HHS Public Access

Author manuscript

J Hypertens. Author manuscript; available in PMC 2014 April 14.

Published in final edited form as:

J Hypertens. 2013 July ; 31(7): 1431–1436. doi:10.1097/HJH.0b013e3283611bdf.

Soluble ST2 predicts elevated SBP in the community

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Abstract

Background—Soluble ST2 (sST2) is an emerging prognostic biomarker in patients with existing cardiovascular disease. ST2 and its ligand, interleukin-33 (IL-33), are expressed in endothelial cells, and may play an important role in the development of early atherosclerosis and vascular biology. We sought to investigate the association of sST2 and progression of blood pressure (BP), as well as the development of hypertension.

Methods—Circulating sST2 concentrations were measured in 1834 participants (mean age 56 years, 57% women) of the community-based Framingham Offspring study. Participants were free of hypertension at baseline. Multivariable linear and logistic regression models were used to evaluate the association of sST2 concentrations and subsequent BP outcomes.

Results—Higher sST2 concentrations were associated with incident hypertension over 3 years of follow-up [multivariable-adjusted odds ratio per 1 standard deviation increase in sST2 1.22, 95% confidence interval 1.05–1.42, P =0.01]. Individuals in the upper sST2 quartile had a 2.6 mmHg greater increase in SBP compared with those in the lowest quartile (P for trend across quartiles

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Conflicts of interest

J.L.J. has received research grant funding from Critical Diagnostics, and has served on the advisory board for Critical Diagnostics.

0.002) and a 1.8 mmHg greater increase in pulse pressure (*P* for trend 0.005). In contrast, sST2 concentrations were not associated with changes in DBP (*P* =0.27).

Conclusion—These findings suggest that sST2 concentrations predict changes in BP physiology typically seen with aging and progressive arterial stiffness. Further studies are needed to elucidate underlying mechanisms by which the ST2/IL-33 pathway may contribute to BP physiology.

Keywords

biological markers; blood pressure; epidemiology; hypertension; immune system; risk factors

INTRODUCTION

Hypertension affects over a quarter of all men and women over the age of 18 years [1], and it is the single most important risk factor for cardiovascular disease in older individuals [2]. An estimated seven out of 10 patients with incident myocardial infarction or incident heart failure have preceding hypertension [2].

The ST2 pathway is emerging as an important component of cardiovascular response to mechanical stress. ST2 is a member of the interleukin (IL)-1 receptor family, whose expression in cardiomyocytes is upregulated in response to stress [3]. The membrane-bound form of ST2 interacts IL-33 (released from fibroblasts), leading to antihypertrophic and antifibrotic effects in the myocardium [4,5]. IL-33 is also expressed in endothelial cells, in which it induces expression of adhesion molecules and inflammatory activation, and expression of IL-33 has been detected in human atherosclerotic plaque, suggesting an important role in vascular biology; in this regard, IL-33 activity has been theorized to retard atherosclerotic progression [6]. Soluble ST2 (sST2) consists of the extracellular domain of the ST2 molecule, and may act as a decoy receptor for IL-33, blocking myocardial and vascular benefits, experimentally leading to progressive myocardial remodeling and atherosclerosis, respectively [4,6].

In clinical studies, circulating sST2 concentrations are associated with a worse prognosis in patients with heart failure [7–11], acute dyspnea [12], and acute coronary syndrome [13,14]. Although higher sST2 concentrations have previously been weakly correlated with hypertension and SBP cross-sectionally [9,11,15], the relation of sST2 to incident hypertension is unknown. Therefore, we evaluated the association of sST2 concentrations to longitudinal blood pressure (BP) changes and incident hypertension in an ambulatory community-based population, in order to explore a possible pathophysiologic pathway, by which ST2/IL-33 may contribute to cardiovascular risk.

METHODS

Study sample

The Framingham Heart Study (FHS) Offspring study is a prospective, observational community-based study [16]. Children (and spouses of the children) of FHS original-cohort participants were enrolled in 1971 and have been followed with serial examinations. Of 3532 participants attending the sixth examination (baseline, 1995–1998), 3273 participants

returned for follow-up at the seventh examination (1998–2001). Of these, 52 were excluded due to missing BP data, 1305 were excluded due to prevalent hypertension at the baseline examination, 34 due to missing sST2 measurement, eight due to heart failure, 33 due to coronary heart disease, one due to stage IV chronic kidney disease [defined as estimated glomerular filtration rate (eGFR) <30 ml/min per 1.73 m^2], and six due to missing covariates, leaving 1834 for inclusion in this study. All participants provided informed consent and the study was approved by the appropriate Institutional Review Board.

Clinical assessment

BP was measured in the left arm using a mercury sphygmomanometer, with the participant in a seated position after at least 5 min of rest. The examination BP was the average of two physician-obtained measurements. Hypertension was defined as a SBP at least 140 mmHg, a DBP at least 90 mmHg, or current use of antihypertensive medication. Change in SBP, DBP, and pulse pressure was defined as the continuous change between the baseline and follow-up examinations.

BMI was calculated using weight and height (kg/m^2). Participants regularly smoking cigarettes during the prior year were considered current smokers. Diabetes mellitus was defined as a fasting glucose at least 126 mg/dl, non-fasting blood glucose at least 200 mg/dl, or the use of insulin or oral hypoglycemic medications. Total and high-density lipoprotein cholesterol levels were obtained, and eGFR was calculated using the Modification of Diet in Renal Disease equation [17]. Cardiovascular events were adjudicated by a three-physician panel after review of medical records. History of major coronary heart disease was defined as prior myocardial infarction or acute coronary insufficiency (prolonged ischemic symptoms with new electrocardiographic abnormalities in the absence of biomarker elevations indicative of infarction). Heart failure was defined using FHS criteria [18].

Laboratory testing

sST2 concentrations were measured on blood samples (plasma) collected at the sixth examination. Samples were collected after an overnight fast, and were immediately centrifuged for storage at −80°C. sST2 concentrations were measured using a high-sensitivity sandwich immunoassay (Presage ST2; Critical Diagnostics, San Diego, California, USA) [19]. The assay has a lower detection limit of 2 ng/ml, and within-run and total coefficients of variation are 2.4% or less and 4.0% or less, respectively.

Statistical analysis

sST2 concentrations were log-transformed due to a right-skewed distribution. Multivariable linear regression models were used to examine the association of sST2 concentrations and change in SBP, DBP, and pulse pressure between the baseline and follow-up examination. Models were first adjusted for age and sex, and further adjusted for baseline SBP and DBP, BMI, diabetes, and smoking status. Multivariable logistic regression was used to examine the association of baseline sST2 concentrations and incident hypertension. Incident hypertension and change in BP were also examined across sST2 quartiles, with the lowest quartile serving as the referent. We tested for a trend of increasing risk of hypertension and

greater increase in BP across quartiles of sST2 (coded values 1, 2, 3, 4). Analyses were conducted using SAS, version 9.1.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

The baseline characteristics of our sample are shown in Table 1. A total of 1834 participants were included in this analysis, with a mean age of 56 years and 57% women. Baseline SBP was 119 ±12 mmHg and DBP was 73±8 mmHg.

Soluble ST2 and change in blood pressure parameters

For the overall sample, the SBP changed by 2.3 ±12.4 mmHg (P <0.0001), and the DBP by 0.4 ±7.7 mmHg (P =0.03) over a mean follow-up period of 3 years. Each one SD increase in log-sST2 concentration was associated with a 0.9 mmHg increase in SBP [multivariable-adjusted β estimate 0.94, standard error (SE) 0.30, P =0.002; Table 2]. Each increasing sST2 quartile was associated with a greater increase in SBP over the follow-up period, with individuals in the highest sST2 quartile having a 2.6 mmHg greater increase in SBP compared with those in the lowest quartile (β estimate 2.61, SE 0.86, P for trend 0.002).

sST2 was similarly associated with increasing pulse pressure over the course of 3 years, with individuals in the highest sST2 quartile having a 1.8 mmHg greater increase in pulse pressure when compared with participants in the lowest quartile (β estimate 1.78, SE 0.68, P for trend 0.007). In contrast, sST2 concentrations were not associated with changes in DBP over the follow-up period (P =0.27).

Soluble ST2 and incident hypertension

During a mean follow-up period of 3 years, 296 individuals developed new-onset hypertension. Each one standard deviation (SD) increase in log-sST2 concentration was associated with a 2% increased odds of incident hypertension [multivariable-adjusted odds ratio (OR) 1.22, 95% confidence interval (CI) 1.05–1.42, P =0.01; Table 3]. The odds of new-onset hypertension increased across sST2 quartiles (P for trend 0.008) as displayed in Fig. 1. The incidence of hypertension over the 3-year follow-up period was 12% in quartile 1, 15% in quartile 2, 18% in quartile 3, and 20% in quartile 4. Specifically, the highest sST2 quartile was associated with a 1.8-fold increased odds of hypertension when compared with the lowest quartile (multivariable-adjusted OR 1.79, 95% CI 1.17–2.73, P =0.01).

Secondary analyses

Exclusion of individuals with wheezing, asthma, or those taking glucocorticoids for inflammatory conditions (n =186) did not materially change results (Supplemental Digital Content, http://links.lww.com/HJH/A254).

DISCUSSION

Our findings indicate that sST2 is associated with BP-related outcomes in the community. Notably, sST2 predicted increases in SBP and pulse pressure, but not DBP, consistent with changes in BP physiology typically seen with aging and concomitant progressive increase in arterial stiffness [20]. Prior clinical studies have demonstrated the prognostic role of sST2 in

cardiovascular disease, and sST2 in combination with other novel biomarkers appears to improve risk prediction of cardiovascular events in the community [21]. We sought to explore a possible physiologic mechanism by which sST2 may be linked to cardiovascular disease, and observed a strong association with BP progression, suggesting a potential pathway by which the ST2/IL-33 pathway may contribute to increased cardiovascular risk.

Prior clinical studies have focused on participants with existing cardiovascular disease, wherein sST2 was only weakly associated with SBP [11,13] and hypertension [9] cross-sectionally, with other studies showing no such association [14,22]. These seemingly discrepant data are not surprising, given the fundamental differences in patient cohorts: the association of sST2 and BP may be obscured in patients with acute heart failure or acute coronary syndrome, as other mechanisms may be predominantly determining both BP and sST2 levels in these settings. Our cohort, in contrast, is the first to examine sST2 in relation to incident hypertension in a stable, carefully characterized and ostensibly healthy community-based cohort, wherein elevated sST2 concentrations may be more clearly linked to underlying pathways leading to hypertension.

ST2 is emerging as an important mediator of ventricular remodeling, as well as a valuable prognostic marker in cardiovascular disease [7–9,11,13,22–24]. In addition to mediating myocardial response to stress [4,7], the ST2/IL-33 pathway may also play an important role in vascular biology. ST2 and its ligand IL-33 are both expressed in human endothelial cells [25,26], and IL-33 is also expressed in human atherosclerotic plaque [6].

Whether the ST2/IL-33 pathway confers protective or harmful vascular effects, remains unclear. Recent studies indicate possible protective effects [27], which may be immune-mediated, as membrane-bound ST2 is expressed on Th2 but not Th1-type T-helper cells [28]. IL-33 drives the production of Th2 cytokines [29], and as atherosclerosis is predominantly a Th1-driven process [30], it would imply that IL-33 might have potential vasculoprotective effects. This has indeed been shown in an apolipoprotein $E^{-/-}$ mouse model given a high-fat diet, in which IL-33 reduced the development of atherosclerosis and formation of foam cells [31,32]. In this model, IL-33 caused a shift in immunological response from Th1 to Th2, and reduced the development of atherosclerosis; conversely, treatment with sST2 had a neutralizing effect on IL-33 and resulted in greater atherosclerosis [31]. In contrast, IL-33 in human endothelial cells promoted angiogenesis, vascular permeability, and endothelial activation with expression of vascular adhesion molecules, an important contributor to endothelial dysfunction and early atherosclerosis [6,33]. A pro-atherogenic effect was also supported by studies demonstrating modulation of ST2 and IL-33 expression in endothelial cells via IL-1β and tumor necrosis factor-α [34,35], and IL-33-mediated release of IL-6 and IL-8 by endothelial cells [36].

Although further work is needed to reconcile and understand these experimental data and the role of sST2 in vascular biology, our findings support a robust link between sST2 and multiple BP measures. Our observational data clearly cannot infer underlying biological mechanisms; however, it is possible that vascular effects of the ST2/IL-33 pathway – either immune or atherogenic – may lead to progression of predominantly SBP found in our study. It is unclear whether atherosclerosis leads to increased arterial stiffness and isolated systolic

hypertension [37,38]; however, it is becoming increasingly clear that inflammatory and immune mechanisms may contribute to hypertension [39], and it is plausible that ST2/IL-33 may play a role in this process. Contemporaneous assessment of arterial stiffness was not performed in our cohort, and further studies are needed to elucidate potential underlying mechanisms.

Our study has several limitations worth mentioning. First, sST2 concentrations were measured only at the baseline examination, and the relation of changes in sST2 concentrations to BP is not known. Furthermore, measurement of circulating IL-33 relative to sST2 concentrations would have been of mechanistic interest [40], and would have allowed for more meaningful interpretation of the sST2 data, but was not technically feasible in this cohort. Our analysis included only participants who were seen at follow-up examinations to ascertain BP-related outcomes, which may have resulted in survivor bias. However, these potential limitations would have likely biased our results toward the null. Finally, the changes in BP observed over the 3-year follow-up period were small, and clinical implications of our findings remain to be determined. Our study sample was predominantly white and generalizability to other populations is not known, as mechanisms of hypertension may vary across different ethnicities. Further analyses of multiethnic groups are needed to confirm our findings.

CONCLUSION

In summary, we found that circulating sST2 concentrations predicted both progression in SBP and pulse pressure in relatively healthy, community-dwelling adults. These findings suggest that the ST2 pathway may play an important part in BP physiology, and thus may in part contribute to cardiovascular risk. Future studies, including investigations focused on the role of IL-33 in modifying the association of sST2 and BP outcomes, are needed to elucidate the underlying mechanism by which ST2/IL-33 leads to clinical vascular disease.

Acknowledgments

Measurement of the sST2 assay was performed by Critical Diagnostics Inc.

This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195). J.E.H. is supported by an American Heart Association Clinical Research Program award. S.C. is supported by an award from the Ellison Foundation.

Abbreviations

BP	blood pressure
CI	confidence interval
eGFR	estimated glomerular filtration rate
FHS	Framingham Heart Study
OR	odds ratio
sST2	soluble ST2

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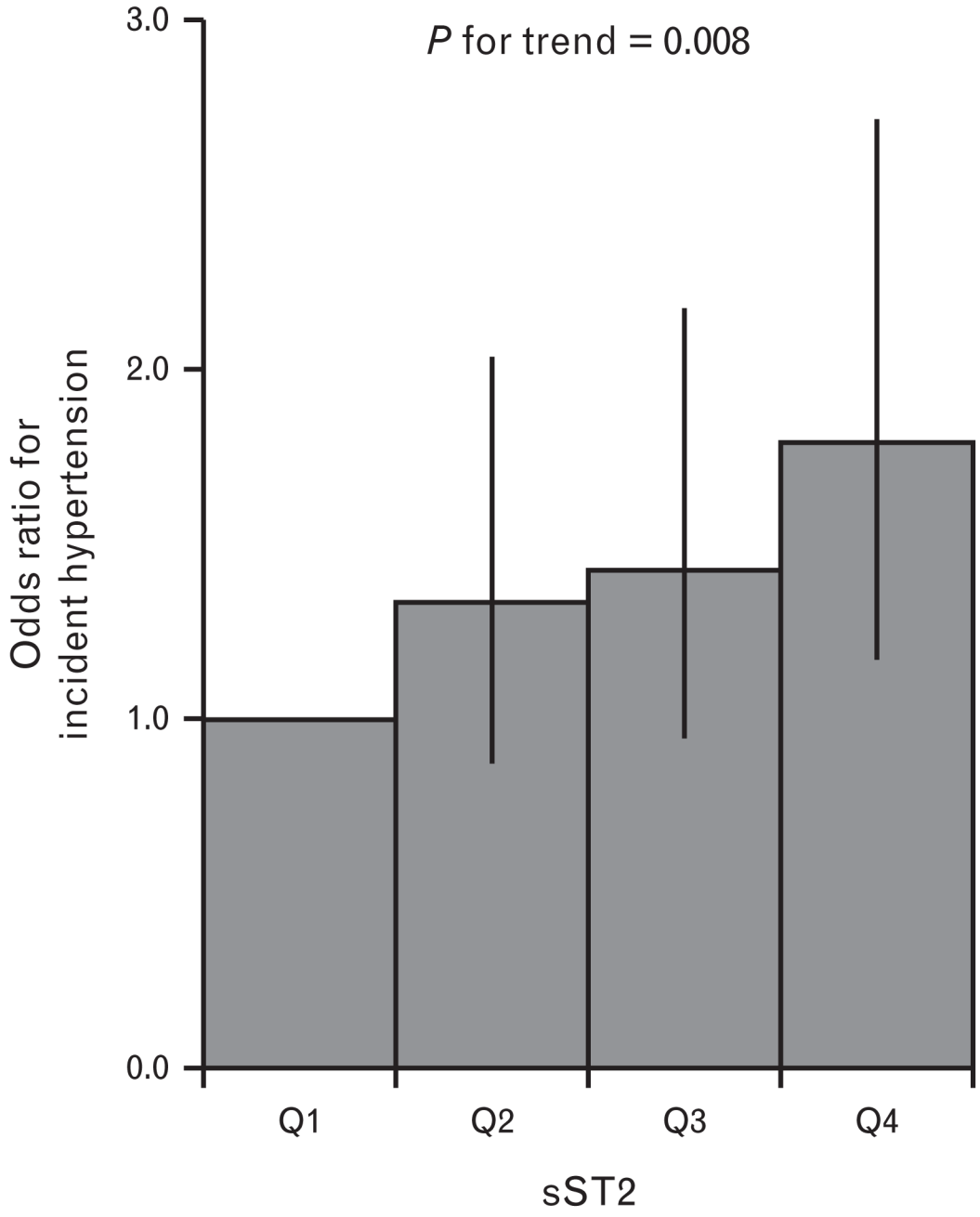

FIGURE 1.

Odds ratios of incident hypertension by soluble ST2 quartiles. Soluble ST2 (sST2) quartile cut-points are 16.0, 19.9, and 24.8 ng/ml. Error bars represent 95% confidence intervals.

TABLE 1

Baseline characteristics of 1834 Framingham Heart Study participants free of hypertension

	Total sample (*n* =1834)
Age, years	56 (9)
Women, *n* (%)	1049 (57)
SBP, mmHg	119 (12)
DBP, mmHg	73 (8)
BMI, kg/m^2	27 (5)
Diabetes mellitus, *n* (%)	81 (4)
Current smoker, *n* (%)	303 (17)
Laboratory characteristics	
Total cholesterol, mg/dl	205 (38)
HDL cholesterol, mg/dl	53 (16)
sST2 concentration, ng/ml, median (25–75%ile)	19.9 (16.1–24.8)

GFR, glomerular filtration rate; HDL, high-density lipoprotein; sST2, soluble ST2. Values are mean (standard deviation), unless otherwise indicated.

TABLE 2

Association of soluble ST2 concentration and change in blood pressure

		Age-adjusted and sex-adjusted model		Multivariable-adjusted model[a]	
Predictor	**Outcome**	**β estimate (SE)**	***P***	**β estimate (SE)**	***P***
Log-sST2[b]	SBP	0.94 (0.31)	0.002	0.94 (0.30)	0.002
Log-sST2[b]	DBP	0.21 (0.19)	0.27	0.20 (0.18)	0.27
Log-sST2[b]	Pulse pressure	0.73 (0.26)	0.005	0.75 (0.24)	0.002
Quartile 1	SBP	Referent		Referent	
Quartile 2		0.26 (0.82)		0.31 (0.80)	
Quartile 3		0.94 (0.83)		1.08 (0.81)	
Quartile 4		2.61 (0.86)		2.58 (0.85)	
P for trend			0.002		0.002
Quartile 1	Pulse pressure	Referent		Referent	
Quartile 2		0.46 (0.69)		0.37 (0.64)	
Quartile 3		0.77 (0.70)		0.87 (0.65)	
Quartile 4		1.82 (0.73)		1.78 (0.68)	
P for trend			0.01		0.007

sST2 quartile cut-points are 16.0, 19.9, and 24.8 ng/ml. BP, blood pressure; MAP, mean arterial pressure; sST2, soluble ST2.

[a] Adjusted for age, sex, SBP and DBP at baseline, diabetes mellitus, BMI, and smoking.

[b] Odds ratio listed is per 1 standard deviation increase in log-sST2.

TABLE 3

Association of soluble ST2 concentration and incident hypertension

	Age-adjusted and sex-adjusted model		Multivariable-adjusted model[a]	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Log-sST2[b]	1.21 (1.06–1.39)	0.006	1.22 (1.05–1.42)	0.01
Quartile 1	Referent		Referent	
Quartile 2	1.28 (0.87–1.90)		1.34 (0.88–2.04)	
Quartile 3	1.52 (1.03–2.23)		1.43 (0.94–2.18)	
Quartile 4	1.77 (1.20–2.62)		1.79 (1.17–2.73)	
P for trend		0.003		0.008

sST2 quartile cut-points are 16.0, 19.9, and 24.8 ng/ml. CI, confidence interval; OR, odds ratio; sST2, soluble ST2.

[a] Adjusted for age, sex, SBP and DBP at baseline, diabetes mellitus, BMI, and smoking.

[b] Odds ratio listed is per 1 standard deviation increase in log-sST2.