Influence of Right Ventricular Hemodynamics on Left Ventricular Diastolic Pressure-Volume Relations in Man

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with the technical assistance of Frank R. Reed

SUMMARY To clarify the mechanism of displacement of the left ventricular diastolic pressure-volume function with alteration of loading conditions, the effects of nitroglycerin on pressure-volume relations in 13 patients were compared with those of amyl nitrite in 13 other patients during cardiac catheterization. After nitroglycerin, average systemic mean arterial pressure declined by 15.1 mm Hg (17%) and left ventricular end-diastolic pressure by 9.4 mm Hg (49%); right ventricular systolic and end-diastolic pressures fell 11.6 mm Hg (36%) and 5 mm Hg (41%), respectively. In all patients diastolic pressure-volume curves were significantly displaced downward and leftward. After amyl nitrite, average systemic mean arterial pressure fell 20.1 mm Hg (22%), but left ventricular end-diastolic pressure and right ventricular systolic and end-diastolic pressures were not significantly reduced. No significant displacement of diastolic pressure-volume curves occurred. Both the rate constant of the exponentially fit diastolic pressure-volume curve, and the rate of diastolic isovolumic relaxation (T) were unchanged after each drug. Thus downward displacement of diastolic pressure-volume functions after nitroglycerin appears to be dependent more upon reduction of right ventricular filling dynamics than coronary perfusion pressures. More favorable effects upon left ventricular function may be associated with reduction of both left ventricular filling pressures and systemic impedance (reflecting both “preload” and “afterload”) than of systemic arterial pressures (“afterload”) alone.

BENEFICIAL EFFECTS of pharmacologic manipulations of left ventricular loading conditions upon the decompenated ventricle appear to be attributable, at least in part, to favorable effects of reduction of preload and afterload upon the left ventricular diastolic pressure-volume relationship. Downward displacement of the pressure-volume function reflects an indirect beneficial effect of reduction of loading conditions on left ventricular function, because of the diminution of myocardial oxygen consumption accompanying the smaller ventricular volume, and consequently reduced wall tension. Thus, downward displacement has been observed with reduction of ventricular preload and afterload induced by nitroprusside and nitroglycerin. Conversely, upward shifts of the diastolic pressure-volume function have been reported with acute systolic loading of the left ventricle by administration of methoxamine and angiotensin, and with induction of angina by rapid atrial pacing.

Displacements of the pressure-volume relation of this type contradict traditional concepts of left ventricular pressure-volume relations, which have assumed that the ventricle adheres to a specific pressure-volume curve, characterized experimentally in the canine model and empirically in man, by a monoexponential function specific to each ventricle independent of load, and imply the existence of a family of diastolic pressure-volume curves for each ventricle, the “position” of the curve being dependent upon immediate loading conditions. Despite the important implications of such shifts, especially with regard to assessment of changes in ventricular systolic function based on classical ventricular function curves in which end-diastolic pressure is incorporated as an estimate of end-diastolic volume or fiber length, their underlying mechanisms are controversial. Thus, changes in myocardial relaxation, passive myocardial elastic stiffness, sustained myocardial contraction, perfusion pressure within the coronary vascular bed exerting “erectic” effects upon the myocardium, varying impingement of the aortic root upon the left ventricular cavity, and changes in the behavior of the anatomical constraints to left ventricular distension produced by the pleural pressure, right ventricle, and pericardium have all been suggested as causes of load-dependent shifts of the diastolic pressure-volume function. To further delineate the mechanism of the downward displacement of the pressure-volume curve in response to nitroglycerin administration, we examined three potential etiologic factors — myocardial relaxation, right ventricular chamber pressures, and coronary perfusion pressures — on left ventricular pressure-volume relations in man.

The circulatory effects of nitroglycerin and amyl nitrite differ: nitroglycerin results in a reduction of both systemic arterial pressure and venous return, and thus of right ventricular filling pressure; amyl nitrite

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Supported by Ischemic Heart Disease SCOR grant HL-17646, National Heart, Lung, and Blood Institute.
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results in a similar diminution of systemic arterial pressure, but conversely, in an unchanged or even augmented venous return. We considered the possibility that the individual contribution of changes in right ventricular hemodynamics, and systemic arterial pressures to the observed changes in left ventricular pressure-volume relations could be assessed by comparing the effects upon the pressure-volume function of nitroglycerin and amyl nitrite administration.

**Methods**

**Patient Population**

Twenty-six patients (20 male, six female), with a mean age of 51.9 years (range 39 to 68 years) were selected from those scheduled for diagnostic cardiac catheterization for evaluation of chest pain suggestive of coronary artery disease. An additional six male patients (mean age 53 years) were studied as controls, without pharmacologic intervention. All patients were in normal sinus rhythm. Patients with significant hypertension, cardiomyopathy, or left ventricular hypertrophy were excluded from the study. Informed consent was obtained in all cases. No complications were experienced by any of the patients studied.

**Catheterization Procedure**

Right and left heart catheterization was performed using standard techniques, via the brachial or femoral approach, with patients in the fasting state. Premedication with 50-100 mg of hydroxyzine hydrochloride was administered intramuscularly 60 minutes before the procedure. Whenever possible, all cardioactive medications were withdrawn at least 18 hours before the study. Cardiac output was measured by the Fick or indicator dilution (indocyanine green) technique. After assessment of hemodynamics, left ventriculography was performed with patients in the right anterior oblique (RAO) projection in the basal state, and after administration of nitroglycerin or amyl nitrite, or was repeated without drug administration in patients studied as controls. Selective coronary arteriography was then performed via the brachial or femoral artery approach.

**Data Acquisition**

Details of the techniques employed to obtain optimal simultaneous measurements of high fidelity ventricular diastolic pressures and volumes have been described previously. Simultaneous measurement of left ventricular pressure and volume during angiography is essential to avoid experimental artifact due to the small, though significant, elevation of left ventricular pressure induced by the contrast injection itself. Left ventricular pressure was measured with \#5-\#7 French micromanometer tip catheters (Millar Instruments Inc.) introduced via the left femoral artery with the use of a percutaneous arterial introducer equipped with a secondary port through which systemic arterial pressure was measured (Cor
dis Corp). Contrast injection was performed through a left ventricular angiographic catheter (\#7 or \#8 French pigtail) introduced percutaneously via the right femoral artery. A dual catheter system has been found necessary to avoid artifact attributable to pressure of the contrast injection on the atmospheric reference air tube of the micromanometer system. The necessity for the use of micromanometer tip catheters to avoid resonance artifacts observed during diastole with fluid-filled systems, and for accurate measurement of \(dP/\text{dt}\), has recently been emphasized.

The micromanometer system was calibrated electronically after equilibration against the pressure recorded via the fluid-filled catheter. Instantaneous \(dP/\text{dt}\) was obtained by direct differentiation of the left ventricular pressure signal (Accudata 132; Honeywell, Inc.). Right ventricular pressure was recorded continuously on a scale of 0-50 mm Hg with a \#7 French Swan-Ganz catheter positioned carefully within the right ventricle to avoid stimulation of ectopic beats.

Left ventricular systolic (scale 0-200 mm Hg) and diastolic (scale 0-50 mm Hg) pressures, systemic arterial pressure (scale 0-200 mm Hg), \(dP/\text{dt}\), ECG, cine frame pulse, and angiographic injector pulse were recorded simultaneously with the use of a multichannel recording system at a paper speed of 200 mm/sec (Honeywell, Inc.) (fig. 1).

**Experimental Protocol**

After measurement of resting right and left heart hemodynamics and equilibration of the micromanometer and fluid-filled catheter systems, the U-arm radiographic system (Siemens Cardioskop) was positioned precisely in the 45° RAO projection. Right and left ventricular pressures were then recorded during held submaximal inspiration without injection of contrast, to permit evaluation of the effects of the contrast agent alone upon resting hemodynamics. Inadvertent performance of the Valsalva maneuver was avoided by prior instruction of the patient, fluoroscopic observation of the diaphragm, and monitoring of right and left ventricular pressures. Left ventriculography was then performed under similar respiratory conditions, by injection of 30 ml of sodium and meglumine diatrizoate (Hypaque 76) via the pigtail catheter over a 3-second period with an ECG-triggered injector (Conrac; Siemens Corp). Angiography was performed with a 25 cm cesium iodide image intensifier (Siemens Corp) at a frame rate of 60/sec.

After a pause of 20 minutes to allow for dissipation of the hemodynamic and myocardial effects of the contrast agent, during which initial hemodynamics and heart rate were restored, the intervention ventriculogram was performed under similar respiratory conditions: 1) at the moment of maximal reduction of systolic left ventricular pressure, approximately 20-30 sec after standardized inhalation of amyl nitrite (amyl nitrite vaporole, 0.3 ml, Eli Lilly and Co); 2) after administration of sufficient nitroglycerin sublingually
(0.8–1.6 mg) to achieve a significant reduction (20–30 mm Hg) of left ventricular systolic pressure; and 3) without drug administration in patients studied as controls, to assess the effects of contrast injection alone upon left ventricular diastolic pressure-volume relations.

To exclude "drift" in the micromanometer system, the pressure registered by the transducer tip catheter was equilibrated with that recorded through the fluid-filled catheter immediately before drug administration. Both the patient and the x-ray equipment were maintained in precisely the same position and projection between the two ventriculograms.

Data Analysis

Ventricular volume was determined serially from consecutive frames of the cineventriculograms throughout diastole with the use of the standard area length method.\textsuperscript{15} Patients whose left ventriculograms

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**FIGURE 1.** Hemodynamic data recording in a representative patient in the resting state (PRE NG) and after nitroglycerin administration (POST NG). Injector Pulse = marker indicating commencement of ECG triggered contrast injection at preselected time during cardiac cycle; ECG = surface electrocardiogram; Cine Pulse = electronic signal recorded simultaneously with each cine frame exposed; dP/dt = first differential of left ventricular pressure with respect to time (200 mm Hg sec\textsuperscript{-1} cm\textsuperscript{2}); RFA = right femoral artery (10 mm Hg/cm); LV (high gain) = left ventricular pressure (10 mm Hg/cm); LV (low gain) = left ventricular pressure (5 mm Hg/cm); RV = right ventricular pressure (5 mm Hg/cm). Vertical time lines = 1 sec.
revealed moderately, or severely asynergic contraction patterns (involving more than one myocardial segment), or segmental early diastolic relaxation, were excluded from the study. In each instance, the first adequately opacified sinus beat was used, excluding premature contractions, as well as the first or second sinus beats thereafter. Analyses were performed within the first five beats of initiation of the injection, when the effects of contrast agent on myocardial function are negligible.16-18 Simultaneous serial high fidelity pressures were measured at 16.7-msec intervals from the high gain (0-50 mm Hg) ventricular pressure tracing at intervals synchronized precisely with each ventriculographic frame. Left ventricular pressure-volume data were analyzed by fitting (least squares technique) to the first order exponential function

\[ P = be^{kt} \]

where \( P \) = pressure in mm Hg, \( b = \) data constant, e = base of natural log, \( V = \) volume in ml, \( k = \) rate constant of the exponential function.7, 8, 10, 19-21 The rate constant "k" of this function has previously been used as an index of left ventricular chamber stiffness in individual patients.22

In each instance, the intercept on the pressure axis at zero volume was derived by exponential extrapolation, and was used to indicate the relative position of the curve on the pressure-volume plot.1 This value represents a mathematical expression intended solely to define the position of the pressure-volume curve on a coordinate system under selected hemodynamic circumstances. It does not entail direct physiological connotations, since actual measurements of pressure at zero volume are not possible in the clinical setting.

Early diastolic left ventricular relaxation was analyzed by the technique of Weiss et al.,23 and Karliner et al.24 and expressed as "T," an index of the time-course of left ventricular relaxation. Left ventricular pressure was analyzed at 5-msec intervals during isovolumic diastolic relaxation, and T derived from the rate constant of the exponential fit (least squares) to the serial diastolic pressures during this interval.23, 24 Unlike peak negative dP/dt per se, T has been shown to be independent of peak systolic pressure and end-systolic volume and fiber length.23 Recent studies in canine models also indicate that T is independent of systolic myocardial shortening within the physiologic range of cardiac output (Weisfeldt ML: personal communication).

Mean systemic arterial pressure, which approximates the pressure drop across the coronary bed since coronary venous pressure is low, was used as an estimate of mean coronary perfusion pressure.25

Statistical comparisons between initial data and that obtained during the drug intervention were performed using the paired t test; we compared control data between the groups of patients receiving nitroglycerin and amyl nitrite, respectively, using the t test for difference between group means. Statistical comparison of pressure-volume relations between in-

### Table 1. Changes in Hemodynamics and Left Ventricular Function after Nitroglycerin

<table>
<thead>
<tr>
<th></th>
<th>Pre NG</th>
<th>Post NG</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial systolic pressure (mm Hg)</td>
<td>125.8 ± 5.0*</td>
<td>99.4 ± 3.9*</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Systemic arterial diastolic pressure (mm Hg)</td>
<td>70.4 ± 2.3</td>
<td>61.0 ± 1.9</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>88.9 ± 2.8</td>
<td>73.8 ± 2.3</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>125.2 ± 8.4</td>
<td>101.4 ± 6.7</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV minimal diastolic (mm Hg)</td>
<td>10.8 ± 1.8</td>
<td>6.02 ± 1.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV peak a wave pressure (mm Hg)</td>
<td>19.0 ± 2.0</td>
<td>10.0 ± 1.5</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV end diastolic pressure (mm Hg)</td>
<td>19.3 ± 1.8</td>
<td>9.9 ± 1.5</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Peak +dP/dt (mm Hg/sec)</td>
<td>1095 ± 58</td>
<td>1206 ± 59</td>
<td>NS</td>
</tr>
<tr>
<td>Peak -dP/dt (mm Hg/sec)</td>
<td>1179 ± 93</td>
<td>973 ± 67</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>T (msec)</td>
<td>75.9 ± 8.2</td>
<td>69.8 ± 10.7</td>
<td>NS</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>32.6 ± 2.8</td>
<td>21.0 ± 2.1</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>RV minimal diastolic pressure (mm Hg)</td>
<td>6.7 ± 1.6</td>
<td>2.8 ± 1.0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>RV peak a wave pressure (mm Hg)</td>
<td>11.6 ± 1.6</td>
<td>6.4 ± 1.5</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>RV end diastolic pressure (mm Hg)</td>
<td>12.2 ± 1.3</td>
<td>7.2 ± 1.3</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV end diastolic volume index (ml/m²)</td>
<td>89.2 ± 5.9</td>
<td>70.4 ± 5.5</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV end systolic volume index (ml/m²)</td>
<td>36.2 ± 6.2</td>
<td>25.3 ± 4.4</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>RR interval (msec)</td>
<td>897 ± 47</td>
<td>753 ± 24</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.61 ± 0.05</td>
<td>0.66 ± 0.04</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Mean circumferential fiber shortening rate (circ/sec)</td>
<td>0.96 ± 0.13</td>
<td>1.20 ± 0.13</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Mean = standard error of the mean.
†Statistical significance (paired t test).

Abbreviations: LV = left ventricle; RV = right ventricle; NG = nitroglycerin; NS = not statistically significant; T = rate of diastolic isovolumic relaxation.
individual patients was not performed, in view of the unresolved question of appropriate normalization for individual cardiac dimensions.26

Results

Anatomical Findings

Significant coronary artery disease was documented in all patients studied. Significant coronary artery disease was also detected in the six patients studied as controls without drug administration. Normally synergic left ventricular contraction occurred in all patients, except for three receiving nitroglycerin and two receiving amyl nitrite, in whom mild asynergy involving only one myocardial segment was detected.

No statistically significant difference in initial systemic arterial systolic, diastolic or mean pressures, left ventricular systolic or end-diastolic pressures, end-systolic and end-diastolic left ventricular volumes, ejection fraction, mean circumferential fiber shortening rate, right ventricular systolic or end-diastolic pressures was observed between the groups of patients receiving nitroglycerin and amyl nitrite, respectively. No patient developed symptomatic, hemodynamic, or electrocardiographic evidence of acute myocardial ischemia during the study.

Effects of Nitroglycerin on Hemodynamics (table 1, fig. 1)

We observed a significant reduction in systemic arterial systolic, diastolic and mean pressures, and in left ventricular systolic, minimal, and end-diastolic pressures, in all patients after nitroglycerin. Average right ventricular systolic and end-diastolic pressures also declined significantly. Although average peak positive dP/dt was not significantly altered, peak negative dP/dt fell significantly in each patient. A small but statistically significant reduction of average RR interval was recorded.

Effects of Amyl Nitrite on Hemodynamics (table 2)

As after administration of nitroglycerin, after inhalation of amyl nitrite average systemic arterial systolic, diastolic and mean pressures, and left ventricular systolic pressure fell significantly in all patients. In contrast to the effects of nitroglycerin, no significant decline occurred in average left ventricular minimal or end-diastolic pressures, while a slight but significant increase was observed in average right ventricular systolic, minimal, and end-diastolic pressures. Although average peak positive dP/dt remained unchanged, we recorded a significant reduction in peak negative dP/dt after amyl nitrite, similar to that observed after nitroglycerin. A small but significant reduction in average RR interval was noted after amyl nitrite as was the case after nitroglycerin.

Effects of Nitroglycerin and Amyl Nitrite

Early Diastolic Relaxation (tables 1 and 2)

The average coefficient of determination for the exponential fit to the rate of pressure decline during the

**Table 2. Changes in Hemodynamics and Left Ventricular Function after Amyl Nitrite**

<table>
<thead>
<tr>
<th></th>
<th>Pre AN</th>
<th>Post AN</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial systolic pressure (mm Hg)</td>
<td>128.7 ± 6.0*</td>
<td>90.6 ± 4.4*</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Systemic arterial diastolic pressure (mm Hg)</td>
<td>70.9 ± 2.8</td>
<td>58.8 ± 2.2</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>90.5 ± 3.4</td>
<td>70.4 ± 2.6</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>128.4 ± 5.9</td>
<td>90.8 ± 4.1</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV minimal diastolic (mm Hg)</td>
<td>7.1 ± 1.6</td>
<td>7.0 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>LV peak a wave pressure (mm Hg)</td>
<td>14.5 ± 2.0</td>
<td>14.8 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>LV end diastolic pressure (mm Hg)</td>
<td>15.1 ± 1.9</td>
<td>15.9 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Peak +dP/dt (mm Hg/sec)</td>
<td>1180 ± 40</td>
<td>1135 ± 57</td>
<td>NS</td>
</tr>
<tr>
<td>Peak −dP/dt (mm Hg/sec)</td>
<td>1193 ± 94</td>
<td>753 ± 78</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>T (msec)</td>
<td>57.7 ± 4.7</td>
<td>59.7 ± 6.9</td>
<td>NS</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>33.2 ± 2.4</td>
<td>38.0 ± 2.9</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>RV minimal diastolic pressure (mm Hg)</td>
<td>4.4 ± 1.0</td>
<td>5.1 ± 1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RV peak a wave pressure (mm Hg)</td>
<td>11.2 ± 1.0</td>
<td>12.4 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>RV end diastolic pressure (mm Hg)</td>
<td>11.2 ± 1.2</td>
<td>12.5 ± 1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV end diastolic volume index (ml/m²)</td>
<td>90.7 ± 7.2</td>
<td>88.2 ± 5.4</td>
<td>NS</td>
</tr>
<tr>
<td>LV end systolic volume index (ml/m²)</td>
<td>39.3 ± 4.2</td>
<td>28.7 ± 4.8</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>RR interval (msec)</td>
<td>895 ± 44</td>
<td>765 ± 29</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.57 ± 0.03</td>
<td>0.69 ± 0.05</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Mean circumferential fiber shortening rate (circ/sec)</td>
<td>0.87 ± 0.06</td>
<td>1.43 ± 0.15</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
†Statistical significance (paired t test).
Abbreviations: LV = left ventricular; RV = right ventricular; AN = amyl nitrite; NS = not statistically significant; T = rate of diastolic isovolumic relaxation.
isovolumic period of diastole was 0.98, before and after both nitroglycerin and amyl nitrite. Peak negative dP/dt declined significantly after both nitroglycerin and amyl nitrite. However, peak negative dP/dt has been found to be predominantly a function of peak aortic pressure, and in the presence of the altered hemodynamic conditions induced by each drug in the present study, may not per se indicate an alteration in ventricular relaxation.

Conversely, there was no statistically significant or directionally consistent change in T after administration of either drug, implying that at any given level of pressure at the time of peak negative dP/dt, the rate of pressure decline during the isovolumic period of diastole was unchanged. Since T has been proposed as an index of the time-course of left ventricular early diastolic relaxation which, unlike peak negative dP/dt is relatively insensitive to concomitant hemodynamic changes, the absence of a significant change in T suggests the absence of any significant myocardial relaxation changes in response to either nitroglycerin or amyl nitrite.

Effects of Nitroglycerin and Amyl Nitrite on Left Ventricular Volume

Prominent and statistically significant reductions in both average end-diastolic and end-systolic volume indices occurred after nitroglycerin administration. After amyl nitrite, the average end-systolic volume index declined significantly also, but in contrast to the results obtained after nitroglycerin, no significant alteration in average end-diastolic volume index was observed (tables 1 and 2).

Comparison Between Average Changes in Hemodynamics and Left Ventricular Volumes after Nitroglycerin and Amyl Nitrite

Statistical analysis (t test for difference between group means) showed no significant difference between average changes in systemic arterial pressures, left ventricular systolic pressure, RR interval, peak negative dP/dt, ejection fraction, mean circumferential fiber shortening rate, left ventricular systolic and end-diastolic volumes, or T, between the patients receiving nitroglycerin and amyl nitrite, respectively. Thus, the observed changes in diastolic pressure-volume relationships do not appear to be attributable to differences in the magnitude of hemodynamic or left ventricular volume alterations between the two patient groups.

Effects of Nitroglycerin and Amyl Nitrite on Left Ventricular Pressure-Volume Relations

We analyzed left ventricular pressure-volume relationships during the period of diastole between minimal diastolic and peak a wave pressures. The configuration of the pressure-volume relationships conformed generally to a first order exponential function with an average coefficient of determination of 0.94. Comparison of the exponential fits to the pressure-volume functions before and after nitroglycerin (left), and before and after amyl nitrite (right) in two representative patients is shown in figure 2. The left panel shows prominent downward and leftward displacement of the pressure-volume function after nitroglycerin. Substantial reduction of pressure throughout a range of volumes common to both pre- and post-nitroglycerin functions, reflects an absolute change in overall diastolic ventricular pressure-volume characteristics.

Diastolic pressure-volume functions were compared quantitatively and qualitatively only with respective control values in each patient (paired t test). Pressure-volume functions were not normalized for individual patients, in view of the unresolved question of the most appropriate normalization factors for individual cardiac characteristics. Thus, we observed substantial quantitative and qualitative differences between pressure-volume curves in individual patients. We did not find a statistically significant difference in the control values for the extrapolated pressure intercept at zero volume between the two groups of patients.

The downward displacement of the pressure-volume relationship after nitroglycerin was confirmed in all cases by a statistically significant decline in the value of the extrapolated intercept of the pressure-volume function on the pressure axis at zero volume (paired t test), regardless of the initial level of left or right ventricular diastolic pressure (table 3). In contrast, downward displacement of the pressure-volume function was not observed in any patient after amyl nitrite (fig. 2, right panel), though a slight leftward shift without downward displacement occurred in one patient in whom significant reduction of left ventricular end-diastolic volume occurred. In confirmation of this observation, no statistically significant alteration occurred in the value of the extrapolated pressure intercept of the pressure-volume function at zero volume after amyl nitrite (table 3).

In the six patients studied as controls without drug administration, diastolic pressure-volume curves obtained during serial ventriculograms were virtually superimposable, excluding any direct effect of radiographic contrast medium alone on left ventricular pressure-volume relationships in this study.

In all patients, including those receiving nitroglycerin and those receiving amyl nitrite, no statistically significant change occurred in the rate constant of the exponential fit to the observed pressure-volume data before and after the drug intervention, suggesting, within the limitations of the simple exponential model used, no significant change in intrinsic chamber distensile properties of the left ventricle which contribute to the pressure-volume relationship.

Discussion

Our study confirms previous observations of prominent downward displacement of left ventricular diastolic pressure-volume functions after administra-
tion of nitroglycerin in patients with significant coronary artery disease. Such shifts suggest the existence of a family of pressure-volume curves, the "position" of which depends on the immediate loading conditions. In view of the disparate results obtained after nitroglycerin compared with those after amyl nitrite, these observations suggest that a major factor accounting for such shifts in the left ventricular pressure-volume relation is an alteration in left ventricular diastolic behavior effected by a change in right ventricular diastolic filling patterns.

In order to confirm the observed displacement statistically, pressure-volume curves were fitted to a first order exponential function with a satisfactory mean coefficient of determination \(r = 0.94\). The exponentially fit pressure-volume function was extrapolated to the pressure axis at zero volume, since actual measurement of the pressure intercept of the pressure-volume function is impossible in the clinical setting. Though the experimentally verified exponential nature of the length-tension curve in isolated cardiac muscle supports the fitting of diastolic pressure-volume relations to an exponential function in the intact dog heart, application of exponential analysis to the clinical situation has not been validated. Simple exponential expressions cannot be used to quantitate myocardial stiffness in absolute terms, or as a basis for comparison between patients because of the difficulty of normalization for individual cardiac dimensions, however they may provide a useful and quantifiable description of diastolic pressure-volume relations in the intact ventricle in individual patients.

Although the limitations of single plane left ventricular cineangiography, particularly in patients with coronary artery disease and asynergic contraction patterns, are well-known, erroneous estimations of ventricular geometry and dimensions incurred by failure of the single plane view to demonstrate asynergic segments appear most likely to influence parameters of systolic performance; there is little evidence that estimation of diastolic function may be subject to such artifact. Furthermore, although mild asynergy was present in five patients in our study, patients with moderate or severe asynergy were excluded, and we did not observe segmental early

![Figure 2](image-url)

**Figure 2.** Left ventricular pressure-volume functions before (PRE NG) and after (POST NG) nitroglycerin (left), and before (PRE AN) and after (POST AN) amyl nitrite (right), in two representative patients. Significant downward and leftward displacement of the pressure-volume function after nitroglycerin is illustrated. In contrast, diastolic pressure-volume curves before and after amyl nitrite were virtually superimposable.

| Table 3. Changes in Rate Constant (k) of the Exponential Fit Left Ventricular Diastolic Pressure-Volume Function, and Extrapolated Pressure Intercept at Zero Volume, Before and After Nitroglycerin and Amyl Nitrite |
|-------------------------------------------------|-----------------|-----------------|------|
| Nitroglycerin | Pre NG | Post NG | p† |
| Rate constant "k" (mm Hg/ml) | 0.0099 ± 0.002* | 0.0110 ± 0.003 | NS |
| Pressure intercept (mm Hg) | 4.62 ± 1.4 | 2.40 ± 0.8 | <0.025 |
| Amyl nitrite | Pre AN | Post AN | |
| Rate constant "k" (mm Hg/ml) | 0.0156 ± 0.006 | 0.0145 ± 0.008 | NS |
| Pressure intercept (mm Hg) | 4.47 ± 1.4 | 4.36 ± 1.4 | NS |

*Mean ± SEM.
†Significance (paired t test).
Abbreviations: NG = nitroglycerin; AN = amyl nitrite.
diastolic relaxation. Accordingly, single plane RAO ventriculography provided adequate estimation of changes in ventricular volume in our study, as in several comparable studies of ventricular diastolic function.1, 3, 4, 10, 21, 22, 27, 30

Although downward displacement of the left ventricular diastolic pressure-volume function occurs after administration of nitroprusside4, 7 and nitroglycerin,1, 9 and upward displacement after angiotensin,8 methoxamine,1 β-blocking agents,5 and during pacing-induced angina,6 the mechanisms underlying such shifts are not known. A variety of both intracardiac and extracardiac factors are responsible for determination of left ventricular diastolic properties, including 1) completeness of early diastolic relaxation, 2) passive elastic properties of the myocardium and ventricular chamber, 3) plastic and viscous myocardial characteristics, and 4) extracardiac constraints to ventricular distension by the pericardium, pleural pressure, right ventricle, and coronary vascular perfusion pressure.4, 6 Alterations in any one or all of these factors may play a role in the displacements of the left ventricular diastolic pressure-volume relation.

In view of the evidence that impairment of left ventricular relaxation may modify ventricular diastolic behavior under certain pathological conditions,31, 32 Brodie et al. suggested that improved relaxation may contribute to the downward displacement of the diastolic pressure-volume function observed after administration of nitroprusside.4 Direct relaxant effects of nitroprusside on cardiac muscle, relief of ischemia by favorably influencing the myocardial oxygen supply/demand ratio associated with pre- and afterload reduction, and endogenous catecholamine release were cited as mechanisms for such a change in relaxation.4

In the present study, although peak negative dP/dt was significantly reduced in all patients after nitroglycerin and amyl nitrite, T was not significantly changed. Unlike peak negative dP/dt, which has been shown to be sensitive to concomitant changes in peak systolic pressure and end-systolic volume,23 T has been proposed as an index of the activity of the active myocardial relaxing system relatively insensitive to changes in the hemodynamic factors which may be influenced by nitroglycerin. Thus, the absence of a significant change in T suggests the absence of any significant change in intrinsic relaxation of the ventricular myocardium or chamber in response to nitroglycerin or amyl nitrite.

Since intrapleural pressure is an important determinant of the net transmural pressure across the ventricular wall, changes in pleural pressure may influence ventricular pressure-volume relationships. Based on analysis of esophageal pressures, which correlate closely with pleural pressures,24 Alderman et al.3 have demonstrated that although pleural pressure varied markedly between patients, it remained relatively constant during a state of held inspiration in individual patients. Thus, acute changes in pleural pressures would not be expected to account for the displacement of ventricular pressure-volume curves in specific individuals under the standardized respiratory conditions used in our study.

The role of restriction to expansion of the left ventricle by the pericardium has been considered a cause of alterations in left ventricular pressure-volume relationships.3 Interventions tending to expand ventricular volume may result in ventricular pressures in excess of those predicted from the basal ventricular pressure-volume relationship due to pressure of the ventricular wall against the relatively unyielding pericardium. Conversely, in the setting of an initially distended left ventricle, interventions reducing ventricular dimensions might produce a greater reduction of ventricular pressure than that predicted from the intrinsic left ventricular pressure-volume relationship. In fact, it has been demonstrated that the canine pericardium elevates left ventricular pressure and reduces volume over a range of physiologic pressures24 and appears to support or gently compress the heart depending on the level of left ventricular end-diastolic pressure and systemic venous pressure. Restriction to left ventricular filling by the pericardium, however, is unlikely to play a significant role in the displacement of the pressure-volume curves in our study, since in no patient was initial left ventricular end-diastolic volume index or right ventricular pressure substantially elevated.

While simple expressions involving pressure-volume relationships may provide some quantification of ventricular "stiffness" in individual patients, Mirsky27 emphasized the value of indices of myocardial stiffness based on stress-strain analysis, which permits more valid comparison between hearts of different shapes and sizes. Glantz et al. have derived an equation for myocardial elasticity, validated in the dog model, which defines the ventricular pressure-volume relationship in terms of ventricular volume, wall thickness, and the myocardial exponential stress-strain curve, and have shown that such indices of myocardial stiffness based on pressure-volume relationships in the canine model are essentially similar to those derived using stress-strain relationships in isolated muscle preparations obtained from the same heart.25 Although in a subsequent clinical study, Alderman et al.3 demonstrated that this equation describes the observed diastolic pressure-volume data more closely than the empirical exponential model, use of either expression suggested that observed shifts in the diastolic pressure-volume curve could not be attributed to acute changes in the passive elasticity of the myocardial or intrinsic ventricular pressure-volume relations. These findings agree with our study.

Left ventricular pressure-volume relationships may also be altered by changes in systemic arterial pressure.5 Brodie et al.4 suggested changes in aortic pressure causing altered impingement of the aortic root upon the ventricular cavity as a mechanism of this effect. Salisbury et al. demonstrated an inverse relationship between coronary perfusion pressure and myocardial distensibility in the canine model, whereby
increasing coronary perfusion pressure resulted in an increase in left ventricular end-diastolic pressure at a constant volume, implying reduced myocardial distensibility, presumably due to an "erectile" effect of the coronary vascular tree.36 Similarly, an increase in ventricular wall mass, attributed to coronary vascular engorgement and an erectile effect on the myocardium, have been proposed as a mechanism for the upward displacement of ventricular pressure-volume function by methoxamine.5

Substantial experimental evidence suggests that right ventricular hemodynamics influence left ventricular pressure-volume relationships.97 Thus, directionally concomitant increases or decreases in left ventricular diastolic pressures have been observed in response to elevation or depression of right ventricular diastolic pressures in isolated canine heart preparations with intact pericardia and constant cardiac output and systemic arterial pressure.58, 59 In our study, comparable relationships between the changes in right and left ventricular pressures were observed, though the average reduction in left ventricular diastolic pressure was disproportionately greater than the decline in right ventricular pressure. These phenomena are compatible with the known structural and functional interrelationships of the two ventricular chambers such that changes in right ventricular volume and pressure may result in altered transmural stresses across the interventricular septum, thus modifying the left ventricular pressure-volume relationship.5, 27 Such stresses may be influenced by several factors, including the pressure gradient across the septum, initial levels of right and left ventricular diastolic pressure and distensibility, cardiac output, intrathoracic pressures, and characteristics of the septum itself — its thickness, configuration and propensity to displacement between the two ventricular chambers. Recent two-dimensional echo studies in man have demonstrated net displacement of the septum into the left ventricular cavity during acute right ventricular loading, implying a significant influence upon left ventricular configuration by changes in right ventricular loading.40 In view of the various factors which may influence the interdependence of the two ventricles, a disproportionate relationship between changes in right ventricular diastolic pressure, and the resulting alteration of left ventricular end-diastolic pressure, is not unexpected. In addition, changes in left ventricular compliance in dogs with chronic right ventricular pressure and volume overload are reversible when the hypertrophied right ventricle is filled to a normal end-diastolic pressure, suggesting that the observed changes in left ventricular distensibility are not attributable to alterations in intrinsic myocardial elastic properties,41 confirming the role of right ventricular loading upon left ventricular pressure-volume relations.

Since nitroglycerin reduces both systemic arterial pressure and right heart pressures,42 it is difficult to establish which response is primarily responsible for the shift of pressure-volume functions induced by the drug. Nitrates relax vascular smooth muscle in larger arteries and the arteriolar bed ("resistance vessels"). The ratio of precapillary to postcapillary resistance is unaltered after nitrate administration, suggesting equivalent effects on arterioles and venules.43 However, the dominant cardiovascular effect of nitroglycerin is on the venous bed ("capacitance vessels").44 By comparison, the effects of amyl nitrite on the capacitance vessels are controversial;42 both decreased44 and increased44 venous tone have been reported in man. In conscious dogs, nitroglycerin and amyl nitrite both affect resistance and capacitance vessels.42 These disparate results may be explained by the dual effects of the nitrates upon venous tone: 1) a direct venodilator effect, and 2) a compensatory reflex venoconstrictor sympathetic response initiated by the baroreceptors.42, 44 Whether the direct vascular "relaxing" effects of nitroglycerin and amyl nitrite are similar, the observed net increase in venous tone after inhalation of amyl nitrite probably reflects the very rapid action of this drug and consequent reflex adrenergic compensatory adjustments to the sudden fall in blood pressure.42 In contrast, venous tone and venous return are consistently diminished by nitroglycerin. The reflex-mediated increase in venous return after amyl nitrite, in contrast to the "peripheral venous pooling" effect of nitroglycerin, was used in our study to differentiate effects on the left ventricular diastolic pressure-volume relationship of decreased coronary perfusion pressure and flow, which generally parallels falls in systemic arterial pressure,46 and decreased right ventricular pressure. Reduction of both systemic arterial and thus coronary perfusion pressures, and right ventricular pressure in response to nitroglycerin, resulted in downward displacement of the pressure-volume function. However, reduction of systemic arterial and thus coronary perfusion pressures without a simultaneous reduction of right ventricular pressures resulted in no such downward displacement. These results support the observation of Templeton et al.47 who, using a sinusoidal forcing function in canine hearts, found no change in left ventricular pressure-volume relations expressed in terms of the intrinsic viscoelastic properties of the left ventricle upon alteration of coronary perfusion pressure and flow. The observed downward displacement of the pressure-volume function in the present study was not accompanied by a significant change in T or the rate constant of the exponentially fitted diastolic pressure-volume function, implying no significant change in the rate of diastolic isovolumic left ventricular relaxation, or in individual diastolic left ventricular chamber distensible characteristics.

Several factors influence the left ventricular diastolic pressure-volume function including cardiac geometry, passive mechanical properties of the myocardium, incomplete relaxation, engorgement of the coronary circulation, interaction between the two ventricles48 and pericardial constraints. Functional interrelationships between these factors are complex and incompletely understood; nevertheless, in this study,
downward displacement of the diastolic pressure-volume curve in response to nitroglycerin appears to be due primarily to changes in the constraint to left ventricular distension produced by the right ventricle as imposed by its filling hemodynamics and systemic venous return, rather than to changes in coronary perfusion pressures, intrinsic chamber distensible properties, or rate of diastolic isovolumic relaxation. These results indicate that the function of the impaired left ventricle may be influenced more favorably by combined reduction of both ventricular filling pressures (reflecting “preload”) and systemic vascular impedance (reflecting “afterload”), than by reduction of systemic impedance alone, in view of the downward displacement of the left ventricular pressure-volume function, and the resultant more favorable diminution of myocardial oxygen consumption associated with the reduced ventricular pressure and volume accompanying preload reduction.

Acknowledgments

The authors express appreciation to Burton E. Sobel, M.D., for helpful review of the manuscript, and to Michele Bowman, for her assistance in the preparation of this manuscript.

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Circulation. 1979;59:21-31
doi: 10.1161/01.CIR.59.1.21

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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