Serum Soluble ST2 as a Biochemical Marker of Acute Heart Failure

Future Areas of Research*

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The investigation into biochemical markers is modifying the approach to the diagnosis and management of heart failure (HF). Over the last decade, natriuretic peptides (NPs) have been shown to be particularly useful in confirming or refuting the diagnosis of HF as well as stratifying long-term risk profiles. Several novel cardiac, metabolic, and inflammatory biochemical markers have emerged in the field of HF, such as the soluble ST2 receptor (sST2).

The receptor ST2 is an interleukin (IL)-1 receptor (IL-1R) family member that has 2 primary isoforms regulated by different promoters. The transmembrane ST2 isoform (ST2L) is a membrane-bound isoform with 3 extracellular immunoglobulin G domains, a single transmembrane domain, and an intracellular domain homologous to Toll-like receptors and other IL-1Rs. The sST2 isoform lacks the transmembrane and intracellular domains. Both ST2L and sST2 are transcriptionally induced by mechanical strain in rat cardiomyocytes and cardiac fibroblasts (1,2), as well as by IL-1β, and phorbol ester in cardiomyocytes (1).

Recently, IL-33 has been identified as a functional ligand of ST2L. Sanada et al. (2) reported that IL-33 was transcriptionally induced by mechanical stretch, angiotensin II, and phorbol ester in cardiac myocytes and fibroblasts. IL-33 markedly blocked angiotensin II- and phenylephrine-induced necrosis factor (NF)-κB activation and hypertrophy in cardiomyocytes. After pressure overload by transverse aortic constriction, ST2−/− mice had more left ventricular hypertrophy, myocardial fibrosis, and chamber dilation, and decreased fractional shortening and survival compared with wild-type littermates (2). Furthermore, recombinant IL-33 treatment reduced hypertrophy and fibrosis and improved survival after transverse aortic constriction in wild-type mice, but not in ST2−/− littermates.

It has been found that treatment with sST2 antagonizes the ability of IL-33 to block angiotensin II- and phenylephrine-induced hypertrophy in cardiomyocytes (2). In addition, when cardiac fibroblasts are stimulated with phorbol ester, both sST2 and total IL-33 are induced, but unbound IL-33 diminishes (2). Collectively, these data suggest that sST2 functions in myocardium as a soluble decoy receptor and that the local ratio of IL-33 and sST2 could regulate IL-33-mediated signaling.

Recent experimental and clinical studies have reported an excess of serum sST2 in different cardiac conditions. Transient increase of sST2 has been found after myocardial infarction in mice subjected to coronary artery ligation (1). Increased levels of sST2 have been reported in the circulation of patients 1 day after acute myocardial infarction and correlated positively with creatine kinase and negatively with ejection fraction (1). In addition, it has been shown that high baseline levels of sST2 predicted congestive HF and mortality in patients with acute myocardial infarction at 30 days (3,4). Of interest, the combination of sST2 and amino terminal B-type natriuretic peptide (NT-proBNP) significantly improved risk stratification (4). Increased serum levels of sST2 have been reported in patients with acute dyspnea, whether due or not due to acute destabilized HF (5,6). Baseline serum sST2 level was also a strong and independent predictor of mortality at 1 year in these patients, its predictive ability being higher than the ability of NT-proBNP (5–7). Finally, abnormally high serum sST2 levels have been identified in patients with severe chronic HF (8). Change in sST2 over a 2-week period was a significant predictor of mortality or transplantation in these patients, independent of brain natriuretic peptide (BNP) and pro-atrial natriuretic peptide.

In this issue of the Journal, Rehman et al. (9) have analyzed the patient-specific characteristics with effects on serum sST2 values in a cohort of 346 patients with acute HF. In addition, the authors have explored the association between serum sST2 levels and outcome in these patients. Serum sST2 levels segregated with more severe New York Heart Association functional class symptoms, and presented an independent inverse association with ejection fraction. In addition, serum sST2 levels at presentation strongly predicted mortality from a few months from presentation to at least 1 year. In a multivariate Cox model containing established clinical and biochemical predictors, including BNP and NT-proBNP, sST2 remained a predictor of mortality. When both sST2 and NPs were elevated, the highest rates of death were observed in a cumulative hazard analysis.

Determination of disease severity and risk stratification in patients with acute HF is particularly challenging for physicians with currently available tools. Thus, the study by...
Rehman et al. (9) is timely for several reasons: 1) it shows for the first time that serum sST2 levels in acutely decompensated HF represent a biochemical marker of disease severity; 2) it confirms that serum sST2 is a powerful and accurate biochemical marker for prediction of near-term mortality in these patients; and 3) it adds prognostic performance to the standard biochemical marker, namely, NPs. There are, however, several pathological and clinical aspects not covered by the study by Rehman et al. (9) that will require further research.

First, as mentioned above, an excess of sST2 relative to IL-33 might be detrimental to the cardiomyocyte because of its ability to interfere with the cardioprotective effects of the biomechanically activated fibroblast-cardiomyocyte IL-33/ST2L paracrine system. Then, understanding of the true pathophysiological meaning of serum sST2 levels in patients with acute HF requires the simultaneous assessment of the circulating levels of IL-33.

Second, in addition to patients with acute HF and/or acute myocardial infarction, patients with asthma (10) or autoimmune diseases (11) may also have increased serum sST2 levels. Thus, it is necessary to prove that, in patients with acute HF, serum sST2 reflects what is occurring at the cardiac level. That proof will require performing invasive studies aimed to demonstrate the following: 1) that the myocardial expression of sST2 is associated with its serum level; 2) that there is a positive gradient from sST2 level measured in coronary sinus blood toward its level measured in peripheral vein blood; and 3) that serum sST2 is associated with alterations of left ventricular morphology and/or function that develop when the myocardium is submitted to biomechanical stress.

Third, no information is yet available on the impact of treatment-induced longitudinal changes in sST2 levels over time on the clinical outcome and long-term prognosis of the patient with acute HF. Two arguments support that an investigation in this area is important. On the one hand, the possibility exists that, besides its potential detrimental effects on the myocardium, sST2 may be beneficial under an immunological point of view. In fact, sST2 has been shown to inhibit the release of pro-inflammatory cytokines by human immune cells (12,13), and this property could be advantageous, taking into account that immune activation and increased production of pro-inflammatory cytokines play an important role in the progression of HF. On the other hand, among the criteria a biochemical marker should fulfill to be clinically useful is that the knowledge of its measured level should aid in medical decision making, particularly in selection of an appropriate therapeutic intervention. Because of the duality of actions of sST2 at the cardiac and immune levels mentioned here, the role of this molecule in selection of therapy and monitoring of response to therapy must be clarified.

In summary, the article by Rehman et al. (9) provides a strong basis for additional research aimed to definitively prove that circulating sST2 is a biochemical marker of the biomechanical stress of the myocardium, and that its incorporation into the clinical management of patients with acute HF will improve their care.

**Key Words:** biochemical marker • heart failure • soluble ST2.

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**REFERENCES**


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