SUMMARY The previously demonstrated relationship between the mitral valve E-F slope and the rate and timing of early left ventricular (LV) filling has suggested that LV "compliance" is a major determinant of the E-F slope. Accordingly we constructed high fidelity simultaneous pressure-volume (P-V) curves at rest and following the steady state infusion of low dose (33 ± 4 μg/min) nitroglycerin (TNG) for ten patients undergoing cardiac catheterization. The mitral echogram recorded no more than 5 min prior to the resting and TNG left ventriculograms were compared to the P-V curves so obtained. The increases in the mitral E-F slopes observed in all patients with TNG (74 ± 13 mm/sec to 102 ± 16 mm/sec, P < 0.01) were associated with variable downward shifts of the P-V curves. In general, the greater increases in E-F slope were associated with greater downward shifts of the early diastolic P-V curves while smaller increases were associated with less obvious shifts. These early diastolic P-V shifts were associated with increases in the volume of blood entering the LV during the first third of diastole (53 ± 6 ml to 69 ± 8 ml, P < 0.001). Thus the pressure-volume relationship in early diastole is a more important determinant of the mitral E-F slope than the late diastolic P-V relationship and probably explains the poor correlation to "mean diastolic compliance" previously reported.

Therefore we devised a study protocol to determine what effect acute alterations in the LV pressure-volume relationship had on the mitral valve echocardiogram in the intact human ventricle. No theoretical models of compliance or stiffness were employed. Changes in the raw pressure-volume data were compared to changes in the mitral echo in the same patient.

Methods

The study population consisted of ten patients (mean age 53 ± 2 years) with chronic stable angina pectoris undergoing diagnostic cardiac catheterization. Patients with valvular and cardiomyopathic heart disease and patients with either akinetic or dyskinetic left ventricular wall segments were excluded. All were in normal sinus rhythm at the time of study. No patient was taking digitalis. Propranolol and nitrates were withheld for at least 6 hours prior to study. Patients were catheterized in the fasting state following light sedation with oral diazepam. Retrograde left heart catheterization was performed using high fidelity micromanometer tipped angiographic catheters (Millar Mikro-tip) externally calibrated against a mercury reference. High fidelity left ventricular pressure was frequently compared to simultaneously recorded fluid pressure to detect baseline drift. Radial artery, mean right atrial pressure, and high fidelity left ventricular systolic and diastolic pressures were continuously recorded on an 8 channel direct writing recording device immediately prior to, during and following left ventricular angiography. The pressure recording was electronically marked at 10 msec intervals during the left ventriculogram. Similar time markers on the cineangiographic frames allowed for the determination of simultaneous pressure-volume data for each patient.

After the patient was instructed to take a full inspiratory effort, the left ventriculogram was performed in the 30° right anterior oblique projection using 50 ml of meglumine diatrizoate (Renografin 76) and recorded at 60 frames/sec on 35 mm film using a Siemens 7 inch cesium iodide image intensifier. Correction factors for magnification and distortion were obtained for each patient using a standard 1 cm²
angiographic grid filmed at the angiographic center of the left ventricle.\textsuperscript{13} Frame-by-frame ventricular volumes were then calculated from the time of initial mitral valve opening to end diastole using the area-length method of Sandler and Dodge, employing a computer assisted Graf-Pen system.\textsuperscript{14}

Mitral valve opening was marked by the cineangiographic frame first demonstrating entrance of unopacified blood into the left ventricle. End diastole was marked by the frame with the greatest ventricular volume prior to the onset of left ventricular contraction. Premature ventricular contractions and beats immediately following a premature beat were excluded. Only those sinus beats following the completion of contrast injection were analyzed because of the artificial displacement downward of the recorded left ventricular pressures during the injection. Patients with excessive ventricular irritability or incomplete ventricular opacification were excluded. Mean right atrial pressure was measured immediately prior to and once again during the left ventriculogram. Any patient performing the Valsalva maneuver as recorded by a greater than 5 mm Hg rise in mean right atrial pressure during the ventriculogram was also excluded.

Twenty minutes following the acquisition of baseline hemodynamic and pressure-volume data, an intravenous infusion of nitroglycerin was started using a Harvard constant infusion pump. The initial dose of nitroglycerin was 20 \( \mu \)g/min. It was titrated upward every five minutes in increments of 10 \( \mu \)g/min until at least a 10\% reduction in left ventricular end-diastolic pressure was attained, while attempting to avoid wide swings in systemic arterial pressure. At this point the infusion was held constant for an additional 10 min. When a steady state was attained the measurements of hemodynamic and pressure-volume data were repeated.

Two additional patients with coronary artery disease served as controls. They received no nitroglycerin between two determinations of hemodynamic and pressure-volume data obtained 20 min apart.

The volume of blood entering the left ventricle during the first third of diastole was calculated from the sequential volume data both at rest and following the nitroglycerin infusion. The angiographic stroke volume was taken as the difference between the end-diastolic and end-systolic volumes.

Each patient underwent echocardiography in the supine position in the cardiac catheterization laboratory no more than 5 min before the resting and again before the nitroglycerin left ventriculogram. Since deep inspiration frequently interposes interfering air-containing lung between the transducer and the heart, all recordings were made during quiet respiration. All echocardiograms were obtained with an Ekoline 20 Smith-Kline ultrasonoscope using a 10 cm focused transducer held perpendicularly to the chest wall. Recordings of the anterior mitral valve leaflet echo with the maximal diastolic excursion were made with a Honeywell 1856 strip chart recorder at 50 mm/sec. Care was taken to insure that the resting and nitroglycerin tracings were taken from exactly the same position on the chest wall and that the ultrasound beam was directed through the same portion of the mitral valve free edge. The early diastolic closure slope (E-F\textsubscript{0}) was measured as illustrated in figure 1. The values recorded were the average of ten consecutive beats.

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** A schematic drawing of a mitral valve echogram demonstrating the method of measuring the early diastolic closure slope (E-F\textsubscript{0} slope).

Statistical calculations were performed by Student's \( t \)-test for paired data.

**Results**

The resting and nitroglycerin data are summarized in table 1. The mean TNG infusion rate was 33 ± 4 \( \mu \)g/min (range 20–60 \( \mu \)g/min). There was no significant change in heart rate, angiographic stroke volume, left ventricular ejection fraction and mean right atrial pressure following the nitroglycerin. An 11 mm Hg reduction in left ventricular systolic pressure and 6 mm Hg reduction in mean arterial pressure did not reach statistical significance.

In the ten study patients the nitroglycerin produced a significant reduction in the left ventricular volume and pressure at the time of mitral valve opening: 80 ± 16 ml to 70 ± 17 ml (\( P < 0.05 \)) and 14 ± 2 mm Hg to 9 ± 1 mm Hg (\( P < 0.01 \)) respectively. In addition there was a significant reduction in left ventricular volume and pressure at end diastole: 206 ± 21 ml to 195 ± 21 ml (\( P < 0.05 \)) and 18 ± 2 mm Hg to 9 ± 2 mm Hg (\( P < 0.01 \)), respectively.

An example of the resting and TNG pressure recordings for one of the study patients is illustrated in figure 2. The left ventricular diastolic pressure data thus recorded was used to construct simultaneous pressure-volume curves, an example of which is illustrated in figure 3. The downward shift of the pressure-volume curve was associated with a significant increase in the mitral valve E-F\textsubscript{0} slope as illustrated in the same figure. The pressure-volume curves of all ten study subjects were shifted downward to a varying degree. In each case the downward shift was associated with a significant increase in the mitral valve E-F\textsubscript{0} slopes (fig. 4). Strict quantification of the change in the pressure-volume curves was not attempted because of the theoretical objections previously stated. However, examination of the pressure-volume curves demonstrates that in general those patients with the greatest reduction in left ventricular volume and pressure during the first third of diastole had the greatest increases in the echocardiographic E-F\textsubscript{0} slopes. Conversely small changes in early diastolic pressure and volume were associated with smaller changes in the E-F\textsubscript{0} slopes (fig. 5). There was no consistent relationship between the changes in the E-F\textsubscript{0} slopes and the changes observed in pressure and volume during the last third of diastole. Furthermore, the rate of rise of the late
diastolic pressure-volume curve was greater in four of the ten patients following the TNG infusion. In spite of these steeper late diastole pressure-volume curves with TNG the E-F₀ slope increased in each instance.

The nitroglycerin infusion was associated with a significant increase in the volume of blood entering the left ventricle during the first third of diastole: 53 ± 6 cc to 69 ± 8 cc (P < 0.001) (fig. 6).

In the two control patients receiving no TNG, the P-V curves and the E-F₀ slopes were identical (fig. 7). No change

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TABLE 1. Patient, Hemodynamic, and Echographic Data on Patients Studied with and without Nitroglycerin.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age/Sex</th>
<th>CAD</th>
<th>HR (Rest)</th>
<th>TNG (Rest)</th>
<th>LVV at MV O (ml)</th>
<th>LVP at MV O (mm Hg)</th>
<th>Min LVP (mm Hg)</th>
<th>EDV (ml)</th>
<th>ED P (mm Hg)</th>
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</table>

**Control**

- **Age/Sex**: 39/M, 68/M, 41/M, 51/M, 58/M
- **HR (Rest)**: 91, 94, 33, 35, 70, 69
- **LVV at MV O (ml)**: 33, 55, 21, 21, 51, 60
- **LVP at MV O (mm Hg)**: 35, 21, 17, 17, 55, 60
- **Min LVP (mm Hg)**: 8, 7, 5, 5, 21, 21
- **EDV (ml)**: 15, 14, 11, 11, 10, 10
- **ED P (mm Hg)**: 140, 135, 143, 145, 143, 145

**Mean ± SEM**

- **LVV at MV O (ml)**: 66 ± 3, 66 ± 3, 80 ± 16, 70 ± 17, 14 ± 2, 9 ± 1
- **LVP at MV O (mm Hg)**: 6 ± 2, 6 ± 2, 70 ± 17, 70 ± 17, 6 ± 2, 6 ± 2
- **Min LVP (mm Hg)**: 195 ± 21, 195 ± 21, 18 ± 9, 18 ± 9, 8 ± 9, 8 ± 9
- **EDV (ml)**: 53 ± 3, 53 ± 3, 65 ± 3, 65 ± 3, 66 ± 3, 66 ± 3
- **ED P (mm Hg)**: 21 ± 10, 21 ± 10, 20 ± 10, 20 ± 10, 20 ± 10, 20 ± 10

**Abbreviations**: HR = heart rate; LVV = left ventricular volume; LVP = left ventricular pressure; EDV = end-diastolic volume; EDP = end-diastolic pressure; SV = stroke volume; EF = ejection fraction; MAP = mean arterial pressure; MRAP = mean right atrial pressure; MV O = mitral valve opening; TNG = nitroglycerin.
was noted in the volume of blood entering the LV during the first third of diastole in these two patients.

**Discussion**

We have demonstrated that an acute intervention which results in a variable downward shift of the pressure-volume relationship in the intact human ventricle uniformly results in a significant increase in the mitral valve echocardiographic E-F₀ slope. Furthermore, by examining the raw pressure-volume data from the time of mitral valve opening to end diastole, it is apparent that the increase in the E-F₀ slopes observed in all ten study patients was related to the degree of reduction of early diastolic pressure and volume and has no constant relationship to the late diastolic pressure-volume alteration induced by the nitroglycerin. These changes cannot be ascribed to a nonspecific effect of the angiographic contrast agent. The two control patients who received no nitroglycerin had identical pressure-volume curves and echocardiographic E-F₀ slopes.

The effects of the low dose intravenous nitroglycerin on heart rate, stroke volume, mean arterial pressure and left ventricular filling pressure observed in the present study are similar to those reported by Flaherty et al., using a similar infusion rate in patients with acute myocardial infarction. Since left ventricular volumes were not measured, these investigators could not exclude a nitroglycerin-induced downward shift of the pressure-volume curve as a contributing factor to the reduction in left ventricular filling pressure observed. The present study confirms their suspicion that, at these infusion rates, the nitroglycerin-induced reduction in filling pressure is in part mediated by a reduction in preload and in part by an alteration of the pressure-volume relationship of the left ventricular chamber.

Although the present study was not designed to investigate the mechanism of the nitroglycerin induced downward shift in the pressure-volume relationship, several points can be made. Since mean right atrial pressure did not differ significantly immediately prior to and during the acquisition of the resting and nitroglycerin pressure-volume data, differences in intrathoracic pressure that might have been caused by unnoticed Valsalva maneuvers cannot account for the acute alterations observed. It has been demonstrated that left ventricular pressure can be significantly altered by changes in the filling pressure of the right ventricle, presumably through an effect on the interventricular septum. By increasing venous capacitance and decreasing

**Figure 3.** The diastolic pressure-volume curve at rest and during the nitroglycerin infusion for patient 7. Data points extend from the time of mitral valve opening to end diastole. The mitral echogram on the left was obtained at rest; the one on the right during the nitroglycerin infusion. Note the change in the early diastolic closure slope (E-F₀) with the nitroglycerin infusion. TNG = nitroglycerin.
venous return, nitroglycerin may reduce right ventricular diastolic pressure, and therefore left ventricular diastolic pressure more than would be expected for any reduction in left ventricular diastolic volume. Since venous capacitance and right ventricular diastolic pressure were not measured in the present study, we cannot exclude the possibility that nitroglycerin induced right ventricular diastolic pressure and volume shifts may be contributing to the observed left ventricular pressure-volume shifts. Since the nitroglycerin increased the volume of blood entering the left ventricle during the initial third of diastole, it seems unlikely that viscous effects could explain the lower pressures observed. The data from the present study cannot exclude the possibility that nitroglycerin either directly or indirectly enhances left ventricular relaxation. Lastly nitroglycerin may alter the elasticity of cardiac muscle either directly or indirectly by altering the volume and/or distribution of coronary blood flow.

Regardless of the mechanisms involved, the variable downward shift of the pressure-volume relationship produced by the nitroglycerin resulted in a significant increase in the mitral valve E-F0 slope. If the rate of early left ventricular filling is indeed a major determinant of the mitral E-Fo slope7, 8 one would expect changes in early diastolic pressure and volume to exert a more important effect on this slope than late diastolic pressure and volume. This hypothesis is supported by the data of the present study. In general, those patients demonstrating the greater reductions in pressure and volume with nitroglycerin during the first third of diastole had the greater increases in the E-F0 slopes while smaller reductions in pressure and volume resulted in smaller increases in the E-F0 slopes. No similar relationship could be demonstrated for the late diastolic pressure-volume curves. In fact four of our ten patients actually had steeper late diastolic pressure-volume curves with nitroglycerin, yet all demonstrated an increase in the E-F0 slope. This primacy

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**Figure 4.** Mitral E-F0 slope at rest and during the nitroglycerin infusion for each study patient. TNG = nitroglycerin.

**Figure 5.** Representative resting and nitroglycerin pressure-volume curves for four study patients. The change in the mitral E-F0 slope with nitroglycerin is indicated for each patient.
of early diastolic pressure and volume may in part explain the poor correlation observed by DeMaria et al.8 between measures of "mean diastolic compliance" and the E-Fo slope.

In 1974 Quinones et al.8 demonstrated a relationship between the mitral valve E-Fo slope and two measures of diastolic compliance: the end-diastolic distensibility index (dV/dP)0d and the slope of the log pressure-volume curve. These investigators9 and others9,11 have more recently pointed out the technical and theoretical limitations of such an analysis which requires several assumptions about the left ventricular pressure-volume relationship. It should be emphasized that in the present study alterations in the raw pressure-volume curves were examined in the same patient following an acute intervention. These changes were related to observed changes in the E-Fo slopes. No assumptions about the exponential nature of the pressure-volume relationship or derived indices of left ventricular compliance were made.

Although great care was taken to insure that the resting and nitroglycerin echocardiograms were obtained from the same position on the chest wall and through the same portion of the mitral valve, small variations in the path of the echo beam through the heart cannot be entirely excluded. However if such variations had been playing a significant role in the changes observed in the E-Fo slopes with nitroglycerin, one would expect a totally random distribution of change. Yet each patient uniformly demonstrated an increase in the E-Fo slope with nitroglycerin which was related to the degree of downward displacement of the early diastolic pressure-volume curve. In addition the measured E-Fo slopes were identical in the two control patients who received no nitroglycerin. These findings suggest that any small effect subtle differences in transducer angulation produced on the E-Fo slopes was overshadowed by the more important nitroglycerin-induced changes.

The subjects of the present study were patients with chronic stable angina pectoris. Since patients with valvular heart disease and patients with either hypertrophic or congestive cardiomyopathy were specifically excluded, the results of the present study should not be extrapolated to these disease states. Alteration in papillary muscle orientation and chordae tendineae insertion and traction on the mitral leaflets might contribute to the attenuated mitral valve E-Fo slopes commonly seen in these disease states independent of early diastolic pressure and volume.25

The early diastolic closure of the mitral valve is a complex event. In the absence of intrinsic mitral valve pathology and grossly disordered left ventricular geometry, the rate of mid-diastolic mitral closure has previously been shown to be related to the rate of early left ventricular filling. Although the exact mechanism of this relationship remains unclear, it

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**Figure 6.** The volume of blood entering the left ventricle during the first third of diastole at rest and with nitroglycerin for each study patient.

**Figure 7.** The pressure-volume curve at rest and following a control period during which no nitroglycerin was given. The two curves are superimposable. The mitral E-Fo slope at rest (on the left) and following the control period (on the right) are similar.
has been ascribed to the greater development of turbulence and vortices on the undersurface of the leaflets following rapid left ventricular filling. In keeping with this hypothesis we have demonstrated that the pressure-volume relationship in the left ventricle in early diastole plays an important role in determining the rapidity of mid-diastolic closure. The lack of correlation to the late diastolic pressure-volume relationship is not surprising and probably explains the poor correlation of the E-F slope to measures of “mean diastolic compliance” previously reported.

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