Association Between Mitral Annulus Calcification and Carotid Atherosclerotic Disease

Yehuda Adler, MD; Arnon Koren, MD; Noam Fink, MD; David Tanne, MD; Renato Fusman, MD; Abid Assali, MD; Jakov Yahav, MD; Avigdor Zelikovski, MD; Alex Sagie, MD

Background and Purpose—It has been established that mitral annulus calcification (MAC) is an independent predictor of stroke, though a causative relationship was not proved, and that carotid artery atherosclerotic disease is also associated with stroke. The aim of this study was to determine whether there is an association between the presence of MAC and carotid artery atherosclerotic disease.

Methods—Of the 805 patients in whom the diagnosis of MAC was made by transthoracic echocardiography between 1995 and 1997, 133 patients (60 men and 73 women; mean age, 74.3±8 years; range, 47 to 89 years) underwent carotid artery duplex ultrasound for various indications; the study group comprised these patients. They were compared with 129 age- and sex-matched patients without MAC (57 men and 72 women; mean age, 73.6±7 years; range, 61 to 96 years) who underwent carotid artery duplex ultrasound during the same period for the same indications. MAC was defined as a dense, localized, highly reflective area at the base of the posterior mitral leaflet. MAC was considered severe when the thickness of the localized, highly reflective area was ≥5 mm on 2-dimensional echocardiography in the 4-chamber view. Carotid artery stenosis was graded as follows: 0%, 20%, 40%, 60%, 80%, and 100%.

Results—Compared with the control group, the MAC group showed a significantly higher prevalence of carotid stenosis of ≥40% (45% versus 29%, P=0.006), which was associated with ≥2-vessel disease (23% versus 10%, P=0.006) and bilateral carotid artery atherosclerotic disease (21% versus 10%, P=0.011). Severe MAC was found in 48 patients. More significant differences were found for the severe MAC subgroup (for carotid stenosis of ≥40%) in rates of carotid artery atherosclerotic disease (58% versus 29%, P=0.001), and ≥2-vessel disease (31% versus 10%, P=0.001), in addition to bilateral carotid artery stenosis (27% versus 10%, P=0.004) and even bilateral proximal internal carotid artery stenosis (21% versus 8%, P=0.015). Furthermore, significant carotid artery atherosclerotic disease (stenosis of ≥60%) was significantly more common in the severe MAC subgroup than in the controls (42% versus 26%, P<0.05) and was associated with higher rates of ≥2-vessel disease (19% versus 7%, P=0.02) and bilateral carotid artery stenosis (17% versus 7%, P=0.05). On multivariate analysis, MAC and age but not traditional risk factors were the only independent predictors of carotid atherosclerotic disease (P=0.007 and P=0.04, respectively).

Conclusions—There is a significant association between the presence of MAC and carotid artery atherosclerotic disease. MAC may be an important marker for atherosclerotic disease of the carotid arteries. This association may explain the high prevalence of stroke in patients with MAC. (Stroke. 1998;29:1833-1837.)

Key Words: carotid artery diseases ■ mitral annulus calcification ■ stroke

Mitral annulus calcification (MAC) is a chronic, non-inflammatory, degenerative process of the fibrous support structure of the mitral valve.1,2 It occurs more often in women and the elderly.3 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.4-11 Its association with stroke has been suspected1,2,6-21 since the 1946 report of Rytand and Lipsitch.3 However, whether MAC 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 unclear.

Previous pathological studies22 have claimed that MAC in the elderly is a form of atherosclerosis and suggested that coronary atherosclerosis, MAC, and aortic valve calcium in the elderly have a similar etiology.23 We recently demonstrated24 a highly significant association between the presence of MAC and aortic atheroma, and Demopoulos et al25 found a very strong association between the presence of aortic atheroma and carotid artery atherosclerotic disease. Therefore, theaim of the present work was to determine whether an
association exists between MAC and carotid artery atherosclerotic disease.

**Subjects and Methods**
Between 1995 and 1997 our laboratory made a diagnosis of MAC by transthoracic echocardiography in 805 patients. Of these, 133 (73 women and 60 men; age range, 47 to 89 years; mean, 74.3 ± 8 years) underwent carotid artery duplex ultrasound for various indications. This group was compared with 129 age- and sex-matched patients (72 women and 57 men; age range, 61 to 96 years; mean, 73.6 ± 7 years) without MAC who underwent carotid artery duplex ultrasound during the same period. Patients with rheumatic valvular disease, cardiomyopathy, or prosthetic valves were excluded.

Complete 2-dimensional and Doppler color flow examinations were performed in all patients with the 2.5-MHz transducer of a Hewlett-Packard phased array sector scanner (model 77020 A). The 2-dimensional echocardiographic criteria for MAC included an intense echo-producing structure located at the junction of the atrioventricular groove and posterior mitral valve leaflet on the parasternal long axis and apical 4-chamber views or an intense echo-dense structure located posterior to the posterior mitral valve leaflet on the parasternal short-axis view. MAC was considered severe when the thickness of the intense echo-producing structure was ≥ 5 mm measured by 2-dimensional echocardiography in the 4-chamber view. Forty-eight patients were found to have severe MAC (32 women and 16 men; age range, 50 to 87 years; mean, 75 ± 8 years).

All studies were recorded on super-VHS tape and evaluated independently by 2 cardiologists with expertise in echocardiography. In case of disagreement, a third examiner was consulted. The observers who made the diagnosis of MAC were blinded to the presence or absence of carotid artery atherosclerotic disease.

Carotid artery duplex ultrasonography was performed (ATL-HDI 3000, Siestel) with the patient in the supine position, head slightly rotated to the side. Imaging was begun in the transverse plane at the most proximal level obtainable in the common carotid artery (CCA). After the CCA was scanned, the subclavian artery was identified in its long axis by sliding the transducer inferiorly and angling it slightly underneath the clavicle. The transducer was then advanced cephalad toward the carotid bifurcation to identify the internal (ICA) and external carotid arteries. During imaging of the carotid vessels in the transverse orientation, the most stenotic area was carefully evaluated and measured for the percent area/diameter stenosis and/or residual lumen diameter.

Sagittal images were obtained next. Imaging was begun with the proximal CCA. The transducer was aligned so that the CCA appeared in a horizontal position on the screen, without either end angled up or down. This allowed for the best acoustic reflection from the vessel. The transducer was then moved in a cranial fashion to image the bifurcation.

Carotid artery stenosis (CCA and ICA) was graded as follows: 0%, 20%, 40%, 60%, 80%, and 100%. Bilateral carotid artery stenosis was defined as the presence of carotid artery disease in both right and left carotid arteries (either CCA or ICA) above a specific limit of stenosis for both sides (for example, right CCA and left ICA with stenosis of ≥ 40%); disease ≥ 2-vessel disease was defined as bilateral disease or disease involving both the CCA and the ICA on the same side above a specific limit of stenosis for all vessels.

Atherosclerotic risk factors considered in this study were diabetes mellitus, hypertension, hypercholesterolemia, and history of smoking. Diabetes mellitus was defined as hyperglycemia requiring previous or ongoing pharmacological therapy. Hypertension was defined as either systolic or diastolic elevation of blood pressure (> 140/90 mm Hg) or the need for ongoing antihypertensive pharmacological therapy. Hypercholesterolemia was defined as a total cholesterol level of ≥ 200 mg/dL. Significant smoking history was defined as 10 or more pack-years of cigarette use.

### Statistical Analysis
Numerical values are reported as mean ± SD or as a proportion of the sample size. Comparisons between the study and control groups were made with the χ² test for categorical data and Student’s t test for continuous data. Multivariate analysis was used to identify predictors for carotid artery disease. The following variables were entered into the model: age, sex, MAC, diabetes mellitus, hypertension, hypercholesterolemia, and history of smoking. The univariate correlation coefficients for these variables were determined and then entered into a multivariable model for prediction of carotid artery atherosclerotic disease with use of the RS1 Statistical Package (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.

### Results

#### Patient Characteristics
The MAC group included 133 patients (73 women and 60 men; mean age, 74.3 ± 8 years; range, 47 to 89 years) (see Table 1). The control group included 129 age- and sex-matched patients (72 women and 57 men; mean age, 73.6 ± 7 years; range, 61 to 96 years). There were no intergroup differences in hypercholesterolemia and positive smoking history. Diabetes mellitus and hypertension were significantly more frequent in the MAC patients (30% versus 8%, P = 0.001, and 66% versus 53%, P = 0.03, respectively).

Severe MAC was found in 48 study patients (32 women and 16 men; mean age, 75 ± 8 years; range, 50 to 87 years) (see Table 2). There were no differences between this subgroup and the control group in age and sex distribution or in hypercholesterolemia and positive smoking history. Diabetes mellitus and hypertension were also more frequent in

### Table 1. Clinical Characteristics of MAC Subjects and Controls

<table>
<thead>
<tr>
<th></th>
<th>MAC Group (n = 133)</th>
<th>Control Group (n = 129)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range), y</td>
<td>74.3 ± 8</td>
<td>73.6 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(47–89)</td>
<td>(61–96)</td>
<td></td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>73/60</td>
<td>72/57</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88 (66%)</td>
<td>68 (53%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>10 (8%)</td>
<td>10 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40 (30%)</td>
<td>10 (8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>30 (23%)</td>
<td>26 (20%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2. Clinical Characteristics of Severe MAC Subjects and Controls

<table>
<thead>
<tr>
<th></th>
<th>Severe MAC Subgroup (n = 48)</th>
<th>Control Group (n = 129)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range), y</td>
<td>75 ± 8</td>
<td>73.6 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(50–87)</td>
<td>(61–96)</td>
<td></td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>32/16</td>
<td>72/57</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 (77%)</td>
<td>68 (53%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>4 (8%)</td>
<td>10 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (31%)</td>
<td>10 (8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>12 (25%)</td>
<td>26 (20%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
the severe MAC patients (31% versus 8%, $P=0.001$, and 77% versus 53%, $P=0.003$, respectively).

**Indications for Carotid Artery Duplex Ultrasound**

There were no significant differences between the MAC and control groups regarding indications for referral for carotid duplex ultrasound: stroke, 67 patients (50.3%) versus 58 (45%); carotid bruit or screening before cardiac surgery, 66 patients (49.7%) versus 71 (55%). This was also true when the severe MAC subgroup was compared with the controls: stroke, 24 patients (50%); carotid bruit or screening before cardiac surgery, 24 patients (50%).

**Mitral Annulus Calcification and Carotid Artery Disease**

Carotid artery stenosis of $\geq 40\%$ was found in 37 of the 129 patients without MAC (29%) compared with 60 of the 133 with MAC (45%, $P=0.006$) and in 28 of the 48 patients with severe MAC (58%, $P=0.001$) (see Tables 3 and 4). A significant difference was also found for the presence of carotid artery stenosis of $\geq 60\%$ between the controls (26%) and the severe MAC subgroup (42%, $P<0.05$). Disease $\geq 2$-vessel disease with carotid artery stenosis of $\geq 40\%$ was found in 13 control patients (10%) compared with 30 MAC patients (23%, $P=0.006$) and 15 severe MAC patients (31%, $P=0.001$). The differences in the rate of disease $\geq 2$-vessel disease with significant stenosis of $\geq 60\%$ between the severe MAC patients (19%) and the control patients (7%) was also significant ($P=0.02$). Bilateral carotid artery disease with stenosis of $\geq 40\%$ was found in 13 control patients (10%) compared with 28 MAC patients (21%, $P=0.01$) and 13 severe MAC patients (27%, $P=0.004$). Bilateral carotid artery disease with stenosis of $\geq 60\%$ was found in 9 controls (7%) and 8 severe MAC patients (17%, $P=0.05$). Bilateral proximal ICA stenosis of $\geq 40\%$ was also found significantly more often in the severe MAC subgroup compared with the control group (21% versus 8%, $P=0.015$). No carotid artery atherosclerotic disease was significantly more common in the controls compared with both the MAC group and the severe MAC subgroup (66% versus 46%, $P=0.001$, and 66% versus 35%, $P=0.001$), respectively.

Univariate analysis was performed. In the MAC subgroup, MAC ($P=0.006$) and age ($P=0.03$) were the only significant predictors for carotid artery stenosis of $\geq 40\%$. Multivariate analysis also identified MAC ($P=0.007$) and age ($P=0.04$) as the only independent predictors for carotid artery stenosis of $\geq 40\%$. Univariate analysis of the severe MAC subgroup identified MAC ($P=0.0001$), hypercholesterolemia ($P=0.01$), and age ($P=0.014$) as the only significant predictors for carotid artery stenosis of $\geq 40\%$. Similar results were identified in the multivariate analysis: MAC ($P=0.0002$), hypercholesterolemia ($P=0.009$), and age ($P=0.019$) for carotid artery stenosis of $\geq 40\%$.

**TABLE 3. Prevalence and Characteristics of Carotid Artery Atherosclerotic Disease in Patients With and Without MAC**

<table>
<thead>
<tr>
<th></th>
<th>MAC Group (n=133)</th>
<th>Control Group (n=129)</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Carotid artery stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 60%$</td>
<td>42 (32%)</td>
<td>34 (26.4%)</td>
<td>0.35</td>
</tr>
<tr>
<td>$\geq 40%$</td>
<td>60 (45%)</td>
<td>37 (29%)</td>
<td>0.006</td>
</tr>
<tr>
<td>$\geq 20%$</td>
<td>72 (54%)</td>
<td>44 (34%)</td>
<td>0.001</td>
</tr>
<tr>
<td>$\geq 2$-vessel disease ($\geq 40%$ stenosis)</td>
<td>30 (23%)</td>
<td>13 (10%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Bilateral carotid artery disease ($\geq 40%$ stenosis)</td>
<td>28 (21%)</td>
<td>13 (10%)</td>
<td>0.01</td>
</tr>
<tr>
<td>No carotid artery atherosclerotic disease</td>
<td>61 (46%)</td>
<td>85 (66%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**TABLE 4. Prevalence and Characteristics of Carotid Artery Atherosclerotic Disease in Patients With and Without Severe MAC**

<table>
<thead>
<tr>
<th></th>
<th>Severe MAC Group (n=48)</th>
<th>Control Group (n=129)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid artery stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 60%$</td>
<td>20 (42%)</td>
<td>34 (26%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$\geq 40%$</td>
<td>28 (58%)</td>
<td>37 (29%)</td>
<td>0.001</td>
</tr>
<tr>
<td>$\geq 20%$</td>
<td>31 (65%)</td>
<td>44 (34%)</td>
<td>0.001</td>
</tr>
<tr>
<td>$\geq 2$-vessel disease ($\geq 60%$ stenosis)</td>
<td>9 (19%)</td>
<td>9 (7%)</td>
<td>0.02</td>
</tr>
<tr>
<td>$\geq 2$-vessel disease ($\geq 40%$ stenosis)</td>
<td>15 (31%)</td>
<td>13 (10%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bilateral carotid artery disease ($\geq 60%$ stenosis)</td>
<td>8 (17%)</td>
<td>9 (7%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Bilateral carotid artery disease ($\geq 40%$ stenosis)</td>
<td>13 (27%)</td>
<td>13 (10%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Bilateral proximal ICA disease ($\geq 40%$ stenosis)</td>
<td>10 (21%)</td>
<td>10 (8%)</td>
<td>0.015</td>
</tr>
<tr>
<td>No carotid artery atherosclerotic disease</td>
<td>17 (35%)</td>
<td>85 (66%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Discussion
The present study is the first to show a strong and significant association between the presence of MAC and carotid atherosclerotic disease. Patients with severe MAC had more severe atherosclerotic disease in the carotid arteries.

Association Between Mitral Annulus Calcification and Stroke
Since the report by Rytand and Lipsitch, numerous studies have suggested an association between MAC and stroke. In a 4.4-year follow-up study of 107 MAC patients and an equal number of matched control patients, Nair et al noted a 10% rate of cerebrovascular events in the first group compared with a 2% rate in the second (P<0.01). Benjamin et al examined the relationship between MAC and the incidence of stroke in a population-based study from the Framingham cohort. They concluded that in the elderly, MAC was associated with a doubled risk of stroke, independent of traditional risk factors for stroke. 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.

Mitral Annulus Calcification and Atherosclerosis
Pathological studies have proved that foam cells representing early atherosclerotic lesions can be found in affected patients already during adolescence and in the second and third decades of life on the endothelium of the epicardial coronary arteries, the ventricular surface of the posterior mitral leaflet, and the aortic aspects of each of the aortic valve cusps.

Experimentally induced systemic arterial atherosclerosis is also associated with the deposition of fatty plaques on the aortic surface of the aortic valve cusps and the ventricular surface of the posterior mitral leaflet. These findings suggest that coronary atherosclerosis, MAC, and aortic valve calcium in the elderly have a similar etiology: as the fatty plaques grow, their nutritional needs fail to be fulfilled, and they degenerate into calcific deposits. Roberts, in an editorial on the senile cardiac calcification syndrome, claimed 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 MAC in the elderly is a form of atherosclerosis.

Carotid Artery Atherosclerotic Disease and Stroke
Carotid artery atherosclerotic disease has been found with high prevalence in elderly patients with hypertension, hyperlipidemia, a history of smoking, and diabetes mellitus. Its association with coronary artery disease and abdominal aortic aneurysm has also been noted, in addition to a possible link with stroke. A review of hospital and community stroke registries revealed that 25% to 33% of all ischemic strokes can be attributed to atherothrombotic disease that affects the major arteries to the brain in their extracranial and intracranial courses. Demopoulos et al also found a very strong association between the presence of aortic atheromas and carotid artery disease. Our group recently demonstrated a highly significant association between the presence of MAC and aortic atheroma, suggesting that this association may explain the high incidence of stroke in patients with MAC.

In the present study, we found a significant association between the presence of MAC and carotid artery atherosclerotic disease (stenosis of ≥40%, P=0.006), and even association between the presence of severe MAC and significant carotid artery atherosclerotic disease (stenosis of ≥60%, P<0.05). This supports our previous hypothesis that MAC is a marker for the systemic atherosclerotic processes that are responsible for stroke. We also found that MAC eliminated hypertension and diabetes mellitus, both known to be risk factors for carotid disease, from the multivariate analysis of risks for carotid atheromatous disease. A possible reason for this is that since MAC, carotid artery disease, and aortic atheroma presumably have a common etiologic basis (namely, atherosclerosis), they express the summation of atherosclerotic risk factors such as hypertension and diabetes mellitus. It is therefore not surprising that MAC is a stronger predictor of carotid artery atherosclerotic disease than these individual risk factors. It should be noted that our study design was not planned to examine the association between MAC and stroke subtypes believed to be due to atherothrombotic carotid disease; this awaits further investigation.

Conclusions and Clinical Implications
MAC can be detected by transthoracic echocardiography, a simple, noninvasive imaging method. Using MAC as a marker, we can define a subgroup of patients with a high prevalence of carotid artery disease. We suspect the association between MAC and carotid artery disease explains the high incidence of stroke in MAC patients. A prospective study is mandatory to prove this hypothesis. The presence of MAC probably indicates a systemic atherosclerotic process that involves the aorta, aortic valve, coronary system, and probably the carotid arteries. This information is important to candidates for cardiac surgery, since this procedure is associated with an increased risk of stroke in patients with carotid artery atherosclerotic disease. Carotid artery duplex ultrasound should be considered in patients with MAC before cardiac surgery is performed.

Acknowledgments
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References


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