Mechanism of Atrial Fibrillation and Increased Incidence of Thromboembolism in Patients With Hypertrophic Cardiomyopathy

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To elucidate the morphologic characteristics of the left ventricle in patients with hypertrophic cardiomyopathy who developed atrial fibrillation, we studied left ventricular geometry by two-dimensional echocardiography in 92 patients with hypertrophic cardiomyopathy. These patients were divided into two groups; 24 patients with transient or persistent atrial fibrillation (group I) and 68 patients with sinus rhythm (group II). Left ventricular chamber size in group I was significantly smaller than that in group II. Left ventricular chamber size was correlated positively with stroke volume, and was correlated negatively with left ventricular end-diastolic pressure. The incidence of systemic thromboembolism in group I was 7.1% per patient year.

In hypertrophic cardiomyopathy, the size of the left ventricle appears to have major pathophysiologic significance in the development of atrial fibrillation. In addition, since patients with hypertrophic cardiomyopathy who develop atrial fibrillation have a potential risk of systemic thromboembolism, prophylactic anticoagulant therapy should be performed in these patients.

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In the clinical setting, we often encounter patients with hypertrophic cardiomyopathy who develop atrial fibrillation. Many authors have shown that atrial fibrillation develops in approximately 15% of patients with hypertrophic cardiomyopathy. Atrial fibrillation deteriorates the functional status of patients with hypertrophic cardiomyopathy by eliminating the important contribution of atrial systole to left ventricular end-diastolic volume, and is believed to herald a poor prognosis. Moreover, atrial fibrillation is associated with embolic complications. However, to our knowledge, there has been no evaluation of the incidence of embolic complications in patients with hypertrophic cardiomyopathy who developed atrial fibrillation.

Hypertrophic cardiomyopathy is characterized by decreased left ventricular distensibility, which may be related to the development of atrial fibrillation. The morphologic characteristics of the left ventricle in patients with hypertrophic cardiomyopathy who are at high risk of atrial fibrillation remain unclear.

Wide-angle, two-dimensional echocardiography permits accurate visualization of the left ventricle. Using two-dimensional echocardiography, we measured the left ventricular chamber size and investigated its significance in predicting the development of atrial fibrillation.

Key words:
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fibrillation in patients with hypertrophic cardiomyopathy. The incidence of systemic thromboembolism in patients with hypertrophic cardiomyopathy who developed atrial fibrillation was also examined.

METHODS

Study Patients
A retrospective analysis of the association of systemic thromboembolism and atrial fibrillation was performed in 128 patients with hypertrophic cardiomyopathy who were diagnosed at Ehime University Hospital between April 1983 and March 1986. The diagnosis of hypertrophic cardiomyopathy was based on the presence of typical clinical and electrocardiographic findings in association with a hypertrophied, non-dilated left ventricle on two-dimensional echocardiography in the absence of hypertension, valvular heart disease, or any other systemic conditions which might cause cardiac hypertrophy. Of these 128 patients, 92 met the following criteria and were included in this study: (1) a recording of a technically satisfactory two-dimensional echocardiogram, (2) no complication of coronary artery disease, (3) no persistent atrial fibrillation at the time of diagnosis, and (4) a follow-up period of more than 3 years. Twenty-four patients had atrial fibrillation documented on physical examination and resting and/or ambulatory electrocardiography (ECG) during the fol-

![Fig.1. A stop frame of two-dimensional echocardiogram obtained in the parasternal long-axis view at end-diastole (A) and a schematic diagram (B). The portion of the left ventricular chamber which is surrounded by the interventricular septum (IVS), aortic valve (Ao), mitral valve leaflets (ML), posterior wall (PW) and the most outward border of papillary muscles (PM) was considered the left ventricular effective chamber size (LVECS). Abbreviations: LV = left ventricle; LA = left atrium.](image-url)
Atrial Fibrillation and Thromboembolism in HCM

Informed consent.

Patients were divided into two groups on the basis of their development of atrial fibrillation during the follow-up period: 1) group I (n=24); 8 patients with persistent atrial fibrillation (duration ≥1 week) and 16 patients with transient atrial fibrillation (duration ≥1 min and <1 week), and 2) group II (n=68); patients with sinus rhythm throughout the entire follow-up period. With respect to sex and age, there were no significant differences between the persistent and transient atrial fibrillation groups, or between group I and group II, respectively (Table I).

Assessment of Systemic Thromboembolism

All patients who were suspected of having systemic thromboembolism were admitted to the hospital for evaluation and treatment. The diagnosis of systemic thromboembolism was based on the patient’s history, physical findings and brain computed tomography. All patients with stroke fulfilled the diagnostic criteria for cerebral embolism proposed by Hart et al.14 In group I, the incidence of systemic thromboembolism was calculated by the following formula: Number of systemic thromboembolism events/sum of the follow-up periods (years) for each patient×100.

Echocardiography

Echocardiographic studies were carried out using an SSD-870 echocardiograph with a 3.5 MHz transducer (ALOKA Inc, Tokyo, Japan). M-mode echocardiographic recording was carried out after the cardiac anatomy was visualized by two-dimensional echocardiography. The M-mode echocardiographic cursor was first positioned at the level of the mitral valve, where the interventricular septum, the left ventricular posterior wall, and the point of separation of the mitral leaflets were best imaged. The thicknesses of the interventricular septum and left ventricular posterior wall, and the left ventricular internal dimensions at end-diastole and end-systole were measured according to the criteria of the American Society of Echocardiography.15 The M-mode echocardiographic cursor was then moved to the level of the aortic valve to measure the left atrial dimension. M-mode echocardiograms were

Fig.2. Stop frames of two-dimensional echocardiograms (left) obtained in the parasternal long-axis view at end-diastole and respective schematic diagrams (right). A is a normal heart, B is obstructive-type hypertrophic cardiomyopathy, C is non-obstructive type and D is so-called apical hypertrophic cardiomyopathy. In contrast to the normal heart, papillary muscles are clearly observed in hypertrophic cardiomyopathy. The left atrium is much larger in patients with a small left ventricular effective chamber (B and C).

low-up period. Ambulatory ECG monitoring was performed at the time of diagnosis and at least 6 months later.

The 92 study patients with hypertrophic cardiomyopathy ranged in age from 16 to 70 years (mean 54) and 77 (84%) were male. Fifty-two patients were asymptomatic, 35 had a mild functional limitation (New York Heart Association functional class II), and 5 had a moderate functional limitation (class III). Echocardiographic evaluation was performed in sinus rhythm at the time of diagnosis without medications. All patients participated in this study after giving their
recorded at a paper speed of 50 mm/sec.

Assessment of Left Ventricular Effective Chamber Size

After a thorough examination of the left ventricular long-axis view in each patient, a representative stop-frame image was photographed directly. As illustrated in Fig. 1, we referred to that portion of the left ventricular cavity which was surrounded by the aortic valve, interventricular septum, posterior left ventricular wall, mitral valve leaflets and the most outward border of papillary muscles which could be defined as chordal and papillary muscle attachments, as the left ventricular effective chamber size. To avoid underestimating left ventricular effective chamber size, great care was taken to examine an accurate long-axis left ventricle to ensure a maximal left ventricular size. Measurements were made at end-diastole after careful localization of endocardium, and the area of the innermost margin of the left ventricular effective chamber size was quantified with a planimeter. We tested the intraobserver variability of the measurement of left ventricular effective chamber size in a series of 20 patients. The coefficient of variation was 3.7%. In these 20 patients, the correlation coefficient between duplicate measurements was 0.99.

To assess left ventricular geometry, patients were also divided according to the pattern of left ventricular hypertrophy (Fig. 2). In group I (n=24), 6 patients were classified as obstructive-type hypertrophic cardiomyopathy (B), 16 patients were non-obstructive type (C), and 2 patients were so-called apical hypertrophic cardiomyopathy (D). On the other hand, 2 patients were classified as B, 54 patients as C, and 12 patients as D in group II (n=68). The proportion of patients who were classified as B in group I was greater than that in group II.

Assessment of Early Diastolic Time Intervals

We measured early diastolic time intervals as indices of left ventricular diastolic function. As previously reported\textsuperscript{10,12} the echocardiogram, apexcardiogram, and phonocardiogram were recorded simultaneously at a paper speed of 100 mm/sec. All measurements were averaged over five cardiac cycles. The following definitions were used:

1. II\textsubscript{A}-MVO time. The interval from the onset of the aortic component of the second heart sound to the point of mitral valve opening (MVO). This phase corresponds to the isovolumic relaxation time.

2. MVO-O time. The interval from MVO to the O point in the apexcardiogram.

In 28 patients with hypertrophic cardiomyopathy who underwent diagnostic cardiac

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catheterization, relationships between left ventricular effective chamber size and both stroke volume (measured by the dye-dilution method using a cuvette densitometer) and left ventricular end-diastolic pressure were evaluated without medications. As illustrated in Fig. 3, left ventricular effective chamber size correlated positively with stroke volume ($r = 0.63; p < 0.01$) and negatively with left ventricular end-diastolic pressure ($r = -0.54; p < 0.01$). Thus, this index seems to be suitable for reflecting stroke volume and left ventricular end-diastolic pressure in patients with hypertrophic cardiomyopathy.

**Statistical Analysis**

All values are expressed as the mean ± SD. A two-tailed Student's $t$-test was used to compare means, while the chi-square test was used to assess differences in categorical variables. Differences with $p$ values of $<0.05$ were considered significant. Relations between variables were assessed using univariate linear regression analysis and Pearson's correlation coefficient. A correlation coefficient was considered to be significant at $p < 0.05$.

**RESULTS**

**Comparison of Echocardiographic Indices between Group I and Group II**

As shown in Table I, left atrial dimension in group I was markedly greater than that in group II. However, there were no significant differences in either left ventricular wall thickness or left ventricular internal dimension between the 2 groups. Fractional shortening and early diastolic time intervals ($T_{A-MVO}$ and $MVO-O$ times) also showed no significant differences between the 2 groups. The left ventricular effective chamber size in group I ($19.7 ± 2.8 \text{cm}^2$) was significantly smaller than that in group II ($25.1 ± 3.8 \text{cm}^2$) ($p < 0.01$) (Fig. 4). The left ventricular effective chamber size was clearly greater in the normal control than in patients with hypertrophic cardiomyopathy (Fig. 2). Fig. 5 shows the relationship between the left atrial dimension and the left ventricular effective chamber size in patients with hypertrophic cardiomyopathy. A significant negative correlation ($r = -0.68; p < 0.01$) was observed.
between the 2 indices.

The Incidence of Systemic Thromboembolism in Hypertrophic Cardiomyopathy

Eleven patients in group I (46%) had systemic thromboembolism during the follow-up period, whereas none of the patients in group II had systemic thromboembolism. Cerebral embolism occurred in 10 patients and femoral artery embolism occurred in the remaining patient. An average follow-up period of 6.5 years was achieved and the incidence of systemic thromboembolism was 7.1% per patient year in group I. There was no significant difference in the incidence of thromboembolism between patients with transient atrial fibrillation (44%) or persistent atrial fibrillation (50%).

DISCUSSION

The present results indicate that left atrial size in patients with hypertrophic cardiomyopathy is negatively correlated to the effective chamber size of the left ventricle, and that the development of atrial fibrillation is closely related to a smaller left ventricular effective chamber size. This is new evidence regarding the development of atrial fibrillation in hypertrophic cardiomyopathy. In addition, patients with hypertrophic cardiomyopathy who developed atrial fibrillation have a potential risk of systemic thromboembolism.

It is well recognized that papillary muscle hypertrophy is common in hypertrophic cardiomyopathy and the distal cavity of the left ventricle is eliminated by hypertrophied left ventricular wall and papillary muscles. In contrast to the parasternal long-axis view in a normal subject, papillary muscles were clearly observed in patients with hypertrophic cardiomyopathy (Fig. 2). While our method certainly has limitations, left ventricular effective chamber size may be appropriate for assessing the stroke volume in hypertrophic cardiomyopathy. Our data regarding the distribution of hypertrophy show that papillary muscle hypertrophy and a reduction in the left ventricular outflow tract appear to be the major source of small left ventricular effective chamber size.

Considering these morphologic characteristics of the left ventricle, conventional methods using M-mode echocardiography may overestimate left ventricular chamber size in hypertrophic cardiomyopathy. In this study, we found an important association between the area which we designated as the left ventricular effective chamber size and stroke volume, as shown in Fig. 3. Although left ventricular diastolic dimension showed no significant difference between group I and group II, left ventricular effective chamber size was significantly reduced in group I. If we consider that the echocardiographically determined percent fractional shortening showed no significant difference between the 2 groups, cardiac output in group I was low. Thus, smaller left ventricular chamber has a major pathophysiologic significance in the low cardiac output in patients with hypertrophic cardiomyopathy.

The left ventricular effective chamber size was positively correlated with stroke volume and negatively correlated with left ventricular end-diastolic pressure. Thus, smaller left ventricular chamber size in hypertrophic cardiomyopathy reflects a high left ventricular chamber stiffness, which produces a left atrial overload and eventually atrial fibrillation. Atrial fibrillation usually occurs when left ventricular systolic function decreases and left ventricular chamber size enlarges with high left ventricular end-diastolic pressure. However, in patients with hypertrophic cardiomyopathy who develop atrial fibrillation, left ventricular chamber size is very small. This difference in left ventricular chamber size between hypertrophic cardiomyopathy and other heart diseases might be attributed to the qualitative difference in the myocardial characteristics between hypertrophic cardiomyopathy and other heart diseases. Thus, the measurement of left ventricular diastolic dimension may be insufficient for detecting patients with hypertrophic cardiomyopathy who will develop atrial fibrillation.

In addition, atrial fibrillation in hypertrophic cardiomyopathy was independent of age. This finding differs from a previous observation in mitral stenosis that age was an etiological factor in the production of atrial fibrillation. During an average observation period of 6.5 years, 11 thromboembolic events developed in the 24 patients of group I. Most of these thromboembolic events

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affected the brain. The incidence of systemic thromboembolism in group I was 7.1% per patient year, which is similar to that in patients with mitral stenosis who had atrial fibrillation (over 6% per patient year).\textsuperscript{18,19} On the other hand, no thromboembolic events developed in group II. These findings lead us to conclude that atrial fibrillation is a major factor in the development of thromboembolism in patients with hypertrophic cardiomyopathy. The Framingham study\textsuperscript{20} found that stroke was five times more common in patients with atrial fibrillation than in an age-matched group in sinus rhythm. Regardless of the underlying risk factors, intracardiovascular clotting is increased in patients with atrial fibrillation.\textsuperscript{21} Therefore, prophylactic anticoagulant therapy should be recommended to prevent intracardiovascular thrombus in hypertrophic cardiomyopathy patients who may develop atrial fibrillation. A limitation of this retrospective study is the fact that clinical, ECG and ambulatory ECG assessments were performed during routine clinical follow-up and not according to a fixed protocol. Using this clinical follow-up, we cannot totally deny the occurrence of transient atrial fibrillation in group II.

In this study, we also found that the incidence of systemic thromboembolism in patients with transient atrial fibrillation was similar to that in patients with persistent atrial fibrillation. Thus, the duration of atrial fibrillation was not directly related to the risk of thromboembolism. This finding agrees with other observations.\textsuperscript{22,23} We previously reported 2 patients with hypertrophic cardiomyopathy who experienced left atrial mobile thrombus shortly after transient atrial fibrillation.\textsuperscript{8} Morphologic and hemodynamic characteristics in these patients were a small left ventricular chamber, a large left atrium and a low cardiac output. These observations suggest that, in addition to atrial fibrillation, a low cardiac output is an important risk factor for the occurrence and development of left atrial thrombus. The combination of a stagnant blood flow in the left atrium due to atrial fibrillation and a low cardiac output may predispose a patient to thrombus formation.

In conclusion, our results show that small left ventricular chamber size and high left ventricular chamber stiffness in patients with hypertrophic cardiomyopathy produce conditions which may lead to atrial fibrillation. In addition, a high incidence of systemic thromboembolic events was observed in patients with hypertrophic cardiomyopathy who developed atrial fibrillation. Thus, prophylactic anticoagulant therapy should be performed in patients with hypertrophic cardiomyopathy who may develop atrial fibrillation.

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