Systolic dysfunction of the left ventricle is the most common cause of elevation of left ventricular (LV) diastolic pressure, which often results in congestive heart failure. However, diastolic dysfunction also occurs in the absence of systolic dysfunction, producing pulmonary congestion and congestive heart failure (1,2). Although Doppler echocardiography permits noninvasive measurement of transmitral flow velocity and thereby the assessment of LV diastolic function, altered LV preload, among other factors, affects the Doppler derived transmitral flow velocity indices (3,4). Thus, a noninvasive and cost-effective method that is less dependent on the preload is desirable in evaluating LV diastolic function in clinical settings.

Tissue Doppler imaging (TDI) is a noninvasive, ultrasound technique that has enabled direct measurement of myocardial velocity in real time (5–8). In contrast to the conventional echocardiography, TDI directly derives velocity information not only from the myocardial boundaries but from within the myocardial wall without the need of exact boundary tracings and the subsequent differentiation processes. Nevertheless, TDI measurements are affected by the translational motion of the heart because TDI measures velocity against the transducer (8). Accordingly, others as well as ourselves have previously introduced myocardial velocity gradient (MVG) as a new indicator of regional myocardial contraction (9,10) that is independent of the translational motion (10,11). We define MVG as the slope of the regression line for the transmural velocity profile between the endocardium and epicardium across the myocardial wall, thereby reflecting myocardial thick-
Methods

Study subjects. We enrolled 69 consecutive subjects comprising 13 normal subjects, 25 patients with hypertensive heart disease (HHD) and 31 patients with dilated cardiomyopathy (DCM) in this study. Normal subjects were healthy hospital personnel presenting normal echocardiographic study. Inclusion criteria for the HHD group were: 1) history of systemic hypertension (a casual diastolic pressure >100 mm Hg and a casual systolic pressure >160 mm Hg) and 2) echocardiographically normal fractional shortening (>28%) except for those enrolled in the follow-up study protocol. Inclusion criteria for the DCM group were: 1) LV enlargement and contractile dysfunction of unknown etiology and 2) angiographically normal coronary arteries. Exclusion criteria for the enrollment were: 1) localized LV asynergy, 2) valvular diseases, 3) pericardial diseases, 4) coronary artery disease and 5) myocardial diseases of specific etiology. Hence, the HHD group had impaired diastolic function with the systolic performance maintained (14) except for those enrolled in the follow-up study protocol, whereas the DCM group had both diastolic and systolic abnormalities (15–17). The study protocol conformed to the institutional guidelines for the medical ethics and all subjects provided written informed consent.

Of the 69 subjects, 58 included normal subjects as well as patients in a stable condition in whom congestive heart failure had been well controlled and were enrolled in the comparative study protocol. Fifteen were subsequently excluded because of inadequate image quality in nine and complication of arrhythmia in six. Thus, patients finally enrolled in the comparative study protocol included 43 patients comprising 12 normal subjects, 12 patients with HHD and 19 patients with DCM (Table 1). There was no statistical difference in age among the groups. The other 11 patients (8 men and 3 women, mean age = 46 years, range 27 to 68 years), who demonstrated apparent signs and symptoms of congestive heart failure at the initial examination, were recruited for the follow-up study protocol. This subgroup of patients comprised seven patients with DCM and four patients with HHD (Table 2). These patients received treatment with digoxin, vasodilators, angiotensin-converting enzyme inhibitors and diuretics after admission. All had normal sinus rhythm.

Comparative study protocol. Standard echocardiography including the measurement of transmitral flow velocity indices was performed at rest. The LV short axis dimensions, fractional shortening and LV posterior wall thickness were measured by standard M-mode echocardiography (18,19). Transmirtal flow velocity patterns were assessed by a standard tissue Doppler imaging.}

Table 1. Clinical and Echocardiographic Data for Subjects Enrolled in the Comparative Study

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 12)</th>
<th>HHD (n = 12)</th>
<th>DCM (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>48 ± 18</td>
<td>58 ± 14</td>
<td>44 ± 13</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>5/7</td>
<td>8/4</td>
<td>13/6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>61 ± 6</td>
<td>59 ± 12</td>
<td>68 ± 12</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>47 ± 4</td>
<td>49 ± 6</td>
<td>68 ± 12*</td>
</tr>
<tr>
<td>FS (%)</td>
<td>39 ± 6</td>
<td>41 ± 10</td>
<td>15 ± 5*</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>8.5 ± 1.2</td>
<td>13.1 ± 2.2*</td>
<td>8.9 ± 2.6</td>
</tr>
</tbody>
</table>

*p < 0.01 versus normal. Values are expressed as mean ± SD.

Abbreviations and Acronyms

A = peak late diastolic filling velocity
DCM = dilated cardiomyopathy
DcT = deceleration time of the early diastolic filling velocity
E = peak early diastolic filling velocity
HHD = hypertensive heart disease
IRT = isovolumic relaxation time
LV = left ventricular
MVG = myocardial velocity gradient
TDI = tissue Doppler imaging
pulsed-wave Doppler technique in the apical four-chamber view (3). Doppler measurements were averaged from three consecutive beats: peak early diastolic filling velocity (E), peak late diastolic filling velocity (A), the ratio (E/A), the deceleration time of the early diastolic filling velocity (DcT) and the LV isovolumic relaxation time (IRT). On completion of the standard echocardiographic measurements, TDI was done to obtain peak negative MVG in early diastole at rest.

**TDI system.** The TDI system used in this study has been described in detail elsewhere (6,8,10–12). In brief, a color Doppler sector scanner capable of TDI (SSA-380A; Toshiba Corp.) was connected to a personal computer (Macintosh 8100; Apple Computer) via a high-fidelity Red, Green and Blue (RGB) interface (IG24; Neotec Ltd.). Importantly, this system enabled the direct transfer and digital saving of the images without the loss of color intensity. A pair of a conventional gray-scale echocardiographic image and the corresponding color-coded velocity mapping image in a bi-directional red and blue mode specifically designed for the computer analysis was respectively transferred to the computer. Velocity ranges were adjusted to maximize sensitivity of low velocity values while avoiding saturation of the highest velocity during diastole. In this study, the standard M-mode echocardiographic view of the LV posterior wall was used with the guidance of two-dimensional echocardiography so that the ultrasound beam would be aligned perpendicular to the LV posterior wall. Use of the M-mode TDI permitted high temporal resolution as high as 4 ms.

**Concept of peak negative MVG.** We define MVG as the slope of the regression line for the transmural velocity profile between the endocardium and epicardium across the myocardial wall, which reflects regional wall thickening and thinning dynamics (9,10). The MVG forms a steep negative peak in early diastole, corresponding to the peak rate of wall thinning. However, peak negative MVG and the peak rate of wall thinning are not identical because MVG is derived from the regression line for the transmural velocity profile rather than derived from the endocardial and epicardial point velocity difference.

**Calculation of MVG in M-mode TDI.** Endocardial and epicardial boundaries of the LV posterior wall were manually traced in an M-mode gray-scale image, and the velocity data between the two lines were extracted from the corresponding color-coded image. At each time point, as indicated by the vertical line in early diastole (Fig. 1, top left), the velocity profile across the myocardial wall was obtained and provided for the least squares linear regression analysis (Fig. 1, right). The slope of the regression line was determined as the instantaneous MVG. The MVG calculations were repeated at each time point throughout the cardiac cycle. Peak negative MVG in early diastole was subsequently determined (Fig. 1, bottom left) and was averaged for three consecutive beats. The MVG was analyzed off line and approximate time required for measuring an entire cardiac cycle was 50 s, including manual tracings.

**Passive leg lifting maneuver.** Passive leg lifting was performed to investigate the effects of preload increase on TDI as well as standard Doppler transmitral flow velocity measurements in a subgroup of 30 patients (10 normal subjects, 10 patients with hypertension and 10 patients with dilated cardiomyopathy) extracted from the 43 patients enrolled in the comparative study protocol. Leg lifting was not done in 13 patients because of the unavailability of personnel in 8, inadequate image quality during the maneuver in 1 and possible volume overloading suspected by a standard echocardiographic examination in 4. First, both legs of the study subject were lifted up to 45° from the horizontal position by another examiner while the transmitral flow was continuously recorded with a pulsed-wave Doppler. The timing of the maximum changes occurring in the transmitral flow velocity pattern was determined. After resting for 5 min, TDI examination was performed both at rest and during leg lifting, and peak negative MVG was determined both at rest and at the time maximum changes occurred in the transmitral flow velocity pattern.

![Figure 1. Calculation of peak negative MVG in early diastole. See text for details.](image-url)
pattern. Finally, leg lifting was repeated during pulsed-wave Doppler transmitral flow recording to confirm the reproducibility of the timing of the changes in the transmitral flow pattern.

Follow-up study protocol. In the 11 patients presenting overt congestive heart failure at the initial examination, both standard echocardiographic and TDI examinations were repeated on 26 ± 16 days after the initial examination to assess the effect of volume reducing therapy for congestive heart failure, particularly preload reduction, on the TDI as well as on the transmitral flow velocity indices. Changes in the clinical and echocardiographic status of these patients by the therapy were shown in Table 2. Body weight significantly decreased and the fractional shortening increased after the treatment.

Intraobserver and interobserver variability of peak negative MVG. Reproducibility of peak negative MVG measurements was assessed in eight subjects randomly allocated from the comparative study group. Intraobserver variability was assessed by a single observer (Y.S.) on two separate occasions. Interobserver variability was assessed by two independent observers (Y.S. and M.U.). The mean difference between the measurements by a single observer was 0.2 ± 0.2/s. The mean interobserver difference was 0.5 ± 0.5/s.

Statistical analysis. Data are expressed as mean value ± SD. Multiple comparison was performed by two-way analysis of variance, followed by a Scheffe’s post hoc test. Paired comparison was done by Student’s paired t test. Differences were considered to be statistically significant at p < 0.05.

Results

Comparative study. Transmitral flow velocity indices and peak negative MVG could be derived from all 43 subjects. Transmitral flow velocity pattern in patients with HHD demonstrated an abnormal relaxation pattern, in which E and E/A decreased, and DcT and IRT increased (Fig. 2). Peak negative MVG was also attenuated in patients with HHD as compared with normal subjects (Fig. 2). In contrast, transmitral flow velocity pattern in patients with DCM did not necessarily differ from normal subjects due to the pseudonormalization occurring in some patients (Fig. 2). Peak negative MVG was significantly attenuated in patients with DCM as compared with normal subjects (Fig. 2). Comparisons of the transmitral flow velocity indices and the peak negative MVG among the groups were summarized in Table 3. Peak negative MVG was attenuated both in HHD and in DCM, whereas the transmitral flow velocity pattern varied among patients with DCM. The attenuation of E and the prolongation of DcT and IRT (an abnormal relaxation pattern) were seen in patients with HHD. Hence, peak negative MVG was attenuated in HHD as well as in DCM, reflecting the impairment of diastolic function in both groups, regardless of the presence or absence of impaired systolic performance.

Peak negative MVG in early diastole demonstrated minimal overlap between the normal and the abnormal (HHD and DCM) as compared with peak negative endocardial velocity in

| Table 3. Transmitral Flow Velocity and Tissue Doppler Indices in the Comparative Study |
|---------------------------------|-----------------|-----------------|
| Normal (n = 12) | HHD (n = 12) | DCM (n = 19) |
| E (cm/s) | 72 ± 10 | 54 ± 16* | 63 ± 18 |
| A (cm/s) | 58 ± 22 | 71 ± 21 | 58 ± 21 |
| E/A | 1.5 ± 0.7 | 0.8 ± 0.3† | 1.2 ± 0.6 |
| IRT (ms) | 66 ± 14 | 87 ± 25* | 73 ± 27 |
| DcT (ms) | 164 ± 15 | 211 ± 31† | 157 ± 37 |
| Peak negative EV (cm/s) | −11.4 ± 2.2 | −8.1 ± 2.3† | −7.4 ± 2.9† |
| Peak negative MVG (s) | −7.7 ± 1.5 | −3.9 ± 1.3† | −4.4 ± 1.4† |

* p < 0.05 versus normal. † p < 0.01 versus normal. Values are expressed as mean ± SD. A = peak late diastolic filling velocity; DcT = dilated cardiomyopathy; DCM = peak early diastolic filling velocity; EV = endocardial velocity; HHD = hypertensive heart disease; HR = heart rate; IRT = isovolumic relaxation time; MVG = myocardial velocity gradient; Normal = normal subjects.
early diastole (Table 3). Hence, the sensitivity and specificity of peak negative MVG for discriminating the abnormal from the normal were 90% and 100%, respectively, when a cutoff MVG of -5.7/s was used. Those of peak negative endocardial velocity were 81% and 92%, respectively, when a cutoff velocity of -8.9 cm/s was used.

Responses to passive leg lifting. The E and E/A of the transmitral flow velocity pattern markedly increased by leg lifting, changing from an abnormal relaxation pattern to a near normal pattern as demonstrated in a case of HHHD (Fig. 3, top). Peak negative MVG, on the other hand, remained unchanged (Fig. 3, bottom). Similar directional changes occurred by leg lifting in all 30 patients studied (Fig. 4). The E and E/A increased and DcT shortened significantly, reflecting the preload increase due to the transient increase of venous return from the lower extremities. In contrast, peak negative MVG did not alter significantly even under such circumstances (Fig. 4). Heart rate and blood pressure were not significantly altered by the maneuver (heart rate from 62 ± 11 to 64 ± 11/min; systolic blood pressure from 136 ± 22 to 138 ± 24 mm Hg).

Follow-up study. In the subgroup of patients presenting congestive heart failure, volume overloading was corrected by medical therapy, as indicated by the significant decrease in body weight (Table 2). The E and E/A decreased and DcT increased with the improvement of heart failure as demonstrated in a representative case of HHHD (Fig. 5, top). Hence, the transmitral flow velocity pattern apparently changed from a normal or a pseudonormal pattern to an abnormal relaxation pattern, accompanied by the clinical improvement of congestive heart failure. Peak negative MVG improved in spite of the suggested preload reduction (Fig. 5, bottom). The peak negative MVG as well as the transmitral flow velocity indices demonstrated similar directional changes in all patients receiving volume reducing therapy for congestive heart failure (Fig. 6). Thus, with the clinical improvement of the signs and symptoms of congestive heart failure, the transmitral flow velocity indices were apparently worsened from a normal or a near normal pattern toward an abnormal relaxation pattern,

![Figure 3](image1.png) **Figure 3.** Transmitral flow velocity patterns (top) and MVG curves (bottom) obtained at rest and during passive leg lifting in a representative case of hypertensive heart disease. E significantly increased and E/A apparently normalized, thus transmitral flow velocity pattern changing from an abnormal relaxation pattern to a near normal pattern by leg lifting. In contrast, peak negative MVG was not significantly altered by the maneuver.

![Figure 4](image2.png) **Figure 4.** Changes in the transmitral flow velocity indices and peak negative MVG by passive leg lifting maneuver. E and E/A significantly increased while DcT shortened by leg lifting. In contrast, peak negative MVG was unaltered by the maneuver. The same directional changes were observed among different groups. **Solid circles** = normal subjects; **open circles** = patients with hypertensive heart disease; and **solid squares** = patients with dilated cardiomyopathy. Lifting = during passive leg lifting. Rest = at rest.
whereas the peak negative MVG demonstrated an improvement.

**Discussion**

In this study we sought to assess the clinical significance of peak negative MVG derived from TDI as a noninvasive indicator of LV diastolic function. By comparing peak negative MVG among patients with or without impairment of systolic and diastolic performance, we have demonstrated that peak negative MVG reflected diastolic abnormalities in these patients. We have also found that peak negative MVG was relatively independent of preload alterations because peak negative MVG was unaltered, while the transmural flow velocity indices were significantly altered, by passive leg lifting maneuver. Finally, we have found that peak negative MVG showed an improvement by volume-reducing therapy in contrast to the transmural flow velocity indices, which apparently worsened toward an abnormal relaxation pattern. Thus, peak negative MVG may be a noninvasive indicator of LV diastolic function that is relatively independent of preload alterations, and thereby could be used for the follow-up of patients with nonischemic myocardial disease presenting congestive heart failure.

The MVG was introduced by Fleming et al. (9) and Uematsu et al. (10) as a new noninvasive indicator of myocardial function. The myocardial velocity information was derived from each pixel, between the endocardium and epicardium across the myocardial wall, as opposed to only two values being considered in digitized M-mode echocardiography. Therefore, the accuracy of MVG is less dependent on the accuracy of endocardial and epicardial boundary traces. The MVG has been analyzed in patients with impaired systolic function as well as in healthy subjects (9,10,20). More recently, Palka et al. (13) have analyzed diastolic MVG in patients with myocardial hypertrophy to conclude that diastolic MVG is useful in differentiating hypertrophic cardiomyopathy and athletes' hearts when the thickness of the myocardium is within borderline limits. Nevertheless, diastolic MVG in other cardiac diseases and the effects of preload alterations on the diastolic MVG remained to be elucidated. Accordingly, we examined patients with the impairment of both systolic and diastolic
performance (DCM) as well as patients with impaired diastolic function with maintained systolic performance (HHD), along with normal subjects, to assess the significance of peak negative MVG in this study. Furthermore, effects of preload alterations on MVG were assessed by performing passive leg lifting and by following up on patients with congestive heart failure on volume-reducing therapy.

If the transmural velocity profile is approximated as linear, MVG is equivalent to the rate of change in wall thickness normalized by the instantaneous wall thickness (10). This normalization by the wall thickness could lessen the effects of systolic function or elastic recoil of the left ventricle on the diastolic index. In fact, patients with HHD constantly demonstrated lower than normal peak negative MVG although systolic performance was maintained in these patients.

The LV diastolic function has also been assessed by mitral annulus velocity as well as by myocardial velocity using a spectral TDI technique (21–23). Restrictive and constrictive physiology was differentiated with this methodology (24,25). Sohn et al. (26) demonstrated that mitral annulus velocity determined by this technique is a relatively preload-independent variable. However, because this technique detects the velocity of the myocardium or the mitral annulus against the transducer with a fixed sample volume, the influence of translational motion cannot be ruled out. The MVG, on the other hand, has been shown independent of the translational motion of the whole heart in clinical settings (11) as well as by theoretical considerations (10). The results from the comparative study suggest peak negative MVG is more specific than peak negative endocardial velocity to differentiate abnormal diastolic function.

**Passive leg lifting.** In this study, we performed passive leg lifting as a means of increasing preload (27). This simple maneuver has several advantages over pharmacologic interventions or volume loading for the purpose of assessing the directional changes because it does not significantly affect afterload and heart rate, and the duration of the effect is short. As opposed to transmitral flow velocity indices, peak negative MVG remained substantially unchanged by leg lifting.

**Influence of volume-reducing therapy on the indices.** Body weight was significantly decreased during the follow-up period, indicating the effective volume reduction for treating congestive heart failure. The transmitral flow velocity patterns apparently worsened from a normal or a near normal pattern to an abnormal relaxation pattern by the therapy. These changes are understandable because preload reduction will result in lowering E and prolongation of DcT under unaltered LV diastolic function (3,4). Therefore, the apparent worsening of the transmitral flow velocity pattern during the therapy implies preload reduction rather than worsening of the diastolic function. However, it is difficult to determine from the transmitral flow indices alone whether the changes observed are due to the preload reduction or due to the impairment in relaxation. No change may be seen if both preload reduction and the improvement in relaxation occur at the same time to a certain extent. Hence, a noninvasive indicator of LV diastolic function that is less dependent on the preload is desirable. Peak negative MVG demonstrated a slight but significant improvement during the follow-up, while transmitral flow velocity patterns apparently worsened toward an abnormal relaxation pattern. Together with the results from the leg lifting, these data imply that peak negative MVG may be an indicator of diastolic function less dependent on preload alterations.

The mechanisms responsible for the relative preload independence of peak negative MVG remain unclear. It is interesting to speculate, however, that peak negative MVG may reflect the process of active myocardial relaxation. Although peak negative MVG occurs shortly after the isovolumic relaxation period during the rapid filling phase, the LV relaxation still continues in this phase. Hence, depressed peak negative MVG may at least in part indicate the diastolic dysfunction reflecting slow relaxation. This is in accordance with the earlier finding that the time constant of the LV pressure decay (tau), an invasive indicator of LV relaxation, is not significantly influenced by preload alterations within a physiologic range (28).

**Clinical implications.** Assessment of diastolic function by a transmitral flow velocity pattern alone is sometimes confusing in patients presenting congestive heart failure because transmitral flow velocity patterns are determined by the instantaneous pressure gradient between the left atrium and the left ventricle, thereby largely influenced by preload (4). Peak negative MVG may be considered as a more specific indicator of LV diastolic function than the transmitral flow indices because peak negative MVG appears to be less dependent on the preload. Peak negative MVG may be useful to avoid misinterpretation of transmitral flow velocity patterns, particularly in the follow-up of patients presenting congestive heart failure. Further studies should be needed to address its usefulness in evaluating a variety of therapeutic interventions in the long-term follow-up of patients presenting congestive heart failure.

**Study limitations.** Patients associated with localized LV asynnergy had been excluded from the study. Although most patients with DCM demonstrate generally reduced LV wall motion, some patients with DCM reveal localized LV asynnergy. Peak negative MVG may not be applied to such patients for the assessment of LV diastolic function because we derived peak negative MVG from the LV posterior wall to represent the entire left ventricle. Nevertheless, the directional changes may be assessed by this methodology during the follow-up of these patients.

This study does not include the direct validation of peak negative MVG by comparing it with a gold standard for the assessment of LV diastolic function. The time constant of the LV pressure decay (tau), an indicator of LV isovolumic relaxation, may serve as one of the candidates for the comparison, which was not done in this study. However, tau is derived from the pressure decay in the isovolumic relaxation phase, whereas peak negative MVG is derived from myocardial velocity after the mitral valve opening. Therefore, an identical
standard of reference for the validation of peak negative MVG is not currently available.

We utilized M-mode TDI in this study to maximize the temporal resolution, thereby detecting a steep peak of the diastolic MVG. M-mode measurements have limited spatial resolution and the effects of asynchrony were not assessed. With the improvement of the technology, however, diastolic MVG measurements could be done with two-dimensional TDI. Thus, measurements of peak negative MVG may be applied to multiple locations of the left ventricle, which would allow comparison of the regional diastolic function of the myocardium in the near future.

Conclusions. Peak negative MVG derived from TDI may be a noninvasive indicator of LV diastolic function that is less affected by preload alterations than the transmitral flow velocity indices, and thereby could be used for the follow-up of patients with nonischemic LV dysfunction presenting congestive heart failure.

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