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Importance of Left Ventricular Minimal Pressure as a Determinant of Transmitral Flow Velocity Pattern in the Presence of Left Ventricular Systolic Dysfunction

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Objectives. This study was designed to assess whether the transmitral flow velocity pattern provides an estimation of left atrial pressure irrespective of the presence of left ventricular systolic dysfunction and, if not, to clarify the mechanism.

Background. The pulsed Doppler transmitral flow velocity pattern, particularly peak early diastolic filling velocity, has been shown to change in parallel with left atrial pressure. However, extremely elevated left atrial pressure in association with heart failure does not necessarily cause an increase in peak early diastolic filling velocity in patients.

Methods. Left atrial pressure was elevated with intravenous saline infusion in 11 dogs (normal left ventricular function group) and hemodynamic, transesophageal Doppler echocardiographic and M-mode echocardiographic variables were recorded at three different loading levels. In another 12 dogs, left atrial pressure was elevated by production of left ventricular systolic dysfunction with the stepwise injection of microspheres into the left coronary artery (left ventricular dysfunction group) and the same set of recordings was obtained at three different levels of dysfunction.

Results. Peak early diastolic filling velocity increased with left atrial pressure in the normal left ventricular function group and

correlated with mean left atrial pressure ($r = 0.61$, $p < 0.01$) and early diastolic left atrial to left ventricular crossover pressure ($r = 0.71$, $p < 0.01$). In contrast, peak early diastolic filling velocity did not increase with left atrial pressure in the left ventricular dysfunction group and did not correlate with mean left atrial pressure ($r = -0.05$) or the crossover pressure ($r = 0.06$). Peak early diastolic filling velocity correlated well with the difference between the crossover pressure and left ventricular minimal pressure in the left ventricular dysfunction group ($r = 0.64$, $p < 0.01$). In contrast to peak early diastolic filling velocity, deceleration time of the early diastolic filling wave correlated with mean left atrial pressure and the crossover pressure irrespective of the primary cause of preload alteration ($r = -0.54$, $r = -0.59$, $p < 0.01$ respectively, $n = 69$ for all data).

Conclusions. Preload dependency of the Doppler transmitral flow velocity pattern is hampered if an increase in left atrial pressure is due to left ventricular systolic dysfunction. In this setting, the increase in left ventricular minimal pressure due to left ventricular systolic dysfunction cancels the effect of the increase in left atrial pressure on the flow velocity pattern.

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The pulsed Doppler transmitral flow velocity pattern in patients with diastolic dysfunction usually shows decreased peak early diastolic filling velocity, slowed deceleration of the early diastolic filling wave and increased peak filling velocity at atrial contraction (1-7). The characteristic abnormal pattern can be normalized in association with concomitant congestive heart failure. Observations in such patients include increased peak early diastolic filling velocity, fast deceleration of the early diastolic filling wave and decreased

peak filling velocity at atrial contraction (4,5,8). The increased peak early diastolic filling velocity in such patients has been considered to imply the elevation of left atrial pressure, because several groups (9-15) have shown that peak early diastolic filling velocity correlates with left atrial pressure. However, although left atrial pressure might be extremely high in such patients, higher than normal peak early diastolic filling velocity is not necessarily observed (4,8). These findings suggest that peak early diastolic filling velocity does not simply change in parallel with left atrial pressure in patients with left ventricular dysfunction and that the estimation of left atrial pressure from the transmitral flow velocity pattern is misleading.

This study was designed to assess whether transmitral flow velocity pattern provides the estimation of left atrial pressure irrespective of the presence of left ventricular systolic dysfunction and, if not, to clarify the mechanism.

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Methods

Animal preparation and data collection. This study conforms to the guiding principles of Osaka University School of Medicine with regard to animal care and to the "Position of the American Heart Association on Research Animal Use." Twenty-three mongrel dogs (12 to 35 kg) were sedated with morphine sulfate (3 mg/kg body weight subcutaneously) 30 min before induction of general anesthesia with alpha-chloralose (50 mg/kg intravenously). After the induction of general anesthesia, intravenous infusion of alpha-chloralose (30 mg/kg per h) was continued until the end of the experiment. Each dog was intubated and artificially ventilated in the supine position with a Harvard type respirator (R-60, Aika, Japan) utilizing room air. A central thoracotomy was performed, and the pericardium only around the right atrium was incised. The right atrial appendage was paced to keep heart rate constant throughout the experimental protocol after crushing of the sinus node. The pacing rate was adjusted to be higher than an idioventricular rate. An 8F high fidelity manometer-tipped catheter (Sentron, Roden, Netherlands) was introduced into the left ventricle through the left carotid artery. A 6F high fidelity manometer-tipped catheter (Millar Instruments) was introduced into the left atrium through the left pulmonary vein. The manometers were calibrated relative to atmospheric pressure before introduction of the catheters into the cardiac chambers. A 7F flow-directed pulmonary artery catheter (Gould) with a fluid-filled lumen was connected to a fluid-filled pressure transducer (model TP-400T, Nihon Kohden) positioned at the midthoracic level and was advanced into the right ventricle through the right jugular vein. Continuous lead II electrocardiographic (ECG) tracing, left atrial and left ventricular pressures, right ventricular pressure and first derivative of left ventricular pressure (dP/dt) were displayed on the eight-channel recorder (Nihon Kohden) and all recordings were made at a paper speed of 100 mm/s.

A commercially available echocardiograph (SSH-65A, Toshiba) was used to record the pulsed Doppler transmitral flow velocity pattern and M-mode echocardiograms of the left atrial and left ventricular cavities. These were recorded simultaneously with high fidelity left atrial and left ventricular pressure signals transmitted from the eight-channel recorder.

The pulsed Doppler transmitral flow velocity pattern was obtained by using a transesophageal two-dimensional phased array echocardiographic 3.75-MHz transducer with pulsed Doppler capabilities (ESB-37SR, Machida, Japan). After the stable two-dimensional image of mitral valve inflow was obtained, the sample volume was placed at the tip of the mitral valve leaflets so that the maximal velocity across the mitral valve would be measured.

Two-dimensional targeted M-mode echocardiograms of the left atrial and left ventricular cavities were obtained with a 5-MHz transducer on the surface of the heart. To obtain an M-mode echocardiogram of the left atrium, the trans-

ducer was placed near the outflow tract of the right ventricle so that a two-dimensional view similar to the parasternal long-axis view was obtained. The transducer orientation was adjusted to make the ultrasound beam transect the aorta and the aortic valve and to obtain an adequate recording for the measurements of anteroposterior left atrial diameter. An M-mode echocardiogram of the left ventricle was obtained at the midpapillary muscle level. Pressures were monitored with and without the transducer placed on the heart to ensure no or minimal influence of the transducer manipulation on the measurements. All Doppler and M-mode echocardiographic recordings were made at a paper speed of 100 mm/s using a strip chart recorder (LSR-20B, Toshiba).

Before each recording, the manometric left ventricular pressure was aligned with the pressure measured by its fluid-filled lumen connected to a TP-400T transducer positioned at the midthoracic level, and the difference between manometric left atrial and left ventricular pressures during mid-diastole of long diastolic cycles was recorded. All measurements were made during the end-expiratory portion of the respiratory cycle.

Experimental protocol. The dogs were assigned to either a normal left ventricular function or a left ventricular dysfunction group. The former group consisted of 11 dogs (13 to 35 kg), and the latter group consisted of the other 12 dogs (12 to 35 kg).

Preload augmentation (normal left ventricular function group). First, pulsed Doppler transmitral flow velocity pattern, M-mode echocardiograms of the left atrium and left ventricle, high fidelity left atrial and left ventricular pressures, left ventricular dP/dt and right ventricular pressure at the control study were recorded. Saline solution was then intravenously infused, and the same set of recordings was obtained at two different stable levels in each dog, that is, at left ventricular end-diastolic pressures of 12 to 17 mm Hg (moderate preload augmentation) and of ≥ 18 mm Hg (advanced preload augmentation). The recordings were obtained 10 to 15 min after a stable state was obtained.

Production of left ventricular systolic dysfunction (left ventricular dysfunction group). After control Doppler echocardiographic, M-mode echocardiographic and hemodynamic recordings were obtained, a 5F Judkins left coronary catheter (Schneider Inc.) was introduced through an arterial sheath (Terumo, Japan) into the right femoral artery and advanced into the left coronary ostium under echocardiographic guidance. A bolus injection of a small amount of hand-agitated saline solution into the left coronary artery was used to verify homogeneous staining of the left ventricular wall with a contrast echocardiogram. Then plastic microspheres ($50 \pm 2 \mu\text{m}$ in diameter, 3M) were injected into the left coronary artery to induce acute ischemic left ventricular dysfunction according to previous methods (16,17). The microspheres were continuously agitated in a saline solution suspension and injected every 5 to 10 min as a bolus

injection of 5 ml (24,000 microspheres/ml). A sequence of injections was made to first produce mild left ventricular dysfunction (left ventricular end-diastolic pressure 12 to 17 mm Hg) and then severe left ventricular dysfunction (left ventricular end-diastolic pressure \geq 18 mm Hg). After 10 to 15 min of a stable state, the same recordings obtained in the control study were performed at the stages of mild and severe left ventricular dysfunction, respectively.

Data analysis. A personal computer system (NEC) was used to digitize pressure tracings and the pulsed Doppler transmitral flow velocity pattern. The transmitral flow velocity pattern was traced along the darkest portion of the velocities to obtain peak early diastolic filling velocity and peak filling velocity at atrial contraction, mean acceleration and deceleration rates of the early diastolic filling wave, acceleration and deceleration times of the early diastolic filling wave and time-velocity integrals of the early diastolic filling wave and the filling wave at atrial contraction. Acceleration and deceleration times of the early diastolic filling wave were defined as twice the intervals between the point at peak velocity and that at half of the peak velocity in the acceleration and deceleration phases, respectively. The time-velocity integrals of the early diastolic filling wave and the filling wave at atrial contraction were the areas under the traced transmitral velocity profile during the early diastolic filling period and the filling period at atrial contraction, respectively. When the early diastolic filling wave and the filling wave at atrial contraction overlapped, the integral of the early diastolic filling wave was measured to the onset of the filling wave at atrial contraction, and the residual area was measured as the integral of the filling wave at atrial contraction.

Simultaneous tracings of high fidelity left atrial and left ventricular pressures were digitized for measurements of mean left atrial pressure, left atrial to left ventricular crossover pressure (the first early diastolic crossover point of left atrial and left ventricular pressures), peak instantaneous difference between left atrial and left ventricular pressures in early diastole, left ventricular minimal pressure in early diastole, left ventricular end-diastolic pressure and left ventricular systolic pressure. Right ventricular pressure was traced to obtain right ventricular end-diastolic pressure. The difference between left atrial and left ventricular pressures during mid-diastole of long diastolic cycles was subtracted from the recorded left atrial pressure to adjust left atrial and left ventricular pressures to a common baseline when these two pressures were reconstructed on the computer system to calculate mean left atrial pressure, the crossover pressure and peak instantaneous difference between left atrial and left ventricular pressures in early diastole. Left and right ventricular end-diastolic pressures were defined as left ventricular and right ventricular pressures at the R wave on the ECG. Left ventricular systolic pressure was defined as maximal left ventricular pressure. Left ventricular isovolumetric relaxation was assessed with use of the least squares method, using pressure points from the time of peak negative

dP/dt until 5 mm Hg above left ventricular end-diastolic pressure on the basis of a model of exponential decay with variable asymptote: $P(t) = P_A \exp(-t/T_D) - P_B$, where $P(t)$ is left ventricular pressure, t is time and P_A , T_D and P_B are constants determined by the data. T_D was computed from this formula as a time constant of the decrease in isovolumetric pressure (18,19). Although the decrease in isovolumetric pressure is not exactly exponential (20), the time constant derived from the exponential approximation provides an index of the rate of left ventricular relaxation (21).

Left atrial diameter at mitral valve opening was measured at the crossover pressure. Left atrial diameter just before atrial contraction was measured at the onset of the A wave of left atrial pressure. Left ventricular end-diastolic diameter was measured at the R wave on the ECG. Left ventricular end-systolic diameter was measured at the peak downward motion of the interventricular septum. Average values of three consecutive cardiac cycles were used for the quantitative analysis.

Statistical analysis. Values are expressed as mean value \pm SD. The statistical significance of the difference in the data among different conditions in a group or between the two groups was tested with an analysis of variance (ANOVA) and Scheffé F test. Bivariate correlations between Doppler echocardiographic and hemodynamic variables were performed with simple least-squares linear regression analysis. Multiple linear regression analysis was performed to identify the responsibility of the crossover pressure and the time constant or that of the crossover pressure and left ventricular minimal pressure for the determination of peak early diastolic filling velocity. Specifically, we entered peak early diastolic filling velocity as the dependent variable into a multiple regression with the crossover pressure and the time constant or the crossover pressure and left ventricular minimal pressure as independent variables. To examine whether the associated regression coefficient was significantly different from zero and whether it contributed significantly to the multiple regression, the t value of each variable was calculated as $t =$ the associated regression coefficient of each variable/the standard error of the coefficient. Results were considered significant at a probability value < 0.05 . All calculations were performed with the STATVIEW II (Abacus Inc.) statistical program.

Results

There was no significant difference in body weight (21 ± 7 kg in the normal left ventricular function group and 23 ± 7 kg in the left ventricular dysfunction group) or control Doppler echocardiographic, M-mode echocardiographic and hemodynamic variables between the two groups (Tables 1 and 2).

Effects of elevated left atrial pressure during preload augmentation in hearts with normal left ventricular function (Table 1). In the group with normal function, as mean left atrial pressure and left atrial to left ventricular crossover

Table 1. Changes in Doppler Echocardiographic, M-Mode Echocardiographic and Hemodynamic Variables Associated With Preload Augmentation in the Group With Normal Left Ventricular Function

	Control Period	Preload Augmentation	
		Moderate	Advanced
HR (beats/min)	93 ± 12	93 ± 12	93 ± 12
A (cm/s)	34 ± 9	42 ± 5*	42 ± 7‡
E (cm/s)	58 ± 16	71 ± 17‡	80 ± 19‡‡
E/A	1.7 ± 0.3	1.7 ± 0.4	1.9 ± 0.6
TVI-A (cm)	1.3 ± 0.5	1.6 ± 0.5*	1.7 ± 0.6‡
TVI-E (cm)	7.9 ± 1.8	9.4 ± 2.1‡	9.7 ± 2.2‡
Diastolic TVI (cm)	9.2 ± 2.0	11.0 ± 2.4‡	11.4 ± 2.3‡
Acceleration time (ms)	80 ± 14	97 ± 20*	96 ± 15*
Acceleration rate (cm/s ²)	721 ± 151	763 ± 224	834 ± 162
Deceleration time (ms)	153 ± 23	132 ± 32	118 ± 21‡
Deceleration rate (cm/s ²)	397 ± 162	578 ± 215*	712 ± 259‡
LAD ₁ (mm)	16 ± 4	20 ± 3‡	24 ± 3‡‡
LAD ₂ (mm)	14 ± 4	18 ± 4‡	20 ± 4‡
LVEDD (mm)	18 ± 7	20 ± 7‡	22 ± 7‡§
LVEDD (mm)	30 ± 6	35 ± 6‡	38 ± 6‡‡
LVEDP (mm Hg)	6 ± 2	14 ± 1‡	19 ± 1‡‡
LV minP (mm Hg)	3 ± 2	5 ± 2‡	8 ± 2‡‡
mLAP (mm Hg)	5 ± 2	10 ± 2‡	14 ± 2‡‡
XP (mm Hg)	7 ± 2	12 ± 3‡	16 ± 3‡‡
XP - LV minP (mm Hg)	5 ± 2	7 ± 3‡	8 ± 3‡§
Peak ΔP (mm Hg)	3 ± 1	5 ± 2*	5 ± 2‡
LVSP (mm Hg)	117 ± 19	127 ± 20	132 ± 15‡
Peak + dP/dt (mm Hg/s)	2,855 ± 961	2,716 ± 837	2,633 ± 756
Peak - dP/dt (mm Hg/s)	2,277 ± 588	2,194 ± 431	2,186 ± 417
T _D (ms)	37 ± 9	42 ± 10*	41 ± 11*
RVEDP (mm Hg)	6 ± 3	12 ± 2‡	16 ± 3‡‡

*p < 0.05 versus control. †p < 0.01 versus control. ‡p < 0.01 versus moderate preload augmentation. §p < 0.05 vs. moderate preload augmentation. Data are expressed as mean value ± SD. A = peak filling velocity at atrial contraction; ΔP = instantaneous difference between left atrial and left ventricular pressures in early diastole; Diastolic TVI = the sum of the time-velocity integral of the early diastolic filling wave and the filling wave at atrial contraction; E = peak early diastolic filling velocity; E/A = a ratio of E to A; HR = heart rate; LAD₁ = left atrial diameter at mitral valve opening; LAD₂ = left atrial diameter before atrial contraction; LVEDD = left ventricular end-diastolic diameter; LVEDP = left ventricular end-diastolic pressure; LVEDD = left ventricular end-systolic diameter; LV minP = left ventricular minimal pressure in early diastole; LVSP = left ventricular systolic pressure; mLAP = mean left atrial pressure; -dP/dt and +dP/dt = negative and positive first derivative of left ventricular pressure, respectively; RVEDP = right ventricular end-diastolic pressure; T_D = a time constant of left ventricular isovolumetric pressure fall; TVI-A = time-velocity integral of the filling wave at atrial contraction; TVI-E = time-velocity integral of the early diastolic filling wave; XP = left atrial to left ventricular crossover pressure; XP - LV minP = the difference between the crossover pressure and left ventricular minimal pressure.

pressure increased during volume infusion, peak early diastolic filling velocity, peak filling velocity at atrial contraction and the time-velocity integral of the early diastolic filling wave increased and deceleration time of the early diastolic filling wave shortened (Fig. 1). Left atrial and left ventricular diameters, left ventricular minimal pressure and right ventricular end-diastolic pressure also increased with left atrial pressure. The time constant of left ventricular pressure was slightly, although statistically significantly, prolonged as left atrial pressure increased. The difference between the crossover pressure and left ventricular minimal pressure and peak instantaneous difference between left atrial and left ventricular pressures in early diastole increased with left atrial pressure.

Effects of elevated left atrial pressure during the production of left ventricular systolic dysfunction (Table 2). In the group with ventricular dysfunction, peak positive and negative dP/dt decreased and the time constant was prolonged with the depression of left ventricular function. The increase in mean left atrial pressure and the crossover pressure accompanied by the production of left ventricular systolic dysfunction in this group was comparable to that accompanied by preload augmentation in the normal left ventricular function group. Nevertheless, neither peak early diastolic filling velocity nor peak filling velocity at atrial contraction increased in this group (Fig. 2). Deceleration time of the early diastolic filling wave shortened with an increment in left atrial pressure during the production of left ventricular systolic dys-

Table 2. Changes in Doppler Echocardiographic, M-Mode Echocardiographic and Hemodynamic Variables Associated With the Depression in the Level of Left Ventricular Function in the Dysfunction Group

	Control	LV Dysfunction	
		Mild	Severe
HR (beats/min)	96 ± 9	96 ± 9	96 ± 9
E (cm/s)	57 ± 15	48 ± 13	49 ± 17
A (cm/s)	38 ± 12	40 ± 8	34 ± 7
E/A	1.6 ± 0.6	1.2 ± 0.5	1.5 ± 0.6
TVI-E (cm)	8.4 ± 2.5	6.3 ± 2.2*	5.7 ± 2.5†
TVI-A (cm)	1.6 ± 0.6	1.5 ± 0.4	1.3 ± 0.3
Diastolic TVI (cm)	10.0 ± 2.9	7.8 ± 2.3*	7.0 ± 2.7†
Acceleration time (ms)	89 ± 22	87 ± 21	84 ± 19
Acceleration rate (cm/s ²)	667 ± 206	573 ± 193	584 ± 173
Deceleration time (ms)	156 ± 14	121 ± 25‡	99 ± 22‡§
Deceleration rate (cm/s ²)	369 ± 99	398 ± 85	499 ± 139*
LAD ₁ (mm)	18 ± 6	24 ± 7†	29 ± 8†‡
LAD ₂ (mm)	17 ± 7	22 ± 7†	26 ± 8†‡
LVESD (mm)	21 ± 6	30 ± 7†	34 ± 6†§
LVEDD (mm)	33 ± 5	38 ± 6†	41 ± 5†‡
LVEDP (mm Hg)	8 ± 3	14 ± 4†	21 ± 4†‡
LV minP (mm Hg)	3 ± 1	7 ± 2†	12 ± 2†‡
mLAP (mm Hg)	6 ± 2	10 ± 3†	15 ± 3†‡
XP (mm Hg)	7 ± 2	11 ± 2†	16 ± 3†‡
XP - LV minP (mm Hg)	5 ± 2	4 ± 1	5 ± 3
Peak ΔP (mm Hg)	3 ± 1	3 ± 1	3 ± 1
LVSP (mm Hg)	130 ± 18	126 ± 20	122 ± 23
Peak + dP/dt (mm Hg/s)	3,002 ± 511	2,214 ± 358†	1,961 ± 365†
Peak - dP/dt (mm Hg/s)	2,376 ± 508	1,647 ± 355†	1,329 ± 326†§
T _D (ms)	39 ± 6	56 ± 10†	72 ± 9†‡
RVEDP (mm Hg)	8 ± 4	11 ± 3†	13 ± 4†§

*p < 0.05 versus control. †p < 0.01 versus control. ‡p < 0.01 versus mild left ventricular dysfunction. §p < 0.05 versus mild left ventricular dysfunction. Abbreviations as in Table 1.

function. Left atrial and left ventricular diameters, left ventricular minimal pressure, right ventricular end-diastolic pressure and the time constant increased with the increase in left atrial pressure as a result of left ventricular systolic dysfunction. The difference between the crossover pressure and left ventricular minimal pressure or peak instantaneous difference between left atrial and left ventricular pressures in early diastole did not change with the increase in left atrial pressure due to left ventricular systolic dysfunction.

It is noted that the increases in left ventricular minimal pressure and left ventricular end-systolic diameter associated with the increase in left atrial pressure were greater and the increase in right ventricular end-diastolic pressure was smaller in this group than in the normal left ventricular function group.

Correlations between hemodynamic and Doppler echocardiographic measurements. In pooled data taken from all 33 experimental stages in the 11 dogs from the normal left ventricular function group, peak early diastolic filling velocity correlated with mean left atrial pressure ($r = 0.61$, $p < 0.01$) and the crossover pressure ($r = 0.75$, $p < 0.01$, Fig. 3). Better, although not significant, correlation was observed between peak early diastolic filling velocity and the differ-

ence between the crossover pressure and left ventricular minimal pressure ($r = 0.85$, $p < 0.01$). Multiple linear regression analysis of the crossover pressure and the time constant yielded a high correlation with peak early diastolic filling velocity ($r = 0.84$, $p < 0.01$), and the calculation of the t value indicated that the crossover pressure and the time constant added significantly to the relation (the crossover pressure $t = 6.543$, $p = 0.0001$; the time constant $t = -3.743$, $p = 0.0008$). Multiple linear regression analysis of the crossover pressure and left ventricular minimal pressure also yielded a high correlation with peak early diastolic filling velocity ($r = 0.86$, $p < 0.01$), and the calculation of the t value indicated that the crossover pressure and left ventricular minimal pressure added significantly to the relation (the crossover pressure $t = 8.596$, $p = 0.0001$; left ventricular minimal pressure $t = -4.522$, $p = 0.0001$). Deceleration time of the early diastolic filling wave correlated with mean left atrial pressure ($r = -0.55$, $p < 0.01$), the crossover pressure ($r = -0.65$, $p < 0.01$) and the difference between the crossover pressure and left ventricular minimal pressure ($r = -0.56$, $p < 0.01$).

In pooled data taken from all 36 experimental stages in the 12 dogs from the left ventricular dysfunction group, peak

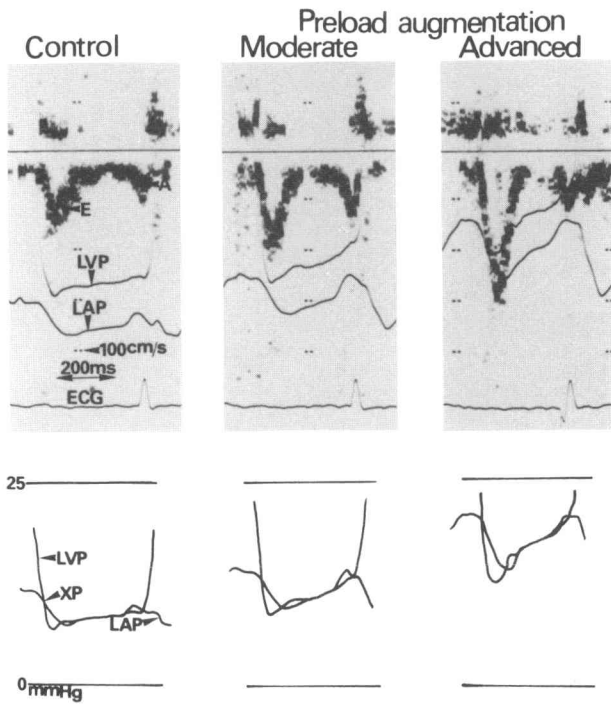


Figure 1. Normal left ventricular function group. Example of simultaneous recording of transmitral flow velocity pattern, high fidelity left atrial (LAP) and left ventricular (LVP) pressures and electrocardiogram (ECG) during preload augmentation. Left atrial and left ventricular pressures were traced and superimposed on each other with left atrial pressure shifted for the difference between left atrial and left ventricular pressures during middiastole of long diastolic cycles as shown below the original recordings. In this case, peak early diastolic filling velocity (E) increased with left atrial to left ventricular crossover pressure (XP). A = peak late diastolic filling velocity.

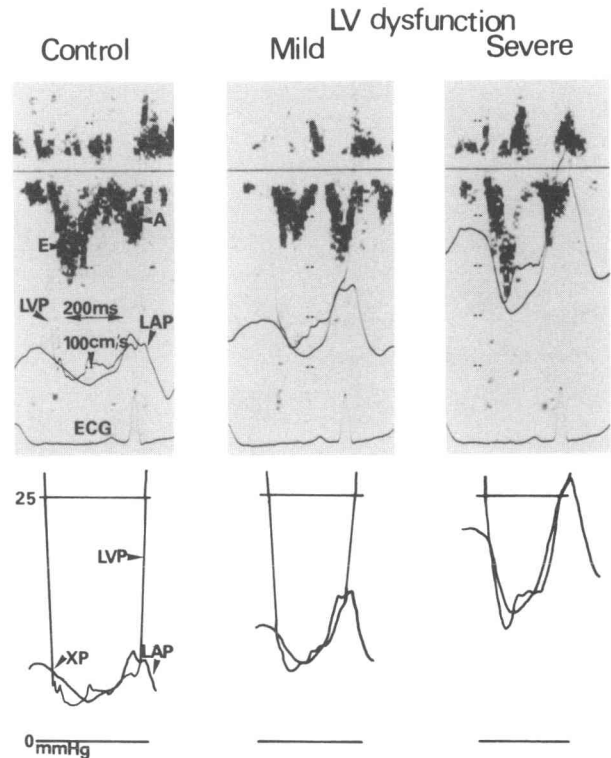


Figure 2. Left ventricular (LV) dysfunction group. Example of simultaneous recording of transmitral flow velocity pattern, high fidelity left atrial (LAP) and left ventricular (LVP) pressures and electrocardiogram (ECG) during the production of left ventricular systolic dysfunction. Left ventricular pressure and shifted left atrial pressure are shown below the original recordings. In this case, peak early diastolic filling velocity (E) did not increase despite the consistent increase in left atrial to left ventricular crossover pressure (XP). Abbreviations as in Figure 1.

early diastolic filling velocity did not correlate with mean left atrial pressure ($r = -0.05$) or the crossover pressure ($r = 0.06$, Fig. 4). Significant improvement in the correlation was obtained if peak early diastolic filling velocity was compared with the difference between the crossover pressure and left ventricular minimal pressure ($r = 0.64$, $p < 0.01$). Multiple linear regression analysis of the crossover pressure and the time constant yielded no improvement in the correlation with peak early diastolic filling velocity ($r = 0.37$). However, the analysis of the crossover pressure and left ventricular minimal pressure yielded a significant improvement in the correlation with peak early diastolic filling velocity ($r = 0.69$, $p < 0.01$), and the calculation of t value indicated that the crossover pressure and left ventricular minimal pressure added significantly to the relation (the crossover pressure $t = 4.945$, $p = 0.0001$; left ventricular minimal pressure $t = -5.462$, $p = 0.0001$). Deceleration time of the early diastolic filling wave correlated with mean left atrial pressure ($r = -0.53$, $p < 0.01$) and the crossover pressure in this group ($r = -0.56$, $p < 0.01$); however, it did not correlate with the difference between the crossover pressure and left ventricular minimal pressure ($r = 0.15$).

In pooled data taken from 69 experimental stages in the 23 dogs from the two groups, peak early diastolic filling velocity did not correlate with mean left atrial pressure ($r = 0.19$) or correlated poorly with the crossover pressure ($r = 0.38$, $p < 0.05$). Significantly better correlation was observed between peak early diastolic filling velocity and the difference between the crossover pressure and left ventricular minimal pressure ($r = 0.81$, $p < 0.01$, Fig. 5). Deceleration time correlated with mean left atrial pressure ($r = -0.54$, $p < 0.01$) and the crossover pressure ($r = -0.59$, $p < 0.01$, Fig. 5); however, it did not correlate with the difference between the crossover pressure and left ventricular minimal pressure ($r = -0.14$).

Discussion

In this study, we examined whether preload dependency of the pulsed Doppler transmitral flow velocity pattern is altered if preload changes in association with left ventricular systolic dysfunction. Peak early diastolic filling velocity increased with left atrial pressure, and a significant correla-

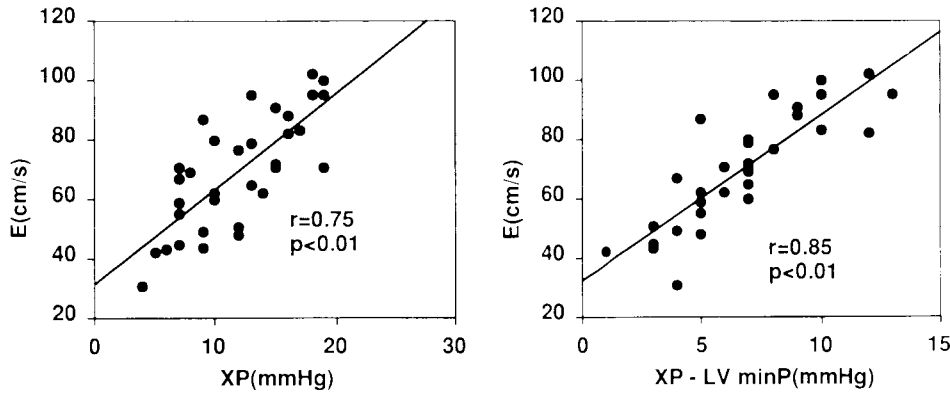


Figure 3. Normal left ventricular function group. Peak early diastolic filling velocity (E) was compared with the crossover pressure (XP) (**left panel**) and the difference between the crossover pressure and left ventricular minimal pressure (XP - LV minP) (**right panel**) in this group, in which left atrial pressure was altered by volume infusion. There were good correlations between peak early diastolic filling velocity and the crossover pressure and between peak early diastolic filling velocity and the difference between the crossover pressure and left ventricular minimal pressure.

tion between peak early diastolic filling velocity and mean left atrial pressure or the crossover pressure was observed if left atrial pressure was manipulated with volume infusion. In contrast, peak early diastolic filling velocity did not increase with left atrial pressure, and the correlation between peak early diastolic filling velocity and mean left atrial pressure or the crossover pressure was poor if left atrial pressure was increased by producing left ventricular systolic dysfunction. Improvement in the correlation coefficient was obtained if peak early diastolic filling velocity was compared with the difference between the crossover pressure and left ventricular minimal pressure. As left atrial pressure increased, deceleration time of the early diastolic filling wave shortened independently of the cause of the elevation of left atrial pressure.

Early diastolic filling and left ventricular minimal pressure.

Peak early diastolic filling velocity correlated with mean left atrial pressure and the crossover pressure if left atrial pressure was altered by volume infusion in normal hearts. This finding is consistent with those of the previous studies (9-15) in which preload was altered without changes in left ventricular function. In contrast to the results in normal

hearts, peak early diastolic filling velocity did not correlate with mean left atrial pressure or the crossover pressure if left atrial pressure was increased by the production of left ventricular systolic dysfunction. These results suggest that preload dependency of peak early diastolic filling velocity is not maintained if preload changes in association with left ventricular systolic dysfunction.

Now questions arise regarding why peak early diastolic filling velocity did not correlate with left atrial pressure when left atrial pressure was elevated by the production of left ventricular systolic dysfunction. Choong et al. (9) showed that left atrial V wave pressure and the time constant are the major variables in determining peak early diastolic filling velocity in *normal hearts*. Because the time constant was prolonged with the increase in the crossover pressure in the left ventricular dysfunction group, one might think that the correlation would be improved if the time constant were taken into account. However, multiple linear regression analysis of the crossover pressure and the time constant yielded no improvement in correlation with peak early diastolic filling velocity ($r = 0.37$). Thus, the lack of correlation between peak early diastolic filling velocity and the

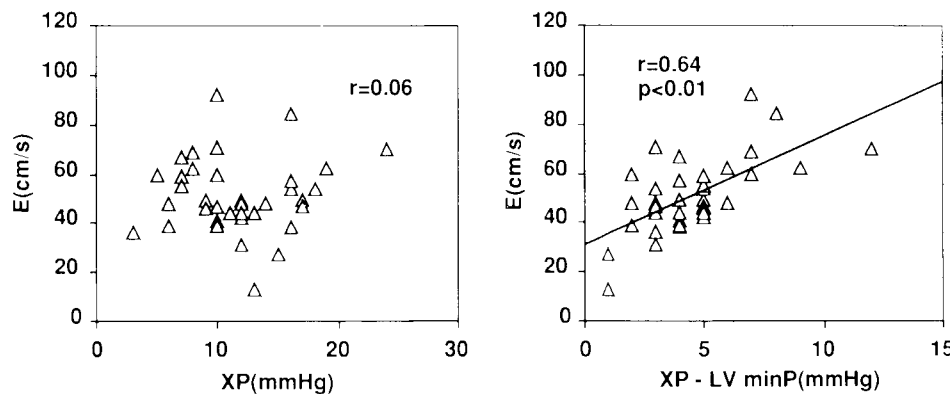
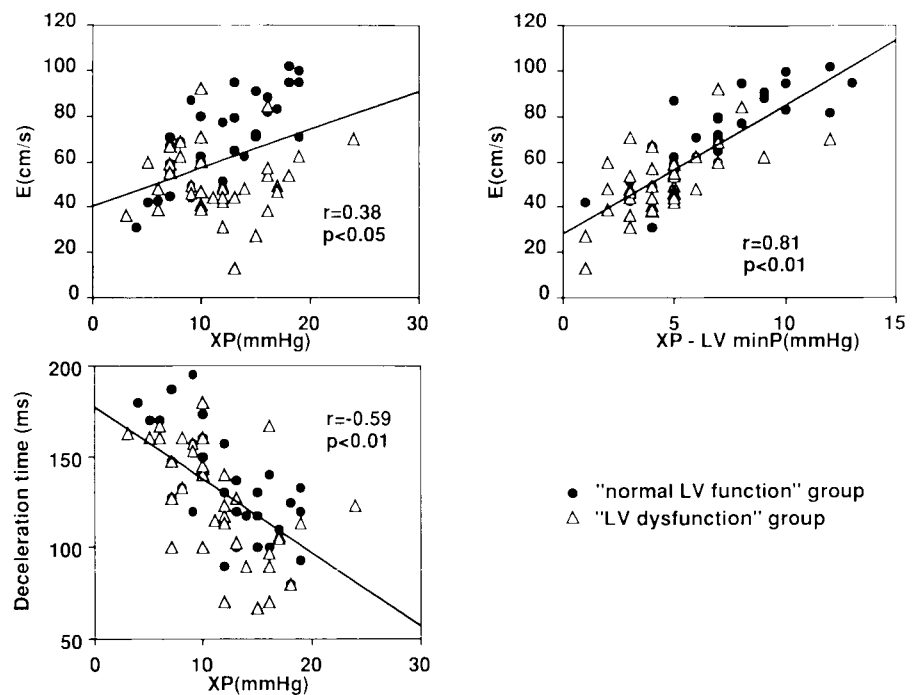


Figure 4. Left ventricular dysfunction group. Peak early diastolic filling velocity (E) was compared with the crossover pressure (XP) (**left panel**) and the difference between the crossover pressure and left ventricular minimal pressure (XP - LV minP) (**right panel**) in this group, in which left atrial pressure was altered by the production of left ventricular systolic dysfunction. There was no significant correlation between peak early diastolic filling velocity and the crossover pressure. However, improvement in the correlation was observed when peak early diastolic filling velocity was compared with the difference between the crossover pressure and left ventricular minimal pressure.

Figure 5. Combined groups. Peak early diastolic filling velocity (E) was compared with the crossover pressure (XP) (**left upper panel**) and the difference between the crossover pressure and left ventricular minimal pressures (XP - LV minP) (**right upper panel**) from the pooled data of both groups. There was a weak correlation between peak early diastolic filling velocity and the crossover pressure: a significantly better correlation was observed when peak early diastolic filling velocity was compared with the difference between the crossover pressure and left ventricular minimal pressure. Deceleration time of the early diastolic filling wave was also compared with the crossover pressure from the pooled data of both groups (**left lower panel**) and a significant correlation was observed.



crossover pressure during the production of left ventricular systolic dysfunction cannot be explained only by the contribution of the prolongation of the time constant.

The concomitant increase in left ventricular minimal pressure due to left ventricular systolic dysfunction was a most likely explanation for the lack of correlation between the crossover pressure and peak early diastolic filling velocity because the improvement in the correlation coefficient was observed if peak early diastolic filling velocity was compared with the difference between the crossover pressure and left ventricular minimal pressure (Fig. 4). The good correlation between peak early diastolic filling velocity and the difference between the crossover pressure and left ventricular minimal pressure during the production of left ventricular systolic dysfunction may not only imply that peak early diastolic filling velocity is determined by left atrial to left ventricular pressure gradient in early diastole. The good correlation may also imply that left ventricular minimal pressure is an important determinant of left atrial to left ventricular pressure gradient in early diastole and is one of the most important contributors to the changes in peak early diastolic filling velocity. This may be particularly true when the elevation of left atrial pressure is due to left ventricular systolic dysfunction because the increase in left ventricular minimal pressure was considered to cancel out the effects of elevated left atrial pressure and to reduce left atrial to left ventricular pressure gradient in early diastole. The good correlation between peak early diastolic filling velocity and the crossover pressure during volume infusion may be because the associated elevation of left ventricular minimal pressure was small and negligible.

Determinants of left ventricular minimal pressure. Left ventricular minimal pressure is mainly affected by left ventricular elastic recoil (left ventricular suction), extracardiac constraining force and left ventricular relaxation (21-23). In particular, left ventricular elastic recoil may be a most important determinant of left ventricular minimal pressure in failing hearts with left ventricular systolic dysfunction because left ventricular elastic recoil is largely affected by left ventricular systolic function. At end-systole, the myocardium is compressed to the length below its equilibrium length and left ventricular end-systolic volume is smaller than the equilibrium volume. This compression of myocardium stores elastic energy and the stored energy causes left ventricular elastic recoil. Therefore, the smaller difference between left ventricular end-systolic volume and the equilibrium volume is associated with the smaller recoil force. In the presence of left ventricular systolic dysfunction, left ventricular end-systolic volume increases and the difference between left ventricular end-systolic volume and the equilibrium volume decreases, resulting in decreased restoring force and hence decreased left ventricular elastic recoil. The decreased elastic recoil works toward an increase in left ventricular minimal pressure (23). In this study, the increase in left ventricular end-systolic diameter was larger in the group with abnormal than in the group with normal left ventricular function, although the increases in left ventricular end-diastolic diameter were similar in the two groups. Further, left ventricular minimal pressure positively correlated with left ventricular end-systolic diameter in the left ventricular dysfunction group ($r = 0.72, p < 0.01$). Therefore, the increase in left ventricular minimal pressure asso-

ciated with the production of left ventricular systolic dysfunction may be largely due to poor left ventricular contractility and a consequent decrease in left ventricular elastic recoil.

It is well known that an increase in extracardiac constraining force shifts the left ventricular diastolic pressure-volume curve upward (24). Therefore, the increase in extracardiac constraining force is another possible factor of elevating left ventricular minimal pressure, which is the most likely cause of the lack of correlation between the crossover pressure and peak early diastolic filling velocity. To clarify the contribution of the extracardiac constraining force in this study, the changes in left ventricular minimal pressure were compared with those in right ventricular end-diastolic pressure because the latter pressure reflects extracardiac constraining force (25,26). During volume infusion, the mean increase in left ventricular minimal pressure was 5 mm Hg, and the mean increase in right ventricular end-diastolic pressure was 10 mm Hg. During the production of left ventricular systolic dysfunction, the mean increase in left ventricular minimal pressure was 9 mm Hg, and the mean increase in right ventricular end-diastolic pressure was 5 mm Hg. The increase in left ventricular minimal pressure was larger and the increase in right ventricular end-diastolic pressure was smaller during the production of left ventricular systolic dysfunction than during volume infusion. These results imply that the contribution of extracardiac constraining force to the increase in left ventricular minimal pressure should be much smaller during the production of left ventricular systolic dysfunction than during volume infusion. Thus, the increase in extracardiac constraining force is unlikely to be responsible for the increase in left ventricular minimal pressure and the poor correlation between peak early diastolic filling velocity and the crossover pressure during the production of left ventricular systolic dysfunction.

Left ventricular relaxation also affects left ventricular minimal pressure (21). If the impairment of left ventricular relaxation were responsible for the increase in left ventricular minimal pressure and for the poor correlation between peak early diastolic filling velocity and the crossover pressure during the production of left ventricular systolic dysfunction, the consideration of the time constant should improve the correlation between the crossover pressure and peak early diastolic filling velocity. However, multiple linear regression analysis of the crossover pressure and the time constant yielded a poor correlation with peak early diastolic filling velocity, although the analysis of the crossover pressure and left ventricular minimal pressure yielded a significant correlation with peak early diastolic filling velocity in the left ventricular dysfunction group in this study. In contrast, the consideration of the time constant improved the correlation between the crossover pressure and peak early diastolic filling velocity (in the group with normal left ventricular function). Thus, although these results cannot deny that the impairment of left ventricular relaxation might

partially contribute to the increase in left ventricular minimal pressure, increased left ventricular minimal pressure responsible for the poor correlation between the crossover pressure and peak early diastolic filling velocity during the production of left ventricular systolic dysfunction cannot be attributed solely to the effect of left ventricular relaxation on left ventricular minimal pressure in this study.

Deceleration time of the early diastolic filling wave. Deceleration time of the early diastolic filling wave shortened as left atrial pressure increased. Deceleration time correlated with mean left atrial pressure and with the crossover pressure in both groups in this study. Furthermore, the correlation between deceleration time and mean left atrial pressure or the crossover pressure was significant, although not as good, in pooled data from the two groups. In contrast to peak early diastolic filling velocity, deceleration time did not correlate with the difference between the crossover pressure and left ventricular minimal pressure in the left ventricular dysfunction group. A previous clinical report (4) showed that deceleration time is shorter in patients with cardiomyopathy and elevated crossover pressure than in normal subjects although peak early diastolic filling velocity was not different between patients and normal subjects. These findings suggest that preload dependency of deceleration time is less affected by the cause of preload alteration than is that of peak early diastolic filling velocity.

The correlation between deceleration time and left atrial pressure was not good in this study. The Stanford investigators (4,8,22) showed that a large and steep left ventricular rapid filling wave is largely responsible for the shortening of deceleration time. As noted in Figure 2, there is a steeper increase in early diastolic left ventricular pressure after left ventricular minimal pressure consistent with loss of left ventricular compliance. This is more prominent in severe than in mild left ventricular dysfunction and during preload augmentation without left ventricular ischemic dysfunction. The rapid increase in early diastolic left ventricular pressure causes more rapid equilibration between left atrial and left ventricular pressures and accounts for the rapid decline in deceleration time. Thus, the modest correlation between deceleration time and left atrial pressure may be explained by the contribution of left ventricular compliance as shown in the configuration of the left ventricular rapid filling wave.

Study limitations. Our study has several limitations. 1) Left ventricular dysfunction was produced by an injection of microspheres into the left coronary artery in this study (16,17). Although this model demonstrated global systolic and diastolic dysfunction, it did not completely reflect human cardiomyopathy. However, the observed changes in the transmitral flow velocity pattern were analogous to those observed in clinical practice, and the relation between Doppler echocardiographic and hemodynamic variables was discussed in this study. Thus, errors in relating the results of this study to clinical practice may be small.

2) Acute alteration in loading condition or left ventricular

function was produced in this study. In patients with chronic heart failure, chronic adaptation may occur and this adaptation cannot be produced in the acute left ventricular dysfunction model of this experiment. Thus, further examinations may be needed to take account of chronic adaptation.

3) A progression of mitral regurgitation and an enlargement of mitral anulus area may have been associated with the intervention in this study, and such changes can affect the results of this study. However, the Doppler color flow jet area of mitral regurgitation was small, and a giant V wave of left atrial pressure was not observed throughout our experiment. Thus, changes in mitral regurgitation and mitral anulus area are unlikely to affect the conclusions of this study.

Clinical implications. The results of this study show that a concomitant increase in left ventricular minimal pressure due to left ventricular systolic dysfunction is responsible for the impairment of left ventricular diastolic filling. Thus, low peak early diastolic filling velocity may be observed in patients with elevated left atrial and left ventricular minimal pressures, and the transmitral flow velocity pattern should not provide an estimation of left atrial pressure in such patients. These results suggest that a reduction of left ventricular minimal pressure associated with medical therapy may play an important role in recovering left ventricular diastolic filling and hence stroke volume in patients with heart failure. For example, an increase in stroke volume produced by administration of vasodilators or arteriodilators in patients with heart failure may be at least partially explained by an associated decrease in left ventricular minimal pressure. This is because even a small decrease in afterload may decrease left ventricular end-systolic volume, increase elastic recoil, decrease left ventricular minimal pressure and improve left ventricular diastolic filling, particularly in failing hearts with a low left ventricular end-systolic elastance (a slope of left ventricular end-systolic pressure-volume relation). Thus, strategies of decreasing left ventricular minimal pressure may be effective in improving left ventricular diastolic filling and stroke volume in patients with heart failure.

Much attention has been paid to peak early diastolic filling velocity in assessing left ventricular diastolic function and loading conditions from the transmitral flow velocity pattern. This study showed that the deceleration time of the early diastolic filling wave correlates with left atrial pressure rather than left atrial to left ventricular pressure gradient both in normal and failing hearts, although peak early diastolic filling velocity correlates with left atrial to left ventricular pressure gradient rather than left atrial pressure. Clinical observations showed that deceleration time is shorter in patients with heart failure and increased left atrial pressure than in normal subjects, although peak early diastolic filling velocity does not differ between patients and normal subjects (4). Thus, although peak early diastolic filling velocity has been used as an estimate of left atrial pressure (5,9,11), the results of this study imply that the

estimate of left atrial pressure might be more accurate if deceleration time in addition to peak early diastolic filling velocity or isovolumic relaxation time were taken into account. In this context, future studies are warranted to develop a noninvasive means of estimating left atrial pressure by the combination of some of mitral flow-related Doppler variables.

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