The Furosemide Stress Test and Predicting AKI Outcomes

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In the distant past, the distinction between oliguric and nonoliguric ARF was headline news that was featured in a prominent medical journal.[1] That series of 92 patients was underpowered by modern standards and used an increase in serum creatinine of 2.0 mg/dl to define ARF, which corresponds to stage 3 AKI in the modern parlance.[2] Previously, nonoliguric ARF was associated with conditions that markedly increased catabolism (*e.g.*, burns), other causes of osmotic diuresis (*e.g.*, mannitol), or postobstructive diuresis. With the advent of widespread aminoglycoside antibiotic use, the prevalence of nonoliguric ARF increased and the contributions of exogenous toxins to AKI were better recognized. Most importantly, the observations on a well studied relatively small group of patients demonstrated that inpatient mortality was much better for nonoliguric ARF (26%) compared with oliguric ARF (50%).[1]

As is too often the case with association studies, the inference was drawn that fluid administration would convert oliguric to nonoliguric ARF and that short-term outcomes would be improved. It turns out this is not the case. Although fluid overload during AKI is associated with worsened outcome,[3–7] so is the aggressive administration of diuretics during the course of AKI. When adjusted for the fluid balance status, any apparent beneficial effect of diuretics in AKI can be explained by correction of fluid overload for which the diuretic was being administered.[7] In addition to the lack of any appreciable benefit of diuretic administration on clinical outcomes,[8] the ill-advised use of diuretics may delay the institution of more appropriate therapies.[6] In retrospect, the association described by Anderson *et al.*[1] is probably best explained by selection bias or confounding by severity.[9]

Nevertheless, there is a role for a diuretic challenge (in contrast with continued administration) in the management of AKI. Furosemide is an interesting agent; in addition to its obvious effect on the Na^+-K^+-Cl^-_2 cotransporter at the luminal surface of the thick ascending limb, its availability at that site requires renal blood flow and organic anion secretion in the proximal tubule, and the diuretic response requires no limitation to increased urine flow by downstream obstruction.[10] When faced with the patient with persistent oliguric AKI, administration of a single dose of furosemide was thought to be informative. If 200 mg of furosemide given intravenously was accompanied by a 200-ml increase in urine output over the next 4 hours in an oliguric euvolemic patient, then the clinical impression was that the patient was likely to recover sufficient renal function to avoid the need for inpatient dialysis. Conversely, the failure to respond to the diuretic challenge was felt to be ominous. This empirical approach was logically on the basis of the integrated functional requirements needed for a diuretic response, but it was never assessed in a prospective fashion, much less subjected to the rigors of peer review.

In the current issue of the *JASN*, Koyner and colleagues compare a furosemide stress test (FST) to a series of *au courant* biomarkers for predicting the severity of AKI in the hospital setting.[11] This article follows up on their previous report that defined and standardized the FST.[12] In brief, this diuretic challenge was developed in the setting of early AKI and consists of a one-time dose of 1.0–1.5 mg/kg intravenous furosemide in critically ill patients with stage 1 or 2 AKI. The primary outcome measure was progression to stage 3 AKI (need for renal replacement therapy, increased serum creatinine three times baseline, or urine output 0.3 ml/h per kg×24 hours) within 14 days of the diuretic challenge.[12] The area under the receiver operator characteristic curve for total urine output within 2 hours after the diuretic challenge was 0.87 for predicting progression to stage 3 AKI. The ideal cutoff for predicting AKI progression was urine output $<$100 ml/h for the first 2 hours after the diuretic challenge.[12] In this exercise, an extensive list of biomarkers was compared with the previously described FST results. None of the individual biomarkers significantly improved on the FST for predicting progression to stage 3 AKI, the subsequent need for inpatient renal replacement therapy, or inpatient mortality.[11] Perhaps most telling, the reported pilot study results did not demonstrate any statistically improved risk prediction when a biomarker panel was added to the FST results, but when FST was combined with the other biomarkers of AKI there was in improvement in risk prediction for all outcomes. There may have been a potential source of confounding because patients included in this study already had kidney injury; therefore, the performance of damage biomarkers may have been compromised by this *a priori* selection bias.

Even though limited by small numbers of patients (n=77), we can harken back to the classic study of Anderson *et al.* with 92 patients.[1] It is well recognized that urine output is an important characteristic related to the severity and even duration of AKI, and urine output criteria are included in the most current consensus definitions of AKI.[2] There are important limitations to obtaining urine flow rates. Although the most accurate assessment of urine flow is readily available in the critical care setting, the reality is that most patients with less severe AKI occur outside of the critical care setting.[13] An important strength of the FST is that it can be performed

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outside of a critical care unit where the possibility of obtaining a timed urine collection over 2 hours, even if bladder catheterization is needed, is more likely than obtaining complete collections over 24-hour intervals.

There did not seem to be any difference in response comparing furosemide-naïve patients with those who had previously been exposed to furosemide, albeit at least 6 hours elapsed between the prior furosemide exposure and the FST, in keeping with the dictum that "Lasix lasts 6 hours."[14] Realizing the FST is more than a test of renal reserve, but an assessment of integrated renal function (blood flow, organic acid secretion, thick ascending function, luminal patency, *etc.*), it seems likely that prior exposure to furosemide[15] may affect the sensitivity or dose response of the FST.

There is an issue in the definition of AKI that this study should bring into focus. The diagnostic criteria for AKI incorporate a time-dependent change in serum creatinine from the baseline value or a change in the urine flow rate. The baseline serum creatinine is a bit of a challenge[16]; it is operationally defined with reference to some antecedent outpatient value. In this work, the baseline serum creatinine is defined as the nadir of outpatient serum creatinine values for the 6 months before admission, or if those were not available, then the nadir of at least two serum creatinine values obtained before the FST was used to define the baseline value. The baseline creatinine is used to define the absolute or relative increase in serum creatinine that underlies the staging of AKI. In this respect, the previous work by Siew *et al.* is noteworthy,[17] where admission serum creatinine and nadir inpatient serum creatinine were compared with the outpatient creatinine obtained >7 days before admission. Using the first admission serum creatinine appeared to underestimate the incidence of AKI, whereas the last measured serum creatinine overestimated the incidence of AKI.[17] Some patients may have developed AKI before admission, which would explain the shortcomings of the first and last measured inpatient serum creatinine values as baseline. This area needs more evaluation because the use of previous outpatient serum creatinine is plagued by ascertainment bias (who has a serum creatinine measured, and why was it measured?). Furthermore, AKI is a global health problem,[18] and in many parts of the world previous outpatient creatinine values are simply not available.

This pilot study by Chawla and associates[11,12] obviously needs confirmation and prospective extension to more study sites and a larger number of participants. It will be important to see if the predictive power of the FST remains informative for patients who are not in the critical care setting and critically ill patients. It should not be surprising that larger numbers of less severe AKI patients are found in the noncritical care setting, and it is exactly for this group of AKI patients that the FST is designed to provide prospective risk stratification and prediction of AKI outcome. Perhaps perform an FST will join the usual nephrologic advice to match input and output and avoid nephrotoxins on the standard AKI consultation report for all patients developing AKI, whether they are in a critical care setting or not.

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DISCLOSURES

None.

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See related article, "Furosemide Stress Test and Biomarkers for the Prediction of AKI Severity," on pages 2023–2031.