Risk of Stroke in Patients With Mitral Annulus Calcification

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SUMMARY 63 patients with mitral annulus calcification (MAC) were followed for an average of 3.4 years. Two patients experienced TIA, both ipsilateral to a previous endarterectomy site, and IV-DSA demonstrated normal extracranial vessels. There were 3 strokes (5%), all fatal, but none could be attributed to embolism. Embolic stroke due to MAC is rare and difficult to prove due to coexistent atherosclerosis. Associated cardiac conditions such as atrial fibrillation, which might increase the risk of embolism, usually occur with MAC ≥ 5 mm. In many patients, MAC may be better viewed as a marker of generalized calcific atherosclerosis rather than as an immediate embolic source.

ALTHOUGH MITRAL ANNULUS CALCIFICATION (MAC) has been implicated as a cause of embolic stroke, no natural history studies have addressed this issue. We studied the frequency of cerebrovascular events in 63 patients with MAC diagnosed by echocardiography and cardiac catheterization.

Methods

Between 1977 and 1981, 65 patients with MAC demonstrated on echocardiography (M-mode or 2 dimensional) were seen at the Cleveland Clinic Foundation. The echocardiographic criteria for the diagnosis of MAC included the presence of a dense band of echoes behind the posterior cusp of the mitral valve, anterior to the posterior wall of the left ventricle, and moving in parallel with the left ventricular endocardium. Fifty six patients also underwent cardiac catheterization, which confirmed the presence of MAC.

Follow-up dated from the time of echocardiography and was accomplished using available medical records, telephone interviews and a standardized questionnaire.

Results

Follow-up averaged 3.4 years and was achieved in 63 patients (97%). There were 32 men and 31 women with a mean age of 65 years (range, 47–78 years).

Presenting symptoms included: angina pectoris, 50 patients (79%); congestive heart failure, 34 patients (54%); cardiac dysrhythmia, 22 patients (35%); syncope, 15 patients (24%). Associated medical conditions are given in table 1.

Four patients presented with amaurosis fugax and 2 with hemispheric transient ischemic attacks (TIA). All of these patients had hypertension and coronary atherosclerosis, 3 had left atrial enlargement, 5 had compensated congestive heart failure, and 1 had atrial fibrillation. Four of the patients with TIA underwent intravenous digital subtraction angiography (IV-DSA); none underwent intraarterial angiography. IV-DSA demonstrated mild irregularity of the internal carotid artery (ICA) origins in 2 patients. In 2 patients IV-DSA showed significant ulcerated stenosis of the ipsilateral ICA origin; both underwent carotid endarterectomy.
Fourteen patients (22%) died during follow-up. Thirteen of the patients who died had moderate to severe MAC (>5 mm), and the cause of death was cardiac-related in 7 patients (congestive heart failure, 3; myocardial infarction, 4).

During follow-up, 2 patients experienced TIA after an average interval of 2 years. In both the patients the TIA were ipsilateral to a previous carotid endarterectomy, and 4-D SA demonstrated normal extracranial vessels. Three patients (5%) suffered a stroke, all fatal (cerebellar hemorrhage on warfarin, 1; primary intracerebral hemorrhage, 1; pontine infarction, 1).

Discussion

Mitral annulus calcification is a frequent cause of apical systolic heart murmurs in the elderly. The average age at diagnosis is 65 years or older; patients with rheumatic calcification of the mitral valve present at a younger age. There is a female sex predilection. Autopsy studies of patients over age 50 have demonstrated a frequency of MAC of about 10%, and one postmortem series found a frequency of 27% in patients over age 90.3,4

The pathogenesis of non-rheumatic MAC is uncertain. The female preponderance suggests an endocrine disturbance. No abnormality of calcium metabolism has been identified in patients with MAC, although recent data suggest an alteration in parathyroid hormone metabolism in patients with MAC associated with chronic renal failure undergoing hemodialysis.5 An association between MAC, coronary atherosclerosis and peripheral arterial disease has been made; both diabetes mellitus and hypertension seem to accelerate the process.7 It is thus tempting to view MAC as a degenerative aging process analogous to atherosclerosis.8,9

Cardiac conditions associated with MAC, some of which increase the risk of embolism, include mitral insufficiency, mitral stenosis, congestive heart failure, conduction disturbances, atrial fibrillation, and aortic valve sclerosis. In two studies which included the patients in this report, associated cardiac conditions were correlated with MAC ≥5 mm thickness.5,10 Fulkerson et al found 11 patients (14%) with mitral valve prolapse among their series of 80 with MAC, and the mean age was significantly lower (64 versus 75 years) than the patients without mitral valve prolapse.11

MAC provides a setting which could predispose to either calcific or platelet/fibrin embolization, yet this potential complication has rarely been well-documented in the literature. Valvular ulceration with extrusion of calcific material, thrombus formation and frank caseation have been described in postmortem studies.3 The only pathologically proven case of brain infarction related to embolization from a calcified mitral annulus was reported by Ridolfi and Hutchins in 1976.12 At postmortem there was severe calcification of the mitral valve annulus with endotheil ulceration and exposure of underlying calcific debris; there were numerous calcific brain and systemic emboli. De Bono and Warlow1 later popularized the concept of MAC as a source of brain embolism. Among 151 consecutive patients presenting with a cerebrovascular event, 8 patients (5%) had MAC. This compared with no cases of MAC among 146 control patients matched only for age and sex. This difference must be interpreted with caution. A 5% frequency of MAC is not unexpected in an elderly patient population with cerebrovascular disease and presumably atherosclerotic risk factors; there is no indication that the control group was comparable in this regard. Also, only 2 of the 8 patients with MAC underwent angiography. Stroke accompanied by MAC has been associated with a high frequency of angiographic evidence of appropriate atherosclerotic lesions in the carotid arteries.13

In our MAC population stroke was uncommon (5%) and could not be ascribed to embolization. All of the patients with TIA had coexistent atherosclerotic disease or other cardiac conditions in addition to MAC. Several conclusions therefore seem warranted: 1. Brain embolization from isolated MAC is rare and difficult to prove due to coexistent atherosclerosis. 2. Embolization from MAC should be considered if there is no other apparent cause for a cerebrovascular event. Confidence in a diagnosis of embolism from MAC is higher in patients with an associated cardiac condition such as atrial fibrillation, most of whom have MAC ≥5 mm in thickness. 3. In many cerebrovascular patients, MAC may be better viewed as a marker of generalized calcific atherosclerotic disease rather than as an immediate embolic source.

References

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SUMMARY  The pathophysiology of postischemic encephalopathy is complex, and includes tissue acidosis, edema, hypoperfusion, membrane dysfunction, impaired energy production, and possibly hypermetabolism. We tested the hypothesis that this multifactorial clinical problem must be approached with multifaceted therapy, with specific treatment aimed at each of the above postischemic changes. Eighteen minutes of complete global brain ischemia was produced with a higher pressure neck cuff in pigtailed monkeys. Control treatment postischemia (n = 9): 1) Normotension (MAP $\leq 80$ mmHg) restored within 2 min postischemia, 2) controlled ventilation for 24 hours with PaCO$_2 = 25$ mmHg, 3) normothermia, and 4) phenytoin seizure prophylaxis from 20 hours postischemia. Experimental treatment (n = 10): Control treatment plus the following modifications: 1) Hemodilution to hematocrit 25% at 1-4 min postischemia, 2) brief hypertension (MAP 130 mmHg for 5 min) after accomplished hemodilution, 3) hypothermia for 6 hours, 4) pentobarbital 30 mg/kg i.v., 5) dexamethasone 4 mg/kg i.v. Outcome was evaluated at 96 hours postischemia by overall performance categories (OPC) (OPC I = normal, OPC V = brain death), neurologic deficit (ND) scores (100% ND = brain death, 0% ND = normal), and histologic damage scores of the brains. Results: Brain death developed in 1/9 control and 0/10 treated animals. The number of awake monkeys (OPC I and II) at 96 hours postischemia was significantly higher in the treated group (7/10) than in the control group (2/9) (p = 0.05). The median ND scores for the two groups were 16 and 35% respectively (p > 0.05). The results strongly suggest that postischemic treatment may be beneficial and that a multifaceted therapeutic approach is worth pursuing.

IN SPITE OF INTENSIVE RESEARCH, no specific therapy has so far been identified and generally accepted for use after complete global brain ischemia (GBI). Treatment with large doses of barbiturates was initially considered beneficial when given before1 as well as after2 the ischemic episode, but these encouraging results have not been reproduced in later studies,3,4 and the value of barbiturate treatment after GBI remains questionable. Research in cerebral resuscitation has been encouraged by an improved understanding of pathophysiologic events in the brain during and after ischemia.5,6 Changes occurring after ischemia, when normal perfusion pressure is restored, are believed to cause further damage,8 and therapeutic intervention in the early postischemic period might be of value in preventing at least part of the ensuing brain damage. Identified changes in the brain after ischemia include: 1) Reflow problems, multifocal and generalized hypoperfusion,9-14 2) brain tissue acidosis,15 3) brain edema,11,16,17 4) membrane failure,5,7,18,19 5) impaired restitution of energy production,12,19-21 6) hypermetabolism with a mismatch between oxygen supply and cerebral metabolic demands,13,19,22,23 Furthermore, there may be postischemic seizures24 that may cause additional brain damage.25 With such a complex, multifactorial problem, we chose to test the hypothesis that treatment after GBI also will have to be multifaceted in order to be effective. The aim was to treat each and all of the above postischemic (PI) changes to determine if this would improve final neurologic outcome. We studied a combination of the following modes of treatment PI: 1) Hemodilution, 2) hypertension, brief and moderate, 3) hypothermia, 4) pentobarbital anesthesia, and 5) dexamethasone. Although none of these treatment modalities alone have been shown to improve neurologic outcome after GBI, there is experimental evidence that each of these treatments has a beneficial effect on one
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Stroke. 1984;15:801-803
doi: 10.1161/01.STR.15.5.801
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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