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ORIGINAL ARTICLE

Lower Body Weight in Men, an Epidemiological Predictor of Enlarged Left Atrium in Sinus Rhythm Patients with Dilated Heart

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ABSTRACT

Background/Aims: The source of thrombi in patients with dilated cardiomyopathy is not necessarily from the dilated left ventricle. Left atrium (LA) and left atrial appendage (LAA) might be in charge for relatively high rate of systemic embolizations in these patients. The main aim of our study was to identify epidemiological predictors in sinus rhythm patients with dilated heart for LA and LAA dilation and/or dysfunction. **Patients and Methods:** This was a prospective cross-sectional study conducted from 2009 to 2014 in 101 sinus rhythm patients with dilated heart. We excluded patients with swallowing problems, acute myocardial infarction, atrial fibrillation/flutter, severe systolic dysfunction, mechanical valves, oral anticoagulation therapy, and/or patients with a history of stroke/systemic thromboembolic event. **Results:** Mean patient age was 58.13 ± 12.66 years and 69.3% were men. Hypertension was encountered in 51% of our patients, 56% of them had a history of coronary artery disease, 30% had diabetes, 25% had dyslipidemia, 30% were smokers, whereas 10% were alcoholics. Mean LA dimensions resulted higher than reference values, whereas 86% of our patients had LAA dysfunction. Male gender was an independent predictor for LA diameter dilation (95% confidence interval [CI]: 1.765–9.078, P = 0.005), while lower body weight was a predictor for enlargement of LA area (95% CI: 0.044–0.351, P = 0.014) and LA volume (95% CI: 0.160–2.067, P = 0.024). **Conclusion:** Male patients with dilated cardiomyopathy at sinus rhythm with lower body weight tend to have larger LA and consequently might be at higher risk of developing atrial thrombus and its subsequent consequences.

Key Words: Body weight, dilated cardiomyopathy, left atrial appendage, left atrium, stroke prevention

INTRODUCTION

The annual risk of systemic embolization in patients with dilated cardiomyopathy is 1.4–12%.[1,2] However, the source of thrombi in these patients is not necessarily from the dilated left ventricle (LV).[2] Several studies have documented that dilated LV is associated with dilated left atrium (LA) and left atrial appendage (LAA).[3-6] On the other hand, LA size serves as a significant and useful clinical predictor for ischemic stroke or all-cause mortality.[7] Furthermore, LAA size, flow velocity, and ejection fraction (EF) have been shown to correlate very well with LAA presence of thrombus and subsequent thromboembolic events.[4,8]

The aim of our study was to analyze epidemiological features of our patients with dilated heart of mild to moderate systolic dysfunction, who were at sinus rhythm. Our main aim was to analyze the relationship and prediction of these epidemiological data to LA and LAA size and function as predisposing features of thromboembolic events.

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PATIENTS AND METHODS

This was a prospective cross-sectional study conducted in University Clinical Center of Kosova from 2009 to 2014. The study included 101 patients with dilated LV (regardless of its etiology) in sinus rhythm. We excluded patients with swallowing problems, acute myocardial infarction, atrial fibrillation/flutter, severe systolic dysfunction, mechanical valves, oral anticoagulation therapy, and/or patients with a history of stroke/systemic thromboembolic event.

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

Epidemiological data, physical examination, laboratory tests, electrocardiography (ECG), chest X-ray, transthoracic echocardiography (TTE), and transesophageal echocardiography (TEE) were obtained for every patient that entered the study.

Echocardiography

TTE (Phillips iE 33) examinations and measurements were performed according to the recommendations of the American Society of Echocardiography.[9] Left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter, septal wall, and posterior wall thickness were measured from parasternal M-mode view according to standard criteria. LV EF was determined from apical views with modified Simpson's rule. LV EF <50% was considered as systolic dysfunction, whereas LV EF under 30% was considered as severe LV dysfunction. LA diameter was measured in two-dimensional projection at end-ventricular systole in parasternal short axis view at the level of the aortic valve. Measurement of LA volume was done with area-length (L) method using apical 4-chamber and apical 2-chamber views at ventricular end-systole (maximum LA size), whereas L was measured from back wall to line across hinge points of mitral valve. Calculation of LA volume was made by the following formula: $8/3\pi$ ([A1][A2]/L).

TEE (Phillips iE 33, Agilent Image-Point Hewlett Packard or Toshiba NEMIO XG SSA-580A) was performed in all patients that entered this study, with the main aim at analyzing LAA. The LAA was visualized from the 2-chamber longitudinal view of the left cavities. Maximum and minimum LAA area was measured by planimetry method by tracing the LAA starting from the top of the limbus of the upper pulmonary vein along the entire appendage endocardial border. The maximal area of the LAA was measured during LAA diastole, while the LAA minimal area was measured at systole. The LAA EF was calculated from the following equation: LAA EF (%) = 100 (LAAmax − LAAmin)/LAAmax.

Patients with LAA peak emptying velocity <40 cm/s and/or spontaneous echo contrast (SEC) and/or thrombus in LAA were considered as having LAA dysfunction. LAA flow velocities were obtained with pulsed-wave Doppler interrogation by placing the sample volume at the orifice of the LAA. Four waves were identified: "e" wave, which represents the early diastolic emptying flow; "a" wave, which corresponds to the LAA intrinsic late diastolic contraction; early systolic negative wave, which presents the LAA filling; and the systolic reflection waves, which appear if the heart rate is slow enough and if the LAA function is normal.[10,11] Peak "a" wave and peak systolic wave were determined. SEC was identified if dynamic "smoke-like" echos with swirling motion in the cavity were seen. Thrombus was diagnosed in case of the presence of a distinct, well contoured echogenic mass, which was identifiable in at least two different views.

Statistical analysis

All data were expressed as mean ± standard deviation and percentages. Correlation of selected variables was estimated using Spearman's correlation coefficient as we assumed nonlinear correlation existence. Multiple regression analysis was used as a prediction model, and the data were expressed as odds ratio with 95% confidence intervals (CIs) and probability value adjusted for all other measured risk factors. Variables with a value of $P < 0.05$ were considered significant. All data analysis was performed using the SPSS version 13.0 (IBM SPSS, Inc., Chicago, IL, USA).

RESULTS

One hundred and one patients ($n = 101$) were selected to enter our study, and their basic characteristics are presented in Table 1. The main inclusion criterion for our patients was dilated LV, with the mean LVEDD being 66.6 ± 6.07 mm, and the mean LV EF 39.02 ± 6.4%.

They were on an average age of 58.13 ± 12.66 years and predominantly male (69.3%). According to the body mass index (BMI) World Health Organization classification, our study population was in the preobese group (principal cut-off limits: 25.0–29.99 kg/m^2), while taking gender into account, the female patients were classified in obese class I group (principal cutoff limits: 30.0–34.99 kg/m^2) and statistically were more obese than males ($P = 0.0001$).

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As for risk factors for cardiovascular diseases, hypertension was present in half of our study population (51.5%) without any difference between genders, while smoking (29.7%) and especially diabetes mellitus (29.7%) were presented with similar frequency and rather remarkably. Smoking was significantly more frequent in males (38.6% males vs. 9.7% females; $P = 0.002$) while the frequency of diabetes mellitus was without any difference between genders. History of coronary artery disease (CAD) was rather frequently present in our study population (56.4%) with statistical difference between genders in favor of males (67.1% vs. 32.3%; $P = 0.001$).

As for LA dimensions, areas, and volumes, analysis of mean values showed greater than reference values for all parameters [Table 2]. LA diameter and its normalization for body surface area (BSA) were significantly greater in favor of patients with a history of CAD (46.93 ± 4.98 mm vs. 44.70 ± 4.68 mm, $P = 0.024$; 24.10 ± 3.16 mm/m^2 vs. 22.68 ± 2.76 mm/m^2, $P = 0.02$, respectively).

As for characteristics of LAA size and function assessed by TEE, mean values showed normal LAA EF [Table 3]. Besides that LAA dysfunction was documented in 86.1% of patients, considering the definition of dysfunction: LAA peak emptying velocity <40 cm/s and/or presence of SEC and/or thrombus in LAA.

Analysis of relationship among epidemiological parameters and TTE assessed LA diameter, area, and volume [Table 4] showed that male gender, older age, lower body weight, lower BMI, presence of diabetes, and history of CAD were related to higher LA diameter and LA/BSA. Higher LAV was related to older age, whereas higher LAV/BSA was related to older age, lower weight and BMI, and history of CAD.

Analysis of relationship among clinical parameters and TEE assessed LAA area and function [Table 5] showed that older age, lower weight, lower BMI, and presence of hypertension were significantly related to lower LAA EF. Hypertension was related also to lower filling wave. None of the clinical parameters were related to LAA dysfunction.

Taking into account that LA enlargement could be a source of thrombus formation, we analyzed if there were independent predictive epidemiological variables that could affect LA size and indirectly lead to thrombus formation. Results of multiple linear regression analysis showed that male gender was responsible for 25.5% LA diameter change ($R^2 = 0.255$), which means that for every male patient

Table 1: Basic characteristics of all patients in the study (*n*=101)

Basic features	mean±SD or *n* (%)
Age	58.13±12.66
Gender	
Male/female (%)	70/31 (69.3/30.7)
Weight (kg)	82.43±12.72
Height (cm)	170.41±7.68
BMI (kg/m^2)	28.39±4.04
Male	27.46±3.64
Female	30.47±4.15
BSA (m^2)	1.97±0.17
Smoking (%)	30 (29.7)
Smoking duration (years)	17.76±17.03
Alcohol (%)	10 (9.9)
HT (%)	52 (51.5)
Duration of HT (years)	8.06±6.11
DM (%)	30 (29.7)
Duration of DM (years)	6.83±6.23
Dyslipidemia (%)	25 (24.8)
History of CAD	57 (56.4)
History of vascular disease	6 (5.9)
History of AF	None

Data are presented as mean±SD or *n* (%). AF=Atrial fibrillation, BMI=Body mass index, BSA=Body surface area, CAD=Coronary artery disease, DM=Diabetes mellitus, HT=Hypertension, SD=Standard deviation

Table 2: Characteristics of left atrium size assessed by transthoracic echocardiography in all patients (*n*=101)

LA features	mean±SD
LA (mm)	45.96±4.95
Male	47.32±4.70
Female	42.90±4.12
LA/BSA (mm/m^2)	23.48±3.06
LA A1 (cm^2)	25.43±6.92
LA A2 (cm^2)	25.36±6.18
LA area average (cm^2)	25.39±6.28
LA long axis (mm)	6.38±0.81
LA volume (ml)	88.06±37.98
LA volume/BSA (ml/m^2)	44.87±18.75

Data are presented as mean±SD. LA=Left atrium, BSA=Body surface area, LA A1=Left atrial area at 4-chamber view, LA A2=Left atrial area at 2-chamber view, SD=Standard deviation

Table 3: Characteristics of left atrial appendage size and function assessed by transesophageal echocardiography in all patients (*n*=101)

LAA features	mean±SD or *n* (%)
LAA maximum area (cm^2)	4.73±1.59
LAA minimum area (cm^2)	2.55±1.41
LAA EF (%)	47.50±20.92
"a" wave (cm/s)	54.11±24.44
Filling wave (cm/s)	44.86±20.97
LAA dysfunction (%)	87 (86.1)

Data are presented as mean±SD or *n* (%). LAA=Left atrial appendage, EF=Ejection fraction, SD=Standard deviation

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Table 4: Relevant relationships among epidemiological and echocardiographic parameters of left atrium diameter, area, and volume assessed by transthoracic echocardiography in all patients (*n*=101)

	Age (years)	Gender (male/female)	Weight (kg)	BMI (kg/m^2)	DM duration (years)	History of CAD (%)
LA (mm)	r=0.197; P=0.048	r=0.423; P=0.0001	-	-	-	r=0.254; P=0.010
LA/BSA (mm/m^2)	r=0.203; P=0.042	r=0.253; P=0.011	r=−0.594; P=0.001	r=−0.539; P=0.0001	r=0.379; P=0.043	r=0.222; P=0.025
LA area aver.(cm^2)	r=0.202; P=0.043	-	-	-	-	-
LAV (ml)	r=0.206; P=0.039	-	-	-	-	-
LAV/BSA (ml/m^2)	r=0.206; P=0.038	-	r=−0.263; P=0.008	r=−0.229; P=0.021	-	r=0.200; P=0.045

CAD=Coronary artery disease, BMI=Body mass index, BSA=Body surface area, DM=Diabetes mellitus, LA=Left atrium, LAV=Left atrial volume

Table 5: Relevant relationships among epidemiological and echocardiographic parameters of left atrial appendage area and function assessed by transesophageal echocardiography in all patients (*n*=101)

	LAA maximum area (cm^2)	LAA minimum area (cm^2)	LAA EF (%)	"a" wave (cm/s)	Filling wave (cm/s)	LAA dysfunction
Age (year)	-	-	r=−0.203; P=0.042	-	-	-
Weight (kg)	-	r=−0.218; P=0.029	r=0.219; P=0.028	-	-	-
BMI (kg/m^2)	-	r=−0.292; P=0.003	r=0.263; P=0.008	-	-	-
HT (%)	-	r=−0.262; P=0.0008	r=0.236; P=0.018	-	r=−0.222; P=0.026	-

BMI=Body mass index, EF=Ejection fraction, HT=Hypertension, LAA=Left atrial appendage

the LA diameter (on the average) increases by 5.421 mm (95% CI: 1.765–9.078) (P = 0.005). When LA area average was taken into account, then weight appeared responsible for 20.5% LA area average change (R^2 = 0.205), which means that for every decrease of one kilo body weight, the LA area average (on the average) increases by 0.197 cm^2 (95% CI: 0.044–0.351) (P = 0.014). These results were almost identical when LA volume was used as dependent variable. Weight was responsible for 17.5% LA volume change (R^2 = 0.175), which means that for every decrease of one kilo body weight the LA volume (on average) increases by 1.113 ml (95% CI: 0.160–2.067) (P = 0.024).

Binary logistic regression analysis showed a lack of any significant independent predictive clinical variables for LAA dysfunction.

DISCUSSION

Our study population was dominated by men (69.3%), and this is similar to most of the studies with heart failure patients. Under-representation of women has been a consistent finding in heart failure trials.[12] In this context, Rossi *et al*. in a meta-analysis of 18 studies, with 1157 patients with heart failure demonstrated an 82% representation of male patients.[13] On the other hand, we found a similar ratio of gender representation to ours in a study by Galrinho *et al*., where 34% of patients with dilated cardiomyopathy were women.[14] The reasons for this are yet unclear although the incidence of heart failure is higher in men than in women, whereas the prevalence is equal.[15]

Mean age (58 ± 13 years) of our heart failure patients was somewhat younger than the mean patient age in most heart failure trials. Thus, the meta-analysis research group in echocardiography heart failure meta-analysis, which included data of 3540 patients from 18 studies, revealed a mean patient age of 62 ± 13 years.[16] Perhaps, the younger patient age in our study population could be explained by the fact that patients with severe LV systolic dysfunction were not included in our study that might have been in more advanced age. The second explanation might be that our sample patient population reflects the overall age demographics in Kosovo, where around 50% of population represents those <24 years of age.

Our data demonstrated that female patients had significantly higher BMI compared to males. Obesity is known to be associated to cardiovascular disease. The Framingham Heart Study has shown that as BMI increases so does the risk for congestive heart failure.[17]

As far as our patients' habits are concerned, we found that around 30% of our patients were current cigarette smokers, predominantly males. Smoking is not known to be related to dilated cardiomyopathy; however, it is related to CAD, which was present in ~56% of our patients and was responsible for ischemic cardiomyopathy. Consumption of alcohol as another habit taken into account was present in ~10% of our patients, all of them being men. Only one of them was a heavy alcohol consumer. Otherwise, it is known that long-term heavy alcohol consumption is the leading cause of a nonischemic, dilated cardiomyopathy, referred to as alcoholic cardiomyopathy.

Among the cardiovascular risk factors, high blood pressure was the most prevalent in our study population. Hypertension is known to be highly prevalent in the

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general population, and it is the main contributor for the incidence of heart failure as it increases threefold the risk for heart failure. However, the incidence of heart failure in relation to high blood pressure increases with the severity of hypertension.[18] Despite the high prevalence of hypertension in cardiovascular and heart failure patients, after thorough investigation of etiology of heart failure, the role of hypertension decreases as opposed to increase the impact of CAD.[19] Furthermore, LV dilation with impaired contractility is the least frequent form of hypertensive heart disease.[20] There are reports that pure dilated cardiomyopathy due to hypertension was present in only 4% of patients with congestive heart failure.[19] Other risk factors for cardiovascular disease, such as diabetes and dyslipidemia, were relatively frequent in our patients (30% and 25%, respectively), which may be justified by a high proportion of patients with CAD in our study population (~56%). History of CAD was documented by either coronary angiography information or by hospital discharge list confirming experienced myocardial infarction at least 3 months prior to entering the study. Dilated cardiomyopathy of ischemic origin is known to be the most common type of dilated cardiomyopathies.[21]

The role of left atrium and left atrial appendage for stroke

Framingham Heart Study investigators found that LA size remained a significant predictor of stroke in men and death in both genders after adjusting for age, hypertension, diabetes, smoking, ECG LV hypertrophy, prevalent atrial fibrillation, and prevalent congestive heart failure or myocardial infarction.[7] The Northern Manhattan Stroke Study also showed that LA size was associated with an increased risk of ischemic stroke.[22]

Several theories have been proposed to find explanations for the relationship of LA enlargement and stroke or all-cause mortality. One of the theories states the possible cause of thrombus formation in patients with dilated LA might be blood stasis.[7] Increased LA size occurs as a result of raised intra-atrial pressure, which in turn influences a reduction in LAA flow velocity, resulting in an increased risk of thrombus formation and potential subsequent embolic stroke.[7] On the other hand, dilation of the LA may serve as an indicator for structural heart disease, hypertension, or increased LV mass and by this means, it may be related to augmented risk for stroke and mortality.[7]

The LAA, on the other hand, is the most common cardiac location of thrombi formation. Three specific variables of the LAA have been studied with respect to thrombus formation and stroke, which include: LAA size, flow pattern, and flow velocity. As mentioned earlier, 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. LAA is also demonstrated to be larger in patients with SEC in LAA.[23] LAA has also been found to be of larger size in patients with LAA thrombus.[8] Reduced or absent LAA inflow and outflow velocities and LAA low EF are also strongly correlated to LAA SEC and thrombus formation.[8]

Epidemiological features of patients with dilated heart and their relation to left atrium and left atrial appendage

Atrial fibrillation is a well-known risk factor for embolic stroke and mortality.[7] That is why we included in the study only patients in sinus rhythm to avoid the influence of atrial fibrillation on thrombus formation and LA size.

Several studies have demonstrated that obesity is associated with increased LA dimension independent of hypertension.[24,25] Obesity has been linked to thrombosis. Patients with higher BMI have higher fibrinogen levels, which are associated with the presence of LA/LAA thrombus.[26] Interestingly, our results showed that body mass correlated inversely with both, LA and LAA size. However, chronic heart failure is known to induce general wasting in heart failure patients.[27] This might be the reason that in our patients with dilated hearts, the relationship of body weight to LA and LAA size did not correspond to findings by other authors, in contrary it showed a significant inverse relation. Furthermore, reduction of body weight resulted to be an independent predictor of LA area and volume enlargement in our study population. We believe to be the first authors to notify that lower body weight in patients with dilated cardiomyopathy, in sinus rhythm, should raise doubts regarding larger LA.

Our data showed a positive relationship between age and LA size (diameter, area, and volume). Likewise, a relation between LA dilation and aging, even in healthy patients, has been documented.[28]

Male gender is found to be in relationship to LA diameter, but it also resulted to be an independent predictor of LA size in our study population. As discussed earlier, Framingham Heart Study investigators found that LA size remained a significant predictor of stroke in men.[7]

Diabetes and coronary disease were related to LA size in our patients, and this is comparable to results reported by other authors.[29,30]

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Unfortunately, we were unable to find epidemiological predictors that could suggest us for LAA dilation or dysfunction.

CONCLUSIONS

Male patients with dilated cardiomyopathy at sinus rhythm with lower body weight tend to have larger LA and consequently might be at higher risk of developing atrial thrombus and its subsequent consequences. Therefore, these patients should be watched more carefully and possibly initiate the anticoagulation therapy, despite the fact that they are in sinus rhythm and their LV systolic function is not severely impaired.

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Conflicts of interest

There are no conflicts of interest.

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