

## A New Approach for Evaluation of Left Ventricular Diastolic Function: Spatial and Temporal Analysis of Left Ventricular Filling Flow Propagation by Color M-Mode Doppler Echocardiography

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**Objectives.** To evaluate left ventricular diastolic function and differentiate the pseudonormalized transmitral flow pattern from the normal pattern, the propagation of left ventricular early filling flow was assessed quantitatively using color M-mode Doppler echocardiography.

**Background.** Because the propagation of left ventricular early filling flow is disturbed in the left ventricle with impaired relaxation, quantification of such alterations should provide useful indexes for the evaluation of left ventricular diastolic function.

**Methods.** Study subjects were classified into three groups according to the ratio of early to late transmitral flow velocity (E/A ratio) and left ventricular ejection fraction: 29 subjects with an ejection fraction  $\geq 60\%$  (control group); 34 with an ejection fraction  $< 60\%$  and E/A ratio  $< 1$  (group I); and 25 with ejection fraction  $< 60\%$  and E/A ratio  $\geq 1$  (group II). The propagation of peak early filling flow was visualized by changing the first aliasing limit of the color Doppler signals. The rate of propagation of peak early filling flow velocity was defined as the distance/time ratio

between two sampling points: the point of the maximal velocity around the mitral orifice and the point in the mid-left ventricle at which the velocity decreased to 70% of its initial value. High fidelity manometer-tipped measurement was performed in 40 randomly selected subjects.

**Results.** The rate of propagation decreased in groups I and II compared with that in the control group ( $33.8 \pm 13.8$  [mean  $\pm$  SD] and  $30.0 \pm 8.6$  vs.  $74.3 \pm 17.4$  cm/s,  $p < 0.001$ , respectively) and correlated inversely with the time constant of left ventricular isovolumetric relaxation and the minimal first derivative of left ventricular pressure (peak negative  $dP/dt$ ) ( $r = 0.82$  and  $r = 0.72$ , respectively).

**Conclusions.** Spatial and temporal analysis of filling flow propagation by color M-mode Doppler echocardiography was free of pseudonormalization and correlated well with the invasive variables of left ventricular relaxation.

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Pulsed Doppler measurement of transmitral flow has been widely used to assess the left ventricular relaxation abnormality noninvasively in patients with failing hearts (1-5). However, pulsed Doppler-derived indexes are affected by multiple factors, including active relaxation and distensibility of the left ventricle, the pressure gradient between the left ventricle and atrium, and altered loading conditions (2,6,7). The abnormality of left ventricular relaxation is concealed in some patients because the transmitral flow pattern is normalized by an increased atrioventricular pressure gradient (pseudonormal-

ization) (8-10). In these patients, pulsed Doppler-derived indexes show poor correlations with invasive variables of left ventricular diastolic properties (11-13).

This study sought to validate the feasibility of our new index, the rate of propagation of left ventricular peak filling flow velocity in early diastole, for the evaluation of left ventricular diastolic function, particularly with a pseudonormalized transmitral flow pattern, using color M-mode Doppler echocardiography with a baseline-shifted first aliasing limit.

### Methods

**Study group.** We studied 93 subjects with sinus rhythm. All subjects underwent echocardiography and cardiac catheterization, including left ventriculography and coronary angiography for their diagnosis. Study subjects were classified into three groups. The control group included 31 patients with no evidence of apparent left ventricular systolic dysfunction (left ventricular ejection fraction  $\geq 60\%$ , age range 21 to 78 years,

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mean age 58). Fifteen of them had stable angina pectoris, and the others did not have clinically significant cardiac disease.

Sixty-two patients had systolic dysfunction (left ventricular ejection fraction <60%). Of these, 34 had an old myocardial infarction (12 anterior, 10 inferior, 2 lateral, 10 combined anterior and inferior), and 28 had idiopathic dilated cardiomyopathy. According to the ratio of early to late transmitral peak velocities (E/A ratio), these patients with systolic dysfunction were classified into two groups, group I (E/A ratio <1, 37 patients, age range 39 to 74 years, mean age 59) and group II (E/A ratio  $\geq$ 1, 25 patients, age range 31 to 72 years, mean age 56), representing a pseudonormalized transmitral flow pattern.

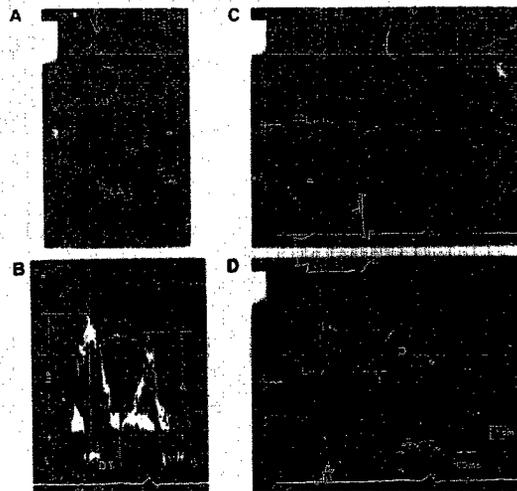
Subjects with atrial fibrillation, mitral stenosis, severe mitral regurgitation, aortic valve disease, congenital heart disease, hypertrophic cardiomyopathy with end-diastolic left ventricular wall thickness >12 mm or hypertension with systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg were excluded from the study. The study was approved by the human subjects review committee of our institution.

**Doppler echocardiography.** Echocardiograms were obtained using an Aloka SSD 870 equipped with a 2.5-MHz transducer. On the apical long-axis view, the sample volume of pulsed Doppler was located at the tip of the mitral valve leaflets to obtain the transmitral flow velocity in this study. The sample volume was 2 mm. Peak early and late transmitral flow velocities (E and A velocities), the ratio of early to late peak velocities (E/A ratio), and deceleration time of early transmitral flow velocity were obtained (Fig. 1A,B).

A color M-mode Doppler image of left ventricular filling flow in early diastole was obtained from the apical long-axis view (Fig. 1A). The ultrasound beam was interrogated from the apex of the heart toward the center of the mitral orifice as parallel to the filling flow as possible. By changing the first aliasing limit sequentially at intervals of 2 cm/s with the use of the baseline shift (14) (Fig. 2), a flow velocity higher than the aliasing velocity could be displayed in blue within red filling flow signals. First, we located the point of the maximal velocity around the mitral orifice in early diastole, which was obtained at the center of the minimized aliasing area (Fig. 1C). Next, we changed the first aliasing limit to 70% of the maximal velocity and located the point nearest to the apex on the aliasing boundary (Fig. 1D). The distance/time ratio, that is, the upward slope of the line connecting these two points, was measured and defined as the rate of propagation of peak early filling flow velocity (Fig. 1D).

In a preliminary experiment, we tested several different first aliasing limits, such as 90%, 80%, 70% and 60% of the maximal velocity (Fig. 2). The limit of 70% was adopted mainly because 70% ( $1/\sqrt{2}$ ) of the velocity represents the one-half pressure gradient, according to the simplified Bernoulli's equation;  $\Delta P = \frac{1}{2}\rho v^2$ , where  $\Delta P$  is the pressure gradient (i.e., the driving force of the filling flow),  $\rho$  blood density and  $v$  velocity of the blood flow.

To correct the influence of various peak early transmitral flow velocities, the rate of propagation of peak early filling flow



**Figure 1.** Definition of Doppler indexes. A, A two-dimensional color flow image: LV = left ventricle; LA = left atrium. B, Pulsed Doppler transmitral waveform: E and A = peak early and late transmitral flow velocity, respectively; DT = deceleration time of early transmitral flow velocity. C, D, Color M-mode Doppler images of left ventricular filling flow. The small arrows adjacent to the color bars indicate the first aliasing limit in each image.  $L_{max}$  = the point with the maximal filling flow velocity;  $L_{70}$  = the point with 70% velocity of  $L_{max}$ . The slope of the arrow  $L_{max}-L_{70}$  (D/t) was defined as the rate of propagation of peak early filling flow velocity.

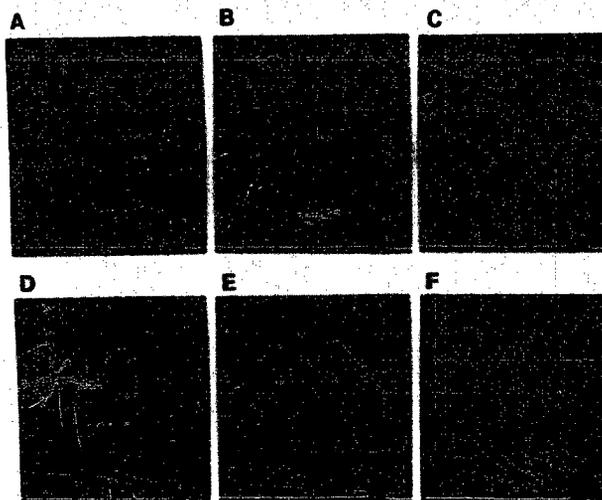
velocity was divided by E velocity, which was defined as the propagation ratio (the rate of propagation/E velocity).

Doppler echocardiograms were recorded on a video with a sweep speed of 100 mm/s and then digitized and analyzed by an image-processing system (TomTec Imaging Systems, Prism 5000). To cancel beat to beat variations, five different cardiac cycles were analyzed, and mean values were used for each parameter.

**Cardiac catheterization.** All subjects underwent left ventriculography. The ventriculograms were obtained in the 30° right anterior oblique projection. Left ventricular ejection fraction was calculated by Simpson's method.

In 40 randomly selected subjects (13 subjects of the control group, 14 subjects of group I and 13 subjects of group II) of 93 study subjects, hemodynamic data were obtained before left ventriculography using a high fidelity micromanometer-tipped catheter system (Camino Laboratories, System M 420) (15). Left ventricular minimal pressure in early diastole, left ventricular end-diastolic pressure and the minimal first derivative of left ventricular pressure (peak negative dP/dt) were measured at a paper speed of 100 mm/s (Fig. 3). The time constant T of left ventricular pressure decay in isovolumetric relaxation was calculated on a Macintosh Quadra 840AV according to the method of Weiss et al. (16). The pressure decrease every 5 ms from the peak negative dP/dt to 5 mm Hg above left end-diastolic pressure was applied to the exponential decay,  $P = \exp(At + B)$ , where P is pressure; A is the slope of ln P versus

**Figure 2.** Color M-mode images of left ventricular filling flow. The aliasing velocities of panels A, B, C, D, E and F are 64, 58, 52, 47, 41 and 35 cm/s in the same cardiac cycle, respectively.



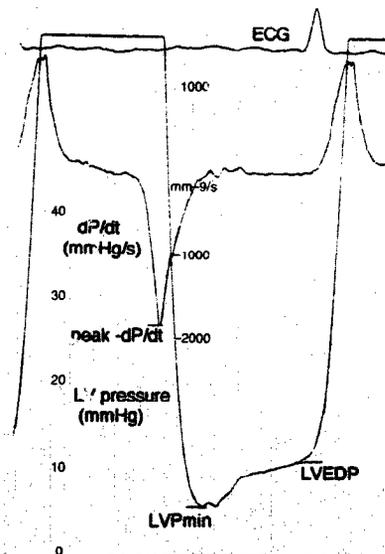
t; t is the time after the peak negative  $dP/dt$ ; and the time constant T is represented by  $-1/A$ . The intervals between echocardiography and hemodynamic examination ranged from 2 to 18 h. There were no significant differences in basal hemodynamics (heart rate and blood pressure), and the medical therapy was kept constant in both examinations.

**Reproducibility of measurements.** To test the intraobserver variability, the rate of propagation of peak early filling

velocity was measured twice from the data obtained from 14 randomly selected patients by a single observer after a 2-week interval. To examine the interobserver variability, two observers independently measured the rate of propagation in the same 14 patients.

**Statistical analysis.** Results are expressed as mean value  $\pm$  SD. The significance of differences among the groups was assessed by analysis of variance. Statistical relations were assessed by linear regression analysis. Differences and correlations were considered significant when the p value was  $<0.05$ .

**Figure 3.** Measurement method for invasive parameters. LV pressure = left ventricular pressure;  $LVP_{min}$  = left ventricular minimal pressure in early diastole; LVEDP = left ventricular end-diastolic pressure; peak  $-dP/dt$  = the minimal first derivative of left ventricular pressure (peak negative  $dP/dt$ ); ECG = electrocardiogram.



## Results

We obtained satisfactory color M-mode images and measured the rate of propagation of peak early filling flow velocity in 88 (95%) of 93 subjects. In two patients of the control group and three patients of group I, the quality of color M-mode images was not good enough for the measurement. These five subjects were excluded from further analysis.

**Clinical characteristics.** As indicated in Table 1, there were no significant differences in age, heart rate and systolic blood pressure among the three groups. In group II, left ventricular end-diastolic dimension obtained echocardiographically was the largest, and left ventricular ejection fraction was the lowest, among the three groups. Although the E/A ratio was reduced and deceleration time of early transmitral flow velocity was prolonged in group I compared with that in the control group, no differences of E/A ratio and deceleration time were found between group II and the control group because of the pseudonormalized transmitral flow pattern in group II.

**Color M-mode Doppler echocardiography.** Representative color M-mode images of each group are shown in Figure 4. The rate of propagation of peak early filling flow velocity is indicated by the line with an arrowhead in the blue aliasing

**Table 1.** Characteristics and Measured Variables of Study Patients

	Control Group (n = 29) (mean $\pm$ SD)	Group I (n = 34) (mean $\pm$ SD)	Group II (n = 25) (mean $\pm$ SD)
Age (yr)	58.2 $\pm$ 13.0	59.4 $\pm$ 8.4	55.7 $\pm$ 10.7
HR (beats/min)	67.0 $\pm$ 7.4	66.6 $\pm$ 9.1	66.4 $\pm$ 10.3
SBP (mm Hg)	124 $\pm$ 14	126 $\pm$ 15	120 $\pm$ 14
LVDd (mm)	47.0 $\pm$ 4.5	54.0 $\pm$ 8.6*	62.1 $\pm$ 11.6*†
LVEF (%)	70.2 $\pm$ 5.7	45.2 $\pm$ 9.9*	34.4 $\pm$ 6.2*†
E (cm/s)	60.6 $\pm$ 13.0	47.0 $\pm$ 12.6*	66.8 $\pm$ 17.9†
A (cm/s)	56.7 $\pm$ 14.4	68.9 $\pm$ 14.8*	50.2 $\pm$ 14.8†
E/A	1.13 $\pm$ 0.40	0.69 $\pm$ 0.15*	1.37 $\pm$ 0.46
DT (ms)	168 $\pm$ 39	216 $\pm$ 56*	158 $\pm$ 33†

\*p < 0.001 versus control group. †p < 0.001. ‡p < 0.05 versus group I. DT = deceleration time of early transmitral flow velocity; E/A = ratio of peak early (E) and late (A) transmitral flow velocities; HR = heart rate; LVDd = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

area. The upward slope of the line in the control group is steeper than that in groups I and II.

The maximal velocity around the mitral orifice obtained by the color M-mode Doppler technique had a good correlation with E velocity obtained by the pulsed Doppler technique ( $y = 0.98x + 0.625$ ,  $r = 0.98$ ,  $p < 0.001$ ,  $n = 88$ , data not shown).

The rate of propagation in group I or group II was lower than that in the control group (control group  $74.3 \pm 17.4$ ; group I  $33.8 \pm 13.8$ ; group II  $30.0 \pm 8.6$  cm/s) (Fig. 5A). Although there were no differences in E/A ratio and in deceleration time between group II and the control group, the rate of propagation was significantly reduced in group II. The propagation ratio (the rate of propagation/E velocity) in group II showed the lowest value among the three groups (control group  $1.27 \pm 0.36$ ; group I  $0.74 \pm 0.32$ ; group II  $0.47 \pm 0.13$ ) (Fig. 5B).

**Comparison with hemodynamic data.** In groups I and II, the time constant T was prolonged, and the peak negative dP/dt increased compared with the control group. Left ventric-

ular minimal pressure and end-diastolic pressure in group II were the highest among the three groups (Table 2). Although E/A ratio and deceleration time showed poor correlations with the time constant T ( $r = 0.01$  and  $r = 0.18$ ,  $n = 40$ , respectively), the rate of propagation correlated well with the time constant T, the peak negative dP/dt and left ventricular minimal pressure, respectively ( $y = -1.88x + 134$ ,  $r = 0.82$ ,  $p < 0.001$ ;  $y = -0.056x - 33.0$ ,  $r = 0.72$ ,  $p < 0.001$ ; and  $y = -4.91x + 74.2$ ,  $r = 0.61$ ,  $p < 0.001$ ,  $n = 40$ ) (Fig. 6).

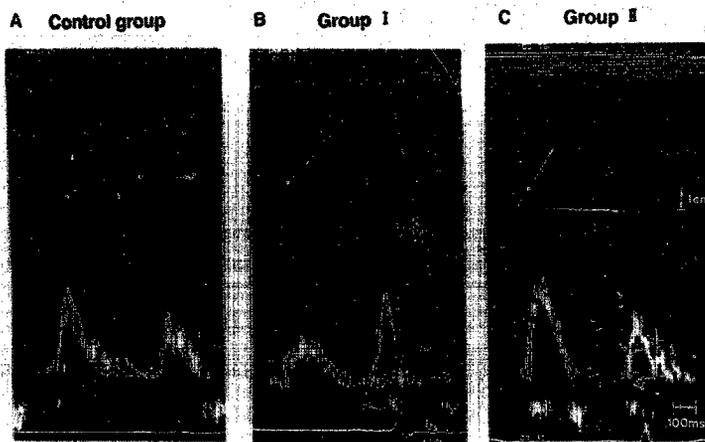
**Reproducibility.** The intraobserver and interobserver variations were within an acceptable range (intraobserver difference  $1.0 \pm 3.4$  cm/s; interobserver difference  $-1.0 \pm 6.2$  cm/s, mean  $\pm$  SD).

## Discussion

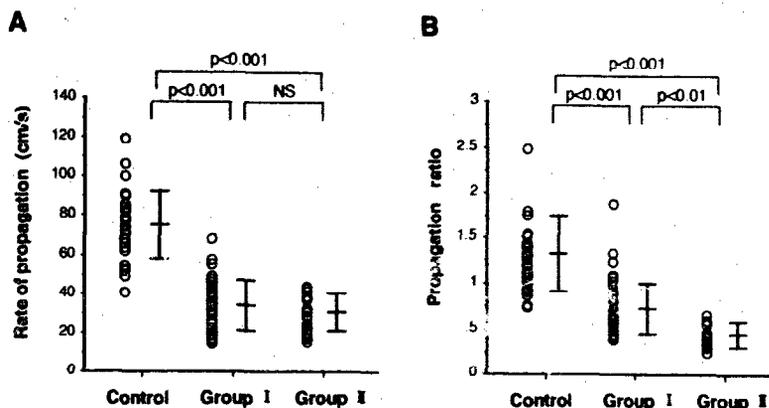
**Color M-mode Doppler-derived indexes.** Color M-mode Doppler echocardiography with the baseline shift technique enabled us to trace the propagation of peak early filling flow into the left ventricle. The validity of the baseline shift technique was proved by the fact that there was a good correlation between the initial peak filling velocity obtained by color M-mode Doppler and that by pulsed Doppler.

The rate of propagation of peak early filling flow velocity was decreased in both groups I and II. Although the E/A ratio in group II was not different from that in the control group because of pseudonormalization, the rate of propagation was significantly lower in group II.

In the normal state of left ventricular diastolic filling as seen in the control group, rapid left ventricular relaxation generates a dynamic pressure gradient, initially at the mitral orifice (6,9,17). The intraventricular minimal pressure does not increase significantly, and the pressure gradient is still maintained in the mid-left ventricle during early diastole (17,18). According to the Bernoulli equation, this pressure gradient generates the driving force to fill the blood volume deep into the left ventricle. Thus, the peak left ventricular filling can be



**Figure 4.** Relations between the rate of propagation and transmitral flow pattern in representative patients from three study groups. These images were obtained from a control subject (A), a group I patient (B) and a group II patient (C), respectively.



**Figure 5.** Comparison of rate of propagation of peak early filling flow velocity (A) and propagation ratio (the rate of propagation/E velocity) (B) among the three groups.

rapidly propagated sequentially from the mitral orifice toward the left ventricle.

Generally, in the state of diastolic dysfunction, the transmitral pressure gradient diminished by the impaired relaxation process results in a decreased early transmitral flow velocity (9,10,19). As described by Courtois et al. (18), the early diastolic intraventricular pressure gradient is lost because of rapidly increased left ventricular minimal pressure. Such a damped intraventricular pressure gradient may lead to slower propagation of early filling flow.

The state of pseudonormalized transmitral flow, as seen in group II, is characterized by concealed relaxation abnormalities because of the increased early transmitral velocity that is caused by an elevated transmitral pressure gradient (8-10). In the setting of severely reduced left ventricular distensibility, ventricular pressure increases immediately after the filling of a small amount of the blood volume into the left ventricle (6,20). Thus, the large atrioventricular pressure difference decays rapidly, and the driving force of the ventricular filling may be stalled at the near mitral orifice (8,17). Consequently, the filling flow propagation is rapidly attenuated in spite of increased early transmitral velocity.

To cancel the preload effect on the early transmitral flow velocity and to compare patients with different early transmi-

tral flow velocities, the rate of propagation of peak early filling flow velocity was corrected for the E velocity. Group II showed a higher E velocity than group I. However, the propagation ratio in group II was significantly reduced compared with group I, suggesting that left ventricular distensibility in patients with pseudonormalized transmitral flow pattern was the most advanced stage of left ventricular diastolic dysfunction.

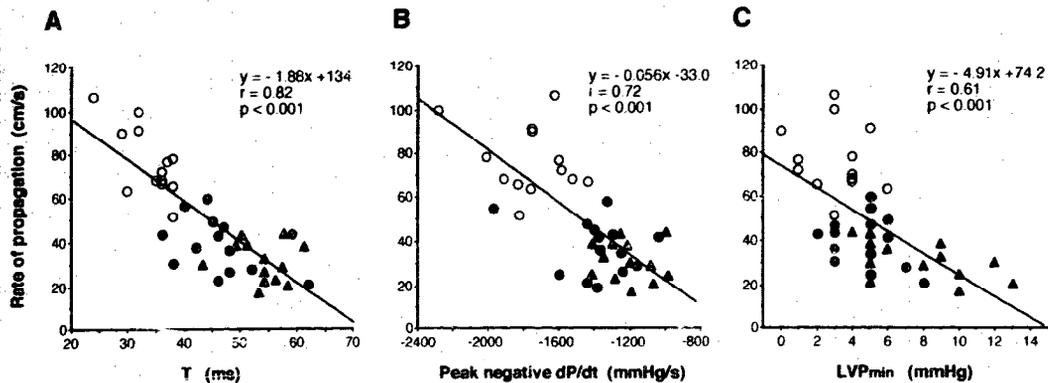
Jacobs et al. (21) represented the qualitative analysis of delayed propagation of early filling flow by color M-mode Doppler echocardiography in patients with dilated cardiomyopathy. Quantitative evaluation of the filling flow delay using the color M-mode technique was reported by Brun et al. (22). They found that the propagation of the filling wave front in early diastole was reduced in patients with impaired left ventricular relaxation. However, blurred wavefront signals sometimes make it difficult to determine its margin and do not reflect the transition of the peak of early filling flow propagation. Stugaard et al. (23) reported a delay in the time that the filling flow reached several sampling points in the left ventricle by computer analysis of color flow distribution. Although these studies reported the validity of filling flow propagation to assess left ventricular diastolic function, they did not verify the feasibility of such color M-mode indexes in cases with pseudonormalized transmitral flow pattern.

**Comparison with invasive indexes.** The isovolumetric time constant T is generally acknowledged to be an invasive index of left ventricular relaxation characteristics in early diastole and is not much affected by loading conditions (16,24). Appleton et al. (8) mentioned that Doppler-derived indexes, such as E/A ratio, isovolumetric relaxation time and the deceleration time of early transmitral flow, had poor correlations with the time constant T. Choong et al. (9) also reported that the relation of early transmitral velocity to the time constant T was shifted in association with altered loading conditions. In our study, the rate of propagation of peak early filling flow velocity correlated well with the time constant T and the peak negative dP/dt, suggesting that the rate of propagation is a more reliable

**Table 2.** Hemodynamic Data of Study Patients Obtained by Micromanometer

	Control Group (n = 13) (mean ± SD)	Group I (n = 14) (mean ± SD)	Group II (n = 13) (mean ± SD)
T (ms)	33.4 ± 4.2	46.6 ± 7.7*	55 ± 4.9*†
Peak -dP/dt (mm Hg/s)	-1,759 ± 225	-1,380 ± 218*	-1,212 ± 140*
LVP <sub>min</sub> (mm Hg)	3.2 ± 1.9	4.7 ± 1.7	7.8 ± 3.0*†
LVEDP (mm Hg)	11.0 ± 3.1	14.3 ± 7.4	18.5 ± 5.3‡§

\*p < 0.001, †p < 0.01 versus control group. ‡p < 0.01, §p < 0.05 versus group I. LVEDP = left ventricular end-diastolic pressure; LVP<sub>min</sub> = left ventricular minimal pressure in early diastole; Peak -dP/dt = peak negative dP/dt; T = time constant T of left ventricular isovolumetric relaxation.



**Figure 6.** Correlations between the rate of propagation of peak early filling flow velocity and the time constant T (A), peak negative dP/dt (B) and left ventricular minimal pressure (LVP<sub>min</sub>) (C). Open circles = control group; solid circles = group I; triangles = group II.

variable to assess the characteristics of left ventricular diastolic dysfunction than the transmitral flow pattern is.

Left ventricular minimal pressure is an important determinant of early transmitral flow velocity (17). The rate of propagation also showed a fair correlation with left ventricular minimal pressure. Study patients who had higher left ventricular minimal and end-diastolic pressures had a lower rate of propagation, suggesting that a decreased rate of propagation might be one of the indexes reflecting elevated left ventricular pressure in diastole.

**Limitations of the study.** The color M-mode Doppler beam should be interrogated as parallel as possible to the filling flow. However, in cases with a significantly dilated left ventricle, the flow will progress along the posterior wall with the swirling ventricular current. We might have underestimated the value of the rate of propagation in these cases. In some cases, the rate of propagation was not measured. It was difficult to display a clear aliasing boundary when the peak early filling velocity was decreased to <25 cm/s or the aliasing area appeared first in the mid-left ventricle, not around the mitral orifice.

The rate of propagation is supposed to be, in part, dependent on altered loading conditions, heart rate and age. Thus, further investigations are needed to clarify the effects of the changes of loading conditions on the propagation of early filling flow. We should also verify the validity of this new color M-mode Doppler-derived index in various conditions, such as hypertension, hypertrophic cardiomyopathy, atrial fibrillation and valvular or congenital heart disease.

**Conclusions.** The rate of propagation of left ventricular peak filling flow velocity in early diastole was obtained by color M-mode Doppler echocardiography with the baseline shift technique. It appears to be a simple and useful noninvasive

variable to evaluate more precisely left ventricular diastolic function. In contrast to the conventional Doppler-derived indexes, the rate of propagation of peak early filling flow velocity does not show pseudonormalization and may provide a new Doppler echocardiographic index that correlates well with invasively obtained variables of left ventricular relaxation.

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