

## Does Mitral Regurgitant Flow Affect Left Atrial Thrombus Formation in Patients with or without Atrial Fibrillation ?

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**Abstract :** The aim of this study was to examine whether the presence of mitral regurgitation (MR) affects left atrial thrombus (LAT) formation in patients with or without atrial fibrillation (AF). The frequency of LAT formation detected with transesophageal echocardiography was significantly lower in the subjects with sinus rhythm (18/447) in comparison to that of AF patients (82/150). A single factor analysis for whole subjects revealed that higher age, the existence of AF, greater left atrial and left ventricular systolic diameters, and a lower ejection fraction were all associated with LAT formation, whereas a stepwise multiple regression analysis revealed that a low ejection fraction alone was an independent contributor for LAT formation. Among the patients with AF, none of the echocardiographic parameters showed any significant influence on LAT formation, however, the existence, but not the severity, of MR slightly decreased the incidence of LAT formation, whereas, in patients with sinus rhythm, a left ventricular dysfunction appeared to be a contributing factor to LAT formation.

**Key words :** transesophageal echocardiography, cardiac function, sinus rhythm, atrial fibrillation

### Introduction

LAT formation in patients with atrial fibrillation (AF) is a fatal clinical problem associated with systemic embolization.<sup>1)</sup> Several studies have shown a close relationship between AF and left atrial thrombus (LAT) formation. However, it remains inconclusive whether the regurgitant flow due to mitral regurgitation (MR) is inhibitory for LAT formation.<sup>2)-7)</sup> In the present study, we examined

the effect of MR and its severity on LAT formation in Japanese patients with or without AF.

### Methods

#### *Study Subjects*

Non-rheumatic patients (415 males and 182 females) were selected from 752 subjects who had undergone transesophageal echocardiography (TEE) at Fukuoka University Hospital between April 1993 and March 1996. The patients suffered from obvi-

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Foot notes

AF, atrial fibrillation ; LAT, Left atrial thrombus ; TEE, transesophageal echocardiography ; TTE, transthoracic echocardiography

ous rheumatic valvular heart diseases based on past history, multiple valvular disease diagnosed by transthoracic echocardiography (TTE) and TEE were not included. Furthermore, the following exclusion criteria were applied : poor visualization on TTE or TEE, insufficient echocardiographic data, or the presence of spontaneous echo contrast in a TEE analysis. Spontaneous echo contrast was noted in 6 (1.0%) patients ; this pattern is known to closely related to LAT.<sup>(6)(8) - 13)</sup> Since it was rather difficult to distinguish spontaneous echo contrast from a real LAT, subjects with spontaneous echo contrast were excluded from the present study.

Among the 597 patients, 447 subjects were in sinus rhythm at the time of admission to the hospital without a history of sustained or paroxysmal AF as diagnosed by a routine ECG or Holter ECG. The remaining 150 subjects had been previously diagnosed to have AF (defined as an episode that lasted all day based on 24-hours ECG). Informed consent for participation in this study was obtained from all subjects prior to performing the echocardiographical examinations.

### **Echocardiography**

TTE and TEE were performed in all subjects using commercially available equipment (Aloka SSD-870, Toshiba SSH-140). Lead II recording was used to monitor electrocardiograms, TTE was performed before TEE in all patients with 2.5 or 3.5 MHz transducer and TEE was performed with a 5 MHz biplane transesophageal probe (9 mm in diameter and 100 cm in length). TTE studies included a standard parasternal long - axis, apical two-chamber and apical four-chamber views using a 2.5 MHz transducer. The diameters of the left atrium, the aorta, and the left ventricle (LV) as well as the wall thickness were measured according to the American Society of Echocardiography guidelines.<sup>14)</sup> The severity of MR was scored quantitatively according to conventional Doppler flow-mapping criteria in TTE.<sup>15)</sup> A four-point scale was used to designate determine the severity of regurgitation by mapping the systolic turbulent flow within the left atrium in the parasternal long-axis or apical four-chamber view (Fig. 1). The severity of MR was classified as absent (0 or I), mild

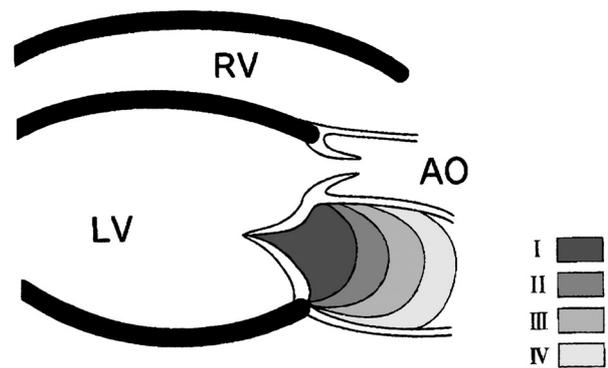


Fig. 1 Quantitation of mitral regurgitation using color doppler mapping.  
RV, right ventricle ; LV, left ventricle ; AO, aorta.

(II), moderate (III), or severe (IV) because grade I regurgitation has been found in patients without valvular MR.

The presence of LAT was evaluated by TEE. After at least a 4-hours fast, the patients were sedated with an intravenous injection of 15 mg pentazocine and 10 mg diazepam, they then received an intramuscular injection of 20 mg scopolamine. TEE was usually performed with the patients in the left lateral decubitus position. A transesophageal probe was introduced after the upper pharyngeal region had been anesthetized with 8% xylocaine spray. Cardiac images were obtained in the transesophageal position. The left atrium and the left atrial appendage were inspected closely for the presence of LAT. We defined LAT as a well-circumscribed echogenic mass, distinct from the atrial wall, which was consistently recognized in several views. Spontaneous echo contrast was defined as the presence of diffuse smoke-like echoes present the atrium. Echocardiographic examinations were recorded on videotape and reviewed independently by three echocardiographers.

### **Statistical analysis**

The analyzed data were presented as the mean  $\pm$ SD. A one way-analysis of variance (ANOVA) was used to compare echocardiographical parameters in patients with or without LAT. The chi-square test was used to analyze the effect of MR or its severity on LAT formation. A two-tailed p value less than 0.05 was regarded as statistically

significant. The interaction between AF and LAT was examined by multiple regression analysis. A multiple regression analysis was used to evaluate the interaction between the presence or absence of AF and the grade of MR. Statistical were performed using the Statistical Analysis System (SAS).<sup>16)</sup>

## Results

LAT was identified in 100 (17%) of the 597 patients by TEE, but not at all by TTE. When the analysis was performed on all patients examined, two clinical parameters were found to be significantly different between the subjects with or without LAT. These were age ( $64 \pm 12$  vs.  $61 \pm 11$  years,  $p < 0.05$ ) and the prevalence of AF (82 vs. 14%,  $p < 0.01$ ). Among echocardiographic parameters, the left atrial diameter and ventricular systolic diameter were significantly greater in the patients with LAT than in those without (Table 1). The

EF was significantly lower in patients with LAT. These differences were further examined by a stepwise multiple regression analysis which identified only a low EF ( $p < 0.05$ ), as an independent contributor for LAT formation (Table 2).

In patients with sinus rhythm, LAT was found in 18 subjects (4%), whereas in patients with AF, LAT was detected 82 patients (67%,  $p < 0.01$ ). Based on these data, the participating patients were divided into two groups, namely those with a sinus rhythm and the those with AF. In the patients with a sinus rhythm, the systolic LV diameter was significantly larger in those with LAT. EF in patients with LAT was smaller than those without LAT (Table 3). On the other hand, in patients with AF, there was no significant difference in TTE parameters in those with or without LAT.

We also determined the effect of MR on LAT formation in patients with or without AF, independently by a chi-square analysis. The first analysis was for the effect of MR itself and the

**Table 1.** Transthoracic echocardiographic parameters (M-mode) relative to the left atrial thrombus

Variable	LAT absent	LAT present	p-value*
n	497	100	
Aortic diameter (mm)	$32.3 \pm 4.7$	$32.9 \pm 4.5$	0.23
Left atrial diameter (mm)	$36.8 \pm 8.8$	$43.2 \pm 8.4$	$< 0.01$
LV diastolic diameter	$49.7 \pm 8.8$	$50.9 \pm 7.6$	0.19
LV systolic diameter (mm)	$31.5 \pm 9.2$	$35.5 \pm 9.7$	$< 0.01$
Thickness of IVS (mm)	$9.9 \pm 2.1$	$9.6 \pm 1.8$	0.23
Thickness of LVPW (mm)	$9.7 \pm 1.9$	$9.6 \pm 1.6$	0.87
Ejection fraction (%)	$72.6 \pm 13.0$	$65.7 \pm 15.5$	$< 0.01$
Fractional shortning (%)	$37.2 \pm 11.1$	$30.8 \pm 14.5$	0.87

LV : left ventricle, IVS : interventricular septum, LVPW : left ventricular posterior wall  
Data are expressed as the mean  $\pm$  SD

\* : unpaired t-test

**Table 2.** Multiple logistic regression analysis of several clinical parameters on left atrial thrombus (LAT) formation

Variable	Oddsratio	CI	p-value
Age	1.01	0.99–1.04	0.39
Sex (male vs female)	0.99	0.54–1.82	0.98
AF	35.21	0.81–1537.51	0.06
MR grade	0.75	0.53–1.07	0.11
Left atrial diameter	1.05	0.99–1.12	0.10
Ejection fraction	0.96	0.987–1.00	0.01

CI, 95% confidence interval ; AF, atrial fibrillation ; MR, mitral regurgitation

second was for the effect of MR severity (Table 4). These analyses were performed separately in patients with or without AF. The existence of MR slightly, but not significantly, decreased LAT formation only in patients with AF. Furthermore, the severity (mild, moderate, or severe) of MR did not affect the incidence of LAT in patients with sinus rhythm and with AF. In a separate analysis, in order to examine the effect of higher or lower stirring effect of MR flow on LAT formation, whole patients were recategorized into 2 groups consisting of 1) a lower degree of MR (absent or mild degree) of and 2) a higher degree of MR (moderate to severe). Next, the same analyses were performed, but we could not find any protective effect of a higher MR flow on LAT formation in both patient categories (data not shown).

### Discussion

The use of TEE has significantly improved the detection of LAT, which may be associated with fatal thromboembolism.<sup>17)18)</sup> Therefore, the detection of clinical parameters that promote LAT formation is an important clinical target. Our study reconfirmed that the systolic dysfunction and AF *per se* increase the incidence of LAT formation.

A statistical analysis of the data of the entire group showed that the regurgitant flow due to MR did not significantly affect the incidence of LAT. Our results indicated that the factors contributing to LAT formation might differ in patients with or without AF. Since AF has a potent independent effect on LAT formation as shown in both the present and previous studies,<sup>6)8)</sup> the relationship between MR-associated regurgitant flow and LAT formation in AF may be different from that in patients with sinus rhythm. If left atrial stasis is

Table 3. Echocardiographic parameters in the patients in sinus rhythm or with atrial fibrillation

Parameters	Sinus rhythm		p*	atrial fibrillation		p*
	LAT (-) n=429	LAT (+) n=18		LAT (-) n=68	LAT (+) n=82	
Aortic diameter (mm)	32.2±4.8	32.9±4.3	0.56	33.0±4.4	33.0±4.6	0.93
Left atrial diameter (mm)	35.3±7.6	38.1±5.6	0.12	46.0±10.1	44.3±8.6	0.22
LV diastolic diameter (mm)	49.3±8.6	52.6±10.6	0.12	52.0±9.5	50.6±6.8	0.30
LV systolic diameter (mm)	30.9±9.1	36.5±14.4	0.01	35.2±9.2	35.2±8.4	0.99
Thickness of IVS (mm)	9.8±2.1	9.6±2.3	0.57	10.0±2.1	9.6±1.7	0.25
Thickness of LVPW (mm)	9.6±1.8	9.8±2.0	0.73	9.9±2.0	9.6±1.7	0.28
Ejection fraction (%)	73.7±12.4	65.9±19.9	0.01	65.5±14.5	65.7±14.5	0.95
Fractional shortening (%)	38.0±11.1	32.7±13.8	0.53	32.7±9.7	30.4±14.6	0.27

Values are the mean±SD. LV : left ventricle, IVS : interventricular septum wall, LVPW : left ventricular posterior wall  
\*Unpaired t-test.

Table 4. Incidence of left atrial thrombus (LAT) among the different severity grades of mitral regurgitation (MR)

MR Severity	Patient category			
	Sinus rhythm		Atrial fibrillation	
Absent	14/356	(3.9)	50/81	(61.7)
Present	4/91	(4.4)	32/69	(46.4)*
Mild	2/59	(3.4)	18/40	(45.0)
Moderate	2/21	(9.5)	11/23	(47.8)
Severe	0/11	(0)	3/6	(50)

Numbers in brackets are the percentages. \*,  $\chi^2$ p=0.08 v.s. MR absent group.

the essential mechanism for LAT formation, existence of MR and its severity should not have a major impact on LAT formation in patients with sinus rhythm, in which atrial stasis is unlikely to be a major problem. Our study showed that a larger left systolic ventricular diameter and lower ejection fraction had an independent effect on LAT formation in the patients with sinus rhythm. Although only few subjects had LAT with a sinus rhythm (n=22), our data suggested that a cardiac dysfunction has a greater impact on LAT formation than the presence of MR.

In patients with AF, however, there were no marked differences in the echocardiographic parameters associated with LAT formation. This finding indicates that AF itself is a strong independent contributor for LAT formation. Our data further suggested that the existence of MR slightly, but not significantly, decreased the incidence of LAT formation in patients with AF. On the other hand, the severity of MR did not affect the incidence of LAT formation. These findings suggest that the stirring effect of MR does not have a protective effect on LAT formation in patients with AF, where atrial stasis appears to be a major determinant of LAT formation. Therefore, it is critically important for patients with AF to take anti-coagulation drugs regardless of existence of MR.

To explain the tendency for the inhibitory effect of MR on LAT formation, one may think about other factors such as the direction of the regurgitant flow, which may affect the local blood status in the left atrial appendage. In this study, however, the direction of the regurgitant MR flow was not analyzed. This problem should be considered in future studies.

Although a number of previous studies showed that MR has an inhibitory effect on LAT formation and thromboembolic events,<sup>2)-5)</sup> other studies have showed no association between MR and LAT formation.<sup>6)7)19)</sup> One of the reasons explaining the discrepancy between these studies could be patient selection. In the present study, broad selection criteria were applied for patient selection. For example, patients with rheumatic heart disease including mitral stenosis, and aortic regurgitation and stenosis were excluded to eliminate the effects of

any changes associated with rheumatic valvular diseases. Furthermore, LAT identified by TEE was the criterion used for the study incorporation and spontaneous echo contrast was excluded to avoid a false positive LAT by TTE. Such study management was necessary to compare the effect of MR in patients with and without AF.

LAT was found in a relatively large number of patients with sinus rhythm (18/447, 4%). This frequency was similar to that of previous studies.<sup>19)-21)</sup> However, the total number of patients examined in previous studies was at most 50, and no statistical comparison between the patients with or without LAT was performed. To our knowledge, this is the first report to show a difference in the echocardiographic parameters between patients with or without LAT in sinus rhythm. However, the results regarding this issue were not surprising because the parameters contributing to LAT formation in patients with sinus rhythm were not novel. A left ventricular dysfunction was the major determinant of LAT formation, which correlated with the results of previous studies.<sup>1)22)</sup>

### Conclusions

AF appeared to be an independent contributor to the development of LAT in patients without rheumatic valvular heart diseases. Among the patients with AF, none of echocardiographic parameters had any significant influence on LAT formation. In addition, the existence or its severity of MR did not significantly protect LAT formation, whereas left ventricular dysfunction appears to be an important factor contributing to LAT formation in patients with a sinus rhythm.

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