RENAL EFFECTS OF CRITICAL ILLNESS

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INTRODUCTION

Acute renal failure (ARF) is broadly defined as deterioration of renal function over days to weeks, a common occurrence in intensive care unit (ICU) patients; incidence and mortality estimates vary according to ARF definition and associated morbidities.\(^1\) The mortality of ARF is 50–80% in ICU populations, and has not declined significantly since the initial marked benefit of acute dialysis therapy, despite numerous advances in renal replacement technologies and critical care over several decades.\(^4\) Although multiple system organ failure (MSOF) and other comorbidities contribute to its high mortality rate, ARF independently increases morbidity and mortality.\(^5\) The mechanisms by which ARF contributes to nonrenal organ dysfunction and death are incompletely understood. Emerging data suggest that isolated renal ischemia–reperfusion injury causes injury and dysfunction of distant organs in experimental ARF.\(^5\) Apart from obviously lethal ARF sequelae such as severe hyperkalemia, the identities and precise effects of ‘uremic’ toxins have not been identified, particularly in ARF. Accordingly, it is likely that renal replacement therapy in its current form is only a partial solution to the multisystem problems caused by ARF.

Prevention or early diagnosis and amelioration of ARF are clearly the preferred approaches to diminishing the contribution of renal dysfunction to adverse outcomes in critically ill patients. Most ARF in ICU patients is caused by either prerenal azotemia (reversible renal insufficiency due to renal hypoperfusion) or acute tubular necrosis (ATN). ATN results from a variety of ischemic and nephrotoxic insults, often in additive or synergistic combination.\(^12\) Multiple causes of renal hypoperfusion and injury are commonplace in the ICU, including systemic hypoperfusion (shock), the effects of mechanical ventilation,\(^13\) renal vasoconstriction in patients with cirrhosis and sepsis,\(^14,15\) increased intra-abdominal pressure,\(^16\) and a variety of nephrotoxins (endogenous and exogenous). Because renal hypoperfusion plays a role in the pathogenesis of prerenal azotemia and ATN, and shock is common in critically ill patients who develop ARF, much attention is paid to optimization of renal perfusion, attempting to prevent or ameliorate ARF in the ICU. This chapter reviews the effects of critical illness on renal perfusion and function, and the impact of renal insufficiency on outcome in the ICU.

RENAI L PERFUSION AND FUNCTION

The kidneys perform a variety of homeostatic functions, including regulation of fluid and electrolyte balance and tonicity, excretion of endogenous and exogenous wastes and toxins, and several endocrine functions such as the synthesis of erythropoietin (EPO) and renin and the activation of vitamin D. Much of the homeostatic and detoxification work of the kidneys is done through high-volume hemofiltration and selective filtrate reabsorption or modification. The best global index of renal function is the glomerular filtration rate (GFR), which is normally in the range of 100–125 ml/min. Of the 150–180 L filtered daily, only a small fraction (≤1%, 1.5–1.8 L) typically appears as urine output (UOP). This is consistent with the concept that, beyond filtration, the major renal homeostatic function is the selective mass reabsorption of filtered fluid and electrolytes, apart from toxic nitrogenous wastes. Urine volume is
determined by the requirement to excrete daily obligate solute load (electrolytes and nitrogenous wastes) in appropriately concentrated urine. Assuming maximal urine-concentrating ability (1400 mOsm/kg), the minimum daily urine output required to excrete the average daily solute load is 400 ml, below which positive solute balance and azotemia develop, thus the standard definition of oliguria (<400 ml/24 h). In terms of monitoring urine output, if urine is maximally concentrated (1.4 mOsm/ml), and excretion of 10 mOsm/kg/day (700 mOsm/day in a 70-kg person) is required to avoid solute retention, this mandates urine output of 500 ml daily (21 ml/h or 0.3 ml/kg/h). Of course, if solute appearance increases (patient size, hypercatabolism, hyperalimentation) or maximal urinary concentrating ability is diminished (renal dysfunction, age), higher urine volumes are required to maintain adequate solute excretion. Since such conditions are more the rule than the exception, it seems more appropriate to expect solute retention at urine outputs below the more typical ICU monitoring target of 0.5-1.0 ml/kg/h (840-1680 ml/day). Of course, urine output targets must be sufficient to control fluid balance as well as solute excretion, so higher UOP values may be required for patients with large obligate fluid intakes. In a large study of 13,152 ICU patients, Le Gall and colleagues found that mortality increased with urine output below 750 ml/24 h, or above 10 L/day.17 The cause–effect relationship between oliguria and adverse outcome, and the relative importance of solute retention vs fluid overload are unknown, but it seems clear that the higher minimum urine output target used in critically ill patients is justified. Of course, urine output must be assessed in context, relative to fluid intake, extrarenal fluid loss, diuretic use, systemic hemodynamic parameters, and overall fluid balance. Nonetheless, it is probably appropriate to use graded levels of oliguria, along with markers of GFR, to define the presence and severity of acute renal dysfunction. This approach underlies the recently proposed RIFLE criteria (risk, injury, failure, loss, end-stage) suggested for ARF definition by the ADQI group3 (Fig. 4.1).

The kidneys normally receive 20–25% of cardiac output (CO), although their combined weight is less than 1% of total body weight, resulting in the highest tissue perfusion in the body. Basal renal oxygen consumption is 400 μmol/min/100 g of kidney, but this high value results in an arteriovenous oxygen content difference of only 1.7 vol%.18 The vast majority of renal oxygen consumption is utilized to support tubular sodium reabsorption. As illustrated in Figure 4.2,18 the kidneys are unique in having physiologic supply-dependent oxygen consumption. Decreasing renal oxygen delivery results in decreased oxygen consumption throughout a wide range,19 because diminished GFR and sodium filtration requires proportionately less tubular oxygen consumption for reabsorptive work, and arteriovenous O2 content difference is unchanged down to a renal blood

Figure 4.1 RIFLE classification system for acute renal failure. A new graded classification system has been proposed to ‘stage’ acute renal dysfunction, proposed by the Acute Dialysis Quality Initiative (ADQI) consensus group, incorporating levels of oliguria in addition to fractional serum creatinine elevation. The more severe of the GFR or UOP criteria is selected to determine ARF severity. a Serum creatinine increments must be abrupt (within 1–7 days) and sustained (>24 h). b Persistent ARF = 1–3 months of renal replacement therapy (RRT). ESRD = >3 months or more of RRT. (Reproduced with permission from Kellum et al.)
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**Figure 4.2** Renal oxygen consumption. Decreasing renal oxygen delivery results in decreased oxygen consumption throughout a wide range, because diminished glomerular filtration rate (GFR) and sodium filtration requires proportionately less tubular oxygen consumption for reabsorptive work. As renal blood flow is progressively decreased, renal oxygen consumption follows a triphasic pattern: Stage 1: renal oxygen consumption is decreased and arteriovenous (a–v) O₂ content difference is unchanged down to a renal blood flow of 150 ml/min/100 g of tissue. Stage 2: as renal blood flow and oxygen delivery decrease further below 150 ml/min/100 g, GFR ceases but the minimum threshold for supporting parenchymal oxygen consumption and viability is reached, oxygen extraction increases, and a–v content difference widens. Stage 3: Finally, as maximal oxygen extraction is exceeded (below a renal blood flow of 75 ml/min/100 g of kidney tissue), anaerobic metabolism, ATP depletion, and ischemic tubular injury ensue. This phenomenon of physiologic supply dependence of renal oxygen consumption throughout a wide range of oxygen delivery underlies the distinct difference in renal tolerance of ischemic insults; renal artery cross-clamp is better tolerated than insults of similar duration in the cerebral, coronary, or mesenteric circulations, but profound renal ischemia does cause ischemic injury.

Renal blood flow (RBF) is approximately 1.1 L/min (20–25% of CO), providing renal plasma flow (RPF) of 605 ml/min (assuming hematocrit of 45%). There are three main determinants of RBF:

1. cardiac output (CO)
2. renal perfusion pressure (RPP)
3. renovascular resistance (RVR), which is primarily regulated by glomerular hemodynamic factors (afferent and efferent arteriolar tone).

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RBF = \frac{RPP}{RVR}
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RPP is the difference between renal arterial (inflow) and venous (outflow) pressures. Outflow pressure is negligible under normal circumstances, but may be increased by venous return impedance from extremely raised intrathoracic pressure (mechanical ventilation, discussed below) or intra-abdominal pressure (see discussion of abdominal compartment syndrome in Ch. 5). Thus, RPP is proportional to mean arterial pressure (MAP) for practical purposes. The primary site of renovascular resistance is the afferent arteriole (Fig. 4.3). Afferent arteriolar resistance is modulated by several influences, both intrinsic (autoregulation) and extrinsic (neurogenic, paracrine, endocrine). Autoregulation maintains RBF (and GFR) over a wide range of MAP levels by modulation of afferent arteriolar resistance. RBF increases by only 10% when MAP increases by 50% from 100 to 150 mmHg (Fig. 4.4). This regulatory process is achieved by modulation of afferent arteriolar tone by two influences: a local myogenic reflex in the afferent arteriolar wall (increased stretch causes reflex vasoconstriction) and a process called tubuloglomerular feedback (TGF) (Figs 4.5 and 4.6). The TGF mechanism functions as follows: the macula

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Concepts related to renal function, oxygen consumption, and regulation include:

- Glomerular filtration rate (GFR)
- Renal perfusion pressure (RPP)
- Renal vascular resistance (RVR)
- Cardiac output (CO)
- Oxygen consumption
- Tubuloglomerular feedback (TGF)
- Renal plasma flow (RPF)
- Mean arterial pressure (MAP)
- Myogenic reflex
- Afferent arteriolar tone

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Flow of 150 ml/min/100 g of tissue. This contrasts with other organs (notably myocardium, brain, and intestine) in which progressively increased O₂ extraction is required to maintain basal O₂ consumption and aerobic metabolism when delivery decreases. For example, the myocardium has the highest O₂ consumption in the body, associated with a much higher basal arteriovenous oxygen content difference of 11 vol%, so that decreased coronary flow rapidly leads to anaerobic metabolism. In contrast, as renal blood flow and oxygen delivery decrease further below 150 ml/min/100 g, GFR ceases but the minimum threshold for supporting parenchymal oxygen consumption and viability is reached, oxygen extraction increases, and arteriovenous O₂ content difference widens.
Figure 4.3 Renovascular resistance sites. The hydrostatic pressure profile in the canine renovascular tree is shown. The bulk of renovascular resistance occurs at the afferent and efferent arterioles. (Reproduced with permission from Valtin H, Schafer JA: Renal function. Mechanisms preserving fluid and solute balance in health. Little, Brown and Company, Boston, 3rd edn, 1995. In: Chapter 6: Renal hemodynamics and oxygen consumption (figure 6–1, page 97); adapted from another chapter.)

densa is a chloride-sensing nephron segment distal to the thick ascending limb of the loop of Henle (TALH); increased chloride delivery past the TALH results in afferent arteriolar vasoconstriction due to TGF, which normally serves to defend intravascular volume, by limiting GFR when salt excretion is excessive (see Fig. 4.6). Conversely, when renal perfusion, GFR, and tubular chloride concentration decrease, TGF and afferent tone are down-regulated. However, these mechanisms act to maintain RBF only in the range of 80–90 mmHg, and autoregulation fails precipitously at MAP levels below 80 mmHg. RBF and GFR decrease linearly below 70–80 mmHg, and RBF ceases at a RIP of 30 mmHg (the critical closing pressure of the renal circulation; see Fig. 4.4).

Of course, GFR is not solely determined by renal plasma flow. The renal circulation is unique in featuring postcapillary (efferent) in addition to pre-capillary (afferent) arterioles. The efferent arteriole is the second major site in the renal circulation which determines renovascular resistance (see Fig. 4.3). The rate at which a portion of RPF traverses the filtration apparatus (GFR) is determined by the balance of hemodynamic (Starling) forces in the glomerular capillary (GC). Since the hydrostatic and oncotic pressures in Bowman’s space are ordinarily negligible, the net filtration pressure (NFP) driving the GFR is the balance of intracapillary hydrostatic and oncotic pressures (Fig. 4.7). Early in the GC, hydrostatic pressure dominates and NFP and GFR are maximal. NFP progressively diminishes as hydrostatic pressure falls and oncotic pressure increases (by hemoconcentration), resulting in cessation of filtrate formation before blood enters the efferent arteriole (Fig. 4.8). The fraction of renal plasma flow which is filtered is called the filtration fraction (FF):

$$FF (%) = \frac{\text{GFR (ml/min)}}{\text{RPF (ml/min)}}$$

FF is normally approximately ≤20% (GFR 125 ml/min ÷ RPF 605 ml/min), determined by the balance of afferent and efferent arteriolar resistance (Fig. 4.9). Both afferent and efferent tone are increased by catecholamines, and back pressure from efferent resistance partly offsets decreased GC

Figure 4.4 Autoregulation of renal blood flow (RBF). Autoregulation maintains RBF, and glomerular filtration rate (GFR), over a wide range of mean arterial pressure (MAP) levels by modulation of afferent arteriolar resistance. RBF increases by only 10% when MAP increases by 50% from 100 to 150 mmHg, but decreases precipitously when MAP falls below 70–80 mmHg. (Reproduced with permission from Vander AJ: Renal physiology, 5th Edn, McGraw-Hill, New York, 1995. In: Chapter 2: Renal blood flow and glomerular filtration (figure 2–4, page 34).)
Figure 4.5 The juxtaglomerular apparatus (JGA) and tubuloglomerular feedback (TGF). The JGA consists of three components: (1) the granular cells (JG), which secrete renin; (2) the macula densa; and (3) the extraglomerular mesangial cells (EGM). (A) The effect of increasing salt (NaCl) delivery to the distal nephron (macula densa) increases levels of adenosine in the JGA interstitium, causing adenosine 1 receptor (A1AR)-mediated constriction of the afferent arteriolar smooth muscle cells. (B) The effect of decreasing salt delivery to the macula densa increases vasodilatory PGE₂ (made by cyclooxygenase-2, COX-2) in the JGA, along with renin release from granular cells (stimulated by PGE₂ receptor subtype EP4), resulting in vasodilation. (Reproduced with permission from Schnermann J.²¹)

hydrostatic pressure due to catecholamine-induced afferent constriction, helping to augment FF and preserve GFR. In contrast, angiotensin II preferentially constricts the efferent arteriole, markedly increasing filtration fraction; this occurs because the efferent arteriole has only vasoconstrictor AT₁ receptors, and lacks the AT₂ receptors which release vasodilatory nitric oxide (NO) and partly reverse angiotensin II-induced constriction in the afferent arteriole.²⁶ Various combinations of altered afferent and efferent arteriolar tone can change RBF and GFR, sometimes in opposite directions (see Fig. 4.9).
It is important to understand the renal hemodynamic responses to shock. In response to hypotension, baroreceptor stimulation increases sympathetic outflow. Sympathetic outflow also indirectly activates the renin–angiotensin–aldosterone axis, through beta-adrenoceptor-stimulated renin release from the juxtaglomerular apparatus (JGA) in the afferent arteriolar wall (see Fig. 4.5). Renin release from the JGA is also stimulated locally by decreased afferent arteriolar stretch, and by autoregulation-dependent stimulation from the macula densa, sensing decreased distal salt delivery. Together, these influences augment filtration fraction, which tends to preserve GFR relative to decreased renal blood flow. In this setting, the combination of diminished RBF (inflow) and increased filtration fraction (outflow) results in concentration of unfilterable plasma proteins and increases glomerular capillary oncotic pressure; thus, NFP falls and glomerular filtration ceases earlier in the GC. The blood which traverses the efferent arteriole and peritubular capillaries...
has a higher oncotic pressure, increasing resorption of sodium and water in the proximal tubule, a phenomenon called **glomerulotubular balance** (Fig. 4.10). In the setting of systemic hypoperfusion, the pressor effects of catecholamines and angiotensin II also act to preserve systemic and renal perfusion pressure, and the same hormones promote sodium reabsorption throughout the nephron (angiotensin II both directly and via aldosterone). In addition, renal blood flow distribution is shifted from the superficial to the juxtamedullary nephrons, further facilitating salt retention (see below). In severe hypotension, nonosmotic vasopressin release has both pressor and fluid (water)-retaining effects. Thus, the renal effects of the systemic pressor response to hypotension and hypoperfusion act to preserve GFR (by augmenting filtration fraction), and maximize salt and water retention to maintain intravascular volume. All of these systemic and renal responses are of course highly appropriate in response to a classic cause of shock and prerenal azotemia such as major hemorrhage, but increased systemic vascular resistance (SVR) and salt retention are maladaptive in congestive heart failure (CHF). The renal vasoconstrictor and salt-retaining effects of catecholamines and the renin–angiotensin–aldosterone axis are antagonized by activation of a variety of vasodilators (atrial natriuretic peptide [ANP], kinins, prostaglandins) and natriuretic substances (prostaglandins, ANP). Stimulation of afferent arteriolar release of vasodilator prostaglandins by catecholamines and angiotensin II partially offsets renal vasoconstriction in shock: thus, the adverse renal hemodynamic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with systemic hypoperfusion and renal vasoconstriction. ANP is released in response to atrial stretch, and helps relieve the maladaptive salt retention and increased afterload caused by the other active hormonal systems in CHF.

There is a further level of sophistication in the design of the renal circulation which underlies the remarkable fluid-retaining capacity of the kidney. Solute and water retention are favored by the unique design of the intrarenal circulation. The

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**Figure 4.9** Effects of afferent- and efferent-arteriolar constriction on glomerular capillary hydraulic pressure ($P_{GC}$) and renal blood flow (RBF). RBF is altered additively by changes in total renal arteriolar (afferent and efferent) resistance, irrespective of site. Constriction of either the afferent (B) or efferent (C) arterioles decreases RBF, with additive effects of constricting both together (D). Glomerular capillary hydrostatic pressure ($P_{GC}$) and glomerular filtration rate (GFR) are differentially affected by increases in afferent tone (B, decreases $P_{GC}$ and GFR) vs efferent tone (C, increases $P_{GC}$ and GFR). Simultaneous constriction of afferent and efferent arterioles tends to decrease RBF, $P_{GC}$, and GFR, but efferent constriction helps maintain $P_{GC}$ and GFR in this setting (D), by increasing filtration fraction. (Reproduced with permission from Vander AJ: Renal physiology, 5th edn. McGraw-Hill, New York, 1995. In: Chapter 2: Renal blood flow and glomerular filtration (Figure 2-3, page 32).)
Figure 4.10 Glomerulotubular balance. Glomerulotubular balance is maintained by changes in filtration fraction (FF) and resulting Starling forces in the proximal tubules and peritubular capillaries. If glomerular filtration rate (GFR) increases without a change in renal plasma flow (RPF) (Step 1) (e.g., afferent dilation with efferent constriction), then FF increases and more plasma water is filtered. This hemoconcentrates plasma proteins in the peritubular capillaries, raising plasma oncotic pressure (πc), while hydrostatic pressure in the peritubular capillaries (Pc) is falling (due to efferent constriction) (Step 2). These changes in peritubular capillary Starling forces favor increased reabsorption of sodium and water in the proximal tubule (Step 3). Thus, although an unchanged fraction (approximately two-thirds) of the glomerular filtrate continues to be reabsorbed, the amount reabsorbed is greater, in proportion to the increase in GFR and FF. (Reproduced with permission from Valtin H, Schafer JA: Renal function. Mechanisms preserving fluid and solute balance in health. Little, Brown and Company, Boston, 3rd edn. 1995. In: Chapter 6: Renal hemodynamics and oxygen consumption (figure 7–10, page 141).

The majority of nephrons are cortical (90%), but 10% are located deeper in the juxtamedullary region. Juxtamedullary nephrons have a different efferent circulation than their superficial counterparts. Specifically, in cortical nephrons the efferent arteriole branches into a peritubular capillary network, which subsequently forms the renal venous system. In contrast, juxtamedullary efferent arterioles form long hairpin vessels called the vasa recta, which penetrate deep into the medulla and supply the thick ascending loops and distal proximal tubules of the deep nephrons (Fig. 4.11). The hairpin nature of the vasa recta is important to maintain the medullary solute concentration gradient, which permits maximal urinary concentration. However, the combination of major tubular oxygen consumption and countercurrent exchange of oxygen between vasa recta limbs makes the deep medulla a very hypoxic environment under normal circumstances. Although renal oxygen consumption is driven largely by reabsorption of filtered sodium, as discussed above, the relationship between oxygen delivery and consumption described above is not homogeneous throughout the kidneys. Although the kidneys are the most perfused organs in the body, this statement applies only to the cortex, not the medulla. The medulla receives only 6% of total renal blood flow (0.3 ml/min/g vs 5 ml/min/g to the cortex), and exists in a baseline hypoxic state (pO₂ 10 mmHg vs 50 mmHg in cortex), despite containing two sites where a large proportion of tubular work and oxygen consumption occurs (the “S₃” distal segment of the proximal tubule, and the TALH) (Fig. 4.12). It is not surprising that medullary hypoperfusion will predominate injury of the TALH and S3 segment among the recognized models of ischemic ATN.

**RENALEFFECTSOFSHOCKANDVASOACTIVE DRUGS**

It is obvious that many cases of ARF in the ICU are caused by prerenal azotemia, which is decrease GFR resulting from diminished renal perfusion often associated with shock. Prerenal azotemia
marked by decreased renal blood flow, renal vasoconstriction, increased filtration fraction, and avid salt and water reabsorption, through the mechanisms described above. In patients with prerenal azotemia, complete reversal of shock can normalize renal perfusion and function. Persistent systemic and/or renal hypoperfusion with unreversed prerenal azotemia may result in ischemic renal injury and ATN. It is unclear to what extent ATN is caused by ischemic injury in critically ill patients, an assumption which underlies most of the therapeutic approaches to the prevention or therapy of ARF over the past several decades. Systemic hypotension with shock is certainly a common precursor of ATN in humans, prerenal azotemia often precedes ATN, and decreased renal perfusion (renal vascular crossclamp, high-dose norepinephrine infusion) is a recognized model of renal injury in animals. Nonetheless, decreased renal perfusion has not been documented to be of etiologic significance in the development of ATN in critically ill humans, apart from some clearcut insults such as surgical aortic crossclamp before ICU transfer. However, although other documented etiologic factors such as circulating nephrotoxins (drugs, pigments, cytokines), acidosis, and hypoxemia coexist in this population, it seems likely that ischemic (± reperfusion) injury plays an important role in the pathogenesis of much ATN in the ICU. Furthermore, since the vasoactive therapies which are used in the hemodynamic management of ICU patients may also alter renal blood flow, optimization of renal perfusion and function is a major endpoint in resuscitation. Taken together, available data suggest that optimization of renal perfusion is an important cornerstone of attempts to prevent and treat ARF in the ICU.
Although improving renal perfusion may reverse prerenal ARF (by definition), and diminish ischemic contributions to the pathogenesis of ATN, it is quite conceivable that in many cases ATN develops despite appropriate resuscitation and adequate renal perfusion. Zager and colleagues have shown in an endotoxemic rat model of septic ARF that paired combinations of insults (renal crossclamp, systemic endotoxin, aminoglycoside, temperature elevation) cause azotemia and renal pathologic findings of ATN, but these insults individually cause no renal dysfunction or injury.\textsuperscript{12} We suspect that this synergistic injury model accurately reflects the pathogenesis of much ARF in the ICU. Other experimental data have shown that endotoxin, tumor necrosis factor, and numerous other inflammatory mediators are directly cytotoxic to renal endothelial and tubular cells.\textsuperscript{14,31-33} Although ARF may be prevented or ameliorated by judicious use and monitoring of nephrotoxic drugs, and perhaps evolving cytoprotective and anti-inflammatory therapies, the major focus in ARF prophylaxis and therapy remains optimization of renal perfusion. The primary causes of renal hypoperfusion differ between the major types of shock, and therapies vary accordingly.

**Renal effects of 'low-flow' shock (low CO states)**

Decreased CO due to hypovolemia or cardiac dysfunction diminishes renal perfusion both directly and indirectly. Decreased CO not only directly lowers RBF (via inadequate CO, RPP, or both) but also activates a number of renal vasoconstrictor systems which increase RVR. Baroreceptor stimulation resulting from decreased CO activates neurohumoral responses (sympathetic nervous system, renin-angiotensin system, and vasopressin secretion) that have opposing effects on renal perfusion, tending to augment RPP but also cause renal vasoconstriction. Any intervention restoring CO and systemic perfusion therefore augments renal perfusion by reversing the aforementioned influences. Volume loading to prevent hypovolemia is probably the most effective preventive measure to avoid prerenal azotemia as well as ischemic and nephrotoxic ATN. As discussed elsewhere in this book, there are a variety of tools to guide fluid and vasoactive drug management in the ICU. It is important not to administer excessive fluid to avoid complications such as pulmonary edema, intra-abdominal hypertension.
and poor wound healing with subcutaneous edema. It remains unresolved whether crystalloids or colloids are the preferred fluids to use to maintain adequate preload and renal function in hypovolemic shock.

The choice among available inotropes or vasodilators to improve renal function in patients with renal hypoperfusion secondary to CHF is similarly unclear. It is clear that the use of inotropes to achieve supranormal cardiac output and oxygen delivery does not improve renal function in critically ill patients. and of course fails to improve or increase mortality. Gattinoni and colleagues studied 762 ICU patients and found no difference in mortality or renal function (creatinine, urine output) with either supranormal CO/oxygen delivery or maintenance of mixed venous oxygen saturation (SvO₂) ≥70% with dobutamine vs control management. Hayes and colleagues found (in 100 ICU patients) that supranormal oxygen delivery (dobutamine) vs control resulted in increased mortality (54% vs 34%), and this approach has fallen out of favor in the management of critically ill patients. However, as discussed in Chapters 1 and 5, there is a growing interest in early goal-directed therapy of septic shock, including the use of transfusion and inotropes to optimize oxygen delivery. It is unknown if this approach will reduce the incidence of ARF.

The commonsense approach of using fluids and vasoactive drugs to achieve an adequate cardiac output, based on assessment of available hemodynamic and tissue perfusion markers (cardiac filling pressures, thermodilution or other cardiac output measurements, venous oxygen saturation), remains the primary approach to the prevention and reversal of ARF due to prerenal azotemia. However, restoration and maintenance of adequate intravascular volume and CO does not guarantee adequate renal perfusion. Renal blood flow is only optimized when CO is adequate and renal perfusion pressure is sufficient to distribute an appropriate proportion of systemic oxygen delivery to the kidneys. This requires a renal perfusion pressure above the lower autoregulatory threshold. It is particularly important to balance these factors when systemic vasodilators are used for afterload reduction to augment CO in CHF; excessive vasodilation may lower MAP and RPP below the renal autoregulatory threshold and negate some of the potential benefit of increased CO. Conversely, the use of vasopressors to support perfusion pressure in patients with vasodilatory shock may adversely affect tissue perfusion by creating excessive cardiac ‘afterload’ in the presence of significant myocardial dysfunction (pre-existing or acquired), in addition to any potential adverse effects on regional blood flow distribution (see below).

Renal effects of ‘high-flow’ (vasodilatory) shock

Although not generally regarded as a controversial critical care issue to the same degree as oxygen delivery strategies, the appropriate MAP and RPP target for titration of hemodynamic support is another area of clinical uncertainty. Importantly, the logic for defending renal perfusion pressure with vasoactive agents presumes both pressure-dependent renal flow and flow-dependent renal function. Standard recommendations have traditionally suggested that fluids and vasoactive drugs should be titrated to maintain an MAP ≥60 mmHg, In the recent trial of goal-directed therapy in early septic shock, the target MAP range of 65–90 mmHg was (along with other parameters) associated with improved outcome, but renal function was not a reported endpoint in this study. Although generally accepted as the target MAP in shock resuscitation and perioperative management, 60–65 mmHg is on the steep portion of the renal autoregulation curve (see Fig. 4.4), and is associated with a precipitous decrement in RBF and GFR from normal, in dogs and healthy human subjects.

The data demonstrating that 80 mmHg is the lower autoregulatory threshold in the renal circulation are primarily derived from animal studies. Limited human data are consistent with prior experimental findings in animals, but definitive data from healthy humans are lacking. Stone and Stahl demonstrated that hemorrhage in healthy humans, which decreased MAP from 80 to 67 mmHg, was associated with a 20% decrement of RBF and a 30% fall in GFR; this study did not control for the contributory effects of decreased blood volume and CO on renal perfusion, however. It is certainly true that autoregulation extends predominantly over a high range of MAP (80–180 mmHg), impeding hypertensive renal injury, rather than truly protecting against decrements in RPP, RBF, and GFR. In patients with chronic hypertension, in whom the curve is right-shifted, this problem is probably exacerbated, but current recommendations for hemodynamic management do
not account for this potential issue. In contrast, young healthy patients commonly have low normal baseline MAP and RPP values which are associated with shock and renal hypoperfusion in others. Apart from hypertension, other comorbidities, drugs, and other therapies may impair autoregulation. For example, experimental data suggest that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers may specifically impair autoregulation of GFR (but not renal blood flow) by blunting efferent arteriolar tone (Fig. 4.13). In addition, it appears that RBF autoregulation is impaired by conditions such as sepsis and cardiopulmonary bypass (CPB). Furthermore, if renal injury does result in ATN, experimental data suggest that autoregulation is lost, and that RBF becomes linearly pressure-dependent, resulting in recurrent ARF with subsequent hypotension. Limited human biopsy data support the hypothesis that fresh ATN lesions develop with subsequent hypotension and hypoperfusion insults in humans with ATN. Thus, maintenance of adequate MAP is important not only for prevention of renal injury/ATN but also its supportive management, in which maintenance of adequate RPP may become even more critical than in the presence of uncomplicated prerenal azotemia.

There are some precise experimental data examining the role of perfusion pressure in the pathogenesis of renal dysfunction in CPB patients. Animal studies support the concept that RBF during CPB is dependent on renal perfusion pressure, suggesting loss of autoregulation, but pressor-induced increased MAP does not augment renal perfusion if pump flow is low. Similarly, small studies in on-pump CABG (coronary artery bypass graft) patients suggest that increasing MAP by augmenting pump flow or adding a pressor in the presence of normal flow increases renal perfusion, but pressor use is ineffective for this purpose when pump flow is low. There has not been a trial of higher vs lower renal perfusion pressure for the prevention of perioperative ARF in CABG patients at risk, and this was not examined as an endpoint in a trial which showed improved cardiovascular and neurologic outcomes.

Uncertainty regarding the potential adverse renal effects of pressors is greatest in septic shock patients. In septic shock, recent consensus recommendations have suggested adoption of the MAP target from the early goal-directed therapy protocol (≥65 mmHg) for initial resuscitation, with specific guidance for later-phase pressor titration. CO is normal or elevated in the majority of patients with fluid-resuscitated septic shock.

**Figure 4.13** Angiotensin II and autoregulation of glomerular filtration rate (GFR). Reducing perfusion pressure is associated with preserved renal blood flow (RBF) (A) and GFR (B) in control dogs (open squares), until autoregulation falls below 105 mmHg (RBF) or 80 mmHg (GFR). RBF and GFR are expressed as a percentage of control values. In dogs receiving intrarenal infusion of angiotensin II antagonist (closed symbols), baseline RBF is higher (A), and RBF autoregulation is maintained. In control autoregulation of GFR is impaired by intrarenal angiotensin II antagonist (B, closed circles), falling below 105 mmHg. (Reproduced with permission from Hall et al. In Rose BD, Post TW: Clinical physiology of acid-base and electrolyte disorders, 3rd edn. McGraw-Hill, New York, 2001. Chapter 2, page 41, figure 2–8.)
Prerenal azotemia in septic shock is caused by a wide-ranging variety of derangements, including hypovolemia (venodilation, capillary leak), vasoparesis causing refractory hypotension and decreased RPF, and relative myocardial depression (CO and stroke work are less than they should be, suggesting myocardial depression). In addition, occult renal vasoconstriction is a major cause of renal hypoperfusion in septic shock (see below). Clinically, refractory arteriolar vasoparesis with pressor-resistant hypotension dominates management. In many patients, despite adequate preload and ventricular function, refractory hypotension develops with vasodilatory shock. The role of MAP/RPP in the pathogenesis of ARF in the ICU has not been explicitly evaluated in a prospective trial, and experimental data are limited. In experimental sepsis models, it is clear that administration of pressors to animals with inadequate fluid resuscitation is harmful, increasing the incidence of ARF and cardiovascular failure. Treggiari and colleagues showed in volume-resuscitated endotoxemic pigs that administration of pressors to raise MAP from about 50 mmHg to about 60 mmHg resulted in increased cardiac output and renal blood flow. In this study, the use of higher doses to achieve MAP values of about 70 mmHg did not seem to improve renal perfusion, resulting in further increased cardiac output but also increased renovascular resistance and unchanged renal blood flow. This is perhaps surprising in view of the fact that 60–70 mmHg is on the descending limb of the renal autoregulation curve, as discussed above (see Fig. 4.4). In any case, it is unlikely that the threshold MAP to optimize renal perfusion is identical in animals and humans, so these experimental data are of limited relevance. More important is the concept that the use of alpha-adrenergic agonists in the presence of fluid-resuscitated, hyperdynamic, vasodilatory shock with refractory hypotension results in improved renal perfusion, rather than precipitating ARF. This was best shown in elegant studies by Bellomo and colleagues, who clearly demonstrated in canine endotoxemic shock that norepinephrine increased renal blood flow, not only increasing perfusion pressure but also lowering renovascular ohmic resistance and critical closing pressure.

Clinical studies of patients in septic shock suggest that renal function and urine output improve once MAP is increased above 60 mmHg by the use of catecholamine vasopressor therapy. These studies are of poor quality (see recent extensive reviews), however, and were hampered by the lack of a tool to measure blood flow in ICU patients. Of the available techniques to assess renal perfusion, p-aminohippuric acid (PAH) clearance is not a valid method to assess renal plasma flow, because tubular PAH extraction is impaired in critical illness, CPB, postrenal transplantation, and ATN. In fact, it has never been documented whether or not renal autoregulation is intact in animal or human sepsis, and (if so) over what MAP/RPP range. Similarly, the choice of vasopressor is largely a matter of personal preference, without guidance from definitive prospective studies. Specific clinical scenarios and drug characteristics may lead to particular choices (e.g. norepinephrine for dopamine-refractory vasodilatory shock, phenylephrine for vasodilatory shock with arrhythmias on dopamine or norepinephrine). The hypothesis that higher perfusion pressures might prevent or reverse renal dysfunction in resuscitated patients with septic shock is untested by comparative clinical trials. There has only been one randomized trial comparing the effects of catecholamine pressor agents on renal function in septic shock; Martin and colleagues found that the use of norepinephrine was an effective pressor alone, and reversed shock refractory to high-dose dopamine, resulting in increased urine output, but GFR was not measured. Several other descriptive studies have documented improving urine output in patients treated with norepinephrine, but only a few also measured GFR, and none of these included comparison groups. Desjars and colleagues showed that initiation of norepinephrine in 22 of 25 septic shock patients increased MAP (54 to 80 mmHg), UOP (23 ml/h to 66 ml/h), and creatinine clearance (29 ml/min to 71 ml/min) after 24 hours of norepinephrine therapy. Martin and colleagues similarly found that norepinephrine raised MAP in 24 patients refractory to fluids and dopamine and/or dobutamine, reversed oliguria in the majority (20/24), and was associated with increasing creatinine clearance. Redl-Wenzel and colleagues studied 56 septic shock patients refractory to fluids and dopamine/dobutamine, and found that increased MAP (56 to 82 mmHg) was associated with increased creatinine clearance over 48 hours (75 ml/min baseline, 89 ml/min 24 hours, 102 ml/min 48 hours). More recently, LeDoux and colleagues found that titration of norepinephrine to raise MAP from 65 mmHg to 85 mmHg in 10 patients resulted in significantly increased cardiac output, but no change in urine output (GFR was not measured). Although recommendations for titration of catecholamine pressor therapy to
MAP targets of 60–70 mmHg have become routine, these are clearly not evidence-based guidelines.

Vasopressin is emerging as an alternative pressor for vasodilatory shock, and may have some advantages over catecholamines with respect to renal function. Vasopressin is a peptide hormone synthesized in the hypothalamus, stored in the posterior pituitary gland, and secreted in response to increased plasma osmolality, baroreflex activation (hypotension, hypovolemia), and other non-osmotic stimuli. Vasopressin activates renal collecting duct V2 receptors (increased tubular water reabsorption; 'ADH', antidiuretic hormone), and vascular V1 receptors (vasoconstriction). Initial reports of successful use as a rescue agent in patients failing standard vasopressor therapy were followed by data showing that vasopressin deficiency (failure to adequately increase circulating vasopressin concentrations in response to hypotension), rather than altered vascular vasopressin responsiveness, was the underlying cause of this phenomenon. Landry and colleagues have also demonstrated clinical utility of vasopressin for reversal of refractory vasodilation post-cardiac bypass, which is a clinical syndrome with many similarities to septic shock. There is also an extensive literature suggesting advantages of vasopressin over epinephrine in cardiac arrest resuscitation. Emerging data suggest that vasopressin deficiency plays a role in septic shock and in post-CPB hypotension. A small study suggested that prophylactic vasopressin administration reduces post-bypass hypotension and use of other vasoconstrictors.

Data with regard to the effects of vasopressin on renal function in septic shock are promising. These data suggest that vasopressin may augment GFR not only by raising MAP and RPP but also by increasing glomerular efferent arteriolar tone and filtration fraction, compensating for the counter-regulatory effect of septic afferent arteriolar vasoconstriction. Most compelling is in-vitro work that demonstrates an exclusive (preferential) efferent arteriolar constriction by vasopressin in renal glomerular microvessels. This effect would tend in vivo to increase glomerular hydraulic pressure and GFR, and may explain the frequent observation that this agent increases UOP in septic shock, despite an anticipated ADH effect of water conservation/antidiuresis. Preliminary data from a prospective, blinded study by Patel and colleagues suggest that vasopressin increases UOP and GFR compared with norepinephrine titrated to similar systemic endpoints. Since other data showed similar effects of adding vasopressin to norepinephrine or other pressors, we favor a direct glomerular hemodynamic effect of vasopressin as the explanation for improved UOP in human septic shock. This is further supported by the recent work examining the effect of vasopressin on systemic and renal perfusion in septic animals. Guzman and colleagues showed in a canine endotoxemia model that vasopressin increased renal blood flow towards baseline values, whereas norepinephrine titrated to similar systemic hemodynamic parameters did not. In endotoxemic rats, vasopressin or L-canavanine (an inhibitor of inducible nitric oxide synthase) improved renal function, whereas norepinephrine titrated to similar MAP did not. In septic sheep (cecal ligation and puncture), vasopressin therapy (alone or in combination with norepinephrine) improved urine output, renal histology, and survival compared to control or norepinephrine therapy. Vasopressin seems to be a promising drug to improve renal function in vasodilatory shock, but in view of the potential for adverse effects on systemic and regional perfusion (notably skin necrosis and mesenteric ischemia), definitive outcome trials are required before recommending routine use in pressor-requiring vasodilatory shock. The 2000 VASTT trial of vasopressin vs norepinephrine/placebo in septic shock is past 50% enrollment, and should provide the required data to determine safety and effectiveness (Dr Keith Walley pers. comm).

Concerns for use in septic shock include potential for V2-stimulated water intoxication/hyponatremia (not observed to date and V2-stimulated pulmonary arterial, coronary, cerebral, and mesenteric vasoconstriction. Pulmonary hypertension was not seen in any of the septic or other vasodilatory shock patients studied by Landry and colleagues or Tsuneyoshi and colleagues, and in the preliminary report by Patel and colleagues pulmonary artery pressures were lower in septic patients treated with vasopressin than norepinephrine. Extrapolation from the cardiac arrest literature suggests that coronary and cerebral perfusion should not be compromised by vasopressin any more than by epinephrine or other catecholamines. As noted above, there is ongoing concern regarding potential effects of vasopressin on mesenteric perfusion. Although mesenteric ischemia was not specifically addressed by Tsuneyoshi et al’s study, they did find that of the patients treated with vasopressin for septic shock, those that survived had decreased levels of lactate...
from baseline (a marker of more adequate systemic perfusion or improved liver function) compared to those that did not, and no correlation was found between vasopressin infusion and development of lactic acidosis. More recent studies have not provided consistent conclusions regarding the effects of vasopressin therapy on splanchic perfusion in human septic shock, perhaps in part due to differences in perfusion measurement techniques and vasopressin dosing. Improved splanchic perfusion was found in human septic shock studies of terlipressin by Morelli and colleagues, and of vasopressin by Dunser and colleagues. Similarly, vasopressin therapy in ovine sepsis improved splanchic perfusion and survival. On the other hand, some studies in animals and humans suggest that vasopressin may cause splanchic hypoperfusion in septic shock. Of course, these concerns must be balanced against the known systemic and regional adverse effects of conventional catecholamine vasopressors, which have been well-described to cause arrhythmias and regional tissue ischemia (by vasoconstriction and hypermetabolism) in human sepsis, particularly in the splanchic circulation. Recent literature also highlights the known potential for pressor therapy (catecholamines, vasopressin, or both in combination) to cause or contribute to skin necrosis in vasodilatory shock. In particular, peripheral intravenous administration increases the risk of skin necrosis, accordingly, only central vein administration is recommended. Based upon available data, the use of vasopressin for vasopressor support in septic shock potentially represents the first major advance in this area since the introduction of catecholamine agents for this purpose. Results of the VASST trial are eagerly awaited.

Taken together, the literature suggests that maintenance of adequate renal perfusion pressure is an important goal in optimizing renal blood flow, particularly in critically ill patients in whom autoregulation of RBF and GFR is probably impaired (sepsis, CPB, chronic hypertension, ACE inhibitors). Whether the benefit of any pressor in improving renal function is caused by increased global renal blood flow, alterations in renal blood flow distribution, or some other pressure-dependent mechanism is unclear, but it is agreed that patients with vasodilatory shock require pressor therapy if hypotension is refractory to fluids and perhaps inotropic support. The literature does not provide a precise MAP target to achieve this goal, apart from specific circumstances such as aiming for 65 mmHg in protocol-driven resuscitation in early septic shock. It appears that a minimum MAP target of 60-70 mmHg is appropriate for drug titration in patients with vasodilatory shock requiring pressors. However, some patients with myocardial dysfunction may require lower MAP targets (less afterload), whereas others (with prior hypertension in particular) may benefit from a higher renal perfusion pressure. Titration of therapy to individual response may require modifications of published protocols or guidelines.

Optimization of glomerular hemodynamics

Beyond provision of adequate CO and systemic oxygen delivery, and maintenance of optimal RPP, reversal of local renal vasoconstrictor influences is the third potential therapeutic component ensuring renal perfusion in shock. As discussed above, renal vasoconstriction occurs in shock, through multiple mechanisms. Even in septic shock and cirrhosis, two states marked by diminished SVR and hypotension, renal vasoconstriction occurs and is well documented to be the cause of hepatorenal syndrome. Specifically, in hepatorenal syndrome ARF occurs in cirrhotic patients with normal kidneys but profound renal vasoconstriction, which critically impairs renal perfusion and glomerular filtration; renal effects of chronic liver disease are further discussed in Chapter 5. Renal vasoconstriction is also thought to play a role in the pathogenesis of septic ARF, along with hypovolemia (septic venodilation, capillary leak) and impaired systemic oxygen delivery, leading to development of prerenal azotemia. Indeed, some evidence suggests that much septic ARF is in fact severe, unreversed prerenal azotemia, without apoptosis or necrosis on autopsy. These data suggest that septic ARF can have a purely hemodynamic, vasoconstriction-mediated etiology, without apoptosis or necrosis, akin to hepatorenal syndrome. In combination, additive or synergistic nephrotoxic insults (inflammatory mediators, pigments, drugs, etc.) may then precipitate ATN when prerenal azotemia is not effectively prevented or reversed. The relative importance of selective renal vasoconstriction and regional hypoperfusion vs systemic hypoperfusion or nephrotoxin exposure in causing ARF in critically ill patients has not been precisely defined. Theoretically, any agent which offsets renal vasoconstriction might decrease the
incidence of prerenal azotemia and ATN in high-risk patients. It seems preferable to adopt a prophylactic strategy for prevention or reversal of vasoconstriction-induced prerenal azotemia, reversing an often clinically inapparent contributor to the pathogenesis of ATN, rather than attempting to intervene after frank renal injury has occurred. This concept, though theoretically attractive, remains unproven at this time. Increased renal vascular resistance may be reversed by use of generalized renal vasodilators, or by specific pharmacologic antagonists of known renal vasoconstrictor substances. Although the latter approach has been shown to increase renal perfusion and GFR in experimental ARF, with positive results using pharmacologic antagonists of endothelin, leukotrienes, thromboxane, and platelet-activating factor, definitive clinical studies have not been performed with any of these agents in critically ill humans. Of note, endothelin antagonism increased the rate of ARF in chronic renal insufficiency (CRI) patients receiving radiotracuent in a placebo-controlled study. The former approach is best represented by the use of dopaminergic agonists and other vasodilators for renal vasodilation in high-risk patients, an approach which has proven unsuccessful in numerous clinical trials.

Prolonged or severe prerenal azotemia may result in ATN, caused by ischemia alone or in combination with nephrotoxic insults. When ATN develops, decreased GFR results from a combination of renal vasoconstriction and parenchymal renal injury. Several mechanisms probably account for the decrease in GFR in ATN, including the direct results of tubular injury (intratubular obstruction by necrotic tubular cell debris and 'backleak' of glomerular filtrate through damaged tubular epithelium) and a major functional element – renal afferent arteriole vasoconstriction via tubuloglomerular feedback (TGF). The effect of TGF is to decrease RBF and GFR in ATN as follows: afferent arteriolar vasoconstriction is an adaptive response to the increased delivery of solutes to the macula densa in the distal tubule, preventing mass fluid loss past injured proximal convoluted tubule and loop of Henle segments which have become incapable of reabsorptive work. If normal glomerular filtration of 150 L/day of isotonic saline has continued in the presence of impaired tubular sodium reabsorption, the adverse implications are obvious. The problem of inappropriate salt-wasting is exacerbated by the loss on cellular polarity in injured/apoptotic renal tubular cells, which actively transfer sodium into the lumen. Indeed, the phenomenon whereby TGF-mediated afferent arteriolar constriction shuts down GFR in the presence of ATN has been termed 'acute renal success', because hypovolemic death would be the alternative outcome.

Vascular contributions are important not only in the initiation of ATN and the subsequent vasoconstrictor-mediated decrement in GFR but also in extension and maintenance (see Chs 5 and 8). ATN also involves inflammatory mediators, reactive oxygen species formation, and leukocyte infiltration, all of which further damage the kidneys. Current strategies to prevent or treat ARF by increasing renal perfusion may be ineffective or even harmful in the presence of established ARF with ATN, because the phenomenon of physiologic supply-dependency of renal oxygen consumption dictates that increased RBF and GFR accordingly increase O2 consumption. If renal vasodilators are to prove successful in ARF prevention and therapy, it is important that they favorably affect intrarenal blood flow distribution and the balance of regional O2 delivery and consumption. Importantly, the potential for imbalance between oxygen supply and delivery in the medullary circulation suggests that the use of renal vasodilators is not without risk in ARF patients. Increased cortical blood flow favors glomerular filtration, but inadequate medullary blood flow may continue to deprive the S3 and TALH segments (which must absorb this filtrate) of the necessary oxygen and nutrient supply to simultaneously perform reabsorptive work and remain viable. This may explain the failure of low-dose dopamine and a variety of other renal vasodilators to achieve benefit in ARF prophylaxis or therapy studies to date, despite the documented capacity to increase RBF.

It is possible that current resuscitation endpoints do not optimize renal perfusion, by failing to correct reversible septic myocardial depression, aiming for an inappropriately low renal perfusion pressure, and leaving renal vasoconstrator influences unopposed, which results in the common occurrence of uncorrected prerenal azotemia. As mentioned above, uncorrected prerenal azotemia is the common substrate for synergistic renal injury and ATN, and recurrent hypotension exacerbates renal injury in established ATN. Therefore, although not guided by a comprehensive, evidence-based approach, the use of fluids and vasoactive drugs to optimize systemic and renal perfusion remains the mainstay of our efforts to prevent and reverse ARF in critically ill patients.
EFFECTS OF MECHANICAL VENTILATION ON RENAL FUNCTION

Positive pressure mechanical ventilation alters renal perfusion and function through a variety of mechanisms.\(^1\)\(^3\) Elevation of intrathoracic pressure impedes venous return from the periphery, and may result in hypovolemic shock in patients with diminished effective arterial blood volume, particularly in the initial post-intubation period. Even in the absence of frank hypovolemia with hypotension, positive pressure ventilation alters a variety of neurohormonal systems. Positive pressure ventilation stimulates increased sympathetic outflow, activation of the renin-angiotensin-aldosterone axis, and nonosmotic vasopressin release, while suppressing ANP release. These effects lead to systemic and renal vasoconstriction, decreased renal blood flow and GFR, and fluid retention (salt and water) with oliguria. Increased pressure in the inferior vena cava and renal veins may also play a role in ventilator-induced renal dysfunction and fluid retention. Other data suggest that a shift of intrarenal perfusion from cortex to medulla is a mechanism of intrathoracic pressure elevation that impedes venous return from the periphery, and may result in hypovolemic shock in patients with diminished effective arterial blood volume, particularly in the initial post-intubation period. Even in the absence of frank hypovolemia with hypotension, positive pressure ventilation alters a variety of neurohormonal systems. Positive pressure ventilation stimulates increased sympathetic outflow, activation of the renin-angiotensin-aldosterone axis, and nonosmotic vasopressin release, while suppressing ANP release. These effects lead to systemic and renal vasoconstriction, decreased renal blood flow and GFR, and fluid retention (salt and water) with oliguria. Increased pressure in the inferior vena cava and renal veins may also play a role in ventilator-induced renal dysfunction and fluid retention. Other data suggest that a shift of intrarenal perfusion from cortex to medulla is a contributor to the salt-retaining/oliguric effects of positive pressure ventilation,\(^9\),\(^9\) but this has not been a consistent finding.\(^7\)

Small studies have shown that fluid administration\(^7\), the use of vasoactive drugs, including norepinephrine (5 \text{ mg/kg/min}) or fenoldopam (a pure vasodilator),\(^1\),\(^9\),\(^1\)\(^0\) can ameliorate the renal hypoperfusion and decreased GFR associated with positive pressure ventilation and positive end-expiratory pressure (PEEP). However, hemodynamic and neurohormonal mechanisms may not be the major cause of ventilator-induced renal injury. A growing body of evidence suggests that pro-inflammatory effects of positive pressure ventilation, particularly with (lung-) injurious ventilatory strategies, may be a source of acute renal injury.\(^1\)\(^0\),\(^1\)\(^0\)\(^4\) Imai and colleagues elegantly demonstrated in a rabbit model of acute lung injury that injurious ventilatory strategy led to increased acute renal failure, with pathologic evidence of renal tubular cell (and intestinal) apoptosis, and significant lung epithelial cell necrosis.\(^1\)\(^0\)\(^1\) They further demonstrated that plasma from rabbits ventilated with injurious strategy induced increased apoptosis when incubated with cultured rabbit proximal renal tubular cells. In the ARDSNet Trial, in addition to improved survival and ventilator-free days, the low tidal volume group had more days without circulatory, and renal failure (renal: 20 ± 11 vs 18 ± 11 days, \(p = 0.005\)).\(^1\)\(^0\)\(^4\) Similarly, Ranieri and colleagues showed that a 'lung-protective' mechanical ventilation strategy (lower tidal volume, higher PEEP) caused less systemic and intrapulmonary inflammation than standard management,\(^1\)\(^0\)\(^5\) along with fewer patients with organ system failure, including markedly fewer with renal failure (\(p < 0.04\)) at 72 hours.\(^1\)\(^0\)\(^3\) This topic is further discussed in Chapter 7. In summary, recent developments have shown us that a combination of appropriate hemodynamic support and lung-protective ventilatory strategies is the best current approach to minimize ventilator-induced renal dysfunction.

EFFECT OF RENAL INSUFFICIENCY ON FUNCTION OF OTHER ORGANS AND OUTCOME IN THE ICU

The mortality of ARF remains high, but it has often been said that modern ICU patients die 'with rather than of' ARF. The precise contribution of 'uremia' to their morbidity and mortality has been difficult to dissect, in part because severity of illness scores have performed poorly in predicting ARF outcome. It is unclear how best to predict or stratify mortality in patients with ARF in the ICU, but there is sufficient evidence to doubt the predictive value of scores such as APACHE II and APACHE III, which seem to underestimate mortality in the presence of ARF.\(^1\)\(^0\),\(^1\)\(^0\)\(^5\),\(^1\)\(^0\)\(^6\) Predictive scores designed specifically for ICU patients with renal failure, such as the Cleveland Clinic Score and the Liao Score, have better accuracy, but may not be applicable to other medical centers.\(^1\)\(^0\),\(^1\)\(^0\)\(^5\),\(^1\)\(^0\)\(^6\) Renal failure-specific severity of illness scoring systems have been validated to predict prognosis in ICU ARF, accounting for both severity of renal failure and associated MSOF, but it is not known if these systems perform accurately outside of the institutions in which they were developed.\(^1\)\(^0\),\(^1\)\(^0\)\(^7\)

It is becoming more apparent that increasing prevalence of septic ARF is the major impediment to improving ARF survival. For example, a recent prospective multicenter ICU study of ARF found that subjects with septic ARF had a far higher unadjusted mortality rate (74% vs 45%, \(p <0.001\)) than those without sepsis.\(^1\)\(^0\)\(^8\) Another prospective study of septic surgical ICU patients found that inhospital mortality was 57% in those with ARF vs 28% without.\(^1\)\(^0\)\(^6\) These findings are in agreement with the practical experience of every intensivist and nephrologist. Patients with hemodynamic...
instability are at greatest risk for developing ARF, are more difficult to provide renal replacement therapy for, and are most likely to die. Patients with septic shock, along with those with cardiogenic shock, remain our greatest management challenge, driving the current trends in ICU technology for RRT. Although MSOF and other comorbidities contribute to its high mortality rate, ARF independently increases morbidity and mortality. Studies in patients with radiocontrast nephropathy and ARF post-cardiac surgery have found that ARF independently increases mortality.5,6 More recently, Metnitz and colleagues found that severe ARF requiring renal replacement therapy increased the risk of in-hospital death to a degree beyond that expected based on severity of illness scores.7 Clermont and colleagues demonstrated that acute renal failure carries a higher odds ratio of death in critically ill patients than chronic renal failure with end-stage renal disease (ESRD), and this was unaccounted for by severity of illness scoring.8 APACHE III scoring predicted outcome accurately in patients without renal failure, overestimated mortality in critically ill ESRD patients, but underpredicted mortality in those developing ARF after ICU admission. ARF patients had a higher mortality than ESRD patients even if they did not similarly require dialysis. Taken together, these and other studies have found that we lack a severity of illness scoring system which accurately predicts ARF outcome in ICU patients, and this is an impediment to appropriate stratification of multicenter, prospective trials in this population.

Many of the effects of ARF are difficult to identify and quantify independently. It is obvious that problems such as refractory hyperkalemia, pulmonary edema, or clearcut uremic manifestations such as pericarditis are related to ARF when they develop acutely in the appropriate setting. Other uremic manifestations may have several explanations (encephalopathy, acidosis), or may be occult causes of other complications (bleeding diathesis and gastrointestinal bleed, leukocyte dysfunction with immunosuppression, and nosocomial infection). In addition to the emergence of data which appear to confirm an independent role of ARF in increasing mortality in the ICU, it is also clinically obvious that ARF is a cause of significant morbidity and severely complicates ICU management. Many of these complications of renal dysfunction will be discussed in subsequent chapters of this book. Renal dysfunction (acute or chronic) impairs regulation of fluid and water balance, resulting in a tendency to develop volume overload and hyponatremia. A variety of other clinically apparent biochemical and acid-base disorders also develop in ARF patients, apart from accumulation of nitrogenous wastes, azotemia, and uremia. Other effects of renal dysfunction are more subtle. Elimination of many drugs, metabolites, and nephrotoxins is impaired in the presence of renal impairment. Nonrenal elimination (hepatic metabolism) of drugs may also be suppressed. The loss of proximal tubular function also prevents vitamin D hydroxylation at the 1α-position, contributing to hypocalcemia (along with hyperphosphatemia). Vitamin D may also play an immunoregulatory role. Similarly, renal tubules play a role in the removal of pro-inflammatory cytokines and the production of anti-inflammatory cytokines. As detailed in Chapter 7, renal ischemia–reperfusion injury may even cause acute lung injury.10,11 Other data suggest that ARF causes injury to a variety of other distant organs. Interstitial renal cells produce EPO, with deficiency causing anemia and perhaps contributing to multiple organ dysfunction (decreased oxygen delivery, EPO receptors on end-organs such as the brain), and EPO therapy may even improve outcome. Our attempts at renal replacement therapy probably fall far short of the goal of compensating for the loss of diverse renal functions. More sophisticated techniques may provide better acute RRT in the future; a bioartificial renal tubule assist device containing human proximal tubular cells is already entering phase II trials.10,11 While our RRT options evolve, prevention (see Ch. 5) or amelioration (see Ch. 8) of ARF in the ICU is a major goal to improve outcome in critically ill patients.

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