THE ANALYSIS OF ATHEROSCLEROTIC CAROTID INVOLVEMENT IN SYMPTOMATIC CORONARY PATIENTS WITH MITRAL/AORTIC ANNULUS CALCIFICATION

Silvia Georgiana Ionescu\(^1\), Irina Popescu\(^2\), Adina Ionac\(^1\), Sorin Pescariu\(^1\), Stefan Iosif Dragulescu\(^1\)

ABSTRACT

Introduction: Preclinical atherosclerotic markers are also risk factors for mitral/aortic annulus calcification, characterized by lipid and calcium deposits within its fibrous skeleton. Aims: To determine if the presence of mitral/aortic annulus calcification (echocardiographic study) is associated with significant coronary artery disease (angiographic study) and/or carotid artery disease (echocardiographic study). Material and methods: We included 123 coronary patients (66.20 ± 8.11 years) with indication for angiography (angina pectoris or ECG changes or positive stress testing) that were also evaluated by using echocardiography and carotid ultrasonography. The quantification of coronary lesions was made using the Gensini score, for the carotid lesions we used a plaque score and the calcific annulus lesions were defined according to the Guidelines. Results: The entire population analyzed was characterized by the presence of pro-atherogenic cardio metabolic profile. The prevalence of coronary artery disease was 72.4%, with a median of the Gensini Score of 26. Patients with significant carotid stenosis (>50%) and mitral/aortic annulus calcification had higher Gensini scores vs those without annulus lesions: 43.17 ± 33.96 vs. 26.62 ± 38.06, p < 0.05; respectively 43.08 ± 38.04 vs 26.69 ± 32.17, p < 0.01. Subjects with carotid occlusion, no matter the site of annulus calcification - the Gensini score and annulus calcification based on the metabolic syndrome or on the carotidmetabolic risk components. Conclusions: our study proves the association between mitral/aortic annulus calcification with atherosclerotic lesions at the coronary and carotid site, in a group of selected patients. Identification of carotid stenosis among coronary patients with annulus calcification might allow a more accurate risk stratification with better therapeutic decisions.

Key Words: mitral/aortic annulus calcification, coronary artery disease, carotid atherosclerosis

INTRODUCTION

Preclinical atherosclerotic markers are also risk factors for mitral/aortic annulus calcification, characterized by lipid and calcium deposits within its fibrous skeleton. Framingham Heart Study has proven that those with echocardiographic evidence of mitral annulus calcification have had higher Odds ratio for cerebral stroke (2.10), cardiovascular event-
fatal coronary event, non fatal coronary event requiring hospitalization or revascularization procedure (1.5), overall cardiac death after 16 years follow up (1.6). The nature of these vascular events has proven to be embolic. A question arises: could mitral annulus calcification be a direct source of embolism or is it a marker of a clinical status associated with thrombembolism: age, arterial hypertension, hypercholesterolemia, diabetes mellitus, chronic peripheral arterial disease, atrial fibrillation and heart failure? 

Cardiovascular Health Study showed that the severity of annulus calcification had a direct correlation with the presence of cerebral infarction (MRI study): OR=1.24. 

Future studies will have to clarify the underlying mechanisms and, if we can slow the process of annulus calcification, would we be able to reduce the incidence of stroke? 

In the ARIC (Atherosclerosis Risk in Communities Study) cohort, carotid atherosclerotic plaque detection was a marker of advanced atherosclerosis and had a strong predictive value for cerebral stroke. 

In light of this evidence, we made the following hypothesis: the presence of mitral annulus calcification could be a sign of high susceptibility for the development of atherogenic vascular processes, due to similar aggregation of cardiovascular risk factors. 

**AIM**

Our study aims to determine whether the presence of mitral/aortic annulus calcification is associated with significant coronary or carotid artery disease. 

**MATERIAL AND METHODS**

Patient selection: we enrolled 792 patients at high cardiovascular risk, which were evaluated using the echographic method, prior to angiography. The inclusion criteria were as follows: all patients were admitted to the Institute of Cardiovascular Disease, Timisoara, with indication of angiography for signs and symptoms suggestive for coronary artery disease; coronary artery disease diagnosed by ECG changes or positive exercise stress testing; preserved left ventricular ejection fraction; sinus rhythm. Exclusion criteria: acute myocardial infarction (defined by creatin-kinase and troponin elevation), congenital heart disease, heart failure NYHA III, IV. We thus included 123 coronary patients with indication for angiography. All patients have signed the informed consent. The study was approved by the Ethic Committee at The Institute of Cardiovascular Disease Timisoara. 

Data collection: we have used the clinical charts for data collection: demographic data, anthropometric data, anamnesis, clinical examination and paraclinical data: metabolic profile, hemodynamic profile: systolic and diastolic blood pressure, pulsed pressure. 

The echocardiographic evaluation was made using a General Electrics Vingmed Ultrasound System, a Vivid 7 and a Vivid 9 machine, with MS4 and MS5 transducers. Annulus calcifications were analyzed by 2D transthoracic echo, parasternal long axis and short axis view and apical views. They were defined according to the ACC/AHA guidelines 2006 and EAE/ASE guidelines. In view of the recommendations of The American Society of Echocardiography 2006, we performed the measurements for the evaluation of the carotid intimae-media thickness and we defined carotid atherosclerosis through the plaque score: 0=no calcific lesions; 1 = calcific. atherosclerotic plaques, no stenosis; 2 = stenosis < 50%; 3 = stenosis > 50%; 4 = carotid occlusion. 

The angiography was done using a Siemens Coroskop standard machine, in order to detect coronary atherosclerotic lesions. We calculated the Gensini Score for each enrolled patient, and we applied this score in relationship with the coronary lumen narrowing, according to the reference. 

**Statistical analysis**

The data were collected and electronically deposited using The Epiinfo Program, 2001, version 6. The statistical analysis was done with The SPSS program, 2010, version 18. Results were considered statistically significant for p < 0.05; strong statistical significance was considered for a p < 0.01. For parametric data we applied the t student test; for the non-parametrical data we applied the Mann-Whitney test and the Kruskal-Wallis test; and for the categorical data we used the chi squared test. 

**RESULTS**

Mitral annulus calcification was detected in 71 cases out of the 123. The proportion of aortic annulus calcification was 56.1%. (Table 1) The prevalence of mitral and aortic annulus calcification was maximum, 70% respectively 80% among patients with carotid score of 4. Carotid stenosis higher than 50% was present in 25 patients out of 50 with annular calcification (50%). 5 out of 20 patients with annulus calcification had a carotid score of 4 (25%). 

The variation of the Gensini score in the presence of aortic or mitral annulus calcification in patients with a carotid score of 3 and 4: the prevalence of coronary artery disease defined by the angiographic criteria was
Table 1. The frequency of annulus calcification and the carotid plaque score.

<table>
<thead>
<tr>
<th>Carotid score</th>
<th>Anulus calcification</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent(Ao)</td>
<td>Present(Mi)</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>51</td>
</tr>
</tbody>
</table>

72.4%. The Gensini score had a median of 26.

Relation between the Gensini score and the carotid score

The mean Gensini Score was significantly higher among those with carotid artery occlusion (score 4) compared to those without carotid lesions (score 0): 36.13 ± 31.13 vs 19.11 ± 21.31, p < 0.01. (Fig. 1)

Relation between the Gensini score - the carotid score - aortic and mitral annulus calcification

In subjects with carotid stenosis higher than 50%, the mean Gensini score was significantly higher in those with mitral annulus calcification (43.08 ± 38.04 vs 26.29 ± 32.17, p < 0.01) or aortic annulus calcification (43.17 ± 33.96 vs 26.62 ± 36.08, p < 0.05) compared to those without degenerative annular lesions. (Fig. 2)

No matter the site of the annulus calcification (aortic or mitral), subjects with carotid occlusion (score 4) have had a significantly lower Gensini score compared to those with carotid score of 3: 36.13 ± 31.14 vs 43.17 ± 33.96, p < 0.01; 36.14 ± 32.85 vs 43.08 ± 38.04, p < 0.05.

The cardiovascular profile in the presence of carotid occlusion and annulus calcification

a. Metabolic profile: the entire population analyzed was characterized by the presence of proatherogenic cardio metabolic profile: total cholesterol= 209.75 ± 53.97 mg/dl, LDLc = 137.5 ± 55.56 mg/dl, triglycerides = 147.88 ± 41.97 mg/dl, HDLc = 37.00 ± 9.20 mg/dl, fasting plasma glucose = 159.38 ± 74.58 mg/dl. We found no statistically significant differences between those with carotid score 4 and 0, p > 0.05. furthermore, there was no significant relationship between the metabolic syndrome and aortic or mitral annulus calcification, p>0.05.

b. Hemodynamic profile: the subjects with carotid occlusion had a hypertensive profile characterized by a mean SBP of 175 mm Hg ± 22.67 mmHg, and a mean DBP of 89.38 mm Hg ± 15.22 mmHg. The entire group was characterized by a mean value of the pulsed pressure of 68.38 ± 19.73 mm Hg. The histogram of frequency distribution showed a high prevalence of the pulsed pressure above 60mm Hg: 90 out of 123 cases. The behaviour of mean pulsed pressure among the subgroups of subjects with degenerative annulus lesions was higher among those with aortic annulus calcification:

- aortic valve sclerosis: mean PP = 57.12 ± 17.91 mm Hg;
- mitral valve fibrosis: mean PP = 61.72 ± 3.53 mm Hg;
- mitral annulus calcification: mean PP = 56.35 ± 20.43 mm Hg;
- aortic annulus calcification: mean PP = 66.36 ± 15.10 mm Hg;
- atherosclerotic plaques on the ascending aorta mean PP = 49.12 ± 18.68 mm Hg.

The variation analysis of the mean PP value in patients with annulus calcification and carotid lesions has found statistically significant differences only in the group with carotid score of 4 and aortic annulus calcification: 85.63 ± 17.61 mm Hg vs. 62.50 ± 3.53 mm Hg, p < 0.01. (Tables 2,3)

DISCUSSION

Our study clearly proves the association between vascular atherosclerosis and degenerative lesions found at the mitral/aortic annulus site. The prevalence of annulus calcification was maxim among patients with more severe coronary lesions. Furthermore, in the presence of significant carotid artery stenosis, the coronary lesions were more severe in patients with annulus calcification vs those without.

An interesting observation refers to the quantitative analysis of the coronary lesions, expressed as the Gensini score: in patients with carotid stenosis higher than 50% and annulus calcification, the coronary lesions were more severe than in patients with carotid stenosis only.
First of all, the coexistence of carotid atherosclerosis and mitral annulus calcification could bring to light new information in regard to the incidence and severity of coronary artery disease.9

Second of all, atherosclerosis is a systemic disease: the distribution of the atherosclerotic lesions is most defiantly heterogeneous. A question arises at this point: which site is more protected from atherosclerosis? The brain or the myocardium? Rosengarten B. et al, by correlating the stenosis of each coronary artery (as a uni-/bi-/tri- vessel disease) with carotid artery stenosis, found no association whatsoever.9 Only the severity of coronary artery disease assease as the Gensini score has been proven to correlate with cerebrovascular disease.

Third of all, the patients with mitral annulus calcification are at high risk for arterial calcifications in other vascular territories, and are therefore at high risk for fatal/nonfatal cardiovascular event.10,11 Further research in the field of calcification, both vascular and valvular, could offer new solutions for cardiovascular risk stratification and management. Roger J.M.Rennenberg consider vascular calcification as the result of a complex interaction between stimulating proteins-BMP-2, RANKL and inhibiting ones-matrixGlc proteins, BMP-7, A-fetuin, thus launching new therapeutic insights.12

Fourth of all, the relation between valvular annulus calcification and atherothrombotic cardiovascular disease has not been well established. In MESA Study, mitral annulus calcification was statistically significant associated with atherosclerosis risk factors: age, diabetes mellitus, body mass index, especially in women and independently of etnic origins.13

It seems of intrest the fact that we found a significant association between pulsed pressure and aortic annulus calcification. It is well known and proven the value of pulsed pressure as a marker of cardiovascular risk, along with aortic annulus calcification.14-16

As cerebral hemorrhage represents 15% of the total number of cerebral strokes in Europa, Safar's conclusion remains valid: independently of systolic blood pressure, diastolic blood pressure and mean blood pressure, pulsed pressure is an important cardiovascular risk factor needed to be taken into account especially in hypertensive patients undergoing treatment.17

Agnon et colab. underline the pathogenic similarities between atherosclerosis and pulsed pressure; he is also the one to issue the hypothesis that aortic valve sclerosis and annulus calcification are atherosclerotic-like processes.18,19

Although our study can not prove the implication of traditional cardiovascular risk factors in the genesis of mitral/aortic annulus calcification, the metabolic and hemodynamic profile of the patients justifies an aggressive management of modifiable risk factors, in order to reduce the global cardiovascular risk and, obviously, the number of cardiovascular events.
CONCLUSIONS

Our study proves the association between mitral/aortic annulus calcification with atherosclerotic lesions at the coronary and carotid site, in a group of selected patients. The echografic detection of annulus calcification might improve the algorithm for the evaluation of the arterial function and therefore, the management of the cardiovascular risk. Identification of carotid stenosi among coronary patients with annulus calcification might allow a more accurate risk stratification with better therapeutical decisions.

The limitations of our study regard the selection criteria. Our results should be interpreted in a given context: we included in our study only high risk patients, that were evaluated ECHO before the angiography. It's highly possible for the prevalence data to be overestimated; but our proven associations reflect once again the natural history of atherosclerosis.

REFERENCES