Cardiac Abnormalities in Ischemic Cerebrovascular Disease Studied by Two-Dimensional Echocardiography

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SUMMARY In the study of cardiac abnormalities responsible for the development of cerebral embolism two-dimensional echocardiography was performed on 350 patients with ischemic cerebrovascular disease. The results were compared with those obtained from 350 controls without any history of stroke. Atrial fibrillation was detected on ECG in 115 cases (33%) of the patients and in 35 cases (10%) of the controls (p < 0.001).

The structural cardiac diseases observed in stroke patients were: rheumatic heart disease (RHD) in 37, congestive cardiomyopathy (CCM) in 7, hypertrophic cardiomyopathy (HCM) in 19, mitral annulus calcification (MAC) in 29, mitral valve prolapse (MVP) in 9, and myocardial infarction (MyI) in 10 patients. Controls were found to have these lesions in 11, 2, 3, 12, 4 and 9 patients respectively. RHD (p < 0.001), HCM (p < 0.01) and MAC (p < 0.01) were significantly more frequent in patients with ischemic cerebrovascular disease, but not MyI, CCM or MVP. Intracardiac thrombi were diagnosed in 29 cases of patients and in 4 cases of controls (p < 0.001).

Our data suggested that nonrheumatic heart diseases such as MAC and HCM could also be considered as causes of embolic stroke. The reasons for the variable frequencies of cardiac abnormalities reported in the literature for stroke patients are discussed.

THE ROLE OF THE HEART IN CEREBRAL EMBOLISM HAS been well known since the 17th century. Until recently, however, rheumatic heart disease (RHD), which can be usually diagnosed from physical findings, has been the commonest reported cardiac disease leading to cerebral embolism. The incidence of cardiac abnormalities in patients with ischemic cerebrovascular disease has also been extensively studied. The somewhat different opinions among investigators as to the nature of the cardiac abnormalities causing embolism, are possibly due to differences in patient populations and in the methods of diagnosing cardiac abnormalities. Differences arise as well because of the difficulty of differentiating embolism from thrombosis. Recent equipment, such as echocardiography, has enabled noninvasive and accurate diagnosis of cardiac abnormalities other than RHD. A variety of cardiac disorders can be found frequently in patients diagnosed as having ischemic cerebrovascular disease. These disorders include mitral valve prolapse (MVP)¹,² left atrial myxoma,³ and mitral annulus calcification (MAC).⁴ These reports have urged us on a detailed study of embolism-prone cardiac lesions utilizing newly developed technology. The present study was designed to investigate the incidence of cardiac abnormalities in a large number of patients suffering from ischemic cerebrovascular disease utilizing two-dimensional echocardiography (2DE). The relationship between the severity of ischemic cerebrovascular disease visualized by CT-scan and the type of cardiac abnormality was studied.

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Materials and Methods
Two-dimensional echocardiography (2DE, Toshiba, electronic sector scanner, SSH-11A) has been used at the Division of Cerebrovascular Diseases of Hanwa Memorial Hospital since June, 1978. Between December, 1978 and October, 1981, 2120 patients with cerebrovascular disease were admitted to our division, 720 cases within 48 hours of the onset. All were diagnosed with physical and neuroradiological findings including CT-scan. Three hundred and seventy-five patients were considered to have ischemic cerebrovascular disease and 305 had hemorrhage strokes, (cerebral hemorrhage and subarachnoid hemorrhage); the remaining 40 cases were suspected as having cerebrovascular disease but other pathological conditions could not be completely excluded. 2DE studies were performed upon 375 consecutive patients who were diagnosed definitely as having ischemic cerebrovascular disease. In 25 patients the 2DE examinations were technically unsuccessful. In the remaining 350 patients, 318 had completed, progressing stroke or reversible ischemic neurological deficit (RIND), and 32 had TIA only. The diagnosis of TIA and other types of stroke were based on the definition of the Ad Hoc Committee.⁵ Another 350 patients, matched for sex and age by the decade, were selected as controls from hospital inpatients who had no history of cerebrovascular disease or systemic embolism. The selection of the control group was performed in a blind manner by other clinical groups in the hospital. The control patients originated from about 1,000 patients admitted because of other diseases: gastro-intestinal disease, trauma, cancer, metabolic disorder, heart disease, etc. and were available for study by 2DE concurrently with the study of the stroke patients between 1978 and 1981. Of 350 stroke patients, 195 were male and 155 female. Their mean age was 66.2 years (range 20-96). In the control group, 195 were male and 155
female and their mean age was 69.5 years (range 25–97).

The 2DE studies were done with a wide angle 78° phased array sector scanner. M-mode echocardiography was performed simultaneously with 2DE observing echo sources. Parasternal, apical and subxiphoid windows were used in order to investigate the pathological changes of the left atrium, left ventricle, aortic valve, mitral valve and their appendages (mitral annulus, papillary muscle, etc.). Every image was recorded on videotape for post examination analysis. The single-image was obtained by electrocardiogram gated photography utilizing a Polaroid camera. The criteria of each structural cardiac abnormality on 2DE were as follows:

Rheumatic heart disease (RHD) was diagnosed as having the typical M-mode and 2DE findings of the mitral and/aortic valves.

Congestive cardiomyopathy (CCM) was diagnosed as dilated poorly contracting left ventricles but the wall thickness was within normal limits. Other echocardiographic findings were decreased cardiac output with a poorly moving aorta, decreased mitral valve opening, gradual closure of the aortic valve, dilatation of the left atrium, and abnormal closure of the mitral valve indicative of an elevated left ventricular diastolic pressure. Although cases with CCM had no clinical signs of congestive heart failure, to differentiate CCM from congestive heart failure, 2DE was performed two or three times and the findings were confirmed.

The criterion for hypertrophic cardiomyopathy was septal hypertrophy (greater than 1.5 cm in thickness at end-diastole). Additional criteria, not sufficient for diagnosis in themselves, were: 1) the ratio of septal to posterior left ventricular wall thickness was 1.5 or greater (ASH), 2) systolic anterior motion (SAM) of the anterior mitral leaflet was present, 3) anterior displacement and slowing of the early diastolic closing motion of the anterior mitral leaflet in diastole, 4) a decrease in transverse left ventricular diameter at the level of the mitral valve, and 5) systolic semiclosure of the aortic valve.

The M-mode echocardiography of mitral annulus calcification (MAC) showed a dense and linear echo behind the mitral valve that moved anteriorly with systole, a phenomenon similar to the motion of the posterior left ventricular wall. In scanning from the left ventricle to the left atrium this dense band of echoes stopped abruptly at the junction between the left ventricle and left atrium. However, because of the difficulty in differentiating this band of echoes from the posterior mitral valve leaflet and from the posterior wall of the left ventricle, MAC was diagnosed by 2DE as a bright echo between the mitral valve and the posterior left ventricular wall.

Mitrail valve prolapse (MVP) was diagnosed as anterior or posterior mitral leaflet bulging through the line that extends from the base of the aortic valve to the arterioventricular junction by long-axial view using 2DE irrespective of M-mode echocardiographic findings.

Myocardial infarction (Myl) was diagnosed when abnormal movement of left ventricular motion (akinesia or dyskinesis) was shown by echocardiography in association with abnormal Q waves on the ECG.

Evaluation of the echocardiographic findings, both in stroke patients and controls, was done in a blinded manner by a member of the Department of Cardiology and a member of the Division of Cerebrovascular Diseases. In addition to 2DE, left ventriculography, coronary angiography, phonocardiography and an analysis of carotid pulse wave were performed if necessary for the diagnosis.

In order to detect atrial fibrillation, a 12-lead ECG was used and an ECG was obtained for all cases, every day in the acute stage and once a week in the chronic stage, for both stroke patients and controls. In total, 1 ECG was done more than seven times in both groups of patients during their admission, although the mode of ECG follow-up was somewhat different for the two groups. 2DE was performed as often as possible on relatives of patients having MVP or HCM.

To study the relationship between cardiac abnormalities (including atrial fibrillation, structural cardiac disease, and intracardiac thrombi seen by 2DE) and the severity of ischemic cerebrovascular disease, the findings on CT-scan were studied in all 308 patients with supratentorial ischemic cerebrovascular disease. The 42 patients with infratentorial ischemic stroke were excluded because of the difficulty in judging the size of the low density area on CT-scan. The severity of ischemic cerebrovascular disease divided into two groups according to the extent of low density area (LDA) on CT-scan: a large infarction was designated as one with an LDA larger than the area of the middle cerebral artery territory, and a small infarction as one with an LDA smaller than the area of the middle cerebral artery territory, including those with a CT having a normal appearance. Large infarction on CT-scan was diagnosed in 106 of the 308 patients with supratentorial ischemic cerebrovascular disease.

Results

The incidence of intracardiac thrombi and structural cardiac disease by 2DE was significantly more frequent in stroke patients than in the control group (p < 0.001). Atrial fibrillation on ECG was more frequent in stroke patients (p < 0.001). Among the 29 patients having intracardiac thrombi, demonstrable by 2DE, 17 had both structural cardiac disease and atrial fibrillation, 2 had structural cardiac disease (myocardial infarction) only, 7 had atrial fibrillation without structural cardiac disease and 3 had no structural cardiac disease or atrial fibrillation. Of 4 patients with intracardiac thrombi in the control group, two were diagnosed as having both rheumatic heart disease and atrial fibrillation, and the other two had atrial fibrillation only (table 1).

The frequency of individual structural cardiac disease is shown in table 2. RHD (p < 0.001), HCM (p < 0.01) and MAC (p < 0.01) were significantly more frequent in patients with ischemic cerebrovascular dis-
cases, but MyI, CCM and MVP were not. No patients with myocardial infarction had major cardiac ischemic events within six months of the stroke. Other structural cardiac diseases identified in the patients were, left atrial myxoma in 1, rupture of the chordae tendinae in 2, hypertensive left ventricular hypertrophy in 5, atrial septal defect in 2, aortic regurgitation in 2, protruded vegetation on the mitral valve in 2, aortic stenosis in 3 and aortic valve replacement in 2 cases.

Autopsy was performed in 5 of 10 fatal cases with RHD, 3 of 5 with HCM, 3 of 6 with MAC, 1 of 3 with CCM, 2 of 4 with MyI and in both of the two fatal cases with MVP; the diagnosis by 2DE was confirmed in all of them. Intracardiac thrombi diagnosed by 2DE were verified in 11 cases by autopsy but there were other two cases (1 with RHD and the other with HCM) that had intracardiac thrombi undetected by 2DE. Figure 1 shows an intracardiac thrombus in a patient with RHD in whom a postmortem examination was performed and the 2DE findings were confirmed.

Figure 2 shows the age distribution of all the stroke patients with structural cardiac disease. RHD, CCM and MVP occurred in relatively younger patients, and MAC in older patients. Most of the patients with MyI were in their 7th decade; HCM was distributed uniformly in each decade. The mean ages of patients with each structural cardiac disease were 61.0 in RHD, 55.0 in CCM, 69.3 in HCM, 77.9 in MAC, 60.3 in MVP and 71.7 years old in MyI, respectively.

Table 3 shows the relationship between the cardiac abnormalities and the severity of ischemic cerebrovascular disease diagnosed by CT-scan. In the patients with large infarction, each cardiac abnormality (atrial fibrillation, structural cardiac disease and intracardiac thrombi) was diagnosed more frequently than in the patients with a small infarction (p < 0.001).

Discussion

It is widely accepted that patients with cardiac abnormalities are at risk for permanent embolic sequelae in the brain, eyes and other organs. This observation has been reported both from prospective and retrospective observations on patients with heart disease or cerebrovascular disease.

Atrial fibrillation, with or without valvular heart disease, is implicated in the development of embolism. Aberg et al. reported the incidence of emboli in an autopsy study of 642 cases with atrial fibrillation: 53.5% of cases with valvular or congenital disease, 54.3% with combined valvular and ischemic heart disease, and 41.7% with other conditions (such as ischemic heart disease, hypertensive heart disease, malignancies and other miscellaneous types); the incidence in the control group without atrial fibrillation was 18.7%. Cerebral emboli, either isolated or with emboli at other sites, occurred in 77% of their embolic cases. In the Framingham study, the incidence of stroke increased 5.61 times in patients with atrial fibrillation, regardless of the duration of atrial fibrillation. In an autopsy study of 333 patients with atrial fibrillation, Hinton et al. found emboli to be nearly as common without RHD (59 of 171, 35%) as with RHD (29 of 70, 41%).

In the past, RHD in particular has been reported to be the predominant cause of cerebral embolism even in patients with a stable sinus rhythm. Systemic embolism occurs over several years in 9–49% of RHD patients and 20–70% of these emboli are cerebral. Some nonrheumatic heart diseases such as MVP, MAC, cardiomyopathy and left atrial myxoma, also

Discussion

A high proportion of patients with atrial fibrillation, structural cardiac disease and intracardiac thrombi have cerebral embolism.

Table 1 shows the relationship between the cardiac abnormalities and the severity of ischemic cerebrovascular disease diagnosed by CT-scan. In the patients with large infarction, each cardiac abnormality (atrial fibrillation, structural cardiac disease and intracardiac thrombi) was diagnosed more frequently than in the patients with a small infarction (p < 0.001).

Table 2 shows the structural cardiac disease diagnosed by 2DE.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Frequency of Structural Cardiac Disease, Intracardiac Thrombi and Atrial Fibrillation</th>
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<tbody>
<tr>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>(n = 350)</td>
<td>(n = 350)</td>
</tr>
<tr>
<td>Structural cardiac disease</td>
<td>130 (37.1%)</td>
</tr>
<tr>
<td>Intracardiac thrombi</td>
<td>29† (8.3%)</td>
</tr>
<tr>
<td>Atrial fibrillation (Af)</td>
<td>115 (32.9%)</td>
</tr>
</tbody>
</table>

*p < 0.001 (χ² test).
19 cases with structural cardiac disease, 7 cases with only Af and 3 cases without structural cardiac disease or Af.
32 cases with RHD and Af, 2 cases with only Af.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Structural Cardiac Disease Diagnosed by 2DE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>with ischemic cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>Af</td>
<td>(+)</td>
</tr>
<tr>
<td>Rheumatic heart disease*</td>
<td>32</td>
</tr>
<tr>
<td>Congestive cardiomyopathy</td>
<td>2</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy†</td>
<td>7</td>
</tr>
<tr>
<td>Mitral annulus calcification†</td>
<td>15</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
</tr>
</tbody>
</table>

*p < 0.001, †p < 0.01 χ² test Yates' correction.
A few previous reports have described the most significant nonrheumatic heart diseases associated with cerebral emboli. MAC has been well documented from the autopsy studies of aged patients, and was found in about 10% of autopsied patients. A few recent studies have suggested that MAC was associated with cerebral or retinal embolism in the elderly and reported that the frequency of MAC in patients with ischemic cerebrovascular disease was significantly higher than in a control group. Although not described here in detail, we have observed that nearly 80% of MAC patients who have had cerebral ischemic events have had concomitant carotid atherosclerotic lesions, including stenosis or ulcerative atheroma. Further studies are necessary to confirm MAC as an embolic source in any given patient and even then the role played by the carotid atheromatous lesion and that played by the MAC may remain uncertain.

Another major condition in the present study was HCM. Recent reports have pointed out that HCM is not rare in the elderly. The etiology of HCM has not been completely elucidated; it appears to be of congenital etiology in the young, while hypertension and/or aging have been suggested as the cause in older people. Fifteen families of our patients with HCM were examined by 2DE but no hereditary evidence was found. HCM in the elderly, may indeed have a different etiology from that in the young, a matter requiring further investigation.

In our study no significant difference was shown in Table 3. Relationship between Cardiac Abnormalities and Size of Infarction on CT Scan

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Large Infarction (N = 106)</th>
<th>Small Infarction (N = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>63 (59.4%)</td>
<td>41 (20.3%)*</td>
</tr>
<tr>
<td>Structural cardiac disease</td>
<td>64 (60.4%)</td>
<td>51 (25.2%)*</td>
</tr>
<tr>
<td>Intracardiac thrombi</td>
<td>22 (20.8%)</td>
<td>8 (4.0%)*</td>
</tr>
</tbody>
</table>

(*p < 0.001 χ² test)

MVP has been reported, however, as a cause of cerebral embolism. The condition of MVP has been known since the 19th century but, had not attracted neurologists' attention until the papers of Barnett, Woldoff et al. and of Barnett et al. reported two cases of retinal stroke accompanying MVP. Barnett reported 4 cases and then 12 cases of TIA or partial nonprogressing stroke with MVP and their following report emphasized that MVP must be taken into consideration when investigating the embolic source, especially in younger patients. The lack of significant difference in the incidence in our patients and in our controls may be due to the fact that only a small number of TIA or young patients were included in our study.

Myocardial infarction, with ventricular mural thrombi going as emboli to the arterial circulation, is a traditionally recognized cause of embolism. The phenomenon is encountered particularly within the first three months of an acute myocardial infarction, thereafter few embolic events occur. This is one of the important reasons for the lack of significant incidence of myocardial infarction in our two groups. The myocardial infarcts had occurred prior to this period of susceptibility and this study was conducted on patients admitted to hospital because of cerebral ischemic symptoms.

One of the reasons which probably accounts for the rarity of CCM is that patients with CCM are generally referred to a general medical or cardiological service rather than to a neurologist. Cardiac symptoms tend to be severe and frequent before cerebral events occur. A number of reports have detailed the cardiac abnormalities found in patients with cerebral embolism, but only recently have researchers utilized echocardiography. The studies of Friedman et al. Fisher, Wells, Hinton et al. did not use echocardiography while those of DeBono et al., Lovett et al. did. In these reports, somewhat different opinions about the nature and the frequency of cardiac abnormalities are encountered. This difference is dependent on several factors: e.g. difference in diagnostic methods utilized to determine the cardiac abnormalities, different patient populations, differing severity of cerebral dis-
ease, differences in the types of ischemic cerebrovascular disease, etc. In our study, the more serious the extent of the ischemic cerebrovascular disease on the CT-scan, the more frequently were cardiac abnormalities diagnosed. Cerebral emboli from these such cardiac abnormalities as atrial fibrillation and structural cardiac disease tend to cause cerebral infarction of a very severe degree. As shown in figure 2, each structural cardiac disease has a different age distribution. The difference in age of the patient population under study is an influential factor in determining the nature of cardiac disease diagnosed in any reported group of patients. In our study, patients with RHD, CCM or MVP were relatively younger than patients with MAC (mean age: 77.9 y.o.).

Patients with cerebral or retinal ischemia resulting from cardiac lesions may be regarded as a distinct group in terms of both treatment and prognosis. Previous reports, as well as our findings have demonstrated that a variety of cardiac abnormalities are common in ischemic stroke patients. Several questions arise in the interpretation of the importance of cardiac abnormalities in patients with ischemic cerebrovascular disease. 1) Can stroke in patients with cardiac disease always be diagnosed as resulting from cerebral embolism? May they not be suffering from cerebral thrombosis caused by co-existing atherosclerotic cerebrovascular disease? 2) Is the cerebral embolism the direct result of structural cardiac disease or is it due to a functional abnormality such as subsequent atrial fibrillation? 3) Is cerebral embolism in a given patient caused by heart disease alone? As described above for MAC, concomitant atherosclerotic lesion in the carotid artery may give rise to emboli and this confusing situation must be taken into consideration especially in the elderly.

Accurate answers to these questions are needed to clarify the mechanism and the accurate assessment of the prevalence of embolism due to heart conditions. With further technological advance these problems will become better understood.

Acknowledgment

We would like to thank Professor H.J.M. Barnett who inspired the present study and gave helpful advice.

References

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