CHAPTER 10

Renal Energy Consumption and Metabolism

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OBJECTIVES

This chapter will:

1. Describe normal renal oxygenation and energy metabolism.
2. Explore renal bioenergetics during experimental acute kidney injury.
3. Discuss the role of bioenergetic failure and renal oxygenation during acute kidney injury in critically ill patients.
4. Review interventions with potential impact on renal oxygen delivery and consumption in critically ill patients.

The kidneys are among the most metabolically active organs in the body. Most of the energy consumed by the kidneys is used to maintain fluid and electrolyte homeostasis and, while clearing waste products from the entire body's metabolism, prevent important nutrients from being lost in the urine. Emerging evidence suggests that disruption of renal bioenergetics is a major pathophysiologic event during development of acute kidney injury (AKI). In recent years, thanks to improved techniques to quantify regional real-time changes in renal oxygenation and energy metabolism, the effects of common intensive care management strategies on such parameters have been unraveled. Identification of optimal therapies to improve renal bioenergetics therefore has become a major focus in AKI research.

NORMAL RENAL BIOENERGETICS

Renal Oxygenation and Energy Consumption

Although the kidneys constitute only approximately 0.5% of the total body weight, they are responsible for almost 10% of the total body oxygen consumption and resting energy expenditure (approximately 150 kcal/day).[1,2] Renal oxygen and energy consumption is a function of primary active transepithelial transport of filtered solutes and basal consumption necessary for cell survival. Basal consumption is required for maintaining ion gradients across cell membranes, "housekeeping" (removal of dysfunctional organelles from the cytoplasm), and support of progression of the cell cycle (through the G0, G1, S, G2, and M phase) in preparation for mitosis. However, under normal conditions, most of the energy, around 80%, is consumed during reabsorption of filtered solutes from the tubular lumen and back into the blood circulation. Among primary active transporters, Na^+/K^+-ATPase is the most abundant, explaining why active sodium reabsorption is responsible for most of the renal oxygen and energy consumption.

Although increased renal blood flow (RBF) improves renal oxygen delivery, parallel changes in glomerular filtration rate (GFR) and sodium filtration increase tubular reabsorptive work and oxygen consumption. Therefore, unlike other major organs, the kidneys display a linear relationship between oxygen supply (RBF) and demand (sodium reabsorption). Consequently, oxygen extraction

Nephron segment	Mitochondrial density (%)	ATPase activity	QO_2/ TNa (cal/mEq)	Glycolytic capacity	Gluco-neogenesis
Proximal tubule (S1, S2 segments)	33	High	0.36	Low	High
Proximal tubule (S3 segment)	22	Low	NR	Low	High
Thin descending and ascending limbs	6-8	Low	NR	Moderate	Low
Thick ascending limb	44	High	1.4	Moderate	Low
Distal convoluted tubule	33	High	2.7	High	Low
Cortical collecting duct	20	Low	4.6	High	Low
Medullary collecting duct	10	Low	4.6	High	Low

FIGURE 10.1 Mitochondrial density, ATPase activity, metabolic efficiency (QO_2/TNa), and major metabolic pathways in different nephron segments. (Modified from Sekine et al: Solute transport, energy consumption, and production in the kidney. In Alpern R, Hebert S, ed: *Seldin and Giebisch's the kidney.* Boston, MA: Academic Press; 2008.)

(i.e., the difference in oxygen content between renal artery and vein) remains unchanged below 2 volume percent down to a level of RBF when GFR ceases and RBF only supports basal metabolic requirements needed for tubular cell survival. Further reductions in RBF increase oxygen extraction until anaerobic metabolism ensues.

Renal perfusion, energy consumption, metabolic efficiency, and hence the tolerance for hypoxic stress vary across the nephron. Normally, 85% to 90% of renal perfusion circulates through the cortical region. The S1 and S2 segments of the proximal convoluted tubule have a high Na^+/K^+-ATPase activity, maintaining the sodium gradient necessary for secondary reabsorption of glucose, amino acids, and water. This part of the nephron is also the most metabolically efficient; i.e., the energy and oxygen consumption (QO_2) needed to reabsorb sodium (TNa) is lower than in the more distal segments. In fact, metabolic efficiency (QO_2/TNa) progressively decreases downstream from the proximal tubule (Fig. 10.1).

In contrast to the cortical region, the renal medulla receives only 10% to 15% of RBF. In addition, because of the countercurrent exchange of oxygen between the ascending and descending limb of the vasa recta, the effective medullary oxygen supply is relatively low. Yet, the medullary thick ascending limb (mTAL) has a high Na^+/K^+-ATPase activity and mitochondrial density and consumes a significant amount of oxygen to maintain the medullary osmotic gradient. In their aggregate, high oxygen consumption together with low oxygen supply logically could explain the low medullary tissue pO_2 observed in studies on anesthetized rats, dogs, and humans. However, a recent study on awake sheep found similar tissue pO_2 in cortex and medulla despite significantly lower perfusion in the medullary compartment. Furthermore, a reduction in global RBF during partial renal artery occlusion caused a proportionally greater decrease in medullary perfusion and tissue pO_2.[3] This novel finding suggests that anesthetic agents may have influenced the observed corticomedullary pO_2 gradient in previous investigations by causing increased oxygen consumption in mTAL, decreased medullary perfusion, or both. However, further studies are needed to explore this hypothesis.

Renal Energy Production

Renal ATP is (95%) generated predominantly via oxidative phosphorylation in the mitochondria (Fig. 10.2). Amino acids, glucose, fatty acids, and ketone bodies are the major substrates used for such ATP production. However, the substrate preference varies along the nephron. For example, although more distal parts of the nephron have a high glycolytic enzyme activity, the proximal tubule poorly metabolizes glucose and mainly relies on fatty acids, ketone bodies, and amino acids as energy fuels. In contrast, the proximal tubule is the only part of the nephron where net gluconeogenesis takes place, mainly by using lactate as substrate (see Fig. 10.1). Such glucose production contributes significantly to whole body gluconeogenesis and also may provide important energy substrate to the more distal parts of the nephron.

To meet the energy demands from active sodium transport, the S1 and S2 segments, mTAL and distal convoluted tubule are rich in mitochondria. Among these segments, mTAL needs special attention because it, despite dwelling in a hypoxic environment, has the highest mitochondrial density and Na^+/K^+-ATPase activity (see Fig. 10.1). In contrast to ATP production in the proximal tubule, which is highly oxygen dependent, anaerobic glycolytic capacity is high in the mTAL-supporting ATP production required to maintain the Na^+/K^+-ATPase machinery in a hypoxic environment. In fact, even during short-term (10 minutes) renal anoxia, more than 70% of cellular ATP was maintained in the mTAL segment in an animal model.[4]

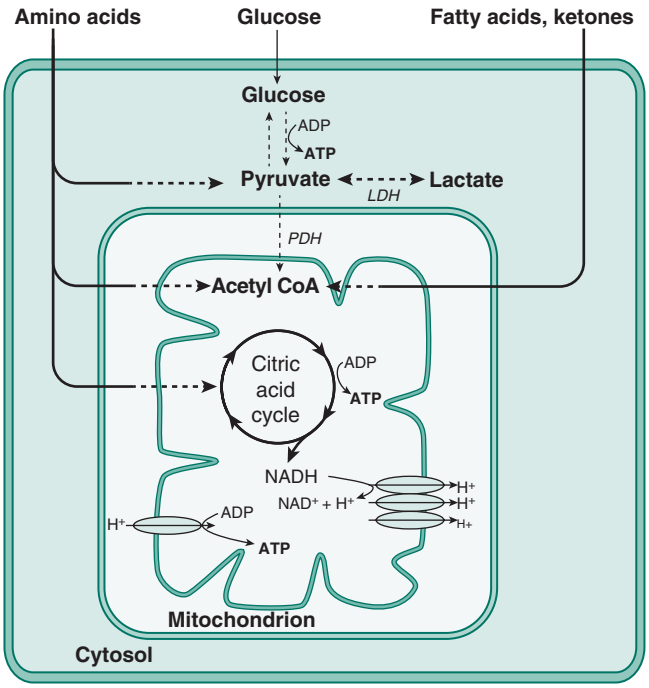

FIGURE 10.2 Adenosine triphosphate (ATP) production in kidney tubular cells. ATP is generated (1) via breakdown of glucose to pyruvate and, during aerobic respiration, through (2) oxidation of acetyl coenzyme A (CoA) generated from amino acids, pyruvate (decarboxylation catalyzed by pyruvate dehydrogenase [PDH]), fatty acids and ketones, and via (3) electron transport phosphorylation. Under anaerobic conditions, pyruvate is metabolized by lactate dehydrogenase (LDH) to lactate. *ADP,* Adenosine diphosphate; *NADH,* reduced nicotinamide adenine dinucleotide; *NAD+,* oxidized nicotinamide adenine dinucleotide; *PDH,* pyruvate dehydrogenase.

RENAL BIOENERGETICS IN ACUTE KIDNEY INJURY

Regional Oxygenation and Energy Metabolism During Experimental AKI

Decreased GFR, the major functional event during AKI, is a highly protective mechanism during renal stress. Reduced GFR lowers oxygen and energy demands as less sodium must be reabsorbed actively by the tubules. Moreover, transition of Na^+/K^+-ATPase from the basal to the apical or lateral membrane has been observed in response to ischemia-reperfusion injury.[5] Such relocation inhibits the Na^+/K^+-ATPase machinery, potentially causing a further reduction in oxygen consumption. However, this idea is controversial as recent data suggest reduced metabolic efficiency during Na^+/K^+-ATPase relocation causing increased oxygen and ATP consumption. Finally, even basal oxygen and energy consumption can be reduced during severe renal stress or injury, leading to a state of cellular "hibernation." This process, orchestrated by the mitochondria, involves pausing the cell cycle before transition from the G1 to the S (DNA synthesis) phase, thereby significantly reducing energy consumption until renal stress/injury has abated.[6]

However, despite marked reductions in GFR during AKI and the possibility of reduced energy consumption on a cellular level, a reduction in total renal oxygen consumption, which is a function of the venoarterial oxygen content difference, has not been confirmed consistently in animal AKI models (Table 10.1). Moreover, even when renal oxygen extraction ratio is low, indicating adequate global renal oxygenation, regions with impaired tissue oxygenation still can be seen (see Table 10.1). This contradicting observation has potential explanations. First, because of relatively low baseline oxygen extraction, the oxygen saturation in renal

TABLE 10.1

Kidney Perfusion and Tissue Oxygenation During Experimental Acute Kidney Injury

REFERENCE (YR, AUTHOR, PAGE)	ANIMAL	SETTING	RENAL BLOOD FLOW			GLOBAL RENAL OXYGENATION			TISSUE PO_2	
			TOTAL	CORTEX	MEDULLA	RDO_2	RVO_2	$RERO_2$	CORTEX	MEDULLA
2009 Johannes, 97–103	Rat	LPS sepsis	Decreased	NR	NR	Decreased	Unchanged	Increased	Decreased	Decreased
2011 Dyson, 83–89	Rat	LPS sepsis	Decreased	NR	NR	Decreased	Unchanged	Increased	Decreased	Decreased
2015 Calzavacca, e431–e439	Sheep	*E. coli* sepsis	Increased	Increased	Decreased	Increased	Unchanged	Decreased	Increased	Decreased
2016 Lankadeva 100–108	Sheep	*E. coli* sepsis	Increased	Increased	Decreased	Increased	Unchanged	Decreased	Increased	Decreased
2009 Legrand, F1109	Rat	IRI	Decreased	NR	NR	Decreased	Decreased	Increased	Decreased	Decreased
2011 Legrand 192–198	Rat	IRI	Decreased	NR	NR	Decreased	Decreased	Increased	Decreased	Decreased
2014 Abdelkader, F1026	Rat	IRI	Decreased	Decreased	Unchanged	Decreased	Decreased	Unchanged	Unchanged	Unchanged
2010 Siegemund, 345	Pig	IRI	Decreased	NR	NR	Decreased	Unchanged	Increased	Decreased	NR

IRI, Ischemia-reperfusion injury; *LPS,* lipopolysaccharides; *NR,* not reported; *RDO_2,* renal oxygen delivery; *RVO_2,* renal oxygen consumption; *$RERO_2$,* renal oxygen extraction ratio.

venous blood is normally high (approximately 80%). Therefore regional changes in consumption may have little or no impact on the total renal venous saturation, a component of the total renal oxygen consumption calculation. Second, as mentioned in the previous section, sodium reabsorption becomes less metabolically efficient during renal stress (increased QO_2/TNa). This was illustrated in rats in which the amount of oxygen required to reabsorb 1 mmol of sodium more than doubled after ischemia-reperfusion injury.[7,8] More recent work suggests that such bioenergetic failure may be caused by mitochondrial injury and/or dysfunction, possibly via reduced nitric oxide activity. In fact, various kidney insults—septic, ischemic as well as nephrotoxic—can cause mitochondrial swelling, a widespread reduction in electron transport enzyme activity, and, as a consequence, reduced ATP synthetic capacity.[9] It is possible, although not confirmed, that greater oxygen consumption will follow mitochondrial damage to sustain cellular ATP production.

Studies measuring renal tissue ATP during AKI have shown divergent results. During hypotensive gram-negative sepsis causing AKI in sheep, total renal ATP levels did not change despite marked reductions in RBF. Although renal oxygen consumption was not measured in that study, it is possible that it increased and thereby prevented significant renal ATP depletion.[10] In contrast, in a canine endotoxin shock model causing hyperdynamic sepsis and augmented RBF, ATP levels decreased in the renal cortex, whereas medullary levels were unchanged.[11] This finding agrees with the ability of the medullary part of the nephron to maintain ATP production via anaerobic glycolysis during renal stress.

Significant changes in metabolic functions with potential impact on ATP synthesis are observed during AKI. In the proximal tubule, gluconeogenesis from pyruvate is stimulated by short-term ischemia (and other AKI forms), providing glucose as a substrate for anaerobic ATP production in the distal nephron.[12] Importantly, enhanced gluconeogenesis contributes to pyruvate depletion in this nephron segment, which may have implications for AKI pathophysiology. In light of its key position in aerobic and anaerobic energy pathways (see Fig. 10.2) and its antioxidant and potentially antiinflammatory effects,[13] pyruvate therapy may have a role in future AKI therapy (see later section).

Renal Oxygenation and Energy Metabolism During Clinical AKI

Data on renal oxygen delivery, consumption, and extraction in clinical AKI are limited. However, renal oxygenation during cardiac surgery–associated AKI, a condition triggered by ischemia reperfusion injury after cardiopulmonary bypass circulation, has been explored in a series of experiments by Ricksten et al.[13a] This group used the retrograde renal vein thermodilution technique, paraaminohippuric acid (PAH) infusion clearance with correction for renal extraction of PAH, and renal extraction of 51chromium-ethylenediaminetetraacetic acid (51Cr-EDTA) for quantification of RBF, GFR, and renal oxygen supply/demand.

In cardiac surgery patients with AKI, a significant reduction in RBF, GFR, and oxygen delivery was observed despite normal cardiac index. In contrast, despite halved GFR and sodium reabsorption, which logically should reduce renal oxygen consumption to the same degree, oxygen consumption was similar in patients with and without AKI. Metabolically inefficient sodium reabsorption likely explains this finding. In fact, similar to previous observations during experimental AKI,[14] AKI patients required twice the amount of oxygen to reabsorb the same amount of sodium as the control patients without AKI.

The clinical implications of such detectable oxygen supply-demand mismatch are yet to be confirmed. In fact, a large body of evidence challenges the view that oxygen debt is a major trigger of renal injuries. First, even short-term interruption of RBF appears to have limited impact on the kidney structure and function.[15] For example, up to 60 minutes of total ischemia during aortic aneurysm repair or renal revascularization caused only a mild and transient increase in serum creatinine, no change in serum cystatin C, and minimal histologic changes. In addition, minimal release of urinary AKI biomarkers (NAG, LFABP, NGAL, IL-18, albumin) was observed. Importantly, neither of these changes correlated with ischemia duration. However, despite apparent tolerance to ischemia, mitochondrial swelling did occur, supporting the potential role of bioenergetic stress during AKI.

Second, it is well established that severe AKI can occur despite early restoration of RBF with fluids, vasopressors, and inotropes in patients with septic shock. Third, although patchy areas of necrosis can be seen on postmortem analysis in septic patients with severe AKI,[16] most renal tubular cells appear normal on histopathologic examination.[17]

Finally, our ability to monitor real-time changes in renal oxygenation is limited. Estimation of renal oxygen extraction is an attractive approach but requires placement of a renal vein catheter, which may not be feasible outside clinical research protocols. However, novel data suggest that the partial pressure of urinary oxygen, which can be measured easily by an oxygen probe inserted via the urinary catheter, accurately reflects intrarenal oxygenation. Furthermore, experimental septic AKI causing reduced medullary perfusion and oxygenation was detected by parallel changes in urinary pO_2.[18] Whether urinary pO_2 reflects clinically important changes in renal oxygenation during human AKI and whether modification of such changes produces clinical advantages over standard care remains to be seen.

INTERVENTIONS AFFECTING RENAL BIOENERGETICS

Loop Diuretic Agents

It is well established that loop diuretic agents such as furosemide, bumetanide, and ethacrynic acid inhibit the $Na^+/K^+/Cl^-$ pumps located in the mTAL and consequently reduce sodium reabsorption and oxygen consumption in this part of the nephron. In addition, in animal experiments, administration of furosemide before and/or after renal artery occlusion attenuated short-term[19] and longer-term[20] development of ischemia-reperfusion induced renal failure.

Moreover, in healthy humans, using blood oxygenation level–dependent (BOLD) MRI to assess the level of oxygenation in the kidney, an intravenous dose of 20 mg furosemide significantly increased medullary oxygenation.[21] Finally, in a subsequent study by Swärd et al., a furosemide bolus (0.5 mg/kg) followed by infusion (0.5 mg/kg/hr) after cardiac surgery decreased sodium reabsorption by more than 20% and caused an associated decrease in global renal oxygen consumption.[22]

However, despite such promising animal and human data, clinical benefits of using loop diuretics as renoprotective agents have not been established. A meta-analysis of nine

randomized trials showed that furosemide was not effective in the prevention or treatment of AKI.[23] Moreover, continuous furosemide infusion failed to improve renal recovery after RRT in general intensive care unit (ICU) patients.[24] Finally, more recent studies even suggest increased AKI incidence and RRT requirements after diuretic therapy.[25,26]

Physiologically, inhibition of the $Na^+/K^+/Cl^-$ pumps in mTAL raises the downstream urinary sodium concentration, which may trigger the tubuloglomerular feedback (TGF) mechanism causing preglomerular vasoconstriction and decreased GFR. This hypothesis was supported by an observed 12% decrease in GFR after furosemide therapy after cardiac surgery.[22] Together with a potentially reduced circulating plasma volume after furosemide-induced diuresis, TGF activation may counteract potential benefits of reduced kidney cellular oxygen consumption. These effects should be considered by clinicians when prescribing loop diuretics to critically ill patients with or at risk of AKI.

Vasopressors

Cardiac output, intrarenal vascular resistance, and renal perfusion pressure (RPP) are key determinants of RBF and hence renal oxygen delivery. Effectively, RPP is determined by the difference between mean arterial pressure (MAP) and central venous pressure (CVP).[27] Although retrospective data suggest that higher indexed systemic oxygen delivery together with higher MAP during vasopressor therapy attenuates AKI progression,[28] the optimal individual MAP target and the optimal use of vasopressors to achieve this target are uncertain.

Noradrenaline

Experimental data in awake, healthy sheep demonstrate that, although RBF and oxygen delivery were maintained during noradrenaline infusion, oxygen consumption increased, whereas medullary flow and tissue oxygenation decreased.[29] Conversely, in patients with vasodilatory shock after cardiac surgery, noradrenaline-infusion to increase MAP from 60 to 75 mm Hg improved renal oxygenation by increasing oxygen delivery without affecting oxygen consumption. Importantly, this beneficial effect on the oxygen supply-demand relationship occurred despite an almost 30% increase in GFR.[30]

Finally, in almost 800 patients with septic shock randomized to higher (80 to 85 mm Hg) versus lower (65 to 70 mm Hg) target MAP using noradrenaline infusion, no overall difference in renal replacement therapy requirements was observed. However, in a subpopulation of patients with chronic hypertension, a target MAP of 80 to 85 decreased the need for RRT.[31]

In view of these clinical findings, administration of clinically relevant doses of noradrenaline during vasodilatory shock appears to attenuate the risk of renal injury in selected populations. Whether this apparent renoprotective effect is mediated via the noradrenaline-dependent increase in glomerular hydraulic pressure, via improved delivery of oxygen and nutrients to the kidney parenchyma, or both remains to be determined.

Vasopressin

Vasopressin and its analogue terlipressin are potent renal vasoconstrictors acting mainly on postglomerular vessels, causing increased hydraulic glomerular pressure and GFR. In the aforementioned study on awake sheep,[29] infusion of vasopressin at a dose (mean 13 units/hr) that reduced global RBF and oxygen delivery did not significantly alter renal oxygen consumption, cortical and medullary blood flow, or tissue oxygenation. A significant increase in MAP and therefore RPP may have preserved renal oxygenation in that experiment.

Clinically, vasopressin in combination with noradrenaline improved urine output and creatinine clearance compared with noradrenaline alone despite similar cardiac index and MAP in a small (n = 24) randomized trial.[32] However, a dose-dependent increase in GFR and sodium reabsorption in combination with decreased RBF was observed during low-dose vasopressin infusion (1.2–4.8 units/hr) after cardiac surgery, collectively reducing renal oxygenation.[33]

Despite concern about the renal safety of vasopressin resulting from oxygen supply-demand imbalance, observational data suggest beneficial effects on renal outcomes. For example, in a secondary analysis of the Vasopressin and Septic Shock Trial (VASST), septic shock patients with mild AKI randomized to receive low-dose vasopressin (0.6–1.8 units/hr) were less likely to progress to severe AKI or to require RRT than patients randomized to receive noradrenaline infusion.[34] Furthermore, in patients with hepatorenal syndrome, another condition characterized by vasodilatory shock, administration of terlipressin attenuated AKI progression compared with placebo.[35] Such promising clinical data must be confirmed or refuted in future randomized controlled trials, including critically ill patients at high risk of AKI.

Angiotensin II

Angiotensin II (ATII) is a renal vasoconstrictor mainly affecting efferent arteriolar resistance, thereby causing increased GFR in the setting of reduced RBF during hyperdynamic sepsis.[36] Consequently, increased sodium reabsorptive work (increased sodium filtration) together with reduced oxygen delivery (reduced RBF) could lead to oxygen supply-demand mismatch. Indeed, in awake sheep ATII reduced global RBF and caused an isolated decline in medullary pO_2, suggesting reduced oxygen delivery and/or increased consumption in that region.[29] More relevant to a clinical setting was the observation that in sheep with gram-negative sepsis causing profound hypotension and reduced RBF, a 2-hour infusion of ATII restored blood pressure without causing further reductions in RBF or negatively affecting renal tissue ATP levels.[10] In view of such limited and contradictory evidence, ATII therapy currently is not recommended for use outside clinical studies.

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) mainly dilates preglomerular resistance vessels, causing a poised increase in RBF (oxygen delivery), GFR, and sodium reabsorption (oxygen consumption), hypothetically preserving renal oxygen balance during stimulated diuresis. Indeed, after uncomplicated cardiac surgery, ANP-infusion (25–50 ng/kg/min) increased GFR and oxygen consumption. However, in combination with decreased oxygen delivery (RBF dropped because of systemic hypotension), renal oxygen extraction increased refuting the oxygen-conserving hypothesis in this setting and using these doses.[22]

Even so, in patients undergoing high-risk surgery known to cause a high rate of ischemia-reperfusion kidney injuries,

ANP-infusion attenuated postoperative AKI and reduced the need for renal replacement therapy.[37,38] Importantly, in these trials, the use of low-dose ANP (12.5 ng/kg/min) prevented systemic hypotension, which may have produced a favorable bioenergetic milieu in face of enhanced renal excretory function. Larger multicenter randomized studies are required to explore the feasibility, safety, and clinical benefits of low-dose ANP infusion as a renoprotective agent in critically ill patients.

Intravenous Fluid Therapy

Intravenous fluid administration is used commonly to treat hemodynamic instability to improve organ perfusion and oxygen delivery. However, contemporary studies on healthy sheep during normovolemic hemodilution in pigs and in rats subjected to hemorrhagic shock have demonstrated impaired renal tissue oxygenation after fluid therapy despite improved cardiac output and RBF.[39–41] Importantly, even restoration of baseline hemoglobin using blood transfusion after hemorrhage failed to fully restore tissue oxygenation in one study.[41] Irreversible metabolic inefficiency to reabsorb sodium (increased QO_2/TNa), as observed by the authors, may explain this finding.

Similarly, despite improved cardiac index and RBF during postoperative plasma volume expansion with clinically relevant fluid volumes (either 20 mL/kg of crystalloids or 10 mL/kg of colloids) after uncomplicated cardiac surgery, impaired renal oxygen delivery resulting from hemodilution was observed. However, although oxygen extraction increased with crystalloid therapy suggesting renal oxygen supply-demand mismatch, colloid bolus did not affect oxygen extraction.[42] Because a large body of data now suggests that uncritical fluid administration is common and may impair renal outcomes,[27] defining optimal fluid strategies in critically ill patients should be a priority for future studies.

Pyruvate

Based on the assumption that bioenergetic failure is a major mechanism during AKI development and that pyruvate depletion is a feature of experimental AKI, the role for pyruvate therapy was explored recently in separate AKI models. Persistent renal cortical tissue pyruvate depletion was observed during unilateral kidney ischemia in mice and up to 18 hours after reperfusion. In addition, glycerol-induced AKI (nephrotoxic AKI model) produced similar results as well as a marked reduction in renal tissue ATP levels.

Compared with saline, treatment with pyruvate almost completely prevented AKI development as demonstrated by an attenuated increase in BUN levels, improved ATP levels, and a marked reduction in renal neutrophil gelatinase-associated lipocalin (NGAL) mRNA levels. Furthermore, although glycerol induced histologic evidence of AKI (proximal tubule brush border membrane blebbing and cellular necrosis in cortex and outer medulla), normal histopathology was seen after glycerol injection in combination with pyruvate treatment.[43] Finally, in a sepsis model in mice, administration of ethyl pyruvate even as late as 12 hours after sepsis initiation attenuated renal injury as suggested by decreased serum creatinine and reduced tubular damage on histologic examination.[13]

These findings support the role of pyruvate as a key substrate of cellular energy production. They also reinforce the view that bioenergetic failure plays an important role in ischemic, nephrotoxic, and septic AKI. However, future studies must confirm or refute the importance of pyruvate depletion in human AKI and whether treatment with pyruvate preserves kidney structure and function in patients at risk.

CONCLUSION

Bioenergetic failure is emerging as a potentially important pathophysiologic mechanism during development of AKI from various causes in critically ill patients. Although much evidence comes from animal experiments, little is known about regional metabolic changes in the human kidney during AKI. In addition, in the critically ill patient treated in the ICU, changes in renal oxygen delivery, renal oxygen consumption, renal ATP production, and renal ATP consumption are not only affected by the underlying illness but also modified by a complex interaction of therapies such as nutrition, vasoactive drug therapy, fluid management, blood transfusion, and oxygen therapy. Therefore the optimal use of such therapies to achieve maximum clinical benefit must be systematically explored in future randomized controlled trials.

Key Points

1. Renal metabolic activity is high mainly because of active reabsorption of sodium along the nephron.
2. Renal mitochondrial injuries, pyruvate depletion, and inefficient sodium reabsorption are associated with bioenergetic failure and AKI.
3. Loop diuretics appear to reduce renal oxygen consumption but do not prevent AKI in humans.
4. Although experimental data suggest that noradrenaline improves renal oxygenation and vasopressin impairs renal oxygenation, both these vasopressors may prevent renal injuries during treatment of vasodilatory shock.

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

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