

Relationship between extent and complexity of coronary artery disease and different left ventricular geometric patterns in patients with coronary artery disease and hypertension

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ABSTRACT

Objective: The relationship between severity of coronary artery disease (CAD) and left ventricles (LV) hypertrophy in hypertensive patients is well known. However, the association between the extent and complexity of CAD assessed with SYNTAX score (SS) and different LV geometric patterns has not been investigated. We aimed to investigate the association between SYNTAX score and different LV geometric patterns in hypertensive patients.

Methods: The study had been made in our clinic between January 2013 and August 2013. We studied 251 CAD patients who had hypertension and who underwent coronary angiography (147 males, 104 females; mean age 61.61±9.9 years). Coronary angiography was performed based on clinical indications. SS was determined in all patients. Echocardiographic examination was performed in all subjects. Four different geometric patterns were determined in patients according to LV mass index (LVMI) and relative wall thickness (RWT) (Groups: NG- normal geometry, CR- concentric remodeling, EH- eccentric hypertrophy, and CH- concentric hypertrophy). Biochemical markers were measured in all participants.

Results: The highest SS values were observed in the CH group compared with the NG, CR, and EH groups ($p<0.05$ for all). Also, the SS values of the EH group were higher than in the NG and CR groups ($p<0.05$ for all). Multivariate linear regression analysis showed that SS was independently associated with LV geometry ($\beta=0.316$, $p=0.001$), as well as age ($\beta=0.163$, $p=0.007$) and diabetes ($\beta=-0.134$, $p=0.022$).

Conclusion: SYNTAX score is independently related with LV geometry in hypertensive patients. This result shows that LV remodeling is parallel to the increase in the extent and complexity of CAD in our study patients. (*Anatol J Cardiol* 2015; 15: 789-94)

Keywords: SYNTAX, geometry, hypertrophy, hypertension

Introduction

The Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score quantifies the extent and complexity of angiographic disease (1). SYNTAX score (SS) has been used to make revascularization decisions and predict long-term mortality and morbidity in patients with coronary artery disease (CAD) (2, 3). Moreover, SS has the power to predict adverse cardiac events, such as contrast-induced nephropathy and no-reflow in patients with ST elevation myocardial infarction (MI) treated with primary percutaneous intervention (4). On the other hand, SS is strongly associated with left ventricle hypertrophy (LVH) in hypertensive patients and different patient groups (5-9).

There are four different geometric patterns of the left ventricle (LV) in hypertension (HT), and these geometric patterns are different for prognosis and LV function (6-8). LV geometric patterns incorporate normal LV structure (NG) and concentric remodeling (CR), in addition to LVH [eccentric hypertrophy (EH) and concentric hypertrophy (CH)] (7). Previously, it has been shown that higher systolic blood pressures are associated with CH (7). Demographic factors, such as age and gender, diabetes mellitus, neurohormonal activation, or coronary artery disease can also modulate the development of different LV geometric patterns (8).

Although SS is associated with LVH in hypertensive patients (7, 9, 10), it has not been investigated in different LV geometric patterns. Therefore, we aimed to investigate the association

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between the extent and complexity of CAD, assessed by SYNTAX score, and different LV geometric patterns in patients with CAD who have hypertension.

Methods

Study populations

The study had been made in our clinic between January 2013 and August 2013, we evaluated 251 CAD patients who had hypertension and underwent coronary angiography (147 males, 104 females; mean age 61.61 ± 9 years). Coronary angiography was performed for the investigation of ischemic heart disease based on clinical indications (typical chest discomfort and/or abnormal stress test results, such as positive treadmill test, dobutamine stress echo, and myocardial perfusion scintigraphy). Patients with coronary lesions with a diameter stenosis of $\geq 50\%$ in ≥ 1.5 -mm vessels were included in the study. All patients were clinically stable and had a history of hypertension. In each subject, blood pressure (BP) was measured on at least three separate days after 15 min of sitting comfortably and was then averaged. Individuals who had systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg in the office setting were diagnosed as hypertensive (11). Only 70% of hypertensive individuals selected for the present analysis had regularly used anti-hypertensive therapy with one or more medications.

The exclusion criteria were the presence of neoplastic disease, heart failure, recent major surgical procedure, or chronic liver or kidney disease. Patients with previous MI and angina episodes 48 hours before hospitalization, those who had previous coronary angioplasty or bypass surgery, and those with valvular, myocardial, or pericardial disease were also excluded. The study was conducted according to the recommendations set forth by the Declaration of Helsinki on biomedical research involving human subjects. The institutional Ethics Committee approved the study protocol, and each participant provided written informed consent.

After a detailed medical history and complete physical examination, each participant was questioned for major cardiovascular risk factors, such as age, sex, diabetes mellitus, smoking status, previous medications, and hypertension. In addition, body mass index was calculated, and systolic BP (SBP) and diastolic BP (DBP) were recorded.

Also, fasting venous blood samples were obtained from all patients to determine their plasma levels of fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, creatinine, and hemoglobin.

Coronary angiography and SYNTAX score

All patients underwent coronary angiography with the Judkins technique. Coronary angiography was performed with a standard femoral approach with a 6-F diagnostic catheter. Coronary lesions leading to $\geq 50\%$ diameter stenosis in ≥ 1.5 -mm vessels were scored separately and added together to provide

the cumulative SYNTAX score, which was prospectively calculated using the SYNTAX score algorithm on the baseline diagnostic angiogram (1). Two experienced interventional cardiologists analyzed the SYNTAX score; the opinion of a third analyst was obtained, and the final judgment was made by consensus in cases of a disagreement. The final score was calculated from the individual lesion scores by analysts who were blinded to the procedural data and clinical outcome.

Echocardiography

Standard two-dimensional and Doppler echocardiographies were performed using a commercially available echocardiographic machine (Vivid 7R GE Medical System, Horten, Norway) with a 2.0-3.5-MHz transducer. Measurements were made during normal breathing at end-expiration. LV end-systolic (LVESD) and end-diastolic diameters (LVEDD), end-diastolic interventricular septal thickness (IVSth), and end-diastolic LV posterior wall thickness (PWth) were measured at end-diastole according to established standards of the American Society of Echocardiography. LV ejection fraction (EF) was determined by the biplane Simpson's method (12). LV mass (LVM) was calculated using the Devereux formula (13).

$$LVM = (1.04 [(LVEDD + IVSth + PWth)^3 - (LVEDD)^3] - 13.6).$$

Then, the LV mass index (LVMI, g/m^2) was obtained with the following formula: LVM/body surface area. LVH was defined according to more stringent criteria as LVMI values exceeding $125 g/m^2$ in men and $110 g/m^2$ in women (14). Relative wall thickness (RWth, cm) was measured at end-diastole as the ratio of $(2 \times PWth)/LVEDD$. Increased RWth was defined as ≥ 0.45 .

All echocardiographic measurements were repeated by a second observer (MG) who was blinded to the values obtained by the first observer (HU). Interobserver variability was assessed by calculating the coefficient of variation. The coefficient of variation was $< 8\%$ for all measurements. Any discrepancy was resolved by consensus. All echocardiographic measurements were repeated 1 week later by an observer (HU) who was blinded to the results of the previous measurements, and the intraobserver variability was $< 5\%$ for all measurements.

Patterns of left ventricular geometry

Geometric patterns were based on the upper normal limits for LVMI and RWth: (i) normal geometry (NG; normal LVMI and normal RWth); (ii) concentric remodeling (CR; normal LVMI and increased RWth); (iii) concentric hypertrophy (CH; increased LVMI and increased RWth); and (iv) eccentric hypertrophy (EH; increased LVMI and normal RWth) (8).

Reproducibility

All echocardiographic measurements [except coronary flow reserve (CFR)] were repeated 1 week later by the same sonographer (H.U.), and the intraobserver variability was calculated as the difference in the 2 measurements of the same patient by the observer divided by the mean value. Intra-observer variabilities were less than 5% for all measurements.

Statistical analysis

All analyses were conducted using SPSS 17.0 (SPSS for Windows 17.0, Chicago, IL, USA). The distribution of continuous variables was assessed with the one-sample Kolmogorov-Smirnov test. Comparison of categorical variables between the groups was performed using the chi-square test. Analysis of variance (ANOVA) was used in the analysis of continuous variables. Spearman's test was performed to identify bivariate correlation between continuous and categorical variables. A stratified post hoc analysis of echocardiographic, clinical, and laboratory variables was performed according to the LV geometric patterns. The associations of SYNTAX score were assessed by the Pearson's correlation test. Multiple linear regression analysis was performed to identify the independent associations of the SYNTAX score. A two-tailed $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline clinical, laboratory, echocardiographic, and angiographic characteristics of the groups are shown in Table 1. In the present study, four different geometric patterns were determined according to LVMI and RWth: (1) 79 patients with NG, (2) 64 patients with CR, (3) 39 patients with EH, and (4) 69 patients with CH. Age, body surface area (BSA), and SBP and DBP values were significantly different among the groups ($p < 0.05$ for all).

The comparison of SS values among the groups is shown in Table 1 and Figure 1. The highest SYNTAX score values were observed in the CH group compared with the other groups ($p < 0.05$ for all). Also, SS values of the EH group were higher than in the NG and CR groups ($p < 0.05$ for all). However, SS values of the NG and CR groups were similar ($p > 0.05$).

IVSth, PWth, RWth LVMI, and EF values were different among the groups. The highest LVMI and RWth values were detected in the CH group compared with the other groups ($p < 0.05$ for all).

Bivariate and multivariate relationships of SYNTAX score

The bivariate and multivariate relationships of the SYNTAX score are demonstrated in Table 2. SS was associated with BMI ($r = -0.129$, $p = 0.041$), age ($r = 0.150$, $p = 0.017$), diabetes ($r = 0.144$, $p = 0.023$), HDL ($r = 0.132$, $p = 0.036$), creatinine ($r = 0.138$, $p = 0.028$), EF ($r = -0.180$, $p = 0.004$), LVMI ($r = 0.252$, $p < 0.001$), RWth ($r = 0.152$, $p = 0.016$), and LV geometry ($r = 0.331$, $p < 0.001$) in the bivariate analysis.

Multivariate regression analysis showed that SS was independently associated with age ($\beta = 0.163$, $p = 0.007$), diabetes mellitus (DM) ($\beta = 0.134$, $p = 0.022$), and LV geometry ($\beta = 0.316$, $p = 0.001$).

Discussion

This is the first study that has investigated the relationship between SYNTAX score and different LV geometric patterns in hypertensive CAD. The present study shows that SS is indepen-

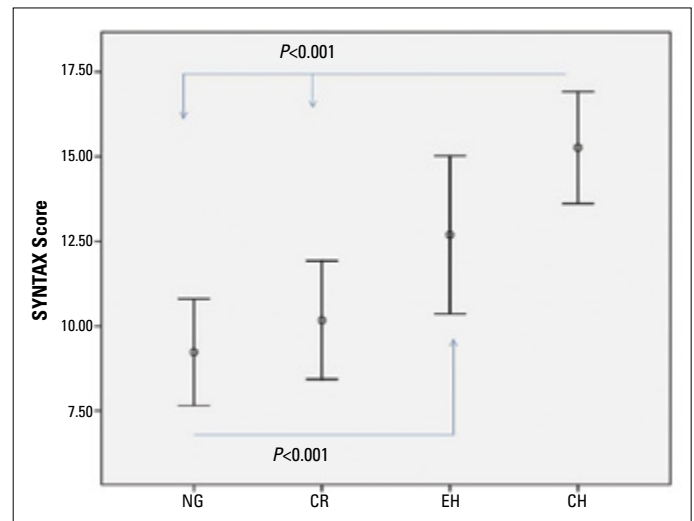


Figure 1. SYNTAX score in different left ventricle geometry patterns
CH - concentric hypertrophy; CR - concentric remodeling; EH - eccentric hypertrophy; NG - normal geometry

dently associated with left ventricle geometry, as well as age and diabetes. In the present study, the CH group had the highest SS values among all study groups. Also, the SS values of the EH group were higher than in NG and CR groups.

An association between SS and LVH in hypertensive patients has been showed in previous studies (6, 7). Several mechanisms have been proposed for this relationship (15). There is evidence that several factors may induce parallel changes in LV mass and atherosclerotic lesions (16). Hypertension stimulates both LVH and atherosclerosis (16, 17). The renin-angiotensin-aldosterone system can be the most important mechanism. Angiotensin II and angiotensin II type 1 receptor activation promotes intracellular reactions that may lead to both cardiac hypertrophy and the progression of complex atherosclerotic lesions through the proliferation of vascular smooth muscle cells and the production of extracellular matrix protein (18, 19). LVH in hypertensive patients leads to shifts toward glycolytic metabolism, disorganization of the sarcomere, alterations in calcium handling, changes in contractility, loss of myocytes with fibrotic replacement, systolic and diastolic dysfunction, and electrical remodeling, resulting in alterations in myocardial metabolism, structure, and function with increasing severity of LVH (20). These structural, metabolic, and functional alterations possibly increase the extent of atherosclerosis.

Although the association between LVH and SS is well known in hypertensive patients (6, 7, 10), the relationship between LV geometry and SS has not been investigated previously. The present study shows that SS is associated with LV geometry independently of LVH. Also, in our study, SS values were associated with LV geometry but not with LVMI or RWth alone in the multivariate analysis. Previous studies have reported that abnormal LV geometric patterns are associated with a greater risk of hypertensive complications (6, 7). A subgroup study of the Framingham heart study (21) demonstrated that patients with concentric LVH had the worst prognosis, followed by those with

Table 1. Comparison of baseline, laboratory, echocardiographic, and angiographic characteristics among the groups

Variables	NG Group	CR Group	EH Group	CH group	ANOVA P
Age, years	60.1±9.04	58.46±9.6	61.7±9.8	66.10±9.8 ^a	<0.001
Gender ^a male	38 (46.0%)	31 (45.8%)	21 (37.5%)	37(46.2%)	0.852
BMI, kg/m ²	29.01±4.4	29.6±5.3b	29.3±5.2	28.8±5.3	0.911
BSA, m ²	1.87±0.17	1.93±0.21	1.83±0.17	1.83±0.17	0.020
SBP, mm Hg	145.2±15.8	146.7±18.5	149.4±18.1	157.0±17.1 ^c	<0.001
DBP, mm Hg	92.2±11.3	94.2±11.2	95.6±11.3	104.6±13.2 ^d	<0.001
Heart rate, beats/minute	76.5±12.3	75.2±8.5	76.1±13.0	75.4±9.7	0.332
Diabetes ^e , n (%)	36 (45.6%)	23 (31.9%)	21 (43.8%)	31 (44.9%)	0.345
Hyperlipidemia ^e , n (%)	36 (45.6%)	35 (54.7%)	17 (33.6%)	35 (50.7%)	0.628
Smoking ^e , n (%)	24 (27.6%)	23 (35.9%)	22 (46.3%)	31 (44.9%)	0.152
Family history ^e , n (%)	26 (32.9%)	21 (31.8%)	13 (23.3%)	16 (23.2%)	0.518
Laboratory findings					
Glucose, mg/dL	140.8±8.2	148.3±9.3	149.3±13.6	147.4±10.3	0.740
LDL-C, mg/dL	117.7±23.1	111.2±24.8	109.4±20.9	110.7±33.1	0.170
HDL-C, mg/dL	44.4±6.7	42.4±6	43.7±8.5	44.2±7.2	0.463
Triglyceride, mg/dL	162.12±53	158.64±65	151.41±37	145.52±42	0.237
Hemoglobin, mg/dL	15.5±1.4	13.8±1.3	14.1.0±1.4	15.2±1.3	0.767
Creatinine, mg/dL	0.92±0.4	0.88±0.27	0.92±0.31	0.97±0.49	0.636
Echocardiographic findings					
LVEDD, cm	5.1±4.6	4.3.2±3.6	5.1±3.9	4.7.2±3.6	0.238
IVSth, cm	0.98±0.1 ^e	1.12±0.11 ^f	1.15±0.12 ^g	1.23±0.1	<0.001
PWth, cm	0.9±0.08 ^h	1.08±0.1 ^k	1.02±0.1 ⁱ	1.21±0.09	<0.001
EF, %	54.8±8.4 ^{aa}	55.8±7.6 ^{bb}	50.6±8.7	53.7±6.8	0.011
RWth, cm	0.39±0.03 ^{cc}	0.50±0.04 ^{dd}	0.40±0.04 ^{ee}	0.51±0.04	<0.001
LVMI, g/m ²	96.3±17.6 ^{ff}	102.3±17.8 ^{gg}	146.1±32.3	147.6±23.9	<0.001
Angiographic findings					
SYNTAX score	9.2±7.02 ^{hh}	10.1±6.9 ^{kk}	12.6±7.1	15.2±6.8	<0.001
Previous medications					
ACE-I use, n (%)	24 (27.6%)	21 (31.8%)	21 (53.8%)	31 (44.3%)	0.153
ARB use, n (%)	26 (32.9%)	23 (35.9%)	17 (43.6%)	35 (50.7%)	0,164
Beta-blocker use, n (%)	24 (27.6%)	23 (35.9%)	22 (46.3%)	31 (44.3%)	0.347
Statin use, n (%)	36 (45.6%)	35 (54.7%)	17 (33.6%)	35 (50.7%)	0.628
OAD use, n (%)	36 (45.6%)	23 (31.9%)	21 (43.8%)	31 (44.9%)	0.345
ACE-I - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BMI - body mass index; BSA - body surface area; CH - concentric hypertrophy; CR - concentric remodeling; DBP - diastolic blood pressure; EF - ejection fraction; EH - eccentric hypertrophy; HDL-C - high-density lipoprotein cholesterol; IVSth - interventricular septal thickness; LDL-C - low-density lipoprotein cholesterol; LVEDD - left ventricle end-diastolic diameter; LVMI - left ventricle mass index; NG - normal geometry; OAD - oral antidiabetic; PWth - posterior wall thickness; RWth - relative wall thickness; SBP - systolic blood pressure ^a Chi-square ^b P<0.001 vs. NG, CR, and EH groups; ^c P=0.014 vs. EH group, P=0.005 vs. CH group; ^d P<0.001 vs. NG, CR, and EH groups; ^e P<0.001 vs. NG, CR, and EH groups; ^f P<0.001 vs. CR, EH, and CH groups; ^g P<0.001 vs. EH and CH groups; ^h P<0.001 vs. CH group; ⁱ P=0.007 vs. EH group; ^j P=0.001 vs. EH group; ^k P<0.001 vs. CR and CH groups; ^l P<0.001 vs. EH group; ^m P<0.001 vs. CH group; ⁿ P<0.001 vs. EH and CH groups; ^o P=0.012 vs. EH group; P<0.001 vs. CH group; ^p P<0.001 vs. CH group					

EH, CR, and normal geometry. In the LIFE study (10), the prevalence of CAD was almost twice as high in patients with CH as in the other subgroups. The lowest cardiovascular risk was observed in the group with NG (7). Therefore, the highest SS in the CH group may contribute to a poorer prognosis compared

with the other geometric patterns. A CH geometric pattern is the endpoint of hypertension, and both LVMI and RWth increase in this geometric pattern. Our study revealed that the SS values were significantly higher among hypertensive subjects with CH and EH compared to those in the CR and NG groups. This result

Table 2. Bivariate and multivariate relationships of SYNTAX score

Variables	Pearson correlation coefficient	P	Standardized β -regression coefficients	P
BMI, kg/m ²	-0.129	0.041	-0.004	0.82
Age, years	0.150	0.017	0.163	0.007
Diabetes, n (%)	0.144	0.023	0.134	0.022
HDL, mg/dL	0.132	0.036	0.107	0.065
Creatinine, mg/dL	0.138	0.028	0.111	0.060
EF, %	-0.180	0.004	-0.132	0.034
LVMI g/m ²	0.252	<0.001	-0.032	0.710
RWth, cm	0.152	0.016	0.025	0.721
LV Geometry	0.331	<0.001	0.316	0.001

BMI - body mass index; EF - ejection fraction; HDL - high-density lipoprotein; LV - left ventricle; LVMI - left ventricular mass index; RWth - relative wall thickness

suggests that LVMI is a more important parameter than RWth. Increased left ventricle mass, volume and pressure overloads, or a combination of both cause different LV geometric adaptations, including NG, CR, EH, and CH. Geometric patterns identify distinctive pathophysiologic patterns and may be added to LV mass for risk stratification (6, 7, 21, 22).

The pathophysiological mechanisms underlying the association between different LV geometry with the extent and complexity of CAD are still unclear. Traditionally, it was thought that the activation of neuro-humoral mechanisms triggers a progressive increase in LVMI and the progression of atherosclerosis in hypertensive patients. The increase in LV mass needs to compensate for increased cardiac load when the LV geometry is concentric or eccentric (23, 24). Also, it is known that increased oxidative stress has been regarded as one of the most important contributors to the progression of atherosclerosis in hypertensive patients with different LV geometries (25, 26). Oxidative stress alters normal endothelial function, supporting proinflammatory, prothrombotic, proliferative, and vasoconstrictor mechanisms that support the atherogenic process (27, 28). In addition, patients with EH and CH were older, which may also have affected the severity of CAD.

Also, in our study, SS was independently associated with DM. A relationship between diabetes and SYNTAX score was shown in previous studies (29, 30). DM appears to be involved in each step of the atherosclerotic process. It triggers endothelial dysfunction in humans in vivo (31) and leads to adverse modifications in lipid (32-35) and coagulation factors (33, 36). Chronic hyperglycemia can damage the kidneys, leading to vascular damage and secondary hypertension (32, 33, 37). It may also exert direct toxic effects on the vasculature, potentiating the development of atherosclerosis (37, 38).

Study limitations

Two-dimensional echocardiography is limited in its accuracy for measuring LV mass, because all methods assume a uniform

LV thickness. However, the M-mode methods that are based on the simple cube-function formula have repeatedly been shown to give reasonably accurate LV mass measurements in necropsy validation studies. In addition, the simplicity and ease of this technique have made it possible to apply it to large-scale clinical and epidemiological studies and to relate LV mass and its change over time to clinical outcomes (39).

Conclusion

In hypertensive patients with coronary artery disease, the severity and complexity of coronary artery disease progressively increase from normal geometry to concentric hypertrophic geometry. So, it can be thought that ventricular remodeling in hypertensive patients may be parallel to the severity of coronary artery disease.

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Peer-review: Externally peer-reviewed.

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