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Left Atrial Appendage Function In Patients with Mitral Stenosis in Sinus Rhythm

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Aims: Left atrial appendage thrombi are believed to be the source of embolism in patients with rheumatic mitral stenosis in atrial fibrillation. There are a few studies which search the effects of left atrial appendage dysfunction in patients with mitral stenosis in sinus rhythm.

Methods and Results: Left atrial appendage function and flow patterns in 41 patients with rheumatic mitral stenosis in sinus rhythm and 11 healthy subjects were studied by transoesophageal echocardiography. Left atrial appendage flow profiles were recorded within the proximal third of the appendage. The left atrial appendage ejection fraction was expressed as (maximal area of appendage minimal area of appendage)/maximal area of appendage. In addition, two-dimensional imaging was used to determine the presence of spontaneous echocardiographic contrast and thrombus formation. Patients with mitral stenosis in sinus rhythm had significantly decreased left atrial appendage emptying and filling velocities compared to controls ($0{\cdot}40 \pm 0{\cdot}15$ m/s vs $0{\cdot}82 \pm 0{\cdot}19$ m/s and $0{\cdot}42 \pm 0{\cdot}21$ m/s vs $0{\cdot}68 \pm 0{\cdot}28$, respectively, $P<0{\cdot}001$ and $P<0{\cdot}05$). Compared with the control subjects, patients with mitral stenosis had significantly greater maximal area of the appendage and had reduced left atrial appendage ejection fraction ($5{\cdot}3 \pm 2{\cdot}2$ cm^2 vs $2{\cdot}4 \pm 0{\cdot}5$ cm^2 and $50 \pm 16\%$ vs $70 \pm 7\%$, respectively, $P<0{\cdot}001$ and $P<0{\cdot}05$). Of the patients with mitral stenosis in sinus rhythm, seven patients had spontaneous echocardiographic contrast and one of these had left atrial appendage thrombus. Compared with patients without spontaneous echocardiographic contrast, patients with spontaneous echocardiographic contrast had decreased left atrial appendage ejection fraction ($33 \pm 21\%$ vs $54 \pm 13\%$, $P<0{\cdot}01$). One of the patients with mitral stenosis had central retinal artery occlusion, but thrombus was not observed in left atrial appendage.

Conclusion: The study found that left atrial appendage dysfunction may occur in patients with mitral stenosis in sinus rhythm.

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Key Words: Mitral stenosis; left atrial appendage; sinus rhythm; thrombus.

Introduction

Cardiogenic embolism accounts for an important number of ischaemic strokes. Especially, left atrial and left atrial appendage thrombi are important sources of embolism[1]. Left atrial appendage is a blind-ended pouch and usually has a multilobed anatomic structure. Effective blood flow in the appendage cavity prevents thrombus formation[2], but various pathophysiologic states like atrial fibrillation and/or rheumatic mitral valve disease may cause left atrial appendage dysfunction which is known as an important risk factor in thrombus formation[3–5]. Therefore attention has been focused recently on the detection of left atrial appendage function by transoesophageal echocardiography to assess the risk of thrombus formation. Most of these studies have been conducted in patients with atrial fibrillation and mitral valve disease or stroke[3–6]. However, studies about the role of left atrial appendage function in patients with rheumatic mitral valve disease in sinus rhythm are limited[7,8]. Our study was designed to examine left atrial appendage function in patients with rheumatic mitral stenosis in sinus rhythm and to define relation between left atrial appendage function

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and thrombus and/or spontaneous echo contrast in the left atrial appendage cavity in these patients.

Methods

A total of 56 patients with rheumatic mitral valve disease in sinus rhythm were enrolled into the study. Fifteen patients with moderate or severe mitral regurgitation were excluded. Forty-one patients (32 female, nine male, mean age of 41 ± 9 years) with mitral stenosis in sinus rhythm were assessed. These patients underwent clinical, electrocardiographic, roentgenologic, transthoracic and transoesophageal echocardiographic examinations. None of the patients was receiving oral anticoagulants or antiplatelets at the time of the study. Age- and gender-matched (seven female, four male, mean age of 34 ± 10 years) 11 healthy subjects were included in the study as a control group who had normal transthoracic and transoesophageal echocardiographic examinations and none had cardioembolic disease history. Presence of sinus rhythm was confirmed by 12-lead electrocardiograms in all patients.

Echocardiography

Transthoracic studies were performed with GE Vingmed system fiVe and a 2·5 MHz transducer. Left ventricle end-diastolic and end-systolic diameters and end-systolic left atrial diameter were measured from M-mode in the parasternal long axis views[9]. Mitral stenosis was quantified by planimetry of two-dimensional images, Doppler measurement of transvalvular gradients, and estimation of valve area by the pressure half-time method[10–12]. The mean transmitral pressure gradient was calculated from the maximal transvalvular flow velocity using modified Bernoulli equation[12]. Mitral regurgitation was categorized semiquantitatively on the basis of the size of the Doppler colour flow area (0= absent, 1=trivial, 2=mild, 3=moderate, 4=severe) and patients with mitral regurgitation above grade 2 were excluded from the study.

Transoesophageal studies were performed with a 5 MHz multiplane transducer. Lidocaine was used for local anaesthesia of the hypopharynx. Left atrial appendage was visualized from the horizontal short-axis view at the base of the heart and the two-chamber longitudinal view of the left atrium and the ventricle. The presence of spontaneous echo contrast and thrombus in the left atrium and left atrial appendage was carefully searched. Blood flow velocities were assessed with pulsed Doppler by placing the sample volume within the proximal third of the appendage and so that peak emptying and filling Doppler waves of the left atrial appendage were measured (Fig. 1). The values of three measurements in consecutive cardiac cycles were averaged. The area of the left atrial appendage was measured by computer-assisted planimetry from the two-dimensional echocardiographic images at the orifice of the appendage in the transverse view, immediately before mitral valve opening (left atrial appendage max), at atrial end-diastole (after mitral valve opening but before left atrial appendage contraction), and at atrial end-systole [minimum diameter observed after the *P* wave (left atrial appendage min)]. Left atrial appendage ejection fraction (%) was calculated by using the formula: [(left atrial appendage maximum area–left atrial appendage minimum area)/left atrial appendage maximum area] × 100.

Statistical Analysis

Data were analysed with the SPSS for Windows statistical package and are presented as mean ± SD. Differences between mean values were analysed by Student's unpaired *t*-test. The Chi-square test and Fischer's probability test were used to compare proportions. Differences were considered significant when $P<0{\cdot}05$.

Results

Patients with mitral stenosis in sinus rhythm did not differ significantly from the control group regarding age, sex and body surface area. Clinical and echocardiographic characteristics of the patients and control group are shown in Table 1. Left atrial appendage spontaneous echo contrast was detected in seven (17%) of the 41 patients with rheumatic mitral stenosis in sinus rhythm by transoesophageal echocardiography. One of the patients who had grade 2 spontaneous echocardiographic contrast had also thrombus in the left atrial appendage cavity. One patient had history of left central retinal artery emboli, no thrombus was found in the left atrial appendage or left atrium of this patient, but grade 2 spontaneous echocardiographic contrast was present. As shown in Table 1, patients with mitral stenosis in sinus rhythm had significantly lower left atrial appendage peak emptying and filling velocities and lower left atrial appendage ejection fraction than control subjects ($0{\cdot}40 \pm 0{\cdot}15$ m/s vs $0{\cdot}82 \pm 0{\cdot}19$ m/s and $0{\cdot}42 \pm 0{\cdot}21$ m/s vs $0{\cdot}68 \pm 0{\cdot}28$, and $50 \pm 16\%$ vs $70 \pm 7\%$ respectively, $P<0{\cdot}001$ and $P<0{\cdot}05$, and $P<0{\cdot}05$). Also, left atrial appendage maximal and minimal area of the patients were larger than that of the control subjects ($5{\cdot}3 \pm 2{\cdot}2$ cm^2 vs $2{\cdot}4 \pm 0{\cdot}5$ cm^2 and $2{\cdot}8 \pm 2{\cdot}0$ cm^2 vs $0{\cdot}7 \pm 0{\cdot}2$ cm^2 respectively, $P<0{\cdot}001$). In the study group patients with mitral valve area less than or equal to $1{\cdot}5$ cm^2 had significantly lower left atrial appendage peak emptying velocities compared to patients with mitral valve area larger than $1{\cdot}5$ cm^2 ($0{\cdot}32 \pm 0{\cdot}07$ m/s vs $0{\cdot}48 \pm 0{\cdot}16$ m/s, $P<0{\cdot}001$). In addition, left atrial appendage function was compared in patients with and without spontaneous echo contrast (Table 2). left atrial appendage peak emptying velocities and left atrial

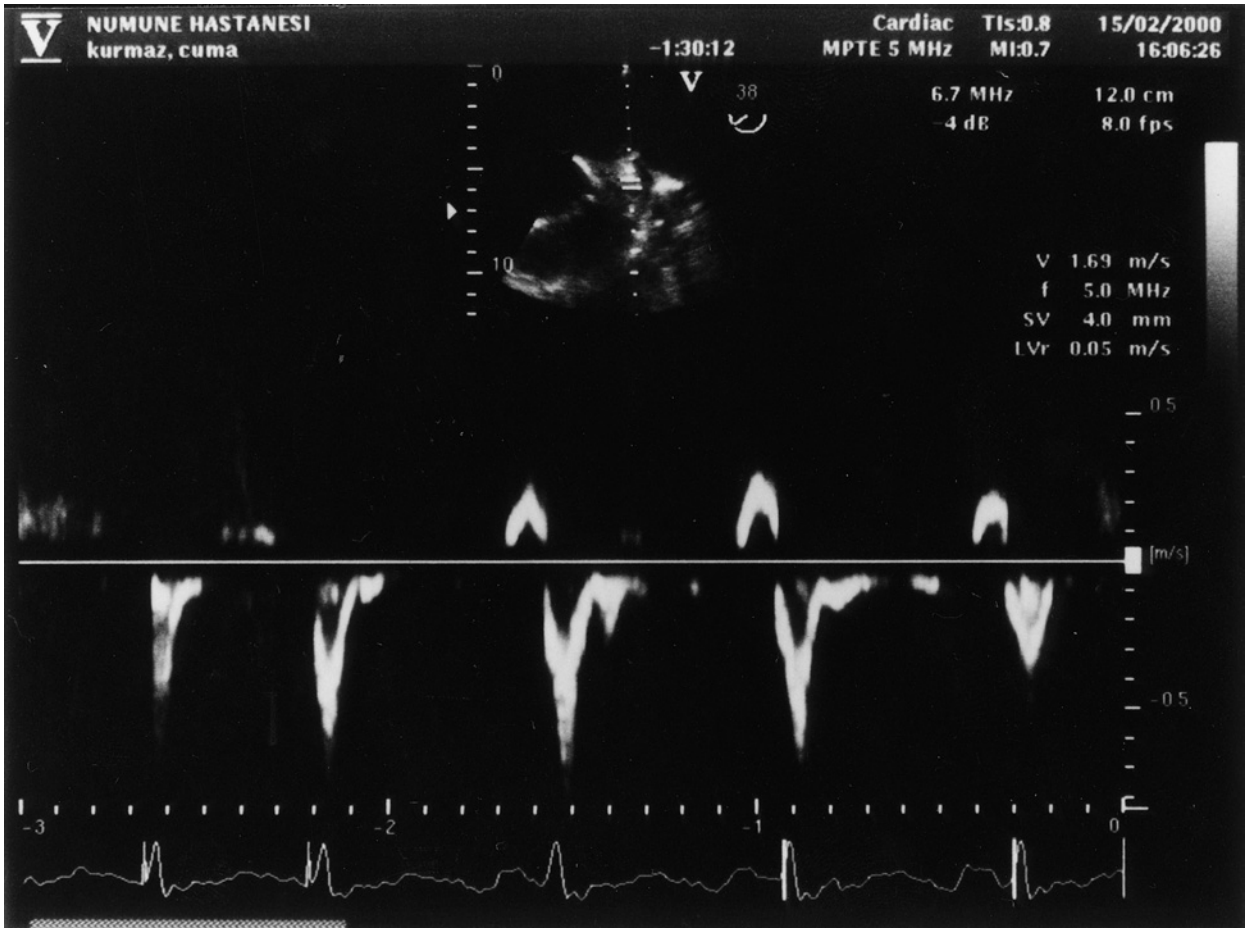

Figure 1. Reduced left atrial appendage peak emptying and filling velocities in a patient with mitral stenosis in sinus rhythm who had spontaneous echo contrast.

appendage ejection fractions were found to be lower in patients with spontaneous echo contrast ($0{\cdot}27 \pm 0{\cdot}1$ m/s vs $0{\cdot}45 \pm 0{\cdot}1$ m/s and $33 \pm 21\%$ vs $54 \pm 13\%$, respectively, $P<0{\cdot}01$ and $P<0{\cdot}05$). Patients with spontaneous echo contrast had greater mean transmitral pressure gradient and smaller mitral valve area as compared with the patients without spontaneous echo contrast ($12{\cdot}1 \pm 3{\cdot}9$ mmHg vs $7{\cdot}3 \pm 2{\cdot}9$ mmHg and $1{\cdot}2 \pm 0{\cdot}2$ cm^2 vs $1{\cdot}9 \pm 0{\cdot}9$ cm^2, respectively, $P<0{\cdot}05$ and $P<0{\cdot}001$). In addition, no correlation was observed between spontaneous echo contrast and left ventricular ejection fraction or left atrial area.

Discussion

Left atrial appendage is a small muscular sac of atrial wall and frequent location of thrombus formation in patients with mitral valve disease. In this study, we found that patients with mitral stenosis in sinus rhythm had left atrial appendage contractile dysfunction compared with normal subjects. Furthermore, patients with spontaneous echo contrast had marked left atrial

Table 1. The clinical and echocardiographic characteristics of patients and control group.

	Patients (n=41)	Control (n=11)
Characteristics		
Age (years)	41 ± 9	34 ± 10
Sex (female/male)	32/9	7/4
Body surface area (m^2)	$1{\cdot}7 \pm 0{\cdot}2$	$1{\cdot}6 \pm 0{\cdot}1$
Transthoracic echocardiography		
Mitral valve area (cm^2)	$1{\cdot}8 \pm 0{\cdot}6$	
Mean diastolic gradient (mmHg)	$8{\cdot}3 \pm 3{\cdot}6$	
Left atrial diameter (cm)	$4{\cdot}8 \pm 0{\cdot}7$	
Thrombus	1	
Spontaneous echo contrast	7	
Mitral regurgitation (absent/trivial/mild)	24/5/12	
Transoesophageal echocardiography		
LAA peak emptying velocity (m/s)	$0{\cdot}40 \pm 0{\cdot}15$*	$0{\cdot}82 \pm 0{\cdot}19$
LAA peak filling velocity (m/s)	$0{\cdot}42 \pm 0{\cdot}21$**	$0{\cdot}68 \pm 0{\cdot}28$
LAA maximal area (cm^2)	$5{\cdot}3 \pm 2{\cdot}2$*	$2{\cdot}4 \pm 0{\cdot}5$
LAA minimal area (cm^2)	$2{\cdot}8 \pm 2{\cdot}0$*	$0{\cdot}7 \pm 0{\cdot}2$
LAA ejection fraction (%)	50 ± 16**	70 ± 7

*$P<0{\cdot}001$, **$P<0{\cdot}05$, LAA=left atrial appendage.

Table 2. Echocardiographic characteristics of patients with and without spontaneous echo contrast.

	Present ($n=7$)	Absent ($n=34$)
LAA peak emptying velocity (m/s)	$0{\cdot}27 \pm 0{\cdot}1$*	$0{\cdot}45 \pm 0{\cdot}1$
LAA peak filling velocity (m/s)	$0{\cdot}36 \pm 0{\cdot}2$**	$0{\cdot}48 \pm 0{\cdot}19$
LAA ejection fraction (%)	33 ± 21**	54 ± 13
Mitral valve area (cm^2)	$1{\cdot}2 \pm 0{\cdot}2$***	$1{\cdot}9 \pm 0{\cdot}9$
Mean diastolic gradient (mmHg)	$12{\cdot}1 \pm 3{\cdot}9$**	$7{\cdot}3 \pm 2{\cdot}9$

*$P<0{\cdot}01$, **$P<0{\cdot}05$, ***$P<0{\cdot}001$, LAA=left atrial appendage.

appendage contractile dysfunction compared with those without spontaneous echo contrast.

Studies about patients with atrial fibrillation and cardioembolic stroke or mitral stenosis showed that patients with atrial fibrillation had lower left atrial appendage flow parameters compared to control subjects and, lack of active left atrial appendage flow had been found to be correlated with left atrial appendage spontaneous echo contrast and thrombus formation[3–5]. Our study suggested that even if the patients with mitral stenosis are in sinus rhythm, active left atrial appendage blood flow and contractile function may be disturbed. This might be the result of significant increase in left atrial pressure caused by afterload elevation. Left atrial appendage contractile dysfunction may cause blood stasis in the left atrial appendage cavity and this might be one of the mechanisms for the formation of spontaneous echo contrast and thrombus in left atrial appendage[2]. It has been shown that in patients with severe hypertension and hypertrophic cardiomyopathy in sinus rhythm, a marked elevation in the left atrial pressure reduces the left atrial appendage peak emptying velocities and these changes may be accompanied by an increase incidence of thrombus formation in the left atrial appendage[13–15].

Compared with other studies performed in patients with mitral stenosis and sinus rhythm, mean mitral valve area of our patients was larger[6,7]. This indicates that mild mitral stenosis can also cause left atrial appendage dysfunction in sinus rhythm which may predispose spontaneous echo contrast and/or thrombus formation in the left atrial appendage cavity. Also, lower incidence of spontaneous echo contrast and thrombus in our study may be explained by larger mitral valve area in our patients.

Time to begin prophylactic anticoagulant treatment in patients with mitral stenosis in sinus rhythm is not clear[16]. In a study left atrial appendage flow profile is suggested to be used to define a subset of mitral stenosis patients at an increased risk of embolization[8]. In our study left atrial appendage emptying velocities were found to be significantly lower in patients with spontaneous echocardiographic contrast and/or thrombus which may predispose embolization. Left atrial appendage blood flow velocities may be used as a criterion to begin prophylactic anticoagulant treatment in patients with mitral stenosis in sinus rhythm. Although our patients were not followed in respect of atrial fibrillation development, left atrial appendage blood flow velocities may be useful to determine the risk for future development of atrial fibrillation in these patients. Further prospective studies are needed to confirm these hypotheses.

Endocardial damage occurs in the atrial appendages of patients with mitral valve disease[17]. Potentially thrombogenic changes are shown in the left atrial appendage of patients with mitral stenosis, such as decreased release of prostaglandin I_2 from left atrial appendage endocardial cells compared with that of the right ventricle and pulmonary artery[18]. These anatomic appearances may contribute to the risk of intraatrial thrombus formation in patients with mitral stenosis in sinus rhythm. In addition, some studies have shown that patients with rheumatic valvular disease exhibit abnormalities of haemostatic markers like fibrinogen and fibrin d-dimer[19]. These markers were found to be significantly higher in patients with valvular atrial fibrillation than in patients with nonvalvular atrial fibrillation and in patients with sinus rhythm and mitral stenosis[19–21]. Thus, underlying heart disease may affect coagulation activity. However, we didn't measure fibrinogen, fibrin d-dimer or von Willebrand factor to correlate with spontaneous echocardiographic contrast and thrombus in the left atrial appendage. Further studies are required to investigate how haemodynamic abnormality and endothelial dysfunction of left atrium mainly affect the coagulation state in patients with mitral stenosis in sinus rhythm.

It is concluded that left atrial appendage contractile function is disturbed in patients with mitral stenosis in sinus rhythm especially in patients with spontaneous echo contrast. As a result, left atrial appendage contractile dysfunction is one of the indicator of probable spontaneous echo contrast and/or thrombus formation in left atrial appendage cavity in these patients.

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