Chapter 2

Mechanical ventilation and acute renal failure

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Abstract

Objective: To review the current literature on possible mechanisms by which mechanical ventilation may initiate or aggravate acute renal failure.

Data Source: A Medline database and references from identified articles were used to perform a literature search relating to mechanical ventilation and acute renal failure.

Data Synthesis: Acute renal failure may be initiated or aggravated by mechanical ventilation through three different mechanisms. First, strategies such as permissive hypercapnia or permissive hypoxemia may compromise renal blood flow. Second, through effects on cardiac output, mechanical ventilation affects systemic and renal hemodynamics. Third, mechanical ventilation may cause biotrauma — a pulmonary inflammatory reaction that may generate systemic release of inflammatory mediators. The harmful effects of mechanical ventilation may become more significant when a comorbidity is present. In these situations, it is more difficult to maintain normal gas exchange, and moderate arterial hypoxemia and hypercapnia are often accepted. Renal blood flow is compromised due to a decreased cardiac output as a consequence of high intrathoracic pressures. Furthermore, the effects of biotrauma are not limited to the lungs but may lead to a systemic inflammatory reaction.

Conclusions: The development of acute renal failure during mechanical ventilation likely represents a multifactorial process that may become more important in the presence of comorbidities. Development of optimal interventional strategies requires an understanding of physiologic principles and greater insight into the precise molecular and cellular mechanisms that may also play a role.
Introduction

Mechanical ventilation can induce or aggravate lung injury and is thought to contribute to the development of distant organ failure.\(^1,2\) Clinical trials have demonstrated that ventilator management can alter the degree of organ failure and the mortality rate in patients with acute respiratory distress syndrome.\(^3,4\) An early manifestation of organ failure in the intensive care unit is acute renal failure (ARF),\(^5-7\) with a prevalence ranging from 4% to 16%, which is associated with increased mortality rates.\(^8,9\)

A number of physiologic and biological mechanisms could link mechanical ventilation and the onset of ARF, but the specific contributions in any patient are difficult to ascertain because the underlying disease process necessitating mechanical ventilation may also have an adverse effect on renal function. This perspective will review the links between ventilation and ARF, with a brief focus on the pathophysiology of acute tubular necrosis since this is the most common mechanism leading to ARF in the intensive care unit.\(^7\)

Pathophysiology of Acute Tubular Necrosis

Acute tubular necrosis is most often ischemic or toxic in origin. Many clinical conditions can lead to kidney ischemia as a result of either extrarenal or intrarenal factors that compromise renal blood flow (RBF).\(^7\) Different segments of the kidney vary in their sensitivity to ischemic injury.\(^10\) The proximal tubules depend almost entirely on mitochondrial respiration for their energy supply and are therefore more susceptible to ischemic renal injury.\(^11\) Also, the medulla becomes far more hypoxic than the cortex following a decrease in RBF.\(^10\) After ischemia, toxins (e.g., various antibiotics used in the intensive care unit) account for the largest number of cases of acute intrinsic renal failure by directly damaging tubular cells or by various other mechanisms.\(^7\)

The mechanism of cell death induced by ischemic and cytotoxic events is in general determined by the severity of injury, with severe insults causing necrosis and similar, milder insults causing apoptosis.\(^11,12\) It is now well recognized that much of the acute tubular necrosis-induced renal dysfunction is due to both mechanisms.\(^13,14\) It is not yet possible to quantify the relative contributions made by necrosis and apoptosis to acute tubular necrosis in vivo. There are,
however, important therapeutic consequences; whereas necrosis is difficult to reverse, the apoptotic pathway can potentially be modulated to maintain cell viability.

Mechanical Ventilation and Acute Renal Failure

Mechanical ventilation may induce acute tubular necrosis leading to ARF by three proposed mechanisms: a) through effects on arterial blood gases; b) through an effect on systemic and renal blood flow; and c) by triggering a pulmonary inflammatory reaction—biotrauma—and the systemic release of mediators generated during biotrauma.

Effect of Mechanical Ventilation on Pao2 and Paco2.

In most mechanically ventilated patients, normal gas exchange is targeted; however, in many patients with acute lung injury or acute respiratory distress syndrome, maintenance of normal gas exchange may be impossible or may require ventilatory settings that may further injure the lungs, leading to ventilation-induced lung injury. In such cases, a lower than normal Pao2 or a higher Paco2 is accepted. In particular, there is evidence that permissive hypercapnia may be beneficial in critically ill patients. However, changes in Pao2 and Paco2 can affect renal hemodynamics.

Hypoxemia.

Severe hypoxemia (Pao2 <40 mm Hg) is generally thought to reduce RBF and can lead to functional renal insufficiency in humans and animals. However, there are conflicting reports on the renal effects of moderate hypoxemia. Several studies suggest that mild hypoxemia without concomitant hypercapnia exerts no significant effect on renal hemodynamics. Other studies have demonstrated that acute normocapnic hypoxemia increases renal vascular resistance, leading to renal hypoperfusion and a decreased glomerular filtration rate (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, angiotensin II, endothelin, and bradykinin, as well as a chemoreceptor-mediated sympathetic reflex.
Hypercapnia.
The effect of hypercapnia on RBF is well documented in animal studies,\textsuperscript{31-41} in normal subjects,\textsuperscript{26} and in subjects with respiratory failure\textsuperscript{26,31,32} or chronic obstructive pulmonary disease.\textsuperscript{26,29-32} Paco2 levels have been found to correlate inversely with RBF.\textsuperscript{44} Hypercapnia can reduce RBF by direct and indirect mechanisms. Hypercapnia directly causes renal vasoconstriction\textsuperscript{26,45} and stimulates noradrenaline release acting on the sympathetic nervous system.\textsuperscript{46,47} Increased sympathetic activity can also reduce RBF and, to a lesser extent, GFR and may contribute to nonosmotic release of vasopressin.\textsuperscript{58} Indirectly, hypercapnia causes systemic vasodilation that decreases systemic vascular resistance,\textsuperscript{49} “inactivating” the baroreceptors with a subsequent release of noradrenaline and stimulation of the renin-angiotensin-aldosterone system,\textsuperscript{50,51} leading to a decrease in RBF.\textsuperscript{44,52} Human, postrenal transplant, and animal studies suggest that local neurogenic mechanisms play a role in the RBF response to hypercapnia.\textsuperscript{53,54} In addition, other factors such as circulating catecholamines and neuropeptides also affect the renovascular response to hypercapnia in addition to effects on renal innervation. Of importance clinically, the rapid and marked decrease in RBF in response to hypercapnia also occurs in the presence of normal or increased Pao2.\textsuperscript{54} This suggests that changes in Paco2, independent from Pao2, play a pivotal role in determining the renovascular response to changes in arterial blood gas pressures. However, in an in vitro model of renal ischemia, ischemia-induced apoptosis of rat renal tubular cells required both a low Pao2 and a high Paco2.\textsuperscript{55}

Effects of Mechanical Ventilation on Systemic and Renal Blood Flow.
Based largely on renal ischemia/reperfusion studies, it is well known that a compromised RBF contributes to renal vascular and tubular damage and influences long-term renal function.\textsuperscript{56-58} Although the precise mechanisms remain unclear, apoptosis and necrosis play pivotal roles in the development of renal hypoxic/ischemic damage.\textsuperscript{59,60} The proposed mechanisms by which mechanical ventilation alters renal perfusion include reduction in cardiac output, redistribution of intrarenal blood flow, and stimulation of hormonal and sympathetic pathways.\textsuperscript{61,62}

Reduction in Cardiac Output.
Mechanical ventilation exerts systemic hemodynamic effects through a complex interaction between intrathoracic pressure, intravascular volume, and cardiac performance. Mechanical ventilation decreases cardiac output by decreasing preload, affecting both 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 increasing levels of positive end-
expiratory pressure (PEEP). Hemodynamic studies demonstrated an immediate decline in
urinary output after the start of mechanical ventilation (an effect that appears to be exacerbated
by PEEP). During mechanical ventilation, a decreased cardiac output may lead to decreased
renal perfusion and is associated with reduced renal function, for example, sodium handling,
GFR, urinary output, and urea and creatinine clearance, in various animal models and patients
with respiratory failure. The reported effects of mechanical ventilation on GFR and RBF are
variable and may reflect differences in hydration status, patient acuity, possible underlying
pulmonary dysfunction, anesthetics used, and species variation. Dispute exists about the
relative contribution of effects of cardiac output and stimulation of water- and sodium-retaining
hormonal systems. In addition, these effects were studied for a maximum period of 2 hrs
in humans, and the observed renal dysfunction appears to be reversible.

Redistribution of Intrarenal Blood Flow.
A number of studies have demonstrated redistribution of blood flow from the cortical to the
juxtamedullary nephrons during ventilation with PEEP, whereas total RBF remained
unchanged. This was associated with decreased urinary output and creatinine clearance and
increased fractional resorption of sodium, suggesting that no, or small, decreases in RBF can
seriously affect renal function. However, the effect of PEEP on intrarenal redistribution of blood
flow was not confirmed in another study.

Stimulation of Hormonal and Sympathetic Pathways.
Various regulatory mechanisms that affect renal function during mechanical ventilation have
been proposed. Thus far, no definite correlation between antidiuretic hormone levels, prostaglandin,
catecholamine, atrial natriuretic factor, or vasoactive peptides and renal function during mechanical ventilation has been established. Mechanical ventilation with PEEP increases sympathetic tone resulting in increased plasma renin activity, hence decreasing GFR by reducing blood flow. Mechanical ventilation also has a transient effect on aortic blood pressure, which by reflex activates the sympathetic nervous system through aortic and (sino)carotid baroreceptors and, more slowly, affects intravascular volume by changing renal
function. Whether the effect of atrial stretch receptors on renal vascular tone also alters
renal function during mechanical ventilation remains to be evaluated.
Mechanical Ventilation and Biotrauma.

Two independent pathways of the biotrauma hypothesis are distinguished: a) Ventilation may cause release of mediators in the lung and into the systemic circulation; and b) these mediators have biological actions. Most research has focused on the first part of the hypothesis, and it has become clear that the release of inflammatory mediators during mechanical ventilation depends on the underlying lung disease and on the ventilatory strategy. The second part of this hypothesis has only recently begun to be addressed.

Biotrauma and ARF.

There are only a few studies addressing the role of biotrauma in ARF. Gurkan and colleagues, comparing different ventilation strategies in an acid-induced lung inflammation rat model, demonstrated histologic lung damage and increased levels of pulmonary, hepatic, and renal interleukin (IL)-6 levels after mechanical ventilation with high tidal volumes. However, both renal function and blood IL-6 levels were not studied. Using an in vivo animal model of acid aspiration, Imai et al. demonstrated that an injurious ventilatory strategy increased epithelial cell apoptosis in the kidney and led to increased levels of biochemical markers indicating renal dysfunction. They performed an in vitro study suggesting that soluble Fas ligand (sFasL) was an important mediator causing apoptosis in their study, and using samples from patients with acute respiratory distress syndrome, they also demonstrated a significant correlation between changes in sFasL and changes in creatinine, supporting the hypothesis that mechanical ventilation-induced lung injury may lead to renal dysfunction via a sFasL-mediated mechanism. 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 hrs in patients with acute respiratory distress syndrome, whereas the inflammatory response was attenuated by a lung-protective strategy. The latter group had significantly lower concentrations of a number of cytokines (tumor necrosis factor [TNF]-α, IL-1β, IL-6, IL-8, soluble TNF receptors, IL-1 receptor-antagonist) in plasma and bronchoalveolar lavage fluid at 36 hrs. A post hoc analysis revealed that an increase in IL-6 plasma concentrations correlated with the development of acute renal failure. Recently, Simmons et al. found significant correlations between increased pro- and anti-inflammatory cytokine levels, including IL-1β, IL-6, IL-8, IL-10, and TNF-α, and mortality in patients with ARF compared with healthy controls and patients with end-stage renal disease. In the aforementioned studies, several issues need to 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. However, these mediators may also be produced locally in the kidneys as a result of a compromised RBF and exert their effect directly in the

**Table 1.** The potential effects on ARF of several systemically expressed mediators which have been shown to be increased during mechanical ventilation in animal and human studies.

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Potential effects contributing to ARF</th>
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<tbody>
<tr>
<td>IL-1β (123)</td>
<td>Upregulation of FAS on renal cells (116), stimulation of production TNF-α, IL-6, IL-8 and PAF. Glomerular and tubulointerstitial neutrophil sequestration, upregulation of leukocyte adhesion molecules. Alterations in vascular tone, mediated by (released) prostaglandins, PAF, endothelin, NO and adenosine, additionally resulting in decreased filtration fraction (118, 119). Procoagulant activity, inhibition of neutrophil apoptosis and chemotaxis of macrophages (120).</td>
</tr>
<tr>
<td>IL-6 (105, 124, 125)</td>
<td>Central role in mediating effects of IL-1β and TNF-α (120), stimulation of tubular regeneration (126).</td>
</tr>
<tr>
<td>IL-8 (MIP-2) (104, 105, 127, 128)</td>
<td>Chemotraction of neutrophils, promotion of leukocyte adhesion, contribution to glomerular neutrophil sequestration (118).</td>
</tr>
<tr>
<td>IL-10 (125)</td>
<td>Down-regulation of the synthesis of proinflammatory mediators like TNF-α, IL-1, IL-8, nitric oxide, reactive oxygen species by monocytes or macrophages (113, 129-131).</td>
</tr>
<tr>
<td>TNF-α (105, 121, 124, 125, 127, 132, 133)</td>
<td>Upregulation of FAS on renal cells (116), stimulation of production TNF-α, IL-6 and IL-8 (119). Glomerular and tubulointerstitial neutrophil sequestration, upregulation of leukocyte adhesion molecules. Alterations in vascular tone, mediated by (released) prostaglandines, PAF, endothelin, NO and adenosine, additionally resulting in decreased filtration fraction (118).</td>
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<tr>
<td>FasL (104)</td>
<td>The FasL-Fas system induces glomerular cell apoptosis in-vivo associated with decreased number of mesangial cells, proteinuria, and hematuria in the absence of glomerular inflammation. Tubular epithelial cells were protected from apoptosis. Renal injury may also be limited by activation of Fas through limiting of injurious immunological responses (116).</td>
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<tr>
<td>Soluble IL-1RA (105, 125)</td>
<td>Antagonization of IL-1, potentially protective (134).</td>
</tr>
<tr>
<td>Soluble TNF receptors (105)</td>
<td>Binding to and inactivating the biological activity of TNF-α, potentially protective (134).</td>
</tr>
<tr>
<td>MCP-1 (104)</td>
<td>Promotion of apoptosis of renal tubular cells and renal dysfunction (115). Amplification mechanism in the context of acute renal failure, attraction and activation of neutrophils during renal inflammation (135). Association with renal dysfunction, hypotension and increased mortality in rabbits (136).</td>
</tr>
<tr>
<td>GRO (104)</td>
<td>Enhancing endothelial survival (138), suppression of thrombosis (139), exertion of anti-inflammatory effects (140) and induction of synthesis of vasodilating agents (141, 142). Likely involved in vascular protection.</td>
</tr>
<tr>
<td>VEGF (137)</td>
<td>Enhancing endothelial survival (138), suppression of thrombosis (139), exertion of anti-inflammatory effects (140) and induction of synthesis of vasodilating agents (141, 142). Likely involved in vascular protection.</td>
</tr>
</tbody>
</table>

IL = interleukin, TNF = tumor necrosis factor, MIP = macrophage inflammatory protein, PAF = platelet activating factor, NO = nitric oxide, MCP = monocyte chemotactic protein, GRO = growth-regulated oncogene, VEGF = vascular endothelial growth factor

Second, it is important to prove that there is a cause and effect relationship between mediators and renal dysfunction, rather than simply an association. A number of mediators have been reported to increase in the systemic circulation during mechanical ventilation and may potentially contribution to ARF (Table 1). The simultaneous
detection of both proinflammatory (severe inflammatory response syndrome) and anti-inflammatory (counter anti-inflammatory response syndrome) mediators may reflect altered regulation of the inflammatory response. A persistent activation of the inflammatory response is associated with organ failure.\textsuperscript{114} Inflammatory mediators may affect renal function through several mechanisms, some of which may be synergistic. Suggested mechanisms include a direct effect on RBF through the release of several vasoactive mediators or through induction of a local renal inflammatory response. sFasL is known to induce apoptosis of glomerular cells, whereas monocyte chemotactic protein promotes macrophage-mediated tubular injury.\textsuperscript{115,116} IL-1β, IL-6, and TNF-α may facilitate this process by activating platelet-activating factor and inducing an inflammatory reaction, both contributing to the apoptotic effects of sFasL (Table 1).\textsuperscript{116-120} A combination of the aforementioned processes may also be involved. By compromising RBF, a critical threshold may be reached and inflammatory mediators may exert a direct effect on renal cells, thereby inducing or contributing to ARF.

**Conclusions and Hypothesis**

Mechanical ventilation of healthy lungs in normovolemic patients most likely does not exert any major effects on renal function. If there is any mild inflammatory reaction, it would remain compartmentalized to the lungs.\textsuperscript{121,122} Under these circumstances, an effect on the renal microcirculation cannot be excluded but this has not been studied.

The harmful effects of mechanical ventilation become more significant when comorbidities are present. In the presence of acute lung injury, it is more difficult to maintain normal gas exchange, and moderate arterial hypoxemia or hypercapnia is often accepted. RBF is further compromised due to a decreased cardiac output as a consequence of 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 further compromised. This series of events may reflect a multifactorial process (summarized in Fig. 1) that eventually may result in the development of ARF.
Despite difficulties in differentiating between the effects of mechanical ventilation per se and the underlying disease on renal function, review of the current literature suggests that mechanical ventilation itself may play a pivotal role in the pathogenesis of ARF in mechanically ventilated patients.
Although some of these mechanisms have been studied for decades, the mechanisms at the cellular and molecular levels have only recently been addressed. The precise mechanisms described require further study to delineate more precisely the contribution of each proposed factor and their interrelationships and to suggest novel therapeutic approaches to prevent and treat ARF in critically ill patients.\textsuperscript{123-142}

**Acknowledgments**

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References


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