Is Carotid Atherosclerosis More Important in Patients With Mitral Annular Calcification Than in Those Without?

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SUMMARY

It has been suggested that mitral annular calcification (MAC) may be a manifestation of generalized atherosclerosis. However, how the incidence and extent of coronary artery disease (CAD) are affected by the coexistence of carotid atherosclerosis (CAS) in patients with versus without MAC have not yet been studied.

We studied 101 patients with echocardiographic MAC and 52 controls without MAC to investigate the clinical impact of CAS on the frequency and severity (defined as the number of obstructed vessels) of CAD in patients with MAC. Carotid Doppler ultrasonographic examination was performed on all patients before coronary angiography. In patients with both MAC and CAS, the incidences of CAD and multivessel disease (≥ 2 vessel or left main coronary artery disease) were significantly higher than in the control group with CAS alone (91% versus 68%, $P = 0.008$ and 76% versus 44%, $P = 0.004$, respectively). On the other hand, among study and control patients without CAS, although the frequencies of CAD and multivessel disease were higher in patients with MAC, interestingly, the differences were not statistically significant (37% versus 58% and 15% versus 26%, respectively, $P > 0.05$ for both). Stepwise multiple logistic regression analysis revealed that CAS ($P < 0.001$), MAC ($P < 0.01$) and, to a limited extent hypertension ($P = 0.054$), were independent predictors for the presence of CAD.

In conclusion, the coexistence of CAS is more important in patients with MAC than in those without as it provides valuable information about the incidence and severity of underlying CAD. In cases with MAC but without CAS, MAC could be caused by factors other than atherosclerosis. (Jpn Heart J 2004; 45: 603-611)

Key words: Mitral annular calcification, Coronary artery disease, Carotid atherosclerosis

MITRAL annular calcification (MAC) is a fibrous, chronic degenerative calcification of the mitral valve support ring.[1)] It is more frequent in female and elderly

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patients.[2,3] Several studies have associated MAC with atrial fibrillation, endocarditis, conduction disturbances, left atrial enlargement, mitral regurgitation/stenosis, and hypertrophic cardiomyopathy.[4-8] Also, in recent studies, a close relationship has been established between MAC and carotid atherosclerosis (CAS) or coronary artery disease (CAD).[9-11] In view of these reports, it has been suggested that MAC is a manifestation of diffuse atherosclerosis of the vascular system. In patients with MAC, cardiovascular risk factors such as hypercholesterolemia, hypertension, and diabetes mellitus are also common, which lends further support to this hypothesis.[12] On the other hand, autopsy studies have shown a strong correlation between carotid and coronary atherosclerosis and parallel findings were found in several clinical studies.[13-18] However, the clinical importance of coexisting CAS in patients with MAC, in terms of its implications on the frequency and severity of CAD, has not been extensively studied. In this study, we investigated how the incidence and extent of CAD are affected by the coexistence of carotid atherosclerosis in patients with MAC as compared to those without.

METHODS

Between September 2001 and March 2003, 101 patients with echocardiographically determined MAC admitted for coronary angiography were studied. Fifty-two age- and sex-matched patients without MAC, who were also admitted for coronary angiography in the same period, were enrolled as the control group. Patients with rheumatic valve disease, a cerebrovascular accident, cardiomyopathy, valvular prosthesis, history of recent infective endocarditis, carotid surgery, or known coronary artery disease were excluded.

Echocardiography: A Hewlett Packard Sonos 2500 echocardiographic system with a 3.5 MHz transducer was used. The M-mode echocardiographic criterion used for the diagnosis of MAC was the presence of dense echoes behind the posterior mitral leaflet and anterior to the left ventricular posterior wall. The 2-dimensional echocardiographic criterion for MAC was 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.[7] All echocardiograms were interpreted without the knowledge of other clinical or laboratory information.

Carotid Doppler ultrasonography: Bilateral carotid Doppler ultrasonography was performed on all patients before coronary angiography using an ATL 3500 system (ATL, Bothell, WA) and a linear array transducer. The common, bulbar, and proximal portions of the internal carotid artery were assessed in the longitudinal and transverse planes. CAS was defined as the presence of a plaque which

was at least 50% thicker than the vessel wall or associated with mineralization in any segment of any carotid artery.[19,20]

Coronary angiography: The standard Judkins method was used for the angiographic assessment. Data were assessed by two cardiologists blinded to the echocardiographic and carotid Doppler ultrasonographic findings. For the purpose of this study, the presence of more than 50% stenosis in one or more major epicardial artery or in the left main coronary artery was accepted as CAD. Patients with CAD were also assigned to one of two groups as having univessel or multivessel disease (≥ 2 vessel or left main coronary artery). A 50% or greater stenosis of vessels other than the major epicardial arteries was regarded as obstruction of the major vessel from which they arose.

Cardiovascular risk factors: Diabetes mellitus (fasting blood glucose level > 126 mg/dL or being on antidiabetic medication), hypertension (at least 3 blood pressure measurements above 140/90 mmHg), hypercholesterolemia (values above 200 mg/dL), low HDL-cholesterol (values below 40 mg/dL), a positive family history of CAD (CAD in first-degree relatives before age 55), and smoking (at least 1 cigarette per day) were assessed as risk factors in all groups.

Statistical analysis: All data were analyzed using the SPSS 10.01 (SPSS Inc., Chicago, IL) statistical package program. Numeric values are reported as the mean ± SD or as a proportion of the sample size. Comparisons between the study and control groups were conducted with the chi-square test or, when needed, Fischer's exact test for categorical data and with Student's *t* test for continuous data. Stepwise multiple logistic regression analysis was used to identify independent predictors for coronary artery disease. The following variables were entered into the model: age, sex, MAC, CAS, diabetes mellitus, hypertension, hypercholesterolemia, low HDL-cholesterol, family history of premature coronary artery disease, and history of smoking. The level of significance was defined as $P < 0.05$.

RESULTS

CAS was more frequent in patients with MAC (69% versus 48%, $P = 0.010$). No differences were found between the control and study groups in terms of indications for coronary angiography and cardiovascular risk factors other than diabetes mellitus. Diabetes mellitus was more frequent in the study group (39% versus 21%; $P = 0.029$) (Table I). Smoking was more prominent in patients with CAS in the control group (44% versus 19%, $P = 0.047$), whereas hypertension was more frequent in patients with CAS in the MAC group (63% versus 36%, $P = 0.011$). Patients with CAS were significantly older both in the control and study groups (69 ± 6 versus 57 ± 9, $P < 0.001$ and 67 ± 6 versus 59 ± 9, $P < 0.001$ respectively) (Tables II and III).

Table I. Clinical Characteristics of the Study and Control Patients

	Control group [MAC (-)] (n = 52)	Study group [MAC (+)] (n = 101)
Age (years)	63 ± 9	64 ± 7
Female/male, *n* (%)	34/18 (65/35)	61/40 (60/40)
Hypertension, *n* (%)	21 (40)	55 (55)
Diabetes mellitus, *n* (%)	11 (21)	39 (39)*
High total cholesterol, *n* (%)	12 (23)	32 (32)
Low HDL-cholesterol, *n* (%)	7 (14)	10 (10)
Smoking, *n* (%)	16 (31)	30 (30)
Family history, *n* (%)	5 (10)	9 (9)
CAS, *n* (%)	25 (48)	70 (69)**
Reasons for coronary angiography		
a) Chest pain, *n* (%)	21 (40)	45 (45)
b) Positive treadmill testing, *n* (%)	22 (42)	38 (38)
c) Positive Tc-99m scintigraphy, *n* (%)	9 (17)	18 (18)

*P = 0.029; **P = 0.010; MAC = mitral annular calcification; CAS = carotid atherosclerosis.

Table II. Clinical Characteristics of the Control Group

	CAS (-) (n = 27)	CAS (+) (n = 25)
Age (years)	57 ± 9**	69 ± 6
Female/male, *n* (%)	20/7 (74/26)	14/11 (56/44)
Hypertension, *n* (%)	8 (30)	13 (52)
Diabetes mellitus, *n* (%)	3 (11)	8 (32)
High cholesterol, *n* (%)	7 (26)	5 (20)
Low HDL-cholesterol, *n* (%)	2 (7)	5 (20)
Smoking, *n* (%)	5 (19)*	11 (44)
Family history, *n* (%)	2 (7)	3 (12)

*P = 0.047; **P < 0.001. CAS = carotid atherosclerosis.

Table III. Clinical Characteristics of the Study Group

	CAS (-) (n = 31)	CAS (+) (n = 70)
Age (years)	59 ± 9 **	67 ± 6
Female/male, *n* (%)	22/9 (71/29)	39/31 (56/44)
Hypertension, *n* (%)	11 (36) *	44 (63)
Diabetes Mellitus, *n* (%)	10 (32)	29 (41)
High cholesterol, *n* (%)	9 (29)	23 (33)
Low HDL-cholesterol, *n* (%)	4 (13)	6 (9)
Smoking, *n* (%)	6 (19)	24 (34)
Family history, *n* (%)	2 (7)	7 (10)

*P = 0.011; **P < 0.001. CAS = carotid atherosclerosis.

CAD and multivessel disease were more frequent in patients with MAC as compared to the control group (81% versus 52%, $P < 0.001$ and 60% versus 29%, $P < 0.001$, respectively) (Table IV). In both the study and the control groups, the frequencies of coronary artery and multivessel disease were higher in patients with CAS than in those without CAS (68% versus 37%, $P = 0.026$ and 44% versus 15%, $P < 0.020$ in the control group, respectively; 91% versus 58%, $P < 0.001$ and 76% versus 26%, $P < 0.001$ in the MAC group, respectively) (Tables V and VI).

Among patients with CAS, the frequencies of CAD and multivessel disease were higher in the study group compared to the control group (91% versus 68%, $P = 0.008$ and 76% versus 44%, $P = 0.004$, respectively). On the other hand, among study and control group subjects without CAS, although the frequency

Table IV. Frequency of Coronary Artery Disease and its Severity in Groups

	Control group [MAC (-)] ($n = 52$)	Study group [MAC (+)] ($n = 101$)	*P*
CAD *n* (%)	27 (52)	82 (81)	< 0.001
Single vessel disease, *n* (%)	12 (23)	21 (21)	NS
Multivessel disease, *n* (%)	15 (29)	61 (60)	< 0.001

CAD = coronary artery disease; NS = not significant; MAC = mitral annular calcification.

Table V. Frequency of Coronary Artery Disease and its Severity in Patients With and Without CAS in the Control Group

	CAS (-) ($n = 27$)	CAS (+) ($n = 25$)	*P*
CAD *n* (%)	10 (37)	17 (68)	0.026
Single vessel disease, *n* (%)	6 (22)	6 (24)	NS
Multivessel disease, *n* (%)	4 (15)	11 (44)	< 0.020

Table VI. Frequency of Coronary Artery Disease and its Severity in Patients With and Without CAS in the Study Group

	CAS (-) ($n = 31$)	CAS (+) ($n = 70$)	*P*
Coronary artery disease, *n* (%)	18 (58)	64 (91)	< 0.001
Single vessel disease, *n* (%)	10 (32)	11 (16)	NS
Multivessel disease, *n* (%)	8 (26)	53 (76)	< 0.001

Table VII. Coronary Artery Disease and its Severity in Relation to CAS in the Study and Control Groups

		Control group [MAC (-)]	Study group [MAC (+)]	
		(n = 27)	(n = 31)	P
Patients without CAS (n = 58)	CAD n (%)	10 (37)	18 (58)	NS
	Single vessel, n (%)	6 (22)	10 (32)	NS
	Multivessel, n (%)	4 (15)	8 (26)	NS
		(n = 25)	(n = 70)	P
Patients with CAS (n = 95)	CAD n (%)	17 (68)	64 (91)	0.008
	Single vessel, n (%)	6 (24)	11 (16)	NS
	Multivessel, n (%)	11 (44)	53 (76)	0.004

and extent of CAD were higher in patients with MAC, interestingly, the differences were not statistically significant (37% versus 58%, $P > 0.05$ and 15% versus 26%, respectively, for both $P > 0.05$) (Table VII).

Stepwise multiple logistic regression analysis revealed that CAS (RR = 4.65, $P < 0.001$), MAC (RR = 3.21, $P < 0.01$), and to a limited extent hypertension (RR = 2.26, $P = 0.054$), were independent predictors for the presence of CAD.

DISCUSSION

We found that CAD and multivessel disease were more frequent in patients with MAC than in those without. Similarly, Adler, *et al* reported that CAD and multivessel disease were more frequent in these patients.[10] In our study, however, we have shown for the first time that the presence or absence of CAS in these patients causes significant differences in the severity and frequency of the CAD. CAD and multivessel disease were significantly more frequent in MAC patients with CAS than in subjects without MAC but with CAS. On the other hand, in the absence of CAS, the presence of MAC alone did not result in a significant increase in the frequency and extent of CAD.

CAS has been evaluated with a variety of methods. Intima-media thickness has been reported to be closely related to asymptomatic myocardial ischemia.[15] Rosfors, *et al* have shown that increased carotid intima-media thickness was associated with advanced atherosclerosis at the carotid bifurcation.[21] In some studies, the severity of the stenosis of the carotid atheroma plaques and the number of these plaques were taken into consideration.[18,22] In our study, we defined

CAS as the presence of carotid atheroma plaques, instead of measurement of carotid intima-media thickness, as reported previously by Khoury, *et al*.[16)]

Various studies have shown that MAC and cardiovascular calcification, as assessed by multiple modalities including electron beam computerized tomography, echocardiography, and conventional chest x-ray film, are associated with cardiovascular disease risk factors.[2,23,24)] Also, an association between MAC and aortic plaque and/or coronary calcification has been shown previously.[25-27)] Recent data also suggest that cardiovascular calcification is a strong predictor for the presence of CAD and it was suggested that MAC is a manifestation of diffuse atherosclerosis of the vascular system.[10,17,20,24)] The pathophysiology of cardiovascular calcification is not clear, but may be caused by metabolic derangements.

MAC is more frequent in osteoporotic postmenopausal women where it is attributed to ectopic calcium deposits related to the severe bone loss caused by postmenopausal osteoporosis.[28)] In support of this view is the finding that the amount of bone mineral is lower in elderly women with MAC.[29)] Therefore, although development of MAC in men could be related mainly to atherosclerosis and its risk factors, an additional mechanism related to osteoporosis may be operative in postmenopausal women. It is well established that atherosclerosis is more prevalent in males; however, MAC is more prevalent among postmenopausal women.[2)] This gender paradox, again, implies different pathogenetic mechanisms for MAC.

MAC was found in more than 26% of patients with chronic renal failure in whom calcium metabolism is seriously disturbed.[30-32)] In light of these reports, derangements in calcium and/or phosphate metabolism may also lead to development of MAC without an underlying atherosclerotic disease. Nair, *et al* showed that the mean serum phosphorus and the product of serum calcium and phosphorus were higher in patients with MAC.[33)] Furthermore, the mitral annular area can be considered as part of the vascular bed, whose calcification is known to be regulated by some of the same processes that regulate bone calcification.[34)] Thus, considering MAC to almost always be a manifestation of severe atherosclerosis may not be appropriate. From this point of view, it may be more accurate to keep in mind that the development of MAC in patients without CAS may not be a manifestation of generalized atherosclerosis. In the study by Nair, *et al*, the prevalence of coronary heart disease was similar in patients with MAC and age- and sex-matched control subjects, all of whom were younger than 60 years.[33)] Also in our study, among patients without CAS, although the frequency and extent of CAD in patients with MAC were higher than in those without, the differences were not statistically significant. The existence of CAS in patients with MAC may increase the likelihood that MAC is a manifestation of diffuse atherosclero-

sis of the vascular system and hence may increase the clinical value of MAC for the presence of coronary artery and multivessel disease.

In conclusion, the findings of the present study imply that both CAS and MAC are associated with the presence of CAD and multivessel disease and that they are more predictive if both are present simultaneously compared to the presence of either MAC or CAS alone. Noninvasive investigation of CAS in patients with MAC provides valuable clinical information on possible underlying CAD and multivessel disease and thus could be beneficial for avoiding unnecessary invasive interventions in these patients.

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