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Association between the level of serum soluble ST2 and invasively measured aortic pulse pressure in patients undergoing coronary angiography

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Abstract

Despite the well-documented value of ST2 in heart failure and myocardial infarction, the role of ST2 in vascular biology has not yet been well defined. This study was performed to investigate the association between serum soluble ST2 (sST2) and invasively measured aortic pulse pressure (APP). A total of 167 consecutive patients with suspected coronary artery disease (CAD) (65.1 ± 9.8 years; men, 65.9%) referred for invasive coronary angiography was prospectively enrolled. APP was measured at the ascending aorta with a pig-tail catheter, and arterial blood samples for the measurement of sST2 were collected before coronary angiography. Serum sST2 levels were quantified by radioimmunoassay. Most of the patients (73.9%) had significant CAD (stenosis ≥ 50%) on coronary angiography. Patients with higher APP (≥76 mmHg) showed a significantly higher sST2 level compared to those with lower APP (<76 mmHg) (31.7 ± 13.9 ng/mL vs 26.2 ± 10.2 ng/mL, $P < .001$). In simple correlation analysis, there was a significant positive correlation between sST2 levels and APP ($r = 0.413$, $P < .001$). In multiple linear regression analysis, sST2 had an independent association with APP even after controlling for potential confounders ($\beta = 0.331$, $P < .001$). The serum sST2 level may be independently associated with invasively measured APP in patients undergoing coronary angiography. The result of this study gives insight into the role of sST2 in aortic stiffening, and suggests that the sST2 level may be a useful marker of aortic stiffness.

Abbreviations: APP = aortic pulse pressure, BMI = body mass index, BPP = brachial pulse pressure, cfPWV = carotid-femoral pulse wave velocity, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, ICA = invasive coronary angiography, IL-33 = interleukin-33, LDL = low-density lipoprotein, SD = standard deviation, sST2 = soluble ST2, ST2 = suppression of tumorigenicity 2, VIF = variance influence factor.

Keywords: aortic pulse pressure, aortic stiffness, cardiac catheterization, soluble ST2

1. Introduction

The suppression of tumorigenicity 2 (ST2) receptor is a member of the interleukin-1 receptor family, expressed in various tissues including cardiomyoctyes and endothelial cells, and secreted in response to cell damage.[1] Interleukin-33 (IL-33) was identified as a functional ligand for the ST2 receptor.[2] In response to cardiacstress and injury, IL-33 binds to the ST2 receptor, and play a cardioprotective role through anti-fibrotic and anti-inflmmatory actions.[3] This cardioprotective IL-33/ST2 signaling pathway is neutralized by soluble ST2 (sST2), which acts as a decoy receptor of IL-33.[3] As a result, the high level of sST2 is associated with increased hemodynamic stress of the heart. Recently, the clinical importance of sST2 in cardiovascular disease has been highlighted because the prognostic value of sST2 has been revealed, especially in patients with ischemic heart disease and heart failure.[4–9] Recently, sST2 has emerged as a new prognostic biomakrer in myocardial infarction and heart failure. To a lesser extent, the role of the ST2/IL-33 pathway in vascular biology has also been suggested in a few studies. Demyaets et al have shown that IL-33 was detected in human atheromatous plaque, and suggested that the ST2/IL-33 system involves in the progression of atherosclersosis.[10]

Aortic pulse pressure (APP) reflects the pulsatile component of blood pressure and aortic stiffness. When the aorta is stiff in clinical conditions, such as ateriosclerosis, arteriosclerosis, or arterial injury, APP increases proportionally.[11] APP is clinically important, because it is associated with organ damage and clinical prognosis independent of traditional risk factors.[12–16] Brachial pulse pressure (BPP) is inaccurate in representing APP, because of systolic amplification, and less powerful in predicting of cardiovascular risk than APP.[17] Several noninvasive methods have been applied to derive APP by analyzing applanted carotid or raidal pulses[18]: however, their estimation of APP have some

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range of errors. Although invasive cardiac catheterization is still the gold standard for calculating APP, it is impractical in clinical settings. Therefore, there has been liminted data on APP obtained by invasive hemodynamic studies.

Considering the role of ST2 in the modulation of inflammation and fibrosis in the cardiovascular system, its influence on aortic stiffening can be expected. However, no study has been conducted to investigate the association between ST2 and aortic stiffness. Therefore, this study was performed to test whether there was a correlation between ST2 levels and APP.

2. Methods

2.1. Study population

This single-center study was performed at Boramae Medical Center (Seoul, Korea). Between January 2013 and July 2014, patients who underwent elective invasive coronary angiography (ICA) were prospectively recruited. ICA was performed for suspected coronary artery disease. A total of 232 paitents were initially screened, however, patients with following conditions were exclued: 1) acute or old myocardial infarction, 2) ongoing chest pain, 3) unstable vital signs, 4) left ventricular ejection fraction <50%, 5) the presence of regional wall motion abnormalies, 6) valvular dysfunction greater mild degree, and 7) the presence of pericardial effusion. Finally, a total of 167 patients were analyzed in this study. We obtained information on demographic characteristics, including age and body mass index (BMI), as well as traditional risk factors, including history of hypertension, diabetes mellitus, dyslipidemia, and ischemic heart disease. BMI was calculated using wieght and height (kg/m^2). Diabetes mellitus was defined as a previous hsitory of diabeters or anti-diabetic medications at the time of the study. Hypertension was defined as a previous history of hypertension or anti-hypertensive medications at the time of the study. Dyslipidemia was defined as a previous history of dyslipidemia or anti-dyslipidemic medicationsat the time of the study. Current smokers were defined as paitents who regularly smoked cigarettes during the last 12 months were considered. Venous blood samples for laboratory tests were collected after overnight 8-h fasting, and white blood cell count, hemoglobin, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglyceride, and serum creatinine were measured. The estimated glomerular filtration rate (eGFR) was calculated using the following formula: $175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$ ($\times 0.742$, if woman).[19] Transthoracic echocardiography was performed and left ventricular ejection fraction was calculated using Simpson's biplane method. Information on concomitant mediations was obtained, which included calcium channel blocker, beta-blocker, renin-angiotensin system blocker, nitrate, and statin. The study protocol was approved by the Institutional Review Board of Boramae Medical Center (Seoul, Korea), and informed consent was obtained from each study patient.

2.2. Cardiac catheterization

Measurements of APP were made immediately before ICA as previously described.[20] Briefly, aortic pressure was measured using a fluid-filled pigtail catheter placed in the ascending aorta within the patient supine. The catheter was flushed with saline and confirmed the absence of bubbles or clots before pressure recording. Pressure tracing was recorded using a hemodynamic monitoring system (Horizon XVu-hemodynamic monitoring system, Mennen Medical, Haifa, Israel). APP was calculated as the difference between the peak systolic pressure and the pressure at end-diastole. The average value of 3 to 5 consecutive beats was used for the analysis. During the APP measurement, brachial systolic and diastolic blood pressures were also measured using oscillometric method, and BPP was calculated as the difference between the brachial systolic blood pressure and diastolic blood pressure. ICA and percutaneous coronary intervention were performed in accordance with current guidelines. CAD extent was classified on the basis of ICA findings. Luminal narrowing more than 50% of the major epicardial coronary artery or main branches with diameter ≥2 mm was considered significant coronary artery stenosis. Cardiac catheterization was performed by a single experienced interventional cardiologist.

2.3. Measurement of soluble ST2

Patients were overnight fast for at least 8 h. Arterial blood was drawn from the femoral or radial artery in the supine position before coronary angiography. Blood samples were immediately cooled and centrifuged at 3000 rpm for 15 min, and the serum was frozen and stored at −70 °C until assayed. Serum sST2 levels were measured in the banked serum samples using a commercially available kit (The Presage ST2 Assay, Critical Diagnostics, San Diego, CA, USA). The minimum detectable concentration was 3.1 to 200.0 ng/mL. The intra-assay and inter-assay coefficients of variations for sST2 were 5.1% and 5.2%, respectively.

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are expressed as percentages. Patients were stratified into 2 groups according to the median value of APP (=76 mm Hg), and clinical characteristics of these 2 groups of patients were compared with Pearson's chi-square tests for categorical variables or Student's t tests for continuous variables. Univariate associations between APP and other variables were assessed using Pearson's bivariate correlation analysis. Scatter plots were used to demonstrate linear correlations between sST2 levels and APP. Multiple linear regression analysis was performed to examine independent relationships between sST2 and APP. Variables having a significant correlation ($P < .05$) with APP in simple correlation analysis were adjusted during the multivariable analysis. When the study population was stratified into the 2 groups by the presence of hypertension, only variables showing statistically highly significant association with APP ($P < .001$) in univariable comparison were controlled during multivariable analysis. Variance influence factor (VIF) was used to overcome multicollinearity problems during multivariable analysis.[21] All independent variables entered in multiple regression analysis indicated that VIF was <3.0. This seemed to exclude serious problems with multicollinearity. A P value of <.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 18.0 (IBM Co., Armonk, NY, USA).

3. Results

3.1. Baseline characteristics of the study patients

The mean age of the study patients was 65.1 ± 9.8 years; and the majority (65.9%) were male. The baseline characteristics of the study patients according to the median value of APP (=76 mm

Table 1

Baseline characteristics of study patients.

Characteristic	Patients with APP < 76 mm Hg (n = 83)	Patients with APP ≥ 76 mm Hg (n = 84)	P
Age, years	60.5 ± 10.1	69.6 ± 7.0	<.001
Female sex, n (%)	15 (18.1)	42 (50.0)	<.001
Weight, kg	69.0 ± 10.1	65.1 ± 11.6	.021
Height, cm	164 ± 7	159 ± 9	<.001
Body mass index, kg/m^2	25.6 ± 3.0	25.3 ± 3.5	.554
Risk factors, n (%)			
Hypertension	46 (56.8)	69 (82.1)	<.001
Diabetes mellitus	21 (25.9)	34 (41.0)	.041
Dyslipidemia	30 (37.0)	40 (47.6)	.169
Cigarette smoking	28 (34.6)	12 (14.3)	.002
Laboratory findings			
Total cholesterol, mg/dL	147 ± 35	146 ± 34	.857
LDL cholesterol, mg/dL	83.4 ± 32.5	86.3 ± 32.7	.578
HDL cholesterol, mg/dL	42.0 ± 10.8	42.2 ± 9.7	.917
Triglyceride, mg/dL	127 ± 87	108 ± 45	.096
Estimated GFR, mL/min/1.73 m^2	82.3 ± 20.1	70.4 ± 23.2	<.001
LVEF, %	63.8 ± 10.1	65.3 ± 9.0	.304
Concomitant medications, n (%)			
Calcium channel blocker	23 (28.4)	21 (25.0)	.622
Beta-blocker	39 (48.1)	36 (46.4)	.825
RAS blocker	39 (48.1)	40 (47.6)	.946
Nitrate	13 (15.6)	18 (21.4)	.377
Statin	57 (70.4)	55 (65.5)	.501
The results of ICA, n (%)			.706
Insignificant stenosis	23 (28.4)	20 (23.8)	
One vessel disease	26 (32.1)	24 (28.6)	
Two vessel disease	14 (17.3)	20 (23.8)	
Three vessel disease	18 (22.2)	20 (23.8)	
Hemodynamic parameter, mm Hg			
Brachial SBP	124 ± 18	140 ± 19	<.001
Brachial DBP	75.8 ± 17.1	75.7 ± 10.4	.984
Brachial PP	46.7 ± 12.7	64.0 ± 16.5	<.001
Aortic SBP	131 ± 15	166 ± 17	<.001
Aortic DBP	74.2 ± 11.6	74.3 ± 12.8	.956
APP	57.0 ± 11.8	92.9 ± 13.4	<.001

APP = aortic pulse pressure, DBP = diastolic blood pressure, GFR = glomerular filtration rate, HDL = high-density lipoprotein, ICA = invasive coronary angiography, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, PP = pulse pressure, RAS = renin–-angiotensin system, SBP = systolic blood pressure.

Hg) are shown in Table 1. Patients with higher APP (≥76 mm Hg) were older (69.6 ± 7.0 years vs 60.5 ± 10.1 years, $P < .001$) and more frequently female (50% vs 18%, $P < .001$) than those with lower APP (<76 mm Hg). Patients with higher APP (≥76 mm Hg) were lighter (65.1 ± 11.6 kg vs 69.0 ± 10.1 kg, $P = .021$) and shorter (159 ± 9 cm vs 164 ± 7 cm, $P < .001$) but had a similar BMI (25.3 ± 3.5 kg/m^2 vs 25.6 ± 3.0 kg/m^2, $P = .554$) compared to those with lower APP (< 76 mm Hg). The prevalences of hypertension (82.1% vs 56.8%, $P < .001$) and diabetes (41.1% vs 25.9%, $P = .041$) were significantly higher in patients with higher APP (≥76 mm Hg) than those with lower APP (<76 mm Hg). Otherwise, smokers were more frequent in patients with lower APP (<76 mm Hg) (34.6% vs 14.3%, $P = .002$). Among laboratory parameters, estimated GFR was signficantly lower in patients with higher APP (≥ 76 mm Hg) as compared to those with lower APP (< 76 mm Hg) (70.4 ± 23.2 mL/min/1.73 m^2 vs 82.3 ± 20.1 mL/min/1.73 m^2, $P < .001$). Concomitant medications and CAD extent were not different between the 2 groups ($P > .05$ for each). In hemodynamic parameters, brachial systolic blood pressure (140 ± 19 mm Hg vs 124 ± 18 mm Hg, $P < .001$) and pulse pressure (64.0 ± 16.5 mm Hg vs 46.7 ± 12.7 mm Hg, $P < .001$), and central aortic systolic blood pressure (166 ± 17 mm Hg vs 131 ± 15 mm Hg, $P < .001$) and pulse pressure (92.9 ± 13.4 mm Hg vs 57.0 ± 11.8 mm Hg, $P < .001$) were significantly higher in patients with higher APP (≥ 76 mm Hg) than those with lower APP (<76 mm Hg). Otherwise, diastolic blood pressures measured at both brachial artery (75.7 ± 10.4 mm Hg vs 75.8 ± 17.1 mm Hg, $P = .984$) and central aorta (74.3 ± 12.8 mm Hg vs 74.2 ± 11.6, $P = .956$) were similar between the 2 groups.

3.2. Univariate associations between APP and sST2

Patients with higher APP (≥76 mm Hg) showed a significantly higher sST2 level compared to those with lower APP (<76 mm Hg) (31.7 ± 13.9 ng/mL vs 26.2 ± 10.2 ng/mL, $P < .001$) (Fig. 1). The sST2 level had a significant positive correlation with APP ($r = 0.413$, $P < .001$). Although BPP also showed a positive correlation with sST2, its correlation power was weaker than APP ($r = 0.159$, $P = .042$) (Fig. 2).

3.3. Independent association between APP and sST2 levels

Multiple linear ligression analysis showed that the sST2 level was independently associated with APP even after controlling for potentinal confounders including age, sex, height, hypertension,

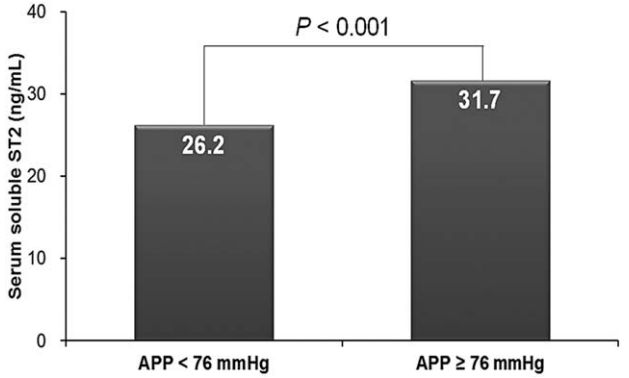

Figure 1. Scatter plot showing the linear associations of sST2 with aortic pulse pressure (A) and brachial pulse pressure (B).

diabetes, smoking, estimated GFR ($\beta = 0.331$, $P < 0.001$) (Table 2). Independent association between sST2 and APP remained significant in both group of patients with ($\beta = 0.384$, $P < .001$) and without ($\beta = 0.362$, $P = .007$) hypertension (Table 3). Age, sex, height and estimated eGFR were considered as potential confounders and controlled in this multivariable analysis.

Table 2

Independent factors associated with aortic pulse pressure.

Variable	β	*P*	VIF
Age	0.456	<0.001	1.356
Female sex	0.218	.023	2.709
Height	0.032	.736	2.682
Hypertension	0.126	.049	1.220
Diabetes mellitus	0.088	.146	1.096
Smoking	−0.030	.639	1.199
Glomerular filtration rate	0.073	.272	1.340
Soluble ST2	0.331	<0.001	1.068

VIF = variance inflation factor.

4. Discussion

In the present study, we explored the association between sSTs levels and APP. The serum sST2 level is independently associated with invasively measured APP. To our knowledge, this is the first report focusing on the association between sST2 level and APP, and suggests that the sST2 may be a new and valuable biomarker of aortic pulsatile hemodynamics and stiffness.

4.1. Association betwween sST2 levels and APP

sST2, a new emerging biomarker, has mainly been investigated with regard to cardiac fibrosis and remodeling in patients with heart failure and myocardial infarction.[4–8] Compared to cardiac disease, however, the role of sST2 in vascular biology is not well defined. Ho et al measured sST2 levels in 1834 healthy adults in the community, and reported that a higher sST2 level correlats with increased brachial systolic blood pressure and brachial pulse pressure during a 3-year follow-up period.[22] Similary, other studies also showed weak and positive associations between sST2 levels and brachial blood pressure.[8,9] Although these data are in line with ours, our study deserves more attention, because it used invasively measured APP, a reliable indicator of central aortic stiffness.[23] Actually, correlation between BPP and sST2 was weaker, supporting the pathophysiological difference between APP and BPP.[24,25] It has generally been accepted that central aortic pressure more accurately reflects loading conditions of the left ventricle, coronary arteries, and cerebral vasculature and thereby, better correlates with cardiovascular target organ damage and other related events than dose brachial pressure.[17,24,26] Recently, Andersson et al investigated 1823 Framingham Heart Study participants, and showed that sST2 was positively associated with carotid-femoral PWV (cfPWV).[27] Given that cfPWV is considered as gold standard nonivasive measure of central aortic stiffness, this finding is consistent with our study result.

Although mechanisms underlying the association between sST2 levels and APP have to be established, several explanations can be suggested with reference to the physiology of ST2 system. It is plausible that impaired regulation of the ST2 system may be involved in aortic stiffening, because ST2 is closely related to organ fibrosis and inflammation,[28] both of which are well-known risk factors for aortic stiffening.[29] In support of this

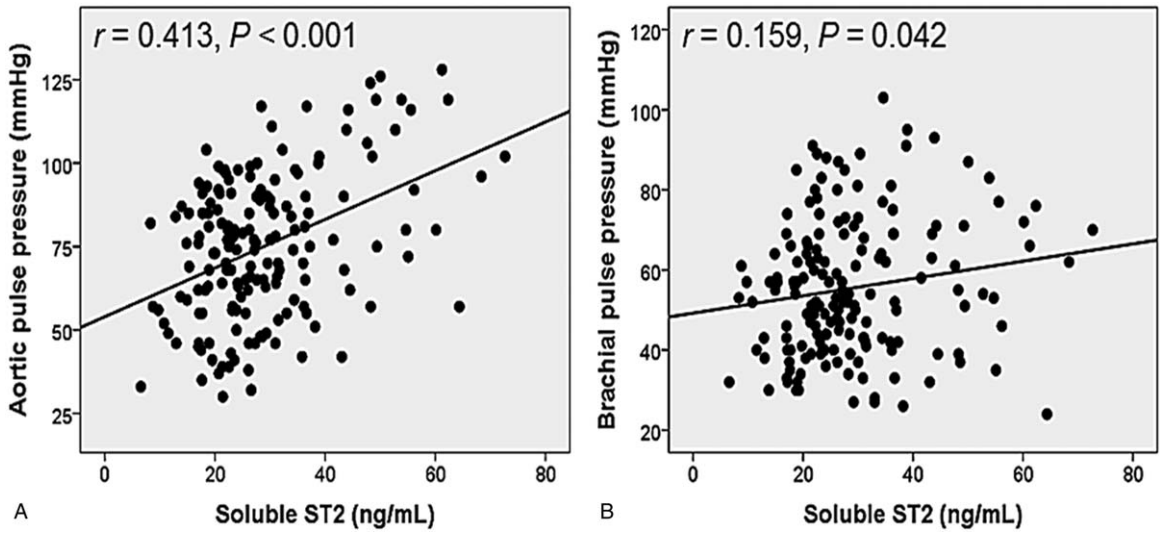

Figure 2. Serum sST2 levels according to APP. APP, aortic pulse pressure.

Table 3

Independent factors associated with aortic pulse pressure according to the presence of hypertension.

	Hypertension (−) (n = 52)			Hypertension (+) (n = 115)		
Variable	β	***P***	**VIF**	β	***P***	**VIF**
Age	0.680	<.001	1.313	0.414	<.001	1.213
Female sex	0.307	.018	2.001	0.165	.205	2.839
Height	−0.122	.338	2.008	0.029	.205	2.847
Glomerular filtration rate	0.258	.015	1.315	0.035	.683	1.270
Soluble ST2	0.362	.007	1.073	0.384	<.001	1.053

VIF = variance inflation factor.

view, it has been reported that the ST2/IL-33 system was activated in atheromatous plaque, and involved in the development of atherosclerosis in humans.[10] A recent animal study also showed that ST2 was expressed in the rat aorta, and promotes extracellular matrix production from vascular smooth muscle cells leading to aortic fibrosis, inflammation and hypertrophy.[30] In ApoE (−/−) mice, treatment of sST2 increased atheroma size in the aorta.[31] On the contrary, it is also possible that the sST2 level can be increased in response to conditions associated with increased aortic stiffness, and that the sST2 level is a marker of aortic stiffening. Additional studies are necessary to test these hypotheses.

4.2. Clinical implications

APP is a reliable indicator of aortic stiffness that is an important indicator of future cardiovascualr events in various populations.[32] Therefore, identification of objective biomarkers reflecting aortic stiffness is clinically valuable. Several potential biomarkers, such as C-reactive protein, have been recognized as markers of aortic stiffness.[33,34] However, reliability of the single biomarker is insufficient. Our study results suggest that sST2 can be a valuable marker of aortic stiffness, and may provide additional information when used in combination with other parameters, but not alone. In addition, the association between sST2 levels and APP suggests a potential pathway how the ST2 system increases cardiovascular risk. Our results provide an important insight into the pathophysiology of aortic stiffness in relation to inflammation and fibrosis, as well as how to use the sST2 level for risk stratification and treatment strategies. Now sST2 level can be obtained during routine blood test, therefore, information on sST2 may help identify high-risk subjects with higher APP, especially in mass screening. This implies that the usefullness of sST2 could be applied to normal subjects or other cardiovascular conditions besides heart failure and myocardial infarction. Furthermore, our results can be extended to the development of a new potential therapeutic target. As there has been lack of effective way to reduce aortic stiffness, investigations focusing on new molecules targeting sST2 for the improvement of arotic stiffness may be valuable.

4.3. Study limitations

This study has several limitations. Firstly, this observational study is inherently limited by lack of randomization, thus, it is difficult to rule out bias and confounding effects of clinical parameters as possible alternative explanatios for the association between sST2 and APP. Secondly, cross-sectional analysis could not identify the causal relationship between sST2 levels and APP. Similary, sST2 levels and APP were measured at the same time, and thus, changes in APP according to serial alterations in sST2 are difficult to evaluate. Longitudinal studies are needed to confirm the changes. Thirdly, acquisition of data on the serum levels of IL-33 or B-type natriuretic peptides, which may help interpret of our data, was not feasible. Fourthly, although we showed a statistically significant correlation between sST2 levels and APP, the correlation power was only modest. Therefore, it is suggested that sST2 is not a unique surrogate of aortic stiffness. Finally, our study population consisted of patients with known or suspected CAD undergoing coronary angiography, therefore, our results may not be applicable to other populations. In fact, both the values of APP and BPP in our study are higher compared to previous studies investigating general population.[35]

5. Conclusion

The sST2 level may be independently associated with invasively measured aortic stiffness in patients undergoing coronary angiography. This result provides an important insight into the role of sST2 in the development of aortic stiffening, and suggests that sST2 may be a useful marker of aortic stiffness. Longitudinal studies with a larger sample size are needed to confirm our results.

Author contributions

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