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Original article

Elevated left ventricular filling pressure estimated by E/E' ratio after exercise predicts development of new-onset atrial fibrillation independently of left atrial enlargement among elderly patients without obvious myocardial ischemia

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ABSTRACT

Objective: To determine whether elevated left ventricular (LV) filling pressure estimated by raised Doppler E velocity to tissue Doppler E' velocity ratio (E/E') after exercise is associated with increased risk of new-onset atrial fibrillation (AF) in non-ischemic elderly patients.
Background: Prognostic importance of exercise induced LV diastolic dysfunction remains uncertain.
Patients and methods: We studied 147 elderly patients (73 ± 5 years) who underwent treadmill stress echocardiography. Patients with exercise induced LV wall motion abnormality were not included. Doppler and tissue Doppler measurements were done before treadmill exercise and immediately after the post-stress image acquisition, and E/E' ratio was measured. Raised E/E' was defined as $E/E' \geq 15$, and left atrial (LA) enlargement was defined as LA volume index $\geq 34\,\text{ml/m}^2$. Using Cox proportional hazards regression analysis, predictor of new-onset AF was determined. Using Kaplan–Meier analysis, we evaluated association between raised post-exercise E/E' or LA enlargement with new-onset AF.
Results: During the follow-up period (median = 67 months), there were 25 new-onset AF. Cox proportional hazards regression analysis demonstrated that male gender [hazard ratio (HR) 3.294; $p = 0.0117$], LA enlargement (HR 3.576; $p = 0.0017$), and raised post-exercise E/E' (HR 3147; $p = 0.0068$) were the best predictors of new-onset AF. Kaplan–Meier survival plot demonstrated that patients with both LA enlargement and raised post-exercise E/E' developed new-onset AF most frequently. There was no significant difference in outcome between patients with isolated raised post-exercise E/E' or isolated LA enlargement.
Conclusions: Raised E/E' ratio after exercise provides significant prognostic information for predicting new-onset AF in non-ischemic elderly patients. This prognostic value of raised post-exercise E/E' is independent of and incremental to the LA enlargement.

Introduction

With aging, prevalence of atrial fibrillation (AF) increases, and AF is the most common cardiac arrhythmia in elderly patients. Additionally, as the population ages, the number of people with AF is rising dramatically [1–4].

AF could be responsible for increased mortality and various morbidities including clinical symptoms, impaired cardiac function, and systemic embolism, particularly ischemic stroke [5–8]. Thus, prediction and prevention of new-onset AF has become intensely investigated, due to its clinical importance.

Left ventricular (LV) diastolic dysfunction has been found to be associated with the development of AF and with major adverse cardiovascular events (MACE) such as cardiac sudden death, acute myocardial infarction (MI), congestive heart failure (CHF) and stroke [9–13]. Assessment of diastolic function used to be performed at rest. However, many elderly patients present with exertional dyspnea, but have normal LV filling pressure at rest. Therefore, it is important to evaluate LV filling pressure with exercise. Diastolic stress echocardiography has been utilized to evaluate diastolic function during exercise or post-exercise [14–18]. It has been reported that elevated LV filling pressure estimated by raised Doppler E velocity to tissue Doppler E' velocity ratio (E/E') after exercise has incremental prognostic value over clinical variables and exercise wall motion analysis [19]. However, there is only a limited study reporting the prognostic importance of exercise-induced LV diastolic dysfunction to predict new-onset AF [20].

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The purpose of this study was to determine whether elevated LV filling pressure estimated by raised E/E' ratio after exercise is associated with increased risk of new-onset AF in elderly patients with no obvious myocardial ischemia.

Methods

Study patients

From January 2005 to December 2008, 342 consecutive patients underwent clinically indicated treadmill stress echocardiography at Takagi Cardiology Clinic, Kyoto, Japan. Patients with unstable angina, decompensated CHF, or severe chronic obstructive pulmonary disease were not included. All patients were referred for exercise stress echocardiography (ExE) to evaluate known or suspected coronary artery disease (CAD) and to evaluate the origin of exertional dyspnea. There were 146 patients with age < 65 years. The remaining 196 elderly patients with age ≥65 years were recruited to the present study. We excluded 10 patients because of significant regional LV wall motion abnormality (WMA) at rest, 2 patients because of documented history of AF, and 3 patients because of more than moderate valvular heart disease. Thirty-four patients who developed new LVWMA after stress were also excluded from the present study. Because LV hypertrophy is an important cause of exertional dyspnea, we did not exclude patients with LV hypertrophy. Finally, 147 elderly patients (73 ± 5 years; 83 males) without inducible myocardial ischemia were enrolled to the present study. All participants gave informed consent before the examinations.

Clinical variables, body mass index [=body weight (kg)/height $(m)^2$], and body surface area (m^2) were recorded at the time of the ExE. Medical treatments and a history of hypertension, diabetes mellitus, lipid disorders, smoking, and CAD were abstracted from the medical record at the time of the ExE. CAD was defined as previous coronary revascularization or history of MI.

Treadmill stress echocardiography

All echocardiographic recordings were performed using two commercially available ultrasound machines (Vivid FiVe with 2.5 MHz transducer from January 2005 to December 2006, and Vivid 7 with M4S transducer from January 2007 to December 2008, GE Health Care, Milwaukee, WI, USA).

The baseline echocardiographic assessment included standard two dimensional measurements of LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV end-diastolic dimension (EDD), intraventricular septal thickness (IVS), left ventricular posterior wall thickness (LVPW), left atrial dimension (LAD), and left atrial (LA) volume. LV volumes were measured using biplane modified Simpson's method and LV ejection fraction (LVEF) was calculated. LV volumes were normalized for body surface area. LV mass was calculated using following formula ($\text{LV mass} = 1.05 \times [(\text{EDD} + \text{LVPW} + \text{IVS})^3 - \text{EDD}^3] - 13.6$) and normalized for body surface area to obtain LV mass index (LVMI) [21]. LAD was also normalized for body surface area. End-systolic (maximum) LA volume was measured using biplane modified Simpson's method and normalized for body surface area to obtain LA volume index (LAVI). LA enlargement was defined as LAVI ≥ 34 ml/m^2 in the present study [22].

Using pulsed-wave Doppler echocardiography, the transmitral flow (TMF) velocity profile was recorded in the apical four-chamber view or apical long-axis view with the sample volume positioned at the level of the mitral valve tips in diastole. The early (E) and atrial (A) TMF velocities, and deceleration time of early left ventricular filling (E-dct) were measured. Using tissue Doppler echocardiography in the apical four-chamber view, peak early diastolic velocity of septal mitral annulus (E') was measured. Increased LV filling pressure at rest was defined as an E/E' ratio ≥15 [23]. Doppler and tissue Doppler parameters were measured as the average of 2–3 cardiac cycles.

Subsequently, all patients underwent maximum symptom limited treadmill exercise test by using the standard Bruce protocol or modified Bruce protocol (Fukuda Denshi Co. Ltd., Tokyo, Japan). Details of the treadmill stress echocardiography in our institution were described previously [17]. Briefly, two dimensional echocardiographic images using standard apical four-chamber view, apical two-chamber view, and apical long-axis view were acquired at baseline and immediately after peak exercise and stored digitally. Immediate post-exercise images were obtained within one minute after the termination of exercise. Regional wall motion of the left ventricle was graded according to 16 segments model, and development of new wall motion abnormality was considered as a marker of exercise-induced myocardial ischemia. As we have previously reported, the sensitivity, specificity, and diagnostic accuracy of the conventional treadmill stress echocardiography for detecting patients with CAD are 87%, 80%, and 84%, respectively, in our clinic [24].

Pulsed-wave Doppler echocardiography and tissue Doppler echocardiography were performed again shortly after the treadmill stress subsequently to the post-exercise image acquisition. Post stress Doppler and tissue Doppler recordings were performed in early recovery (within 2–3 min of cessation of exercise) at the earliest time that the trans-mitral E and A velocities were sufficiently separated to permit measurement. Increased LV filling pressure after exercise was defined as an E/E' ratio ≥15 [16]. Exercise-induced abnormal TMF was defined as post-exercise E/A ratio ≥1.0 [20].

Beta-blockers and other cardiovascular medication were withheld on the day of testing except for short-acting nitrates.

Patient follow-up

Follow-up period was initiated on the day of ExE, and patients were prospectively followed. All patients visited clinic every one to three months, and follow-up data including electrocardiography (ECG) were obtained at each visit. Follow-up period was terminated at January 4, 2012. The primary endpoint for this study was a new-onset AF. New-onset AF was defined by the first presentation of AF that was clinically documented by a physician and confirmed by ECG database (FEV-80, Fukuda Denshi Co. Ltd., Tokyo, Japan). AF was defined as an episode of irregular rhythm with no visible P-wave on the documented ECG recording lasting more than 10 s. Patients with transient symptoms such as palpitations or chest discomfort underwent Holter ECG recording (Holtrec, Nohon Kohden Co., Tokyo, Japan) and/or handheld ECG recording (HCG-801, Omron Healthcare, Kyoto, Japan) to obtain ECG recording when symptoms occur.

Statistical analysis

Categorical variables are expressed as absolute value and percentage (%). Continuous variables are reported as the mean value ± standard deviation (SD).

Differences in categorical variables between two groups were assessed using Fisher's exact test. Differences in continuous variables between two groups were analyzed by Mann–Whitney test. A p-value less than 0.05 was considered to be statistically significant.

To evaluate the incremental benefit of ExE over clinical and resting echocardiographic variables, Cox proportional hazards regression analysis using stepwise method was used. Variables