m-diphosphonate scanning.^{34,35} When visible on the standard chest radiograph, pulmonary calcification most often produces small nodular opacities, which may occasionally coalesce into larger infiltrates.^{36,37}

Urinothorax

Urinothorax, or collection of urine in the pleural space, is a rare complication of obstructive uropathy. As of 2004, 53 cases had been reported in the world's literature.³⁸ Most patients who are found to have urinothorax also have a urine collection (urinoma) in the abdominal cavity or retroperitoneal space.³⁹ Reported underlying causes include obstructing malignancy, retroperitoneal fibrosis, and chronic fibrosis following urinary diversion.³⁸

The pleural fluid in urinothorax is transudative, although the lactic dehydrogenase level can be high, causing misclassification as an exudate.³⁸ The pH and glucose levels tend to be low. An elevated pleural fluid-to-serum creatinine ratio (which should be about 1 but may be 10 or more in urinothorax) confirms the diagnosis.

Sleep Apnea

Sleep apnea is extremely common in patients with chronic renal failure.⁴⁰⁻⁴² Its prevalence is said to be 10-fold higher in patients with end-stage renal disease than in the general population,⁴³ and studies have found that at least 60% of patients on chronic hemodialysis have the disorder.^{18,44} Other sleep disturbances, such as restless-legs syndrome and periodic limb movement disorder, are also very common in this population.⁴⁴ Several potential explanations have been proposed, but the mechanism remains unknown. There appears to be a strong link between sleep apnea and nocturnal hypoxemia and cardiovascular complications in patients with chronic renal failure.^{45,46} Hemodialysis during the night is said to have an ameliorating effect on sleep apnea,^{43,47,48} although the reason for this also remains a mystery. As in obstructive sleep apnea

unassociated with renal disease, treatment with continuous positive airway pressure is effective.

Anemia

Anemia is common and important in chronic renal insufficiency. It contributes to the frequent cardiovascular complications in this condition and negatively affects patients' quality of life.^{49,50} If the anemia is untreated, hemoglobin concentrations typically fall below 10 g/dL, and frequently to half or less of the normal value. With blood-oxygen carrying capacity thus markedly diminished, cardiac output must increase in order to maintain normal tissue oxygen delivery, and even in the absence of pulmonary disease, patients are vulnerable to tissue hypoxia during exertion and at times of acute illness. Treatment with recombinant human erythropoietin corrects anemia, avoids the requirement for blood transfusions and also improves quality of life and exercise capacity.⁵¹

Respiratory Effects of Acute Renal Failure

Acute renal failure is common in the intensive care unit (ICU). A recent observational study of nearly 30,000 patients admitted to the ICUs of 54 hospitals in 23 countries found that 5.7% of all patients had acute respiratory failure during their stay, and that nearly three quarters of these required some form of renal replacement therapy.⁵² Development of acute renal failure predisposes patients to overall fluid overload, and decreased plasma oncotic pressure from hypoalbuminemia and hemodilution promotes leakage of fluid from pulmonary capillaries. The restrictive effects of pulmonary interstitial and alveolar edema, pleural effusion, and chest-wall edema increase the work of spontaneous breathing and may contribute to the development of acute ventilatory failure. In addition, the metabolic acidosis present in most instances of acute renal failure increases the demand for ventilation through compensatory respiratory alkalosis, further disrupting the relationship between the patient's ventilatory needs and capabilities. Pulmonary edema and ventilation at low lung volumes can cause or worsen hypoxemia.

Acute renal failure can necessitate a number of modifications in the management of mechanical ventilation (Table 4). Higher airway pressure is required to maintain the same level of ventilation in the presence of pulmonary edema, pleural effusion, or total-body-fluid overload. Airway mucosal edema can reduce effective airway diameter, predisposing to air trapping and endogenous positive end-expiratory pressure (auto-PEEP), which can reduce venous return, further compromising cardiac function and increasing the risk of alveolar rupture.⁵³

The management of acute lung injury (ALI) and ARDS using lung-protective ventilation is made more difficult in

Table 4. Ways in Which Acute Renal Failure Affects Ventilator Management

Decreased respiratory-system compliance
Intrapulmonary causes
Pulmonary edema
Airway edema
Extrapulmonary causes
Pleural effusion
Pericardial effusion
Chest-wall edema
Clinical implication
Requirement for higher airway pressure
Increased airway resistance
Causes
Airway edema
Decreased lung volumes
Clinical implication
Increased likelihood of dynamic hyperinflation and intrinsic positive end-expiratory pressure
Metabolic acidosis
Causes
Impaired excretion of acid and metabolic products
Clinical implications
Need for compensatory hyperventilation
Worse acidemia with lung-protective ventilation
Increased minute ventilation requirement may interfere with weaning

the presence of metabolic acidosis, which increases ventilatory drive and worsens acidemia related to permissive hypercapnia. Because low-tidal-volume, lung-protective ventilation substantially improves survival in ALI and ARDS, its use should not be abandoned because of acidemia in the face of acute renal failure. Using a dialysate solution with a higher concentration of bicarbonate can facilitate “compensation” for hypercapnia and permit both renal replacement therapy and lung-protective ventilation to be maintained.

Weaning in the face of a metabolic acidosis is a challenge because of the requirement that the patient be able to maintain a higher-than-usual minute ventilation. Otherwise-healthy patients may have no trouble with this requirement, but in patients with severe obstructive lung disease or ARDS, weaning may have to be deferred until either ventilatory function improves or the required hyperpnea diminishes.

Hemodialysis-Related Hypoxemia

Shortly after it was introduced in the treatment of renal failure, most patients undergoing hemodialysis were discovered to develop hypoxemia while connected to the machine. This phenomenon generated much interest among both renal and respiratory clinicians and resulted in dozens

of publications during the 1970s, as its possible mechanisms were investigated. Proposed explanations included: a shift in the oxyhemoglobin dissociation curve due to the increased pH during dialysis; depression of central ventilatory drive; impairment of oxygen diffusion; leukostasis in small pulmonary vessels leading to mismatching of ventilation and perfusion; and alveolar hypoventilation due to diffusion of CO₂ into the dialysate.¹⁸

Studies in both animals and humans demonstrated that leukocytes did accumulate in the lungs during hemodialysis, with activation of complement and other events associated with inflammation.^{54,55} For several years “dialysis lung” was a subject of intense interest, both at the bedside and in the laboratory. It was demonstrated that P_{aO₂} falls within a few minutes of the initiation of hemodialysis, usually by 10–15 mm Hg but sometimes considerably more, reaching a nadir after 30–60 min and then returning to pre-dialysis levels on termination of the procedure.^{18,56} The magnitude of the P_{aO₂}-drop varies according to the chemical composition of the dialysate and the type of membrane used.⁵⁷

Current understanding of dialysis-related hypoxemia is based on the fundamentals of alveolar ventilation, as taught in physiology class. Leukostasis and complement activation do occur during dialysis, but they are almost certainly unrelated to the observed changes in P_{aO₂}. The hypoxemia is explained by decreased alveolar ventilation in response to diffusion of CO₂ into the dialysate, as diagrammed in Figure 3. As CO₂ diffuses into the dialysate, the CO₂ content in venous blood falls. Because ventilation is tightly controlled by the peripheral and central chemoreceptors in response to changes in P_{aCO₂}, this fall in blood CO₂ content diminishes central ventilatory drive and decreases minute ventilation. Because some of the body’s CO₂ production is being eliminated through dialysis, in order to maintain a normal P_{aCO₂}, less CO₂ must be eliminated via the lungs. As alveolar ventilation falls and oxygen extraction remains the same, alveolar P_{O₂} decreases, hence P_{aO₂} falls.

That this basic physiological sequence was in fact responsible for dialysis-associated hypoxemia was finally demonstrated by a series of elegant studies of ventilation and perfusion in several laboratories.^{56,58,59} This mechanism is an example of alveolar hypoventilation without hypercapnia,⁶⁰ something that is possible only if CO₂ is being removed from the body by some route other than the lungs.

How Critical Illness and Mechanical Ventilation Can Damage the Kidneys

Patients may be admitted to the ICU because of illness or injury causing acute renal failure. However, there are several ways in which critical illness not initially involv-

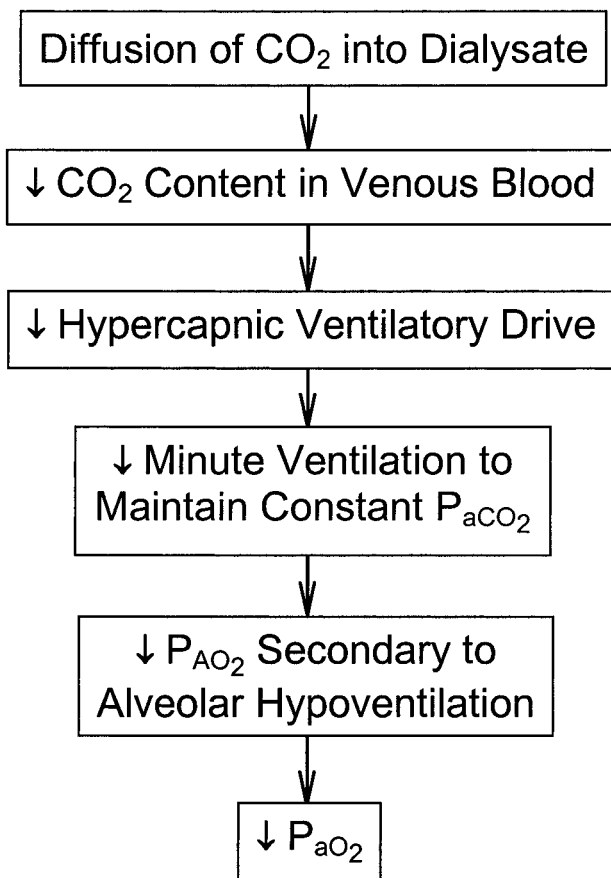


Fig. 3. The pathogenesis of dialysis-associated hypoxemia. For further explanation, see text.

ing the kidneys, and the management of that illness in the ICU, can precipitate iatrogenic renal damage (Table 5). Just as acute processes that precipitate the systemic inflammatory response syndrome predispose patients to ALI and ARDS, these same processes are associated with the development of acute renal failure in the ICU.⁶¹ Urinary-tract infection, the most common hospital-acquired infection, can lead to renal failure, particularly in patients with underlying renal disease. A host of drugs used in the ICU can cause or aggravate renal failure.

Shock from any cause is a known precipitant of acute renal failure, as are conditions that predispose to diminished renal perfusion. One of the latter that has received increasing attention in recent years is the abdominal compartment syndrome.^{62–64} In this syndrome, raised intra-abdominal pressure impairs venous return to the heart, diminishes cardiac output, and causes venous congestion of the abdominal organs, including the kidneys. Clinically, the abdominal compartment syndrome is characterized by hypotension, raised airway pressure, and oliguria. In this clinical setting its presence is confirmed by measurement of pressure in the urinary bladder. Although some authors consider intravesical pressures in excess of 12 mm Hg to

Table 5. Mechanisms by Which Critical Illness and Its Management Can Damage the Kidneys

Systemic effects of sepsis
Intensive-care-unit-acquired urinary tract infection
Drug toxicity
Abdominal compartment syndrome
Ventilator-induced renal injury
Adverse effects of permissive hypercapnia and hypoxia on renal blood flow
Renal hypoperfusion due to decreased cardiac output in the face of raised intrathoracic pressure
Effects of systemic inflammatory mediators released in response to mechanical ventilation

be associated with adverse effects,⁶⁴ others use a pressure of ≥ 30 cm H₂O to diagnose the syndrome.⁶⁵

Although ventilator-induced lung injury is now a widely-accepted entity and a much-investigated subject,^{66–68} until recently much less attention was focused on the potential association between mechanical ventilation and renal injury. However, an increasing body of experimental evidence supports the concept that ventilatory support, particularly with high airway pressure and distending volume, can damage the kidneys as well as the lungs.^{69–71} In addition, permissive hypercapnia and permissive hypoxemia, while potentially protecting the lungs from mechanical and biochemical damage, may be associated with adverse effects on renal perfusion and excretory function.⁶⁹ The emerging concept of biotrauma,⁶⁸ through which mechanical events in the lungs and airways initiate systemic processes that adversely affect other tissues and organs, may apply to the kidneys as well as to the lungs.⁶⁹

Summary

Awareness of the interrelatedness of respiratory and renal function is important in managing patients with diseases of both the lungs and the kidneys. Among the disease processes with both pulmonary and renal manifestations, Wegener's granulomatosis, systemic lupus erythematosus, and Goodpasture's syndrome are most likely to be encountered in respiratory care. Patients with chronic renal failure are subject to several important respiratory complications, including pulmonary edema, pleural effusions and other manifestations of fibrinous pleuritis, and sleep apnea. In managing acute renal failure, the clinician must often contend with respiratory manifestations of volume overload and metabolic acidosis. Mechanical ventilation in patients with renal failure can be especially challenging, particularly with respect to lung-protective ventilation and weaning. Although it was once believed to be caused by pulmonary leukostasis and complement activation triggered by the dialysis membranes,

hypoxemia during dialysis is now understood to be a predictable effect of the loss of CO₂ into the dialysate. Critical illness of any primary cause predisposes patients not only to ALI and ARDS but also to development of acute renal failure. Finally, there is currently an increasing appreciation of the potential for ventilator-induced renal injury, and this subject of investigation is sure to see more activity in the future.

REFERENCES

- Luce JM. Water, solute, and acid-base balance. In: Pierson DJ, Kacmarek RM, eds. *Foundations of respiratory care*. New York, Churchill Livingstone, 1992:115–127.
- Adroge HE, Adroge HJ. Acid-base physiology. *Respir Care* 2001; 46(4):328–341.
- Swenson ER. Metabolic acidosis. *Respir Care* 2001;46(4):342–353.
- Foster GT, Vaziri ND, Sassoon CS. Respiratory alkalosis. *Respir Care* 2001;46(4):384–391.
- Khanna A, Kurtzman NA. Metabolic alkalosis. *Respir Care* 2001; 46(4):354–365.
- Epstein SK, Singh N. Respiratory acidosis. *Respir Care* 2001;46(4): 366–383.
- Kraut JA, Madias NE. Approach to patients with acid-base disorders. *Respir Care* 2001;46(4):392–403.
- Madias NE, Adroge HJ. Cross-talk between two organs: how the kidney responds to disruption of acid-base balance by the lung. *Nephron Physiol* 2003;93(3):61–66.
- Rodriguez W, Hanania N, Guy E, Guntupalli J. Pulmonary-renal syndromes in the intensive care unit. *Crit Care Clin* 2002;18(4):881–895.
- Young KR Jr. Pulmonary-renal syndromes. *Clin Chest Med* 1989; 10(4):655–675.
- von Vigier RO, Trummler SA, Laux-End R, Sauvain MJ, Truttmann AC, Bianchetti MG. Pulmonary renal syndrome in childhood: a report of twenty-one cases and a review of the literature. *Pediatr Pulmonol* 2000;29(5):382–388.
- Schwarz MI, Collard HR, King TE Jr. Diffuse alveolar hemorrhage and other rare infiltrative disorders. In: Mason RJ, Broaddus VC, Murray JF, Nadel JA, editors. *Murray and Nadel's textbook of respiratory medicine*. Philadelphia: Elsevier Saunders, 2005:1656–1678.
- Collard HR, Schwarz MI. Diffuse alveolar hemorrhage. *Clin Chest Med* 2004;25(3):583–592.
- Niles JL, Bottinger EP, Saurina GR, Kelly KJ, Pan G, Collins AB, McCluskey RT. The syndrome of lung hemorrhage and nephritis is usually an ANCA-associated condition. *Arch Intern Med* 1996; 156(4):440–445.
- Channick RN, Rubin LJ. Pulmonary vasculitis and primary pulmonary hypertension. In: Mason RJ, Broaddus VC, Murray JF, Nadel JA, editors. *Murray and Nadel's textbook of respiratory medicine*. Philadelphia: Elsevier Saunders, 2005:1459–1479.
- Fauci AS, Haynes BF, Katz, Wolf SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with patients for 21 years. *Ann Intern Med* 1983;98(1):76–85.
- Zamora MR, Warner ML, Tuder R, Schwarz MI. Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. *Medicine (Baltimore)* 1997; 76(3):192–202.
- Rodriguez-Roisin R, Barbera JA. Pulmonary complications of abdominal disease. In: Mason RJ, Broaddus VC, Murray JF, Nadel JA, editors. *Murray and Nadel's textbook of respiratory medicine*. Philadelphia: Elsevier Saunders, 2005:2223–2241.
- Grassi V, Malerba M, Boni E, Tantucci C, Sorbini CA. Uremic lung. *Contrib Nephrol* 1994;106:36–42.
- Gavelli G, Zompatori M. Thoracic complications in uremic patients and in patients undergoing dialytic treatment: state of the art. *Eur Radiol* 1997;7(5):708–717.
- Rackow EC, Fein IA, Sprung C, Grodman RS. Uremic pulmonary edema. *Am J Med* 1978;64:1084–1088.
- Rocker GM, Morgan AG, Pearson D, Basran GS, Shale DJ. Pulmonary vascular permeability to transferrin in the pulmonary oedema of renal failure. *Thorax* 1987;42(8):620–623.
- Zidulka A, Despas PJ, Milic-Emili J, Anthonisen NR. Pulmonary function with acute loss of excess lung water by hemodialysis in patients with chronic uremia. *Am J Med* 1973;55(2):134–141.
- Stanescu DC, Veriter C, De Plaen JF, Frans A, Van Ypersele de Strihou C, Brasseur L. Lung function in chronic uraemia before and after removal of excess fluid by hemodialysis. *Clin Sci Mol Med* 1974;47(2):143–151.
- Prezant DJ. Effect of uremia and its treatment on pulmonary function. *Lung* 1990;168(1):1–14.
- Fairshter RD, Vaziri ND, Mirahmadi MK. Lung pathology in chronic hemodialysis patients. *Int J Artif Organs* 1982;5(2):97–100.
- Nidus BD, Matalon R, Cantacuzino D, Eisinger RP. Uremic pleuritis—a clinicopathological entity. *N Engl J Med* 1969;281(5):255–256.
- Berger HW, Rammohan G, Neff MS, Buhain WJ. Uremic pleural effusion: a study in 14 patients on chronic dialysis. *Ann Intern Med* 1975;82(3):362–364.
- Maher JF. Uremic pleuritis. *Am J Kidney Dis* 1987;10(1):19–22.
- Alpert MA, Ravenscraft MD. Pericardial involvement in end-stage renal disease. *Am J Med Sci* 2003;325(4):228–236.
- Wood JE, Mahnensmith RL. Pericarditis associated with renal failure: evolution and management. *Semin Dial* 2001;14(1):61–66.
- Hussein MM, Mooij JM, Roujouleh H. Tuberculosis and chronic renal disease. *Semin Dial* 2003;16(1):38–44.
- Cheng IK, Chan PC, Chan MK. Tuberculous peritonitis complicating long-term peritoneal dialysis: report of 5 cases and review of the literature. *Am J Nephrol* 1989;9(2):155–161.
- Faubert PF, Shapiro WB, Porush JG, Chou SY, Gross JM, Bondi E, Gomez-Leon G. Pulmonary calcification in hemodialyzed patients detected by technetium-99m diphosphonate scanning. *Kidney Int* 1980;18(1):95–102.
- Ullmer E, Borer H, Sandoz P, Mayr M, Dalquen P, Soler M. Diffuse pulmonary nodular infiltrates in a renal transplant recipient: metastatic pulmonary calcification. *Chest* 2001;120(4):1394–1398.
- Justrabo E, Genin R, Rife G. Pulmonary metastatic calcification with respiratory insufficiency in patients on maintenance hemodialysis. *Thorax* 1979;34(3):384–388.
- Conger JD, Hammond WS, Alfrey AC, Contiguglia SR, Stanford RE, Huffer WE. Pulmonary calcification in chronic dialysis patients. *Ann Intern Med* 1975;83(3):330–336.
- Garcia-Pachon E, Padilla-Navas I. Urinothorax: case report and review of the literature with emphasis on biochemical diagnosis. *Respiration* 2004;71(5):533–536.
- Salcedo JR. Urinothorax: report of 4 cases and review of the literature. *J Urol* 1986;135(4):805–808.
- Fletcher EC. Obstructive sleep apnea and the kidney. *J Am Soc Nephrol* 1993;4(5):1111–1121.
- Zoccali C, Mallamaci F, Tripepi G. Sleep apnea in renal patients. *J Am Soc Nephrol* 2001;12(12):2854–2859.
- Kraus MA, Hamburger RJ. Sleep apnea in renal failure. *Adv Perit Dial* 1997;13:88–92.
- Hanly P. Sleep apnea and daytime sleepiness in end-stage renal disease. *Semin Dial* 2004;17(2):109–114.
- Parker KP. Sleep disturbances in dialysis patients. *Sleep Med Rev* 2003;7(2):131–143.

45. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Candela V, Labate C, Tassone F. Left ventricular hypertrophy and nocturnal hypoxemia in hemodialysis patients. *J Hypertens* 2001;19(2):287–293.
46. Zoccali C, Mallamaci F, Tripepi G. Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. *J Am Soc Nephrol* 2002;13(3):729–733.
47. Mendelson WB, Wadhwa NK, Greenberg HE, Gujavarty K, Bergofsky E. Effects of hemodialysis on sleep apnea in end stage renal disease. *Clin Nephrol* 1990;33(5):247–251.
48. Fein AM, Niederman MS, Imbriano L, Rosen H. Reversal of sleep apnea in uremia by dialysis. *Arch Intern Med* 1987;147(7):1355–1356.
49. Pendse S, Singh AK. Complications of chronic kidney disease: anemia, mineral metabolism, and cardiovascular disease. *Med Clin North Am* 2005;89(3):549–561.
50. Fishbane S. Anemia treatment in chronic renal insufficiency. *Semin Nephrol* 2002;22(6):474–478.
51. Cody J, Daly C, Campbell M, Donaldson C, Khan I, Rabindranath K, et al. Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. *Cochrane Database Syst Rev* 2005 20;(3):CD003266.
52. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005 17;294(7):813–818.
53. Blanch L, Bernabe F, Lucangelo U. Measurement of air trapping, intrinsic positive end-expiratory pressure, and dynamic hyperinflation in mechanically ventilated patients. *Respir Care* 2005;50(1):110–123.
54. Craddock PR, Fehr J, Brigham KL, Kronenberg RS, Jacob HS. Complement and leukocyte-mediated pulmonary dysfunction in hemodialysis. *N Engl J Med* 1977;296(14):769–774.
55. Carlon GC, Campfield PB, Goldiner PL, Turnbull AD. Hypoxemia during hemodialysis. *Crit Care Med* 1979;7(11):497–499.
56. Patterson RW, Nissenson AR, Miller J, Smith RT, Narins RG, Sullivan SF. Hypoxemia and pulmonary gas exchange during hemodialysis. *J Appl Physiol* 1981;50(2):259–264.
57. Munger MA, Ateshkadi A, Cheung AK, Flaharty KK, Stoddard GJ, Marshall EH. Cardiopulmonary events during hemodialysis: effects of dialysis membranes and dialysate buffers. *Am J Kidney Dis* 2000;36(1):130–139.
58. Romaldini H, Rodriguez-Roisin R, Lopez FA, Ziegler TW, Bencowitz HZ, Wagner PD. The mechanisms of arterial hypoxemia during hemodialysis. *Am Rev Respir Dis* 1984;129(5):780–784.
59. Ralph DD, Ott SM, Sherrard DJ, Hlastala MP. Inert gas analysis of ventilation-perfusion matching during hemodialysis. *J Clin Invest* 1984;73(5):1385–1391.
60. Martin L. Hypoventilation without elevated carbon dioxide tension. *Chest* 1980;77(6):720–721.
61. Wan L, Bellomo R, Di Giandomasso D, Ronco C. The pathogenesis of septic acute renal failure. *Curr Opin Crit Care* 2003;9(6):496–502.
62. Burch JM, Moore EE, Moore FA, Franciose R. The abdominal compartment syndrome. *Surg Clin North Am* 1996;76(4):833–842.
63. Walker J, Criddle LM. Pathophysiology and management of abdominal compartment syndrome. *Am J Crit Care* 2003;12(4):367–371.
64. Sugrue M. Abdominal compartment syndrome. *Curr Opin Crit Care* 2005;11(4):333–338.
65. Benditt JO. Esophageal and gastric pressure measurements. *Respir Care* 2005;50(1):68–75.
66. Ranieri VM, Giunta F, Suter PM, Slutsky AS. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. *JAMA* 2000;284(1):43–44.
67. Plotz FB, Slutsky AS, van Vught AJ, Heijnen CJ. Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses. *Intensive Care Med* 2004;30(10):1865–1872.
68. Slutsky AS. Ventilator-induced lung injury: from barotrauma to bio-trauma. *Respir Care* 2005;50(5):646–659.
69. Kuiper JW, Groeneveld AB, Slutsky AS, Plotz FB. Mechanical ventilation and acute renal failure. *Crit Care Med* 2005;33(6):1408–1415.
70. Chien CC, King LS, Rabb H. Mechanisms underlying combined acute renal failure and acute lung injury in the intensive care unit. *Contrib Nephrol* 2004;144:53–62.
71. Pannu N, Mehta RL. Effect of mechanical ventilation on the kidney. *Best Pract Res Clin Anaesthesiol* 2004;18(1):189–203.