Strain Pattern on Electrocardiogram Is Associated with Increased Carotid Intima-Media Thickness in Patients with Aortic Valve Stenosis

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Background: Coronary artery disease is present in at least 30% of patients with degenerative aortic stenosis (AS). Atherosclerosis also performs an important role in the progression of AS, because of the similarities of pathological mechanisms in both conditions. The electrocardiogram (EKG) strain pattern is associated with structural myocardial change and subendocardial ischemia and has been worldwide used as a marker of AS severity. We hypothesized that EKG strain pattern would be a marker of atherosclerosis as well in AS patients. The aim of this study was to associate the presence of EKG strain pattern in AS patients with the carotid intima-media thickness (CIMT).

Methods: Fifty-two consecutive patients referred from the cardiology clinic with moderate or severe AS were included in the study and underwent clinical evaluation, EKG, transthoracic echocardiography, and carotid ultrasonography, following statistical analysis of the results.

Results: There was a significant association between left ventricular EKG strain and increased CIMT ($P = 0.001$). The presence of strain increased the odds of abnormal CIMT ($P = 0.004$, odds ratio 9.7, 95% confidence interval 2.4–45.0), in a model adjusted for age and clinical diagnosis of systemic arterial hypertension. Additionally, EKG strain was associated with the presence of atherosclerotic plaque in at least one carotid artery ($P = 0.011$).

Conclusion: Our results suggest that AS patients with EKG strain pattern should be further investigated for the diagnosis of subclinical atherosclerotic disease.

INTRODUCTION

Degenerative aortic stenosis (AS) is a highly prevalent disease, and when presenting in a severe stage, is associated with increased morbidity and mortality.[1] Recent literature data indicate that at least 30–40% of AS cases are associated with coronary artery disease (CAD).[2] Atherosclerosis also performs

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an important role in the progression of AS. Current studies suggest that the development and progression of disease occurs due to a systemic cellular and molecular process very similar to atherosclerosis, with endothelial dysfunction and vessel calcification.[3–5]

The presence of electrocardiogram (EKG) left ventricle (LV) strain pattern in AS patients is a prognosis-worsening criterion and may be a marker of myocardial structural changes and subendocardial ischemia.[6] Recent study[7] performed in asymptomatic patients with AS showed that the presence of EKG strain is an independent predictor of poor prognosis. The authors argued that, first of all, it occurs because the presence of strain would indicate myocardial ischemia induced by the imbalance between oxygen demand and supply in the hypertrophied heart. Second, the presence of strain would also reflect AS-induced silent myocardial ischemia.

Also, recent data describing an association between severe AS and peripheral atherosclerosis[2,8] are consistent with the concept that atherosclerosis is a systemic disease. This information reinforces the idea that patients with clinically significant AS are at risk of peripheral atherosclerosis. The ultrasonography for evaluation of carotid intima-media thickness (CIMT) and detection of atherosclerotic plaque is considered a practical and relatively inexpensive noninvasive method to assess the presence of atherosclerosis.

In this context, the hypothesis of this study was that the presence of the left ventricular strain on the EKG of AS patients is a marker of subclinical atherosclerosis defined as an increased CIMT. The aim of this study was to investigate an association between EKG left ventricular strain of patients with moderate to severe AS and increased CIMT.

MATERIALS AND METHODS

This is a prospective study including 52 consecutive patients diagnosed with moderate or severe AS and referred from the outpatient cardiology service of Botucatu Medical School —UNESP from May 2012 to May 2013. All patients underwent a same day clinical evaluation, 12-lead EKG, transthoracic echocardiography, and carotid ultrasonography. This study was approved by the ethics committee of Botucatu Medical School (Protocol 4043-2011).

The inclusion criteria were: age over 18 years and presence of moderate or severe aortic valve stenosis. Exclusion criteria were: prosthetic heart valve; congestive heart failure due to other cause than AS; and other associated heart valves lesion greater than mild.

The criteria of unfavorable prognosis of AS[9] were: presence of angina, dyspnea, or syncope in clinical evaluation; echocardiogram revealing reduced LV ejection fraction (less than 0.5); or presence of LV hypertrophy (LV mass indexed to body surface area greater than 95 g/m^2 in women and greater than 115 g/m^2 in men).

The criteria of moderate to severity AS according to the latest guidelines of the American Society of Cardiology[9] were: echocardiogram revealing aortic valve area less than 1.5 cm^2, maximal aortic gradient greater than 36 mm Hg, or mean aortic gradient greater than 25 mm Hg.

Clinical Evaluation

Age, sex, race, and cardiovascular risk factors as defined by the American current guidelines,[10–14] such as hypertension, diabetes mellitus, obesity, dyslipidemia, smoking, CAD, and heart failure, were recorded besides physical examination.

Electrocardiogram

The standard 12-lead procedure was performed and the following variables were considered: cardiac rhythm, atrial or ventricular overload criteria, and left ventricular strain repolarization, according to the current guidelines of the American Society of Cardiology.[15] The left ventricular strain was defined as ST-segment changes on lateral leads (V5 or V6), showing the flattening ST segment depression $\geq$0.05 mV and asymmetric inverted T wave.

Transthoracic Echocardiogram

Complete echocardiograms were performed in all patients by the same examiner, in accordance with the standardization techniques recommended by the American Society of Echocardiography.[9,16]

Carotid Ultrasound

The CIMT was obtained by the automated method, in the posterior wall of the left and right common carotids, following the recommendations of the ‘‘Consensus Statement from the American Society of Echocardiography’’[17] and ‘‘Mannheim Carotid Intima-Media Thickness Concensus.’’[18] The values were adjusted for race and age, according to these consensuses. The detection and quantification of atherosclerotic plaques were also performed.[19]

Statistical Analysis

The minimal sample size was estimated in 50 patients, considering the level of confidence of 95%, power test of 70%, and association between coronary atherosclerosis and AS of 30%. Continuous variables were expressed as means and standard deviations or by medians and interquartile ranges. Categorical variables were expressed as proportions. Comparison between proportions was performed by chi-squared test. The association between CIMT and strain pattern was assessed using the Fisher's exact test. Multivariate logistic regression model was performed to evaluate whether left ventricular strain was an independent marker of CIMT and carotid atherosclerotic plaque, considering the presence of age and hypertension. Level of significance was set at $P < 0.05$.

RESULTS

As shown in Table I, there were no gender-related differences. The mean age of this population was 65.3 ± 15.1 years. Most of the patients were Caucasian with previous diagnosis of systemic arterial hypertension (SAH) and normoglycemic. CIMT was increased in 17 patients.

Table II shows that increased CIMT was not associated with any of the following clinical variables: hypertension ($P = 0.24$), diabetes ($P = 0.46$), dyslipidemia ($P = 0.41$), known CAD ($P = 0.15$), and obesity ($P = 0.37$).

As shown in Table III, the same clinical variables were not associated with the presence of LV strain on EKG.

Table IV demonstrates that there was no association between left atrium or LV overload with increased CIMT. An association between the presence of EKG LV strain and increased CIMT ($P = 0.001$) was observed. This is shown in Figure 1. The sensitivity of EKG strain pattern in predicting CIMT was 52.9% and the specificity was 90.3%, with positive predictive value of 75% and negative predictive value of 77.7%. Considering the high prevalence of hypertension in these patients (76.9%), a multivariate logistic regression analysis was performed to investigate whether the presence of LV strain was an independent factor associated with increased CIMT, in a model adjusted by hypertension and age. It was observed that, in this model, the presence of LV strain increased 9.7 times the odds of an abnormal CIMT ($P = 0.004$, odds ratio 1.03, 95% confidence interval 0.02–0.48).

Table I. Baseline characteristics

$n = 52$	n (%)
Gender (male/female)	30/22 (57.7/42.3)
Race (C/NC)	47/5 (90.4/9.6)
SAH	40 (76.9)
DM	11 (21.2)
Obesity	15 (28.8)
Dyslipidemia	20 (38.4)
Smoking	24 (46.1)
CAD	24 (46.1)
Severity of AS (M/S)	35/17 (67.3/32.7)
CIMT increased	17 (32.7)
Plaque in carotid	29 (55.8)
Strain pattern in EKG	12 (19.2)

C, Caucasian; DM, diabetes mellitus; M, moderate; *n*, number; NC, non-Caucasian; S, severe.

Table II. Association between clinical variables and CIMT

Clinical variables (N)	Normal CIMT ($n = 35$)	Increased CIMT ($n = 17$)	P value
SAH	24	16	0.24
DM	6	5	0.46
Dyslipidemia	14	7	0.91
Diagnosed CAD	13	11	0.15
Obesity	11	4	0.37

DM, diabetes mellitus; *N*, number of patients.

No association was found between the presence of atherosclerotic plaque in at least one carotid artery and either left atrium or LV overload (Table V). Interestingly, an association between LV strain pattern and presence of atherosclerotic plaque ($P = 0.011$), as shown in Figure 2, was observed. Considering that most of the patients included in this study were hypertensive and there was an association between SAH and atherosclerotic plaque in carotids ($P = 0.005$), a multivariate logistic regression analysis was performed to assess whether the presence of strain was an independent marker of peripheral atherosclerosis in a model adjusted for age and SAH. The analysis indicated that the EKG alteration increased the risk of plaque in carotids by 5.6 times, but it was not significant ($P = 0.065$). The presence of strain presented a specificity of 94.7% to predict atherosclerosis plaque in carotids.

Regarding CAD, despite its strong association with peripheral atherosclerosis, we found no association with the presence of strain ($P = 0.217$) and increased CIMT ($P = 0.149$). However, to subtract

Table III. Association between clinical variables and ventricle strain on electrocardiogram

Clinical variables	Absence of strain (*N*)	Presence of strain (*N*)	*P* value
SAH	28	12	0.24
Obesity	13	2	0.23
DM	6	5	0.07
Diagnosed CAD	16	8	0.22

DM, diabetes mellitus; *N*, number of patients.

Table IV. Association between electrocardiogram variables and CIMT

EKG variables	Normal CIMT (*N*)	Increased CIMT (*N*)	*P* value
Left atrium overload	25	12	0.38
Left ventricle overload	19	15	0.08
Strain pattern	3	9	0.001*

N, number of patients.
*$P < 0.05$.

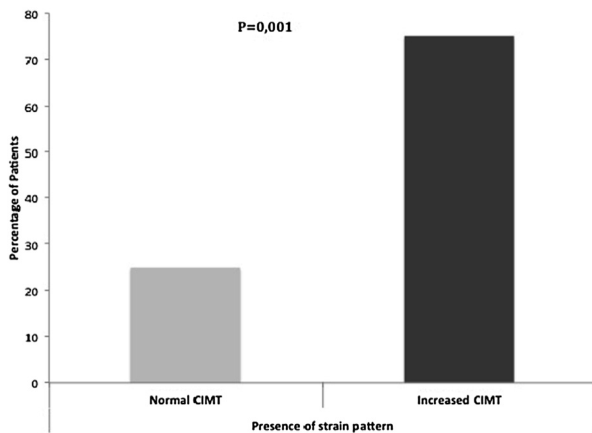

Fig. 1. Association between left ventricle strain pattern of electrocardiogram and increased CIMT.

the possible influence of the presence of CAD in our results, we chose to perform the analysis of a subgroup without diagnosed CAD. We analyzed 28 patients without CAD and found that the presence of strain on EKG was also associated with increased CIMT ($P = 0.008$). The same analyses was performed for presence of plaque and there was not observed association with the presence of strain ($P = 0.057$).

DISCUSSION

Aortic valve stenosis leads to LV pressure overload, causing compensated concentric hypertrophy.

Table V. Association between electrocardiogram variables and atherosclerotic plaque in carotid

EKG variables	Absence of carotid plaque (*N*)	Presence of carotid plaque (*N*)	*P* value
Left atrium overload	14	23	0.741
Left ventricle overload	12	22	0.221
Strain pattern	1	11	0.011*

N, number of patients.
*$P < 0.05$.

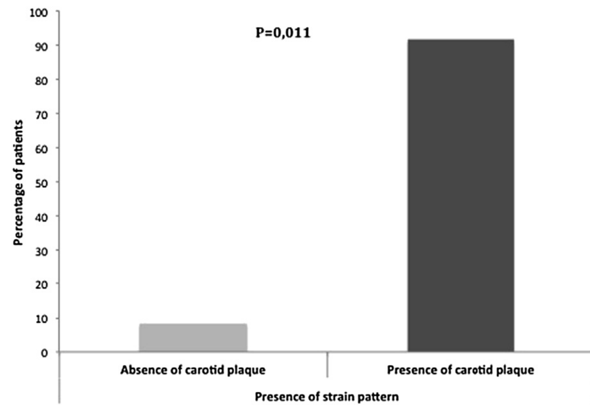

Fig. 2. Association between left ventricle strain pattern of electrocardiogram and presence of carotid plaque.

Increased left ventricular mass may be associated with relative ischemia of cardiac muscle.[1–4] Moreover, due to aortic valve obstruction, there is a decrease in coronary perfusion pressure, which may further accentuate ischemia. Degenerative AS is associated with more than 30% of coronary atherosclerosis, the other contributory to the development of myocardial ischemia.[5]

LV strain pattern on EKG of moderate to severe AS patients is an independent signal of worsening prognosis. Moreover, it is indicative of relative subendocardial ischemia, and in most cases silent ischemia, by imbalance between oxygen demand and supply in the hypertrophied heart.[6–8]

For these reasons, we hypothesized that the strain pattern in aortic valve stenosis may be associated with subclinical atherosclerosis, assuming this as a systemic process. We performed carotid ultrasound to assess CIMT and the presence of atherosclerotic plaque in at least one of the carotid arteries.

In this sample of 52 patients, CIMT adjusted for age, according to previous guidelines,[9–18] has shown a strong association between strain patterns on EKG with increased CIMT. Also, there was an excellent specificity of EKG strain pattern in

predicting CIMT (90.3%). This result suggests that the development of ventricular hypertrophy in AS and the endothelial dysfunction underlying the atherosclerosis have similarities in their physiopathological mechanisms. Tissue growth factors, cytokines, and inflammatory markers, all involved in the process of hypertrophy, would have a systemic effect, also contributing to the increase in CIMT. In addition, these factors may interfere in the progression of AS by perpetuating inflammation.

At this point, some considerations concerning our population and additional statistical analysis would be taken into account and are described in the subsequent paragraphs.

It is already known that patients with degenerative AS have associated cardiovascular risk factors such as SAH and CAD. In our study, we found a high prevalence of hypertensive patients (77.9%), which is also commonly found in clinical practice. Certainly, the presence of SAH is contributive to strain on the EKG, increased CIMT, or peripheral atherosclerotic plaque. This would be considered as a limitation of our study. Therefore, we performed a statistical analysis to assess whether the presence of strain in these AS patients and highly prevalent SAH was independently associated to increased CIMT. Interestingly, we found that the presence of strain enhanced by 9.7 times the odds of increased CIMT and by 5.6 times the odds of carotid plaque in a model adjusted for SAH and age. This collaborated with our hypothesis that EKG is a simple noninvasive method of predicting subclinical peripheral atherosclerosis. These results may be useful for the physicians to recognize AS patients who deserve more aggressive control of risk factors for atherosclerosis.

Another interesting finding in our study was that the presence of comorbidities did not interfere with the presence of strain or increased CIMT, suggesting that, in this population, the presence of AS was the main cause of EKG strain and increase of CIMT.

Despite the strong association with peripheral arteriosclerosis, we found no association between CAD and presence of strain or increased CIMT EMIC.

Further cohort studies should be performed for evaluating EKG strain pattern as a risk factor of CIMT.

CONCLUSION

In moderate-to-severe AS patients, the presence of LV strain in EKG has to be interpreted as a potential indicator of subclinical peripheral atherosclerosis. Therefore, it would be reasonable to suggest that these patients should be further investigated.

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