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Creatinine and Cystatin C: Not the Troponin of the Kidney

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The current perception, based on data from earlier studies,is that worsening renal function (WRF) during diuresis of acute heart failure (HF) patients means that therapy is overzealous and exposes the patients to permanent kidney injury and increased mortality [1]. Underlying this view is the assumption that “increased serum creatinine (sCr) /cystatin C” and “acute kidney injury (AKI)” are interchangeable terms [1]. Recent findings, however, suggest that transient increases in sCr may instead reflect a benign, and potentially reversible hemodynamically-driven reduction in glomerular filtration rate (GFR), reflective of effective decongestion which is associated with improved outcomes [2]. Thus, serious harm continues to be perpetrated against patients with acute illnesses, including HF, by referring to “increased sCr/cystatin C”, “worsening renal function (WRF)”, and “acute kidney injury (AKI)”, as if they were merely different names of the same pathological entity. Ahmad and Colleagues in this issue of Circulation, while attempting to determine if renal tubular injury is the primary mechanism for WRF resulting from aggressive diuresis, came face to face with the reality that increases in either sCr or markers of tubular damage are at best poorly correlated with each other and with the diuretic effect and, at worse, may worsen outcomes due to premature cessation of decongestive therapies [3].

For myocardial infarction cardiac troponins (I and T) are widely considered adequate diagnostic biomarkers based on their myocardial tissue specificity and their association with important clinical outcomes [4].In contrast, assessment of renal status by sCr is not straightforward, as defective excretion of sCr can result from extrarenal hypovolemia, impaired blood perfusion, intrinsic kidney causes (due to sepsis, ischemia, drugs, toxins, interstitial or glomerular causes, or a combination of these conditions) or post-renal disease [5]. It is implausible, therefore, that creatinine, an end-product of muscle catabolism freely filtered by the glomerulus and secreted by the tubule, can discriminate between causes of renal dysfunction. Although measurement of sCr is cheap, widely available and standardized, its disadvantages include not only the many inducers of elevated sCr, but also the large number of conditions affecting its non-GFR determinants, including renal reserve, muscle metabolism, protein intake, volume of distribution, medications, and extra-renal degradation. In fact, equations estimating GFR using sCr have variable bias across populations, are imprecise despite standardization of sCr assays and inclusion of age, sex,

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race and body size as surrogates for creatinine generation [5]. These equations assume that sCr is a steady state marker of creatinine production and disposal, conditions which do not apply to AKI. An alternative to creatinine,cystatin C,is a protein produced in all nucleated cells and distributed in extracellular fluid.It is freely filtered and mostly reabsorbed and catabolized by the proximal tubule. While cystatin C is not affected by muscle mass or diet and less strongly associated with age, sex, and race than creatinine, smoking, inflammation, adiposity, thyroid diseases, malignancy, and glucocorticoids influence cystatin C levels, diminishing their value as a measure of renal excretory performance [5]. In addition, international standardization of the cystatin C assay is not finalized [5]. Estimation of GFR using either creatinine, cystatin C or both have not been validated in acutely ill patients, in whom these estimates appear to be inaccurate compared to 4-hour urinary creatinine clearance for detection of renal function changes [6].It is disappointing, therefore, that the severity of acute kidney injury (AKI) is predominantly classified according to sCr changes or cystatin changes [5, 7].This is because, in the absence of steady state, a patient may have florid tubular damage at presentation without significant changes in sCr due to renal reserve and consequent delay in achievement of detectable changes in this analyte. Conversely, the correlation of an increase in sCr levels with better outcomes during the treatment of HF, suggests that elevation of this analyte identifies physiological, volume-sensitive responses to diuretics, rather than tubular damage [2].

In this issue of Circulation, Ahmad and Colleagues expand the evidence that, in the context of aggressive diuresis of fluid overloaded HF patients, WRF, as defined by creatinine-based estimation of GFR, occurs without obvious renal tubular injury [3]. These findings support the notion that sCr-based AKI stages inaccurately describe the severity of excretory dysfunction and fail to provide information on whether tubular damage, if it occurs at all, is reabsorptive or excretory [7, 8]. Advances in kidney transcriptomics and urinary proteomics suggest that kidney genes and their encoded proteins can be specific for certain stimuli and cellular targets. Serum creatinine is not in this category because it can be elevated to similar extents in different experimental and clinical situations. Xu and Colleagues have found that different genetic signatures are activated by renal ischemia versus volume depletion [9]. Differential gene expression was also shown in thousands of patients presenting with a broad range of illnesses [10]. Hence, the dissociation between kidney cell lines transcriptomics/ urinary proteomics and sCr identified by Ahmad and Colleagues is likely due to differences in the intrinsic characteristics of sCr (delayed, insensitive, not specific to tubular damage) and the genetic responses of the kidney (rapid, sensitive, cell specific, stimulus specific) [8, 9, 11].Then why biomarkers of tubular injury, such as those measured by Ahmad and Colleagues, are not widely used in patients with decompensated HF to distinguish true tubular injury from changes in renal clearance function due to diuresis-driven hemoconcentration?Waikar SS and Colleagues observed that in predictive modeling the performance of biomarkers as measures of tubular injury is undermined by both use of sCr as the “gold standard”comparator and a lack of consideration of disease prevalence in the target population [11]. Assuming that, at a certain cutoff value, sCr is 90% sensitive and 90% specific and disease prevalence is 20%, a new biomarker with 100% sensitivity and 100% specificity, may seem to have only 69% sensitivity and 97% specificity compared with the “imperfect gold standard” [11]. Therefore, changes in therapy of acute HF patients based

only on sCr increases rather than biomarker and clinical data are problematic due to the kinetics and non-GFR determinants of creatinine and because they may trigger adjustments in or discontinuation of symptom- improving and/or life-saving anti-neurohormomal drugs and prevent effective decongestion [1, 8, 9, 11, 12].

Unfortunately, this fact is still viewed with skepticism despite the emerging evidence that unresolved congestion is strongly associated with poor outcomes [2, 12].Compared with normal subjects, even asymptomatic HF patients have decreased sodium excretion in response to volume expansion [1].Abnormal fluid handling is associated with physiological abnormalities in multiple organ systems. Increased myocardial water can lead to ischemia and decreased contractility in animals and humans [1]. Deranged hemodynamics, neurohormonal activation, excessive tubular sodium reabsorption, inflammation, oxidative stress, and nephrotoxic medications are important drivers of harmful cardiorenal interactions in HF patients [1]. Elevation of central venous pressure is rapidly transmitted to the renal veins, causing increased interstitial and tubular hydrostatic pressure, which decreases net glomerular filtration [1]. Increased central venous pressure is independently associated with renal dysfunction and unfavorable outcomes in both acute and chronic HF [1]. Venous congestion itself can produce endothelial activation, up-regulation of inflammatory cytokines, hepatic dysfunction, and intestinal villi ischemia. Bacterial endotoxins can then enter the circulation, magnifying the inflammatory milieu created by venous congestion and neurohormonal activity [1].Thus, the foremost goal in managing decompensated HF patients is to effectively resolve fluid overload [1, 12]. If a decrease in intravascular volume by fluid removal causes small transient increases in sCr, effective decongestion may still be essential to protect the kidney in the long term [1, 12].

While there were no consistent changes in neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-b-D-glucosaminidase (NAG) and kidney injury molecule-1 (KIM-1) suggesting that gross tubular injury cannot account for WRF (particularly since these three biomarkers map to different parts of the nephron and display different mechanisms of activation),Ahmad found that a small subset of patients demonstrated increases in biomarker urinary concentrations in the range of tubular damage seen in previous studies (e.g. the patients with delta NGAL>115ng/mg uCr) [3, 10]. Yet even in these patients, an increase in biomarkers of tubular injury did not worsen outcomes suggesting that fluid overload was a “greater evil” than some degree of renal tubular injury [1, 3, 12]. In addition, NGAL, NAG and KIM-1 levels in the cohort analyzed by Ahmad may have been magnified because they were indexed to urine creatinine (the denominator) which decreases with excretory abnormalities [13]. Hence, it seems premature to equate changes in NGAL, NAG and KIM-1 to injury even in the subset of patients with higher biomarker levels until thorough molecular and histologic characterization is available for all renal cells types. Finally, is there a possibility that NGAL and KIM-1 may be protective during AKI by, respectively, delivering iron and mediating phagocytosis [14,15]?

Unquestionably, Ahmad and Colleagues accomplish two important goals: they confirm that congestion is associated with poor outcomes in acute HF and shed light on the knowledge gaps in the identification of AKI and assessment of its severity, since hemodynamically-driven changes in sCr were not generally accompanied by changes in biomarkers of tubular

damage. While the absence of consistent changes in biomarkers supports continuation of decongestive treatments, increased confidence in these therapies will require documentation of WRF reversibility.

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