

# The Golden Hours of AKI: Is Oxygen Delivery the Key?

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Throughout various fields of scientific investigation, including neonatology and trauma medicine, the idea of the golden hour of treatment has long been debated (1–3). Defined as an interval most critical for successful emergency treatment and improved patient outcomes, the golden hour(s) is contingent on the delivery of early and frequently, protocol-driven care. Although advances in medicine have improved outcomes in these fields, the concept of the golden hour remains loosely applied and increasingly investigated in the setting of AKI. With recent advances in critical care nephrology, including consensus definitions, improved risk stratification, and biomarkers, intensivists and nephrologists are ideally positioned to investigate how best to improve patient outcomes and decrease the severity of renal damage in the golden hours of early AKI (4–6).

In the past, AKI research has focused on the earlier identification of AKI before the rise in serum creatinine or drop in urine output (7,8). Recently, investigators have shifted their focus beyond simply replacing serum creatinine with a new gold standard and have sought to augment the information provided by serum creatinine and urine output, combining them with biochemical biomarkers, functional assessment of urine-making capacity, or both (9–11). Although these studies and others have shown that functional and damage biomarkers with physiologic links to the kidney are useful tools in predicting the risk of progression of early AKI, they were part of observational studies and require additional investigation.

Additionally, an increasing number of controlled trials has shown efficacy when attempting to prevent severe AKI. Judicious intravenous fluid selection of nonhyperchloremic solutions (12) and remote ischemic preconditioning (13) showed renoprotective effects, which decreased the incidence of severe AKI (regardless of the need for RRT). Similarly, a meta-analysis investigating perioperative hemodynamic optimization, Brienza *et al.* (14) showed that trials targeting both supranormal and normal hemodynamic targets decreased the risk of postoperative AKI. However, not every controlled trial targeting hemodynamics parameters has shown a clinical benefit in preventing AKI. Two recent large-scale multicenter investigations of resuscitation protocols in the setting of severe sepsis and septic shock showed relatively low severe AKI event rates (2.8%–13.5%) and no difference in the duration of treatment in those requiring RRT (15,16). Although the ideal resuscitation strategy, intravenous fluid selection,

and hemodynamic parameters to prevent the development of AKI continue to take shape, much less is known about how best to treat and optimize the patient just entering the golden hours that follow a new diagnosis of AKI.

For those with newly diagnosed AKI, there is a dearth of proven interventions to prevent AKI progression. Data surrounding the use of automated, electronic medical record alerts for those with new-onset AKI seemed promising at first (17,18), but when patients were randomized to receive an electronic AKI alert versus usual care, there was no difference in the maximum change in serum creatinine, need for RRT, or inpatient mortality (19). Similarly, although some data point to less progressive AKI for those receiving an early nephrology consultation in the setting of newly diagnosed AKI (20), this has yet to be validated in large randomized trials. Observational data, small prospective studies, and common sense tell us that the avoidance of hypotension (*e.g.*, mean arterial pressure [MAP] <70–75 mmHg) in the setting of early AKI may decrease the incidence of severe progressive AKI (21,22). However, the broad application of such an MAP goal to all patients is not feasible, and the ideal hemodynamic strategy for the prevention of progressive AKI remains unproven. It is with this background that Raimundo *et al.* (23) reported, in this issue of *CJASN*, their findings from a single-center, retrospective cohort study investigating the association between hemodynamic parameters in early AKI and AKI progression and inpatient mortality.

In their 790 patients in the mixed medical-surgical intensive care unit (ICU) with AKI Network Stage 1 AKI, 210 (26.6%) had hemodynamic monitoring in place within the initial 12 hours of AKI onset (23). Importantly, given the retrospective nature of this study, the decision to place hemodynamic monitoring was made at the discretion of the treating teams. Given this lack of randomization, there were empirical differences, perhaps on the basis of treating physician biases, between those with and without hemodynamic monitoring. Those with early monitoring in place had higher severity of illness scores at the time of ICU admission, increased length of ICU stay, and increased mortality. Looking further at the subgroup with hemodynamic monitoring and AKI ( $n=210$ ), there were 85 (40.5%) patients who progressed to AKI Network Stage III AKI, of which 78 required RRT. Those who did not progress had higher cardiac indices (liters per

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minute per meter<sup>2</sup>), higher indexed systemic oxygen delivery (DO<sub>2</sub>I; milliliters per minute per meter<sup>2</sup>; defined as 1.34 × hemoglobin × arterial oxygen saturation × cardiac index), and higher MAP (millimeters of mercury) at the time of first measurement within the first 12 hours of AKI. Thus, although these measures take into account the physician discretion that went into placing the invasive hemodynamic monitoring, they do not account for any treatments or interventions that subsequently followed these initial measures. For every increase of 50 ml/min per meter<sup>2</sup> in DO<sub>2</sub>I, the odds ratio was 0.87 (95% confidence interval, 0.77 to 0.98) for the progression of AKI, and every 5 mmHg higher MAP provided an odds ratio of 0.76 (95% confidence interval, 0.59 to 0.98). Similar associations were seen for central venous pressure and arterial lactate measures, where higher values were associated with a higher risk of progression. However, urine output and fluid balance, vasopressor use, and severity of illness scores were not associated with AKI progression in the multivariate analysis. Importantly, when Raimundo *et al.* (23) looked at many of the hemodynamic parameters over 12–72 hours after AKI and adjusted for the initial hemodynamic measurements, the associations were no longer significant for all indices, except MAP. Not surprisingly, cumulative fluid balance, which has been previously shown to affect AKI outcomes (24,25), was associated with higher risk of AKI progression in 12–72 hours but not over the first 12 hours.

In the setting of patients with AKI, the importance of adequate MAPs and renal perfusion can never be underestimated, because without adequate pressure, it would be unrealistic to expect renal recovery. It should be noted that the initial MAPs in those with and without invasive hemodynamic monitoring were no different ( $P=0.24$ ); however, in those with monitoring, MAPs (mmHg; median [interquartile range]) at the time of AKI were 71 (68–77) in progressors and 74 (70–79) in nonprogressors ( $P=0.01$ ). There was no significant difference in the early MAP between those with and without inpatient mortality, whereas survivors had higher cardiac indices DO<sub>2</sub>I ( $P=0.05$  for both).

This exploratory analysis investigating the role of cardiac index and oxygen delivery is quite exciting. Although this study suffers from all of the limitations of a retrospective, single-center, observational cohort, the idea that higher cardiac indices and/or oxygen delivery (more specifically, renal oxygen delivery) in the setting of very early AKI will improve AKI and patient outcomes is intuitive and attractive from an interventional standpoint.

Interventions aimed at maximizing renal oxygen delivery should be further investigated in the setting of those at high risk for AKI as well as those with the earliest stages of AKI. Investigations that use these baseline hemodynamic parameters should pair them with biochemical biomarkers of renal tubular injury (many of which have been discovered and validated in association with renal hypoxia) (7,9,10) and/or the furosemide stress test (11) (where furosemide has been shown to increase renal blood flow and renal tissue oxygen tension) (26). In combination, these risk prediction tools could trigger protocols designed to further optimize renal and systemic oxygen delivery. This renewed investigation of hemodynamic parameters by Raimundo *et al.* (23) is refreshing and fits with a recent call to better understand the physiology of AKI and to not solely rely on biochemical

biomarkers (27). This continued exploration of hemodynamic and physiologic parameters mirrors other efforts in critical care medicine, where there is a renewed focus on vital signs and other parameters to help risk stratify and prevent adverse patient outcomes (28,29). Although it is important to stress the need for prospective validation of these data, as a field we can remain hopeful that follow-up investigations will validate the findings of Raimundo *et al.* Additional investigation may even expand the window for intervention and modification of the AKI trajectory to a period of time longer than the initial 12 golden hours reported in this study (23).

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