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Invited Review

Is soluble ST2 a new marker in heart failure?

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Abstract

Objectives: The clinical diagnosis of heart failure (HF) is based on a history and a physical examination. Circulating molecules, such as troponin, B-type natriuretic peptide, and N-terminal pro-B-type natriuretic peptide are useful in the management of HF. Recently, it has been reported that a new biomarker, suppression of tumorigenicity (ST2), was associated with the prognosis of HF. ST2 is a cytokine and has 2 isoforms, a soluble (sST2) and a transmembrane receptor (ST2 ligand, or ST2L). The effects of ST2 are related to it binding to interleukin 33, which is a proinflammatory cytokine. sST2 acts as a decoy receptor in these interactions. sST2 plays a role not only in the pathogenesis of HF, but also in the pathogenesis of atherosclerosis. Additionally, an increased blood concentration of sST2 has been reported in several diseases. The most commonly used method is enzyme-linked immunoassay. However, there have been some methodological problems in the analysis of sST2. The aim of this review was to explore the biology and analytical considerations of ST2 and its clinical importance in HF.

Keywords: Cardiac marker, heart failure, inflammation, interleukin 33, soluble ST2

Heart failure (HF) is a chronic, progressive, complex cardiovascular disorder and is a major general health problem. HF results from structural or functional impairment of ventricular filling or ejection of blood. HF, whether due to systolic or diastolic dysfunction, is characterized by ventricular remodeling and variable degrees of myocardial fibrosis in response to cardiac injury or stress. The prevalence of HF has been increasing significantly with the aging population; it is now more than 23 million worldwide, and it remains a leading cause of mortality. To reduce the mortality and morbidity rates, the accurate identification of disease severity is very important in the management of HF [1, 2].

There is no single diagnostic test for HF. A clinical diagnosis of HF is based on a careful history and a physical examination. Some circulating molecules associated with inflammation, oxidative stress, vascular dysfunction, and myocardial and matrix remodeling have been identified and developed for HF management. Among these molecules, troponin, B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are already acknowledged in HF guidelines [3, 4]. According to the 2017 Report of the American College of Cardiology/American Heart Association, measurement of BNP or NT-proBNP is useful in establishing the prognosis or disease severity in chronic HF and is useful in determining the prognosis in acutely decompensated HF. In addition, it was suggested in this guideline that during a HF hospitalization, a predischarge natriuretic peptide level can be useful in establishing a post discharge prognosis. Like natriuretic peptides, the cardiac troponin level may be elevated in the setting of chronic or acute decompensated HF, indicating myocyte injury or necrosis [5].

An elevated plasma level of natriuretic peptide biomarkers is associated with a wide variety of cardiac (HF, acute coronary syndromes, heart muscle disease, valvular heart disease, cardiac surgery, etc.) and noncardiac (obesity, advancing age, anemia, renal failure, critical illness, etc.) causes [6, 7]. Troponins are also similarly increased in acute coronary syndromes and acute decompensated HF [8]. Therefore, the prognostic utility of natriuretic peptides and troponins is limited and their roles in guid-

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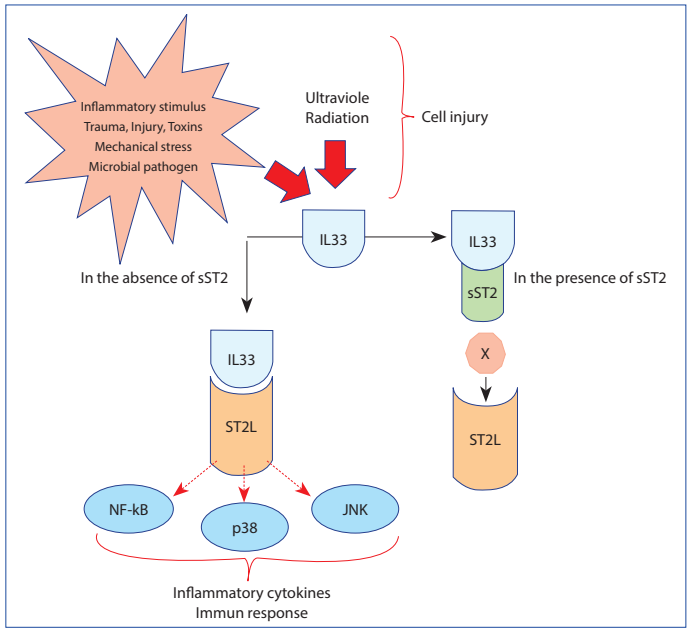

Figure 1. The interaction of interleukin 33 (IL-33) and the transmembrane receptor ST2 ligand (ST2L) activates mitogen-activated protein kinases and several biochemical pathways. The binding of soluble ST2 (sST2) to IL-33 results in the inhibition of the interaction between IL-33 and ST2L; sST2 acts as a decoy receptor in these interactions. An increased concentration of sST2 in the circulation attenuates the systemic biological effects of IL-33 on inflammatory processes.

JNK: C-Jun N-terminal kinase; NF-kB: Nuclear factor-kappa B.

ing treatment have not yet been clearly established. Thus, new molecular biomarker strategies to manage such patients are needed. Recently a new biomarker has become commercially available: suppression of tumorigenicity (ST2) [9, 10].

Biology of ST2

ST2 is a member of the Toll-like/interleukin (IL)-1 receptor superfamily. Due to its cell-signaling capacities, IL-1 plays a central role in the regulation of immune and inflammatory responses and is linked to the processes of infection and inflammation. The ST2 gene is located on human chromosome 2q12. Through alternative splicing, there are 2 isoforms of ST2: a soluble or serum circulating receptor ST2 (sST2) and a transmembrane receptor ST2 ligand (ST2L). ST2L contains an extracellular domain of linked immunoglobulin-like motifs, a transmembrane segment, and an intracellular cytoplasmic domain, whereas sST2 lacks the transmembrane and cytoplasmic domains. The extracellular immunoglobulin domain of ST2 has high homology to the same region of the IL-1 receptor. Although it is known that ST2L is constitutively expressed primarily in hematopoietic cells, the source(s) of circulating sST2 remains unknown. The expression of sST2 is largely inducible and almost ubiquitous in living cells, such as resting fibroblasts. It has been suggested that sST2 is produced by both cardiac fibroblasts and cardiomyocytes in response to injury or stress, and by macrovascular (aortic and coronary artery) and heart microvascular endothelial cells in response to diastolic load [9-12].

Until 2005, it was thought that ST2, as an important mediator in the inflammatory process, was associated with various inflammatory or immune diseases, such as asthma, pulmonary fibrosis, rheumatoid arthritis, vascular diseases, and septic shock [13-15]. The discovery of IL-33 in 2005 offered a new approach regarding the signaling mechanisms of ST2. IL-33 is expressed by a wide variety of cell types, including fibroblasts, mast cells, dendritic cells, macrophages, osteoblasts, endothelial cells, and epithelial cells, and induces helper T cells, mast cells, eosinophils, and basophils to produce type 2 cytokines [16]. IL-33 acts intracellularly as a nuclear factor (independently binding to the ST2L receptor) with transcriptional regulatory properties, and extracellularly as a pro-inflammatory cytokine [17]. In vitro, IL-33 antagonizes the effects of angiotensin-II and phenylephrine-mediated activation of nuclear factor kappa beta (NF-kB) in cardiomyocytes, an effect that is antagonized by ST2. As a cytokine, IL-33 binds to a receptor complex comprised of ST2L (also known as IL1RL1) and IL-1-receptor accessory protein. The interaction of IL-33 and ST2L activates mitogen-activated protein kinases and several biochemical pathways, including the activation of the inhibitor of NF-kB kinase signaling pathways. Thus, IL-33/ST2L signaling is involved in the immune response through the activation of T helper 2 effector cells and the release of T helper 2-related type 2 cytokines. IL-33/ST2L interactions are also related to several inflammatory diseases [18]. On the other hand, the binding of sST2 to IL-33 results in the inhibition of the interaction between IL-33 and ST2L; sST2 acts as a decoy receptor in these interactions. Thus, increased concentrations of sST2 in the circulation attenuate the systemic biological effects of IL-33 on T helper 2-dependent inflammatory processes [19]. Finally, ST2 systems have both inhibiting (through its interaction with sST2) and stimulatory (through its interaction with ST2L) effects on the effects of IL-33 (Figure 1).

In experimental studies, it has been shown that the expression of IL-33 and sST2 in both cardiac fibroblasts and cardiomyocytes increased in response to myocardial stress. Weingberg et al. [20] reported that ST2 was the most highly induced transcript in response to biomechanical stress, and sST2 and ST2L forms were induced in rat neonatal cardiomyocytes subjected to cyclic strain. In myocardial infarction models, myocardial expression of ST2 and serum ST2 was transiently increased in rats. It has been shown experimentally that the interaction between IL33 and ST2L reduces myocardial fibrosis, prevents cardiomyocyte hypertrophy, reduces apoptosis, and improves myocardial function [21, 22]. By blocking the ST2L receptor, the antihypertrophic and antiapoptotic effects of IL-33 were inhibited in cardiomyocytes [23]. Finally, experimental data are indicative of a cardioprotective role for IL-33 and ST2L signaling in cardiomyocytes. In other words, IL-33 shows specific, beneficial effects through the ST2L receptor.

Table 1. Clinical conditions in which soluble ST2 level was evaluated other than heart disease or cardiovascular disease

Disorders	Clinical conditions	References
Infections	Sepsis	13
	HIV infection	54
	Mild or severe influenza	55
Pulmonary diseases	Chronic obstructive pulmonary disease	56
	Allergic airway diseases	57
Liver diseases	Liver failure	58
	Primary biliary cirrhosis	59
Cancer	Gastric cancer	60
	Breast cancer	61
	Hepatocellular carcinoma	62
Endocrine disorders	Type 2 diabetes	63
	Obesity	64
Inflammatory diseases	Bowel disease	65
	Skin disorders, atopic dermatitis	66
Immune diseases	Autoimmune diseases	12
	Rheumatoid arthritis	67
	Sjogren syndrome	68
	Systemic lupus erythematous	69
	Behcet's disease	70
Neurological diseases	Alzheimer's disease-like pathology	71
	Amyotrophic lateral sclerosis	72
	Stroke	73
Renal diseases	End-stage renal disease	74
	Membranous nephropathy	75

In contrast to the cardioprotective effects of IL33/ST2L signaling, it has been reported that the addition of excessive amounts of sST2 result in blocking the beneficial effects of IL-33. In a model with acute myocardial infarction in rats, the mRNA cardiac expression levels of sST2 were rapidly upregulated during the first 4 weeks and positively correlated with the cardiac gene expression of remodeling markers, such as inflammatory and fibrosis markers [24]. In addition, it was reported in that study that no correlation was found between the IL-33 level and cardiac remodeling markers or between sST2 and apoptosis markers. Additionally, in a model of atherosclerosis, IL-33 treatment reduced atherosclerotic plaque size, macrophage, and T cell accumulation in the aortic sinus, and induced T helper 2 cytokines and oxidized-low-density lipoprotein. Furthermore, sST2 co-treatment was related to the development of larger atherosclerotic plaque and increased T helper 1 response [25]. These results suggest that sST2 was involved in not only the pathogenesis of HF but also the pathogenesis of atherosclerosis. The plasma/serum concentrations of sST2 increase in inflammatory conditions, rheumatoid arthritis, type 2 diabetes mellitus, sepsis, autoimmune diseases, liver failure, cancers, fibroproliferative diseases, and ulcerative colitis (Table 1). Therefore, more research is needed to clarify the roles of extracardiac sSH2 in pathological events [26].

Assays of Soluble ST2

There are commercially available, ready-to-use assay kits to measure human sST2 in serum/plasma. Enzyme-linked immunosorbent assays (ELISAs) are frequently used for the measurement of human sST2 in blood. Although more than 20 different ELISA kits for the measurement of human sST2 are commercially available, only 1 method has been cleared by the US Food and Drug Administration (FDA) and received the European Conformity Mark (Presage ST2 assay; Critical Diagnostics, San Diego, CA, USA). Recently, a rapid quantitative lateral flow immunoassay for the measurement of sST2 in human plasma has been developed for point-of-care testing, but it has yet to be approved by the FDA [27].

These assays have a detection limit of 0.002 to 1.3 ng/mL. The measurement ranges from 1.2 to 200 ng/mL. The interassay and intraassay coefficient of variation of these methods is between 6% and 10% and between 6% and 12%, respectively. Regression analysis revealed that there were major differences between methods. Concentrations of sST2 obtained with these assays are not directly comparable [27-28]. Differences between assays have also resulted from different standards and/or different antibodies, as well as different reagents and buffers. For this reason, understanding the distinctions between these assays will be important in the evaluation of published articles. It is unclear if the sum of “free sST2” and

"complexed sST2" were measured by ELISA because of the presentation of both free sST2 and complexed sST2 (sST2 bound IL-33) in blood circulation.

It has been reported that sST2 in plasma/serum was stable for 2 days at room temperature, for at least 1week at 4°C, and for at least 18 months at −20°C and at −80°C. There are no significant analytical interferences reported for ST2 from bilirubin, hemoglobin, triglycerides, cholesterol, total protein, or 49 therapeutic substances [27-30].

Blood Level of Soluble ST2

The most comprehensive study about the blood concentration of healthy subjects was conducted by Dieplinger et al. [27]. They reported that age-independent reference values were 3-28 U/mL in males (n=338), and 2-16 U/mL in females (n=190) and the overall mean for sST2 concentration was 12 U/mL (median: 10 U/mL; range: 5-34 U/mL). Another result of the study was that the difference required for 2 serial measurements of sST2 (referred to as the reference change value, RCV) for healthy individuals was 29.8% (index of individuality was calculated at 2.77; $p<0.05$) and the mean non-fasting sST2 concentration was higher than the fasting concentration (about 5%). Then the assay's manufacturer amended the analyte concentration definition to be in units of ng/mL rather than U/mL. Wu et al. [31] tested the analytical, intraindividual, and interindividual variation for sST2 and found that the RCV and the index of individuality was 30% and 0.25, respectively, and the 95th percentile limit for the Presage assay was 52.1 ng/mL for men and 33.6 ng/ mL for women. The notable points of the studies on biological variability are that the effects of confounding variables such as age, sex, renal function, and body mass index (BMI) are not included.

In a study by Rienstra et al. [32], the reference interval for sST2 was reported as 9-50 ng/mL in males (n=245) and 7-3 ng/mL in females (n=245). Lu et al. [33] reported that the plasma level of sST2 was unaffected by age, but was higher in males compared with females in the US population. Wang et al. [34] suggested that age, BMI, systolic blood pressure, diastolic blood pressure, and smoking did not affect the plasma sST2 level, and that the major influencing factor of sST2 level in the Chinese population was gender.

According to the results of the Framingham Heart Study, there was a significant difference between male and female subjects in plasma sST2 level; the reference interval for sST2 was 11-45 ng/mL in males (n=462) and 9-35 ng/mL in females. Additionally, in this well-characterized, community-based cohort study, it was reported that the plasma concentration of sST2 measured with ELISA increased with age, was associated with diabetes and hypertension, and was not significantly affected by BMI or renal impairment [35].

Mayo Medical Laboratories [36] found a median sST2 plasma concentration of 52.0 ng/mL for males (>18 years) and 38.7 ng/mL for females (>18 years) using ELISA. The median normal concentration of ST2 was reported as 18 ng/mL and concentrations greater than 35 ng/mL were strongly indicative of increased HF risk [36].

In a recently published Korean study, it was reported that gender-specific reference intervals should be used for the Korean population and that the use of a single cut-off value of 35 ng/mL cited in previous studies could be overcautious and result in the possibility of false positivity, especially in men [37]. Mueller et al.[28] measured median sST2 plasma concentration using 3 different assays and found that the median sST2 plasma concentration was 43.5 ng/mL, 0.375 ng/mL, and 0.144 ng/mL. Their results suggested that there was a significant difference in the serum sST2 level according to the used method.

Soluble ST2 and Heart Failure

Despite the potential role played by ST2 in inflammation, it has been suggested that there were significant parallel effects between ST2 and natriuretic peptides. This result indicated that ST2 represented a bridge between the inflammatory and neurohormonal systems [37, 38]. The emergency diagnosis of acute HF starts with clinical presentation and radiographic examination [4, 5]. Although BNP has been accepted as useful in the diagnosis and risk stratification of HF, the diagnostic accuracy of the BNP level between 100 and 500 pg/mL has been limited, and is referred to as the "BNP gray zone." It not clear if the determination of sST2 and BNP level in the gray zone supported the clinical diagnosis. It is noteworthy that there are controversial results in published studies.

The results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study [39] suggested that among dyspneic patients with and without acute HF, ST2 concentration is strongly predictive of mortality at 1 year and might be useful for prognostication when used alone or together with NT-proBNP.

Mueller et al. [40] investigated the sST2 level in patients with acute destabilized HF for 1 year and reported that median concentrations of sST2 were significantly higher in acute HF patients than in those without HF (0.50 vs 0.15 ng/mL) and that there was a strong relationship between sST2 concentration and 1-year mortality.

Henry-Okafor et al. [41] investigated the diagnostic and prognostic roles of sST2 and whether there was a diagnostic contribution of sST2 in patients with suspected HF. They used modified Framingham criteria for acute HF and outcome measures were final diagnosis of acute HF and 5- and 30-day adverse events. The sST2 concentration was higher in patients with HF in unadjusted analyses, but the authors indicated that there was a low diagnostic utility of sST2 after adjusting for a history of aspirin and steroid use, age, gender, race, and BMI. Their results also showed that sST2 did not add significant information to BNP in the diagnosis or prognosis. In another study [42], it was demonstrated that serial sampling of ST2 was predictive of 90-day mortality following acute destabilized HF and that the percent change in ST2 was equivalent to the percent change in NT-proBNP, and that both of these biomarkers

were better at predicting 90-day mortality than the percent change in BNP.

Weinberg et al. [43] reported that a change in ST2 level, but not the baseline ST2, was predictive of 30-day mortality in patients with chronic HF. Rehman et al. [44] suggested that prognostically, ST2 was powerful in acute HF and was synergistic with natriuretic peptides for this purpose, and that the highest rate of death was observed when both ST2 and natriuretic peptides were elevated in cumulative hazard analysis.

Hughes et al. [45] measured high-sensitivity sST2 in 8444 men and women (age range: 25-74 years) in the national FINRISK97 prospective population cohort of Finland. They evaluated the ability of sST2 to predict fatal and non-fatal HF; cardiovascular disease, including coronary heart disease and stroke; diabetes; and death over 15 years of follow-up. Their results indicated that in a healthy population from Finland, sST2 did not improve long-term prediction of cardiovascular events, including HF, or all-cause mortality, and that sST2 did not significantly improve prediction in addition to the Framingham risk factors alone or adjusted for NT-proBNP. They claimed that sST2 should not be considered for incorporation into risk scores for primary prevention of cardiovascular diseases.

Wang et al. [46] found that the use of multiple biomarkers in patients with cardiovascular stress added to the prognostic value of standard risk factors for HF and cardiovascular events. Tomaschitz et al. [47] suggested that there was further exploration to be done of sST2 and molecular mechanisms before they could meet the 9-step criteria (6 of which were recommended by the American Heart Association [48], and 3 were recommended by European Society of Cardiology Working Group [49]) on biomarkers for peripheral circulation.

Recommendations regarding the role of sST2 in general population-based testing, as formulated by the International ST2 Consensus Panel A, were presented by Ho et al. [50] They indicated that there might be a role for sST2 in the prediction of cardiovascular outcomes, potentially in a multimarker strategy including troponins and BNP, but the role of soluble ST2 testing in the general population has not yet been conclusively established. It also noted that future studies are needed to examine the clinical utility of soluble ST2 screening in the general population [50].

Recently, a novel, chronic HF risk tool, the Barcelona Bio-Heart Failure Risk Calculator (www.BCNBioHFcalculator.cat), was developed, and it incorporated clinical and biochemical biomarkers, including sST2, high-sensitivity cardiac troponin T, and NT-proBNP in chronic HF patients [51]. It has been reported that the multiple biomarker approach used by the new HF risk-calculator may be suitable for different pathophysiological pathways involved the prediction of death at 1, 2, and 3 years. However, the clinical routine outcomes of the use of this risk calculator are not yet clear; it requires further validation.

Additionally, the effects of therapy on the level of blood sST2 are not clear, and investigations are limited. Anand et al. [52] reported that, compared with a placebo, an angiotensin-converting enzyme (ACE)-inhibitor or beta blocker significantly reduced the rate of increase in sST2, whereas digoxin and diuretics were associated with higher concentrations ACE-inhibitors and beta-blockers were associated with lower sST2 concentrations in the Valsartan Heart Failure Trial. The results of the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study demonstrated that the mean sST2 level did not change for 3 months in treatment groups of patients with chronic HF [53]. The PROTECT (pro-BNP Outpatient Tailored Chronic Heart Failure Therapy) group assessed the response of sST2 to medications. The investigators found that changing the dose of a beta-blocker might affect the sST2 concentration in HF [54]. Miller et al. [23] published a review indicating a role for IL-33 and its receptor, ST2L, within cardiovascular disease, and the potential use of sST2 as a predictive cardiovascular biomarker.

Conclusion

The ST2/IL-33 pathway is involved in pathophysiology of myocardial dysfunction by potentially attenuating the cardioprotective effects of IL-33 as a result of reducing the extent of cardiac damage after cardiovascular events. sST2 could prevent the effects of IL-33/ST2L interaction. Measurements of blood sST2 level could be of clinical prognostic value in risk stratification of patients with myocardial infarction, HF, and dyspnea. Further studies are needed for a routine use of sST2 in HF. The main points for ST2 are:

1. ST2 is a clinically relevant biomarker reflecting pathophysiological processes bridging the inflammatory and neurohormonal systems, and may provide predictive information in several cardiovascular diseases, especially HF.

2. The utility of sST2 testing in the general population has not yet been established. Both community-based population studies and biological variation studies in patients with healthy and diseased status should be performed.

3. There was a significant difference in the plasma sST2 concentration of healthy patients based on gender in all of the methods examined: the blood sST2 level was higher in males than in females.

4. There are some methodological problems with the sST2 assay. Improving the analytical performance would likely improve the predictive value of the ST2 assay.

5. The method-based variations in blood sST2 levels should not be forgotten in patients with healthy or diseased status.

6. HF may be an important cause of a rise in sST2, but other pathologial processes, including inflammatory diseases (sepsis, heart diseases) may also lead to an increase. Therefore, sST2 may be considered a useful prognostic marker for such diseases.

7. IL-33/ST2L/sST2 proteins have distinct functions in different cells within different biological systems; more knowledge about the regulation of these systems is required. More

research of the role of ST2 for both therapeutic intervention and in the development and progression of atherosclerosis is needed.

8. It seems that the measurement of sST2 on admission might be a strong and independent prognostic biomarker in patients with acute and chronic HF. Serial measurement of sST2 theoretically could assist with therapeutic decisions for patients with HF.

Conflict of interest: None declared.

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