Editorial

Search for a reliable biomarker of acute kidney injury: to the heart of the problem

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Provenance: This is an invited Editorial commissioned by Section Editor Wei Liu, MD (Department of Nephrology, The Affiliated Anqing Hospital of Anhui Medical University, Anqing, China).

Comment on: Ahmad T, Jackson K, Rao VS, *et al.* Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury. Circulation 2018;137:2016-28.

Submitted Aug 16, 2018. Accepted for publication Aug 21, 2018.
doi: 10.21037/atm.2018.08.23
View this article at: http://dx.doi.org/10.21037/atm.2018.08.23

Nephrologists are restlessly looking for an ideal biomarker of acute kidney injury (AKI). In particular, the search for a sensitive and specific "renal troponin" for a timely diagnosis of AKI is still an unmet need in the cardio-nephrology world. Unfortunately, under this premise, there is no one marker at the horizon ready to move into clinics and routine use at the current stage. This is probably due to a different biomarker-tissue selectivity of troponins and cardiac muscular tissue when compared to creatinine and renal tissue.

Troponin I and T are suitable biomarkers for myocardial infarction diagnosis because they reflect myocardial structure (1). To the contrary, renal tissue has a more complicated cellular organization due to concomitant presence of different subtypes of cells with unique function such as the glomerular, mesangial, tubular and interstitial cells. Hence, changes in serum creatinine could be the end result of several patho-physiological clinical conditions such as hypovolemia with reduced renal blood flow, nephrotoxic drugs, glomerular and interstitial diseases, sepsis, toxins and obstructive nephropathy (2).

Although some lines of evidence suggest that aggressive diuretic therapy could be accountable for worsening of renal function (WRF) in acute decompensated heart failure (ADHF), it is also possible that a temporary increase in serum creatinine could reflect a transient and reversible decrease in renal blood flow, not necessarily expression of tubular damage and AKI. Creatinine clearance is the product of glomerular filtration and tubular excretion and it is not an ideal biomarker to evaluate abrupt changes in renal function such as those occurring in AKI patients. Furthermore, serum creatinine (and cystatin-C) assessment is not validated in AKI and muscular metabolism, protein intake and several different drugs (with extra – renal excretion) can modify its distribution's volume biasing its relationship with acute and subtle change of renal function during AKI (3).

To verify the hypothesis that intensive and aggressive diuretic treatment in ADHF patients could lead to WRF due to tubular damage, Tariq Ahmad and coworkers have evaluated for biomarkers of tubular dysfunction 283 patients enrolled in the ROSE-AHF (renal optimization strategies evaluation-acute heart failure) study. In particular, authors simultaneously assayed *N*-acetyl-β-d-glucosaminidase, kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) both at baseline and after 72 hours. Although WRF, defined as a 20% decrease in estimated glomerular filtration rate (eGFR, assessed via cystatin-C) was observed in 21.2% patients no correlation between WRF and biomarkers of renal tubular injury was found (4). Of importance, in the ROSE-AHF furosemide was administered at high dose [median dosage: 560 mg/h i.v. (interquartile range, 300–815 mg)] to target a high urinary output [median: 8,425 mL/day (interquartile range, 6,341–10,528 mL)] questioning the postulated harm of intensive diuretic treatment (4).

Another message that can be derived by the Rose-AHF study is that neither serum creatinine nor cystatin-C are

ideal biomarker to monitor renal function during aggressive diuretic treatment to reduce vascular congestion and increase urinary sodium excretion in hypervolemic patients with heart failure and AKI (4). Indeed, about one in five patients experienced WRF irrespective of serial assessment of either serum creatinine or cystatin-C (4).

In ADHF patients, fluid overload can lead to impaired myocardial contractility and decompensated coronary artery ischemic disease with consequent reduction in effective renal blood flow and increase in sodium tubular reabsorption as well as central venous pressure (5,6). Remarkably, data suggest that venous hypertension can account for some of the impaired renal function by increasing the hydrostatic interstitial and tubular pressures within the kidneys (7). Furthermore, venous congestion has been linked with several pathophysiological changes such as endothelial activation, pro-inflammatory cytokines production as well as intestinal villi ischemia with consequent endotoxins translocation in the blood stream and further triggering inflammation (8). Hence, AKI in ADHF may be the final result of a vicious cycle towards venous congestion and neuro-hormonal hyperactivity rather than an unwanted side effect of aggressive diuretic treatment. In these regards, the ROSE-AHF study suggests that WRF in ADHF patients with fluid overload is not associated to tubular damage (no increase in serum levels of biomarkers of renal tubular injury was observed in WRF) and is unlikely related to the large doses of diuretic administered (WRF detected in only 21% treated patients).

How to put the results of the study by Tariq Ahmad and coworkers into perspectives? First, if the driver of renal outcome in ADHF is fluid overload *per se*, future endeavors are needed to test whether WRF during aggressive diuretic treatment is a real surrogate outcome or an "innocent bystander". Although the ROSE-AHF study failed to demonstrate an association of WRF and markers of renal tubular damage, it does not assess whether WRF is reversible. Hence, future randomized clinical trials (RCTs) are deemed to undoubtedly support the use of aggressive diuretic use (irrespective of serum levels of serum creatinine) to restore an optimal fluid balance in ADHF patients. Second, there is an urgent need for a sensitive biomarker of renal function in heart failure since serum creatinine changes have proved inaccurate and may induce inappropriate diuretic dose reduction or withdrawal.

Until new evidence become available, current results should reassure on the use of diuretics in ADHF patients and fluid overload, although caution should be constantly exerted in managing these fragile patients in consideration of the lack of reliable markers of renal function in this specific setting.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Di Lullo L, Di Iorio BR, Ronco C, Bellasi A. Search for a reliable biomarker of acute kidney injury: to the heart of the problem. Ann Transl Med 2018;6(Suppl 1):S5. doi: 10.21037/atm.2018.08.23

