Minimum Left Ventricular Pressure During β-Adrenergic Stimulation in Human Subjects

Evidence for Elastic Recoil and Diastolic “Suction” in the Normal Heart

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The influence of elastic recoil and restoring forces on diastolic left ventricular pressure decay and minimum left ventricular pressures has been demonstrated in animal models but has not been studied in the human heart. To investigate this issue in the normal human left ventricle, we studied eight patients with chest pain and normal coronary arteries with simultaneous measurement of left ventricular volume (by radionuclide angiography) and pressure (by micromanometer catheter) and coronary sinus blood flow. Electrocardiographic-gated data were obtained in the basal state, during rapid atrial pacing, and during isoproterenol infusion to a similar heart rate. Compared with pacing, isoproterenol increased ejection fraction and reduced end-systolic volume ($p<0.005$), end-systolic pressure ($p<0.005$), and the half-time of pressure decline after peak negative dP/dt (T½) ($p<0.001$). Negative diastolic pressure developed in seven of eight patients during isoproterenol (range, −0.5 to −2.4 mm Hg) but in only one of eight during pacing (−0.2 mm Hg). These reduced diastolic pressures during isoproterenol were accompanied by increased stroke volume (reflecting increased transmitral flow) and diminished pulmonary wedge pressure (reflecting left atrial pressure). The magnitude of reduction in minimum diastolic pressure during pacing and isoproterenol was related to the change in end-systolic volume ($r=0.79$, $p<0.001$), ejection fraction ($r=-0.74$, $p<0.001$), T½ ($r=0.57$, $p<0.02$), and coronary sinus flow ($r=0.73$, $p<0.005$). Stronger correlations were observed in analyzing changes during isoproterenol alone. From similar end-systolic volumes, T½ and the time constant tau were lower (both $p<0.005$), as was minimum diastolic pressure ($p<0.05$) during isoproterenol compared with pacing. Hence, isoproterenol infusion (simulating the catecholamine stimulation during exercise) significantly reduces minimum diastolic pressure in the normal human heart, resulting in the development of negative left ventricular pressures. The reduction in minimum left ventricular pressure is related to changes in left ventricular systolic volume, contractility, and coronary flow, and to the dynamics of isovolumic relaxation. This reduction in early diastolic pressure augments the left atrial–left ventricular pressure gradient during early diastole, enhancing the rate and magnitude of left ventricular filling required to maintain a high cardiac output at elevated heart rates. (Circulation 1990;82:1174–1182)

It is generally accepted that left ventricular relaxation is an active, energy-requiring process, but some controversy exists as to whether the left ventricle is capable of generating a “suction” pressure, thus filling itself or aiding filling when faced with low pressure from the atrium. Several experimental studies have documented the existence of negative left ventricular pressures during diastole. Common to these studies were features such as small end-systolic volumes, low afterload, and mitral orifice occlusion to prevent filling. It has been postulated that the ventricle in this milieu may contract below its “equilibrium volume,”4–7–9 thus calling into play internal restoring forces and elastic recoil that would enhance relaxation of the ventricle, resulting in lower early diastolic pressures.

In humans, negative left ventricular pressures have been recorded when certain elements of the above-noted conditions have been present, such as in patients with mitral stenosis10 or ventricular septal...
Cardiac output and pulmonary capillary wedge pressure were measured with a balloon-tipped thermodilution catheter lying in the pulmonary artery. Arterial and left ventricular pressures and electrocardiographic monitor leads I, aVF, and V_2 were recorded with each flow measurement in the great cardiac vein.

A pigtail catheter (Mikro-Tip, model SPC-780C, Millar Instruments Inc., Houston) with pressure transducers adjacent to and 10 cm proximal to the catheter tip was used to measure left ventricular and aortic pressures. Both transducers were calibrated in normal saline at room temperature (approximately 23° C) before insertion into the arterial system via a femoral artery sheath. The catheter tip was advanced to the apex of the left ventricle. To measure drift of the transducer signal over the time course of the study, systolic and diastolic pressures obtained via the transducers were compared with pressures obtained via the fluid-filled catheter lumen and were recorded at periodic intervals throughout the study in seven patients. Recorded pressures at the time of left ventricular end-diastolic pressure were compared. In six patients, there was either no drift or upward drift of the Millar catheter compared with the fluid-filled catheter (maximum, 2 mm Hg), and in one patient, there was downward drift through the course of the study, with the Millar catheter recording 1 mm Hg below the fluid-filled catheter late in the study.

Atrial Pacing Study

Before the pacing study, all patients underwent diagnostic right and left heart catheterization. Coronary angiography with multiple angulated views then was performed; all patients had normal coronary arteries, as was required for entry into the study. Left ventriculography was performed in four patients; the other four patients had undergone left ventriculography during a previous catheterization, and the procedure was not repeated. All eight patients had normal left ventriculograms.

The study protocol was initiated at least 20 minutes after use of angiographic contrast material so that any effects of the dye on coronary blood flow and metabolism would subside. Great cardiac vein flow was determined at rest, as were measurements of cardiac output, mean pulmonary capillary wedge pressure, and left ventricular peak systolic and end-diastolic pressures. Pacing via the coronary sinus thermodilution catheter was initiated at a heart rate of 100 beats/min and maintained for 3 minutes, followed by pacing at 130 beats/min for 3 minutes. Supraventricular pacing was confirmed in each case by a narrow QRS complex that was unchanged from baseline conditions. Hemodynamic measurements and measurements of coronary flow were repeated at each paced heart rate. Mean pulmonary capillary wedge pressures were recorded during the immediate postpacing beats.
Isoproterenol Study

After a 10-minute pause to allow baseline conditions to be reestablished, isoproterenol was infused at a rate of 1 μg/min and then increased as needed by increments of 1 μg/min at 1-minute intervals to achieve a heart rate of 100 beats/min, which was maintained for 3 minutes. The infusion then was increased to achieve a heart rate of 130 beats/min for 3 minutes. Hemodynamic measurements and measurements of coronary flow were obtained.

Radionuclide Studies

During placement of the right heart catheter, red blood cells were labeled in vivo with 15–25 mCi of technetium-99m.16 Ten minutes after the administration of 99mTc, the patient underwent anticoagulation with heparin (5,000 units, i.v.), and retrograde left heart catheterization was begun. After equilibration of the blood pool tracer and after placement of the catheters in the pulmonary artery and left ventricle, a portable gamma camera equipped with a high-sensitivity parallel-hole collimator was positioned over the left thorax in a modified left anterior oblique position for optimal separation of the left from the right ventricle. Electrocardiographic (ECG)-gated scintillation data were collected to a preset count limit of 10 million counts for the baseline study, and to a preset time comprising the middle 2 minutes of each 3-minute intervention (pacing or isoproterenol). Thus, the baseline study comprised at least 500 cardiac cycles, and the intervention studies at least 250 cardiac cycles. The scintigraphic data were acquired in LIST mode, with exclusion of extrasystolic and postextrasystolic cycles. High temporal resolution (20 msec/frame) left ventricular time activity curves were generated from the cardiac image sequence after background correction, using a fixed left ventricular region of interest that was manually constructed with end-diastolic, end-systolic, and stroke volume functional images.17,18 The time activity curve represents a measure of relative left ventricular volume change with time. End-diastolic counts, end-systolic counts, stroke counts, and ejection fraction were computed for each study after correction for physical decay of the isotope and differences in acquisition time. Changes in end-diastolic, end-systolic, and stroke counts for each intervention were expressed as a percent of control counts to indicate relative changes in left ventricular volumes18,19 in order to compare directional changes in each patient relative to the control values. Baseline thermodilution cardiac output and stroke volume were used to calculate absolute volumes from the radionuclide data for interpatient comparisons.

Left Ventricular Pressure-Volume Analysis

Analysis of the instantaneous left ventricular pressure-volume relation throughout the entire cardiac cycle was performed in all patients. The left ventricular pressure data were obtained via the transducer-tipped catheter simultaneously with the radionuclide data acquisition.18,19 The left ventricular pressure data were collected with LIST mode ECG gating, with subsequent exclusion of extrasystolic and postextrasystolic cycles, such that the average left ventricular pressure-time curve was constructed from the same cardiac cycles used to create the radionuclide angiographic time-activity curve. The pressure data were obtained at an acquisition rate of 250 per second (4 msec/point) and then were condensed to 20 msec/point to correspond to the radionuclide data. The resulting pressure curve and the left ventricular time-activity curve data were combined automatically to create loops representing high temporal resolution (20 msec) instantaneous relations between left ventricular pressure and volume throughout an average cardiac cycle (Figure 1).

Left Ventricular Pressure Analysis

Minimum diastolic pressure was read directly from the digitized pressure record. End-systolic pressure was determined at the time of the aortic dicrotic notch. For analysis of left ventricular isovolumic relaxation, the high temporal resolution left ventricular pressure data (4 msec/point) were analyzed. A value, T1/2, was computed for each acquisition as the time required for the pressure at the time of peak negative dP/dt to decline to one half of its value.20 In addition, the time constant tau (T) was computed using an assumption of monoexponential pressure decay with a nonzero asymptote,21 with data fit over the first 60 msec after peak –dP/dt. Curve fitting for only the first 60 msec after peak –dP/dt was performed because fitting for longer periods at higher heart rates would extend the fitted curve beyond mitral valve opening, after which time pressure fall would no longer be isovolumic.

Statistical Analysis

Differences between interventions were analyzed by a repeated measures analysis of variance (SAS
Effects of Isoproterenol

Consistent with the positive chronotropic and inotropic effects of isoproterenol, heart rate increased significantly to 77±10% compared to baseline values (P<0.0001), and end-diastolic pressure decreased significantly to 57±6%, and both end-diastolic and end-systolic pressures were further decreased by intravenous isoproterenol (Table 2). Generalized volume decreases left ventricular pressure-volume relations shifted to the left, indicating a change in the diastolic distensibility of the heart (Figure 1).

### Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Heart rate (beats/min)</th>
<th>Peak systolic LV pressure (mm Hg)</th>
<th>End-systolic LV pressure (mm Hg)</th>
<th>Minimum diastolic LV pressure (mm Hg)</th>
<th>T½ (msec)</th>
<th>T (msec)</th>
<th>Cardiac index (/min/m²)</th>
<th>Stroke index (ml/m²)</th>
<th>Coronary flow (ml/min)</th>
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<td>13 18 4</td>
<td>0.8 0.5 1.2</td>
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</tbody>
</table>

LV, left ventricular; T½, time required for pressure at peak negative dP/dt to fall to one half its value; T, time constant; B, baseline; P, atrial pacing; I, isoproterenol.
negative pressure during pacing (p<0.005 by Fisher's exact test), to a value less negative than any of the negative pressures recorded during isoproterenol.

Analysis of the left ventricular diastolic pressure-volume relations demonstrated a downward and leftward shift in all patients compared with the baseline and pacing curves (Figures 1 and 2). In addition, the contour of the curve in all patients during isoproterenol demonstrated a more complete decline of pressure before the onset of left ventricular rapid diastolic filling compared with that during pacing (Figures 1 and 2), indicating enhanced left ventricular relaxation before the onset of filling.22,23

The changes in the hemodynamic and radionuclide variables from baseline to both the pacing and isoproterenol interventions were examined to determine their relation to the respective changes in minimum diastolic pressure. The changes in end-systolic volume (r=0.79, p<0.001), ejection fraction (r=−0.74, p<0.001), T½ (r=0.57, p<0.02), and coronary sinus flow (r=0.73, p<0.005) correlated significantly to the magnitude of reduction in minimum diastolic pressure (Figure 3). When the changes in these variables were examined from baseline to isoproterenol alone, the reduction in minimum diastolic pressure correlated with the change in end-systolic volume (r=0.86, p<0.006), ejection fraction (r=−0.92, p<0.002), and T½ (r=0.90, p<0.002).

For each patient demonstrating negative early diastolic ventricular pressure, an equilibrium volume (V₀) was estimated as the intersection of the diastolic pressure-volume relation with the volume axis (i.e., the volume at which pressure is zero). The difference between the estimated equilibrium volume and observed end-systolic volume for each condition (baseline, pacing, and isoproterenol), V₀−ESV, correlated with the minimum diastolic pressures observed (r=−0.67, p<0.001) (Figure 4). These data suggest that restoring forces and elastic recoil resulted from contraction below this estimated equilibrium volume and that enhanced magnitude of such forces results in lower early diastolic pressure.
The correlation between changes in variables of systolic performance and changes in T½ from baseline to both the pacing and isoproterenol interventions also were analyzed (Figure 5). The magnitude of change in T½ was directly related to changes in end-systolic volume (r=0.75, p<0.001) and inversely to ejection fraction (r=-0.93, p<0.0001). These findings indicate that relative and absolute changes in systolic volume profoundly influence the rate of left ventricular relaxation, as reflected by T½. In contrast, the changes in T did not strongly correlate with the magnitude of reduction in minimum diastolic pressure or with changes in end-systolic volume or ejection fraction.

Previous studies have demonstrated the importance of end-systolic volume as a determinant of the rate and extent of pressure decay, mediated through the mechanism of elastic recoil.4,6 It also has been suggested that inotropic stimulation may directly enhance relaxation by augmenting the state of inactivation at a given end-systolic volume. To investigate whether β-stimulation may influence the rate of pressure decay and the minimum diastolic pressure independent of changes in end-systolic volume, patients who achieved the most marked reduction in end-systolic volume indexes during either isoproterenol or pacing were analyzed separately. For this analysis, we selected the seven patients during isoproterenol and the four during pacing whose end-systolic volume index was less than 30 ml/m² and compared the minimum diastolic pressures and time constants at similar end-systolic volumes. During isoproterenol, compared with pacing, end-systolic volume was similar by design (13±7 versus 17±1 ml/m², p=NS), but minimum diastolic pressure was lower (-1.2±1.7 versus 1.1±1.1 mm Hg, p<0.05), as were T½ (24±2 versus 32±5 msec, p<0.005) and T (54±4 versus 77±15 msec, p<0.005). Thus, at a given reduction of end-systolic volume, isoproterenol appeared to enhance the rate and extent of left ventricular pressure decline beyond that achieved by a reduced end-systolic volume alone.

Discussion
The results of this study indicate that elastic recoil and restoring forces are operative in the intact human heart in the absence of significant cardiovascular disease and that these mechanisms result in reduced minimum diastolic pressure and the development of negative left ventricular pressures during β-adrenergic stimulation. The extent of contraction below an estimated equilibrium volume establishes the magnitude of these restoring forces and correlates with the extent of left ventricular pressure decay during early diastole. These data support and extend many previous observations made in both isolated and intact animal heart investigations of the rate and extent of ventricular pressure fall, especially during inotropic stimulation or during conditions associated with reduced end-systolic volume.1-6,24,25 In light of this body of work, Hori et al6 and Sonnenblick6 have suggested that left ventricular diastolic suction may make an important contribution to left ventricular filling during exercise, a condition in which tachycardia and relatively reduced diastolic filling time coexist with demands for augmented cardiac output.

The correlation between end-systolic volume and minimum diastolic pressure in our patients is similar to that observed by Hori et al6 in a canine model using mitral orifice occlusion to separate the effects of relaxation from those of filling. In addition, changes in T½ were closely correlated to changes in end-systolic volume and ejection fraction (Figure 5). These findings suggest that enhanced systolic contraction to a small end-systolic volume facilitated left ventricular relaxation and, hence, a reduction in early diastolic pressure.

**Figure 3.** Magnitude of reduction of minimum diastolic pressure (from baseline study to both pacing and isoproterenol studies) expressed as a function of changes in end-systolic volume (left panel) and ejection fraction (right panel).

**Figure 4.** Minimum diastolic pressure (for all conditions) as a function of difference between end-systolic volume (ESV) and estimated equilibrium volume (Vo).
diastolic ventricular pressure. These data support the concept that ventricular relaxation is an important determinant of the extent of diastolic pressure fall and are consistent with previous reports involving human subjects.26,27

These data also provide evidence in humans for an equilibrium volume—that is, an end-systolic volume below which internal restoring forces and elastic recoil7,9,24,28,29 will result in negative transmural pressures and diastolic suction. This has been studied by Tyberg et al4 and more recently by Nikolic et al7 in dogs. In the latter study, controlled mitral valve occlusion to allow complete relaxation from various end-systolic volumes permitted construction of the entire passive diastolic pressure-volume relation, from which an equilibrium volume could be demonstrated. Such methods were not practical in our patients. However, by examining the intersection of the zero-pressure axis with the pressure-volume axis during ventricular filling, equilibrium volume could be estimated in our patients (Figure 2). When these ventricles were operating below this estimated equilibrium volume, transmitral flow increased (as reflected by enhanced stroke volume), despite reduced left atrial pressure (as reflected by diminished pulmonary wedge pressure). This strongly suggests that diastolic ‘suction’ occurred; that is, elastic recoil arising from restoring forces generated by contraction below equilibrium volume played an important role in left ventricular filling. Indeed, the correlation between the extent of contraction below the estimated equilibrium volume (or lack thereof) and the resulting minimum diastolic pressure (Figure 4) further supports the concept that energy stored during such contraction may be released as elastic recoil and may contribute importantly to the extent of ventricular pressure fall.

In Figures 2 and 4, it is also apparent that the end-systolic volume during pacing is less than the estimated equilibrium volume, yet negative diastolic pressure did not develop. This suggests that reduced end-systolic volume may not be sufficient, in and of itself, to develop negative diastolic pressure in the intact filling heart. Previous studies have suggested an independent effect of β-adrenergic stimulation on the rate and extent of pressure decay,4,6 related to the action of catecholamines to increase calcium ion uptake by the calcium sequestering membranes of the sarcoplasmic reticulum.30 Thus, isoproterenol in our study may have potentiated the relaxation process directly by enhanced inactivation. This effect may have further sensitized the left ventricle to the prevailing loading conditions, resulting in an increased rate and extent of relaxation.8 This concept is supported by our data demonstrating lower values for both time constants and minimum diastolic pressure during isoproterenol compared with pacing in the subset of patients matched for similar reduction in end-systolic volume (and thus similar degree of restoring forces) during the interventions. Hence, this effect of β-stimulation, superimposed on the restoring forces arising from reduced end-systolic volume, would enhance the extent of pressure decay, in agreement with the conclusions of Hori et al6 developed in a dog model.

An additional mechanism for the effect of isoproterenol on pressure decay relates to the lower pulmonary wedge pressures recorded during isoproterenol allowing a more complete isovolumic pressure decline before the onset of filling. Recent data in the dog using controlled mitral valve occlusion have demonstrated that the onset of filling blunts the rate and extent of ventricular relaxation; therefore, the potential extent of pressure fall may have been blunted during atrial pacing compared with isoproterenol by the earlier onset of filling due to a higher atrial pressure.

The current data emphasize the contributions made by restoring forces and elastic recoil, the rate of isovolumic pressure decline, and the onset of filling to early diastolic ventricular pressure. The complex determinants of diastolic pressure also include other factors not accounted for in the present study, such as viscous effects, the rate of rapid early diastolic filling (related in turn to venous return and atrial properties), and external influences such as the right ventricle and pericardium. The absence of negative ventricular pressure during pacing or even at baseline does not necessarily imply the absence of restoring forces, but rather that other factors, such as the onset of filling earlier and at a higher atrial pressure, may have prevented the full extent of ventricular relaxation.7 In this regard, the lower atrial pressures we observed along with the effect of β-adrenergic
stimulation to enhance inactivation may have allowed the influence of elastic recoil and restoring forces to be more fully manifest.

Engorgement of the coronary bed has been postulated to represent an additional loading determinant of left ventricular relaxation, in which early diastolic flow enhances cross-bridge detachment. In this study, the magnitude of change in coronary flow correlated with the reduction in minimum diastolic pressure during both interventions. Although these data may provide support for the concept that coronary flow influences diastolic performance in the normal heart, the changes in coronary flow during pacing and isoproterenol, and hence the correlation between coronary flow and minimum diastolic pressure, could reflect merely the increased metabolic demands of the enhanced chronotropic and inotropic states.

Of the two measures used in this study to describe the time course of ventricular relaxation, T½ correlated better with both systolic shortening and the magnitude of change in minimum diastolic pressure than did T. This may be explained by the fact that the change in pressure with time was not strictly monoexponential after peak negative dP/dt.

Other aspects of our data acquisition and analysis and their influence on the results deserve comment. It is important to recognize that both the pressure and volume data represent the average of the ECG-gated data acquisition comprising more than 250 cardiac cycles such that phasic variations occurring over the course of a few cardiac cycles would not affect the results importantly. Hence, the minimum pressures we recorded (including those pressures less than zero) did not represent the minimum pressures recorded on only a few random cycles. In addition, because each pressure data point represents an average of the pressure data during many cardiac cycles, instantaneous pressures more negative (as well as more positive) must have occurred during the course of data collection. We did not account for the influence of pleural pressures during this investigation. However, previous data from an open- and closed-chest canine study indicate that negative ventricular pressures do not result merely from negative intrathoracic pressures, as negative ventricular pressure was recorded in that study with the chest open.

Enhanced elastic recoil during isoproterenol, contributing to a greater extent of left ventricular pressure decay and lower ventricular pressures during early diastole, has important implications for left ventricular filling. Because mitral valve flow is determined by the instantaneous left atrial–to–left ventricular pressure gradient, the ability of the left ventricle to generate a reduced early diastolic pressure would augment this gradient for any given level of atrial pressure, thus aiding filling in a situation calling for high cardiac output at very rapid heart rates and relatively diminished filling time. More generally, the effect of β-adrenergic stimulation is to enhance filling, even if negative pressures are not achieved, through the mechanism of enhanced relaxation, resulting in lower early diastolic ventricular pressure and hence the establishment of an augmented transmural gradient. Because the effects of β-adrenergic stimulation are similar in many ways to the effects of exercise, the capability of the ventricle to actively reduce early diastolic pressure may be a mechanism for enhanced ventricular filling and augmented stroke volume during exercise independent of changes that might occur in atrial function.

In summary, our data demonstrate that elastic recoil and restoring forces, resulting in negative diastolic left ventricular pressures and implying the potential for ventricular suction, may be generated by the normal human left ventricle during β-adrenergic stimulation. The magnitude of reduction in early diastolic pressure correlates significantly to changes in left ventricular systolic volume and coronary flow and to the dynamics of isovolumic relaxation and restoring forces. An augmented transmural pressure gradient, and hence improved rate and extent of left ventricular filling, would be expected to accompany the reduced ventricular early diastolic pressure, contributing to the maintenance of high cardiac output at elevated heart rates.

References

**KEY WORDS** • left ventricular function • β-adrenergic stimulation • diastolic performance • isoproterenol
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