Simultaneous Doppler Tracing of Transmitral Inflow and Mitral Annular Velocity as an Estimate of Elevated Left Ventricular Filling Pressure in Patients With Atrial Fibrillation

Yasuaki Wada, MD; Kazuya Murata, MD; Takeo Tanaka, MD; Yoshio Nose, MD; Chikage Kihara, MD; Kosuke Uchida, MD; Shinichi Okuda, MD; Takehisa Susa, MD; Yukari Kishida, MD; Masunori Matsuzaki, MD

Background: The time interval between the onset of early transmitral flow velocity (E) and that of early diastolic mitral annular velocity (e') (T<sub>E-e'</sub>) is a good predictor of elevated left ventricular (LV) filling pressure in patients with sinus rhythm. Although the evaluation of LV filling pressure using E/e' has been challenging in atrial fibrillation (AF), the usefulness of T<sub>E-e'</sub> is unknown.

Methods and Results: E and e' were simultaneously recorded using dual Doppler echocardiography in 45 AF patients (30 men; mean age, 69±9 years). E/e' and T<sub>E-e'</sub> were calculated and compared with the pulmonary capillary wedge pressure (PCWP), which was measured invasively. E/e' and T<sub>E-e'</sub> correlated with PCWP (E/e', r=0.57, P<0.001; T<sub>E-e'</sub>, r=0.77, P<0.001). Using receiver operating characteristic analysis, the optimal cut-off for T<sub>E-e'</sub> was 34 ms (sensitivity, 95%; specificity, 88%) and that for E/e' was 14.6 (sensitivity, 50%; specificity, 84%) in order to predict >12-mmHg PCWP. When the combined cut-offs of T<sub>E-e'</sub> >34ms and E/e' >14.6 were used, the sensitivity and specificity of predicting elevated PCWP were improved to 100% and 88%, respectively.

Conclusions: In AF patients, the simultaneous recording of E and e' using dual Doppler echocardiography and the analysis of T<sub>E-e'</sub>, in addition to E/e', improved the accuracy of evaluation of LV filling pressure. (*Circ J* 2012; 76: 675–681)

Key Words: Atrial fibrillation; Left ventricular filling pressure; Tissue Doppler echocardiography

Analysis of the transmitral inflow (TMF) and of the tissue Doppler imaging (TDI)-derived mitral annular velocities is commonly used for evaluating left ventricular (LV) filling pressure,1,2 and these measures provide valuable information for the management of patients with heart failure (HF) and sinus rhythm. In particular, the ratio of the early transmitral peak velocity to the early mitral annular velocity (E/e'), which is used for evaluating LV filling pressure, is widely used in the clinical setting. The E/e' range from 8 to 15 is recognized as a gray or indeterminate zone for the estimation of LV filling pressure.2,3 Furthermore, the measurement of the time interval between the onset of E and the onset of e' (T<sub>E-e'</sub>) has been proposed as another calculation using E and e' that can predict LV filling pressure.4-9 In addition, the clinical utility of T<sub>E-e'</sub> in patients with normal systolic function and an indeterminate E/e' has been reported.10 In contrast, the utilization of TMF and TDI pattern analysis in patients with atrial fibrillation (AF) has not been established because of the lack of atrial contraction and variability of the heart rate. Recently, the usefulness of the simultaneous recording of the ratio of early transmitral peak velocity to flow propagation velocity (E/Vp) and E/e', using a dual Doppler system, for the assessment of LV filling pressure in patients with AF was reported.11-13 The usefulness of T<sub>E-e'</sub> obtained by simultaneous recording of the onset of E and e' for the assessment of LV filling pressure in patients with AF, however, was not evaluated.

The purpose of the present study was therefore to investigate the following: (1) the usefulness of T<sub>E-e'</sub> in patients with AF for the assessment of LV filling pressure using the simultaneous recording of TMF and TDI with a dual Doppler system; and (2) the added benefit of using T<sub>E-e'</sub> to predict LV filling pressure, in addition to the measurement of E/e'.
### Methods

**Subjects**
A total of 45 patients (30 men; mean age, 69±9 years) with chronic AF were evaluated. Patient diagnoses are listed in **Table**. We excluded patients with mitral stenosis, prosthetic mitral valves, moderate to severe mitral regurgitation that was assessed with color Doppler echocardiography, right ventricular dysfunction or renal dysfunction. This study was approved by the institutional ethics review board.

**Echocardiography**
Standard echocardiography was performed using an EUB-7500 digital ultrasound system (Hitachi Medical, Tokyo, Japan) equipped with a 2–4-MHz sector transducer. All images were stored on a hard disk for subsequent analysis. The LV end-diastolic and end-systolic volumes and the LV ejection fraction (LVEF) were calculated using the modified biplane Simpson’s method,[14] and the LV end-diastolic and end-systolic volumes were indexed to body surface area (LVEDVI and LVESVI). Left atrial (LA) volume was assessed using the modified biplane area-length method and was indexed to body surface area. We performed the simultaneous recording of the peak velocity of early transmural flow (E; cm/s) and the tissue Doppler-derived early diastolic mitral annular velocity (e’: cm/s) using the dual Doppler imaging method (**Figure 1**). As shown in **Figure 1**, in order to record the E and e’ velocity profiles in the same cardiac cycles, 2 sample volumes were positioned between the tips of the mitral leaflets and at the mitral annulus, initially at the interventricular septal annulus and then at the lateral annulus. E/e’ and T<sub>e’</sub> were measured for 5 consecutive beats in each of the 2 dual Doppler recordings, and the 10 values were averaged (**Figure 2**). The onset for both Doppler waves was defined as the crossing point of the horizontal axis of the velocity 0 cm/s at the center of the velocity profile line of E or e’.

**Hemodynamic Measurements**
The measurement of the pulmonary capillary wedge pressure (PCWP) was performed within 5 h after echocardiography. Right-sided pressures were obtained with a 6-Fr balloon-tipped pulmonary artery catheter (Swan-Ganz, Baxter Healthcare Corporation) that was introduced through a femoral or jugular vein via a percutaneous approach. The catheter was connected to a strain-gauge pressure transducer and referenced to the midaxillary line in order to obtain the mean PCWP. The pulmonary wedge position was confirmed on chest fluoroscopy, and the balloon tip was gradually inflated until the typical wedge tracing was obtained. Mean PCWP was averaged over 10 consecutive beats during end-expiration apnea.

**Measurement of Brain Natriuretic Peptide (BNP)**
In 30 of the 45 patients, blood samples were drawn from a peripheral vein just after Doppler echocardiography for the measurement of BNP. Blood was immediately placed in chilled glass tubes containing disodium ethylenediamine tetraacetic acid (1.5 mg/ml) and aprotinin (500 KIU/ml). The plasma BNP levels were determined using a highly sensitive immunoenzymometric assay (TOSOH II BNP Assay Kit; Tosoh, Tokyo, Japan).

**Reproducibility**
A total of 10 data points were chosen at random for the re-analysis of T<sub>e’</sub>. A single observer analyzed the data twice at
Assessment of LV Filling Pressure in AF

Figure 1. Measurement of trans-mitral inflow (TMF) and the mitral annular velocity (MAV) using a dual Doppler system. A total of 2 pulsed sample volumes were positioned between the tips of the mitral leaflets and the base of the interventricular septum or left ventricular lateral wall, and E and e’ were measured.

Figure 2. Measurement of T_{E-e’} using a Dual Doppler system. From simultaneous recordings of transmirtal inflow (TMF) and mitral annular velocity (MAV), the time interval was measured between the onset of E and of e’ (T_{E-e’}) for 5 consecutive beats in the same cardiac cycles.
intervals of >1 week apart in order to assess intra-observer variability. Reanalysis was done by a second observer who was blind to the first observer’s measurements. Reproducibility was expressed as the mean percent error (absolute difference divided by the average of the 2 observations).

**Statistical Analysis**

All results are expressed as mean±SD. Statistical analysis was performed using SPSS 16.0J (SPSS Japan, Tokyo, Japan). A linear regression analysis was used to evaluate the correlations between PCWP and the echocardiographic variables and log BNP. The diagnostic utility of T_E-e' in predicting PCWP >12 mmHg was determined using a receiver operating characteristic (ROC) curve. Comparisons of all measurements were made with unpaired Student t-tests. Values were considered significantly different for P<0.05.

**Results**

Subject baseline characteristics are given in Table. Patients were classified into 2 groups: those with PCWP ≤12 mmHg (n=25) and those with PCWP >12 mmHg (n=20). There were no significant differences in gender, heart rate, and systolic and diastolic blood pressure between the 2 groups. The LV diastolic and systolic dimensions, the LA diameter, and the LA volume index were similar between the 2 groups. E/e' was significantly greater and T_E-e' was significantly longer in patients with PCWP >12 mmHg compared to those with PCWP ≤12 mmHg.

**PCWP and E/e’ or T_E-e’**

Significant relationships were observed between PCWP and E/e’ (r=0.57, P<0.001), T_E-e’ (r=0.77, P<0.001), and log BNP (r=0.61, P<0.001; Figure 3). If the cut-off for T_E-e’ was set at >34 ms, the sensitivity and specificity of the prediction of PCWP >12 mmHg were 95% and 88%, respectively. The area under the ROC curve using T_E-e’ to differentiate PCWP >12 mmHg from that of ≤12 mmHg was 0.97 (Figure 4). In contrast, a cut-off of >14.6 for E/e’ predicted a PCWP of >12 mmHg, with 50% sensitivity and 84% specificity. The area under the ROC curve using E/e’ to differentiate PCWP >12 mmHg from that of ≤12 mmHg was 0.71 (Figure 4). The combined criteria of T_E-e’ >34 ms and E/e’ >14.6 produced 100% sensitivity and 88% specificity for detecting PCWP.
Assessment of LV Filling Pressure in AF

Reproducibility
The inter-observer and intra-observer variability, expressed as a mean percent error, of $T_{E-e'}$ was 16.0±14.8% and 6.5±10.3%, and that for $E/e'$ was 11.1±10.1% and 4.3±4.2%, respectively.

Discussion
In the present study we have demonstrated the feasibility of using $E/e'$ and $T_{E-e'}$, obtained with a dual Doppler system, in the evaluation of LV filling pressure in patients with AF and a wide range of LVEFs. The value of the $E/e'$ ratio has been widely used as an index for evaluating LV end-diastolic pressure or LA pressure in cardiac patients with sinus rhythm. In patients with AF, however, the measurements of $E/e'$ and $T_{E-e'}$ are often varied because of the lack of atrial contraction and the irregularity of Doppler parameters due to irregular R-R intervals. Therefore, the non-invasive estimation of LV filling pressure has been challenging.

Dual Doppler System and Evaluation of LV Diastolic Function in AF
A few studies have demonstrated that the $E/e'$ ratio had diagnostic value for LV diastolic function and prognostic value even in patients with AF. Some studies have reported the usefulness of a dual Doppler system for evaluating LV diastolic function in AF. We previously reported that $E/Vp$ was well correlated with neurohormonal and hemodynamic parameters, and was useful for evaluating the severity of HF or a latent HF state, even in patients with AF. Problems with the evaluation of $Vp$, however, have been noted because of the various methods for measuring $Vp$. Kusunose et al and Li et al reported the clinical utility of $E/e'$ obtained using a dual Doppler system for evaluating LV filling pressure in patients with AF. Their subjects, however, were limited to patients with AF and with preserved systolic function.

$T_{E-e'}$ and PCWP
Recently, in addition to $E/e'$, the measurement of the time difference between the onset of mitral inflow and the onset of $e'$ have been proposed for the evaluation of LV filling pres-

Figure 4. Receiver operating characteristic curve for predicting elevated pulmonary capillary wedge pressure (PCWP). The area under the curve (AUC) using $T_{E-e'}$ and $E/e'$ for differentiating PCWP $>12$mmHg from that of $\leq 12$mmHg was 0.97 and 0.71, respectively. $T_{E-e'}$, time interval between the onset of E and of $e'$.

Figure 5. Sensitivity and specificity for predicting elevated pulmonary capillary wedge pressure (PCWP) vs. $E/e'$, $T_{E-e'}$, and both $E/e'$ and $T_{E-e'}$. When the combined criteria of $T_{E-e'}$ $>34$ms and $E/e'$ $>14.6$ were used, the sensitivity and specificity for detecting PCWP $>12$mmHg improved to 100% and 88%, respectively. $T_{E-e'}$, time interval between the onset of E and of $e'$. 

$T_{E-e'}$ (ms)

Sensitivity

Specificity

$E/e'>14.6$  

$T_{E-e'}>34ms$  

$E/e'>14.6$  

$T_{E-e'}>34ms$  

50

84

95

100

88

100
sure. Rivas-Gotz et al first reported a good correlation between Te- e' and the ratio of LV pressure decay (Tau) or LV minimal pressure in a canine model, and they suggested the feasibility of Te- e' as a new index of LV diastolic function. Choi et al reported the usefulness of Te- e' for predicting elevated PCWP in patients with hemodialysis. Additionally, Min et al demonstrated improved accuracy when using Te- e' for the evaluation of LV diastolic pressure in patients with normal systolic function and an indeterminate E/e', which is considered a limitation of E/e' measurement, also known as the gray zone. The study subjects of all previous studies, however, were limited to patients with preserved LVEF and sinus rhythm; that is, they did not evaluate patients with reduced LVEF and AF. In the present study we investigated patients with AF and various degrees of LV systolic function; therefore, the sensitivity and specificity of E/e' or Te- e' for predicting elevated LV filling pressure and BNP might be lower compared to previous studies (Figure 3). Consequently, we used the combined criteria of E/e' and Te- e' in order to improve the accuracy of the temporal analysis of E and e', in addition to E/e', for predicting LV filling pressure.

Combined Analysis of E/e' and Te- e' in Patients With AF

In the present study we were able to calculate E/e' and Te- e' without the influence of heart rate variability because of the simultaneously recording of E and e' in the same cardiac area using a dual Doppler system in AF patients. We also found that if we used the combined criteria of Te- e' >34 ms and E/e' >14.6, the sensitivity and specificity for predicting elevated LV filling pressure were much improved compared to using E/e' or Te- e' alone, even in patients with AF and various degrees of LVEF (Figure 5).

Te- e' and LV Diastolic Dysfunction

As LV diastolic dysfunction progresses, LV relaxation is delayed and early diastolic suction is reduced. In such situations, annular recoil in early diastole is delayed and follows the TMF. The elevation of mean LA pressure facilitates the move of the timing of the mitral opening point forward. The behaviors of the LA, LV pressures, and the mitral annulus that accompany LV diastolic dysfunction may be related to the prolongation of Te- e'.

Clinical Implications

Among the population >65 years of age, approximately 10% have AF, and its incidence increases with age. In particular, in patients with HF greater than class II on the New York Heart Association scale, 10–20% of the patients have AF or paroxysmal AF. Although the importance of LV diastolic function for the management of HF is widely accepted, many HF patients have limitations for non-invasive assessment of LV diastolic function. The new indices measured on dual Doppler systems presented herein may provide clinical utility for point-of-care diagnostics for HF patients with AF and impaired LV systolic function.

Study Limitations

There were a number of limitations in this study. First, the subject group was small because of the difficulty in performing the invasive measurement of PCWP in asymptomatic patients or those with mild symptoms. Moreover, there were only 8 patients with PCWP >18 mmHg out of 20 patients with PCWP >12 mmHg, and no patients with acute HF due to AF tachycardia (heart rate >120 beats/min) because of the echocardiography recordings within 24 h after cardiac catheterization. Second, we excluded patients with significant (moderate or greater) valvular heart disease, which is often accompanied with AF. Third, E/e' and Te- e' were sometimes different between those at the interventricular septal annulus and those at the lateral annulus. In previous studies, e' was obtained on the lateral side of the LV, and we also recommended measuring e' on the lateral side of the LV in patients after cardiac surgery. In the present study, however, the relationship between PCWP and averaged Te- e' was the statistically strongest among correlations between PCWP and septal Te- e' (r=-0.70, P <0.001), lateral Te- e' (r=-0.64, P <0.001) or averaged Te- e' (r=-0.77, P <0.001). In addition, in order to minimize the effect of reduced wall motion caused by myocardial ischemia on e' velocity and delay of onset of e' in patients with coronary artery disease, we used averaged E/e' and averaged Te- e' (lateral and septal) for the estimation of PCWP in the present study.

In conclusion, the present study has demonstrated the feasibility of the non-invasive estimation of LV filling pressure using Te- e' obtained by simultaneous recordings of E and e' in patients with AF and reduced, as well as preserved, LV systolic function. The measurement of Te- e' using a dual Doppler system provided improved accuracy for the estimation of LV filling pressure by E/e' in patients with AF.

References


