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Original article

Myocardial performance index derived from pre-ejection period as a novel and useful predictor of cardiovascular events in atrial fibrillation

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ABSTRACT

Purpose: The pre-ejection period-derived myocardial performance index measured from tissue Doppler echocardiography (PEPa-derived MPI) was reported to be associated with left ventricular systolic and diastolic function in atrial fibrillation (AF). However, its relationship with cardiovascular outcomes in AF has never been evaluated. This study sought to examine the ability of PEPa-derived MPI in predicting adverse cardiovascular events in AF patients.

Methods: In 196 persistent AF patients, we performed comprehensive echocardiography with measurement of PEPa-derived MPI using index beat method. The index beat was defined as the beat following the nearly equal preceding (RR1) and pre-preceding (RR2) intervals. The cycle length of index beat and RR1 and RR2 must be >500 ms and the difference between RR1 and RR2 must be <60 ms. Cardiovascular events were defined as cardiovascular death, nonfatal stroke, and hospitalization for heart failure.

Results: In the multivariate analysis, chronic heart failure and increased ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity (*E*/Ea) and PEPa-derived MPI (per 0.1 increase, hazard ratio, 1.104; 95% confidence interval, 1.032–1.182, $p = 0.004$) were associated with increased cardiovascular events. The addition of PEPa-derived MPI to a Cox model containing chronic heart failure, systolic blood pressure, age, diabetes, prior stroke, left ventricular ejection fraction, and *E*/Ea provided an additional benefit in prediction of adverse cardiovascular events ($p = 0.015$).

Conclusions: In AF patients, the PEPa-derived MPI was a useful predictor of adverse cardiovascular events and could offer an additional prognostic benefit over conventional clinical and echocardiographic parameters.

Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia and its prevalence increases with age, reaching 8% in those older than 80 years [1,2]. AF is associated with an increased risk of stroke, heart failure, and all-cause mortality [3]. Thus, early detection of left ventricular dysfunction in AF patients is important in predicting which patients are at high risk of developing cardiovascular (CV) events and in providing therapeutic intervention to reduce the future incidence of CV events and their accompanied medical and social costs. AF is frequently associated with left ventricular diastolic dysfunction, resulting in a considerable risk of developing heart failure with preserved ejection fraction [3–5]. Inherently, left ventricular ejection fraction (LVEF) is not perfect in prediction of CV outcomes in patients with heart failure with preserved ejection fraction. Thus, concurrent consideration of left ventricular systolic and diastolic function may be important and necessary in improving CV outcome prediction in AF patients [6–8].

Myocardial performance index (MPI), a proposed indicator of combined ventricular systolic and diastolic function, is defined as

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the ratio of the sum of isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) over the ejection time (ET) [9–12]. This index has been demonstrated to be a powerful and independent prognostic indicator in non-AF patients [9,13–15]. IVCT was measured from the end of left ventricular diastolic activity to the onset of left ventricular systolic activity. Because of a loss of mechanical atrial function, the end of left ventricular diastolic activity cannot be determined in patients with AF and thus IVCT cannot be obtained in AF patients. In contrast, although IVCT cannot be measured in patients with AF, pre-ejection period (PEP) can be easily obtained in AF patients. The PEP has been reported to correlate well with left ventricular systolic function [16]. Therefore, using tissue Doppler echocardiography, we can measure PEPa, defined as the interval measured from the onset of QRS to the onset of the systolic mitral annular velocity pattern, ETa, defined as the interval measured from the onset to the end of systolic mitral annular velocity pattern, and IVRTa, defined as the interval measured from the end of systolic mitral annular velocity pattern to the onset of diastolic mitral annular velocity pattern on the same cardiac cycle. Recently, we have demonstrated that the PEPa-derived MPI, defined as the ratio of PEPa + IVRTa to ETa, was significantly associated with echocardiographic left ventricular systolic and diastolic function in AF patients [17]. Because the PEPa-derived MPI can concurrently reflect left ventricular systolic and diastolic function, it has a potential to become a useful parameter in prediction of adverse CV events in AF patients. However, the prognostic value of PEPa-derived MPI in AF patients has never been evaluated. Accordingly, the aim of the present study was to examine the ability of PEPa-derived MPI in prediction of CV outcomes in patients with AF. Besides, we also sought whether PEPa-derived MPI could offer an additional prognostic benefit over conventional clinical and echocardiographic parameters in these patients.

Methods

Study patients

This observational cohort study prospectively and consecutively included patients with persistent AF referred for echocardiographic examinations at Kaohsiung Municipal Hsiao-Kang Hospital from April 2010 to June 2012. Persistent AF was defined as AF lasting for at least 7 days, which was confirmed by 12-lead electrocardiography (ECG), 24-h Holter ECG or ECG recording during echocardiographic examination. Patients with severe mitral stenosis ($n = 2$), severe mitral regurgitation ($n = 5$), moderate and severe aortic stenosis or regurgitation ($n = 4$) and inadequate echocardiographic visualization ($n = 8$) were excluded. Besides, four patients who had no beat fulfilled the requirements of index beat in the stored cardiac cycles were also excluded. Finally, 196 persistent AF patients were included in this study. The study protocol was approved by our Institutional Review Board and enrolled patients gave written, informed consent.

Echocardiographic evaluation

The echocardiographic examination was performed by one experienced cardiologist with a VIVID 7 (General Electric Medical Systems, Horten, Norway), with the participant respiring quietly in the left decubitus position. The cardiologist was blind to the other data. Two-dimensional and two-dimensionally guided M-mode images were recorded from the standardized views. The Doppler sample volume was placed at the tips of the mitral leaflets to obtain the left ventricular inflow waveforms from the apical four-chamber view. All sample volumes were positioned with ultrasonic beam alignment to flow. Pulsed tissue Doppler imaging was obtained with the sample volume placed at the lateral and septal corners of the mitral annulus from the apical four-chamber view. The wall filter settings were adjusted to exclude high-frequency signals and the gain was minimized. On the tissue Doppler images, PEPa, IVRTa, ETa, early diastolic mitral annulus velocity (Ea) and systolic mitral annulus velocity (Sa) were average from septal and lateral ones. LVEF was measured using the modified Simpson's method. Left ventricular mass was calculated using Devereux-modified method [18]. Left ventricular mass index (LVMI) was calculated by dividing left ventricular mass by body surface area. Left atrial volume was measured using the biplane area-length method [19]. Left atrial volume index (LAVI) was calculated by dividing left atrial volume by body surface area. The raw ultrasonic data were recorded and analyzed offline using EchoPAC software (EchoPAC version 08; GE-Vingmed Ultrasound AS GE Medical Systems).

Left ventricular dimensions, LVEF, LAVI, LVMI, PEPa, IVRTa, Eta, and PEPa-derived MPI were measured using the index beat method [20–22]. Because their measurements were easy and rapid, the transmitral E-wave velocity (E), E-wave deceleration time, Ea and Sa were obtained from five beats [4] and the data were averaged to give the mean value for later analysis. If the cardiac cycle length was too short to complete the diastolic process, this beat was skipped. Thus, the selection of E, E-wave deceleration time, Ea, and Sa was not always consecutive. In addition, heart rate was determined from five consecutive beats.

Index beat selection

The index beat taken after the nearly equal preceding and pre-preceding intervals was selected from the stored cardiac cycles (at least 15 beats). The preceding and pre-preceding intervals of the index beat must be >500 ms [23], and the difference between them must be <60 ms [22]. The cardiac cycle of the index beat was also >500 m [23]. If patients had no beat that fulfilled the requirements of the index beat in the stored cardiac cycles, we excluded such patients ($n = 4$). If several beats fulfilled the requirements of the index beat in the stored cardiac cycles, we chose the index beat of first appearance to calculate the echocardiographic data. Fig. 1 illustrates the measurement of PEPa, ETa, IVRTa, and PEPa-derived MPI from index beat in a representative patient.

Assessment of association between index beat and average methods

Fifty-one patients were randomly selected for evaluation of the association between PEPa-derived MPI obtained from index beat and average methods. The PEPa-derived MPI obtained from average method was measured from 13 cardiac cycles and the data were averaged to give the mean value for later analysis.

Collection of demographic, medical, and laboratory data

Demographic and medical data including age, gender, and history of diabetes mellitus, hypertension, coronary artery disease, stroke, and chronic heart failure were obtained from medical records or interviews with patients. Study subjects were defined as having diabetes mellitus if the fasting blood glucose level was greater than 126 mg/dL or hypoglycemic agents were used to control blood glucose levels. Similarly, study patients were considered as having hypertension if the systolic blood pressure was $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg or anti-hypertensive drugs were prescribed. Stroke was defined as a history of cerebrovascular accident including cerebral bleeding or infarction. Coronary artery disease was defined as a history of typical angina with positive stress test, angiographically