Left Atrial Enlargement an Early Predictor for Development of Systolic Dysfunction – Results of a Cross-Sectional Study Conducted in Georgia

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Doi: 10.19044/esj.2017.v13n33p1  URL:http://dx.doi.org/10.19044/esj.2017.v13n33p1

Abstract

Background and Aims: Left ventricular systolic dysfunction, even asymptomatic, is associated with the development of heart failure (HF) and all-cause mortality. Left ventricular ejection fraction (LVEF) is the most commonly used marker of left ventricular systolic function. It is well established that early detection and treatment of reduced LVEF, as well as the aggressive management of predisposing conditions, delays the manifestation of HF. Our study aimed to measure the association between LVEF and other echocardiographic variables in a population with LVEF within the normal range and without symptoms of HF. Methods: We conducted a cross-sectional study in 2008-2009. Results: We analyzed echocardiographic and clinical data of 146 patients: 66.4% were women; mean age was 55 (40 –69 years). LVEF significantly correlated only with left atrium (LA) size (Beta -0.266, p < 0.05). The correlation was inverse and remained significant after adjusting for age, gender, obesity, diabetes, arterial hypertension, left ventricular hypertrophy, pulmonary systolic pressure, mitral regurgitation, and diastolic dysfunction. Conclusions: We found that the earliest structural change associated with LVEF tendency to decrease was LA size. Further research is needed to assess the LA enlargement as an early predictor of systolic dysfunction development.

Keywords: Echocardiography, Left Ventricular Systolic dysfunction, Ejection Fraction, Left Atrium

Introduction

Left ventricular systolic dysfunction, even asymptomatic, is a high risk for development of heart failure (HF), coronary vascular disease (CVD) and all-cause mortality [Yeboah J. et al., 2012, Abhayarantna W. P, 2012,

The predisposing conditions of HF include CVD, smoking, arterial hypertension, obesity, diabetes, valvular heart disease, and male sex [He J et al., 2001, Baldasseroni S, et al., 2002].


This paper describes further analysis of the data collected as part of our study published in 2016 and 2017 [Rukhadze E, Bregvadze-Tabagari N, Tvildiani L, 2016] and between echocardiographic characteristics and the CVD risk groups defined by WHO (World Health Organization) /ISH (International Society of Hypertension) [Rukhadze E, Bregvadze-Tabagari N, Tvildiani L, 2017].

Our study aimed at measuring the association between LVEF and other echocardiographic variables in a population without symptoms of HF and preserved LVEF.

**Material and Method**

The population of our study is a subpopulation of a larger study [Shanthi M, 2005, Toidze M, Tabagari S, Mendis S, Norder P, Bregvadze-Tabagari N, Tvildiani L, Phkhaladze G, Talakvadze T, 2012]. We conducted a cross-sectional study in Sachkhare Medical Center in Georgia from September 2008 to December 2010. The study protocol was approved by the Sachkhare Medical Center and David Tvildiani Medical University Ethics committees. Participation was voluntary. All participants gave written informed consent.

The study group included 177 participants without clinically manifested cardiovascular disease, who underwent routine transthoracic...
echocardiography during the period of “Cardiovascular Risk Assessment of the Georgian Population study” [Toidze M et al., 2012]. We excluded 31 (17.5%) participants from our analysis. For Exclusion we used the following criteria: LVEF < 50 %, severe valvular heart disease defined by European Association of Echocardiography (EAE) and American Society of Echocardiography (ASE) recommendations [ASE COMMITTEE RECOMMENDATIONS for Chamber Quantification, 2005], and atrial fibrillation.

Out of 146 participants included in the final statistical analysis, ??? (66.4%) were women; mean age was 55 (40 –69 years).

Assessment of CVD risk factors
For hypertension we used Joint National Committee (JNC 7) definitions [ESC Committee for Practice Guidelines to improve the quality of clinical practice and patient care in Europe, 2007]; Hyperlipidemia was defined as fasting total cholesterol ≥ 5.2 mmol/L (≥200 mg/dl); diabetes was defined as fasting glucose ≥ 7mmol/L (≥ 126 mg/dl) or use of insulin or oral hypoglycemic medications. Persons who smoked regularly during the previous 12 months were classified as smokers.

Echocardiography assessment
We performed Echocardiography on Philips Sonos 7500 with Secondary Harmonic Imaging by the recommended technique for transthoracic quantitative evaluations [ASE COMMITTEE RECOMMENDATIONS for Chamber Quantification, 2005].

We assessed the mean values and correlation of the following echocardiographic characteristics: left ventricular end-diastolic diameter (LVEDD), interventricular wall thickness (IWS), posterior wall thickness (PWT), left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), left atrium diameter (LAD), and pulmonary systolic pressure (PSP).

We evaluated Left ventricular systolic function by the method of discs (Simpson’s rule) - using area tracings of the LV cavity [ASE COMMITTEE RECOMMENDATIONS for Chamber Quantification, 2005]. For the LA measure, we used LA anteroposterior linear dimension in the parasternal long-axis view by 2 Dimensional (2D) echocardiography [ASE COMMITTEE RECOMMENDATIONS for Chamber Quantification, 2005]. The PSP was assessed by continuous-wave Doppler of tricuspid regurgitation [Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E, 1985]. For assessment of left ventricular diastolic function, we analyzed mitral inflow patterns defined by pulsed wave (PW) Doppler. Additionally, in some cases, we used PW tissue Doppler (DTI) for assessment mitral
annular early and late diastolic velocities [Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography, 2009].

**Statistical Analysis**

We analyzed the data using IBM SPSS Statistics version 21. Descriptive statistics (means, standard deviations, and proportions) were calculated for cardiovascular risk factors and echocardiographic characteristics. Linear regression method was used to establish correlations between EF and other echocardiographic variables. A p-value <0.05 was defined as statistically significant.

**Results**

Our study population is described in table 1. Most of our participants were women; age varied from 40 to 69 (mean age 55). Obesity (OB) was present in 56.80% of study population; Diabetes Mellitus (DM) (12.30%); Hyperlipidemia (19.20%); Smoking (11.60%); Arterial hypertension (47.30%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>97 (66.4)</td>
</tr>
<tr>
<td>Obesity</td>
<td>93 (56.8)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>18 (12.3)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>28 (19.2)</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (11.6)</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>69 (47.3)</td>
</tr>
<tr>
<td>LVH</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>DF (impaired relaxation / pseudonormal)</td>
<td>124 (84.9)</td>
</tr>
<tr>
<td>MR (1st degree / 2nd degree)</td>
<td>146 (94.5)</td>
</tr>
</tbody>
</table>

**Table 1.** Demographic, Clinical and Echocardiographic Characteristics (N=146)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>54.75 (8.9)</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>10.4 (1.5)</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>10.3 (1.5)</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>40.8 (4.5)</td>
</tr>
<tr>
<td>PSP (mmHg)</td>
<td>28.3 (9.5)</td>
</tr>
<tr>
<td>LVD (mm)</td>
<td>48.9 (4.6)</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>102.2 (24.7)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61.5 (4.9)</td>
</tr>
</tbody>
</table>

Mean values of all evaluated echocardiographic variables (LVD, IVS, LVEDV, PSP and EF) except LA were in the normal range, while LA diameter was slightly increased (normal value < 40 mm). Left ventricular Hypertrophy (LVH) defined by left ventricular wall thickness was present only in 4.8 % of study population. Left ventricular diastolic dysfunction (impaired relaxation and pseudonormal type) was presented in 84.9 % of the study population, mitral regurgitation (first and second degree – 94.5 %).

In table 2 is represented the correlation between LVEF and some of the traditional CVD risk-factors and echocardiography characteristics. The LVEF significantly correlated only with LA diameter (inverse correlation). This correlation remains significant (Beta -0.266, p < 0.05) after adjusting for age, gender and presence or absence Obesity, Diabetes Mellitus, Arterial Hypertension and echocardiography defined left ventricular hypertrophy, Pulmonary Systolic pressure, and presence or absence mitral regurgitation and diastolic dysfunction.

**Table 2. Correlation of LVEF with CVD risk-factors and echocardiography characteristics.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Beta</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>-0.266</td>
<td>0.032</td>
</tr>
<tr>
<td>Age</td>
<td>-0.054</td>
<td>0.572</td>
</tr>
<tr>
<td>Gender</td>
<td>0.060</td>
<td>0.498</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.027</td>
<td>0.756</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>-0.067</td>
<td>0.436</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>-0.094</td>
<td>0.283</td>
</tr>
<tr>
<td>LVH</td>
<td>0.039</td>
<td>0.654</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.042</td>
<td>0.627</td>
</tr>
<tr>
<td>MR</td>
<td>0.014</td>
<td>0.900</td>
</tr>
<tr>
<td>DF</td>
<td>0.115</td>
<td>0.317</td>
</tr>
<tr>
<td>PSP</td>
<td>-0.111</td>
<td>0.265</td>
</tr>
</tbody>
</table>

LA, Left atrium diameter; LVD, LVEF, Left ventricular ejection function; PSP, Pulmonary Systolic Pressure; MR, Mitral regurgitation; DF, Diastolic function, LVH, Left ventricular hypertrophy.

**Discussion**

Our study revealed there is a strong correlation between LA size and EF in a population without any clinical presentation of HF, with a slightly increased mean LA size, but a reserved mean EF. The correlation remains significant after adjusting for age, echocardiography evaluated LVH, the presence of Diabetes Mellitus and Obesity. As it was mentioned in our previous studies, LA was the echocardiographic variable that correlated with most CVD risk factors (age, BMI, WC, SBP, and TCH). Age and obesity variables (WC and BMI) correlated with most of the echocardiographic characteristics [Rukhadze E, Bregvadze-Tabagari N, Tvildiani L, 2016]; In
different WHO-ISH risk groups, statistically significant differences were established for LA, PSP, and EF: LA and PSP increased from low to high-risk groups, while EF decreased, but remained in normal range.

It means LA enlargement is a more sensitive marker than EF reduction, can occur earlier, and may be considered as an early predictor of systolic dysfunction.


According to the results of PAMELA study, which estimated the risk of cardiovascular events, cardiovascular mortality, and all-cause mortality associated with the LA enlargement alone or combined with echocardiographic LVH in 1,785 representatives of the general population, subjects with isolated LA enlargement exhibited a significant increase in the adjusted risk of combined fatal and nonfatal cardiovascular events [Bombelli M et al, 2014].

Similar results were obtained in CARDIA study, which included young adults above the clinically established Framingham 10-year global CV risk score. The combined endpoint (incident fatal or non-fatal cardiovascular disease: myocardial infarction, heart failure, cerebrovascular disease, peripheral artery disease, atrial fibrillation/flutter) was determined after 20 years. LA size measurements independently predicted the clinical outcomes, but without altering risk classification [Armstrong A et al., 2014].

We can conclude LA enlargement can be considered an early predictor of reducing EF and thus developing systolic dysfunction. Further studies needed to assess the cost effectiveness of routine echocardiographic examination of patients without clinical manifestation of HF. In patients with increased LA size, but otherwise normal structural echocardiographic parameters, risk modification should be more aggressive to delay the manifestation of HF. Additional study is needed to confirm our hypothesis.
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20. Members of the Chamber Quantification Writing Group are: Roberto M. Lang, MD, FASE, Michelle Bierig, MPH, RDCS, FASE, Richard B. Devereux, MD, Frank A. Flachska, MD, Elyse Foster, MD, Patricia A. Pellika, MD, Michael H. Picard, MD, Mary J. Roman, MD, James Seward, MD, Jack S. Shanewise, MD, FASE, Scott D. Solomon, MD, Kirk T. Spencer, MD, FASE, Martin St John Sutton,
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