Acute Kidney Injury following Cardiac Surgery: A Clinical Model

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Keywords

Clinical model · Acute kidney injury · Cardiac surgery · Mouse model · Statistical power

Abstract

Background: Scientists use preclinical models of acute kidney injury (AKI) to decipher mechanisms and develop therapy, but translation of therapies to patients remains poor. Models that better resemble patients, including those within clinical care, should be considered. **Summary:** Mice provide many advantages to the study of human disease including an ability to dictate precise experimental conditions. To best isolate and measure phenomena, scientists reduce experimental variability – identical animals, environmental conditions, experimental exposures, and outcome assessments. This technique reduces effect size variability and increases power but dissociates these model organisms from the clinical patients they intend to represent, potentially accounting for the poor translation of findings into patient care. Clinical research, conversely, is often plagued by heterogeneous patients, heterogeneous environmental factors, and heterogeneous renal insults. A compromise between these 2 extremes – a model of AKI that is more similar to human disease but still provides opportunities for rigorous investigation – should be utilized. Cardiac surgery provides a clinical model for the study of AKI due to mechanism overlap it shares with other clinical conditions (improved generalizability) and

characteristics that provide distinct opportunities for research. The high rate of AKI following cardiac surgery and the relative homogeneity (decreased variability) of cardiac surgery subjects, their environment, and renal insults increase power and the opportunity to make discoveries and advance care. Moreover, the elective nature of cardiac surgery provides opportunities to perform detailed baseline assessments and pretreat select patients. **Key Messages:** Models that better reflect clinical AKI are needed to decipher mechanisms and develop effective treatments. Cardiac surgery is an important clinical model form for the study of AKI.

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Introduction

Acute kidney injury (AKI) remains one of the most frequent and debilitating complications of hospitalization, surgery, and critical illness. AKI continues to affect a large portion of patients receiving surgery, with sepsis, or admitted to an ICU. The diagnosis of AKI is indepen-

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Table 1. Benefits of murine and clinical models for the study of AKI

Benefits of murine models	Benefits of clinical models
<ul style="list-style-type: none">– Precise experimental conditions– Identical genetic profile among replicates– Identical age, gender, weight, diet– Identical environmental conditions– Precise measured renal insults– Genetic modification of target proteins– Rapid development and lifespan of organisms	<ul style="list-style-type: none">– Results directly applicable to patients– High chronic kidney disease prevalence– Longitudinal tissue sampling– Sex differences and other subgroups– Disease mechanisms reflect clinical conditions– High generalizability of findings
<p>Murine conditions provide excellent opportunity to make discoveries within murine models, but translation of discoveries to patients is lacking. Clinical models yield results more applicable to patients, but reduced ability to manipulate mechanisms impairs assessments of causality, and heterogeneity limits power.</p> <p>AKI, acute kidney injury.</p>	

dently associated with a 5-fold increase in mortality, and in addition, brain, heart, and lung dysfunction and injury [1, 2]. Hospital mortality for AKI patients who require dialysis remains a staggering 30% [3].

To explore mechanisms of AKI and develop preventative and therapeutic treatments, physician scientists have built preclinical models that simulate common causes of AKI. For example, temporary application of a renal pedicle clamp simulates renal ischemia and reperfusion, cecal ligation and puncture simulates systemic infection and sepsis, injection of iohexol or cisplatin simulates exposure to radiocontrast and other nephrotoxins, and intramuscular injection of glycerol models rhabdomyolysis. The insults in these models reliably initiate mechanistic processes that culminate in experimental AKI, but these models generally fail to capture the renal and systemic stimuli that culminate in clinical renal injury because the model organisms and experimental renal insults are dissimilar to patients and their AKI-inducing exposures. The poor fidelity between the insults used in models and those observed clinically and intrinsic differences between humans prone to AKI and experimental animals may partially explain the limited translation of successful preclinical therapies [4]. In addition, common experimental design practices that limit variability may impact translation to human disease.

Models that better reflect clinical AKI are needed to decipher mechanisms and develop effective treatments. Herein, we focus on some of the benefits of preclinical mouse models and clinical model forms of disease, examine some of the statistical premises around the development of a disease model, and make the case that cardiac surgery is a valuable model form for advancing the study of AKI.

Characteristics of an Ideal Model of Disease

The most common model organism for the study of AKI is the mouse. Mice offer many advantages to the study of human disease including an ability to dictate precise experimental conditions; similar biology to humans; rapid lifespan turnover; genetic modification of target protein expression using transgenic, knockout, knockdown, or knock-in techniques; modest facility, feeding, and upkeep costs; and ease of breeding [5]. The benefits of murine models for the study of AKI are limited by differences between mice and clinical patients including dissimilar presentation of disease; discordance between murine AKI models and patients; reduced relative age of experimental mice compared to patients; decreased prevalence and severity of chronic diseases in mice compared to patients; altered immune cell populations and function; different diets; and different gut microbiomes (Table 1). Differences notwithstanding, the widespread use of model organisms to understand physiology and molecular and cell biology have successfully led to the discovery of numerous molecular pathways critical to homeostasis and to the development of effective therapy for many clinical conditions.

To best isolate and measure phenomena within experimental models, scientists reduce variability among model organisms. For example, in murine studies, mice of identical genetic background, age, sex, diet, and environmental exposure are chosen, and treatment/toxin/injury “dose” is carefully prescribed. This strategy reduces the variability of effect among replicates and therefore reduces effect size variability. Experimental conditions that

limit effect size variability improve power to measure the impact of exposures/treatments and to estimate subtle and small effects that otherwise would not be discerned. The following example illustrates the statistical implications of this common technique.

A 10 µg intraperitoneal injection of endotoxin increases circulating blood urea nitrogen 8 mg/dL in 10 mice. In experimental conditions in which the variability of this effect on blood urea nitrogen is small (e.g., 8 ± 5 mg/dL), scientists would have 92% power to detect this treatment effect. However, in conditions in which the variability is greater (e.g., 8 ± 10 mg/dL), scientists would only have 38% power to detect this effect. Note that this large change in power is only the result of the variability in treatment response and not the effect of treatment itself.

Scientists strive to limit variability of all experimental conditions in order to answer questions more efficiently. This reductionist approach narrows the scope of study not only by limiting genetic and environmental confounders but also misrepresents the natural environment of these organisms and further dissociates these model organisms from the clinical patients they intend to represent. The results may not be generalized to clinical patients who contain significant environmental and genetic variability, not to mention intrinsic species differences. These factors, as well as differences between experimental and clinical renal injury, explain, in part, the poor translation of therapy between mice and patients.

In human studies of AKI, however, exploring mechanisms of renal injury and measuring effects of interventions are challenging, for the same reasons that it is simpler to explore mechanisms of renal injury and measure effects of interventions in controlled preclinical experiments – variability in renal insults, variability in genetic and environmental backgrounds, and variability of effect sizes. A compromise between these 2 extremes – a model of AKI that is more similar to human disease but still provides opportunities for rigorous investigation – should provide valuable information to advance the study of AKI.

Cardiac Surgery-Associated AKI

Cardiac surgery provides a clinical model form for the study of AKI – a model that allows scientists to investigate clinically relevant mechanisms of renal injury and test therapies that can be applied directly to and tested in additional patient populations. This is due to the similarity between mechanisms of renal injury fol-

lowing cardiac surgery and other clinical conditions (improved generalizability) and specific characteristics of cardiac surgery patient management that provide distinct opportunities for clinical research (improved experimental conditions compared to other forms of clinical AKI).

Mechanisms of AKI during cardiac surgery are similar to mechanisms of AKI from other clinical conditions, such as renal ischemia/reperfusion, sepsis, radiocontrast, and hemeproteinemia. The kidneys become hypoxic during cardiopulmonary bypass, and following cardiopulmonary bypass have increased oxygen consumption and oxygen exposure [6]. The physiologic perturbations of renal ischemia and reperfusion are accompanied by increased circulating and urinary markers of oxidative damage, specifically products of free-radical induced lipid peroxidation, which have been independently associated with development of postoperative AKI [7]. Ischemia and reperfusion cycles induce reactive oxygen species production from renal mitochondria [8, 9]. Reactive oxygen species and inflammatory mediators impair endothelial function, incite proinflammatory transcription factors including NFκB, and recruit neutrophils and macrophages into the renal interstitium. At the same time, cardiopulmonary bypass and mechanical suction lyse erythrocytes, increase circulating concentrations of free hemoglobin, and lead to a hemeprotein nephropathy akin to rhabdomyolysis [10]. Septic AKI and radiocontrast AKI are also products of altered microcirculation, oxidative damage, and renal inflammation [11, 12]. In addition, patient factors associated with AKI following cardiac surgery are similar to patient factors associated with AKI in other patient populations. These factors include the following preoperative and intraoperative characteristics: chronic kidney disease, advanced age, diabetes, anemia, heart failure, and hypotension. Discoveries within cardiac surgery have mechanistic overlap with other forms of AKI.

As important from a research standpoint, cardiac surgery has additional characteristics that make it favorable as a model for the study of AKI. Cardiac surgery is common, the incidence of AKI following cardiac surgery is high, “experimental conditions” are relatively consistent during cardiac surgery (i.e., a similar degree of renal insult imposed upon a relatively homogenous patient population), and elective surgery provides opportunities to recruit patients, adequately measure baseline parameters, and schedule assessment linked closely to clinical events. In more detail, patients presenting for cardiac surgery frequently share a similar medical profile – hypertension,

Fig. 1. Characteristics of cardiac surgery that increase statistical power and are favorable for its use as a model for the study of acute kidney injury (AKI) in humans. AKI, acute kidney injury.

vascular disease, diabetes, and smoking, and 25 percent of the 500,000 patients who have cardiac surgery each year suffer from AKI [13]. The majority of AKI following cardiac surgery is mild (stage 1), but even mild postoperative AKI is independently associated with significant extrarenal morbidity and a 3-fold increase in postoperative death [14]. A high AKI event rate increases power to detect effects of interventions.

The insults to patients that lead to AKI following cardiac surgery are relatively consistent and controlled compared to other clinical scenarios, further increasing power. Consistency of renal insult within a relatively homogenous patient population reduces effect size variability and provides better opportunities to isolate measurements of mechanisms and treatment effects. Compared to other clinical scenarios such as sepsis or trauma, cardiac surgery procedures are fairly standardized. Patients receive invasive arterial and venous monitoring and access, undergo general anesthesia, positive pressure mechanical ventilation with high oxygen exposure, and cardiopulmonary bypass. Hemorrhage necessitates transfu-

sion of allogenic blood products in nearly 50% of patients. During surgery, blood pressure and cardiac index decrease. Anesthesiologists administer vasopressors (up to 80% of patients receive norepinephrine during surgery) and inotropes which restore global hemodynamic metrics but have conflicting effects on renal parenchyma oxygen delivery. While outliers exist, duration of cardiopulmonary bypass is typically 90 ± 30 min and surgery 5 ± 1 h (Fig. 1).

And finally, cardiac surgery is typically elective. Elective surgery provides opportunities for scientists to selectively recruit patients, perform detailed baseline assessments, and pretreat patients. Scientists can plan data and biospecimen collection at precise timepoints relative to renal insults. These benefits are distinct from other types of clinical AKI, such as AKI associated with sepsis, trauma, or cardiogenic shock. Patients with these latter types of AKI present either with AKI or during development of AKI, precluding opportunity to accurately assess baseline renal function, collect biospecimens, measure circulating or urine makers, or make other clinical assessments.

Conclusion

Preclinical models are important to reduce the burden of AKI, but clinical models that are directly applicable to patients should be exploited. Cardiac surgery has specific characteristics that provide opportunities to decipher pathologic mechanisms of AKI and develop therapy.

Disclosure Statement

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