Are We Barking Up the Wrong Tree? Rise in Serum Creatinine and Heart Failure

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Abstract

A significant subset of patients with heart failure (HF) experience small to moderate rise in serum creatinine (RSC) in the setting of otherwise beneficial therapies such as aggressive diuresis or renin-angiotensin-aldosterone system (RAAS) inhibition. Accumulating data suggest that RSC in this setting is dissimilar from conventional causes of renal insult in that it has a negligible impact on the outcomes. There is also emerging evidence on the lack of association between biomarkers of renal injury and RSC in the setting of aggressive diuresis. A similar pattern has been observed in recent hypertension trials where the RSC in patients with intensive blood pressure control has not been associated with biomarker evidence of renal injury or adverse outcomes. Based on these findings, RSC, rather than acute kidney injury, appears to be the preferred terminology in HF (and possibly in hypertension) because of its purely descriptive nature that lacks any potentially inaccurate implication of mechanistic or prognostic reference. From a pragmatic viewpoint, we believe that small to moderate RSC is to be anticipated and tolerated with RAAS inhibition and/or aggressive diuresis in

acute or chronic HF and should not prompt discontinuation of the therapy unless complications such as hypotension and severe hyperkalemia develop.

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Since 2004, when the term acute kidney injury (AKI) was coined for renal insult represented by a rise in serum creatinine (RSC), our understanding of its pathophysiology in various settings (e.g., sepsis) has exponentially increased. Emergence of biomarkers and development of precision medicine have also helped further shape the field and capture AKI with increased sensitivity.

RSC is often considered somewhat synonymous with biochemically defined AKI, albeit with varying thresholds set or defined for RSC. Based on studies linking RSC to adverse outcomes, it is frequently used as a surrogate safety end point in clinical trials regardless of underlying biology, etiology, or setting. However, a growing body of evidence points to a disconnect between RSC and adverse outcomes in certain clinical circumstances casting doubt on the conventional notion that RSC and AKI are equivalent, represent the same renal process, and portend similar prognostic values. As such, several authors have expressed concerns not only on the accuracy and reliability of using consensus single RSC-based criteria to diagnose AKI but also on its prognostic value. In a meta-analysis

of contemporary trials, interventions that affected risk of mild to moderate RSC in placebo-controlled randomized trials showed no appreciable impact on chronic kidney disease or mortality, raising questions about the value of using small to moderate RSC as an end point in clinical trials altogether [1]. This phenomenon is even more pronounced in the cardiovascular field, especially in heart failure (HF).

Over the last decade, a multitude of studies in patients with acute decompensated HF (ADHF) have found that RSC during hospital admission for decongestion (also called “worsening renal function”, possibly a misnomer) is not associated with untoward outcomes, especially in the face of efficient extraction of excess fluid [2]. This observation seems to be inherent to the clinical setting and not to the decongestive strategy; a pattern similar to diuretic-based regimens has been observed with ultrafiltration therapy [3]. Renin-angiotensin-aldosterone system (RAAS) inhibition is another example that challenges the notion of RSC being equivalent to AKI in HF. RAAS antagonism represents a cornerstone of guideline-directed medical therapy for HF with reduced ejection fraction. RAAS inhibition changes glomerular hemodynamics secondary to a more pronounced vasodilation of the efferent arteriole and reduction of intraglomerular pressure, yielding a decrease in filtration fraction and thus RSC. However, since peritubular capillaries are supplied by the efferent arteriole that is dilated in the presence of RAAS antagonism, better oxygen delivery to the tubules could partially offset their negative effect on filtration. This plus anti-inflammatory effects of RAAS inhibitors could actually protect against renal insult. It has been shown that initiation or uptitration of neurohormonal antagonists, including RAAS antagonists, in patients admitted for ADHF is associated with improved outcomes despite higher rates of RSC [4]. This further reinforces the notion that the small to moderate RSC commonly encountered in the setting of otherwise beneficial HF therapies, such as aggressive diuresis or RAAS inhibition, is dissimilar from conventional causes of genuine AKI and has a negligible impact on the outcomes.

How can we explain this? It could be argued that all forms of RSC do represent renal insult and AKI (and are hence equally detrimental), but those cases of RSC provoked by aggressive diuresis or RAAS inhibition have this disadvantage offset by the mortality benefit of the respective therapeutic intervention. Data suggest that those ADHF patients who present with mild to moderate RSC during decongestion will have outcomes similar to those without RSC only if fluid overload is efficiently treated

(i.e., the confounding impact of lingering congestion) [5]. Similarly, patients with underlying cardiac and renal disease who experience RSC while on RAAS antagonists actually have superior long-term outcomes if RAAS inhibition is continued despite the RSC [6, 7].

An alternative explanation comes from more recent data suggesting that RSC in the context of aggressive diuresis of patients with ADHF does not represent renal insult (i.e., AKI) and is not associated with kidney tubular injury as detected by biomarkers [8]. While this is a novel observation, it is not totally unexpected. It is indeed reminiscent of the findings from Action to Control Cardiovascular Risk in Diabetes-Blood Pressure trial in which intensive blood pressure control was associated with RSC, but not with an increase in the levels of tubular injury biomarkers [9]. Even incident chronic kidney disease (i.e., prolonged RSC) in the setting of intensive BP control has been shown not to be accompanied with an increase in levels of kidney damage biomarkers, hence explaining its lack of correlation with adverse outcomes [10]. To acknowledge the fact that not all forms of RSC in HF are mechanistically and prognostically equivalent, a host of nomenclature has been proposed to distinguish these entities, albeit with uncertain clinical relevance [11].

So, what are the conceptual and practical considerations that could be concluded? First, until there are more data on various forms of RSC in HF, their underlying mechanisms, and their prognostic value, we would suggest not using RSC, AKI, and worsening renal function interchangeably. RSC remains our preferred term due to its purely descriptive nature that lacks any (potentially inaccurate) implication of mechanistic or prognostic reference. More importantly, in light of the data on the salutary impact of RAAS inhibition on mortality in HF even in the presence of RSC, small to moderate RSC is to be anticipated and tolerated and should not prompt discontinuation of RAAS antagonists unless other complications arise (e.g., hypotension or severe hyperkalemia). Despite absence of evidence of benefit, cessation of RAAS antagonists is common in patients admitted with ADHF who develop RSC, while it might conceivably increase the risk of acute hemodynamic deterioration and circulatory congestion in those patients previously stabilized with RAAS inhibition.

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