CHAPTER 122

The Kidney During Mechanical Ventilation

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OBJECTIVES

This chapter will:

1. Describe the epidemiologic relationship between mechanical ventilation and acute renal failure and address the indications for mechanical ventilation.
2. Review the adverse effects of mechanical ventilation on the lung and distant organs.
3. Outline the effects of mechanical ventilation on systemic hemodynamics, local renal blood flow, and on the kidney.
4. Discuss the possible effects of hypercapnia and hypoxemia on kidney function.
5. Describe the effects of mechanical ventilation induced on the kidney.

Mechanical ventilation has been of great value in improving the survival of many patients suffering from respiratory failure. A common cause of respiratory failure is the acute respiratory distress syndrome (ARDS) ranging from mild to severe ARDS, with a mortality rate of 38.5% for severe ARDS.[1] Although the most obvious clinical abnormalities in ALI and ARDS are referable to the lung, the most common cause of death is multiple organ dysfunction including acute kidney injury (AKI).[2] Respiratory failure and mechanical ventilation are risk factors for developing AKI; more than 75% of patients in the intensive care unit (ICU) with AKI receive mechanical ventilation.[3] Also, increased duration of mechanical ventilation increases the risk of developing AKI after cardiac surgery.[4] Mechanical ventilation has been shown to be an independent risk factor for in-hospital death in critically ill patients with AKI, more than tripling the risk of dying in hospital and doubling the risk 1 year after ICU admission.[5] This chapter describes possible mechanisms through which mechanical ventilation affects the kidney in patients requiring ICU management and how these may contribute to the development of AKI.

We dedicate this chapter to the memory of Prof. Groeneveld, a gifted teacher who inspired us greatly. We will miss an excellent scientist and clinician devoted to intensive care medicine. But above all we will miss his warm personality and friendship.

MECHANICAL VENTILATION VERSUS SPONTANEOUS BREATHING

During spontaneous breathing, respiratory muscles establish negative intrathoracic and intrapulmonary pressures and, by downward movement of the diaphragm, a positive intra-abdominal pressure. The resulting intrathoracic pressure–to–ambient pressure gradient allows air to flow into the lungs. The physiologic mechanism of spontaneous breathing facilitates venous return, thereby supporting hemodynamics. In contrast with spontaneous breathing, mechanical ventilation uses positive pressure to inflate the lungs.

In most patients with ARDS, either volume-controlled or pressure-controlled ventilation is used. In the volume control mode, a volume is preset on the ventilator, resulting in a variable airway pressure, whereas in the pressure control mode, the inspiratory pressure is preset, resulting in a certain tidal volume. Thus the airway pressure results from the applied tidal volume or preset inspiratory pressure and on the preset basic end-expiratory volume and depends on lung compliance, airway resistance, and air flow.

During mechanical ventilation, pressure gradients are altered considerably compared with pressure gradients in spontaneously breathing subjects. Intrathoracic, intrapulmonary, and intra-abdominal pressures increase during inspiration and remain positive during the breathing cycle. Only at the end of expiration do they equalize with ambient pressure, when no positive end-expiratory pressure (PEEP) is applied. PEEP usually is applied to prevent the alveoli from collapsing at end expiration. Consequently, mechanical ventilation exerts systemic hemodynamic effects through a complex interaction among intrathoracic pressure, intravascular volume, and cardiac performance. Mechanical ventilation decreases cardiac output by decreasing preload, affecting left ventricular geometry and pulmonary vascular volume and resistance, and, in addition, increasing right ventricular afterload. Evidence for these proposed mechanisms has been known for decades, based on studies in animal models and human subjects during spontaneous ventilation or controlled mandatory ventilation in combination with PEEP.[6,7]

INDICATIONS FOR MECHANICAL VENTILATION

The most common and obvious indication for mechanical ventilation in patients under ICU care is ARDS. This condition can be defined qualitatively as any respiratory pathologic process associated with failure of arterial oxygenation and inadequate alveolar ventilation, with a subsequent decrease in PaO_2 or rise in $PaCO_2$, or both. Although in most mechanically ventilated patients, normal gas exchange is targeted, in many patients with ARDS managed in the ICU, the maintenance of normal gas exchange is impossible. In such cases, to avoid ventilator-associated lung injury (VALI), a low PaO_2 or a high $PaCO_2$ is accepted.[8] The former occurs despite measures to improve oxygenation and despite avoidance of high, potentially toxic inspired oxygen concentrations. The latter may be associated with a strategy of small tidal volume ventilation with adequate mean airway pressure to achieve satisfactory oxygenation, thereby avoiding toxic inspired oxygen concentrations and allowing $PaCO_2$ to increase if necessary. These strategies are called *permissive hypoxemia* and *permissive hypercapnia*, respectively. In this regard, it is important to recognize that patients in the ICU may be subjected to acute changes in PaO_2 and $PaCO_2$, or to mild chronic hypoxemia or hypercapnia, as a result of the applied ventilatory strategy or their underlying condition.

VENTILATOR-INDUCED LUNG INJURY

Besides the adverse effects mechanical ventilation has on systemic hemodynamics, it also can cause direct damage to the lungs, which is termed ventilator-induced lung injury (VILI). *VALI* is used when a causal relationship between mechanical ventilation and lung injury cannot be established, which is usually a clinical setting.[9,10] Initial experimental research on the induction and course of *VILI* focused primarily on the contribution of mechanical factors such as pressure and volume.[11] Based on these studies, innovative and lung-protective strategies have been proposed to avoid VILI by limiting tidal volume and plateau pressure and by maintaining recruitment of alveolar regions with sufficient PEEP. Clinical trials subsequently made clear that ventilator management can alter mortality in patients with ARDS.[8,12] In 2000 the ARDS Network clinical trial revealed that mortality rate was significantly lower in the group managed with lower tidal volumes than for managed with traditional high tidal volumes (31.0% vs. 39.8%).[12]

Mechanical stresses caused by mechanical ventilation can affect cellular and molecular processes in the lung, a mechanism that has been called *biotrauma*.[13] Two independent pathways of the biotrauma hypothesis have been distinguished: (1) Ventilation may cause release of mediators, and (2) these mediators have biologic activity. Ventilation strategies using "large" tidal volumes and zero PEEP in already-injured lungs can promote the release of inflammatory mediators in the lungs. This potentiation of the inflammatory response is supported by evidence from experimental models ranging from mechanically stressed cell systems to isolated lungs and intact animals and humans. The possible pivotal role for biotrauma in the development of multisystem organ failure was based on the suggestion that this inflammatory reaction may not be limited to the lungs but, by way of spillover of mediators in the circulation, also may initiate and propagate a systemic inflammatory response.[14,15] Indirect evidence from experimental models ranging from an isolated perfused and ventilated mouse lung, intact animals with preinjured lungs, and humans with ARDS supports this hypothesis.[16,17] However, conflicting evidence exists.[18,19] In addition, other mechanisms by which mechanical ventilation may affect distant organs include suppression of peripheral immune response and translocation of bacteria and endotoxin from lung and intestine to the systemic circulation.[20]

MECHANICAL VENTILATION AND THE KIDNEY

Acute tubular necrosis most often is ischemic or toxic in origin. Prerenal failure and ischemic tubular necrosis represent points along a continuum, with the former leading to the latter when blood flow is compromised sufficiently.[6] Many clinical conditions can lead to kidney ischemia as a result of either extrarenal or intrarenal factors that compromise renal blood flow.[6] After ischemia, toxins account for the largest number of cases of acute intrinsic renal failure by directly damaging tubular cells or by various other mechanisms.[6]

Mechanical ventilation may contribute to the development of AKI by three different mechanisms (Fig. 122.1): First, the effect of mechanical ventilation on systemic hemodynamics can alter renal blood flow; second, changes in $PaCO_2$ and PaO_2 can affect renal hemodynamics; and

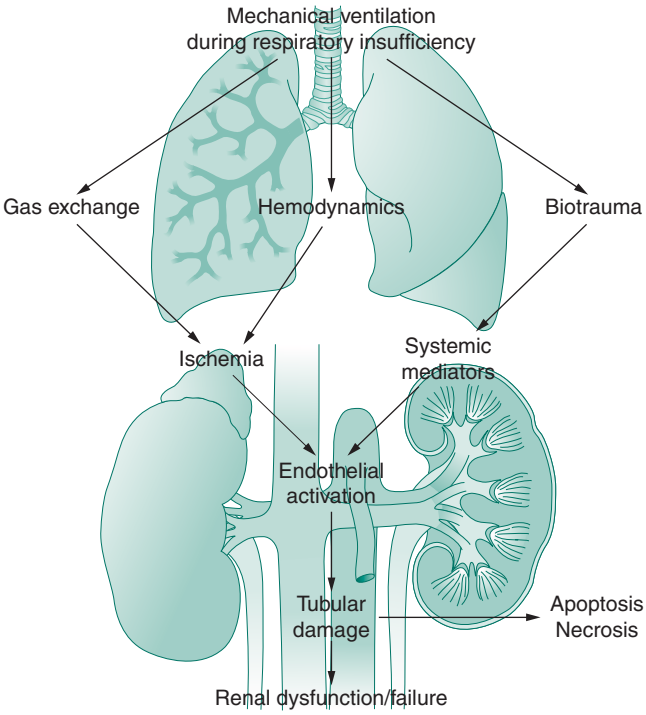

FIGURE 122.1 Mechanical ventilation affects the kidney through three distinct mechanisms: (1) direct effects on gas exchange that can activate vasoactive mechanisms and decrease renal blood flow; (2) depressing effects on systemic hemodynamics, thereby decreasing renal blood flow; and (3) secondary to biotrauma from mechanical ventilation, with the subsequent systemic release of inflammatory and proapoptic mediators that may affect the kidney. These effects may be more pronounced in patients with severe acute respiratory distress syndrome or with circulatory compromise.

third, the systemic release of inflammatory mediators may have biologic activity that affects the kidney.[6]

Effects of Mechanical Ventilation on Renal Blood Flow

Based largely on renal ischemia-reperfusion studies, it is well known that a compromised renal blood flow contributes to renal vascular endothelial and tubular damage and influences long-term renal function. The mechanisms by which mechanical ventilation alters renal perfusion include a reduction in cardiac output and stimulation of hormonal and sympathetic pathways.[6,21]

First, a decreased cardiac output during mechanical ventilation in patients with respiratory failure may lead to decreased renal perfusion and is associated with reduced renal function as reflected in sodium handling, glomerular filtration rate (GFR), urinary output, and urea and creatinine clearance. Hemodynamic studies demonstrated an immediate decline in urinary output after start of mechanical ventilation—an effect that appears to be exacerbated by PEEP.[6,21] The reported effects of mechanical ventilation on GFR and renal blood flow are variable and may reflect differences in hydration status, patient acuity, possible underlying pulmonary dysfunction, and anesthetics used. Dispute exists, however, regarding the relative contribution of effects of cardiac output and the stimulation of water- and sodium-retaining hormonal systems.

Second, various regulatory hormonal mechanisms that affect renal function during mechanical ventilation have been proposed. Thus far, no definite correlation between antidiuretic hormone (ADH), prostaglandin, catecholamine, atrial natriuretic factor (ANP), or vasoactive peptide levels and renal function during mechanical ventilation has been established.[6] In rats, Kuiper et al. found that mechanical ventilation induced decreased RBF, which was associated with increased kidney endothelin-1 levels.[22] Similarly, in rats mechanically ventilated after intratracheal instillation of lipopolysaccharide, renal hypoperfusion and impaired endothelium-dependent vasodilation was shown. This was associated with increased serum creatinine and renal neutrophil gelatinase-associated lipocalin.[23] Mechanical ventilation increased renal endothelial nitric oxide synthase expression, which was correlated with increased renal protein loss and increased vascular permeability.[24] Third, mechanical ventilation with PEEP increases sympathetic tone, resulting in increased plasma renin activity and thereby decreasing GFR by reducing blood flow.[6] Mechanical ventilation also has a transient effect on aortic blood pressure, which reflexively activates the sympathetic nervous system through aortic and (sino)carotid baroreceptors and, more slowly, affects intravascular volume by changing renal function.[6] Whether the effect of atrial stretch receptors on renal vascular tone also alters renal function during mechanical ventilation remains to be evaluated.[6] In conclusion, the effects of a reduced cardiac output on kidney function during mechanical ventilation have been documented extensively. By contrast, the relative role of neurohumoral regulatory systems remains to be investigated.

Pa_2, PaO_2, and the Kidney

Hypercapnia

The effect of hypercapnia on renal blood flow has been well documented in normal persons and in patients in respiratory failure or with chronic obstructive pulmonary disease. $PaCO_2$ levels have been found to correlate inversely with renal blood flow.[6] Hypercapnia can reduce renal blood flow by direct and indirect mechanisms. Hypercapnia directly causes renal vasoconstriction and stimulates norepinephrine release, acting on the sympathetic nervous system.[6] Increased sympathetic activity can reduce renal blood flow and, to a lesser extent, GFR and may contribute to nonosmotic release of vasopressin.[6] Indirectly, hypercapnia causes systemic vasodilation that decreases systemic vascular resistance, "inactivating" the baroreceptors with a subsequent release of norepinephrine and stimulation of the renin-angiotensin-aldosterone system, leading to a fall in renal blood flow.[6]

Human, post–renal transplantation, and animal studies suggest that local neurogenic mechanisms play a role in the response of renal blood flow to hypercapnia.[25] In addition, other factors such as circulating catecholamines and neuropeptides also affect the renovascular response to hypercapnia, in addition to effects on renal innervation (Table 122.1). Of importance clinically, the rapid and marked decrease in renal blood flow in response to hypercapnia also occurs in the presence of normal or increased PaO_2. This finding suggests that changes in $PaCO_2$, independent from PaO_2, play a pivotal role in determining the renovascular response to changes in arterial blood gas pressures.

Hypoxemia

Severe hypoxemia (PaO_2 less than 40 mm Hg) generally is thought to reduce renal blood flow and can lead to functional renal insufficiency.[6] Reports on the renal effects of moderate hypoxemia are conflicting, however. Several studies suggest that mild hypoxemia without concomitant hypercapnia

TABLE 122.1

Inflammatory, Vasoactive, and Proapoptotic Mediators That Potentially Mediate the Effects of Mechanical Ventilation on the Kidney

INFLAMMATORY MEDIATORS	VASOACTIVE MEDIATORS	PROAPOPTOTIC MEDIATORS	COAGULATION
IL-1β	Nitric oxide	Soluble Fas ligand	(a)PAI-1
IL-6	Vasopressin (ADH)	MCP-1	TATc
IL-8	Catecholamines		Active tPA
IL-10	RAAS		
TNF-α	Prostaglandins		
Soluble IL-1RA	ANF		
Soluble TNF receptors	Endothelin		
sICAM-1			
aPC			
MIP-2			
GRO / KC			
VCAM-1			

ADH, Antidiuretic hormone; *ANF,* atrial natriuretic factor; *(a)PAI,* (activated) plasminogen activator inhibitor; *aPC,* activated protein C; *GRO,* growth-related oncogene; *IL,* interleukin; *KC,* keratinocyte chemoattractant; *MCP-1,* monocyte chemotactic protein-1; *MIP,* macrophage inflammatory protein; *RA,* receptor antagonist; *RAAS,* renin-angiotensin-aldosterone system; *sICAM,* soluble intercellular adhesion molecule; *TATc,* thrombin antithrombin complex; *TNF,* tumor necrosis factor; *tPA,* tissue-type plasminogen activator.

exerts no significant effect on renal hemodynamics. Other studies have demonstrated that acute normocapnic hypoxemia increases renal vascular resistance, leading to renal hypoperfusion and decreased GFR. The underlying mechanisms whereby changes in oxygenation induce vasomotor nephropathy are not fully understood. Possible mechanisms include (in)activation of vasoactive factors such as nitric oxide (NO), angiotensin II, endothelin, and bradykinin and a chemoreceptor-mediated sympathetic reflex (see Table 122.1).[6] Although permissive hypercapnia with acidosis has cytoprotective and antiinflammatory properties, no recent studies have addressed the effects of permissive hypercapnia and hypoxemia.

BIOTRAUMA AND THE KIDNEY

An increasing number of mediators have been reported to increase in the systemic circulation during mechanical ventilation and may potentially contribute to AKI (see Table 122.1).[14] These mediators have been identified in clinical studies as well as animal experiments and not only are they proinflammatory by nature but also antiinflammatory mediators have been identified. The simultaneous detection of proinflammatory and antiinflammatory mediators may reflect altered regulation of the inflammatory response. A persistent activation of the inflammatory response is associated with organ failure.[26] Inflammatory mediators may affect renal function through several mechanisms, some of which may be synergistic. Suggested mechanisms include (1) a direct effect on renal blood flow through the release of several vasoactive mediators, (2) induction of a local renal inflammatory response by proinflammatory mediators from pulmonary origin, and (3) the direct induction of apoptosis by proapoptotic factors.[6] Soluble Fas ligand is known to induce apoptosis of glomerular cells, and interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) may facilitate this process by activating platelet-activating factor and inducing an inflammatory reaction, both contributing to the apoptotic effects of soluble Fas ligand.[14] In addition, mediators involved in coagulation and fibrinolysis have been found in plasma after mechanical ventilation, but the evidence for a direct effect on the kidney is limited. Vascular endothelial growth factor also has been found and may have injurious and protective effects.[14] These processes are closely related and a combination of the aforementioned processes is more likely involved than one single process or mediator. By compromising renal blood flow, a critical threshold may be reached and inflammatory mediators may exert a direct effect on renal endothelial and epithelial cells, thereby inducing or contributing to AKI (see Fig. 122.1).

Only a few studies have addressed the role of biotrauma in association with the kidney. In a clinical study, Ranieri et al. observed that a conventional mechanical ventilation strategy was associated with a local and systemic cytokine response that was sustained over 36 hours in patients with ARDS, whereas in a second group of patients, the inflammatory response was attenuated by a lung-protective strategy. Patients in the latter group had significantly lower concentrations of a number of cytokines (TNF-α, IL-1β, IL-6, IL-8, soluble TNF receptors, IL-1 receptor antagonist) in plasma and bronchoalveolar lavage fluid at 36 hours.[27] A posthoc analysis revealed that an increase in IL-6 plasma concentrations correlated with the development of acute renal failure.[17] Most studies on mediator release and effects on the kidney have focused on proinflammatory and chemotactic mediators; in particular TNF-α, IL-6, and MIP-2 have been studied. In vivo, TNF-α can cause and contribute to AKI, but evidence for other proinflammatory mediators is lacking. IL-6 has been shown to be involved in AKI, but its role is incompletely understood. Of all antiinflammatory mediators, only IL-10 appears to have a protective role in the development of AKI. Mediators such as VEGF and activated protein C have been well described in the AKI literature but not in the context of mechanical ventilation. Others, such as ICAM-1, VACM-1, and sFasL have been studied in the context of biotrauma, but their potential effects on the kidney must be elucidated.[14]

In the aforementioned studies, specific issues must be evaluated. First, the source of the mediators remains uncertain. Lung-borne mediators may spill over into the systemic circulation and exert their effect on distant organs.[28] However, these mediators also may be produced locally in the kidneys as a result of a compromised renal blood flow and exert their effect directly in the organs where they are produced. Second, it is important to prove a cause-and-effect relationship between mediators and renal dysfunction, rather than simply recognizing an association.[29]

CONCLUSION

Mechanical ventilation plays an important role in the care of patients in the ICU and is critical to survival in many cases. Despite the emergence of new modes of ventilation and new ventilator strategies, the effects of mechanical ventilation remain complex and extend to organ systems other than the lung. In the ICU, patients usually suffer from ARDS, which significantly alters lung mechanics, thereby aggravating the adverse effects of mechanical ventilation—further depression of hemodynamics and exacerbation of the pulmonary inflammatory processes. In addition, the harmful effects of mechanical ventilation on the kidney become more significant when comorbid conditions are present. In the presence of ARDS, it is more difficult to maintain normal gas exchange, and moderate arterial hypoxemia and hypercapnia often are accepted, which potentially decrease renal blood flow. Renal blood flow is compromised further because of a decreased cardiac output secondary to high intrathoracic pressures. Furthermore, the impact of biotrauma is not limited to the lungs but may lead to a systemic inflammatory reaction. These effects on renal function can be aggravated during sepsis, when prerenal blood flow is compromised further. This series of events may reflect a multifactorial process that eventually may result in the development of AKI. Despite difficulties in differentiating between the effects of mechanical ventilation and the underlying disease on renal function, it is likely that mechanical ventilation greatly affects the kidney.

Key Points

1. Mechanical ventilation has been shown to be an independent risk factor for in-hospital death in critically ill patients with acute renal failure, more than tripling the risk of dying.
2. Through various mechanisms, mechanical ventilation exerts effects on the lungs and extrapulmonary organ systems, including the kidney.

3. Mechanical ventilation exerts effects on systemic hemodynamics and local renal blood flow that may in turn influence renal function.
4. Mechanical ventilation strategies of permissive hypercapnia and hypoxemia may compromise renal blood flow, thereby affecting renal function.
5. Biotrauma, the propagation of a pulmonary inflammatory reaction and spillover of inflammatory mediators into the systemic circulation, also may affect renal function.

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A complete reference list can be found online at ExpertConsult.com.

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