Original Article

J Chin Med Assoc
2004;67:317-322

Non-invasive Determination of Left Ventricular Relaxation Time Constant by Transthoracic Doppler Echocardiography

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Key Words
diastolic function;
diastolic heart failure;
Doppler echocardiography;
isovolumic relaxation time;
pressure-volume loop study

Background. Left ventricular (LV) relaxation time constant (Tau) is a relatively load-independent index of diastolic function in the evaluation of heart failure. However, the requirement of high-fidelity intraventricular pressure recording limits its clinical utility. In the present study, we investigated whether Tau could be estimated noninvasively.

Methods. Thirty-seven patients indicated for cardiac catheterization were recruited for study. Echocardiography and cardiac catheterization with high-fidelity LV pressure recording were performed sequentially within 1 hour. The non-invasive Tau_{Dopp} was derived from the formula: $Tau_{Dopp} = IVRT_{Dopp} / [\ln(Ps) - \ln(10)]$, where IVRT is the isovolumic relaxation time measured by Doppler echocardiography and Ps is systolic blood pressure measured during the echocardiographic examination. The invasive Tau_{LM} was determined by non-linear least-square parameter estimate technique, using the exponential equation: $P_V = P_0 e^{-t/Tau} + b$, where Pv is the instantaneous LV pressure, P_0 is LV pressure at minimal dP/dt, and b is the theoretical asymptote. The difference between Tau_{Dopp} and Tau_{LM} was compared using paired t-test, and their relation was evaluated using simple correlation and intra-class correlation coefficient.

Results. $IVRT_{Dopp}$ was significantly correlated with the invasively derived IVRT (r = 0.42, $p = 0.012$). The completely non-invasive Tau_{Dopp} was significantly correlated with the direct curve-fitted Tau_{LM} (r = 0.41; $p = 0.013$), and the intraclass correlation coefficient was 0.29 ($p = 0.04$). In addition, Tau_{Dopp} was significantly smaller than Tau_{LM} (36 ± 6 ms *vs.* 57 ± 15 ms, $p < 0.001$).

Conclusions. Tau can be estimated noninvasively by transthoracic Doppler echocardiographic method with limited accuracy. The clinical utility of Tau_{Dopp} remains to be determined.

Diastole is a complex process of the cardiac cycle. Diastolic dysfunction may lead to elevated filling pressure and cause symptom/sign of heart failure. Diastolic dysfunction can occur as a primary form of diastolic heart failure.[1-3] Clinical studies have demonstrated that this entity of heart failure occurs more frequently than we expect.[1,4,5] Furthermore, its prognosis and therapeutic strategy are different from those of systolic heart failure.[6] Therefore, the evaluation of diastolic function should be a necessary component in patients presenting with heart failure.

The time constant of left ventricular (LV) relaxation (Tau) is an important quantitative measurement of diastolic performance.[7-9] It is a relatively load-independent parameter for measurement of active myocardial relaxation.[10] However, the requirement for high-fidelity intraventricular pressure recording to estimate Tau has limited its clinical utility. Recently, Scalia *et al.* proposed a noninvasive approach to estimate Tau, based on a Doppler echocardiographic technique.[11] The study used transesophageal echocardiography in the operating room with patients sedated; it does not mirror the routine clinical settings where patients are always examined by transthoracic echocardiography in conscious state. Therefore, the present study examined the validity of the potentially useful noninvasive method

Received: May 19, 2003.
Accepted: June 11, 2004.

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for estimating Tau with transthoracic echocardiography in the routine echocardiographic laboratory.

METHODS

Patient population

We studied 37 patients (28 men and 9 women, aged 39 to 79 years, mean age 65 years) with sinus rhythm and without significant mitral valve disease who were referred for diagnostic cardiac catheterization because of suspected coronary disease or unexplained dyspnea. All patients agreed and gave informed consent before entry into this study.

Echocardiography and hemodynamic evaluation

All patients received a Doppler echocardiographic examination using a 2.5-MHz transducer incorporated in a SONOS 5500 Echocardiograph (Hewlett-Packard) within 1 hour before the catheterization. A pulsed-wave Doppler cursor was placed between tips of the anterior and posterior mitral leaflets for recording of mitral inflow profile. For measurement of the isovolumic relaxation time ($IVRT_{DOPP}$), the Doppler cursor was placed at the junction of the LV outflow tract and the anterior mitral leaflet to capture both LV outflow and mitral valve inflow profiles in the apical 5-chamber view. The spectral images of 4 consecutive heartbeats were stored in a digital optical disk for off-line analysis. The atrial filling fraction (AFF), deceleration time (DT), ratio of early transmitral flow velocity to atrial flow velocity (E/A ratio), and time from termination of mitral flow to the electrocardiographic R wave (MAR) were obtained as previously described.[12] The $IVRT_{DOPP}$ was the interval measured from the aortic valve closing artifact at the end of the LV outflow envelope to the mitral valve opening artifact at the beginning of the mitral E wave. Arterial blood pressure was measured with an oscillometric device during echocardiographic examination. Four measurements of systolic blood pressure were taken and averaged for subsequent calculations.

Cardiac catheterization was performed within 1 hour of the echocardiographic study. No medication was administered to minimize significant fluid shift or hemodynamic change between the noninvasive and invasive studies. After routine coronary angiography, left ventriculography, and right heart catheterization, high-fidelity LV pressure was obtained using a combined pressure-volume catheter (SSD-846, Millar). Data were digitally recorded at 500 Hz, and LV pressure decay analysis was based on data spanning the point at minimal dP/dt to 2 mm Hg above LV end-diastolic pressure (EDP). The invasively-derived isovolumic relaxation time ($IVRT_{INV}$) was measured as the time interval from minimal dP/dt to the onset of ventricular filling from the pressure volume data.

Data analysis

The decay of LV pressure is commonly assumed to be a monoexponential equation.[7] Tau can be determined by non-linear least-square parameter estimate technique (Levenberg-Marquardt method), using the exponential equation: $\mathbf{P_V = P_0 e^{-t/Tau} + b}$, where Pv is the instantaneous LV pressure, P_0 is LV pressure at minimal dP/dt, and b is the theoretical asymptote. This curve-fitted Tau_{LM} is considered as the "gold standard" for comparison (Table 1). Yellin *et al.* have shown that a simplified assumption of a zero asymptote (b = 0) generated values for Tau similar to the true nonzero asymptote.[13] When we assume a zero asymptote, the equation becomes $P_{MV} = P_0 e^{-IVRT/Tau}$ at the mitral valve opening. Therefore, the equation can be rearranged as $Tau = IVRT_{INV} / [\ln(P_0) - \ln(P_{MV})$. Thomas *et al.* have demonstrated that substituting the clinically obtained systolic blood pressure (Ps) for P_0 yields a calculated Tau, which has linear correlation with the Tau_{LM}.[14] With the assumption of $P_{MV} = 10$, Scalia *et al.* further suggested that Tau can be estimated noninvasively with the equation: $\mathbf{Tau_{Dopp} = IVRT_{DOPP} / [\ln(Ps) - \ln(10)]}$, where $IVRT_{DOPP}$ is isovolumic relaxation time obtained by Doppler echocardiographic method.[11] In this study, we firstly validated the basic assumptions of zero asymptote and P_{MV} =10, i.e the validity of the calculated Tau (**Tau_{Calc}**): $\mathbf{Tau_{Calc} = IVRT_{INV}/[\ln(P_0) - \ln(10)]}$, using purely invasive data. For the fully noninvasive determination of Tau, in addition to assuming P_{MV} to be 10 mmHg (**Tau_{DOPP}**), LVEDP was also estimated noninvasively according to the formula: LVEDP = 46 - 0.22 × IVRT - 0.10 AFF - 0.03 × DT - (2 ÷ E/A) + 0.05 × MAR (Tau_{NLVEDP}).[12] Furthermore, the invasively derived pulmonary capillary wedge pressure (Tau_{PCWP}) and LVEDP (Tau_{LVEDP}) were

Table 1. Abbreviations

Tau_{LM} = Isovolumic relaxation time constant determined by non-linear least-square parameter estimate technique.
Tau_{Calc} = Isovolumic relaxation time constant determined by equation $Tau_{Calc} = IVRT_{INV} / [\ln(Po) - \ln(10)]$, whereas $IVRT_{INV}$ is isovolumic relaxation time by pressure-volume analysis and P_0 is the LV pressure at minimum dP/dt.
$Tau_{Calcsbp}$ = Isovolumic relaxation time constant determined by equation $Tau_{Calc} = IVRT_{INV} / [\ln(Ps) - \ln(10)]$, where as Ps is systolic blood pressure during cardiac catheterization.
Tau_{Dopp} = Isovolumic relaxation time constant determined by equation $Tau_{Dopp} = IVRT_{Dopp} / [\ln(Ps) - \ln(10)]$, whereas $IVRT_{Dopp}$ is isovolumic relaxation time by Doppler echocardiography and Ps is systolic blood pressure during echocardiography.
Tau_{LVEDP} = Isovolumic relaxation time constant by equation $Tau_{LVEDP} = IVRT_{Dopp} / [\ln(Ps) - \ln(LVEDP)]$, whereas LVEDP is left ventricular end-diastolic pressure.
Tau_{PWCP} = Isovolumic relaxation time constant by equation $Tau_{PWCP} = IVRT_{Dopp} / [\ln(Ps) - \ln(PWCP)]$, whereas PCWP is pulmonary capillary wedge pressure.
Tau_{NLVEDP} = Isovolumic relaxation time constant by equation $Tau_{NLEDP} = IVRT_{Dopp} / [\ln(Ps) - \ln(NLEDP)]$ whereas NLVEDP is LVEDP estimated by echocardiography.

also used sequentially in the equation to see if the non-invasive Tau estimation could be improved.

Statistics

All variables were summarized as mean ± SD and range. The relationships of the parametric variable IVRT and different Tau values were evaluated by linear regression analysis using Pearson's method. In addition, the intraclass correlation coefficients were also provided for the assessment of agreement.[15] Mean values were compared with the paired Student's t test. A p value < 0.05 was considered to be statistically significant.

Table 2. Clinical characteristics and hemodynamic data

Variables	Min	Max	Mean	SD
Age	39	79	65	11
EF(%)	41	87	71	9
BP_{ECHO}(mm Hg)	94/44	173/93	125/69	19/12
BP_{CATH}(mm Hg)	99/45	209/117	143/74	24/13
NLVEDP (mm Hg)	1	23	12	5
LVEDP (mm Hg)	4	40	14	7
PCWP (mm Hg)	7	23	13	5
$IVRT_{Inv}$(msec)	52	138	95	18
$IVRT_{DOPP}$ (msec)	61	133	91	15
Tau_{LM} (msec)	36	92	56	14
Tau_{Calc} (msec)	29	63	45	8
$Tau_{Calcsbp}$ (msec)	23	51	36	7
Tau_{Dopp}(msec)	26	53	36	6
Tau_{NLVEDP} (msec)	24	45	37	4
Tau_{PCWP} (msec)	26	78	41	11
Tau_{LVEDP} (msec)	28	99	42	13

BP_{CATH} = blood pressure during cardiac catheterization; BP_{ECHO} = blood pressure during echocardiographic examination; EF = LV ejection fraction; NLVEDP = LVEDP estimated by noninvasive method.

RESULTS

The clinical characteristics and hemodynamic data of these patients were summarized in Table 2. There were 12 patients with coronary artery disease, 15 patients with cardiac syndrome x, 7 patients with hypertensive cardiovascular disease, and 3 patients with cardiomyopathy. Blood pressure during cardiac catheterization was slightly higher than that during echocardiographic examination.

Relationships between Tau_{LM} and invasively calculated Tau_{Calc}

The invasively derived $IVRT_{INV}$ showed a linear correlation with the direct curve-fitted Tau_{LM} ($r = 0.63$, $p < 0.0001$) (Fig. 1). The invasively calculated Tau_{Calc} was significantly smaller than Tau_{LM} (45 ± 8 *vs.* 57 ± 15; $p < 0.0001$). However, there was a significant linear correlation between Tau_{LM} and Tau_{Calc} ($r = 0.48$, $p < 0.003$) (Fig. 2). When we substituted the Ps for P_0, the calculated Tau ($Tau_{Calcsbp}$) also showed significant linear correlation with the direct curve-fitted Tau_{LM} ($r = 0.61$, $p < 0.0001$) (Fig. 3). The intraclass correlation coefficient between Tau_{Calc} and $Tau_{Calcsbp}$ was 0.92 ($p < 0.0001$).

Non-invasive Tau_{DOPP} *versus* direct curve fitted Tau_{LM}

The $IVRT_{DOPP}$ was significantly correlated with

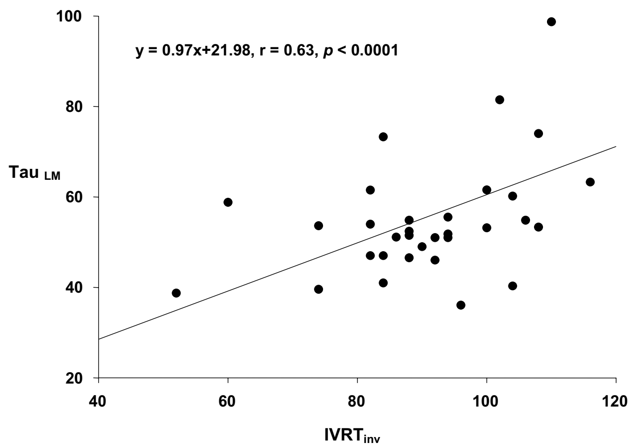

Fig. 1. Scatter plot of the linear regression between the invasively derived $IVRT_{INV}$ and the direct curve-fitted Tau_{LM}.

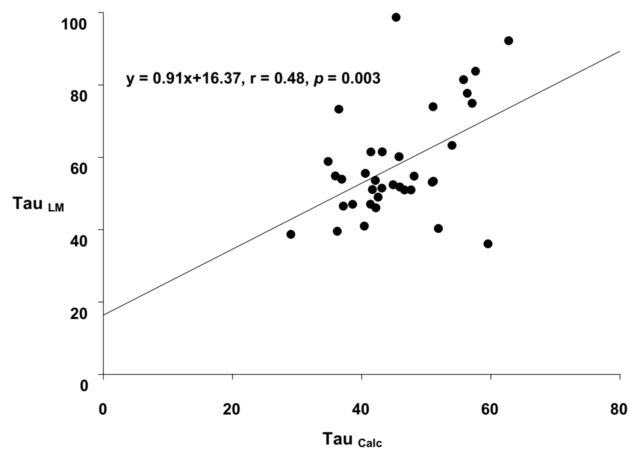

Fig. 2. Scatter plot of the linear regression between the invasively derived Tau_{Calc} and the direct curve-fitted Tau_{LM}.

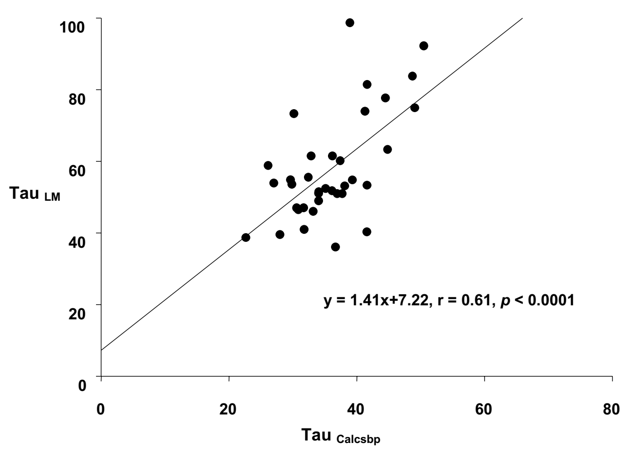

Fig. 3. Scatter plot of the linear regression between the invasively derived $Tau_{Calcsbp}$ and the direct curve-fitted Tau_{LM}.

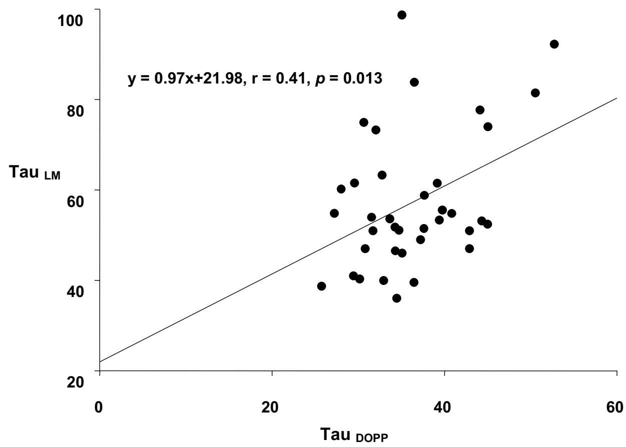

Fig. 4. Scatter plot of the linear regression between the completely non-invasive Tau_{DOPP} and the direct curve-fitted Tau_{LM}.

$IVRT_{INV}$ (r = 0.42, p = 0.012) and Tau_{LM} (r = 0.52, p = 0.001), respectively. The completely non-invasive Tau_{DOPP} showed a significant linear correlation with the invasive direct curve-fitted Tau_{LM} (r = 0.41; p = 0.013) (Fig. 4), and the intraclass correlation coefficient was 0.29 (p = 0.04). Using systolic blood pressure at cardiac catheterization as Ps, the correlation between Tau_{Dopp} and Tau_{LM} slightly improved (r = 0.45, p = 0.005) and the intraclass correlation coefficient was 0.32 (p = 0.03). When we substituted the assumed LA pressure with non-invasively calculated LVEDP, invasively measured PCWP or LVEDP (Tau_{NLVEDP}, Tau_{PCWP}, and Tau_{LVEDP}, respectively), the correlations between the various Tau and the direct curve-fitted Tau_{LM} did not improve (data not shown).

DISCUSSION

Diastolic function is an important component in the evaluation of patients with heart failure, but it remains difficult to quantify with noninvasive techniques. Doppler echocardiographic assessment of mitral and pulmonary vein flow patterns are commonly used to estimate diastolic performance, but they are preload dependent.[16-18] The time constant of LV pressure decay is a well-established preload-independent parameter of diastolic performance.[10,11,19] The present study validated the noninvasive methodology for the determination of Tau proposed by Scalia *et al.*[11] The main results showed that the noninvasive Tau_{DOPP} was significantly correlated with the invasive $Tau_{LM.}$ However, Tau_{DOPP} systematically underestimated Tau_{LM} due to the fact that Ps (arterial systolic blood pressure) is always higher than P_0 (LV pressure at minimal dP/dt).

The foundation of the noninvasive technique for the estimation of tau is the equation: **Tau = IVRT / [ln(Ps) - ln(10)].** Our analysis from the invasive data suggested that the equation appeared to be valid (Fig. 3, r = 0.62, $p <$ 0.0001). Although $Tau_{Calcsbp}$ appeared to have better correlation with Tau_{LM} than Tau_{Calc} (Fig. 2, r = 0.48, $p <$ 0.003), this should not imply that the formula **IVRT / [ln(Ps) - ln(10)]** is more robust than the original formula **IVRT / [ln(P_0) - ln(10)]** in the representation of LV relaxation. Ps and P_0 were highly correlated; so were Tau_{Calc} and $Tau_{Calcsbp}$ (the intraclass correlation coefficient was 0.92, $p < 0.0001$). Since Tau_{LM} was only an estimate of LV relaxation and was subject to error itself, the different correlations between Tau_{LM} and Tau_{Calc} or $Tau_{Calcsbp}$ observed in this study did not represent biological significance.

When Tau was estimated with totally non-invasive parameters, i.e. $IVRT_{DOPP}$ for $IVRT_{INV}$ and the oscillometric Ps, the correlation became weaker (r = 0.41, $p =$ 0.013). One reason for the declined correlation between the noninvasive and invasive Tau values was the change of the hemodynamic condition between the echocardiographic and catheterization procedures, as evidenced by the slightly higher Ps at catheterization. Indeed, substituting the invasively derived Ps during catheterization for the oscillometric Ps during the echocardiographic examination for the calculation of Tau_{DOPP} slightly improved the correlation between Tau_{DOPP} and Tau_{LM} (r = 0.45, $p =$ 0.005).

Interestingly, substituting the non-invasively calculated LA pressure (Tau_{NLVEDP}), invasively measured PCWP (Tau_{PCWP}), or LVEDP (Tau_{LVEDP}) for LA pressure did not improve the correlation between the non-invasive Tau and the curve-fitted Tau_{LM}. Actually, these substitutions weakened the correlation (data not shown). One possible explanation is that none of the LV pressure actually represents LV pressure at the mitral valve opening. According to the equation: Tau = IVRT / [Ln(P_0) - Ln(P_{MV})], P_{MV} is pressure of LV at the mitral valve opening; either PCWP or LVEDP may be a poor estimate of LV pressure at the mitral valve opening. Theoretically, more accurate estimation of LV pressure at the mitral valve opening using a non-invasive method may improve the estimation of Tau by non-invasive technique. Further studies are required to validate this hypothesis.

Limitation of the study

In the present study, the echocardiographic examination and the cardiac catheterization were not simultaneously performed. The hemodynamics might have been affected by intermittent ischemia or spontaneous fluctuation between the noninvasive and invasive measurements. This might partially explain the relatively low correlation coefficients between the noninvasive and invasive measurements, as compared with previous simultaneous studies.

In conclusion, our results show that Tau can be estimated noninvasively by transthoracic Doppler echocardiographic method with an assumed LA pressure of 10 mm Hg with limited accuracy. The clinical application of the noninvasive technique remains to be determined in future studies involving patients with various degrees of diastolic dysfunction.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Taipei Veterans General Hospital (Grant No. VGH-88-304).

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