

Relationship Between Left Ventricular Geometry and Soluble ST2 in a Cohort of Hypertensive Patients

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Left ventricular (LV) hypertrophy (LVH) is classified according to geometric pattern into 4 types: concentric hypertrophy, eccentric hypertrophy, concentric remodeling, and normal geometry. Prevalence of death and cardiovascular complications associated with hypertension depend on the geometric pattern. Although soluble ST2 levels, a novel cardiac biomarker of mechanical strain is increased in hypertension, the relationship with hypertensive LV geometric patterns has not been studied. The authors investigated the relationship between soluble ST2 levels and LV geometric patterns in a cohort of hypertensive

patients. LVH was considered present when echocardiographic LV mass index exceeded 49.2 g/m^{2.7} in men and 46.2 g/m^{2.7} in women. Patients with concentric hypertrophy had higher soluble ST2 levels compared with patients with normal geometry (20.4±8.4 ng/mL vs 14.3±5.4 ng/mL, *P*<.002). Therefore, soluble ST2 level is not only affected by hypertensive LV, but may be a future biomarker in differentiating concentric hypertrophy from normal geometry in hypertension. *J Clin Hypertens (Greenwich)*. 2013;15:899–904. ©2013 Wiley Periodicals, Inc.

Left ventricular (LV) hypertrophy (LVH) is an independent risk factor for all cardiovascular complications of hypertension,¹ and therefore the early detection and management of LVH is important in order to reduce complications. LVH is often classified according to geometric pattern into 4 types: concentric hypertrophy, eccentric hypertrophy, concentric remodeling, and normal geometry.² Patients with concentric LVH have a higher prevalence of associated cardiovascular complications or death than patients with other geometric patterns.³ Such patients also have the most advanced extracardiac target-organ damage compared with other groups.⁴ Thus, there is a need for early diagnosis and therapy for LVH, especially concentric hypertrophy.

Current studies show that the electrocardiographic diagnosis of LVH has a low sensitivity but high specificity in the general population and in African Americans with hypertensive kidney disease.^{5,6} Echocardiography is not generally accessible especially in resource-poor settings, and there may be problems of interpretation in patients with obesity or pulmonary disease.⁷ There is therefore a need for cardiovascular scientists to look for easier and accurate methods, particularly at the bedside, for assessing the cardiac structural changes in hypertension. Another biomarker that is currently of interest to cardiovascular scientists is soluble ST2, which is a member of the interleukin 1

receptor host defense and inflammation family.^{8,9} Soluble ST2 is induced in conditions of myocardial overload such as acute myocardial infarction when the remaining viable myocardium must bear more mechanical stress^{9,10} and has also recently been reported to be increased in patients with hypertension.¹¹ In spite of the usefulness of serum-soluble ST2 in the field of cardiovascular medicine, there are no published data on the relationship between soluble ST2 and LV geometric pattern in hypertension. We therefore studied this relationship in a cohort of hypertensive patients.

METHODS

A total of 133 consecutive patients with a diagnosis of hypertension presenting for the first time to the cardiology clinic of the Department of Medicine at the University of Abuja Teaching Hospital were studied after informed consent was obtained. Ethics approval was obtained from the University of Abuja Teaching Hospital Ethical committee. The study conforms to the principles outlined in the Declaration of Helsinki¹² and wherever possible it also adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for an observational study of this kind.¹³ Hypertension was defined according the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines.¹⁴ Patients with diabetes mellitus, history suggestive of myocardial infarction, regional wall motion abnormality on transthoracic echocardiography, and plasma creatinine levels >170 μmol/L were excluded from the study. Each patient had fasting blood sugar, fasting lipid profile, electrolyte, urea and creatinine, and full blood cell count assessed after an 8- to 12-hour fast. Each patient also

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had blood collected, processed, and plasma stored at -80°C until assay serum-soluble ST2. They also had a transthoracic echocardiography performed the same day the sample was collected for soluble ST2.

Soluble ST2 Analysis

Blood samples were centrifuged and stored at -80°C and the frozen samples were shipped on dry ice to the laboratory at Hatter Institute of Cardiovascular Research in Africa, Cape Town, South Africa, within 3 months of sample collection. Soluble ST2 was measured by a sandwich double monoclonal antibody enzyme-linked immunosorbent assay method, according to manufacturer's instructions (Presage ST2 assay, Critical Diagnostics, New York, NY).¹⁵ Even though most reported studies refer to soluble ST2 levels in serum, plasma ST2 was also increased in patients with acute heart failure.¹⁶ Furthermore, using the Presage ST2 assay as we did, soluble ST2 in frozen plasma samples has long-term stability up to 18 months.¹⁷

NT-proBNP Assay

Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured by a standard electrochemiluminescence immunoassay (BNP Fragment EIA, BIOMEDICA GRUPPE gmbHa Co, Vienna, Austria) according to manufacturer's specification.¹⁸ NT-proBNP concentrations were also determined by experts blinded to the clinical details of the patients.

Transthoracic Echocardiography

Echocardiography was performed by experienced echocardiographers using a commercially available ultrasound system (IVIS-60). Patients were examined in the left lateral decubitus position using standard parasternal, short-axis, and apical views. Studies were performed according to the recommendations of the American Society of Echocardiography.¹⁹ Measurements were averaged over 3 cardiac cycles. The LV measurements taken include interventricular septal thickness at end-diastole (IVSd), the posterior wall thickness at end-diastole (PWTd), and the LV internal dimensions at end-diastole (LVIDd) and at end-systole (LVIDs). LV systolic function was calculated by Teichholz's formula.²⁰ LV mass (LVM) was calculated using the formula²¹: $\text{LVM} = 0.8 (1.04 [\text{IVSTd} + \text{LVIDd} + \text{PWTd}]^3 + 0.6 \text{ g})$. This has been shown to yield values closely related to necropsy LV weight and that has good interstudy reproducibility ($r=0.90$). Relative wall thickness (RWT) was calculated as $2 \times$ posterior wall thickness/LV internal dimension in diastole. LVH was considered when LVMI exceeded 49.2 g/m^2 in men and 46.7 g/m^2 in women.²² Patients were divided into 4 geometric patterns²³ after transthoracic echocardiography. Patients with normal LVMI and relative wall thickness <0.44 were considered to have normal geometry while those with increased LVMI and relative wall thickness >0.44 were considered to have concentric hypertrophy. On the other hand, patients had eccentric

hypertrophy when there was increased LVMI but the relative wall thickness was <0.44 , while patients had concentric remodeling when there was normal LVMI but relative wall thickness >0.44 . Diastolic function was categorized using mitral inflow and tissue Doppler imaging parameters.

Statistical Analysis

SPSS software version 16.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. Continuous variables were expressed as mean \pm standard deviation. Comparison of demographic, clinical, laboratory, and echocardiographic parameters among the geometric patterns was performed by one-way analysis of variance with Sheffe's post hoc test. Correlation coefficients were calculated by linear regression analysis, while multiple regression analysis was applied for analysis of the dependency between variables. $P < .05$ was considered statistically significant. Analysis of variation was performed to determine the sensitivity and specificity of soluble ST2 in differentiating concentric hypertrophy from normal geometry.

RESULTS

One hundred and thirty-three patients with an average age of 48.8 ± 10.7 years were studied; 50.4% were men with an average age of 50.3 ± 10.2 years, while women had an average age of 47.3 ± 11.1 years. Average duration of hypertension was 3.8 ± 1.1 years.

Comparison of Laboratory and Echocardiographic Parameters Between Hypertensive Patients With and Without LVH

Patients with hypertension and LVH (HTLVH) had higher concentrations of soluble ST2 when compared with patients with hypertension without LVH ($23.0 \pm 8.3 \text{ ng/mL}$ vs $14.5 \pm 4.9 \text{ ng/mL}$) (Table I). There was no statistical difference in the NT-proBNP levels

TABLE I. Some Laboratory and Echocardiographic Characteristics in Patients With HTN and LVH and Those Without LVH (HTN)

Variable	HTN (83)	HTN+LVH (50)	P Value
RVD, cm	3.15 (0.42)	3.10 (0.43)	.48
IVSD, cm	0.92 (0.15)	1.30 (0.16)	<.0002
PWD, cm	0.91 (0.13)	1.26 (0.20)	<.0004
EDD, cm	4.38 (0.49)	4.37 (0.95)	.95
ESD, cm	2.51 (0.45)	2.72 (0.95)	.10
LVM, g	202.51 (62.2)	296.1 (151.8)	<.000
Soluble ST2, ng/mL	14.5 (4.9)	23.0 (8.33)	<.001
NT-proBNP, pg/mL	341.0 (95.8)	353.2 (161.4)	.68

Abbreviations: EDD, end-diastolic diameter; ESD, end-systolic diameter; IVSD, interventricular diameter in diastole; LVM, left ventricular mass; NT-proBNP, N-terminal pro-brain natriuretic peptide; PWD, posterior wall diameter in diastole; RVD, right ventricular diameter in diastole. $P < .05$ was considered significant.

between patients with hypertension and those with HTLVH, however, even though patients with HTLVH had higher levels ($P=.68$). Patients with HTLVH also had significantly higher interventricular and LV posterior wall hypertrophy thickness when compared with patients with hypertension and hypertensive heart failure (HHF) ($P<.001$ and $.001$, respectively) and also had higher LVM and LVMI when compared with patients with hypertension.

Pattern of LV Geometry in Patients

Concentric hypertrophy was the commonest form of geometry in 41.4% of cases, followed by eccentric hypertrophy in 30.8% of cases, concentric remodeling in 14.3% of cases, and normal geometry in 13.5% of cases.

Pattern of LV Geometry by Sex

A total of 42.4% of the women in the study had concentric hypertrophy compared with 40.4% of the men. The male population, however, had higher percentages of patients with eccentric and concentric remodeling (32.8% and 14.9%, respectively) compared with those in the female population (28.8% and 13.6%, respectively).

Clinical Features of the 4 LV Geometric Patterns

Patients with concentric remodeling were the oldest (average age, 56.1 ± 8.4 years) compared with patients with normal geometry (average age, 46.3 ± 10.8 years; $P<.004$) (Table II). Patients with eccentric hypertrophy weighed most (mean body mass index [BMI] 29.6 ± 5.0 kg/m²) compared with patients with normal geometry (BMI 25.4 ± 4.1 kg/m²; $P<.003$). Patients with concentric hypertrophy had the second largest BMI (28.7 ± 5.4 kg/m²) compared with patients with normal geometry ($P=.011$). There was no significant difference in the blood pressure profiles of the 4 groups. Patients with concentric hypertrophy had the highest concentrations of soluble ST2 (mean 20.4 ± 8.4 pg/mL) vs patients with normal geometry (14.3 ± 5.4 pg/mL; $P=.002$).

The sensitivity of soluble ST2 in differentiating concentric hypertrophy from normal geometry was

68.2% and the specificity was 88.2% at a cut-off mark of 17.4 ng/mL (Figure 1). The area under the curve (AUC) was 0.76 and positive predictive value (PPV) was 68% ($P<.001$). Figure 2 on the other hand shows that the sensitivity and specificity of soluble ST2 in differentiating hypertension without LVH from hypertension with LVH are 87.0% and 56.7% respectively.

There were no significant differences in the soluble ST2 levels among the other geometric patterns. Patients with concentric hypertrophy had the highest concentration of serum creatinine while patients with normal geometry had the lowest levels, but these differences were not statistically significant.

Echocardiographic Characteristics of the 4 Geometric Patterns

Patients with concentric LVH, eccentric LVH, and concentric remodeling had higher IVSd and PWTd compared with patients with normal geometry, while patients with concentric LVH and concentric remodeling had higher RWT compared with patients

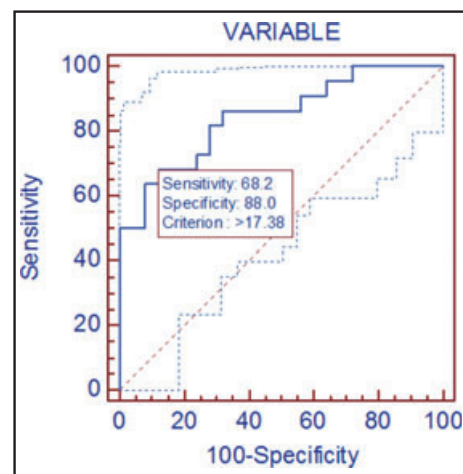


FIGURE 1. Receiver operator curve showing the sensitivity and specificity of soluble ST2 in differentiating concentric hypertrophy from normal geometry.

TABLE II. Clinical Features of the 4 LV Geometric Patterns

Parameter	Normal Geometry	Concentric Hypertrophy	Eccentric Hypertrophy	Concentric Remodeling
Age, y	46.3±10.8	49.3±11.0	45.9±9.8	56.1±8.4 ^a
Women/men, %	15/12	42/40	28/33	13/15
BMI, kg/m ²	25.4±4.1	28.7±5.4 ^a	29.6±5.0 ^a	25.4±5.3
SBP, mm Hg	151.1±20.0	158.5±27.2	148.0±22.4	145.3±19.0
DBP, mm Hg	94.4±11.0	99.2±15.8	94.8±15.0	92.9±13.0
PP, mm Hg	56.7±14.1	59.3±20.9	53.2±14.7	52.3±12.9
MAP, mm Hg	118.1±15.5	122.4±21.9	128.8±16.2	123.3±13.9
Soluble ST2, ng/mL	14.3±5.4	20.4±8.4 ^b	17.8±8.3	16.2±2.9
Serum creatinine	86.1±20.9	98.7±36.1	93.0±24.0	93.0±18.9

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; LV, left ventricular; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure. ^aSignificantly higher compared with normal geometry. ^b $P<.002$.

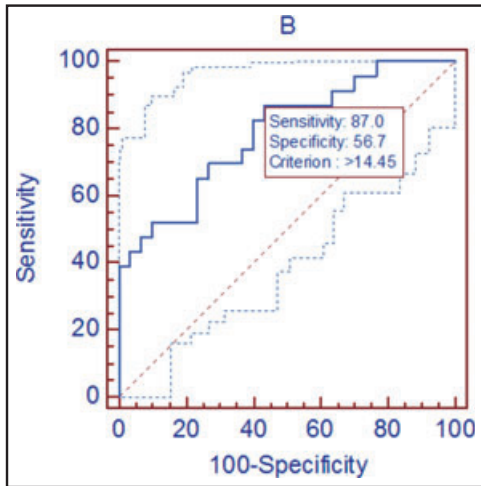


FIGURE 2. Receiver operator curve showing the sensitivity and specificity of soluble ST2 in differentiating hypertension without left ventricular hypertrophy (LVH) from hypertension with LVH.

with normal geometry (Table III). LVMI was highest in concentric LVH followed by eccentric LVH. LVIDD and IVIDS were higher in patients with all other geometric patterns compared with those with normal geometry. Patients with concentric hypertrophy had the lowest LV ejection fraction vs those with normal geometry ($70.7\% \pm 18.6\%$ vs $76.7\% \pm 18.6\%$; $P=.02$).

Univariate Association Between Log-Transformed Soluble ST2 and Clinical and Echocardiographic Parameters

Table IV and Table V show the univariate association between log-transformed ST2 and clinical, laboratory,

and echocardiographic parameters. There was a significant correlation between serum-soluble ST2 and IVSD, LVPWD, LVIDD, LVIDS, right atrial size, LVMI, LV ejection fraction, and transmitral E/A ratio.

Multivariate Analysis of Independent Covariates of Log-Transformed Soluble ST2

In a multivariate analysis, IVSD, LVPWD, LVIDD, and LVIDS remained significant covariates to serum-soluble ST2 concentrations (Table VI).

DISCUSSION

Concentric hypertrophy was the most common geometric pattern in our study cohort, and slightly more common in the female population compared with the male population (42.4% vs 40.4%), similar to previous findings in Nigerian hypertensive patients.^{24,25} The higher prevalence of concentric LVH compared with other geometric patterns is an important finding as the prevalence of death and cardiovascular complications associated with hypertension is higher in hypertensive patients with concentric hypertrophy than in other groups, including patients with eccentric hypertrophy.³ We found that plasma ST2 levels were increased in hypertensive patients with all 3 patterns of abnormal LVH geometry but highest in those with concentric hypertrophy despite comparable blood pressures and LVMI values. These results suggest that there is not only a relationship between hypertensive LVH and soluble ST2, but this relationship is related to the particular geometric pattern, particularly concentric hypertrophy. Therefore, measurement of soluble ST2 could be useful in detecting the particular geometric pattern in hypertension, particularly concentric hypertrophy, thereby facilitating risk stratification. We also found that the diagnostic accuracy of soluble ST2 was greater than that

TABLE III. Echocardiographic Characteristics of the 4 Geometric Patterns

Parameters	Normal Geometry	Concentric Hypertrophy	Eccentric Hypertrophy	Concentric Remodeling
RVD, cm	3.14±0.35	3.19±0.47	3.20±0.34	3.20±0.44
IVSD, cm	0.84±0.14	1.21±0.22 ^a	0.97±0.18 ^a	1.10±0.24 ^a
PWD, cm	0.78±0.08	1.20±0.18 ^a	0.91±0.13 ^a	1.00±0.15 ^a
EDD, cm	4.18±0.26	4.40±0.64 ^a	4.80±0.71 ^a	3.61±0.31 ^a
ESD, cm	2.33±0.34	2.69±0.70 ^a	2.80±0.77 ^a	2.07±0.30 ^a
RWT	0.37±0.04	0.57±0.10 ^a	0.38±0.04	0.57±0.12 ^a
LVM/HT ^{2.7} , g/m ²	40.70±5.20	71.80±21.60 ^a	65.40±32.30 ^a	41.60±5.20
LAA, cm ²	19.30±4.83	20.70±3.80	18.70±3.30	14.00±3.20
RAA, cm ²	15.20±2.40	15.20±3.60	15.20±3.50	14.70±2.90
LVEF, %	76.70±18.60	70.70±18.60 ^a	75.20±15.10	80.10±11.40
Mitral E/A	1.10±0.29	1.10±0.40	1.20±0.44	0.84±0.28 ^a
DT, ms	158.90±22.30	191.20±50.0 ^a	172.0±38.50	201.00±45.60 ^a
TAPSE, mm	22.20±3.30	21.90±5.40	22.60±3.90	22.90±3.20

Abbreviations: DT, deceleration time; EDD, end-diastolic diameter; ESD, end-systolic diameter in systole; HT, height; IVSD, interventricular septal diameter in diastole; LAA, left atrial area; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; MA, atrial filling; ME, early mitral filling; PWD, posterior wall diameter in diastole; RAA, right atrial area; RVD, right ventricular diameter; RWT, relative wall thickness; TAPSE, tricuspid annular pulmonary excursion. ^aSignificantly higher compared with normal geometry ($P<.001$). ^bSignificantly higher compared with concentric remodeling ($P<.001$).

TABLE IV. Univariate Association Between Log-Transformed Soluble ST2 and Clinical Parameters

Parameters	Coefficient of Association (r)	P Value
Age	0.04	.77
Body mass index	0.27	.05
Systolic BP	0.08	.59
Diastolic BP	0.11	.44
Pulse pressure	0.02	.90
Mean arterial pressure	0.04	.70
NT-proBNP	0.38	.003

Abbreviations: BP, blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide

TABLE V. Univariate Association Between Log-Transformed ST2 and Echocardiographic Parameters

Parameters	Coefficient of Association	P Value
RV diameter in diastole	0.11	.45
Interventricular septal diameter in diastole	0.47	<.001
Posterior wall diameter in diastole	0.32	.02
LV internal diameter in diastole	0.29	.03
LV internal diameter in systole	0.32	.02
Relative wall thickness	0.12	.40
LV mass index for HT ^{2,7}	0.37	.006
Left atrial area	0.19	.19
Right atrial area	0.28	.04
LV ejection fraction	0.28	.04
Mitral E/A ratio	0.26	.05
Deceleration time	0.18	.21
Tricuspid annular plane systolic excursion	0.054	.77

Abbreviations: HT, height; LV, left ventricular; RV, right ventricular.

TABLE VI. Multivariate Analysis of Independent Covariates of Log-Transformed Soluble ST2

Parameters	Standardized Coefficient (β)	P Value
Interventricular septal diameter in diastole	0.56	<.0001
LV posterior diameter in diastole	0.43	<.001
LV internal diameter in systole	0.41	<.003
LV mass index for HT ^{2,7}	0.56	<.0001

Abbreviations: HT, height; LV, left ventricular.

of electrocardiography study, which is the most widely used method for the initial assessment of these patients, as evidenced by higher sensitivity and negative predictive value for this marker (Table VII).

Although we found significant correlations between plasma ST2 interventricular septal wall thickness in diastole, posterior wall thickness in diastole, LV internal

TABLE VII. Indexes of Diagnostic Validity for Electrocardiography and ST2 in Left Ventricular Hypertrophy

	ST2 (>14.45 ng/mL)%		P Value
	ECG% (95% CI)	95% CI	
Sensitivity	16.0 (8.62–3.8)	87.0 (75.8–96.4)	<.001
Specificity	95.2 (83.8–99.7)	56.7 (48.7–65.7)	<.001
PPV	51.6 (19.9–82.4)	40.1 (28.7–52.3)	<.001
NPV	77.2 (68.8–84.3)	92.9 (83.2–97.9)	<.001

Abbreviations: CI, confidence interval; ECG, electrocardiographic; NPV, negative predictive value; PPV, positive predictive value.

diameter in diastole and systole, right atrial size, LVMI, LV ejection fraction and transmitral E/A ratio, and plasma NT-proBNP, only interventricular septal wall thickness in diastole, posterior wall thickness in diastole, LV internal diameter in systole and diastole, and LVMI were found to be independent predictors of soluble ST2. The correlation of ST2 with LV wall thickness and chamber sizes is a reflection of the mechanism of secretion of ST2, which is related to mechanical stress.¹⁰ We also observed that our hypertensive patients with concentric hypertrophy had the lowest LV ejection fractions compared with those with normal geometry, further supporting the finding that concentric hypertrophy carries the worst prognosis of the geometric patterns in hypertension.³ Lower LV ejection fraction is an independent marker of worse prognosis in hypertensive heart disease.²⁵ Takeda and Kohno²⁶ reported higher levels of plasma NT-proBNP, which is another biomarker that correlates well with serum soluble ST2 in hypertensive patients with concentric LVH compared with other geometric patterns. In our study, NT-proBNP also correlated with soluble ST2. Soluble ST2 did not correlate well with duration of hypertension. Toda and colleagues²⁷ showed similar findings in patients with essential hypertension in the absence of heart failure using NT-proBNP.

Study Limitations

Our study is limited by the small number of patients. Therefore, the relationship between plasma ST2 and echocardiographic variables seen in this study should be viewed as hypothesis-generating for studies in larger patient cohorts. In addition, since the diagnosis of ischemic heart disease was made clinically using history, troponin I levels, and electrocardiography with no myocardial perfusion imaging and coronary angiography performed, it is possible that subtle coronary artery disease might have been missed which is a confounding factor as ischemic heart disease increases the concentration of soluble ST2.^{9,10} However, there was careful and extensive phenotyping of our study population with respect to clinical, echocardiographic, and biochemical parameters, which reduced the effect of these limitations in this study.

CONCLUSIONS

Our findings suggest that soluble ST2 level is not only affected by hypertensive LVH but may be a future biomarker in differentiating concentric hypertrophy from normal geometry in hypertension.

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