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Left Ventricular Flow Propagation During Early Filling Is Related to Wall Relaxation: A Color M-Mode Doppler Analysis

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Objectives. **This study was designed to evaluate the relation between the velocity of flow propagation and left ventricular relaxation by using color M-mode Doppler echocardiography to analyze flow propagation in the left ventricle.**

Background. **Noninvasive attempts to identify alterations in left ventricular relaxation have been hampered because both the relaxation rate and left atrial filling pressure are the determinants of peak early velocity and filling rate.**

Methods. **Color M-mode velocity data were transferred to a microcomputer and compared with conventional pulsed Doppler data to assess the ability of color M-mode echocardiography to analyze velocity field properties. The velocity of flow propagation was measured as the slope of the flow wave front during early filling in normal subjects (n = 29) and in patients with disease that alters relaxation (dilated cardiomyopathy [n = 31], ischemic cardiomyopathy [n = 8], hypertrophic cardiomyopathy [n = 5], systemic hypertension [n = 22] and aortic valve disease [n = 25]). In nine patients with end-stage dilated cardiomyopathy, echocardiographic and left heart catheterization data were obtained at baseline and during intracoronary dobutamine infusion.**

Results. **Color M-mode and pulsed Doppler echocardiographic data were highly correlated (n = 217, r = 0.94, p < 0.0001, velocity range 0.2 to 1.5 m/s). The velocity of flow propagation was lower in patients than in normal subjects (0.46 ± 0.15 vs. 0.84 ± 0.11 m/s, p < 0.0001). The decrease was significant in all disease forms with or without left ventricular dilation. The velocity of flow propagation was related to peak early velocity in normal subjects (p < 0.001) but not in patients. It varied inversely with the isovolumetric relaxation time constant during dobutamine infusion and the two variables were highly correlated (p < 0.0001).**

Conclusions. **The velocity of flow propagation during early filling seems to be highly dependent on the left ventricular relaxation rate and could be an important tool in studying diastolic function.**

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A delay in flow propagation in the left ventricle was first described in dilated cardiomyopathy by Jacobs et al. (1). Using both two-dimensional color Doppler and color M-mode echocardiography, they showed that early filling reached the apex late in diastole or even during the following systole. The increased dimensions of the left ventricle and a disorientation of flow due to the mitral valve orifice were thought to be the mechanisms explaining the difference between this flow pattern and the rapid progression of flow toward the apex observed in the normal ventricle (1). However, because left ventricular relaxation persists during early diastole (2–6), another possible explanation is a restraint on flow propagation in the ventricular cavity as a result of wall properties. An asynchrony in wall relaxation could modulate flow propagation in the cavity and increased asynchrony could induce the increased delay of flow observed in dilated cardiomyopathy.

The purpose of this study was to test this hypothesis, relating the left ventricular inflow pattern to diastolic myocardial properties. We attempted to analyze the velocity of flow propagation rather than flow propagation delay, because the latter variable is too dependent on ventricular cavity dimensions. Our first objective was to test the feasibility of accurately measuring the velocity of flow propagation with color M-mode echocardiography. Next, we attempted to compare this value in normal subjects with values found in patients with five different diseases known to alter the relaxation process in the presence or absence of left ventricular dilation: dilated cardiomyopathy (7–11), ischemic cardiomyopathy (12–16), hypertrophic cardiomyopathy (17–21), systemic hypertension (7,22) and aortic valve disease (23–26). Our last objective was to determine the significance of the velocity of flow propagation by comparing the values observed in different hemodynamic states with values of the isovolumetric relaxation time constant (27,28).

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Methods

Study patients. We prospectively studied 116 subjects undergoing routine echocardiographic examination and 9 patients who underwent echocardiography during left heart catheterization. Our total study group comprised a normal group (30 subjects with no evidence of heart disease or hypertension) and five groups of patients with disease, inducing delayed left ventricular relaxation: Group I, dilated cardiomyopathy (n = 31, with a subset of 9 patients with end-stage dilated cardiomyopathy who underwent cardiac catheterization during cardiac transplant screening evaluation); Group II, ischemic cardiomyopathy without significant left ventricular dilation (n = 8); Group III, hypertrophic cardiomyopathy (n = 6); Group IV, systemic hypertension (n = 23); and Group V, pre- or postoperative aortic valve lesions (n = 27). Poor technical quality of two-dimensional or Doppler echocardiographic images was an exclusion criterion. Patients with only mild disease, with an uncertain diagnosis or aortic regurgitation impinging on the anterior mitral leaflet were excluded.

Color M-mode and Doppler echocardiographic recordings. Data acquisition was performed during examinations that included pulsed Doppler and color M-mode Doppler echocardiography. An electrocardiographic (ECG) lead was recorded in all patients, and other physiologic tracings could be added. All data were obtained with a Vingmed CFM 750 system. With the use of the apical three- or four-chamber view, the pulsed Doppler sample was placed at the mitral leaflet tips to obtain maximal velocities during the left ventricular filling phase. The sample size was 3 mm. Left ventricular inflow was also recorded with the use of color M-mode echocardiography. We looked for the largest propagation of the color signal in the left ventricular chamber to optimize the recording; peak velocities had to be recorded for ≥2.5 cm in the left ventricle without major velocity loss. The gain was always set to the maximal value, avoiding saturation effects. Pulsed Doppler and color M-mode recordings of left ventricular inflow were obtained within a minimal delay.

Color M-mode characteristics. The ultrasound system used a frequency of 3.25 MHz for the imaging mode and a frequency of 2.5 MHz for the Doppler mode. The color M-mode line contained 128 samples, with a variable depth range (10 to 18 cm). Data were displayed on the system monitor every 5 ms, using 18 color levels for each flow direction.

Data transfer. An interface board developed by the Biomedical Engineering Department of Trondheim University, Norway allowed the transfer of the ultrasound data and physiologic tracings to a microcomputer. Dedicated software (EchoLink, Vingmed Sound, Horten, Norway) ensured the transfer of all echocardiographic modes. Data were first entered into a scrolling memory containing 5 to 10 cardiac cycles and then transferred to the microcomputer. We used a Macintosh IIci with 8 Mbytes of central memory. Data were stored on an optical hard disk (300 Mbyte). One recording sequence (6 to 10 beats) used 0.3 to 1 Mbyte. Each transfer was accomplished in approximately 15 s.

Display and analysis of transferred data. Data handling, processing, display and analysis were performed on the microcomputer monitor with the program EchoDisp (Vingmed Sound). The recordings could be initially displayed in small windows, then expanded to the size of the full monitor screen. Time magnification could also be performed. The color look-up table reproduced the color map of the ultrasound system (18 × 2 levels), but other color maps could be selected. In the color M-mode, the following information was available for each pixel: 1) time, with a 5-ms increment; 2) depth, with a sample size approximating 1 mm (range 0.77 to 1.54 according to the selected depth); and 3) velocity, with a step value approximating 0.04 m/s (range 0.034 to 0.057 according to the Nyquist limit). By shifting the baseline, the maximal recordable velocity could be extended to 2 Nyquist limits (1.22 to 2.03 m/s). The use of low velocity filters appeared unnecessary in color M-mode echocardiography and no temporal or spatial smoothings were performed. Separate windows could be obtained for the spatial velocity (velocity along a depth line) and three-dimensional profiles by referring to a previously defined time-depth area.

Study objectives. The study was designed to 1) validate the quantitative information obtained in color M-mode recordings; 2) provide a spatial description of left ventricular inflow patterns in normal subjects and patients with the different diseases; 3) analyze flow wave propagation, using the information available in the color M-mode documents to provide a quantitative study of flow propagation velocity; and 4) compare the velocity of flow propagation with the isovolumetric time constant of relaxation.

Color M-mode validation protocol. *Comparison with a validated technique.* To validate the quantitative information obtained by color M-mode echocardiography, we selected the peak transmitral velocity values (E wave and A wave) and compared the velocities obtained by conventional single-gate pulsed Doppler echocardiography to similar velocities obtained in the same depth area by color M-mode echocardiography. Because color M-mode echocardiography delivers mean velocities, we utilized modal velocities in pulsed Doppler studies according to the close relation between mean and modal velocities in a laminar flow situation. The comparison was performed for each subject, using one cardiac cycle selected at the end-expiratory phase.

Reproducibility and accuracy. To further test color M-mode quantitative information, we selected a document chosen for optimal technical conditions and smooth appearance of diastolic flow. Six consecutive cardiac cycles were included in a temporal and spatial study. To determine *temporal accuracy*, we compared two successive estimations (t_1 and t_2) during a stable phase of flow. For each depth sample of the M-mode line, we assumed that the flow velocity remained unchanged during the 5-ms time interval. Therefore, any observed change would be considered to be

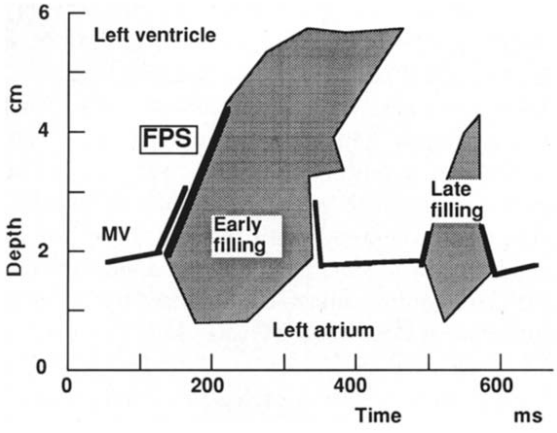


Figure 1. Determination of the velocity of flow propagation (FPS) in the left ventricle by color M-mode echocardiography. The flow pattern in the left ventricle is schematized during diastole. The flow wave front during early filling is shown as a linear segment in the basal zone of the left ventricle. This linear property was observed in most subjects, but is usually lost closer to the apex. Flow propagation velocity is defined as the slope of the linear segment (m/s). MV = mitral valve.

an inaccurate velocity estimation. For *spatial accuracy*, the comparison included the two lines (t_1 and t_2) and was performed on 50 velocity samples situated in the basal and mid portions of the left ventricular cavity. Because important flow velocity changes were observed with changes in depth, we assumed that the average values during six cardiac cycles represented the true velocity. Each individual difference in velocity between adjacent samples was compared with the corresponding mean spatial changes.

Spatial description of left ventricular inflow patterns. The temporal pattern of left ventricular inflow velocity has been widely described in normal conditions and in disease using single-gate pulsed Doppler echocardiography, but these studies are restricted to the transmitral area. Conversely, color M-mode echocardiography permits spatial and temporal visualization of flow propagation inside the whole left ventricular cavity. The extent of this flow propagation was analyzed during early and late filling in the normal group and in patients with disease.

Choice of a method to determine velocity of flow propagation. Different approaches were tested to determine the velocity of flow propagation in the left ventricle during the early filling period. Our choice was to draw a line segment along a color change as displayed on the Macintosh monitor and to read the speed directly. Because use of the highest velocities, gave erratic results, we selected the low velocities outlining the early filling wave front (black to red transition). This wave front had to be reasonably linear (Fig. 1). We always selected the color map that allowed the best low velocity contrast (called the "rainbow without variance" in our software program) and never used low velocity filters. The segment began with the onset of flow in the left ventricular inlet and ended as far as possible in the left ventricular chamber (Fig. 1). In case of significant beat to beat differences, we always selected the highest velocity of flow propagation. Propagation velocity values were expressed in m/s.

In this preliminary study, neither interobserver nor intraobserver variability was measured. As a rule, however, each determination required the agreement of two observers and computer storage of the corresponding image.

Comparison with information obtained during cardiac catheterization. The subset of patients with dilated cardiomyopathy who underwent cardiac catheterization (n = 9) received intracoronary dobutamine infusion to determine their myocardial adrenergic contractile reserve, according to the protocol proposed by Colluci et al. (28). These nine patients were included in Group I. Their data in the control state appear in the general study. In eight of the nine patients, left ventricular pressure recordings were obtained simultaneously with a 5F Millar catheter and transferred with color M-mode data two to five times during the dobutamine infusion (50 to 200 μg/min). We monitored heart rate, left ventricular peak, minimal and end-diastolic pressures, maximal and minimal first derivative of left ventricular pressure (dP/dt) and peak early velocity obtained by color M-mode echocardiography. The time constant of left ventricular isovolumetric relaxation was calculated in two ways. First, we used the natural logarithm method (27) to compute the time constant of isovolumetric relaxation (τ_{ln}) from negative peak dP/dt to mitral valve opening; mitral valve opening was demonstrated by the onset of flow on the color M-mode image. The second method used the direct measurement of pressure half-time (29). With this method, ($\tau_{1/2}$) is measured directly from the pressure tracing as the time required for left ventricular pressure to decrease to half of its value at negative peak dP/dt. Flow propagation velocity was calculated as previously described.

All early filling waves starting after minimal left ventricular pressure were excluded in evaluation of the flow propagation velocity. This condition was found in five instances: the values of the isovolumetric relaxation time constant were always considerably decreased by reference to their basal state values. It was assumed that with left coronary dobutamine infusion, the relaxation process was complete (30) before the onset of early filling. Conversely, the velocity of flow propagation was measured during late filling in one patient because 1) early filling velocity was extremely low; and 2) relaxation was prolonged as evidenced by the isovolumetric time constant. The protocol was approved by the local Ethics Committee of the University Hospital Henri Mondor. All patients provided written informed consent. No complications occurred as a result of the study.

Statistical analysis. Data are expressed as mean value ± SD. The correlations between color M-mode and pulsed Doppler values, between flow propagation velocity and peak velocity variables, between flow propagation velocity and age and between flow propagation velocity and the hemodynamic constant τ were assessed by least squares regression

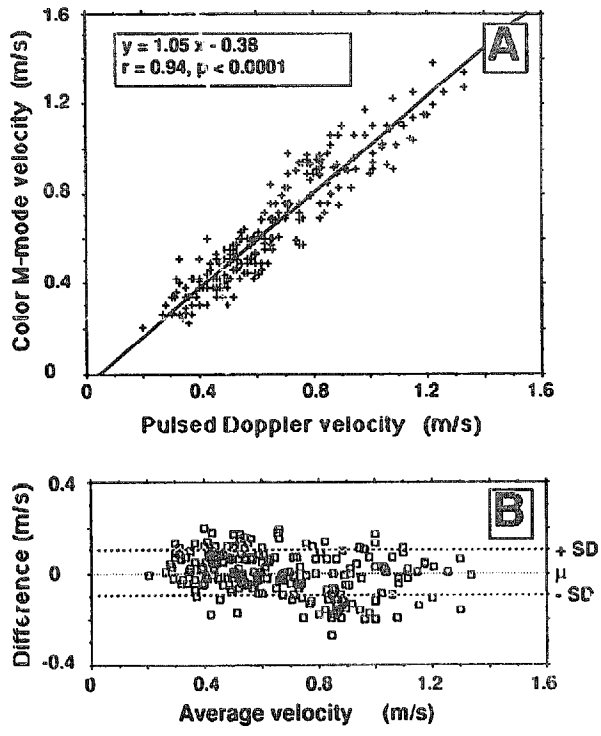


Figure 2. Comparison between peak velocity values measured by single-gate pulsed Doppler and color M-mode echocardiography. This comparison was performed during peak early and late transmitral velocities (n = 217). The correlation between the measurements obtained with both methods is highly significant and close to the identity line. The plot of the difference against the mean of the values confirms the good agreement of the two methods.

analysis. Agreement between color M-mode and pulsed Doppler values was assessed by plotting individual differences against the mean values of the two measurements (31). Comparison of flow propagation velocity in the normal group and in the different groups of patients was accomplished by one-way analysis of variance (ANOVA). If the F value was significant, the Student unpaired *t* test was performed with the use of the Bonferroni correction. Two-term multiple regressions were performed for flow propagation velocity and its potential relations with τ and other variables by using the highest values of partial F. Statistical significance was accepted at a p value < 0.05.

Results

Validation of Color M-Mode Measurements

Comparison of single-gate pulsed Doppler and color M-mode echocardiography. In this comparison, the mean values for E waves (n = 121) were, respectively, 0.72 ± 0.23 and 0.72 ± 0.26 m/s (range 0.30 to 1.33 and 0.26 to 1.38), and the mean values of A wave (n = 96) were 0.61 ± 0.25 and 0.60 ± 0.27 m/s (range 0.20–1.33 and 0.21–1.27). For both E and A waves (n = 217), the mean values were 0.67 ± 0.24 and 0.66 ± 0.27 m/s, respectively. A high correlation was found between pulsed Doppler and color M-mode echocardiography for either peak early velocity, peak late velocity or all values (Fig. 2A). Correlation coefficients are given in Table 1. The regression equations were close to the identity line, despite the wide range of velocities. The mean difference for E wave values was 0.001 m/s, with a 95% confidence interval of +0.097 to −0.95 m/s. The mean difference for A wave values was 0.007 m/s with a 95% confidence interval of +0.103 to −0.89 m/s. The mean difference for combined E and A values was 0.004 m/s, with a 95% confidence interval of +0.100 to −0.92 m/s (Fig. 2B).

Table 1. Correlations Between Peak Early and Late Velocities Determined by Both Single-Gate Pulsed Doppler and Color M-Mode Echocardiography

	No.	r Value	p Value	Slope	Y Intercept
E wave (or unique wave)	121	0.93	0.0001	1.066	−0.050
A wave	96	0.93	0.0001	1.032	−0.026
E and A waves (or E+A)	217	0.94	0.0001	1.052	−0.038

M-mode velocities were measured in samples corresponding to the same depth as the pulsed Doppler volume. The first correlation concerns peak early velocity (E) or peak velocity of a unique wave (E + A). The second concerns peak late velocity (A). All values are included in the third correlation. No. = number of values.

Reproducibility and accuracy. Figure 3A shows two spatial velocity profiles obtained by averaging the data from six consecutive cardiac cycles. The profile at time t_1 and that at time t_2, 5 ms later, are compared. These profiles demonstrate flow acceleration in the left atrium, maximal velocities at the mitral leaflet tips, the slow velocity decrease in the medial region of the ventricle and the velocity decrease near the apex.

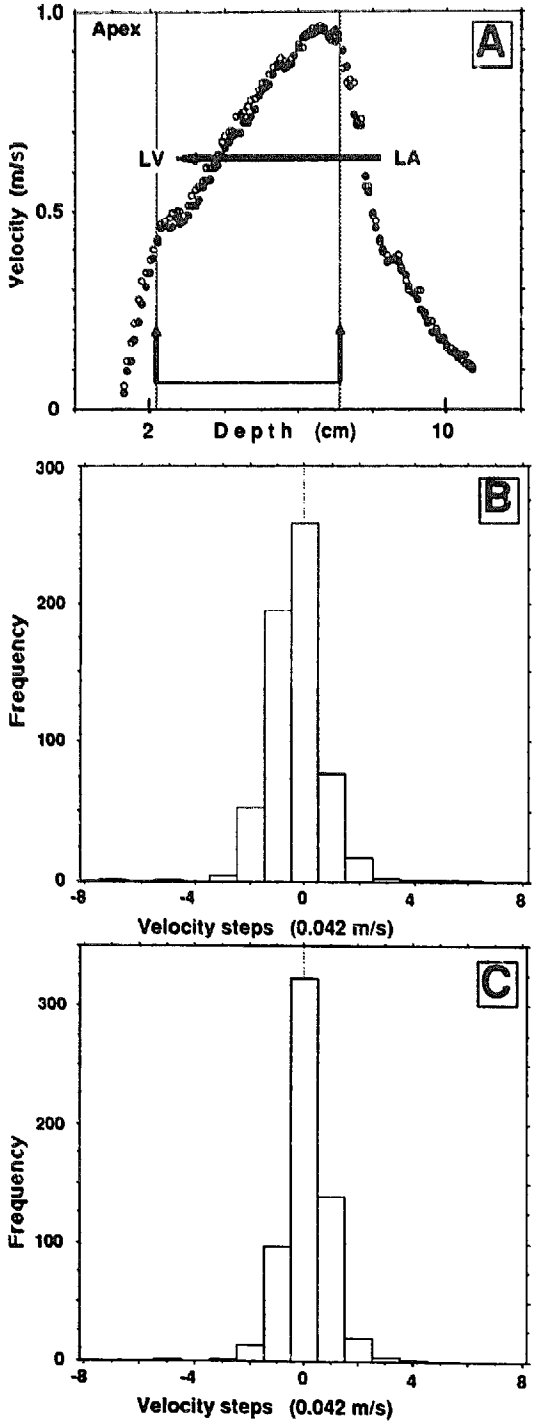
Temporal accuracy. The histogram in Figure 3B shows the results of the comparison between consecutive pixels situated at the same depth during a stable phase of flow (n = 611): the differences did not exceed ±2 velocity steps (or ± 0.08 cm/s) in 99% of the cases. Moreover, Figure 3A suggests that part of the difference is due to a true phenomenon, the progression of flow in 5 ms. The standard deviation of the difference between cycle and mean values was low (±1.07 velocity step or ±0.05 m/s, n = 600).

Spatial accuracy. The histogram in Figure 3C shows the results of the comparison between adjacent velocity samples. The differences did not exceed ±2 velocity steps (or ± 0.08 m/s) in 98% of the cases. The standard deviation of the difference between cycle values and mean values was low (±0.78 velocity step or ±0.03 m/s, n = 600).

Qualitative Description of Flow During the Filling Phase

It was systematically observed in color M-mode recordings that whenever proper alignment had been achieved between left ventricular inflow and the ultrasound beam, the

Figure 3. Temporal and spatial accuracy of color M-mode echocardiography. In **A**, velocity is plotted against depth from the left atrium (LA) on the **right** to the apex of the left ventricle (LV) on the **left. Closed circles** represent the mean of measurements performed just after peak early velocity in six successive cardiac cycles. **Open circles** correspond to the same type of measurements but performed 5 ms after the previous measurements. The two patterns are very similar. **Vertical arrows** limit the zone retained for the spatial study in **C**. In the study of temporal accuracy in **B**, the frequency distribution of the differences between both sets of measurements (n = 611) is shown. The true flow velocities are assumed to remain constant during this short time interval. In the study of spatial accuracy in **C**, the frequency distribution of the differences between adjacent velocity samples is shown. Individual differences are compared with the mean difference, assumed to represent the true velocity profile (n = 600).



highest flow velocity in the left ventricular inlet could be followed downstream for a long distance without a major loss in velocity. As suggested by numeric models (32), the flow streamlines did not diverge when entering the left ventricle and flow remained coherent. Small recirculations were detected at the leaflet tip level, characterized in color M-mode images by flow persisting over time without downstream progression. Further downstream, flow velocity decreased steeply toward the apex. Both models and two-dimensional images suggest that major recirculation takes place between the mid portion of the left ventricle and the apical region. In the apical region of the ventricle, the ultrasound beam orientation becomes inadequate with reference to flow orientation.

In young normal subjects, the flow wave related to early filling progressed rapidly toward the apex. In contrast, filling related to atrial contraction did not pass the mid portion of the ventricle. When flow did reach the apical region during late diastole, it was undoubtly related to early filling (Fig. 4A). In older normal subjects, early and late filling progressed toward the apex at an equal rate (Fig. 4B). In patients with disease, whenever peak early to late velocity ratio remained normal or hypernormal, the color M-mode pattern was similar to the pattern observed in young normal subjects, but the progression toward the apex was delayed (1) and flow could require a full cardiac cycle to reach the apex (Fig. 4C). When the velocity ratio was abnormal (E < A), early filling did not always reach the apical region of the left ventricle, which was instead attained by the flow related to atrial contraction (Fig. 4D). In patients with dilated cardiomyopathy, when both peak early and late transmitral velocities were low, flow was not recorded beyond the mid portion of the ventricle, despite the ability to record very low velocities.

Velocity of Flow Propagation

The linear character of the flow wave front was confirmed in most of the study subjects (96%), and the velocity of flow propagation could be measured according to the requirements of the selected technique.

Flow propagation velocity. The values of flow propagation velocity and transmitral velocity variables determined by color M-mode echocardiography and age are given in Table 2. In the normal group, a high flow propagation velocity was always observed, ranging from 0.68 to 1.05 m/s. It was clearly greater than peak early flow velocity (0.84 ± 0.11 vs. 0.7 ± 0.13 m/s, $p \leq 0.0001$). Flow propagation velocity was also significantly related to age ($r = -0.62$, $p \leq 0.0005$), velocity ratio ($r = 0.70$, $p \leq 0.0001$) with peak early velocity ($r = 0.68$, $p \leq 0.0001$), but not to peak late velocity. A relation between age and both the velocity ratio and peak early velocity (33) was also present in the normal group ($r = -0.42$, $p \leq 0.05$ and $r = 0.71$, $p \leq 0.0001$, respectively).

In contrast, in patients with disease, a low flow propagation velocity was most often observed and there was an

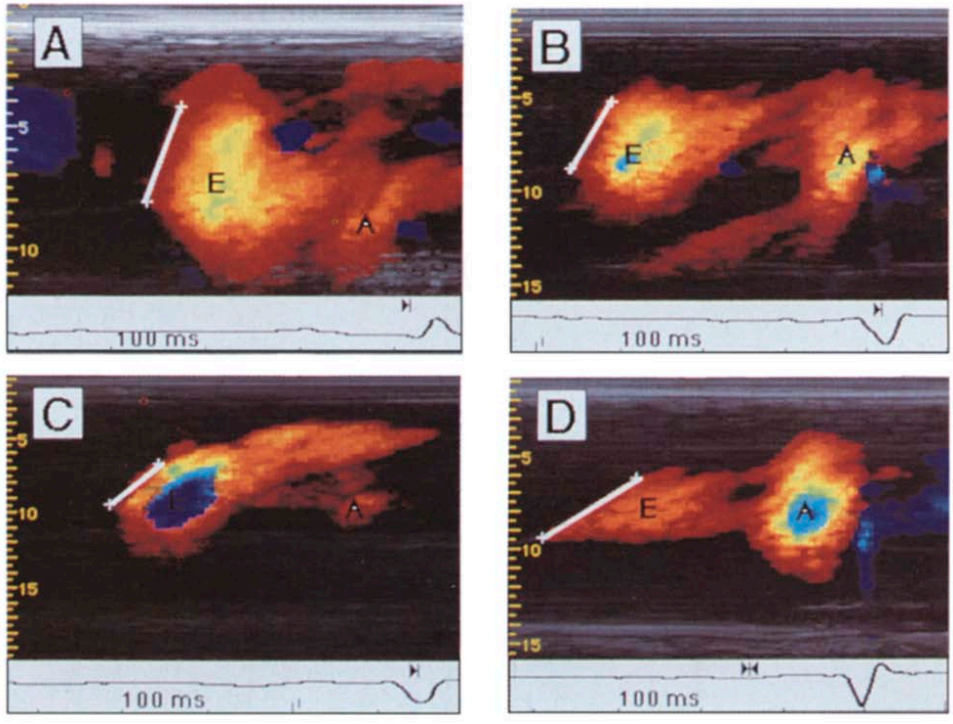


Figure 4. Diastolic flow propagation into the left ventricle. A and B show flow progression in two normal subjects. In A, typical for a young subject, early filling (E) progresses rapidly toward the apex. In contrast, late filling (A) is limited to the basal region of the ventricle. In B, typical for an elderly subject, the progression of early filling and late filling is similar. In both subjects, the early filling wave fronts outlined in white are linear and their slopes are steep (1.05 and 0.7 m/s, respectively). C and D show the flow progression in patients with heart disease. In C, early filling progresses toward the apex, but this progression is slow, despite the high velocities (blue color) observed during the E wave (hypernormal E/A ratio). Late filling progression is extremely limited. In D, early filling does not reach the apex. In contrast, late filling extends to the apex; high velocities are observed during the A wave (abnormal E/A ratio). In both subjects, the early filling wave fronts are linear, but their slopes are low (0.45 and 0.30 m/s, respectively).

overall significant difference compared with results in the normal group (0.46 ± 0.15 vs. 0.84 ± 0.11 m/s, $p < 0.0001$). The normal group differed significantly from all five groups with disease; however, no significant differences were seen among these five groups. In the five groups flow propagation velocity was related to age ($r = -0.35$, $p < 0.005$), but not with peak early and late velocities and their ratio, except for a weak relation ($p < 0.05$) for peak early velocity in Group IV.

Comparison with left ventricular pressure data. The individual results of the nine patients studied in the basal state and during dobutamine infusion are summarized in Table 3. In Patient 4, no distinct early filling was observed, and flow propagation velocity was measured during late filling because its flow wave front took place within the left ventricular relaxation phase (ventricular relaxation was considered complete approximately 3.5 τ after minimal dP/dt or at approximately 320 ms in this patient) (2). In the basal state, all patients had a decreased flow propagation velocity and, accordingly, the isovolumetric relaxation time constants were always increased. Dobutamine induced a significant

Table 2. M-Mode Flow Propagation Velocity and Pulsed Doppler Peak Early and Late Velocity Variables

Group	No.	Age (yr)	FPV (m/s)	E (m/s)	A (m/s)	E/A
Normal	29*	39 ± 13	0.84 ± 0.11	0.70 ± 0.13	0.43 ± 0.07	1.65 ± 0.42
		(19–59)	(0.68–1.05)	(0.42–0.98)	(0.30–0.55)	(0.79–2.79)
Disease	91*	58 ± 17	0.46 ± 0.15	0.74 ± 0.28	0.64 ± 0.32	1.33 ± 1.13
(Groups I to V)		(22–92)	(0.20–1.10)	(0.23–1.48)	(0.11–1.27)	(0.20–6.25)
Group I	31	53 ± 14	0.41 ± 0.11†	0.80 ± 0.27	0.41 ± 0.20	2.00 ± 1.60
		(26–83)	(0.20–0.78)	(0.30–1.35)	(0.11–0.76)	(0.65–6.25)
Group II	8	59 ± 10	0.46 ± 0.11†	0.72 ± 0.21	0.52 ± 0.18	1.35 ± 0.59
		(45–73)	(0.27–0.65)	(0.42–1.01)	(0.34–0.93)	(0.47–2.00)
Group III	5*	66 ± 2	0.58 ± 0.29‡	1.09 ± 0.14	1.15 ± 0.18	1.03 ± 0.14
		(63–67)	(0.40–1.10)	(0.91–1.30)	(1.02–1.27)	(0.94–1.08)
Group IV	22*	55 ± 15	0.50 ± 0.17†	0.61 ± 0.20	0.83 ± 0.20	0.86 ± 0.31
		(22–82)	(0.27–0.92)	(0.38–1.02)	(0.45–1.35)	(0.37–1.73)
Group V	25*	63 ± 22	0.48 ± 0.14†	0.80 ± 0.32	0.75 ± 0.36	1.52 ± 1.40
		(23–92)	(0.29–0.80)	(0.23–1.48)	(0.23–1.25)	(0.20–4.93)

*Correct measurement of flow propagation velocity could not be performed in 5 of 125 subjects. †Difference significant at 99% with respect to normal values. ‡Difference significant at 95% with respect to normal values. Values are reported as mean value ± 1 SD; values in parentheses indicate range. FPV = M-mode flow propagation velocity; Group I = dilated cardiomyopathy; Group II = ischemic cardiomyopathy; Group III = hypertrophic cardiomyopathy; Group IV = systemic hypertension; Group V = aortic valve disease; other abbreviations as in Table 1..

Table 3. Left Ventricular Pressure Results and Color M-Mode Echocardiographic Results in the Basal State and During Dobutamine Infusion

Pt No.	HS	HR (beats/min)	LV Pressure (mm Hg)			dP/dt (mm Hg/s)		τ_{ln} (ms)	$\tau_{1/2}$ (ms)	FPV (m/s)	PEV (m/s)
			Max	Min	ED	Max	Min				
1	1*	100	100	18	26	750	−875	88	59	0.45	1.02
2	1	109	100	10	25	550	−550	64	41	0.45	0.64
	2	103	119	5	19	1,110	−1,100	39	32	0.60	0.58
	3	98	127	−4	3	1,500	−1,550	27	25	DE	0.37
3	1	89	95	29	35	505	−545	110	68	0.44	0.64
	2	87	93	29	34	460	−460	107	80	0.42	0.72
	3	77	97	26	29	670	−700	130	84	0.34	0.57
	4	80	97	20	20	800	−920	140	90	0.26	0.37
	5	102	100	24	24	945	−960	135	103	0.26	0.71
4	1	92	92	24	29	635	−510	99	64	0.35†	0.57
	2	96	98	19	24	720	−595	95	50	0.40†	0.76
	3	96	98	25	29	720	−595	85	67	0.36†	0.68
	4	97	103	24	30	805	−680	85	53	0.41†	0.72
5	1	94	126	19	25	1,105	−1,105	78	41	0.33	0.30
	2	93	139	22	28	1,735	−1,265	77	44	0.34	0.34
	3	95	141	22	25	1,265	−1,580	66	39	0.36	0.34
6	1	69	131	23	24	1,045	−1,290	53	42	0.37	0.24
	2	67	128	28	26	805	−1,290	65	48	0.31	0.20
7	1	73	127	22	23	1,100	−1,170	88	38	0.38	0.94
	2	103	140	6	10	1,600	−1,780	14	13	DE	0.54
	3	90	148	14	22	1,800	−2,000	28	18	0.65	0.92
8	1	111	75	20	18	505	−620	47	33	0.49	1.13
	2	105	75	20	20	505	−660	50	29	0.52	1.13
	3	116	97	6	8	950	−1,010	38	22	DE	0.30
	4	125	67	20	11	505	−545	56	31	0.53	0.95
	5	113	69	24	20	465	−580	55	38	0.57	1.12
9	1	73	90	19	14	705	−750	105	79	0.35	0.49
	2	72	94	8	13	1,080	−1,700	44	17	DE	0.49
	3	81	100	13	13	1,450	−1,950	44	24	DE	0.42
	4	91	101	12	14	1,370	−1,620	52	19	DE	0.42

*Nonsimultaneous. †Flow propagation velocity (FPV) calculated during the A wave (see text). DE = delayed E wave occurring after minimal (Min) left ventricular pressure; dP/dt = first derivative of left ventricular pressure; ED = end-diastolic; HR = heart rate; HS = hemodynamic state; LV = left ventricular; Max = maximal; PEV = peak early velocity except for Patient 4, for whom peak late velocity is given; Pt = patient; τ_{ln} and $\tau_{1/2}$ = isovolumetric relaxation time constants measured according to the natural logarithm method (27) or pressure half-time method (28).

decrease in the time constant of isovolumetric relaxation in five patients, a significant increase in one and no significant change in three; flow propagation velocity behaved in a concordant manner with the time constant of isovolumetric relaxation. These changes in the time constant of isovolumetric relaxation differed from the more homogeneous results reported by Colucci et al. (28). A difference in patient selection could explain this discrepancy.

A strong relation was found between the isovolumetric time constant (τ_{ln} or $\tau_{1/2}$) and flow propagation velocity (Fig. 5 and 6) and among these variables and other hemodynamic or color M-mode variables (Table 4). It is also important to note: 1) the strong relation between the time constant of isovolumetric relaxation and left ventricular minimal pressure and the concordant strong relation between flow propagation velocity and minimal pressure; 2) the relation between flow propagation velocity and peak early velocity, despite the absence of a relation between peak early velocity and the time constant of isovolumetric relaxation; and 3) the relation between flow propagation velocity and heart rate ($p < 0.01$); relations with heart rate were not significant for τ_{ln} and $\tau_{1/2}$. The results of multiple regression analysis are given in Table 5. It is important to recognize the primary importance of the isovolumetric time constant (τ_{ln} or $\tau_{1/2}$) and the weaker though significant importance of the difference between atrial driving pressure and minimal left ventricular pressure.

Discussion

In early diastole, after mitral valve opening, left ventricular pressure continues to decrease even though the chamber is expanding (4,34). Relaxation continues when blood flows into the ventricle and the relaxation rate, ventricular

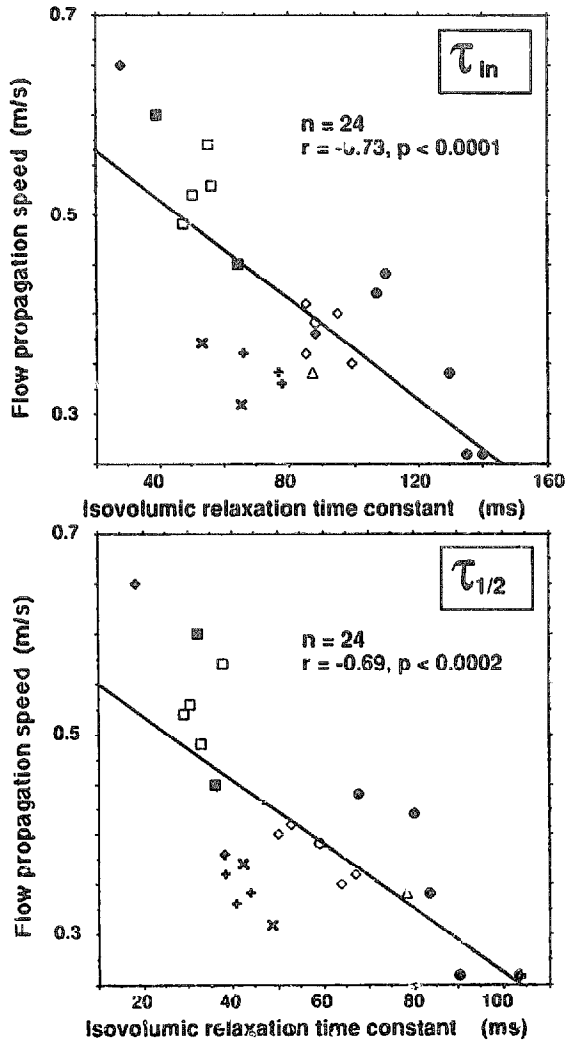


Figure 5. Correlations between velocity of flow propagation and the isovolumetric relaxation rate during intracoronary dobutamine infusion. To allow identification of changes in individual patients (see text and Table 3), each patient is represented by a different symbol. Two methods were used to calculate the time constant of isovolumetric relaxation: the natural logarithm method (τ_{ln}) (**upper panel**) and the pressure half-time method ($\tau_{1/2}$) (**lower panel**). Both methods demonstrated a strong correlation between flow propagation velocity, a noninvasive variable, and isovolumetric relaxation time constant.

diastolic suction and left atrial filling pressure are important determinants of ventricular filling (5,35–41). Relaxation is considered to be complete after a time interval equal to 3.5 times the isovolumetric time constant from the time of minimal dP/dt (2–6). In the normal human heart, the effect of relaxation is essentially over when left ventricular pressure reaches its minimal value. Conversely, in disease, the relaxation process persists after minimal pressure and may occupy the complete diastole.

Early filling is therefore strictly conditioned by the relaxation process. However, relatively few data are available to document this interaction between intraventricular flow and myocardial wall. Lepeschkin (42), studying the ECG U wave, provided a mechanical explanation: afterpotentials could be physiologically generated by the stretching of myocardial *fibers* caused by the ventricle early *filling*. Abnormal U waves could result from an abnormal sequence of relaxation—for instance, during regional myocardial ischemia (42). However, this mechanical explanation has been questioned by others (43).

For theoretic reasons, Brutsaert et al. (44–46) suggested that relaxation is a nonuniform process and that this nonuniformity could be exagerated in disease. Little information is available to support their assessment. Nonuniform wall motion was demonstrated during relaxation by Lew and Le Winter (47), studying regional circumferential lengthening patterns in the left ventricle in normal dog. These investigators observed that the base of the free wall lengthens before the mid portion and the apex and outlined the regional variation in the timing of early diastolic events. Heterogeneous relaxation has also been demonstrated by radionuclide angiography in human control subjects (48). Nonuniformity is increased during isoproterenol infusion into the left anterior descending coronary artery (49,50). Regional left ventricular asynchrony has been demonstrated by radionuclide angiography in hypertrophic cardiomyopathy (51), and beta-adrenergic stimulation resulted in a decrease in the extent of regional nonuniformity (21). Nonuniformity is one possible mechanism that could explain the alterations in relaxation observed in ischemic heart disease (48,52).

Color M-mode echocardiography is a technique potentially able to offer—at least partially—the information required to study the consequences on flow of spatial and temporal nonuniformity in wall relaxation. It has both high temporal resolution (5 ms) and high spatial resolution (approximately 1 mm). High temporal resolution is needed to accurately detect slight asynchronism and high spatial resolution is equally necessary to document on-line flow conditions in different parts of the ventricle. Conventional pulsed Doppler echocardiography can offer the same temporal resolution, but would fail to given simultaneous information in different locations. Two-dimensional color Doppler ultrasound can provide the same spatial resolution but would provide poor temporal resolution (approximately 20 frames/s).

Jacobs et al. (1) were the first to describe a delay in flow propagation in dilated cardiomyopathy using color M-mode echocardiography. They showed that early filling only reached the apex of the ventricle during the next systole. However, they attributed this delay to the geometry of the dilated ventricle and disorientation of transmitral flow. We first confirmed these findings in patients with dilated cardiomyopathy but observed that flow propagation could also be delayed in the absence of left ventricular dilation. In such cases, the delay was less important than in patients with dilated cardiomyopathy but remained significant compared with findings in normal subjects.

Therefore, it appeared necessary to normalize the delay in flow propagation, and we chose to measure the velocity of flow propagation. Our preliminary aim was to validate color

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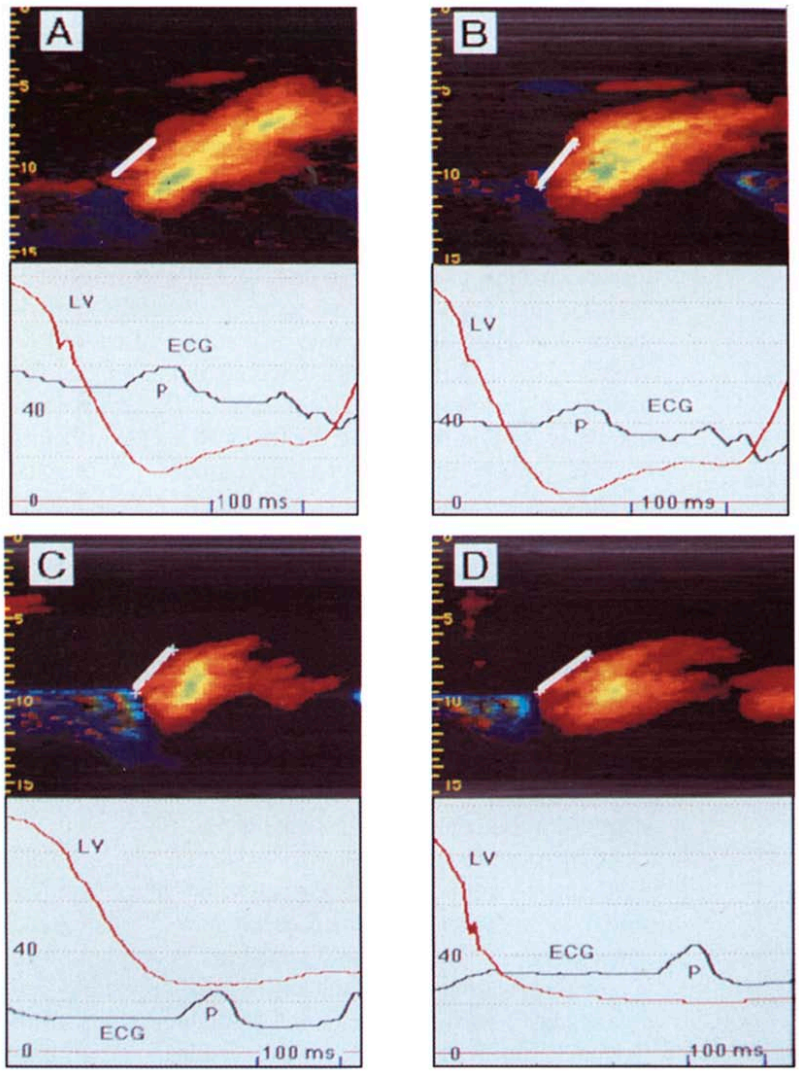

Figure 6. Examples of short-term changes in the velocity of flow propagation during left coronary infusion of dobutamine. In A and B, flow propagation velocity increased from 0.45 m/s (A) to 0.60 m/s (B), whereas the isovolumetric relaxation rate decreased (64 to 39 ms for the time constant of isovolumetric relaxation determined by the natural logarithm method [τ_{in}] and 41 to 32 ms for the time constant of isovolumetric relaxation determined by the pressure half-time method [$\tau_{1/2}$]). Conversely, in C and D, flow propagation velocity decreased from 0.44 m/s (C) to 0.26 m/s (D), whereas the isovolumetric relaxation rate increased (110 to 140 ms for τ_{in} and 68 to 90 ms for $\tau_{1/2}$, respectively). In D, minimal pressure was considerably delayed, a pattern suggesting silent myocardial ischemia. ECG = electrocardiogram; LV = left ventricle; P = ECG P wave.

M-mode quantified data, with two objectives. The first was to perform a validation by reference to single-gate pulsed Doppler ultrasound (53,54). This was accomplished by using either a linear regression method with correlation coefficients ≥0.93 ($p < 0.0001$) and regression line slopes close to 1, or relating individual differences to the mean values of the two measurements. The mean differences for E and A waves were <0.01 m/s and the limits of agreement were small enough for our purpose. Our second objective was to test the accuracy of individual color M-mode measurements by looking for temporal or spatial data heterogeneity during the study of flow with smooth variations. Again, this was accomplished with low temporal and spatial velocity differences between pixels (Fig. 3, B and C).

Another aim was to define the value and limits of the velocity of flow propagation in the normal group. Concurrently, we grouped patients with different cardiac diseases. These diseases have different consequences on left ventricular dimensions but are all known to induce significantly prolonged relaxation. We then compared the velocity of flow propagation in the normal group and in the groups with disease. For this comparison, patients were observed during routine echocardiography and no interruption or modification of their treatment was requested.

Using a one-way analysis of variance, we observed significant differences in the velocity of flow propagation between the normal group and the patients, considered as a whole or in subgroups with different diseases. We could conclude that this velocity was decreased in the patients with disease but that this decrease might have been dependent on geometric factors related to left ventricular hypertrophy despite the absence of dilation in some patients. The next steps in our study were therefore 1) to compare the velocity of flow propagation and the hemodynamic isovolumetric constant reflecting left ventricular relaxation, and 2) to determine whether the velocity flow propagation could change rapidly and in accordance with the time constant of isovolumetric relaxation, thereby demonstrating the independence of the velocity of flow propagation from geometry. These objectives were achieved during a protocol studying

Table 4. Bivariate Correlations Between Left Ventricular Pressure Variables and Color M-Mode Echocardiographic Flow Propagation Velocity and Transmitral Velocity Variables

	No.	r Value	p Value
τ_{ln} and FPV	24	−0.73	<0.0001
$\tau_{1/2}$ and FPV	24	−0.69	<0.0002
τ_{ln} and P_{max}	31		NS
τ_{ln} and P_{min}	31	0.74	<0.0001
τ_{ln} and P_{ED}	31	0.56	<0.005
τ_{ln} and dP/dt_{max}	31	−0.43	<0.02
τ_{ln} and dP/dt_{min}	31	0.45	<0.02
τ_{ln} and PEV	31		NS
τ_{ln} and heart rate	31		NS
$\tau_{1/2}$ and P_{max}	31		NS
$\tau_{1/2}$ and P_{min}	31	0.74	<0.0001
$\tau_{1/2}$ and P_{ED}	31	0.56	<0.005
$\tau_{1/2}$ and dP/dt_{max}	31	−0.49	<0.01
$\tau_{1/2}$ and dP/dt_{min}	31	0.52	<0.005
$\tau_{1/2}$ and PEV	31		NS
$\tau_{1/2}$ and heart rate	31		NS
FPV and P_{max}	24		NS
FPV and P_{min}	24	−0.69	<0.0005
FPV and P_{ED}	24		NS
FPV and dP/dt_{max}	24		NS
FPV and dP/dt_{min}	24		NS
FPV and PEV	24	0.64	<0.005
FPV and heart rate	24	0.54	<0.01

In the absence of peak early filling velocity (PEV), peak late velocity was considered (see text). max = maximal; min = minimal; P = left ventricular pressure; other abbreviations as in Tables 1 and 3.

the contractile reserve of the left ventricle with left coronary dobutamine infusion in patients with dilated cardiomyopathy (29).

Before dobutamine infusion, the velocity of flow propagation was decreased and the isovolumetric relaxation time constant increased in the nine patients studied. Dobutamine induced a significant decrease in the time constant of isovolumetric relaxation in five patients, a significant increase in one and no significant change in three. The two methods used to calculate the time constant of isovolumetric relaxation gave the same results. The velocity and flow propagation behaved in a concordant manner with the time constant of isovolumetric relaxation. There was a strong correlation between the two variables, with $r = -0.74$, $p < 0.0001$ for τ_{ln} and $r = -0.69$, $p < 0.0002$ for $\tau_{1/2}$ (Fig. 5).

Significance of isovolumetric relaxation time constant in humans. In animal experiments, the time course of the isovolumetric pressure decline is determined by a series of interacting factors, including loading conditions, inactivation rate of individual fibers and the degree of inhomogeneity within the wall of the ventricle (44–46,55). However, recent studies (56,57) in patients with normal left ventricular function demonstrated that the rate of isovolumetric relaxation was not affected by modest changes in loading conditions (preload and afterload) when heart rate was maintained constant. Similarly, in patients with pressure overload hypertrophy, no improvement in diastolic relaxation was found during a reduction in left ventricular load (26). Only drastic shifts in afterload slowed the relaxation rate in patients with severe aortic stenosis (58). This slowing could be explained by modifications in the inactivation process or by regional subendocardial ischemia (58). Nonuniformity also seems to be an important and independent determinant of the rate of left ventricular pressure decrease. In dog hearts, nonuniformity can be produced by regional inotropic stimulation of the left ventricle (59). However, in patients with coronary artery disease or hypertrophic cardiomyopathy, the relative magnitude of nonuniformity compared with inactivation in slowing the rate of pressure decrease has not been assessed (21,24).

In summary, two factors affect the time constant of isovolumetric relaxation in humans: the rate of inactivation and nonuniformity. Conversely, the time constant of isovolumetric relaxation does not seem to be affected by moderate changes in loading conditions.

Significance of the flow propagation velocity. In the normal group of patients, the flow propagation velocity was always greater than peak early velocity; however, a significant relation was present between those two variables. In patients with disease, flow propagation velocity was always decreased compared with that in normal subjects, whereas peak early velocity remained in the normal range, despite

Table 5. Multivariate Correlations Between Left Ventricular Pressure Variables and Color M-Mode Echocardiographic Propagation Velocity

Flow propagation velocity with	1) τ_{ln}	2) $\Delta P_{MO\text{-}Mn}$	$r = 0.83$, $p < 0.0001$ ($n = 24$)
Partial p value	0.0001	0.005	
Partial F	25.4	9.7	
Flow propagation velocity with	1) $\tau_{1/2}$	2) $\Delta P_{MO\text{-}Mn}$	$r = 0.78$, $p < 0.0001$ ($n = 24$)
Partial p value	0.0006	0.02	
Partial F	16.2	9.4	
Peak early velocity with	1) $\Delta P_{EF\text{-}Mn}$	2) PMO	$r = 0.74$, $p < 0.0001$ ($n = 31$)
Partial p value	0.0001	0.02	
Partial F	32.4	6.4	

$\Delta P_{EF\text{-}Mn}$ = difference between pressure at the end of early filling and minimal pressure; $\Delta P_{MO\text{-}Mn}$ = difference between pressure at mitral opening (PMO) and minimal pressure; other abbreviations as in Table 4. r and p in the final column refer to the overall significance of the multivariate correlations (n values).

wide individual variations. In the different disease groups, no relations or only weak relations were found between flow propagation velocity and peak early velocity. However, the relation was stronger in the subgroup in which values for the time constant of isovolumetric relaxation were available ($p < 0.005$).

Multivariate analysis (Table 5) showed that flow propagation velocity was mostly dependent on the time constant of isovolumetric relaxation describing the rate of pressure decline, whereas peak early velocity was independent of the time constant of isovolumetric relaxation and related to the difference between left ventricular pressure at the end of early filling and minimal pressure. Therefore, we assume that during the filling period and as long as relaxation is not complete, flow can only progress in the left ventricular chamber according to the speed allowed by the wall relaxation properties.

In normal subjects, the flow propagation velocity is evidently related to a physiologic nonuniformity, and in those with disease this nonuniformity is major (44,46). We admit that the course of relaxation is space dependent and that the relaxation process in the free wall is progressively delayed, spreading from base to apex. The preliminary work of Lew and Le Winter (47), studying mid wall circumferential lengthening in the canine left ventricle, supports this interpretation by demonstrating normal regional variations and a significant delay from base to apex. A recent study (59) using color M-mode echocardiography provides further support. In the canine heart, the delay in the timing of peak early velocity to reach the apex increased significantly during regional myocardial ischemia (59).

The close relation found between the velocity of flow propagation and the time constant of isovolumetric relaxation strongly suggests that the rate of inactivation also plays an important role in determining flow propagation velocity, in different forms of myocardial hypertrophy, for example, or during interventions thought to influence calcium dynamics (60,61) at a cellular level. The influence of heart rate on velocity of flow propagation supports this assumption.

Limitations of the study. The determination of the velocity of flow propagation is strictly dependent on the dedicated interface and associated software proposed by the Trondheim University group. It seems impossible to assess it directly on the ultrasound system monitor. Digital information is necessary to visualize the data with the indispensable time and depth magnification. Moreover, even though the determination of the flow propagation velocity remained manual in this study, full digital information is needed for an automatic determination.

We found only two conditions in which the velocity of flow propagation could not be measured: 1) when it was impossible to obtain a linear wave front for early filling in patients with poor echogenicity or in the presence of an important anterograde flow during the isovolumetric period (62), and 2) in the extraphysiologic condition of an intracoronary dobutamine infusion when early filling started after myocardial deactivation was complete (30).

The alignment between the flow and the ultrasound beam is crucial. A beam incorrectly oriented can lose the flow streamlines close to the mitral orifice and induce a false low propagation speed. It is imperative that the highest flow velocities be followed without major loss from the mitral tip to ≥2.5 cm.

The correlation established between the isovolumetric relaxation time constant and flow propagation velocity has been limited to a subgroup with dilated cardiomyopathy; normal subjects were not considered in this comparison. However, it is obvious that the introduction of normal data for both the time constant of isovolumetric relaxation and flow propagation velocity would have greatly increased the significance of the correlation.

With the use of the flow propagation velocity, the spatial spreading of relaxation is studied along only one path, the base-apex-free wall path; it is not explored in the septal area, according to an apex-base path or to a free wall-septal path, or both.

Clinical implications. These findings have potentially important implications and deserve further investigation in assessing diastolic function in patients with heart disease. The determination of flow propagation velocity seems possible in almost all situations. This constant could noninvasively explore the relaxation process despite "normalized" or hypernormal velocity ratios (9) or in the presence of tachycardia when the velocity ratio cannot be calculated. Moreover, like the time constant of isovolumetric relaxation, flow propagation velocity could follow short- or long-term modifications of left ventricular relaxation. Further studies are necessary to evaluate its sensitivity, accuracy and limits in detecting small changes in the relaxation status. Repeat measurements of flow propagation velocity could easily be made during patient follow-up evaluations or when analyzing the effects of drugs.

Conclusions. Both flow propagation velocity (or early filling velocity constant describing the flow propagation) and the isovolumetric time constant describing the pressure decrease seem to be related to left ventricular myocardial relaxation. The flow propagation velocity could represent a noninvasive challenge to the time constant of isovolumetric relaxation. Color M-mode echocardiography allows an analysis of the flow velocity field along a line in the left ventricular cavity and helps define the relation between flow and wall properties. During the early filling period, progression of flow into the left ventricular cavity is governed by the complex relaxation process taking place in the wall, involving spatial and temporal nonuniformity and myocardial inactivation.

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