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Relationship Between Mitral Annular Calcification and Severity of Carotid Atherosclerosis in Patients With Symptomatic Ischemic Cerebrovascular Disease

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Abstract

Objectives. Many studies have reported the association between mitral annular calcification (MAC) and stroke. MAC has been speculated to be a direct embolic source of stroke. Recently, the association between MAC and atherosclerosis in the coronary artery, aorta, and carotid artery has been reported. This prospective study investigated the association between MAC and severity of carotid atherosclerosis in patients with symptomatic ischemic cerebral disease to evaluate the association between MAC and atherosclerosis as a cause of stroke.

Methods. We studied 377 patients with ischemic cerebral disease (253 men, 124 women, mean age 68 ± 11 years) who underwent echocardiography to determine the presence of MAC and carotid ultrasonography to determine the severity of carotid atherosclerosis. Plaque score was the sum of the maximum intima-media thickness in the common carotid region, the bifurcation bulb region, and the internal carotid artery region, including both right and left arteries.

Results. MAC was found in 86 patients, and was more frequent in women, the elderly, and patients with diabetes or hyperlipidemia ($p < 0.05$). Plaque score was higher in patients with than without MAC (8.3 ± 5.8 vs 5.2 ± 5.2 mm, $p < 0.001$). Multivariate regression analysis identified MAC ($r = 0.26$, $p < 0.0001$), female sex ($r = -0.12$, $p = 0.03$), and age ($r = 0.23$, $p < 0.0001$) as independently associated with plaque score.

Conclusions. MAC is independently associated with severity of carotid atherosclerosis in patients with symptomatic ischemic cerebral disease. This association suggests MAC may be indirectly related to cerebrovascular disease as a marker of the presence of progressive arteriosclerosis for thromboemboli causing stroke.

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Key Words
■Calcium (mitral annular calcification) ■Stroke ■Carotid arteries
■Atherosclerosis ■Ultrasonic diagnosis

INTRODUCTION

Mitral annular calcification (MAC) has become more common with the aging of the population. MAC is a noninflammatory chronic degenerative process involving the fibrous base of the mitral valve[1,2]. Many studies have reported an association between MAC and stroke[3−13]. Recent investigations have linked MAC with atherosclerotic disorders such as coronary artery disease[6,12,14,15], aortic atheroma[16], carotid artery stenosis[5,17−19], and peripheral vascular disease[20]. Previous studies have suggested that MAC might be a marker for carotid atherosclerosis, thus indicating the risk of ischemic cerebral disease[5,17−19,21]. In the Japanese general population, the prevalence of advanced carotid atherosclerosis is essentially similar to that reported in developed Western countries[22]. However, whether carotid atherosclerosis is more advanced when patients with symptomatic ischemic cerebral disease also have MAC has not been determined. The present study examined the association between presence of MAC and patient characteristics, cardiac variables, and severity of carotid atherosclerosis in patients with symptomatic ischemic cerebral disease.

SUBJECTS AND METHODS

Study population

We prospectively examined 377 Japanese patients with ischemic cerebral disease (253 men, 124 women, mean age 68 ± 11 years) who were admitted to the Ibaraki Seinan Medical Center Hospital. Patients with hemorrhagic stroke were excluded. All patients underwent clinical examination and neuroimaging including computed tomography, angiography, and/or magnetic resonance imaging while under the care of the neurosurgeons among the authors (T.K and K.F). All patients underwent echocardiography to evaluate cardiac disease as a possible cause of stroke, and carotid ultrasonography to assess neurologically relevant atherosclerosis. All patients gave informed consent before participation.

Echocardiography

Doppler echocardiographic examinations were performed using a Sonos 2500 system (Agillent Technology) equipped with a 2.5-MHz transducer, or a Vivid 7 system (GE Yokogawa Medical Systems) with a multifrequency transducer. Criteria for MAC included detection of an intense echodense structure in the parasternal and apical long-axis views, located at the junction of the atrioventricular groove and posterior mitral valve leaflet; or in the parasternal short-axis view, located behind the posterior mitral valve leaflet. Left atrial size, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, fractional shortening, and mean left ventricular wall thickness (the mean of septal and posterior wall measurements) were obtained from the parasternal M-mode tracings. Left ventricular hypertrophy was defined as a mean left ventricular wall thickness of at least 12.0 mm.

Carotid artery duplex ultrasonography

Carotid artery duplex ultrasonography was performed using a Sonos 2500 system (Agillent Technology) equipped with a 7.5-MHz linear array transducer, or a Vivid 7 system (GE Yokogawa Medical Systems) with a multifrequency linear array transducer. Carotid atherosclerosis was evaluated as a plaque score[23], with the plaque defined as an area where intima-media thickness exceeded 1.1 mm. The plaque score was the sum of the maximum intima-media thickness in the common carotid region, the bifurcation bulb region, and the internal carotid artery region, including both right and left arteries[22].

Clinical risk factors

Multiple clinical and laboratory risk factors were determined, including presence of hypertension (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or treatment with taking antihypertensive agents); presence of hyperlipidemia (serum cholesterol > 220 mg/d*l* or treatment with antihyperlipidemic agents); presence of diabetes mellitus (fasting glucose > 125 mg/d*l*, hemoglobin A_{1c} > 6.4%, or treatment with antidiabetic); history of smoking; and presence of

Table 1 Demographic, clinical and echocardiographic characteristics of patients with and without mitral annular calcification

	With MAC (n=86)	Without MAC (n=291)	p value
Female (%)	44	29	0.009
Age (yr)	70±10	67±11	0.01
Hypertension (%)	73	65	0.18
Hyperlipidemia (%)	35	23	0.04
Diabetes mellitus (%)	37	23	0.008
Smoking (%)	44	46	0.18
Atrial fibrillation (%)	20	11	0.06
Prior ischemic heart disease (%)	19	15	0.3
Prior heart failure (%)	8	9	0.8
Warfarization (%)	5	3	0.4
Antithrombotic therapies (%)	15	14	0.8
Left ventricular wall thickness (mm)	9.2±1.3	9.0±1.5	0.4
Left ventricular end-diastolic diameter (mm)	47.4±5.6	48.1±5.1	0.3
Left ventricular end-systolic diameter (mm)	30.8±5.5	30.5±5.5	0.7
Fractional shortening (%)	35±7	36±6	0.3
Left atrial dimension (mm)	38.3±7.0	36.2±6.0	0.11

Continuous values are mean±SD.
MAC=mitral annular calcification.

ischemic heart disease.

Statistical analysis

Results are expressed as mean± SD. Comparisons between groups with and without MAC were performed using Student's t-test for continuous variables and the chi-square test for categorical variables. A p value <0.05 was considered to show statistical significance. Multiple linear regression analysis was performed to determine the effects of age, male sex, hypertension, hyperlipidemia, diabetes mellitus, history of smoking, ischemic heart disease, and MAC on plaque score. All calculations were performed using the Stat View J-5.0 statistical program (Abacus Concepts).

RESULTS

Echocardiography showed 86 patients had MAC and 291 patients did not. Comparisons of patient characteristics and echocardiographic data between groups with and without MAC are summarized in **Table 1**. Women made up the larger part of the group with MAC (38/86, 44%) than the group without MAC (85/291, 29%; $p=0.009$). Patients with MAC were older than those without MAC (70 ± 10 vs 67 ± 11 years, $p=0.01$). Among known risk factors for atherosclerosis, diabetes mellitus and hyperlipidemia were significantly more prevalent among patients with MAC than those without MAC (diabetes mellitus, 37% vs 23%, $p=0.008$; hyperlipidemia, 35% vs 23%, $p=0.04$). Among cardiac abnormalities, atrial fibrillation was more prevalent in patients with than without MAC, but the difference was not significant (with MAC 20% vs without MAC 11%, $p=0.06$). Prevalences of other cardiac abnormalities, ischemic heart disease, congestive heart failure, and abnormal echocardiographic variables were essentially similar between the groups. Six patients with hemodialysis were enrolled, and MAC was found in two patients. The plaque score in patients with MAC was significantly higher than in those without MAC (8.3 ± 5.8 vs 5.2 ± 5.2 mm, $p<0.001$). Distributions of plaque scores within various ranges are compared between patients with and without MAC in **Fig.1**. In 44% of patients with MAC, plaque score ranged from 5.1 to 10.0 mm, whereas the score was more than 10.0 mm in 31%. Among patients without MAC, plaque scores in 55% were 5.0 mm or less. Even in a subgroup analysis of 50 patients with atrial fibrillation, plaque score in patients with MAC was higher than in those without MAC (8.7 ± 4.0 vs

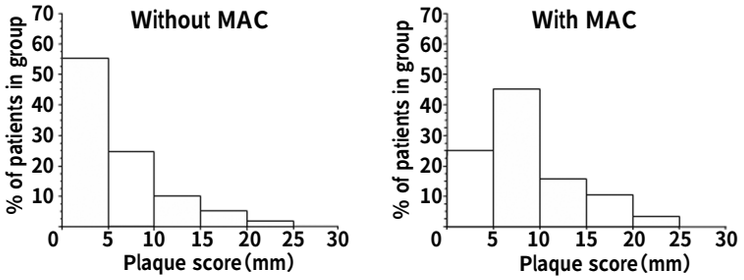

Fig. 1 Comparison of distribution of plaque score between patients with and without mitral annular calcification
Abbreviation as in Table 1.

6.2 ± 4.7 mm, $p = 0.02$).

Table 2 shows the results of multivariate linear regression analyses to identify the independent predictors of plaque score, which were age, sex (female), and MAC.

Table 2 Multivariate correlates of plaque score

	Standardized regression coefficient	p value
Female sex	−0.12	0.03
Age	0.23	<0.0001
Hypertension	−0.01	0.8
Hyperlipidemia	−0.02	0.73
Diabetes mellitus	0.08	0.17
Smoking	0.07	0.21
Prior ischemic heart disease	0.1	0.09
Mitral annular calcification	0.26	<0.0001

DISCUSSION

In this study, MAC was more common in the elderly and in women, although our subjects were limited to patients with ischemic cerebral disease. The prevalence in this study might be similar to those previously reported in the general population[7,24,25]. We found more advanced carotid atherosclerosis in patients with MAC than in those without MAC, and MAC was an independent predictor of carotid atherosclerosis.

Mitral annular calcification and cerebrovascular disease

Numerous studies have suggested an association between stroke and MAC, beginning with the first report of stroke in a patient with MAC in 1946[3]. MAC was found in 8 of 151 patients with cerebral or retinal ischemia, compared with no patients in the control group[4]. The prevalence of MAC in patients with ischemic cerebrovascular disease was 2.5 times that in a control group[5]. In a prospective cohort study, cerebrovascular events occured five times more frequently in patients with MAC than in age- and sex-matched controls over 4.4 years of follow-up[6]. In the Framingham cohort study, the presence of MAC doubled the risk of stroke after adjustment for multiple risk factors, and was an independent predictor of stroke[7]. Strokes in patients with MAC may have an embolic pathogenesis. Funduscopic examination found calcific "white" emboli in the retinal arteries of four patients with MAC as well as evidence of retinal ischemia[4]. Cranial computed tomography showed multiple cerebral calcific densities in a woman, suggesting that the densities were calcific emboli derived from the MAC[8]. Systemic calcific embolization, including emboli to the brain, was verified at autopsy[9]. Two patients had thrombi overlying MAC, suggesting that MAC may serve as a nidus for thrombus formation[10]. Two-thirds of strokes in a group of patients with MAC were embolic, but the embolic source was not determined[7]. Whether MAC was the direct source of emboli or merely a marker for conditions associated with thromboembolism (age, hypertension, hyperlipidemia, diabetes mellitus, peripheral atherosclerosis, atrial fibrillation, and congestive heart failure) remains unsettled.

In the present study, age was greatest, and female sex, diabetes mellitus and hyperlipidemia were more prevalent in patients with than without MAC. Previous studies have shown an association between MAC and various cardiovascular risk factors[6,7,12,13,24,25]. Age, female sex, hypertension, diabetes mellitus, and hypercholesterolemia were independently associated with MAC[25]. Although the prevalence of hypertension did not differ between patients with and without MAC in our study, the population was limited to patients with ischemic cerebral disease, so hypertension may

have been more prevalent overall than in the general population. MAC has been associated with several cardiac conditions including atrial fibrillation, left atrial enlargement, conduction defect, left ventricular enlargement, hypertrophic cardiomyopathy, congestive heart failure, mitral valvular insufficiency, bacterial endocarditis, and aortic calcification[2,6,7,11–13,24–30]. In our study, atrial fibrillation was more prevalent in patients with MAC, but this difference from stroke patients without MAC fell slightly short of significance. Atrial fibrillation is associated with MAC, and the association between atrial fibrillation and cardioembolic stroke is well established[2,7,12,13,24,26]. However, since our patients with both atrial fibrillation and MAC had higher plaque scores than those with atrial fibrillation but not MAC, atherothrombotic factors including carotid atherosclerosis may have contributed to ischemic cerebral disease in patients with both atrial fibrillation and MAC in addition to any contribution from cardioembolism.

Carotid artery atherosclerosis is a direct etiologic factor for stroke[31–35], as atherothrombotic disease is associated with ischemic cerebral disease[36,37]. However, whether carotid plaques merely reflect generalized atherosclerosis or are causally related to subsequent stroke by release of thromboemboli is still controversial. In neurologically asymptomatic subjects, carotid plaques can be considered to be both sources of thromboemboli and markers of generalized atherosclerosis[32], based on the associations of carotid atherosclerosis with coronary artery disease[38–40]and aortic atheroma[41]. Additionally, aortic plaques can give rise to emboli causing stroke[42–44]. Associations between MAC and carotid stenosis have been reported[5,17–19]. In our patients with ischemic cerebral disease, an association between MAC and more advanced carotid atherosclerosis was demonstrated. Multivariate linear regression analysis showed MAC independently predicted a higher plaque score. In this analysis, consideration of MAC eliminated other cardiovascular risk factors including hypertension, hyperlipidemia, smoking, and diabetes mellitus as independent plaque score predictors. This result suggests that MAC is a marker for multiple cardiovascular risk factors strongly related to carotid atherosclerosis[23,45]. Thus, carotid atherosclerosis and MAC share common risk factors[14,25]. Accordingly, we suggest that ischemic cerebral disease in patients with MAC may involve more advanced carotid atherosclerosis, tending to support the previous conclusion that MAC is not an independent risk factor for stroke after adjustment for the presence of carotid stenosis[21].

Sex influence on prevalence of mitral annular calcification

We found a higher proportion of women among ischemic cerebral disease patients who had MAC than those without MAC. A close relationship between MAC and female sex is well established[7,24,25]. On the other hand, male sex was independently associated with carotid atherosclerosis as measured by the plaque score.

Age could play a sex-specific role in the association between MAC and carotid stenosis, as MAC is a stronger marker of carotid artery disease in men younger than 75 years and also in women older than 75 years[19]. MAC in elderly women could be attributed to ectopic calcium deposits related to severe bone loss caused by postmenopausal osteoporosis[46,47]. Therefore, MAC might include a major atherosclerotic component in its etiology in men, with osteoporosis being etiologically important for MAC in women.

Limitations

Since this study was limited to patients with ischemic cerebral disease, no conclusion can be drawn about the determinants of MAC in the general population. We also did not investigate subtypes of ischemic cerebral disease, which may be important in considering the contribution of MAC to cerebral ischemia. Other cardiovascular risk factors for ischemic cerebral disease, such as aortic atheroma and atrial thrombi, were not evaluated because we did not perform transesophageal echocardiography in all patients. This should be pursued in future investigations.

CONCLUSIONS

Since the presence of MAC is associated with increased severity of carotid atherosclerosis, MAC might be a marker of more advanced atherosclerosis as a source of thromboemboli in patients with symptomatic ischemic cerebral disease.

要　　約

症候性脳血管障害例における僧帽弁輪石灰化の存在と頸動脈硬化重症度との関係

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目　的: 僧帽弁輪石灰化と脳卒中との関連について多くの検討がなされており，僧帽弁輪石灰化は心原性の塞栓源との報告がある．一方，近年，僧帽弁輪石灰化と冠動脈，大動脈，そして頸動脈における動脈硬化症との関連についても検討が行われている．そこで我々は，僧帽弁輪石灰化と脳卒中の原因となる動脈硬化症との関連を明らかにするため，僧帽弁輪石灰化と頸動脈硬化の重症度の関係について症候性脳血管障害例において前向きに検討を行った．

方　法: 我々は，症候性脳血管疾患377例(男性253例，女性124例，平均年齢68±11歳)において，経胸壁心エコー図法により僧帽弁輪石灰化の有無を評価し，頸動脈エコー法により頸動脈硬化の重症度を評価した．頸動脈硬化の重症度はプラークスコアにより行った．プラークスコアは両側の総頸動脈体部，球部および内頸動脈における最大内膜中膜複合体厚の総計として算出した．

結　果: 僧帽弁輪石灰化は86例に認められ，女性，高齢者，糖尿病，もしくは高脂血症罹患者においてより多く認められた($p<0.05$)．プラークスコアは僧帽弁輪石灰化を認める症例においてより高値(8.3±5.8 vs 5.2±5.2 mm，$p<0.001$)を示した．多変量回帰分析において，女性($r=-0.12$，$p=0.03$)，年齢 ($r=0.23$，$p<0.0001$)とともに，僧帽弁輪石灰化($r=0.26$，$p<0.0001$)はプラークスコアの独立規定因子であった．

結　論: 症候性脳梗塞症例において僧帽弁輪石灰化の存在は頸動脈硬化の重症度と関連していた．これは，僧帽弁輪石灰化が血栓塞栓症の危険因子である進行した動脈硬化の存在を示唆するマーカーとして，間接的に脳血管障害と関連していることを示唆している．

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