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Modeling human disease: a mouse model of acute kidney injury to chronic kidney disease progression after cardiac arrest

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Acute kidney injury (AKI) is a substantial cause of morbidity and mortality, with over one million patients in the US affected annually. Clinical treatment for AKI primarily focuses on hemodynamic optimization, eliminating risk factors for additional injury, and providing renal replacement therapy if necessary. Despite a sizeable literature on the basic science of AKI, the absence of specific medical therapies for the treatment of AKI is a major shortcoming in the field of nephrology. This has led to increased attention on optimizing preclinical studies to make them more clinically relevant, thereby decreasing barriers that have hindered transition from preclinical discovery to clinical treatment[1]. This has led to a push for AKI studies to use models that better reflect injury seen in patients. As AKI is a major risk factor for the development of chronic kidney disease (CKD), models that evaluate long-term renal outcomes resulting from the transition of injury from AKI to CKD, provide additional insight into an important clinical problem.

Matsushita et al recently reported a novel murine model of AKI to CKD progression following cardiac arrest and cardiopulmonary resuscitation (CA/CPR)[2], a commonly encountered clinical scenario that is a major cause of AKI[3]. Their group has previously shown that the CA/CPR model in mice leads to AKI 24 hours post-arrest, as determined by decreased GFR and elevated serum creatinine[4]. In the current study, the authors use the same model, but for the first time carefully describe unexpectedly dynamic changes in renal functional recovery, tubular injury, inflammation and fibrosis that occur over a seven week period after the initial cardiac arrest. In their model, mice are anesthetized with isoflurane, intubated and ventilated, and cardiac arrest is induced with potassium chloride. Animals remain asystolic for eight minutes following which CPR is performed by finger chest compressions, at a rate of approximately 300 compressions/minute, and epinephrine is administered, following an ACLS-like protocol. CA/CPR animals sustained AKI with near-absent GFR at 24 hours post-arrest. GFR recovered two weeks later, but at seven weeks, post-arrest animals demonstrated reduced GFR, elevated BUN and renal fibrosis,

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suggestive of CKD. Even during the interval recovery of GFR, they show evidence of ongoing renal inflammation and injury from the time of arrest to their final endpoint.

While the authors provide a detailed account of the cellular and molecular dynamics associated with these events, the greater implication of this report lies in their long-term vision. A clinically relevant model of AKI progressing to CKD holds great promise for identifying mechanisms that may be amenable to therapeutic intervention not only for AKI, but also to halt progression to CKD. As this clinical scenario provides a definitive event in time subsequent to which renal injury occurs, the administration of any potential therapeutics could be precisely timed relative to arrest time and integrated with post-arrest protocols. Their long-term model of CKD progression after cardiac arrest also provides a system to identify biomarkers that will predict which patients are most likely to progress to CKD after cardiac arrest, since only a subset of these patients progress to CKD[3]. CA/CPR mice have complete recovery of GFR at two weeks, but tubular injury, KIM-1 positivity, and inflammatory cell infiltrates persist at 24 hours, one week, and seven weeks post-arrest. This suggests that recovery of GFR, signified clinically by normalization of serum creatinine, is inadequate to predict which patients are at risk for progressing to CKD. Several biomarkers have already been proposed as alternatives to serum creatinine due to their higher specificity for the detection of AKI and CKD in certain situations[5]. This model, however, allows for the identification of novel biomarkers that may predict which cardiac arrest patients will progress from AKI to CKD, and may therefore require more intense treatment and observation post-arrest.

Perhaps the strongest physiological component of this model is that it links two vital organs, the heart and the kidney. The authors use primary cardiac dysfunction as a catalyst for renal injury, a clinical scenario referred to as cardiorenal syndrome (CRS). CRS is a descriptive term that applies to any situation in which cardiac and renal dysfunction coexist. This is an important clinical scenario that is commonly encountered and leads to substantial healthcare burden. A CRS classification was proposed by Ronco and colleagues over 10 years ago, and is largely based on chronicity of injury and organ of primary dysfunction[6]. Their broad definition of five CRS subtypes was proposed to highlight the bidirectional relationship between these two organs, but, the optimal clinical application and mechanistic utility of this classification can be unclear.

Matsushita et al use their model to investigate type 1 CRS, the scenario where acute cardiac dysfunction causes acute renal dysfunction. Their claim that they are modeling AKI to CKD progression would also suggest this is a model of progression from type 1 to type 2 CRS (i.e. chronic cardiac dysfunction leading to chronic renal dysfunction). Hemodynamic changes, including decreased forward flow and venous congestion, are often implicated as the predominant factors driving renal dysfunction in acute heart failure. However, the authors report relatively severe AKI, beyond what would have been expected following an equivalent 8 to 10 minute renal pedicle clamp time after surgically induced ischemia-reperfusion-induced AKI. This suggests there are pathogenic differences in this model extending beyond mere renal ischemia. Indeed, Hutchens and colleagues recently reported a possible nephrotoxic role for a circulating factor of cardiac origin, cardiac LIM protein, in

post-cardiac arrest CRS[7]. Future studies using this model will be able to further elucidate these bidirectional cardiorenal signaling pathways.

While there is great potential for this model, several caveats related to this study should be noted. First, post-arrest animals were only followed out seven weeks. While there is no clear definition of CKD in mice, humans are given three months to recover from AKI before they are considered to have CKD. As several markers of injury, including KIM-1 expression, were improving at seven weeks, the possibility that the animals were undergoing a prolonged renal recovery and would return to baseline over the subsequent weeks cannot be excluded. Following these mice beyond three months in the future will answer this question. Second, the pattern and timing of renal injury observed is in the setting of healthy, relatively young mice. This scenario is not typically observed clinically as the majority of patients sustaining cardiac arrest are older and more commonly have some baseline cardiac and/or renal dysfunction. While this study demonstrates what occurs in the setting of normal kidneys, one should be cautious about generalizing these data to the diseased substrate. An earlier study from the Hutchens lab, demonstrated that middle aged male (but not female) C57Bl/6 mice (43–48 weeks) developed more severe AKI 24 hours after CA/CPR than younger mice (10–15 weeks)[8]. Further studies are needed to determine whether differences in short-term renal outcomes in older male vs. female mice are predictive of long-term CKD progression after CA/CPR. Thirdly, the authors achieved return of spontaneous circulation in 87% of their animals, which is higher than is typically observed in patients following cardiac arrest, particularly with nonshockable rhythms. Furthermore, they had approximately 50% survival post-CPR for all groups, which is substantial mortality, but much lower than the 80–90% mortality prior to hospital discharge seen in patients[9]. This is likely to be related to the degree of monitoring under experimental conditions, though an underlying physiological difference between species cannot be excluded. Finally and importantly, this model is technically challenging and so is unlikely to be widely adopted by the AKI research community. Furthermore, because of the relatively high mortality rates encountered over the first week after cardiac arrest (average mortality of 47.1 +/− 14.1% from the three cohorts of mice in the paper), definitive hypothethesis testing studies will require investigators to use larger numbers of mice than are typically used for toxin or ischemia reperfusion-induced AKI studies.

Overall, this model provides an opportunity to investigate the basic science of cardiorenal syndrome with the hope of developing new treatments for renal disease in cardiac arrest patients. By modeling unique pathophysiological events that do not occur in traditional models of AKI, we also anticipate that the long-term CA/CPR model, while technically challenging, is likely to lead to other clinically impactful discoveries including exploration and identification of novel cardio-renal signaling events that enhance renal injury after cardiac arrest, and discovery of novel biomarkers that are predictive of which patients are likely to develop AKI and CKD progression.

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