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Original article

Factors influencing left atrial volume in a population with preserved ejection fraction: Left ventricular diastolic dysfunction or clinical factors?

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ABSTRACT

Background: Increased left atrial volume (LAV) predicts a higher incidence of cardiovascular events and is widely recognized as a major surrogate marker of left ventricular (LV) diastolic dysfunction (DD). Although the pathophysiology of LA enlargement is probably multifactorial, few studies have examined comprehensively the clinical factors that lead to LA enlargement in the absence of valvular disease or LV systolic dysfunction. Therefore, we investigated associations between LAV and several clinical and echocardiographic parameters including DD.

Methods: We enrolled 557 subjects without significant valve disease or LV systolic dysfunction from the health check-up clinic retrospectively. We performed univariable and multivariable linear regression using ln LAV index as the dependent variable and the following independent variables: gender, age, smoking status, drinking habit, hypertension, diabetes, body mass index (BMI), LV ejection fraction, DD, LV mass index, hemoglobin, serum creatinine, serum total cholesterol, serum uric acid, serum sodium, and serum iron.

Results: In multivariable analysis, LAV index was independently associated with BMI, lower hemoglobin, and moderate and severe DD compared with normal diastolic function ($p < 0.001$), but not with mild DD ($p = 0.70$).

Conclusions: LA enlargement was independently associated with moderate and severe DD, but not with mild DD. Furthermore, obesity and lower hemoglobin were associated with LAV independently of DD.

Introduction

Left atrial (LA) enlargement can be easily assessed by echocardiography and is an important predictor of future cardiovascular events including stroke, atrial fibrillation, congestive heart failure, and death [1–4]. Thus, it is important to clarify the clinical factors that are associated with LA enlargement from the viewpoint of preventing LA

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remodeling. In the clinical setting, there are few reports on the factors that lead to atrial remodeling in the absence of mitral valve disease [2,3]. In contrast, experimental studies have shown that LA enlargement is associated with numerous signaling pathways, such as the renin–angiotensin–aldosterone system, transforming growth factor-β1, and oxidative stress [5,6]. Although the pathophysiology of LA enlargement is probably multifactorial, the clinical factors independently associated with LA enlargement have not been well defined. Especially, associations between LA enlargement and the factors that can cause congestive heart failure or atrial fibrillation have not been adequately investigated.

A previous study [7] showed a graded relationship between LA enlargement and the progression of left ventricular (LV) diastolic dysfunction (DD). An increased LA volume is generally accepted as an echocardiographic indicator of DD [8]. Thus, the current guidelines of the European Association of Echocardiography and American Society of Echocardiography recommend the use of LA volume measurements for grading DD (I to III). On the other hand, the current guideline also recommended that one should consider LA volume measurement in conjunction with patients' clinical status [8]. However, the question remains to what extent we should consider patients' clinical status in interpreting LA volume. For instance, when impaired relaxation (DD grade I) occurs, LA volume is unlikely to increase because LA pressure is not elevated at the stage of mild DD [9]. Moreover, some recent studies showed that LA volume might not increase with advancing age [10,11], despite the progression of DD with age [10,12]. These findings suggest there is a clinical necessity to elaborate how much each clinical status can influence dilation of LA volume. In other words, we questioned the extent to which LA enlargement could serve as a surrogate marker of DD.

We sought to determine the major independent clinical factors that are associated with LA enlargement in subjects without valvular disease or LV systolic dysfunction, and to clarify the associations between LA enlargement and DD.

Methods

This retrospective cross-sectional study was approved by the institutional ethics committee of the University of Tokyo.

Subject recruitment and enrollment

A total of 810 subjects underwent echocardiography in the health check-up clinic at the University of Tokyo Hospital between July 2009 and July 2012. Our clinic provides a health check-up for the promotion of health through voluntary medical examinations; the systems are very popular in Japan termed as "Ningen Dock". Our echo laboratory is maintained under the guidelines of the Japanese Society of Echocardiography [13]. The exclusion criteria included the following: a prior/current history of heart valve disease (7 subjects) or myocardial infarction (12 subjects), an LV ejection fraction <50% (7 subjects), atrial fibrillation (15 subjects), or poor echocardiographic images (212 subjects). We reviewed echocardiographic images from the apical windows in all of 810 cases, in order to make sure if they were adequate for measuring LA volume. We eventually had to exclude 212 cases from our analysis. There were 557 subjects who underwent multiple examinations. The numbers of subjects who underwent health check-ups once, twice, three times, four times, and five times were 393, 82, 79, 2, and 1, respectively. Therefore, among a total of 1148 heath check-up studies including echocardiography, a total of 807 examinations were included in our final analysis.

Information regarding gender, birth date, lifestyle, and medical history for each subject was obtained through a self-administered questionnaire and confirmed through an interview with a physician. Blood pressure was measured twice using an automatic device after several minutes of rest in a seated position. Subjects on hypertensive medication or with a blood pressure > 140/90 mmHg were categorized as having hypertension. Patients on diabetic medication or with a hemoglobin A1C > 6.5% were categorized as having diabetes. Prior/current valvular disease or old myocardial infarction was recognized through a self-administered questionnaire. We also confirmed current valve disease by an echocardiographic examination. Body height and weight were measured during hospital visits, and body mass index (BMI) was calculated. We adopted the international classification of adult underweight, overweight, and obesity according to BMI [14]: underweight as BMI < 18.5, normal weight as $18.5 \leq$ BMI < 25, overweight as $25 \leq$ BMI < 30, and obese as $30 \leq$ BMI. Blood samples were collected after an overnight fast.

Echocardiographic imaging

Echocardiography was performed to screen for valvular stenosis or regurgitation using commercially available systems. We excluded subjects with significant regurgitation or stenosis from the analysis since valve disease has a strong influence on LA volume. LV systolic function was assessed in accordance with published guidelines [15]. LV mass was calculated using diastolic measurements of LV internal diameter and wall thickness on 2D echocardiography according to the formula recommended by the American Society of Echocardiography: LV mass $(g) = 0.8 \times \{1.04[(IVST + LVID + PWT)^3 - (LVID)^3]\} + 6\ g$ (IVST, interventricular septal wall thickness; LVID, LV internal diameter; PWT, posterior wall thickness) [16]. LV mass index was calculated as LV mass/body surface area. LA volume was measured by the study investigators (T.N., M.H.) using the biplane area–length method in accordance with the guidelines [8]. Then, LA volume index (LAVI) was calculated as LV volume/body surface area. To estimate inter- and intra-observer variability, two independent observers performed echocardiographic measurements of LAVI in randomly selected 30 subjects and one observer repeated the measurements subsequently. Inter- and intra-observer variability were 12.9 ± 9.6% and 8.3 ± 6.1%, respectively.

We evaluated DD as previously described [17] using transmitral diastolic flow by pulsed-wave Doppler from an apical four-chamber view and pulsed-tissue Doppler imaging (TDI) of LV myocardial velocities. Peak velocities of the early (*E*-wave) and late (*A*-wave) phase of the mitral inflow pattern from Doppler recordings were measured, and their ratio (*E*/*A*) was calculated. We measured the peak systolic (*S*) and peak early diastolic (*E*′) velocities of the septal mitral annulus by pulsed-TDI. We calculated the ratio between the *E* and the *E*′ waves (*E*/*E*′) as a preload-independent index of LV filling pressure. Diastolic function was classified as normal or abnormal (DD) [18], and then DD (when it was present) was assigned one of three grades based on previous studies [17–19]: (i) *E*/*A* ratio ≤ 0.7 (grade I, impaired relaxation); (ii) *E*/*A* ratio > 0.7 and ≤1.5 and *E*′ velocity < 7 cm/s (grade II, pseudo-normalized pattern); or (iii) *E*/*A* ratio > 1.5 and *E*′ velocity < 7 cm/s (grade III, restrictive pattern).

Variable selection

We selected the clinical variables that have prognostic value for cardiovascular events, such as atrial fibrillation, congestive heart failure, or death. We referenced the variables in the Seattle Heart Failure Model [20], which is one of the major predictive models for survival of heart failure patients. We included echocardiographic variables with prognostic significance such as LV ejection fraction, LV mass index, and LV diastolic function [2,3,21–24]. Lastly, we