Clinical Features of Intracardiac Thrombosis Based on Echocardiographic Observation

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The nature of intracardiac thrombi were studied, which were the clinical underlying conditions, relation to systemic embolism, growth of thrombus and effect of anticoagulant therapy on the size of the thrombi, in 818 patients with mitral valve disease and 1000 patients with myocardial infarction by two-dimensional echocardiography. (1) Common underlying conditions were atrial fibrillation, enlarged left atrial cavity and predominance of mitral stenosis in cases with left atrial thrombi, and apical asynergy and low ejection fraction in cases with ventricular thrombi. The blood stasis should be the major factor in the formation of intracardiac thrombi. In a condition of blood stasis, dynamic intracavitary echoes which may represent erythrocyte aggregation were observed. (2) The incidence of systemic embolism in patients with thrombi was higher than that in patients without thrombi in cardiac disease. (3) The intracardiac thrombi were living. They grew and/or reduced their size spontaneously and sometimes became detached from the cardiac wall in the form of ball thrombi. (4) The effect of anticoagulant therapy on the regression of thrombi depends on its age.

ALTHOUGH intracardiac thrombosis may lead to the significant complication of systemic embolism, the life of thrombi has not as yet been determined. Recently, it has been found that intracardiac thrombi can be diagnosed noninvasively with echocardiography.¹⁻⁶ In the present study, the clinical features of left-sided intracardiac thrombosis, which were (1) common underlying conditions, (2) relation to systemic embolism, (3) time of appearance and (4) effect

of anticoagulant therapy on the size of thrombi, were investigated using two-dimensional echocardiography.

SUBJECTS

The subject groups were composed of patients with rheumatic mitral valve disease and those with myocardial infarction.

In rheumatic mitral valve disease, the subjects consisted of 818 patients, 274 males and 544 females, ages 20 to 75 years (average 48.0 years), who received an echocardiographic examination from January 1980 to October 1982. Patients complicated by infective endocarditis were not included in the study. Atrial fibrillation was

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noted in 622 and normal sinus rhythm in the other 196 patients.

In myocardial infarction, the subjects consisted of 1000 patients, 810 males and 180 females, ages 23 to 92 years (average 59.6 years). They underwent an echocardiographic examination from January 1978 to September 1981. Patients with pure non-transmural infarction numbered 60. The site of infarction was the anterior wall of the left ventricle in 527, the inferior in 337, the lateral in 16, and both the anterior and the inferior in 120 patients.

METHODS

The echocardiograph used was a commercially available phased-array system, a Toshiba SSH-11A. The patients were examined in the left recumbent or supine position. The left atrial cavity and left ventricular cavity were examined carefully by shifting, rotating and tilting the transducer, and adjusting the gain control of the equipment if necessary.

The criteria for the echocardiographic diagnosis of intracardiac thrombi were the same as reported previously⁷⁻⁹. The thrombi were diagnosed when a mass echo with clearly defined contour was observed inside of the cardiac cavity, where the endocardial surface echo of the cardiac wall was identified, and when the mass echo concerned was visualized from several positions on the chest wall. According to these criteria, the diagnostic accuracy of the intracardiac thrombi by echocardiography in the preliminary study was as follows: Concerning the diagnosis of thrombi in the left atrial body, left atrial appendage and left ventricular cavity, the sensitivity was 78, 35 and 83%, respectively; the specificity was 100% in all; the predictive value was 96, 86 and 60%, respectively, in patients for whom surgery was performed within 2 weeks after the echocardiographic examination (Table I).

The left atrial dimension was measured as usual from the M-mode echocardiogram in all patients with mitral valve disease.

The left ventricular ejection fraction was calculated using left ventriculography or RI angiography in 576 of the patients with myocardial infarction.

The maximum area of the thrombus echo among the several recordings by various sections was considered to be as the size of thrombus. It was designated as small, medium or large, when the maximum area was under 10 cm², 11–20 cm²

TABLE I ACCURACY OF THE ECHOCARDIOGRAPHIC DIAGNOSIS OF INTRACARDIAC THROMBI

	<i>Left atrium</i>		<i>Ventricle</i>
	<i>Body</i>	<i>APPEND.</i>	
<i>Sensitivity</i>	78	35	83 (%)
<i>Specificity</i>	100	100	100
<i>Predict. Accuracy</i>	100	100	100
<i>Predict. Value</i>	96	86	60

<i>AT surgery</i>						
	(+)	(-)	(+)	(-)	(+)	(-)
<i>2-D (+)</i>	18	0	7	0	10	0
<i>ECHO(-)</i>	5	114	13	79	2	3

<i>LA</i>	<i>Body</i>	<i>LA</i>	<i>APPEND.</i>	<i>LV</i>
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Abbreviations: APPEND. = appendage, 2-D ECHO = two dimensional echocardiography

or over 20 cm², respectively. Growth or reduction of the thrombus was defined as a 15% change in the maximum area of the thrombus echo.

A study of the effect of anticoagulant therapy using warfarin on the size of the thrombus was undertaken retrospectively. Included in the study were the patients who had received echocardiographic examinations at an interval of one month or longer. Patients were also included when the size of the thrombi was changed even if the follow-up period was within one month. The subjects of this study were as follows: In patients with left atrial thrombi, warfarin was administered in 28 and not administered in 27 patients. In patients with left ventricular thrombi, warfarin was administered in 13 and not administered in 28 patients.

RESULTS

1. Incidence of intracardiac thrombi

Left atrial thrombi were noted in 103 of 818 patients (12.6%) with rheumatic mitral valve disease. Atrial fibrillation was shown in all except 2 patients with the left atrial thrombi. Thrombi were noted in 101 of 622 patients (16%) with atrial fibrillation and in 2 of 192 patients (1%) with normal sinus rhythm. The left atrial dimension was 59.5 ± 9.4 mm (average $\pm$ standard deviation) in the patients with thrombi, and 54.3 ± 11.5 mm in the patients without thrombi. The difference was statistically significant ($p < 0.001$).

Fig.1. Relation of the left ventricular ejection fraction to the incidence of the left ventricular thrombus in myocardial infarction. The lower the ejection fraction, the higher the incidence of thrombus.

Fig.2. The dynamic intracavitary echo in the left atrial cavity in mitral valve disease. Sluggish blood flow appears like drifting dregs.

Fig.3. Incidence of left atrial thrombi and their size in patients with dynamic intracavitary echo ("MOYA"). A high rate of incidence of thrombi is shown in patients with a high density of dynamic intracavitary echo.

Mitral regurgitation (MR) was evaluated using left ventriculography in 344 patients on the basis of Seller's criteria, and the average of its grade was 0.8 in 66 patients with thrombi and 1.6 in 278 patients without thrombi (standard deviation was 0.8 and 1.4 respectively). The incidence of left atrial thrombi relative to the grade of MR was as follows: 29, 24, 19% in the patients without MR, with 1st degree MR, and with 2nd degree MR, respectively. None of the patients with 3rd or 4th degree MR had thrombi. When the subjects were limited to those patients with both atrial fibrillation and an enlarged left atrial cavity with a diameter of over 60 mm, but without severe (3rd and 4th degree) MR, left atrial thrombi were observed in 29 of the 58 such patients (50.0%).

Left ventricular thrombi were noted in 89 of the 1000 patients (8.9%) with myocardial infarction (MI); in detail 11.8% of the anterior MI, 0.8% of the inferior MI, 16.8% of the combined cases of anterior and inferior MI, and none of the lateral MI cases. Thrombi were noted at the apical portion where the ventricular wall showed asynergy in all patients. No thrombus existed at the base of the left ventricle, even when the basal portion was a large aneurysm. Among the 576

TABLE II INCIDENCE OF SYSTEMIC EMBOLISM AND INTRACARDIAC THROMBI IN MITRAL VALVE DISEASE AND MYOCARDIAL INFARCTION

Mitral valve disease

		Embolism		
		(+)	(-)	
Thrombi	(+)	40	63	103
	(-)	121	594	715
		161	657	818

Myocardial infarction

		Embolism		
		(+)	(-)	
Thrombi	(+)	10	75	85
	(-)	46	869	915
		56	944	1000

patients examined by left ventriculography or RI angiography, the left ventricular ejection fraction was an average of 47.6% in 519 patients without thrombi (standard deviation was 12.4%), while 35.0% in 57 patients with thrombi (standard deviation was 10.1%). The difference was statistically significant ($p < 0.001$). When the patients were divided into 5 groups according to the left ventricular ejection fraction (under 30%, 30 ~ 39%, 40 ~ 49%, 50 ~ 59% and over 60%), the incidence of thrombi in each group was 19/60, 21/119, 12/149, 4/157 and 1/91 (32, 18, 8, 3 and 1%), respectively, indicating a high incidence of left ventricular thrombi in patients with a low ejection fraction (Fig. 1).

The dynamic intracavitary echoes (like drifting dregs, the so-called "MOYA MOYA" echoes) were demonstrated in the left atrial cavity in some of mitral valve disease patients (Fig. 2). The relationship between the dynamic intracavitary echoes and left atrial thrombs was studied in 116 patients with mitral valve disease, whose echocardiograms were recorded using the same echographic equipment, strip chart recorder (Honeywell FR-06A) and recording chart (Kodak type 1930) in order to avoid variations in the recordings due to equipment. According to the echo density of the dynamic intracavitary echoes, the patients were divided into 3 groups; negative, positive and markedly dense. The incidence of left atrial thrombi in each group was 6/79, 7/27

Fig.4. The first detection of the left ventricular thrombus following the onset of myocardial infarction. (Recurrent myocardial infarction patients were excluded.) The thrombus was formed within 4 weeks after the onset in one half of the patients, but sometimes first appeared at a much later stage of infarction. abbreviation. D = day, W = week, M = month, Y = year

Fig.5. Effect of anticoagulant therapy on the size of intracardiac thrombi in mitral valve disease and myocardial infarction. White, oblique lines and crosshatched columns indicate increase, no change and decrease in size, respectively.

and 6/10 patients (8%, 26% and 60%), respectively, showing a high prevalence of thrombi in patients with the dynamic intracavitary echoes. The size of thrombus tended to be large in the markedly dense group (Fig. 3).

2. Timing of the appearance of thrombus

The timing of the appearance of thrombi was examined retrospectively in 55 patients with left ventricular thrombi who had no recurrent episodes of acute myocardial infarction. In the initial echocardiographic examination after infarction, an absence of left ventricular thrombus was found in 21 of the 55 patients. The thrombi were detected at an early stage within 4 weeks in 26 patients. In one patient, a thrombus was detected just on the first day of his illness. On the other hand, in some patients, new thrombi were shown quite long after the onset of myocardial infarction (Fig. 4).

3. Systemic embolism

In rheumatic mitral valve disease, systemic embolism was noted in 40 of the 103 patients with the left atrial thrombi (39%), in 121 of the 715 patients without thrombi (17%), and in 20% of all 818 patients (Table II). Even in the 196 patients with normal sinus rhythm, systemic embolism was noted in 16 (8%). From a different point of view, left atrial thrombi were demonstrated in 25% of the 161 patients with systemic embolism and in 10% of the 657 patients without systemic embolism (Table II). Among 103 thrombi in the left atrial cavity, 12 thrombi were mobile. Nine of them were pedunculate showing undulating motion with heart beat, and the others were ball thrombi. Systemic embolism was noted in 9 of these patients, in 8 of which, cerebral embolism was noted within 4 weeks before or after the thrombus was detected. All of 3 patients with ball thrombus suffered from cerebral embolism. Two of them died due to systemic shower embolism within a few days after the detection of the ball thrombus.

In myocardial infarction, systemic embolism had been noted in 56 patients (5.6%); in 10 of the 85 patients with left ventricular thrombi (12%) and in 46 of the 915 patients without thrombi (5%). Thrombi were detected in 17.5% of the patients with systemic embolism (Table II).

4. Anticoagulant therapy

The effect of the anticoagulant therapy on the size of thrombus using warfarin was examined.

Among the cases with left atrial thrombi, the thrombi were reduced in 29%, unchanged in 57% and enlarged in 14% of the warfarin group, while reduction, no change and growth of the thrombi was demonstrated in 19, 62 and 19% of the non-warfarin group, respectively. There was no significant difference in reference to the change of thrombus size between these two groups (using the Chi-square test) (Fig. 5). It was significant that a large mobile, but pedunculate thrombus became a ball thrombus, without changing in size, within 20 days during the warfarin therapy. On the other hand, in the cases with left ventricular thrombi, reduction of thrombi was found in 77%, no change in 23% and growth in none of the warfarin group, and 21, 65 and 14% of the non-warfarin group, respectively. There was a significant difference in reference to the change of thrombus size between the two groups (using the Chi-square test) (Fig. 5).

DISCUSSION

1. Accuracy of echocardiographic diagnosis of intracardiac thrombi

The aim of the present study was to investigate the life of intracardiac thrombi, and repeated examinations were needed. In the present study, echocardiography was used because this modality is noninvasive and is best in follow-up studies. However, the echocardiographic criteria of the diagnosis of thrombi were necessarily strict enough to avoid a false positive in any cavity of the heart. The assessment of the growth and reduction of the thrombi, especially, had to be certain. In the preliminary study, the accuracy of echocardiographic diagnosis of thrombi was satisfactory except in the case of thrombi in the left atrial appendage. There was no false positive case in any of the intracardiac cavities. Echocardiographic examination was considered to be sufficient for the present study. The patients were limited to those in which the interval from the echocardiographic study to surgery was within 2 weeks in the preliminary study. This was the reason for the seemingly rapid growth of thrombus as shown in the results of the present study.

2. Blood stasis and thrombosis

Virchow stated that injury of the vessel wall, change of the characteristics of the blood and stasis of the blood flow were the triad of the thrombus formation. In the present study, the

significance of the blood stasis was impressive. The high prevalence of the left atrial thrombi was found accompanied by atrial fibrillation,^{10, 11} predominance of mitral stenosis, and an enlarged left atrial cavity, all of which induce blood stasis. Even if a patient with mitral valve disease showed atrial fibrillation and a giant left atrium, there was no left atrial thrombi when mitral regurgitation was severe. This fact indicates that the stirring of the blood by the mitral regurgitant jet prevents the formation of thrombi.

The underlying conditions of the left ventricular thrombi were the same as those of the left atrial thrombi. The site of the thrombus formation was the asynergic area due to myocardial infarction and, also, localized in the apical region where the blood was not so much moved by the inflow and outflow streams.^{12, 13} No thrombi were found in patients with inferior myocardial infarction, although damage to the endocardial surface was considered to be the same as that in patients with anterior infarction. Moreover, a high incidence of left ventricular thrombi was shown in patients with a low ejection fraction. These facts indicate that the formation of the thrombi is closely related to blood stasis.

We have reported that in clinical and experimental studies the dynamic intracavitary echoes appear with the stagnation of the blood flow^{14, 15} and indicated that the echo source of the dynamic intracavitary echoes was assumed to be aggregated erythrocytes.¹⁴ Erythrocyte aggregation will certainly promote the thrombus formation. These relations may be the reason why a high incidence of left atrial thrombi was shown in patients with dynamic intracavitary echoes. Similar phenomena were observed in the left ventricular cavity in cases with myocardial infarction.¹⁶

3. Birth of thrombi

There is no established theory about the time of the birth of intracardiac thrombus. However, thrombi are thought to be formed not gradually, but comparatively rapidly. In myocardial infarction, in which the blood flow suddenly becomes stagnant, left ventricular thrombi have been shown by echocardiography to be formed soon after the onset of infarction.^{13, 16} However, it is important to recognize that these left ventricular thrombi are formed for the first time *even at a much later stage*.

4. Systemic embolism

Systemic embolism is a fatal complication of

intracardiac thrombosis. The incidence of systemic embolism in patients with thrombi was higher than in patients without thrombi in both mitral valve disease and myocardial infarction. However, patients with both an embolic episode and thrombi appear to be few, indicating that the thrombi detected by echocardiography are not always the embolic source. Undetectable tiny thrombi may play a large part in systemic embolism. Further investigation is needed about the genesis, incidence and clinical course of undetectable and fragile thrombi.

As expected, the mobile thrombi in the left atrium showed high risk of systemic embolism.¹⁷⁻²⁰ Especially, ball thrombus may be equated with fatal thrombus. The echocardiographic examination may be the best for diagnosing it accurately and quickly. It is noteworthy and clinically important that the mobile, but pedunculate thrombi became a ball thrombus in a short period after the administration of warfarin.

5. Effect of anticoagulant therapy

There have been some reports about the effect of anticoagulant therapy on systemic embolism^{11, 21} but none on the size of the intracardiac thrombi. It is noteworthy that the effect of anticoagulant therapy using warfarin was different between the left atrial thrombi in mitral valve disease and the left ventricular thrombi in myocardial infarction. Some thrombi grew and some were reduced in size spontaneously. In mitral valve disease, warfarin did not alter the growth or reduction of thrombi. In myocardial infarction, on the other hand, warfarin did reduce the size of the thrombi. What is the cause of this different effect on the thrombus size between two types of cardiac disease? Most of thrombi in mitral valve disease are old and organized, while most of thrombi in myocardial infarction are fresh and not organized. The effect of anticoagulant therapy may depend on the age of thrombus. Further investigation is needed to diagnose whether the thrombi are fresh or organized.

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