Association between mitral annulus calcification and aortic atheroma: a prospective transesophageal echocardiographic study

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Received 30 June 1999; received in revised form 12 October 1999; accepted 1 December 1999

Abstract

Background and purpose: Although mitral annulus calcification (MAC) has been reported to be a significant independent predictor of stroke, no causative relationship was proven. It is also known that aortic atheroma (AA), especially those ≥5 mm thick and/or protruding and/or mobile are associated with stroke. This study was designed to determine whether an association exists between MAC and AA.

Methods: We prospectively evaluated the records of 279 consecutive patients who underwent transesophageal echocardiography (TEE) for various indications to measure the presence and characteristics of AA. The 105 patients in whom a diagnosis of MAC was made on transthoracic echocardiography (TTE) immediately preceding the TEE, were compared with 174 age-matched patients without MAC. MAC was defined as a dense, localized, highly reflective area at the base of the posterior mitral leaflet. We measured MAC thickness with two-dimensional-TTE in four-chamber view and AA thickness, protrusion and mobility with TEE. AA was defined as localized intimal thickening of ≥3 mm. A lesion was considered complex if there was plaque extending ≥5 mm into the aortic lumen and/or if it was protruding, mobile or ulcerated.

Results: No differences were found between the groups in risk factors for atherosclerosis or in indications for referral for TEE. Significantly higher rates were found in the MAC group for prevalence of AA (91 vs. 44%, P < 0.001), atheromas ≥5 mm thick (68 vs. 19%, P < 0.001), protruding atheromas (44 vs. 15%, P < 0.001), ulcerated atheromas (10 vs. 1%, P < 0.001) and complex atheroma (74 vs. 22%, P < 0.001). Sixty patients had MAC thickness ≥6 mm and 45 > 6 mm. AA thickness was significantly greater in the patients with a MAC thickness of ≥6 mm (6.1 ± 2.8 vs. 5.0 ± 2.6 mm, P = 0.03). On multivariate analysis MAC, hypertension and age were the only independent predictors of AA (P = 0.0001, 0.005 and 0.007, respectively).

Conclusions: There is a significant association between the presence and severity of MAC and AA. MAC may be an important marker for atherosclerosis of the aorta. This association may explain in part the high prevalence of systemic emboli and stroke in patients with MAC.

Keywords: Mitral annulus calcification; Aortic atheroma; Atherosclerosis; Stroke

1. Introduction

Calcification of the mitral annulus is a non-inflammatory, chronic, degenerative process of the fibrous support structure of the mitral valve [1–3]. It occurs more often in women and the elderly [4], especially in the presence of systemic hypertension [2,5–7], hypercholesterolemia [5] and diabetes mellitus [5–7]. Mitral annulus calcification (MAC) has been found to play a role in left atrial enlargement, left ventricular enlargement, atrial fibrillation, conduction defects, mitral regurgitation, mitral stenosis, hypertrophic cardiomyopathy and bacterial endocarditis [3,8–14]. Its association with stroke has been suspected [1–3,10–24] since the 1946 report of Rytand and Lipsitch [9]. In 1981, Nair et al [3] followed two groups of age-and sex-matched patients (n = 107 in each) with and without MAC for a mean of 4.4 years and noted a rate of 10% of cerebrovascular events in the MAC patients as compared with only 2% in the controls (P < 0.01). Benjamin et al [25] in a population-based longitudinal study of the Framing-
Table 1
Clinical characteristics of MAC subjects and controls

<table>
<thead>
<tr>
<th>MAC group (n = 105)</th>
<th>Control group (n = 174)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (range)</td>
<td>74 ± 10 (35–93)</td>
<td>72 ± 7 (61–92)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>45/60</td>
<td>58/116</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>52 (50%)</td>
<td>67 (39%)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>27 (26%)</td>
<td>39 (22%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (24%)</td>
<td>41 (24%)</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>18 (17%)</td>
<td>21 (12%)</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;200 mg/dl)</td>
<td>21 (20%)</td>
<td>27 (16%)</td>
</tr>
</tbody>
</table>

* MAC, Mitral annulus calcification; NS, Not significant; CHD, Coronary heart disease.

2. Methods

2.1. Patients

Between 1997 and 1999, our laboratory prospectively followed 279 consecutive patients who underwent TEE, excluding patients with rheumatic valvular disease or prosthetic valves. The patients were divided into two groups: 105 patients in whom a diagnosis of MAC was made by transthoracic echocardiography (TTE) performed immediately before the TEE (45 females, 60 males, mean age 74 ± 10 years, ranged 35–93 years) and 174 age-matched patients without MAC (58 females, 116 males, mean age 72 ± 7 years, ranged 61–92 years). In order to reach age-matching patients younger than 60 years were excluded from the control group before recruitment. The clinical characteristics of the two groups are shown in Table 1 and the indications for referral for TEE in Table 2.

2.2. Echocardiography study

Complete transthoracic two-dimensional Doppler color flow examinations were performed in all patients using a Hewlett-Packard phased array sector scanner with a 2.5 MHz transducer (77020A). Transesophageal two-dimensional echocardiography was performed immediately after the TTE with a commercially available 5 MHz multiplane transducer (Hewlett-Packard 21363A). The sonographs used were Hewlett-Packard Sonos 1000 and 2000. After the cardiac examination, the transducer was rotated posteriorly to obtain aortic images. The transducer was advanced to the distal esophagus (≈ 40 cm) and slowly withdrawn to obtain images from the distal thoracic aorta to the aortic arch; it was then rotated and advanced to image the ascending aorta. If abnormalities of the aorta were detected, more detailed scanning at that level was performed. These procedures are part of our routine TEE examination. All studies were recorded on super-VHS tape and evaluated independently by two specialists in echocardiography. In cases of disagreement, a third examiner was consulted. MAC was defined as a dense, localized, highly reflective area at the base of the posterior leaflet.
of the mitral valve and was evaluated for both presence and severity (Fig. 1) [34]. The severity of MAC (expressed as maximal thickness in millimeters) was measured with a two-dimensional TTE in four-chamber view [25].

The aortic intima was evaluated for changes in thickening, calcification, protrusion, mobility and ulceration. AA was defined as localized intimal thickening of ≥ 3 mm and was localized to the ascending aorta, the aortic arch or the descending aorta. Complex atherosclerotic plaque was defined as the presence of one or more of the following: (1) focal increase in echo density and thickening of the intima extending ≥ 5 mm into the aortic lumen; (2) disruption or irregularities of the intimal surface (ulceration); (3) overlying, shaggy echogenic material; (4) mobile component of the atheroma; and (5) protruding atheroma [26,35]. The observers who made the diagnosis of AA were blinded to the presence of MAC.

2.3. Risk factors

The atherosclerotic risk factors considered in this study were diabetes mellitus, hypertension, hypercholesterolemia, family history of coronary heart disease and smoking history. Diabetes was defined as hyperglycemia requiring previous or the need for ongoing pharmacologic therapy. Hypertension was defined as either systolic or diastolic elevation in blood pressure (>140/90 mmHg) or ongoing antihypertensive pharmacologic therapy. Hypercholesterolemia was defined as a total cholesterol level of >200 mg/dl. Family history was coded as positive if a first-degree relative had a coronary event at <55 years. Ten or more pack-years of cigarette use was considered significant.

2.4. Statistical analysis

Numeric values are reported as mean ± S.D. or as a proportion of the sample size. Comparisons between the study and control group were made with χ²-square for categorical data and Student’s t-test for continuous data. Multivariate analyses were used to identify predictors for AA. The following variables were entered into the model: age, sex, MAC, diabetes mellitus, hypertension, hypercholesterolemia, positive family history and smoking history. The univariate correlation coefficients for these variables were determined and were then entered into a multivariate model for prediction of AA with use of the RS1 statistical package version 5.3.0 (Bolt, Beranek and Newman, 1997). Forward stepping was used, with the F to enter and F to remove any variable selected so that the corresponding significance level (outer tail area) was < 0.05; no variables were forced into the model.

3. Results

There were no intergroup differences in risk factors for atherosclerosis (Table 1) or in indications for referral for TEE (Table 2). There were significantly more women in the MAC group than in the control group (43 vs. 33%, P = 0.038).

Table 3 and Fig. 1 compare the two groups for prevalence and characteristics of AA. Significantly higher rates were found in the MAC group for presence of AA (≥ 3 mm) (91 vs. 44%, P < 0.001), atheromas ≥ 5 mm (68 vs. 19%, P < 0.001), protruding atheromas (44% vs. 15%, P < 0.001) and ulcerated atheromas (10 vs. 1%, P < 0.001). Complex atheromas were also

### Table 3

<table>
<thead>
<tr>
<th>AA Characteristics</th>
<th>MAC group (n = 105)</th>
<th>Control group (n = 174)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic atheroma (≥ 3 mm)</td>
<td>96 (91%)</td>
<td>77 (44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complex atheroma</td>
<td>78 (74%)</td>
<td>39 (22%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atheroma ≥ 5 mm</td>
<td>71 (68%)</td>
<td>33 (19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protruding atheroma</td>
<td>46 (44%)</td>
<td>26 (15%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ulcerated atheroma</td>
<td>10 (10%)</td>
<td>2 (1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atheromas with mobile components</td>
<td>10 (10%)</td>
<td>8 (5%)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* MAC, Mitral annulus calcification.
MAC has long been suspected to be associated with stroke [1,2,9–24]. Nair et al [3], in a 4.4-year study of 107 MAC patients aged <61 years and an equal number of age and sex-matched control subjects, found that the MAC patients had a five-fold higher incidence of cerebrovascular events. Aronow et al [36] followed 976 MAC patients (mean age 82 years) for 39 months and noted that MAC was associated with a 1.7 times greater risk of new thromboembolic stroke. In a second study of elderly patients with extracranial carotid arterial disease, these authors reported that the presence of MAC increased the incidence of new thromboembolic stroke by 1.5-fold in those with 40–100% extracranial carotid arterial stenosis and by 2.2-fold in those with 0–39% stenosis [37]. In the Boston Area Anticoagulation Trial for Atrial Fibrillation [24], a 2.2-year follow-up of 420 patients (mean age 68 years), MAC was found to increase the incidence of ischemic stroke 4.0 times. Finally, Benjamin et al [25] examined the relationship between MAC and the incidence of stroke in a longitudinal population-based study in elderly patients from the Framingham cohort. They concluded that MAC was associated with a double risk of stroke, independently of traditional risk factors for stroke; on multivariate analysis, each millimeter of calcification increased the relative risk of stroke by 1.24 (95% CI, 1.12–1.37; \( P < 0.001 \)). Yet, whether such calcification contributes causally to the risk of stroke or is merely a marker of increased risk because of its association with other precursors of stroke remains unknown.

Experimentally-induced systemic arterial atherosclerosis is associated with the deposition of fatty plaques on the aortic surface of the aortic valve cusps and on the ventricular surface of the posterior mitral leaflet [38]. Roberts [39], in a necropsy study of persons aged >65 years, showed that 100% of those with MAC or aortic valve calcification had calcific deposits in one or more coronary arteries. This finding was supported by pathological studies [38] showing that collections of foam cells, which represent early atherosclerotic lesions [40] may be observed on the endothelium of the epicardial coronary arteries, on the ventricular surface of the posterior mitral leaflet and on the aortic aspects of each of the aortic valve cusps already in adolescence and the second and third decades of life. These data suggest that coronary atherosclerosis, MAC and aortic valve calcinosis in the elderly have a similar etiology. As the fatty plaques get larger, their nutritional needs fail to be fulfilled and they degenerate into calcific deposits. Roberts [40] claimed, in an editorial on the senile cardiac calcification syndrome, that because calcific deposits in the mitral annular area are observed only in a population that develops significant coronary atherosclerosis, it is reasonable to assume that the cause of MAC in the elderly is similar; that is, MAC in the elderly is a form of atherosclerosis. This explains the

### Table 4

<table>
<thead>
<tr>
<th>Aorta Location</th>
<th>MAC group ((n = 96)^b)</th>
<th>Control group ((n = 77)^b)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending aorta</td>
<td>15 (16%)</td>
<td>2 (3%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Aortic arch</td>
<td>72 (75%)</td>
<td>46 (60%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Descending aorta</td>
<td>70 (73%)</td>
<td>39 (51%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### Notes

- **MAC**: Mitral annulus calcification.
- \(^a\) Total number of patients with atheromas in each group. Percentages and \(P\) values are calculated from the total number of patients with atheromas in each group.

The present study is the first prospective clinical report showing a strong and significant association between the presence of MAC and AA on echocardiography. Complex atheromas were significantly more prevalent in the MAC group compared to the controls and high correlation was found between MAC thickness and AA thickness. These finding support and strengthen our previous observation in a smaller retrospective study [33].
coexistence of MAC and aortic atheroma in the same patients.

We recently demonstrated a significant association between MAC and carotid atherosclerotic disease [41], a well known risk factor for stroke. In a different study we found a highly significant association between MAC and coronary artery disease, including higher rates of 3-vessel disease and left main coronary artery disease among patients with MAC [42]. As a result of the body of evidence obtained from cased control and follow-up studies [26–32], the presence of plaques in the aortic arch can be accepted as a strong independent risk factor for brain infarction, with a causal relationship, particularly for large complex plaques. The significant association between the prevalence and severity of MAC and AA support the view that MAC is a marker of diffuse atherosclerosis, affecting both the aortic arch and the carotid arteries, both capable of causing stroke. Moreover, our results may explain the finding of Benjamin et al [25] regarding the correlation between MAC thickness and the relative risk of stroke.

The absence in our work of any significant differences in risk factors between the MAC group and the controls and the finding on multivariate analysis that only MAC, age and hypertension were an independent predictors for aortic atheroma, further support our hypothesis that MAC and aortic atheroma are an expression of the same systemic process. It is not surprising that the MAC group had significantly more women than the controls. It has been well established that MAC occurs more often in women [4] and our results confirm this finding.

In conclusion, MAC can be detected by TTE, a simple, non invasive imaging method. Using MAC as a marker, can define a subgroup of patients with a very high prevalence of AA. We suspect the association between MAC and atherosclerosis, including aortic atheroma and carotid atherosclerotic disease explains the high incidence of stroke in MAC patients. The presence of MAC probably indicates a systemic atherosclerotic process which involves the aorta, aortic valve, carotid and coronary arteries and perhaps other parts of the arterial systems. This mounting evidence suggests that MAC should likely be considered, in most cases, as an atherosclerotic comorbidity in stroke and not its cause [43].

References


