The influence of left ventricular diameter on left atrial appendage size and thrombus formation in patients with dilated cardiomyopathy

Dilate kardiyomiyopatili hastalarda sol ventrikül çapının sol atriyum apandisi boyutu ve trombüs oluşumuna etkisi

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Objectives: Patients with dilated cardiomyopathy are considered a high risk group for left ventricular (LV) thrombus formation. However, the left atrial appendage (LAA) might be an additional site for thrombus formation in this patient group. We evaluated the association between LV size and left atrium/LAA size and determined the incidence of spontaneous echo contrast (SEC)/thrombus in the LV, left atrium, and LAA in patients with and without enlarged LV dimensions.

Study design: In a prospective design, we examined 45 patients with transthoracic and transesophageal echocardiography. Nineteen patients had an enlarged LV dimension (group 1: LV end-diastolic diameter ≥58 mm), and 26 patients had a normal LV size (group 2). Nonvalvular atrial fibrillation (AF) was present in 13 patients (68.4%) in group 1 and in 14 patients (53.9%) in group 2. Echocardiographic parameters included LV dimension and ejection fraction, left atrial diameter, LAA maximal area, and detection of SEC/thrombus in the LV, left atrium, and LAA.

Results: The two groups were similar with regard to demographic and clinical features. Patients in group 1 had a significantly increased LV end-diastolic diameter (63.5±3.8 mm *vs.* 50.9±0.9 mm; p<0.001) and decreased ejection fraction (45.3±11.7% *vs.* 56.0±10.2%; p=0.002). Left atrial diameter did not differ significantly, but maximal LAA area was significantly greater in group 1 (4.9±2.3 cm^2 *vs.* 3.3±0.8 cm^2; p=0.002). Among the frequencies of SEC and thrombus in the LV, left atrium, and LAA, only the frequency of thrombus in the LAA was significantly higher in group 1 (36.8% *vs.* 7.7%; p=0.05). Compared to patients with a normal LV size and AF, the coexistence of AF with dilated LV was significantly associated with a greater LV end-diastolic diameter (p<0.001) and LAA maximal area (p=0.02).

Conclusion: Patients with a dilated LV have a larger LAA and seem to be at a higher risk for LAA thrombus formation.

Key words: Atrial appendage/ultrasonography; atrial fibrillation/complications; cardiomyopathy, dilated/complications; echocardiography, transesophageal; thrombosis/diagnosis.

Amaç: Dilate kardiyomiyopatili hastalar sol ventrikülde (SV) trombüs oluşumu açısından yüksek risk grubunda kabul edilirler. Ancak, bu hasta grubunda sol atriyum apandisi (SAA) de trombüs oluşumunda bir odak olabilir. Bu çalışmada, SV boyutu ile sol atriyum/SAA boyutu arasında ilişki olup olmadığı araştırıldı ve SV boyutu genişlemiş veya normal olan hastalarda SV, sol atriyum ve SAA'da spontan eko kontrast (SEK)/trombüs varlığı incelendi.

Çalışma planı: Bu prospektif çalışmada, 45 hasta transtorasik ve transözofageal ekokardiyografi ile incelendi. Sol ventrikül boyutu 19 hastada genişlemiş bulunurken (grup 1: SV diyastol sonu çapı ≥58 mm), 26 hastada (grup 2) normal bulundu. Grup 1'de 13 hastada (%68.4), grup 2'de ise 14 hastada (%53.9) kapak hastalığı ile ilgili olmayan atriyum fibrilasyonu (AF) vardı. Ekokardiyografik parametrelerden SV boyutu ve ejeksiyon fraksiyonu, sol atriyum çapı, en büyük SAA alanı ölçüldü ve SV, sol atriyum ve SAA'da SEK ve trombüs varlığı araştırıldı.

Bulgular: İki hasta grubu demografik ve klinik özellikler açısından benzerdi. Grup 1'deki hastalarda SV diyastol sonu çapı anlamlı derecede yüksek (63.5±3.8 mm ve 50.9±0.9 mm; p<0.001), ejeksiyon fraksiyonu düşük (%45.3±11.7 ve %56.0±10.2; p=0.002) bulundu. Sol atriyum çapı iki grup arasında anlamlı farklılık göstermezken, en büyük SAA alanı grup 1'de anlamlı derecede büyüktü (4.9±2.3 cm^2 ve 3.3±0.8 cm^2; p=0.002). Sol ventrikül, sol atriyum ve SAA'da saptanan SEK ve trombüs sıklıkları açısından, SAA'da trombüs görülme sıklığı grup 1'de anlamlı derecede yüksekti (%36.8 ve %7.7; p=0.05). Normal SV boyutu ve AF olan hastalarla karşılaştırıldığında, genişlemiş SV boyutuna AF'nin eşlik ettiği hastalarda SV diyastol sonu çapı (p<0.001) ve en büyük SAA alanı (p=0.02) anlamlı derecede daha yüksek bulundu.

Sonuç: Sol ventrikül genişlemesi olan hastalarda SAA alanı daha büyük ve SAA trombüs oluşma riski daha yüksektir.

Anahtar sözcükler: Atriyum apandisi/ultrasonografi; atriyum fibrilasyonu/komplikasyon; kardiyomiyopati, dilate/komplikasyon; ekokardiyografi, transözofageal; tromboz/tanı.

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Cardiac embolism accounts for more than 15% of embolic strokes, with the left atrial appendage (LAA) being the most predisposed location.[1,2] Patients with ischemic cardiomyopathy, dilated left ventricle (LV), lower ejection fraction, and apical aneurysm seem to be at high risk for LV thrombus formation.[3] However, left atrial thrombi may constitute an alternative source of systemic embolism in dilated cardiomyopathy.[4] Left ventricular end-diastolic dimension correlates well with left atrial diameter in adult patients with atrial fibrillation;[5] on the other hand, an enlarged left atrium on transesophageal echocardiography (TEE) is significantly associated with an enlarged LAA.[6] Dilation of the LAA is a factor that contributes to LAA thrombus formation in patients with sinus rhythm and atrial fibrillation. Intravenous contrast imaging studies has shown that, compared to thrombus-free patients, the LAA is significantly larger in patients with a thrombus.[7,8]

Although there are numerous studies showing that a significant relationship exists between LV systolic function and LAA thrombus formation,[9-12] there is little information, to our best knowledge, in the medical literature on the association between LV size and the incidence of LAA thrombus formation.[4,13]

The aim of our study was to determine whether there was any association between LV size and left atrial/LAA size and to evaluate the incidence of spontaneous echo contrast (SEC)/thrombus in the LV, left atrium, and LAA in patients with enlarged LV dimensions with or without atrial fibrillation. We hypothesized that enlargement of the LV would induce enlargement of the left atrium and LAA, resulting in increased incidence of LAA thrombus formation.

PATIENTS AND METHODS

We conducted a prospective study in 45 patients who underwent TEE examination between February 2006 and October 2006. Nineteen patients who had an LV end-diastolic dimension of ≥58 mm formed the study group (group 1), and 26 patients having a normal LV size comprised the control group (group 2). Thirteen patients (68.4%) in group 1 and 14 patients (53.9%) in group 2 had nonvalvular atrial fibrillation, which was determined by at least two electrocardiograms.

All the patients were evaluated by history, physical examination, laboratory tests, transthoracic echocardiography (TTE), and TEE. Patients who could not tolerate TEE and who refused to participate were excluded. Informed consent was obtained from all the patients and the study protocol was approved by our hospital's ethics committee.

Echocardiographic studies. Conventional transthoracic and transesophageal echocardiography were performed using the Philips iE33 system. All echocardiographic examinations were assessed by two skilled cardiologists and, in case of any discrepancy, the opinion of a third experienced cardiologist was accepted as decisive.

Transthoracic echocardiographic measurements were obtained from the parasternal long-axis view by two-dimensional targeted M-mode tracing according to the recommendations of the American Society of Echocardiography.[14] Left atrial diameter was measured at the end of ventricular systole in the parasternal short-axis view at the level of aortic cusps.

Transesophageal echocardiography was performed with a multiplane probe and a 7.0 MHz transducer connected to the same ultrasound system. All the patients were in the fasting state at the time of the TEE procedure. Intravenous midazolam injection with a dose of 1.5 to 5 mg was administered for conscious sedation and lidocaine spray was used for topical anesthesia of the hypopharynx.

The LAA was visualized from the two-chamber longitudinal view of the left cavities. In patients with sinus rhythm, the maximal and minimal LAA areas were measured during LAA diastole at the onset of the P wave and during LAA systole at the R wave, respectively. In patients with atrial fibrillation, the LAA maximal area was obtained independent of the electrocardiogram.[7]

Thrombus was defined by the presence of a distinct, well-contoured echogenic mass, identified in at least two different views (Fig. 1). The presence of

Figure 1. A large, well-contoured left atrial appendage thrombus in a patient with enlarged left ventricular size and atrial fibrillation.

Table 1. Baseline characteristics and echocardiographic data of the two patient groups

	Group 1 (n=19)			Group 2 (n=26)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			66.4±8.9			62.4±12.9	0.25
Sex							0.52
Females	9	47.4		17	65.4		
Males	10	52.6		9	34.6		
Atrial fibrillation	13	68.4		14	53.9		0.62
Hypertension	16	84.2		18	69.2		0.66
Coronary artery disease	12	63.2		8	30.8		0.18
Diabetes mellitus	5	26.3		3	11.5		0.29
History of stroke	5	26.3		2	7.7		0.15
Left ventricle							
End-diastolic diameter (mm)			63.5±3.8			50.9±0.9	**<0.001**
Ejection fraction (%)			45.3±11.7			56.0±10.2	**0.002**
Left atrium diameter (mm)							
Transthoracic			44.9±6.6			43.2±7.0	0.42
Transesophageal			52.0±8.2			48.9±9.0	0.24
Spontaneous echo contrast							
Left ventricle	9	47.4		4	15.4		0.09
Left atrium	12	63.2		10	38.5		0.34
Left atrial appendage	13	68.4		8	30.8		0.14
Thrombus							
Left ventricle	1	5.3		–			0.25
Left atrial appendage	7	36.8		2	7.7		**0.05**
Left atrial appendage							
Maximal area (cm^2)			4.9±2.3			3.3±0.8	**0.002**
Emptying wave (cm/sn)			49.0±27.5			61.7±33.6	0.18
Filling wave (cm/sn)			39.0±14.3			50.0±21.3	0.06

Group 1: Left ventricle end-diastolic dimension ≥58 mm; Group 2: Normal left ventricle size (controls).

SEC was defined as dynamic smoke-like echos within the cavity, with a swirling motion. The impact of the white noise artifact was eliminated by adjusting the gain setting as required. Left atrial appendage flow velocities were obtained with pulsed-wave Doppler interrogation, by placing the sample volume at the orifice of the LAA. We measured the "a" wave, which corresponds to the LAA intrinsic late diastolic contraction, and early systolic negative wave caused by the LAA filling. In patients with sinus rhythm, the peak "a" wave and the peak systolic wave were noted, whereas in patients with atrial fibrillation, the mean values of three consecutive emptying waves and filling waves were determined.

Statistical analysis. All values were expressed as mean±standard deviation or percentages. Comparison between parametric variables was performed using the two-tailed unpaired t-test, and for categorical variables the chi-square test was used. For all tests, a p value ≤0.05 was considered statistically significant. All statistical analyses were performed using a statistical software (Smith's Statistical Package, version 2.80, 2005).

RESULTS

Baseline characteristics of the patient groups and TTE and TEE findings are shown in Table 1. There were no significant differences between the two groups with regard to age, sex, presence of atrial fibrillation, hypertension, coronary artery disease, diabetes mellitus, or history of stroke.

Patients in group 1 had significantly increased left ventricular end-diastolic diameter (63.5±3.8 mm *vs*. 50.9±0.9 mm; p<0.001) and decreased ejection fraction (45.3±11.7% *vs*. 56.0±10.2%; p=0.002). Left atrium dimension, both measured by TTE and TEE, did not differ significantly between the two groups. Maximal area of the LAA was significantly greater in group 1 (4.9±2.3 cm^2 *vs*. 3.3±0.8 cm^2; p=0.002).

The frequencies of SEC in the LV, left atrium, and LAA, and of thrombus in the LV and LAA were higher in patients with dilated LV, but among all, only the frequency of thrombus in the LAA was of statistical significance (Table 1).

Echocardiographic findings of the patient subgroups according to the presence or absence of atrial

Table 2. Echocardiographic findings of the patient subgroups according to the presence (group 1a) or absence (group 2a) of atrial fibrillation

	Group 1a (n=13)			Group 2a (n=14)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Left ventricle							
End-diastolic diameter (mm)			64.0±4.4			51.0±0.8	**<0.001**
Ejection fraction (%)			42.8±12.3			50.4±9.4	0.08
Left atrium diameter (mm)							
Transthoracic			46.1±6.7			45.5±7.2	0.83
Transesophageal			53.9±6.6			53.6±6.7	0.89
Spontaneous echo contrast							
Left ventricle	6	46.2		4	28.6		0.52
Left atrium	10	76.9		8	57.1		0.63
Left atrial appendage	10	76.9		7	50.0		0.49
Thrombus							
Left ventricle	1	7.7		–			0.31
Left atrial appendage	5	38.5		2	14.3		0.27
Left atrial appendage							
Maximal area (cm^2)			5.3±2.6			3.5±0.5	**0.02**
Emptying wave (cm/sn)			35.9±17.1			46.4±32.2	0.3
Filling wave (cm/sn)			33.4±9.8			41.3±16.5	0.14

Group 1: Left ventricle end-diastolic dimension ≥58 mm; Group 2: Normal left ventricle size (controls).

fibrillation are shown in Table 2. Among the echocardiographic parameters, the coexistence of atrial fibrillation with dilated LV was significantly associated only with greater LV end-diastolic diameter ($p<0.001$) and LAA maximal area ($p=0.02$).

DISCUSSION

Several studies have shown that reduced left ventricular ejection fraction influences LAA dysfunction and LA/LAA thrombus formation. Cemri et al.[11] found that decreased LV systolic function was associated with impaired LA/LAA function and that 75% of patients with LV dysfunction accompanied by atrial fibrillation had LA/LAA thrombus/SEC compared to 18% of patients without LV systolic dysfunction. Handke et al.[9] concluded from their study that patients with a history of stroke, sinus rhythm, and moderate-to-high decrease in ejection fraction presented a risk group for left atrial source of embolism. Our patients had mild systolic dysfunction, thus excluding its possible role on thrombus formation.

There is little emphasis on the role that LV size might play in the incidence of LA/LAA thrombus. About 15% of patients with severe dilated cardiomyopathy and sinus rhythm have atrial thrombi,[4] and the LAA has been reported as the major localization thereof.[13] Our data suggest that patients with dilated LV, with or without atrial fibrillation, are prone to having larger LAA dimensions, as well as a higher incidence of thrombus in the LAA.

The annual risk for systemic embolization in patients with dilated cardiomyopathy varies from 1.4% to 12%.[15,16] Although it is widely thought that the main source of thrombus in patients with dilated cardiomyopathy is the LV, Ciaccheri et al.[16] noted that there was no overlap between the patients that were diagnosed as having LV thrombus and those that experienced an embolic event either prior to entering the study or in the follow-up period. In other words, intracardiac thrombus was not diagnosed by cross-sectional echocardiography in none of the 12 patients that experienced an embolic complication. This observation emphasizes the need to search for other sources of thrombi. Unfortunately, TTE does not offer satisfactory views of the LAA; in contrast, TEE is a reliable, semi-invasive method that gives a clear view of the LAA, with a sensitivity and specificity of 100% and 99%, respectively.[17]

In our study, seven patients (36.8%) with dilated LV had thrombus in the LAA. Of these, two patients (28.6%) were in sinus rhythm and, in group 1, only one patient (5.3%) had thrombus in the LV. In group 2, two patients (7.7%) had LAA thrombus, and both had atrial fibrillation. Of note, LAA thrombi found in group 1 were larger (Fig. 1), and one was mobile. None of the patients were taking oral anticoagulants prior to the examination.

Two limitations have to be mentioned for the study: it was performed in a relatively small number

of cases and patients with larger LV end-diastolic dimensions were not included.

In conclusion, patients with dilated LV chamber size have larger LAA dimensions and appear to be at a higher risk for LA/LAA thrombus formation. Thus, we recommend that this patient group be examined cautiously for thrombus detection. The small size of our study population calls for confirmatory studies.

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