Editorial Commentary

Furosemide responsiveness test—is there any reason to be afraid of diuretic use after cardiac surgery?

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Comment on: Su Y, Zhang YJ, Tu GW, *et al*. Furosemide Responsiveness Predicts Acute Kidney Injury Progression After Cardiac Surgery. Ann Thorac Surg 2024;117:432-8.

Keywords: Acute kidney injury progression (AKI progression); cardiac surgery; furosemide responsiveness; volume status

Submitted Jan 25, 2024. Accepted for publication May 31, 2024. Published online Jul 26, 2024.
doi: 10.21037/jtd-24-153
View this article at: https://dx.doi.org/10.21037/jtd-24-153

Acute kidney injury (AKI) is a common and serious complication in cardiac surgery patients as it carries an increased risk for morbidity and mortality. Post-operative AKI is due to multiple factors, including hemodynamic disturbances, both ischemic and congestive, that compromise renal perfusion, inflammation, oxidative stress and nephrotoxic exposure, among others (1).

Progression of AKI to higher severity stages is associated with poorer outcomes. Predicting the course of AKI can be challenging due to its heterogeneous contributors. There are several risk factors that may provide an increased likelihood of AKI progression and include the severity of AKI itself, worsening underlying illness, hemodynamic instability, fluid management, delayed recognition and treatment, exposure to nephrotoxic drugs, inflammatory response, age and frailty (2). However, physicians still lack the clinical tools to determine the likelihood of AKI progression for those with early stages of AKI. In patients with early AKI, several biomarkers, including plasma neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7) have demonstrated variable ability to predict AKI progression (3). However, the availability of these novel biomarkers may be limited by its expense. In this context, furosemide is being used to establish a triage decision for AKI progression because it is considered the most suitable diuretic for assessing renal tubular function. To achieve a urinary response to furosemide, three components must be considered: (I) furosemide must bind to albumin in the bloodstream, which can be affected by critical illness or low albumin levels; (II) furosemide is actively secreted by proximal tubules using the organic anion transporter (OAT) system, which can be impaired by uremia or metabolic acidosis; (III) transport of the furosemide in the lumen dissolved in the glomerular filtrate transported to the loop of Henle and binding to the Na-K-2Cl apical transporter. Acute tubular injury often disrupts epithelial polarity, causing the redistribution of Na/K ATPase from the basolateral to the apical membrane. This alteration impairs the sodium gradient across the tubule, hampering the secondary active transport of organic acids, including the urinary excretion of furosemide. This methodology to assess the integrity of the renal tubular function in the setting of AKI was first reported by Baek *et al.* in 1973 and later standardized in 2013. Results from the study showed

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that patients who had a poor response to furosemide were at higher risk for developing AKI. The 2-h urine output following the furosemide challenge was found to predict progression to stage 3 AKI and a composite of death or AKI progression within 14 days.

Since the completion of the initial pilot study, there have been several retrospective validations of this cutoff and more recently the publication of a multicenter prospective study, with same results (4). Despite it has also been proven that this test is feasible, safe and well tolerated in critically ill patients, there are concerns related to risk of hypovolemia and hypotension in post-cardiac surgery patients. Volume status has been classically measured by central venous pressure (CVP) but the widespread use of ultrasound among nephrologists and intensivists has created a new scenario. Point-of-care ultrasonography (PoCUS) helps with diagnosis, allowing a more accurate volume assessment, including tissue and vascular congestion in a more objective way (5). But even though these new tools exist, the use of low doses of furosemide are still more common than those proposed in the furosemide stress test (FST) in post-cardiac surgery scenario.

The current article by Su *et al.* (6) explores the possibility of an alternative assessment of furosemide responsiveness in post-cardiac surgery patients to include patients that have received a range of furosemide doses, many of those well below the required for FST. This FST alternative was used in a previous retrospective study in intensive care unit (7), however the quality of the evidence was low due to a small sample and the heterogeneous population (both medical and surgical) compared to the current study. Su *et al.* include the furosemide responsiveness index (FRI) calculated as total urine output (mL) in 2 h divided by dose of intravenous bolus furosemide (mg) and propose for standardization the modified FRI (mFRI) as the total urine output in 2 h divided by the dose of intravenous bolus of furosemide administered and body weight [mL/(mg·kg)/2 h]. They analyzed one prospective observational cohort (Zhongshan) and one retrospective cohort [Medical Information Mart for Intensive Care (MIMIC)-IV] and their key finding is that both FRI and mFRI were inversely associated with the risk of AKI progression and significantly improved prediction for AKI progression based on baseline clinical models that included clinically important variables such as preoperative diuretic exposure, baseline estimated glomerular filtration rate (eGFR), CVP and mean arterial pressure (MAP). Including MAP and CVP in the model is of notable importance since these variables determine mean perfusion pressure (MPP), which can be compromised if non optimal diuretic management is performed, with the subsequent risk of worsening AKI (8). Including previous diuretic use in the model also gives consistency to the results since tubular tolerance is well known to develop during the time that renal tubules are exposed to diuretic (e.g., by adaptive increase in reabsorption in the downstream distal tubule and collecting ducts that offsets ongoing blockade of Na^+ reabsorption in the loop of Henle) (9). In this regard, FST also considers this variable since the dose is adapted from 1.0 to 1.5 mg/kg depending on prior furosemide-exposure. On the other hand, like the FST, urinary output in the FRI and mFRI is also measured 2 h after the administration of the diuretic, without advantages related to time compared to the FST and adding more variables to the formula, which complicates its performance compared to a test that is quick, simple and sensitive.

There are some issues in the article by Su *et al.* (6) worth mentioning. When analyzing the population studied, the lack of homogenization in the two cohorts is notable even in the type of cardiac surgery performed and the non-standardized dose of furosemide evaluated, which varied from 5 to 160 mg. Some of these doses could be comparable to a usual FST, with the same risk of adverse events. This is important since one of the reasons for carrying out this study was analysis of a whole range dose of furosemide, including lower doses presumably administered because of the potential risk of adverse events by using high standardized furosemide dose required in FST. In that sense, data related to subgroup analysis for low doses (e.g., less than 60 mg) would have been interesting as well as evaluation of hemodynamic or volemic data related to adverse events after diuretic administration for the purpose of furosemide response. Unfortunately, there is little data regarding complications of FST and probably would be difficult to obtain in a population that may have received diuretics before and/or after the furosemide response test. In that regard, Rewa *et al.* evaluated the development of adverse events during the FST in 2019 in a prospective observational study and found episodes of hypotension that were satisfactorily resolved by administering parenteral solutions or by using vasopressor (10%), as well as hypokalemia (5%) and hypomagnesemia (5%) but critical life-threatening events were not reported during the FST (7). In order to perform a FST it is important to pay close attention to the underlying causes of oliguria and

the hemodynamic status of the patient. That is why the clinical evaluation and experience of the specialist in the use of diuretics are vital when performing this type of tests, which are usually performed in critically ill patients who may have received resuscitation with parenteral solutions and generally have positive fluid balance. Adverse events are dose and time dependent and in general, if well indicated, the doses established with the FST (up to 1.5 mg/kg) are very likely safe. In general, the risk of using furosemide will likely be high with daily doses higher than 1,000 mg per day of furosemide or its administration in continuous infusion for a long time, well above of that required to assess a furosemide response (10). Therefore, the dreaded adverse events are not supported by the standardized doses of the stress test.

The data obtained by Su *et al.* suggest that the FRI and mFRI are useful in predicting AKI progression in context of cardiac surgery over a wide range of doses, based not only on area under the curve (AUC) but also on the C-index, diuresis threshold, net reclassification, and integrated discrimination improvement index. However, this broad range does not contribute to standardizing the FR, so there is still a long way to go for FRI and mFRI to become a reality in routine practice.

In conclusion, the management of AKI in post-cardiac surgery patients involves a multidisciplinary approach that should address the underlying cause and provide supportive care to prevent progression. Regular assessment, early intervention and collaborative care among healthcare providers are crucial components of a successful prevention strategy. Multicenter prospective cohort studies are required to verify the performance of FRI and mFRI in predicting AKI progression in post-cardiac surgery as well as studies that compare them with FST to validate their efficacy.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article has undergone external peer review.

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-153/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-153/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Martínez-Chillarón M, Cupich AL, Piñeiro GJ, Molina-Andújar A, Poch López de Briñas E. Furosemide responsiveness test—is there any reason to be afraid of diuretic use after cardiac surgery? J Thorac Dis 2024;16(7):4825-4828. doi: 10.21037/jtd-24-153