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Left Ventricular and Left Atrial Thrombi in Sinus Rhythm Patients with Dilated Ischemic Cardiomyopathy

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Introduction: Ischemic dilated cardiomyopathy offers a favorable terrain for left ventricular (LV) thrombus formation; however, left atrial appendage (LAA) may be an additional source of thrombi in patients with dilated heart. The main objectives of this study were to determine the prevalence of LV and LAA thrombi in patients with chronic ischemic dilated cardiomyopathy in sinus rhythm, as well as to reveal echocardiographic predictors for thrombus formation. **Methods:** The study included 57 patients with chronic dilated ischemic cardiomyopathy in sinus rhythm, who were not under oral anticoagulation therapy. Exclusion criteria included patients with: swallowing problems, acute myocardial infarction, idiopathic and/or non-ischemic dilated cardiomyopathy, atrial fibrillation/flutter, severe systolic dysfunction. Transthoracic echocardiography and transesophageal echocardiography were obtained for each patient. **Results:** Mean patient age was 62 ± 10.5 years, mean LV end diastolic diameter was 67.2 ± 5.8 mm, whereas mean LV ejection fraction (EF) was 37.1 ± 4.3 %. LV thrombus was detected in 11 (19.3%) patients; while 23 (40.3%) patients had LAA thrombus. In a multiple regression analysis LV size ($p=0.05$) and lack of aspirin therapy ($p=0.02$) showed to be independent LV thrombus predictors, whereas lower LV EF ($p=0.02$) and larger LAA maximal area ($p=0.004$) demonstrated to be independent predictors of LAA thrombus. **Conclusions:** We consider that our study sheds light to the high possibility of LAA thrombi formation in addition to LV thrombi in patients with chronic dilated ischemic cardiomyopathy in sinus rhythm. LV size, LV EF, LAA maximal area and lack of aspirin therapy are shown to be independent predictors of left heart chamber thrombi in this patient category. **Key words:** thrombus, ischemic disease, dilated cardiomyopathy.

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1. INTRODUCTION

Dilated cardiomyopathy is one of the complications of ischemic disease. Ischemic dilated cardiomyopathy offers a favorable terrain for left ventricular (LV) thrombus formation due to akinesis, dyskinesis and/or aneurysm of myocardial walls, as well as low left ventricular ejection fraction (1). However, we

believe, as we have reported earlier, that left atrial appendage (LAA) may be an additional source of thrombi in patients with dilated heart (2).

The main purpose of this study was to determine the prevalence of LV and LAA thrombi in patients with chronic ischemic dilated cardiomyopathy in sinus rhythm with mild to moderate sys-

tolic dysfunction that were not on anticoagulation therapy. We also aimed to reveal echocardiographic predictors for thrombus formation.

2. PATIENTS AND METHODS

In a prospective cross-sectional study, conducted from December 2009 until January 2012 in University Clinical Center of Kosova, we included 57 patients with chronic dilated ischemic cardiomyopathy in sinus rhythm, who were not under oral anticoagulation therapy. Exclusion criteria included patients with: swallowing problems, acute myocardial infarction, idiopathic and/or non-ischemic dilated cardiomyopathy, atrial fibrillation/flutter, severe systolic dysfunction.

The study was approved by our Ethical Board and written informed consent was taken from every patient enrolled in the study.

Demographic and history data, physical examination, laboratory tests, ECG, chest X-ray, transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were obtained for each patient.

According to their symptoms patients were classified in one of the four New York Heart Association (NYHA) categories.

Ischemic origin of dilated cardiomyopathy was documented by either coronary angiography information or by hospital discharge list confirming experienced myocardial infarction at least three months earlier.

ECG at the time of patient's inclusion in the study as well as minimum of two previous ECGs from outpatient visits were analyzed in order to confirm the chronic nature of ischemic disease, as well as to determine the sinus rhythm over this period. To our best knowledge patients that were included in the study did not have prior episodes of atrial fibrillation.

2.1. Echocardiography

All patients underwent conventional TTE and TEE using commercially available equipment (Phillips iE 33; Bothell, WA, USA). LV end-diastolic/end-systolic diameters, septal and posterior wall thickness and left atrial (LA) diameter were measured according to standard criteria (3). LA volume was calculated by area-length (*L*) method using apical 4-chamber and apical 2-chamber views at ventricular end-systole (3). LV ejection fraction (EF%) was determined with modified Simpson's rule from apical view. Only patient with EF $\geq 30\%$ were included.

Wall motion score index (WMSI) was calculated by the new 17-segment model (3, 4, 5). LV sphericity index in end-diastole and end-systole was defined as the ratio of LV width to LV length in the four-chamber view. Displacement of the mitral annulus (MAPSE) was measured in millimetres (mm) by M-mode echocardiography from four different points (septal, lateral, inferior and anterior mitral annuli) by apical four chamber and apical two-chamber approaches. The average of MAPSE was obtained from the average value of the four annular sites (3).

Thrombus was defined as presence of well defined echogenic intracavity mass with an echo-texture different from that of underlying endocardium, which was identifiable in at least two different views.

TEE, with the multiplane transesophageal transducer, was performed on all patients that entered the study. Intraoral lidocaine spray and intravenous midazolam were administered to every patient. The procedure was always performed by one cardiologist trained for the procedure and another experienced cardiologist observing the course of action. Any discrepancy was resolved by the third cardiologist and consensus.

TEE projections and measurements were completed according to the recommendations (6).

LAA was visualized from the two-chamber longitudinal view of the left cavities. Maximum and minimum LAA area was measured by planimetry method. The maximal area of the LAA was measured during LAA diastole, which corresponds to the onset of the ECG P wave, while the LAA minimal area was measured at R wave. The LAA EF was calculated from the following equation: LAAEF (%) = $100 \times (\text{LAA max} - \text{LAA min}) / \text{LAA max}$. Peak emptying and filling waves were obtained with pulsed-wave Doppler interrogation, by placing the sample volume at the orifice of the LAA.

SEC was diagnosed by the presence of dynamic smoke like echos with swirling motion in the left cardiac cavities distinct from white noise artifact, which was excluded by adjusting the gain setting properly. SEC was classified by "eye-ball" judgment according to qualitative classification introduced by Fatkin et al. into five categories, from 0 (absence of echogenity) to 4+ (severe echogenity) (7).

2.2. Statistical analysis

All data were expressed as mean \pm standard deviation (SD) and percentages. Correlation of selected variables was estimated using Pearson correlation coefficient. Simple and multiple regression analyses were performed to identify factors associated with intracardiac thrombus formation. Using forward selection procedure, we included in the multiple regression models variables with a value of $p \leq 0.05$ in simple regression analysis. For all test, a p value ≤ 0.05 was considered statistically significant. All statistical analysis were performed using statistical software SPS, version 2.80.

3. RESULTS

Mean patient age was 62 ± 10.5 years, whereas the rest of patients' baseline characteristics are presented in table 1. Around 75% of patients were categorized in NYHA II stage of heart failure, having mild limitation of activity. About 89.5% of patients were taking aspirin at the time they entered the study.

Basic ECG and chest X-ray features

	n=57
Age, yr	62.12 \pm 10.6
Female (%)	10/57 (17.54)
Male (%)	47/57 (82.46)
Current smokers (%)	21/57 (36.84)
Alcohol users (%)	6/57 (10.53)
Hypertension (%)	27/57 (47.37)
Diabetes Mellitus (%)	24/57 (42.1)
BMI, kg/m ²	28.09 \pm 4.11
Dyslipidemia (%)	17/57 (29.82)
Peripheral vascular disease (%)	6/57 (10.53)
Heart failure NYHA I (%)	3/57 (5.26)
Heart failure NYHA II (%)	43/57 (75.44)
Heart failure NYHA III (%)	11/57 (19.3)

TABLE 1. Baseline patient characteristics. Data are presented as mean \pm SD or No. (%).

	n=57
Chest X-ray features	
Dilated heart (%)	57/57 (100)
Pulmonary congestion (%)	15/57 (26.32)
Pulmonary effusion (%)	6/57 (10.53)
ECG features	
Heart rate, beats/min.	73.63 \pm 9.72
Left ventricular axis (%)	36/57 (63.16)
LVH (%)	9/57 (15.79)
"Q" wave (%)	39/57 (68.42)
Ventricular repolarization (%)	33/57 (57.89)
Impulse conduction disorders (%)	11/57 (19.3)

TABLE 2. Basic chest X-ray and ECG features. Data are presented as mean \pm SD or No. (%).

	n=57
PT, %	99.74 \pm 12.6
PTT	24.32 \pm 4.34
TT	11.22 \pm 0.9
Hemoglobin, g/dl	129.82 \pm 17.25
RBC, $\times 10^{12}$	4.18 \pm 0.58
Platelets, $\times 10^9$	214.77 \pm 57.21
WBC, $\times 10^9$	9.07 \pm 2.93
ESE rate, first hour	23.33 \pm 15.94
Creatinine, mol/l	106.45 \pm 48.05
Glucose, mmol/l	7.56 \pm 3.64
ALT, IU/l	23.44 \pm 14.32
K, mmol/l	4.53 \pm 0.44
Na, mmol/l	141.28 \pm 3.24

TABLE 3. Basic biochemical and hematological tests*. *Data are presented as mean \pm SD

are presented in Table 2. Around 70% of patients from our study group had evidence of "Q" wave on ECG.

Haemostatis tests were within normal range in all patients included in the study. Basic hematological and biochemical laboratory tests are shown in Table 3. Mean left ventricular end diastolic diameter (LVEDD) of our patients was 67.2 ± 5.8 mm, whereas mean LV EF was 37.1 ± 4.3 %. Two third of the patients had moderate systolic dysfunction, while the rest of patients had mild systolic dysfunction. On the other

	n=57
IVSd, mm	9.89 ± 2.03
PWd, mm	9.93 ± 1.46
LVEDD, mm	67.23 ± 5.77
LVESD, mm	55.14 ± 6.45
LVEF, %	37.14 ± 4.33
Mild systolic dysfunction (%)	19/57 (33.33)
Moderate systolic dysfunction (%)	38/57 (66.67)
Left atrium, mm	46.93 ± 4.98
Left atrial volume, cm ³	92.08 ± 36.89
WMSI	1.62 ± 0.3
Sphericity index d	0.82 ± 0.13
Sphericity index s	0.71 ± 0.12
MAPSE average, mm	8.61 ± 2.25
Peak E wave, cm/s	68.95 ± 22.48
Peak A wave, cm/s	71.66 ± 26.28
E wave DT, ms	198.7 ± 79.83
IVRT, ms	105.39 ± 33.36
MR area, cm ²	4.71 ± 2.95
MR/ LA, %	17.61 ± 10.04

TABLE 4. Echocardiographic data of the study population*. *Data are presented as mean ± SD or No. (%). IVSd: diastolic interventricular septum; PWd: diastolic posterior wall; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; WMSI: wall motion score index; MAPSE: Mitral annular plane systolic excursion; DT: Deceleration time; IVRT: Isovolumic relaxation time; MR: mitral regurgitation; LA: left atrium.

	n=57
LAA maximal area,	4.63 ± 1.62
LAA minimal area,	2.56 ± 1.38
Emptying wave	53.4 ± 22.92
Filling wave	45.91 ± 22.11
LAA EF, %	45.25 ± 21.22

TABLE 5. TEE data of the study population* *Data are presented as No. (%). LAA: left atrial appendage; LAA EF: left atrial appendage ejection fraction.

hand, 39 (68.5%) patients had echocardiographic signs of diastolic dysfunction.

TTE and TEE parameters are shown in Tables 4 and 5, respectively.

LV thrombus was detected in 11 (19.3%) patients. According to size of the thrombus, 4 of them were large and 7 moderate, while one thrombus was protruding and the rest were mural thrombi. Moreover, 23 (40.3%) patients had LAA thrombus, 21 of which were small thrombi and 2 moderate size thrombi. Three patients had thrombi in LV and LAA.

SEC grading detected in LV, LA and LAA is presented in Table 6.

After analyzing echocardiographic

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
LV SEC (%)	3/57 (5.26)	20/57 (35.09)	28/57 (49.12)	6/57 (10.53)	0/57 (0)
LA SEC (%)	2/57 (3.51)	25/57 (43.86)	22/57 (38.6)	8/57 (14.03)	0/57 (0)
LAA SEC (%)	0/57 (0)	7/57 (12.28)	20/57 (35.09)	28/57 (49.12)	2/57 (3.51)

TABLE 6. Prevalence of SEC on the left heart chambers*. *Data are presented as No. (%). LV: left ventricle; LA: left atrium; LAA: left atrial appendage; SEC: spontaneous echo contrast.

	p
LVEDD	0.05
Aspirin therapy	0.02
Coefficient of determination (r ²)=0.115 95% CI: -0.03 ≤ r ² ≤ 0.26	

TABLE 7. Multiple regression analysis of LV thrombus formation. LVEDD: left ventricular end diastolic diameter

	p
LVEF	0.02
LAA maximal area	0.004
Coefficient of determination (r ²)=0.2109 95% CI: 0.03 ≤ r ² ≤ 0.39	

TABLE 8. Multiple regression analysis of LAA thrombus formation. LAA: left atrial appendage; LV EF: left ventricular ejection fraction

data and aspirin usage separately for correlation with LV thrombus, only LVEDD (r=0.21, p=0.05; Figure 1) and aspirin therapy (r=-0.27, p=0.02) resulted significant. In a multiple regression model both parameters, LV size and lack of aspirin therapy, showed to be independent LV thrombus predictors (table 7).

In simple regression analysis LAA thrombus correlated significantly only with LVEF (r=-0.32, p=0.008) and LAA maximal area (r=0.39, p=0.001, figure 2) in our study population. Lower LV EF and larger LAA maximal area, both demonstrated to be independent predictors of LAA thrombus (Table 8).

4. DISCUSSION

LV thrombus was detected in approximately 20% of our sinus rhythm patients with ischemic dilated cardiomyopathy of mild to moderate systolic dysfunction who were not under anticoagulation therapy. Moreover, around 40% of this study population had LAA thrombus. While it is a well known fact that LV thrombi are a frequent incident in patients post myocardial infarction, there are no studies to our best knowledge that searched for LAA thrombi in patients with chronic ischemic dilated cardiomyopathy. LVEDD, lack of aspirin

therapy, LAA maximal area and LVEF were independent predictors of thrombus formation in our study population.

LV thrombus develops in approximately 30% of patients with anterior myocardial infarction and is associated with elevated risk of systemic thromboembolic events [8]. Thrombus formation generally occurs in the anterior wall, particularly in the anteroapical areas, on basis of akinesis or dyskinesis. Less than 5% of patients with myocardial infarction in other areas develop thrombus (1). Other favorable factors for left ventricular thrombus formation include: low ejection fraction, size of the infarct and atrial fibrillation. Intraventricular thrombi post myocardial infarction usually appear by the end of the first week, with peak incidence at day 4 or 5 (1). Echocardiography has 90% specificity and 75-90% sensitivity for detection of left ventricular thrombus (1, 9).

According to the data from several studies, the incidence of stroke following myocardial infarction aver-

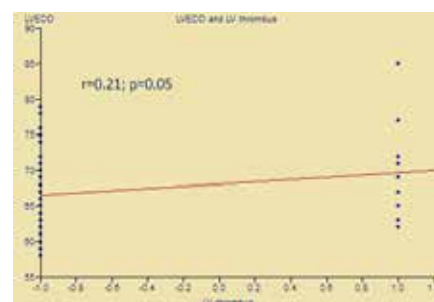


FIGURE 1. Correlation between LV thrombus and LV size

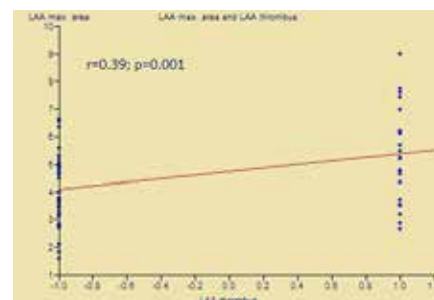


FIGURE 2. Correlation between LAA thrombus and LAA size

ages 2.9%; however usage of antithrombotic and thrombolytic therapy has decreased the incidence of stroke within the first year after myocardial infarction to 1% (1). Studies have shown that frequency of stroke was higher in patients with larger myocardial infarction. The risk of embolism in patients with left ventricular thrombosis is higher in the first week to three months after myocardial infarction. This risk may persist beyond this period, especially in patients with severe left ventricular failure, or in patients with persisting mobile and protruding thrombus (1).

LV aneurysm presents a favorable location for thrombus formation. The frequency of left ventricular thrombi in aneurysms found *post mortem* range from 14-68%, whereas findings of thrombi from aneurysmectomy vary from 50-95% (10). On the other hand the incidence of thromboembolic events in patients presenting with left ventricular aneurysm are reported to be from 0-52% (10, 11). The presence of LV aneurysm presents a risk factor for persistence of thrombus, as well as for its recurrence after cessation of anticoagulation therapy. Studies have demonstrated that thrombus within the LV aneurysm is more vulnerable in the early period, up to 3 months, following myocardial infarction and the risk of stroke at this time accounts for around 10% (12). The incidence of emboli is reported to be very low after this period; however the risk of thromboembolic events continues to be high in patient with LV aneurysm and low EF, or a protruding thrombus (13).

In patients with stroke or transient ischemic attacks the source of the emboli is not routinely determined in 25-50 % of patients (14). That is why we consider the necessity for more thorough investigation of potential embolic sources in order to prevent central ischemic attacks. We believe that LAA, as a common site of thrombus formation, should be examined by TEE in patients with ischemic dilated cardiomyopathy, even in sinus rhythm and with mild to moderate systolic dysfunction. Manning et al. in their study found a 100% sensitivity and 99% specificity for LAA thrombus detection by TEE (15). We excluded from our study patients with

atrial fibrillation and severe LV systolic dysfunction since these features are known to be highly associated with LAA thrombus formation (16, 17, 18). LAA size, determined at surgery or by TEE, has been shown to correlate very well with the LAA presence of thrombus and subsequent thromboembolic events (16, 19). LAA has been found to be of larger size in patients with LAA thrombus, whether they were in atrial fibrillation or sinus rhythm, which was also confirmed by our results (19).

We consider the small population of our study group as the major limitation of this study.

5. CONCLUSIONS

We conclude that our study sheds light to the possibility of LAA thrombi formation in addition to LV thrombi in patients with chronic dilated ischemic cardiomyopathy in sinus rhythm, without anticoagulation therapy. LVEDD, LVEF, LAA maximal area and lack of aspirin therapy are shown to be independent predictors of left heart chamber thrombi in this patient category.

ABBREVIATIONS

- ECG - Electrocardiography,
- EF - Ejection fraction,
- LA - Left atrium/atrial,
- LAA - Left atrial appendage,
- LV - Left ventricle/ventricular,
- LVEDD - Left ventricular end-diastolic diameter,
- MAPSE - Mitral annular plane systolic excursion,
- TEE - Transesophageal echocardiography,
- TTE - Transthoracic echocardiography,
- WMSI - Wall motion score index.

Conflict of interest: none declared.

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