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Original article

Early menopause does not influence left ventricular diastolic dysfunction: A clinical observational study in healthy subjects

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ABSTRACT

Background: The prevalence of left ventricular diastolic dysfunction (LVDD) sharply increases in women after their 50s and may contribute to the high prevalence of diastolic heart failure in elderly women. A decrease in estrogen levels after menopause is postulated to be one of the mechanisms responsible for this phenomenon. However, there is a paucity of data on the relationship between the timing of menopause and the progression of LVDD in the clinical setting; thus, we investigated this relationship in healthy postmenopausal women.

Methods: We enrolled 115 women and divided them into two groups according to median menopause age: 61 who experienced menopause at ≤50 years (early menopause group), and 54 who experienced menopause at >50 years (late menopause group). We compared the echocardiographic and clinical characteristics between the two groups.

Results: There were no significant differences in LV diastolic parameters (mitral E/A, $p = 0.561$; e', $p = 0.052$; E/e', $p = 0.081$; DCT, $p = 0.082$; prevalence of LVDD class, $p = 0.801$), as well as other echocardiographic parameters and clinical characteristics between the two groups. Multivariate linear regression analysis showed that the independent determinants of LVDD were age and body mass index, but not the timing of menopause.

Conclusions: Early menopause did not influence the progression of LVDD in postmenopausal women. The sharp progression of LVDD in elderly women is complex and probably influenced by multiple factors.

Introduction

Almost half of patients with symptomatic heart failure (HF) have been shown to have preserved left ventricular (LV) ejection fraction with diastolic dysfunction [1,2]. Although LV diastolic dysfunction (LVDD), the precursor to diastolic HF, progresses with aging in both men and women, diastolic HF is more prevalent in women than in men, especially postmenopausal women [2–4]. Some previous investigations [5–7] showed a sharp decrease in LV diastolic function in healthy women after 50–60 years of age compared with men, suggesting that menopause may accelerate the progression of LVDD with advancing age in women. Menopause is characterized by the natural cessation of menstruation; and during this time, there is a dramatic decline in the production of ovarian hormones, especially estrogen. Some animal studies [8–10] have shown that estrogen has a cardioprotective effect, and its deficiency may aggravate LVDD. These findings suggest that the loss of the cardioprotective effect of estrogen after menopause may play an important role in the deterioration of LVDD in elderly women [11]. However, few previous studies have addressed whether early menopause influences LVDD in postmenopausal women in the clinical setting. Therefore, we aimed to investigate

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whether age at natural menopause influences the progression of LVDD in healthy postmenopausal women by comparing LV diastolic function between women who experienced early menopause (early menopause group) and those who experienced late menopause (late menopause group).

Materials and methods

Study population

This study was designed as a cross-sectional study, and we enrolled 118 postmenopausal women with a preserved LV ejection fraction who did not suffer from overt heart diseases including a prior/current history of valvular heart disease or myocardial infarction. All subjects enrolled underwent a medical examination in the Epidemiology and Preventive Medicine Department at the University of Tokyo Hospital between June 2007 and July 2012. Subjects with an LV ejection fraction $< 50\%$, atrial fibrillation, or poor echocardiographic images were excluded from the study. Patients with diabetes mellitus and hypertension were also excluded, because these comorbidities could influence LVDD [12,13]. We used the latest data if the subjects underwent multiple medical examinations. We excluded two subjects whose age at the time of menopause was unknown. In addition, we excluded a subject with extreme anemia (hemoglobin 5.2 g/dl), since severe anemia could elevate LV filling pressure through activation of the renin-angiotensin-aldosterone system and increased blood volume [14]. The 115 subjects who were included in the final analysis were divided into two groups according to median menopause age: subjects who experienced menopause at $\leq$50 years old (early menopause group), and subjects who experienced menopause at $>$50 years old (late menopause group). This observational study was approved by the institutional ethics committee of the University of Tokyo.

Clinical and laboratory parameters

Clinical information including, height, weight, systolic blood pressure, diastolic blood pressure, and heart rate were measured, and body mass index was calculated. In addition, subjects were asked to report at what age they experienced menopause defined as the natural cessation of bleeding, and the duration after menopause was calculated. Moreover, history of pregnancy, history of delivery, treatment of hypertension, treatment of diabetes, treatment of dyslipidemia, and smoking status were obtained from a questionnaire completed by all subjects.

Routine laboratory measurements included fasting blood sugar, hemoglobin (Hb) A1c, low-density lipoprotein cholesterol (LDL-cho), high-density lipoprotein cholesterol (HDL-cho), hemoglobin, serum iron, and creatinine were performed using standard assays.

Conventional, 2-dimensional, and Doppler echocardiography

A complete 2-dimensional and Doppler echocardiographic examination was performed using commercially available equipment. Echocardiographic equipment was maintained according to the guideline of the Japanese Society of Echocardiography [15]. LV and left atrial chamber quantification was performed with 2-dimensional echocardiography according to the guidelines of the American Society of Echocardiography (ASE) [16]. The thickness of the intraventricular septum and the LV posterior wall were measured at end-diastole. LV mass was calculated using diastolic measurements of LV diameter and wall thickness on 2-dimensional echocardiography according to the formula provided by the ASE [16] and was indexed by body surface area. LV ejection fraction was calculated using the Teichholz formula. To assess LV diastolic function, pulsed wave Doppler imaging of mitral inflow and tissue Doppler imaging of mitral annular motion at the septum were performed as recommended by the ASE [17]. The peak velocity of early (E) and late (A) diastolic flow, and the early flow deceleration time (DCT) were measured from pulsed wave Doppler imaging of mitral inflow in the apical 4-chamber view. In addition, the E/A ratio was calculated. Early diastolic annular velocity (e') was measured from tissue Doppler imaging of mitral annular motion at the septum in the apical 4-chamber view, and the ratio of peak early diastolic transmitral flow velocity to annular velocity (E/e') was calculated. Maximum left atrial (LA) volume was measured in the apical 4-chamber view and was indexed by body surface area. Furthermore, we classified diastolic function in all subjects into 1 of 4 categories (normal, grade I, grade II, or grade III), according to previous reports [17,18] and clinical status.

Statistical analysis

SPSS software (SPSS Inc., Chicago, IL, USA) version 19 was used for all statistical analyses. All variables are expressed as the mean $\pm$ standard deviation. Unpaired t-tests were performed to compare the baseline characteristics (age at the examination, age of menopause, duration after menopause, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood sugar, hemoglobin A1c, LDL-cho, HDL-cho, hemoglobin, serum iron, creatinine, number of pregnancies, and number of deliveries) and echocardiographic parameters (LV end-diastolic diameter, LV end-systolic diameter, LV mass index, LV ejection fraction, peak E, peak A, E/A, e', E/e', DCT, and LA volume index) between the two groups. Chi-square analysis was used to compare the LVDD grade of the two groups. Pearson's linear correlation analysis was used to determine the correlations between the LVDD parameters and the echocardiographic and clinical variables. Multivariate linear regression analysis was performed to assess the factors that determined the LVDD parameters. Variables with $p < 0.1$ in univariate analysis were incorporated into the multivariate linear regression model. A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The distribution of ages at menopause is shown in Fig. 1. Out of 115 subjects, 61 were classified into the early menopause group and 54 were classified into the late menopause group. Table 1 shows the baseline characteristics of the study population. The mean age at the medical examination was similar between the two groups. There were 16 dyslipidemia patients, and there were no significant differences between the two groups in the mean serum LDL-cho and HDL-cho. In this study, 70% of the subjects had a prior pregnancy and 62% delivered a fetus. In the early menopause group, the duration after menopause was significantly longer than in the late menopause group. There were no significant differences in clinical characteristics except for age at menopause and duration after menopause between the two groups.

Comparison of echocardiographic parameters between the two groups

Table 2 shows a comparison of the echocardiographic parameters between the two groups. All subjects had an LV ejection fraction $>$50% and there were 6 subjects who had LV hypertrophy (LV mass index $>95\ g/m^2$) [16]. There was no significant difference in LV ejection fraction or LV mass index between the two groups. There were also no significant differences in any of the diastolic parameters including the E/A ratio, e', E/e', or LA volume index between the two groups. Although, difference in

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