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Mitral annulus calcification is not an independent risk factor for stroke: a cohort study of 657 patients

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Abstract All studies but one in the past have shown a strong relative risk of mitral annulus calcification for stroke, but the contribution of associated cardiac and vascular risk factors, especially carotid atheroma has not been appreciated. We studied the risk of stroke in selected patients with mitral annular calcification, adjusting for clinical, echocardiographic and therapeutic factors influencing stroke risk. Of 8,160 consecutive patients with echocardiograms, 657 with and 562 without mitral annulus calcification were followed for a mean of 2.4 years (range 1–6.6) to determine stroke risk by means of proportional hazards models with clinical, echocardiographic, and therapeutic variables that influence the risk of stroke. We also determined the association of mitral annulus calcification with subtypes of ischaemic brain lesions generally considered to be specific for an underlying cardioembolic cause. We therefore distinguished between territorial, small deep, and asymptomatic (silent) brain infarcts. Fifty-one patients with mitral annulus calcification and 27 controls had a stroke in the follow-up period. Mitral annulus calcification was not significantly associated with stroke in proportional hazards models (hazard ratio 0.76, 95% confidence interval 0.42–1.36, $P = 0.3$), or with any of the stroke subtypes, or with the presence of silent brain infarcts after adjustments for risk factors for generalized vascular disease Hypertension and carotid atheroma, with or without stenosis, ipsilateral or contralateral to the side of the stroke, were significantly associated with stroke in our patients. This study does not support the view that mitral annulus calcification is a risk factor for stroke. As others have found strong associations between mitral annulus calcification and cardiac and vascular risk factors for stroke, the increased risk of stroke in patients with mitral annulus calcification reported may be explained by these confounding risk factors. Therefore, in our opinion, mitral annulus calcification requires treatment of cardiovascular risk factors, but generally no specific measures such as surgery or oral anticoagulants are required to lower the risk of stroke.

Key words Mitral annulus calcification · Stroke · Risk factors · Stroke subtypes

Introduction

Mitral annulus calcification (MAC) is an age-related degenerative process within the cardiovascular fibrous skeleton, which accelerates in conditions that increase mitral valve stress or activity, such as hypertension, left atrial and ventricular enlargement, atrial fibrillation, hypertrophic cardiomyopathy, aortic valve stenosis, mitral valve prolapse, and mitral valve prosthesis [1–3].

Deposition of calcified material in the valve apparatus in metabolic disorders may also cause MAC [1, 3–10]. The pathological process is hyaline degeneration with fatty depositions, necrosis and calcification of the mitral annulus fibrous tissue, sometimes with bone formation or inflammation [11, 12]. MAC may encompass part or all of the mitral annulus. By direct influence on its surroundings it may cause conduction disorders or mitral stenosis [13, 14]. Prevalence varies considerably between different studies, from 2.8% to 27% [15].

MAC may act as a direct source of emboli or merely as a marker of conditions associated with thrombo-embolism, such as hypertension, general atherosclerosis, advanced age, congestive heart failure, atrial fibrillation and diabetes [1–3, 16–21]. Case reports and epidemiological studies suggest a strong relation between MAC and stroke [3, 22–28]. There is also clinical and pathological evidence of embolism by calcified material in the brain [16], retina, and other organs [3] in patients with MAC. In two studies the prevalence of MAC in patients with systemic or cerebral signs of vascular occlusion was higher than in age- and sex-matched controls [22, 24] but on the basis of the data presented the possibility cannot be excluded that this difference is related to differences in the degree of concomitant cardiovascular disease. In three series systemic or cerebral ischaemic signs occurred more often in patients with MAC than in age- and sex-matched controls [3, 23, 27]. Evidence of a more than doubled risk of stroke in MAC patients comes from a study on the effect of warfarin on stroke risk in atrial fibrillation (the BAATAF study), and from a study that analysed stroke risk in MAC patients [25, 28]. However, in BAATAF relative risk refers to the warfarin effect in atrial fibrillation, and not necessarily to MAC-related stroke. Subgroup analysis, especially in patients selected by the aim of the trial, might also raise the observed stroke risk [29]. Moreover, in both these and other studies the results may be influenced by confounders such as carotid atheroma [26] by the use of antiplatelet drugs or warfarin, or by cardiac factors affecting the risk of stroke.

Vascular disease is common in patients with MAC. Therefore, confounding cannot be prevented by design in a study of MAC-associated stroke. We did a prospective analysis of the risk of stroke in patients with MAC, adjusted for clinical, echocardiographic and therapeutic factors influencing stroke risk. We also analysed the association of MAC with specific stroke subtypes that might suggest an underlying cardio-embolic source.

Patients and methods

Patients

Of 8,160 consecutive patients who had 11,924 echocardiograms between 1 January 1985 and 1 January 1990 at the Department of Cardiology of the University Hospital of Maastricht [30] 663 patients had MAC. These patients entered the study. Six hundred records were selected randomly by the database technician from the remaining 7,600 patients without MAC. Of those, 568 remained after excluding accidental record copies and were entered into the study. Six patients with and six without MAC were lost to follow-up. The cohort therefore consisted of 657 patients with and 562 patients without MAC. For each patient the date of the first echocardiogram after 1 January 1985 indicated the start of the follow-up.

Clinical risk factors at entry

The following risk factors were recorded: age, sex, hypertension (known hypertension treated with anti-hypertensive medication, two or more blood pressure recordings higher than 160/90 mm Hg not measured within 1 week after a stroke), diabetes mellitus (known diabetes treated with diet and/or medication, or either a fasting serum glucose level higher than 7 mmol/l or a postprandial serum glucose level higher than 11 mmol/l measured on at least two separate occasions), ischaemic heart disease (myocardial infarction, angina pectoris), coronary artery bypass grafting, the use of oral anticoagulants or salicylates, prior stroke or TIA, serum cholesterol (the mean of all available values with or without lipid-lowering therapy), hypercholesterolaemia (known treated hypercholesterolaemia), peripheral atherosclerotic disease (symptomatic arteriosclerosis of the extremities), atrial fibrillation, and cardiac valve prosthesis.

Echocardiographic data at entry

The following echocardiographic features were recorded: MAC (defined as bright echoes from the mitral annulus on a two-dimensional echocardiogram with „stone-shadow“; mitral stenosis (defined as rheumatic valvular disease with increased velocities over the valve and a mitral valve area of less than 2.5 cm^2, or non-rheumatic valvular disease if MAC and fibrosis of the mitral valve apparatus was causing a more than physiological gradient, and the mitral valve orifice was smaller than or equal to 2.5 cm^2); mitral insufficiency; calcified aortic valve sclerosis (bright echoes on one or more cusps of 1 mm or more and a maximal pressure gradient below 16 mm Hg); aortic stenosis (a pressure gradient exceeding 16 mm Hg); mitral, tricuspidal or aortic valve prosthesis or bioprothesis; enlarged left atrium (45 mm or more); atrial septum aneurysm; atrial septum defect; reduced left-ventricular ejection fraction (to less than 40%); reduced fractional shortening (to less than 28%); increased left-ventricular mass [31]; posterior-, inferior-, and anterior-wall infarction; wall-motion score; apical aneurysm; cardiac thrombus; and dilated cardiomyopathy. Wall-motion score was a semi-quantitative measure of left-ventricular wall motion. For this purpose, the left ventricle was divided into 13 segments. Wall motion in each segment was scored from 0 to 4 (normokinesia, hypokinesia, hypokinesia to akinesia, akinesia, and dyskinesia). A cutoff point between small and larger asynergy of the left ventricle was chosen at a wall-motion score of 12. Fractional shortening was defined as the difference between left-ventricular enddiastolic and endsystolic diameter. Left ventricular wall-mass cut off points were 175, 200 and 225 g for men, and 165, 190 and 215 g for women [31]. All diameters used were measured according to the recommendations of the American Society of Echocardiography [32–34].

Outcome definitions

Stroke was defined as a supra- or infratentorial brain infarct or intracerebral haematoma. A brain infarct was defined as rapidly developing clinical signs of focal disturbance of cerebral function

lasting longer than 24 h or leading to death, with no other apparent cause than that of vascular origin, while CT showed an area of low attenuation compatible with the clinical signs and symptoms or showed no specific lesion. For symptomatic strokes, when no CT was available, we used the Guy's Hospital Stroke Diagnostic Score (Allen Score) [35] to differentiate between brain infarct and haemorrhage. Symptomatic brain infarcts were divided into small deep (lacunar) and territorial infarcts. A small deep infarct was defined as a lesion visible on CT and compatible with the occlusion of a single perforating artery, i.e. a subcortical, small, sharply marginated hypodense lesion with a diameter of less than 20 mm, or clinically a lacunar syndrome if no specific lesion was visible on CT. We distinguished four lacunar syndromes: pure motor stroke, pure sensory stroke, sensorimotor stroke, and ataxic hemiparesis including dysarthria–clumsy hand cases. A territorial infarct was defined as CT findings compatible with infarction involving the cortex, or clinically a cortical syndrome, i.e. a unilateral motor or sensory deficit, or both, in combination with signs of cortical dysfunction (e.g. aphasia, visual field deficit, visual spatial disturbances, apraxia, neglect or agnosia) if no specific lesion was visible on CT. Patients with a large subcortical infarct were included in this group because of similar pathogenesis. Territorial infarcts were divided into two groups by presumed cause: cardio-embolic and other causes. A cardio-embolic infarct was defined as a territorial infarct in the presence of one or more of the following cardiac sources of embolism: chronic or paroxysmal atrial fibrillation, myocardial infarction less than 6 weeks prior to stroke, prosthetic aortic or mitral valve, endocarditis, dilated cardiomyopathy, mitral stenosis, left-ventricular aneurysm, and intraventricular thrombus. MAC was not defined as a potential cardio-embolic stroke cause. Some patients with a stroke had unrelated low-density areas on CT compatible with previous unperceived brain infarction. Such lesions were defined as silent brain infarcts. We distinguished two types of silent brain infarcts: silent small deep and silent territorial infarcts.

Risk factors at the time of a stroke in the follow-up

Besides age and sex the following risk factors at the time of a stroke were recorded again: hypertension (present before or after stroke but not diagnosed within 1 week after stroke), diabetes mellitus (not measured in the acute phase of stroke, i.e. within 72 h), ischaemic heart disease, and more than 50% carotid stenosis (on either side) on noninvasive carotid studies or angiograms.

Selection

First strokes in the follow-up period were the primary endpoints. The indications for echocardiography in the study and control groups were the usual ones in a university clinic. There were no exclusion criteria, meaning that patients with previous stroke and any TIA were included. A simple questionnaire to general practitioners for all patients enrolled in the study was assembled to verify hospital admissions for stroke, and stroke patients not admitted.

End of follow-up

Follow-up ended with one of the following events, whichever came first: stroke, death, mitral valve replacement with postoperative echocardiogram showing no residual calcification, loss to follow up, or study end.

Acquisition of follow-up data

The clinical and echocardiographic data were recorded at the time of the first echocardiogram for all patients – consecutive patients in a prospective registry – including those lost to follow-up. Patients with stroke were registered in a second and ongoing prospective registry, the Maastricht Stroke Registry. For some patients admitted to other hospitals because they had a stroke, risk factors and CT scans were verified. For all study and control patients after the end of follow-up, we separately performed a double check for possibly missing follow-up data by reviewing all in- and outpatient files and by sending a questionnaire to all general practitioners. Incomplete follow-up of, or uncertainty about, any single or multiple data used as variables in the analysis below was defined as loss to follow-up.

Statistics

Heart surgery, death, more recent patient accrual, withdrawal, and end of follow-up resulted in varying lengths of time of exposure to MAC and other risk factors. We assumed that these exposure times were important for the risk for stroke, but not of stroke subtypes. Therefore, we did a crude analysis of the risk of stroke with incidence density ratios (IDR), and subsequent multivariate analysis with the Cox Proportional Hazard Model (hazard ratios, HR). For comparisons of stroke subtypes, however we did univariate analysis [chi-square test, crude-odds ratios (OR) with 95% confidence intervals (CI)], and subsequent multiple stepwise logistic regression analysis with adjusted odds ratios, to determine the association of MAC with symptomatic or silent small deep or territorial infarcts as dependent variables. Models with different patient subgroups were tested to check the stability of the associations.

Results

Baseline data at entry (Table 1)

Thirty-three patients with MAC and 19 controls had open heart surgery during follow-up. Six patients had MAC after open heart surgery (they had no mitral valve replacement), of whom one had a stroke 1 day after the operation. Mean follow-up was 2.4 years (range 1–6.6). During follow-up 170 MAC patients and 74 controls used aspirin with a mean of 169 and 86 days, respectively, whereas 92 patients with MAC and 161 controls were on anticoagulant therapy during follow-up with a mean of 195 and 210 days, respectively. At the start of follow-up, 122 and 119 MAC, and 64 and 150 control patients, used aspirin or anticoagulants, respectively. Although differential treatment among patients and controls was obvious, MAC was not considered a risk for stroke, and therefore none of the MAC patients received any therapy aimed at reduction of a presumed MAC-related increased stroke risk.

The risk of stroke in patients with MAC (Tables 2 and 3)

Fifty-one MAC patients and 27 controls had a stroke in the follow-up period. Of those patients, 1 control and 5 patients with MAC had had previous strokes, and 1 control and 2 patients with MAC had had prior TIA. Crude analysis (IDR 0.77; 95% CI 0.41–1.41; $P = 0.04$) as well as Cox regression analysis (Table 3) showed no signifi-

Table 1 Baseline data of risk factors among patients with mitral annulus calcification (MAC) and controls

	MAC (n = 657)	Controls (n = 562)
Mean age with standard deviation (median)	72, 10 (74)	53, 18 (58)
Men/women	220/437	338/224
Hypertension	290	96
Ischaemic heart disease	382	225
Diabetes mellitus	124	43
Hypercholesterolaemia	36	10
Mean serum cholesterol	6.6	5.9
Peripheral arteriosclerosis	55	28
Atrial fibrillation	32	30
Prior stroke	40	20
Prior TIA	21	17
Death/mean day's follow-up	104/506	77/524
Dilated cardiomyopathy	30	38
Mitral stenosis	18	19
Mitral regurgitation	220; 64 > grade 2	218; 49 > grade 2
Aortic valve calcification/ with stenosis	289/113	0
Aortic/mitral valve prosthesis in situ	6/3 of which 0/1 bioprosthesis	26/39 of which 3/10 bioprosthesis
Anterior wall infarct/ apical aneurysm/ cardiac thrombus/ atrial septum aneurysm/ atrial septum defect	80/3/5/0/0	82/10/16/3/7
History of coronary artery bypass grafting	67	60

Table 2 Stroke during follow-up in relation with MAC

	MAC (n = 657)	Controls (n = 562)
Stroke 51	(7%) (1 rheumatic valve disease, 1 recent myocardial infarction, 10 atrial fibrillation)	27 (5%) (no cardio-embolic strokes)
Stroke type	34 territorial, 10 small deep, 2 haematomas, 2 infratentorial infarcts, 3 unspecified hemispheric infarcts	13 territorial, 5 small deep (lacunar), 4 unspecified hemispheral infarcts, 3 intracerebral haematomas, 1 had multiple infarcts classified as unspecified

cant association of MAC with stroke. Hypertension and carotid stenosis were significantly associated with stroke.

MAC and stroke subtypes

MAC was not exclusively associated with cortical brain infarction (lacunar vs cortical: OR 1.4; 95% CI 0.18–11.0; P = 0.73) with or without adjustments for risk factors such as carotid stenosis, any cardio-embolic source, and atrial fibrillation. Intracerebral haematoma and infratentorially located infarcts were too sparse for meaningful subanalysis.

Table 3 Risk factors for stroke in the follow-up; proportional hazard analysis (*HR* hazards ratio, *CI* confidence interval, *P P* value, *MAC* mitral annulus calcification, *LVEF* left ventricular ejection fraction, *LV mass*, left ventricular wall mass. The lowest class of LV mass is shown, but results were similar for others)

	HR	95% CI	*P*
MAC	0.76	0.42–1.36	0.3
Age 65 years	1.44	0.55–3.77	0.4
Men vs women	0.82	0.46–1.44	0.5
Hypertension	2.41	1.36–4.26	0.002
Diabetes mellitus	1.35	0.70–2.62	0.4
Ischaemic heart disease	0.80	0.45–1.43	0.4
History of coronary bypass	0.89	0.33–2.36	0.4
Anterior wall infarct	1.59	0.55–4.57	0.4
Apical aneurysm	5.13	0.94–27.9	0.05
Dilated cardiomyopathy	0.98	0.22–4.38	0.9
Generalised vascular disease	0.49	0.17–1.39	0.18
Atrial fibrillation	0.52	0.12–2.23	0.3
Enlarged left atrium	1.16	0.62–2.15	0.63
Hypercholesterolaemia	1.93	0.72–5.19	0.19
Prosthetic valves	1.50	0.47–4.81	0.5
Mitral regurgitation > grade 3	0.77	0.32–1.85	0.5
Anticoagulants	0.66	0.33–1.34	0.2
Aspirin	0.58	0.26–1.28	0.18
LVEF 30%	0.87	0.25–3.03	0.8
Increased LVmass	0.99	0.56–1.73	0.9
Any carotid stenosis	9.8	4.35–22.1	0.000
Prior TIA	1.01	0.23–4.45	0.9

MAC and silent infarcts

MAC was not associated with asymptomatic brain infarcts on CT in patients with a stroke during follow-up (OR 4.28; 95% CI 0.77–23.8; P = 0.13), and probably not with asymptomatic small deep (OR 7.48; 95% CI 0.77–71.2; P = 0.07) or territorial infarcts (OR 3.42; 95% CI 0.18–62.2; P = 0.5) on CT.

Discussion

This study suggests that mitral annular calcification is not a risk factor for stroke. One explanation for this difference from previous reports may be that we adjusted for carotid atheroma, which is associated both with MAC and stroke [26]. We also adjusted for cardiovascular risk factors for stroke, associated with MAC in previous studies [5, 17, 36–40].

Three studies have found an increased prevalence of MAC in selected patients with cerebral ischaemia. De

Bono and Warlow [22] found 8 incidences of MAC in 151 patients with cerebral ischaemia or amaurosis fugax, and none in the control group, a difference probably caused by MAC-related cardiac and carotid disease. Nishide et al. [41] found 2.5 times more MAC in 350 patients with brain infarcts than in controls, not adjusted for the higher prevalence of cardiac disease in the group with brain ischaemia and for carotid atheroma. Jespersen and Egerblad [20] analysed 388 patients with arterial emboli. Forty-nine were suspected of having a cardiac embolic source. Of these, 27% had MAC, compared with 8% in the remaining patients. However, enlarged left atrium and atrial fibrillation were more frequent among the 49 patients, and the contribution of carotid atherosclerosis was not analysed.

Five studies have described stroke risk in MAC patients. Of 80 patients with MAC, 12 had ischaemia in the carotid territory, but patients were not compared with controls [3]. Three strokes occurred during a 3.4-year follow-up of 63 patients, but most had cardiovascular disease [23]. In a univariate analysis [27] of 107 patients aged younger than 61 years with MAC, brain ischaemia occurred five times as much as in age- and sex-matched controls. Cardiac diseases were more frequent in patients with MAC and not adjusted for. Aronow [1] found a 1.7 relative risk of stroke in 526 patients older than 62 years with MAC, unadjusted for the higher incidence of atrial fibrillation and left atrial enlargement in patients with MAC, or for carotid atheroma.

Three epidemiological studies have analysed stroke risk in patients with MAC. BAATAF reported a 4.0 times increased incidence of stroke in 121 patients with MAC from a total of 420 patients with nonrheumatic atrial fibrillation, with or without low-dose warfarin. This risk may be overestimated, as with multivariate analysis of 568 patients with nonrheumatic atrial fibrillation assigned to placebo in the SPAF study, MAC was a no-risk factor for stroke [42]. Firstly, adjustments in BAATAF did not include for carotid disease. Secondly, the number of strokes in the control group might have been underestimated. Thirdly, results apply to atrial fibrillation trial patients, and an interaction between MAC and atrial fibrillation increasing stroke risk cannot be excluded [28]. MAC was associated with a relative risk of stroke of 2.1 in the Framingham study [28] adjusted for age, sex, hypertension, diabetes mellitus, smoking, atrial fibrillation, coronary heart disease and congestive heart failure, also after exclusion of patients with atrial fibrillation. However, limiting outcomes to cerebral infarcts only, reduced the relative risk to 1.78 with a lower limit of the confidence interval of 1.00. Furthermore, inclusion of carotid atheroma in the analysis would probably have reduced the stroke risk attributable to MAC.

As cardio-embolic infarcts may be predominantly territorial [43, 44], we analysed whether MAC was associated with territorial rather than lacunar infarcts, but this was not the case.

Brain CT in healthy volunteers or patients presenting with a stroke often show unexpected previous brain infarction. Some have suggested that such silent infarcts, especially when multiple or territorially located, increase the likelihood that the stroke resulted from cardiogenic embolism, but others strongly doubt this [45–49]. We could not establish a statistically significant association between MAC and silent brain infarcts on CT, although there was a tendency for small deep silent infarcts to be related with MAC, probably because of common underlying vascular risk factors. Obviously, even when stroke patterns, presumed by some to indicate cardio-embolic stroke mechanism, were separately analysed, MAC did not appear as a cardio-embolic source for stroke.

Patients in our study were referred to a cardiologist, undoubtedly increasing the a priori risk of stroke, but equally in the study and control groups. In our analysis we adjusted for clinical and echocardiographic risk factors for stroke. One might argue that it is essentially impossible to adjust completely for the differences of the baseline characteristics between patients and controls, and that this might cause an overestimation of stroke risk in patients with MAC. However, any such residual bias would reject rather than confirm our hypothesis that MAC is a no-risk factor for stroke, and therefore would not influence our conclusion. MAC patients did not use more aspirin or anticoagulants for any reasons associated with MAC, excluding a therapeutic bias.

In conclusion, our data argue in favour of the view that mitral annulus calcification is not an independent risk factor for stroke. Stroke in patients with this valve lesion should be attributed to concomitant cardiovascular and carotid disease, which are strongly associated with MAC, and which therefore should determine the choice for treatment aimed at lowering the risk of stroke in such patients.

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