Alteration of Left Ventricular Diastolic Function During Coronary Angioplasty-Induced Ischemia: A Color M-Mode Doppler Study

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Objectives. The aim of this study was to assess the effects of ischemia on diastolic function by analyzing flow propagation velocity with color M-mode Doppler echocardiography.

Background. Color M-mode Doppler echocardiography has been proposed as a method of assessing left ventricular filling.

Methods. Color M-mode Doppler echocardiography and measurement of hemodynamic data were performed simultaneously at baseline and during angioplasty-induced ischemia. Tau was compared with flow propagation velocity. Late diastolic indexes, left ventricular pressure and flow cessation time were also investigated.

Results. During ischemia, left ventricular relaxation rate (tau) increased, whereas flow propagation velocity decreased, from (mean ± SD) 46.8 ± 10 ms to 72.6 ± 18.3 ms and from 59.8 ± 15.8 cm/s to 30 ± 8 cm/s, respectively (all p < 0.0001). The maximal slowing of flow propagation velocity was observed 20 to 30 s after the beginning of the inflation, coexisting with a notch on the ascending limb of the negative rate of rise of the left ventricular pressure (dP/dt) curve. Flow propagation velocity was correlated with tau both at baseline (r = 0.53, p < 0.05) and during inflation (r = 0.53, p < 0.03). Left ventricular end-diastolic pressure increased during ischemia from 13.5 ± 8 mm Hg at baseline to 27.5 ± 7 mm Hg, while a premature cessation of the entering flow occurred −13.8 ± 23 ms before the next Q wave onset, compared with 4.5 ± 19.6 ms after the Q wave onset at baseline (all p < 0.0001).

Conclusions. The analysis of flow propagation velocity showed that early filling is highly dependent on left ventricular relaxation rate, particularly through the phenomenon of asynchrony. During ischemia, the premature cessation of late filling is associated with increased diastolic pressures.

(J Am Coll Cardiol 1997;29:1246–55) ©1997 by the American College of Cardiology

Brief episodes of acute ischemia and their relief induce complex dynamic changes in myocardial performance. In particular, diastolic properties of the myocardium are altered during ischemia owing to many factors, such as delayed and incomplete left ventricular relaxation (1–3) or extrinsic compression by the right ventricle and the pericardium (4–6). In patients with coronary artery disease, percutaneous transluminal coronary angioplasty induces an interruption of coronary blood flow and provides a unique model to study the effect of transient ischemia in humans. In this setting, Serruys et al. (2) demonstrated that ischemia occurring early during coronary occlusion severely alters filling dynamics owing to essentially an asynchrony in regional filling. The same investigators also showed that ischemia induced by complete occlusion of the left anterior descending coronary artery increased both regional and global chamber stiffness of the left ventricle.

Recently, color M-mode Doppler echocardiography has been proposed as a method for assessing left ventricular filling (7–10). We have previously shown that this technique was potentially able to offer the information required, at least partially, to study the consequences of spatial and temporal nonuniformity in wall relaxation on flow. Stugaard et al. (8) showed that during coronary angioplasty, M-mode Doppler echocardiography revealed a marked delay of apical peak filling velocity and suggested that delayed apical filling was related to dyssnergy of filling, with delayed filling of the ischemic myocardial segment. The present study was conducted to further evaluate the ability of the color M-mode Doppler echocardiographic technique to assess diastolic function during ischemia. Color M-mode Doppler echocardiography was coupled to monitoring of left ventricular pressures by high fidelity catheters.

Methods

Patients. The study group consisted of 16 patients (12 men and 4 women, mean age 57 ± 6 years) selected from a larger group of patients scheduled for percutaneous transluminal...
coronary balloon angioplasty of a proximal left anterior descending coronary artery stenosis. To be included in this study, patients had to have evidence of anterior ischemia, as documented by an exercise test or thallium scintigraphy; one-vessel coronary artery disease with coronary artery stenosis >50%, as assessed by quantitative coronary angiography of the proximal left anterior descending coronary artery, with no angiographic evidence of collaterality of this artery (grade 0); and normal wall motion, as assessed by both two-dimensional echocardiography and left ventriculography. The left ventricular ejection fraction was 58 ± 6%. Patients with unstable angina, recent or previous myocardial infarction, clinical evidence of heart failure or left bundle branch or atrioventricular block were excluded. No patient received beta-adrenergic blocking agents within 72 h before the study. Patients received aspirin; calcium channel blockers and long-acting nitrates were stopped 48 h before coronary angioplasty. Only unrestricted use of short-acting sublingual nitroglycerin was allowed up to 1 h before the study. The study protocol was approved by the local ethics committee, and informed consent was obtained.

**Catheterization procedure.** A 7F guiding catheter was positioned in the ostium of the left coronary artery using the Judkins technique to perform the angioplasty procedure. Non-ionic contrast medium (Omnipaque, Nycomed, Oslo, Norway) was used to avoid a depressant effect during coronary opacification, and hemodynamic measurements were carefully performed without contrast injection. A 5F microtipped catheter transducer (Millar Industries) was placed into the left ventricle through the contralateral femoral artery for measurement of left ventricular pressures (systolic, minimal and end-diastolic pressures) and derivatives (peak positive and negative rate of rise of left ventricular pressure [dP/dt]). Digital signals of hemodynamic recordings were directly entered into the echocardiographic machine and appeared on the screen simultaneously with the electrocardiographic (ECG) traces and the ultrasound data. Zero line and calibration were carefully recorded before any further measurements. Hemodynamic and ultrasound data were transferred at the same time to the computer through the same computer interface. The time constant of the left ventricular isovolumetric relaxation, tau, was calculated using the natural logarithm method to compute tau from peak negative dP/dt to mitral valve opening (11). Before a 50-s inflation, a deformity of the ascending limb of negative dP/dt was present, demonstrating that the time course of the pressure decay deviates substantially from a monoexponential model. However, in the present study, it was not possible to model a biexponential fitting of pressure decay during the early phases of ischemia (2,12). Consequently, we used a monoexponential model by the best fit of all points to calculate tau when the deformity of the ascending limb of negative dP/dt was no longer present; mitral valve opening was demonstrated by the onset of the entering flow at the level of the mitral leaflet leading edge or assumed to coexist with the point where pressure was 5 mm Hg higher than the left ventricular end-diastolic pressure. Aortic pressure was monitored through the guiding catheter and the ECG was continuously recorded.

**Coronary angioplasty procedure.** For each patient, an average of 4.2 inflations (range 3 to 6) with a standard coronary angioplasty balloon catheter was performed. The duration of each inflation was at least 120 s (mean 150 ± 20 s), separated by a 5-min period to allow hemodynamic recovery, determined by the return to baseline values of dP/dt max and dP/dt min, heart rate and mean aortic blood pressure. Angioplasty was considered successful if a residual stenosis <50%, as assessed by quantitative coronary angiography, was obtained.

**Echocardiographic protocol.** After placing the catheters, a 10-min period was observed to ensure hemodynamic stabilization. For each patient, the first and second occlusion periods were analyzed by either color M-mode Doppler echocardiography or pulsed single-gated Doppler echocardiography following a random order. For each inflation, at least three recordings and transfers to the microcomputer were performed: the first one before inflation, the second one 60 s after the beginning of the inflation and the last one 60 to 90 s after deflation. However, in seven patients, recordings were performed as often as possible (every 15 to 20 s) to get the information as continuously as possible; the minimal time for transferring a cine loop of five cycles was 10 s.

To analyze the time course of diastolic alterations occurring during ischemia, the third inflation period was continuously recorded in color M-mode Doppler using a VHS video system. Indeed, because the transfer to the computer was performed from images in the cine loop, none of the images during this third inflation could be transferred to the computer. Consequently, video images and computerized images were never simultaneously obtained. During the study we observed that the time constant of relaxation did not return to the baseline conditions found before the first inflation, so we continuously recorded color M-mode Doppler during a first inflation in three additional patients to ensure that the time course of the relation between invasive hemodynamic and Doppler echocardiographic data was identical irrespective of the inflation period. Finally, in nine patients, transaortic pulsed Doppler was measured to assess cardiac output changes during inflation.

All the echocardiographic data were obtained using a Vingmed CFM 750 system, with a frequency of 3.25 MHz for the tissue imaging mode and 2.5 MHz for the Doppler modes. For the transmural pulsed Doppler mode, the sample size placed at the mitral leaflet tips in an apical four-chamber view was 3 mm. For the transaortic pulsed Doppler mode, velocities were measured at the aortic annulus in an apical three-chamber view, although its diameter was measured in a long-axis parasternal view. For the color M-mode Doppler mode, recordings were performed in an apical three- or four-chamber view to obtain the optimal alignment with the direction of the flow through the mitral valve and inside the left ventricle. As usual, the gain was set to maximal value, avoiding saturation effects. The color M-mode lines contained 128 samples with a variable depth range of 10 to 18 cm (in the depth dimension, the sample size was near 1 mm). Data were
displayed on the system monitor every 5 ms, using 18 color levels for each flow direction, each color level coding for one velocity value; according to the Nyquist limit, the step value was ~4 cm/s (range 3.4 to 5.7). By shifting the baseline, the maximal recordable velocity could be extended to 2 Nyquist limits. The Nyquist limit (0.6 to 0.8 m/s) was determined for each patient in terms of function of depth, wall filtering and frequency, and it remained set to the same level throughout the study.

Echocardiographic analysis. Except for the data recorded on the videotape during the third inflation, which allowed a precise analysis of the time course of the left ventricular filling, all other echocardiographic data were transferred directly to a computer. This computerized method facilitated the storage and blinded analysis of all the Doppler echocardiographic data. Moreover, it allowed a digital analysis of color M-mode recordings.

For computerized analysis, an interface had been developed by the Biomedical Engineering Department of Thordheim University. Dedicated software (Echopac, Vingmed Sound, Horten, Norway) ensured the transfer of all echocardiographic modes to the microcomputer, a Macintosh Quadra 700 with 32 megabytes of central memory. The transfer of color M-mode Doppler data was performed in the data’s original format from the digital converter of the echocardiograph directly into a microcomputer. Data were stored on an optical hard disk. Each transferred sequence comprised 5 to 15 beats present in the cine loop and was performed within 10 to 25 s. Data handling, processing, display and analysis were performed on the microcomputer monitor with the program ECHO-DISP (Vingmed sound).

For the transmitral pulsed Doppler mode, velocity curves were analyzed to obtain heart rate, the maximal velocity of early transmural flow (E) and atrial flow (A) and the E/A ratio, the descending slope of the E wave and the isovolumetric relaxation time in three consecutive beats, and the mean values were calculated as well.

For the aortic pulsed Doppler mode, heart rate and the velocity–time integral of the curve were evaluated in three consecutive beats, and a mean value was calculated to evaluate cardiac output changes during the inflations.

For the color M-mode-Doppler mode, two indexes were calculated to assess left ventricular filling, including transmural and intraventricular flow. The first index was the velocity of the diastolic flow propagation in the left ventricle. It was calculated by three methods. 1) For the video recordings, the detection and slope measurement of the flow wave front (7) on freezez images was the unique method available. However, because this method was too subjective, with poor reproducibility, and did not permit quantitative analysis, this led us to develop automatic computerized techniques. 2) For computerized images, it was possible to visualize isovelocity lines shown by a filtering procedure directly from the ECHO-DISP program. During balloon inflation, these isovelocity lines appeared parallel to each other, although it was not the case before inflation, which made quantitative analysis difficult. 3) Finally, a totally computerized determination of the flow propagation velocity was developed to overcome these limitations. As flow propagation can be demonstrated by the presence in the left ventricle, from the mitral valve to the apex, of particles (red cells) having a similar velocity, flow propagation velocity corresponds to the curve linking, in function of time and depth, the points corresponding to the same isovelocity.

Early filling corresponding to low isovelocities was analyzed because it is assumed to be a reliable measure of relaxation. Moreover, for these low isovelocities, vortex is minimized. The spatial detection zone was found between the mitral tip and the middle of the left ventricle, which was arbitrarily defined as being 3 cm above this mitral tip level. The apical zone was not taken into account because at this level of the ventricle, flow spatial velocity decreases according to a cosine function, which may be interpreted as a change in flow orientation, remaining parallel to the wall and diverging there from the ultrasound beam. In the zone of interest, flow propagation velocity was then defined as the slope of the regression line linking the points of low isovelocity. To get a sufficient number of points for the statistical analysis of the regression line, it was necessary to take into account three close isovelocity groups (Fig. 1). Slope A corresponded to the first three isovelocity lines approximately between 0 and 0.12 m/s, and slope B to the fourth, fifth and sixth isovelocity lines. The values of slope A and slope B appearing in the statistical data corresponded to the mean values of the slopes of three successive flows recorded in the same cine loop. To be accurate, the correlation coefficient (r) between all these points was arbitrarily defined to be higher than 0.9. The best fit allowing the determination of the flow propagation velocity was obtained for slope B (r = 0.95 ± 0.04). With the lowest isovelocities (slope A), the correlation coefficient was lower (r = 0.92 ± 0.05). The choice of a linear or curvilinear model to describe the observed velocity paths depended on the statistical results: For low isovelocities up to the middle region of the ventricle, the flow propagation in the left ventricle adhered to a linear relation.

The second color M-mode index concerned late left ventricular filling related to atrial systole. This index was defined as the measurement of the diastolic time interval between the cessation of inflow at the level of the mitral valve and the end point of the diastolic period. A previous study allowed us to place end-diastolic time at 0 to 30 ms after the beginning of the next QRS interval in a group of normal subjects (13). We never observed flow cessation in normal patients before the beginning of the QRS complex. Accordingly, it was possible to define the onset of the QRS complex as the time reference. The time interval between flow cessation and time reference was positive when the flow stopped after the QRS complex, and negative when it stopped before the QRS complex. Time interval measurements were averaged for three to five consecutive beats. Very low velocities could be unambiguously recorded owing to the use of a specific color Doppler high pass filter that permitted us to minimize but not to suppress flow velocities <8 cm/s. This allowed a very accurate determination.
of time intervals with a temporal definition of the color M-mode Doppler of 5 ms.

Statistical analysis. Results are presented as mean value ± SD. Analysis of variance for repeated measures was used to assess significant changes in hemodynamic and Doppler variables, and the Fisher exact test was then used. The correlations between hemodynamic and echocardiographic data were obtained by least square regression analysis. Statistical significance was accepted at p < 0.05.

Results

Hemodynamic measurements at baseline and during inflation. Heart rate did not change significantly throughout the study, except for a slight and brief increase at 30 s of ischemia (p < 0.05). There was a slightly but statistically significant decrease in mean aortic pressure during each balloon inflation. The magnitude of this decrease was similar, between 3% and 5%, for each ischemic episode (p < 0.05). At baseline, the time constant of relaxation of the left ventricle (tau) was 44.1 ± 8 ms. During the first balloon inflation, tau increased to 74.7 ± 5 ms (p = 0.0001), which was reached within 30 s. Between inflations, we did not observe a complete recovery of tau (52.6 ± 8 ms and 57.2 ± 5 ms after the first and second inflations, respectively [p < 0.05 from baseline]). Individual data are shown in Figure 2. Peak negative dP/dt increased during each inflation period. The magnitude of this increase was similar from the first to the last inflation, and values were close to those observed before balloon inflation within 2 min after the deflation (p = NS). In all patients, a distinct deformation appeared in the ascending limb of the negative dP/dt curve during the initial phase of ischemia for each inflation period. This pattern appeared very soon after the beginning of balloon inflation (from 5 to 20 s), was maximal in between 15 to 40 s after the beginning of inflation and finally disappeared completely after 50 s of inflation (Fig. 3).

Figure 1. Computerized determination of isoveloecies allows the construction of a regression line, slope B, which corresponds to points with the fourth, fifth and sixth isoveloecies chosen to measure the flow propagation velocity (FPV). Under inflation, flow propagation velocity slows and the slope is flattened. In this case we observe complete recovery 2 min after the end of inflation.

Left ventricular end-diastolic pressure increased at each inflation to reach the same maximal value. During the first balloon inflation, left ventricular end-diastolic pressure quickly
increased within 30 s and reached a plateau of 27.5 \pm 6.7 \text{ mm Hg} after 1 min (vs. 13.5 \pm 8 \text{ mm Hg}; p < 0.0001). After balloon deflation, left ventricular end-diastolic pressure decreased within 2 min but did not return to baseline values. Similarly, left ventricular minimal pressure increased significantly from 4.6 \pm 2.6 \text{ mm Hg} to a maximal value of 13.7 \pm 6.3 \text{ mm Hg} (p < 0.002) and from 5.1 \pm 3.2 \text{ mm Hg} to 13.9 \pm 6.7 \text{ mm Hg} (p < 0.002) during the first and second inflations, respectively. Peak positive dP/dt decreased from 2,400 \pm 600 to 2,100 \pm 500 \text{ mm Hg/s} (p < 0.05). Changes were similar during the following inflations, with a recovery of peak positive dP/dt close to the values observed before balloon inflation within 2 min after balloon deflation (p = NS).

**Flow propagation velocity in the left ventricle.** Before inflation, it was neither possible to trace manually and correctly a straight line to determine the flow wave front nor to trace isovelocity lines (interobserver and intraobserver variability >20%). Consequently, the flow propagation velocity could only be correctly calculated by the computerized approach (slope A or B).

During ischemia, flow propagation was dramatically different with a decrease in flow propagation velocity (Fig. 4). In these cases, the different ways of measuring the flow velocity could have been applied, but only computerized measurements have been used for data analysis.

**Quantitative data (Table 1).** Before inflation, slopes A and B were 59.1 \pm 14.7 \text{ cm/s} (range 32 to 73) and 59.8 \pm 15.8 \text{ cm/s} (range 33 to 77), respectively. During inflation, the flow propagation velocity determined both by slope A and slope B decreased to 34.2 \pm 11.6 \text{ cm/s} and to 30 \pm 8 \text{ cm/s}, respectively (all p < 0.0001). Individual variations of slope B are demonstrated in Figure 5. There were weak but significant negative correlations between flow propagation velocity expressed by slope B and tau: At baseline and during inflation, r = 0.53, p < 0.05 and r = 0.53, p < 0.03, respectively. The variations in flow propagation velocity (change in slope B = \pm 29.8 \pm 15.5 \text{ cm/s}) were correlated to those of tau (change in tau = \pm 25.8 \pm 18.8 \text{ ms}) (r = 0.56, p < 0.01). No relation was found between flow propagation velocity (slope A or B) and peak negative dP/dt.

**Figure 3.** Left ventricular (LV) pressure curves. Twenty seconds after the beginning of inflation a deformation in the upstroke of the negative dP/dt curve is evident (arrow). This irregularity disappears after 40 to 60 s of inflation, giving a monoexponential relation between pressure and dP/dt.

**Figure 4.** Flow propagation velocity during ischemia. **Left,** Before inflation, flow enters the left ventricle with a rapid pattern; the slope of the flow wave front appears ambiguous and cannot be used for the determination of flow propagation velocity. **Right,** During ischemia, flow propagation velocity is slowed, and the flow wave front is straight. In this case, it is possible and often easy to manually trace the flow wave front. Only computerized measurements were included in data analysis.
For the inflations where the diastolic events analyzed by color M-mode Doppler echocardiography had been continuously recorded on videotape, the onset of the flow propagation velocity slowing occurred from 10 to 20 s after the beginning of the inflation. The maximal decrease in flow propagation velocity was observed 20 to 30 s after the beginning of the inflation and corresponded to the same time as the notch on the ascending limb of negative dP/dt curves \((r = 0.82, p < 0.001)\). After 40 to 50 s of inflation, while the deformation on dP/dt curve progressively disappeared, the flow propagation velocity progressively improved while always remaining lower than before the inflation. Figure 6 shows the values at 20, 40 and 60 s.

**Premature cessation of flow.** Color M-mode Doppler echocardiography allows the determination of precisely when the flow ceases to enter the left ventricle. Before inflation, the cessation of flow occurred at a mean time interval of 4.5 ± 19.6 ms (range −28 ms before to 33 ms after the Q wave), the interval being positive when the flow stops after Q wave onset and negative when it stops before. During ischemia, the cessation of the flow occurred prematurely (Fig. 7), with a mean time interval of −13.8 ± 23 ms (−65 ms before to 14 ms after the Q wave). This end-diastolic time interval was correlated to the left ventricular end-diastolic pressure both at baseline and during ischemia \((r = 0.53, p < 0.02 \text{ and } r = 0.45, p < 0.05, \text{ respectively})\). Furthermore, the magnitude of the increase in the time interval (change = 18 ± 14 ms), characterized by a premature cessation of the flow during ischemia, was also correlated to the increase in end-diastolic pressure \((change = 13.6 ± 8.3 \text{ mm Hg}, r = 0.57, p < 0.02)\).

**Pulsed Doppler measurements: transmural flow and cardiac output** (Table 2). For the E wave, the maximal amplitude of E significantly decreased at a 30-s inflation but recovered to baseline values at the end of the inflation. The A wave and E/A ratio were not significantly modified. Isovolumetric relaxation time decreased progressively during all the inflations, whereas the descending slope of E increased significantly only at the end of the inflation (Fig. 8). There were no statistical correlations between either tau and isovolumetric relaxation time or between the ischemia-induced variations of these two variables.

In nine patients the ultrasound examination was completed with a determination of the cardiac aortic output before ischemia and at 60 s. It decreased during inflation from 4.7 ± 1 to 4.2 ± 1.2 liters/min \((p < 0.05)\). For these nine patients, this decrease was mostly due to the decrease in velocity–time integral (23 ± 5 cm at baseline vs. 18.8 ± 2.8 cm, \(p < 0.05\)), without significant changes in either heart rate or aortic annulus diameter.

**Discussion**

The present study shows that color M-mode Doppler echocardiography is a new method for assessing the diastolic events that occur during ischemia, in which interactions between wall and flow in particular are documented. The analysis

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**Table 1. Hemodynamic Values at Baseline Before Inflation, 60 s After Beginning of Inflation and After Recovery**

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate (beats/min)</th>
<th>Mean BP (mm Hg)</th>
<th>dP/dt max (mm Hg/s)</th>
<th>dP/dt min (mm Hg/s)</th>
<th>Tau (ms)</th>
<th>LVDP min (mm Hg)</th>
<th>LVDP (mm Hg)</th>
<th>Slope B (cm/s)</th>
<th>Flow Cessation (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>68 ± 13</td>
<td>107 ± 12</td>
<td>2,400 ± 600</td>
<td>−2,300 ± 400</td>
<td>46.8 ± 10</td>
<td>4.6 ± 2.6</td>
<td>13.6 ± 8</td>
<td>59.8 ± 15.8</td>
<td>4.5 ± 19.6</td>
</tr>
<tr>
<td>Inflation</td>
<td>69.7 ± 12</td>
<td>105 ± 15</td>
<td>2,100 ± 500</td>
<td>−1,900 ± 500</td>
<td>72.6 ± 18</td>
<td>13.7 ± 6.3</td>
<td>27.2 ± 7</td>
<td>30 ± 8.2</td>
<td>−13.8 ± 23</td>
</tr>
<tr>
<td>Baseline recovery</td>
<td>69 ± 8.2</td>
<td>108 ± 10</td>
<td>2,400 ± 500</td>
<td>−2,200 ± 400</td>
<td>53.5 ± 10</td>
<td>5.6 ± 4</td>
<td>18 ± 7</td>
<td>58 ± 20</td>
<td>3.8 ± 20</td>
</tr>
<tr>
<td>p value/baseline</td>
<td>NS</td>
<td>&lt; 0.05</td>
<td>&lt; 0.005</td>
<td>&lt; 0.002</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.002</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD. BP = aortic blood pressure; dP/dt max = peak positive dP/dt; dP/dt min = peak negative dP/dt; LVDP min = left ventricular minimal diastolic pressure; LVEDP = left ventricular end diastolic pressure.
of the flow propagation velocity confirms previous observations by Stugaard et al. (8), who showed that early filling was highly dependent on left ventricular relaxation rate. Furthermore, the simultaneity between minimal values of flow propagation velocity and the deformation on the ascending limb of the negative dP/dt curve suggests that the asynchrony of relaxation during early phases of the ischemia influences the flow propagation velocity. In addition, this study shows that the premature flow cessation observed during ischemia was related to the rise in diastolic pressure, which could be partly related to an increased left ventricular chamber stiffness occurring during ischemia.

Alteration of relaxation induced by ischemia. Balloon inflation during coronary angioplasty constitutes a unique model for studying the consequences of transient ischemia on cardiac performance in humans. The sequence of the different hemodynamic events occurring during coronary angioplasty has been well documented: alteration in both diastolic function and wall motion contractility followed by ECG abnormalities and finally chest pain (2,14–18). In these studies, it has been shown that occlusion of the left anterior descending coronary artery (14) is the most effective procedure for studying the effect of ischemia, especially in the absence of collateral channels (18). From a hemodynamic point of view, results observed in the present study are in agreement with previous studies, with a prolongation of tau and a decrease in both peak negative dP/dt (2,3,11,17,19) and peak positive dP/dt (1–3).

In normal subjects, flow propagation is related to a physiologic nonuniformity of relaxation, and in those with cardiac disease, this nonuniformity is major (7), leading to asynchrony of relaxation. The course of relaxation is space dependent, and the relaxation process in the free wall is progressively delayed from base to apex. In physiologic conditions, flow propagation is driven by a pressure gradient between apical and basal regions due to physiologic nonuniformity of relaxation (20) and to early diastolic recoil of the left ventricular wall in conjunction with the release of elastic potential energy stored during systole and generating the phenomenon of suction (21,22). By this last mechanism, the physiologic pressure gradient is clearly mediated by the systolic function of the left ventricle. In the case of ischemia, color M-mode Doppler echocardiography allows visualization of a slowing of the flow propagation speed, which can be a consequence of variations in intracavitary pressure gradients related to the asynchrony of relaxation of adjacent regions and the deterioration of systolic function. If pressure decay induced by relaxation clearly allows

![Figure 6](image6.png)  
**Figure 6.** Evolution of slope B throughout the inflation. Minimal values are detected after 20-s ischemia. *p < 0.05 compared with baseline. †p < 0.05 compared with 20-s inflation.

![Figure 7](image7.png)  
**Figure 7.** Determination of flow cessation using color M-mode Doppler echocardiography. The white line represents the outlined plane of the mitral valve. Time interval is measured between the time when the flow stops entering the left ventricle and the onset of the next QRS interval. Under basal conditions, flow stops entering the left ventricle, close to the onset of the QRS interval. During ischemia, premature cessation of the entering flow is easily observed exactly at the level of the mitral valve. Here, flow cessation was at −35 ms during ischemia. Variations in flow propagation velocity must also be determined.
the setting up of pressure gradients between the left atrium and ventricle and inside the left ventricle, flow propagation is also dependent on myocardial distensibility, which is reduced by the increased rest tension due to impeding wall forces in response to cavity filling. Flow propagation is therefore assumed to depend on the global diastolic properties of the ischemic heart, which are both relaxation and compliance (23).

Effectively, during ischemia, inflow blood propagation is disturbed: In an experimental study using contrast echocardiography, it was shown that during prolonged ischemia, echo contrast medium did not reach the apex within one diastolic period but turned upward to the outflow tract in the middle of the cavity (24). More recently, Stugaard et al. (8,9), using color M-mode Doppler echocardiography, showed a marked delay of apical filling during coronary angioplasty. During coronary angioplasty, the time difference between the occurrence of peak velocity at the mitral tip and in the apical region was prolonged and approximatively multiplied by 3 before and during balloon inflation. In the present study and in agreement with Stugaard et al., we observed a severe modification of flow propagation velocities during ischemia, from a vertical pattern corresponding to rapid flow propagation velocities to a bent pattern corresponding to slowed flow propagation velocities.

The present study also highlights the complex interaction between flow propagation and asynchrony of relaxation. In particular, the analysis of the time course of the alteration of flow velocity showed that it decreased early after balloon occlusion of the coronary artery and was minimal 20 to 30 s after the beginning of this inflation. The maximal decrease in flow propagation velocity occurred simultaneously with the deformity of the ascending limb of the negative dP/dt curve (2,12,17). Progressively, the deformity of the negative dP/dt curve disappeared, whereas flow propagation velocity slightly improved, but always with altered values when compared with baseline. The deformation of the negative dP/dt signal at the early phase of the occlusion is assumed to reflect asynchronous contraction or relaxation at the very beginning of the transmural occlusion: In this case, the time course of left ventricular pressure decay deviates substantially from a monoexponential model. Accordingly, a biexponential fitting of the pressure relation was calculated by Serruys et al. (2) during the early phase of transmural coronary occlusion. In the present study, despite the deformation of the negative dP/dt signal, which always occurred, it was not possible to model a simple biexponential fitting of the course of the pressure decay. Nevertheless, we concurred that the deformation of the negative dP/dt curve was an expression of the asynchrony of relaxation. Finally, the amplitude and chronology of the alteration of flow propagation velocities analyzed by color M-mode Doppler echocardiography can be related to the asynchrony of relaxation, reflecting blood–wall interdependence. In this way, flow propagation velocity has to be interpreted as a result of complex physiologic mechanisms, including relaxation. Its values and especially its variations are coherent but not superimposed on those of the constant tau, which constitutes another approach to studying relaxation but which is at the same time influenced by complex interactions between deactivation and load and is modulated by neurohormonal, metabolic and pharmacologic influences (24).

Detection of flow propagation velocity. The analysis of the left ventricular inflow pattern by color Doppler M-mode echocardiography was initially described by Brun et al. (7) in

![Table 2. Transmitial Pulsed Doppler Values at Baseline, at 30 s of Inflation and at 1 min of Inflation*](Image)

*The inflation episode monitored with pulsed Doppler echocardiography had been randomly determined between the first and the second inflation. †Analysis of variance by the Fisher exact test has been used to compare baseline, ischemia at 30 s and ischemia at 1 min with statistically significant variations for p < 0.05. Data presented are mean value ± SD. A = atrial flow velocity; E = early transmitial flow velocity; IVRT = isovolumetric relaxation time measured with pulsed Doppler echocardiography between the plot of closure of the aortic valve and the plot of opening of the mitral valve.
dilated cardiomyopathies. In this previous study, the slope of the basal flow wave front was measured and found inversely related to tau. However, it appeared that the measurement of this slope was a challenge for a normal flow propagation pattern. This led us to analyze flow propagation velocity with a computerized tracing of low isovelocities slopes by plotting spatial points representing isovelocities linked by the best correlation using simple linear regression analysis. Stugaard et al. (8,9) also showed delay in apical filling by measuring the interval between maximal velocity of E at the mitral tip and in the apical region. Takatsuji et al. (10) used a derived technique by measuring the interval between the maximal rate of increase of action potential upstroke (Vmax) at the mitral level and 70% Vmax in the apical region. Our technique, with computerized detection of isovelocities, appears interesting because it can also be applied when flow does not reach the apex (25) or does not remain in the same tomographic plane throughout diastole. Another reason for our choice is a temporal one, because in some cases when relaxation is slow, the apex is reached in the systolic period, a rather long time after the end of relaxation and after opening of the aortic valves.

For computerized detection of low isovelocities, it is obvious that the slope B obtained with the fourth, fifth and sixth isovelocities (between 0.1 and 0.25 m/s) gave better results than the lowest isovelocities both for the calculation of a linear regression relation between isovelocities and for the relation with tau. It may be hypothesized that very low isovelocities are dependent on other factors such as viscosity or recirculation. However, detection of isovelocity lines by filtering processing can be used to evaluate flow propagation velocity only in case of disease such as dilated cardiomyopathy (7) or during ischemic phases. Finally, and whatever method is used, flow propagation velocity must be measured away from the mitral valve where the flow is directed between the two leaflets that establish a real channel (opened leaflets are not apparent with color M-mode Doppler echocardiography).

Prematurity of cessation of flow. While pacing-induced asynchrony induces an impairment of relaxation, it does not induce end-diastolic pressure changes, suggesting that asynchrony is not sufficient to alter chamber stiffness (26). During angioplasty-induced ischemia, an increase in the global chamber stiffness was previously demonstrated, with an upward shift of the pressure–volume relation but without significant changes in the end-diastolic volumes (17). It has also been shown that this increased stiffness specifically involved myocardial ischemic zones without changes in end-diastolic segmental radii. This shift has been attributed to several factors: changes in intrinsic diastolic myocardial stiffness, including decrease in regional blood flow; delayed left ventricular relaxation; and loss of elastic recoil (22) due to ventricular asynery. In the present study, although evaluation of myocardial stiffness was performed, the increase in end-diastolic pressures could probably be understood as compliance abnormalities based on published data. The M-mode Doppler analysis demonstrated premature cessation of entering flow related to this elevation of end-diastolic pressures, as was previously shown with trans-mitral pulsed Doppler (25) and with pulmonary venous flow (27). Moreover, in recent heart transplant recipients we previously demonstrated that this pattern of interrupted entering flow could be related to structural modifications of myocardium with a positive relation between myocardial fibrosis and premature flow cessation (13).

Interpretation of pulsed Doppler data. With the pulsed Doppler mode, ischemic flow initially was associated with a decrease of E wave and later with an increase of the isovolumetric relaxation time. These abnormalities are in agreement with previous observations of the prolongation of the relaxation rate, which induces a reduced gradient between left atrial and ventricular pressures (1–3,17,28). This abnormal flow pattern is not sustained throughout the inflation for the E wave. Variations of E, A and E/A ratio at the end of the inflation can be related to the alteration of systolic function (29–32) and to the decrease of cardiac output. These pulsed Doppler abnormalities as well as an abrupt pattern of the descending slope of E are known to depend on multiple factors: relaxation lengthening, systolic failure and compliance alteration, as described in the type II of Appleton et al. (29).

Study limitations. Some technical limitations must be addressed. Most are related to the fact that echocardiography was used during a limited number of balloon inflations. Consequently, it was not possible to evaluate the effects of ischemia on left ventricular function for all echocardiographic data. In particular, wall motion abnormalities were not well evaluated, and cardiac output was measured only in a limited number of patients. In addition, it was impossible to simultaneously study different echocardiographic indexes, which meant that we had to randomize pulsed or color M-mode Doppler echocardiography for the two first inflations. The transfer to the computer added other technical difficulties to this study, avoiding a continuous computerized analysis throughout all the inflations. Nevertheless, a precise temporal analysis was performed for the last seven patients.

Conclusions. Color M-mode Doppler echocardiography allows the assessment of the consequences of ischemia on diastolic function. The results are in agreement with invasive hemodynamic data: An immediate alteration of relaxation was related to asynchrony, a color M-mode Doppler transduction resulting in a decrease of the entering flow propagation velocity. Color M-mode Doppler echocardiography also permitted the assessment of premature cessation of entering flow so as to evaluate late diastolic phenomena characterized by an increase in end-diastolic pressure. This technique might help improve our understanding of the diastolic events that occur in clinical practice in situations of ischemia, such as myocardial infarction or stress echocardiography.

We are grateful to Alberto Meguira and Helene Leclerc for technical assistance and help.
References


