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## Contribution of External Forces to Left Ventricular Diastolic Pressure

### Implications for the Clinical Use of the Starling Law

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■ *Objective:* To test whether a substantial proportion of measured resting left ventricular diastolic pressure stems from forces external to the left ventricle (such as right-heart filling) in normal and chronically diseased hearts.

■ *Design:* Nonrandomized study with single intervention.

■ *Setting:* University hospital.

■ *Patients:* 29 patients referred for cardiac catheterization who had normal left ventricles and ejection fractions ($n = 12$); chronic heart disease due to idiopathic dilated cardiomyopathy ($n = 6$); ischemic heart disease ($n = 6$); or left ventricular hypertrophy ($n = 5$).

■ *Intervention:* Acute reduction of external forces imposed on the left ventricle using balloon obstruction of inferior vena caval inflow to the right heart.

■ *Measurements:* Continuous catheter-derived left ventricular pressure-volume data before and after abrupt obstruction of inferior vena caval inflow. Diastolic pressures were measured at the same volume just before atrial systole before and after sudden decrease of external (right-heart and pericardial) forces. The resulting decline in pressure was a measure of the contribution of these external forces to resting left ventricular diastolic pressure.

■ *Results:* The decline in pressure when external forces were released averaged $-19\% \pm 13\%$ with minimal change in left ventricular end-diastolic volume ($-3.66\% \pm 6.7\%$) and cardiac output ($-5\% \pm 8\%$). In all patients combined, the decline in pressure when external forces ($\Delta P_d$) were released correlated with resting left ventricular diastolic pressure ($LVP_d$) given by: $\Delta P_d = 0.38 \times (LVP_d - 6)$ [$r = 0.86$, $P < 0.0001$]. This indicates that when resting diastolic pressure was more than 6 mm Hg, almost 38% of the pressure was due to external factors. This percentage was similar among all subgroups. Furthermore, the left ventricular diastolic pressure could be reduced by this percentage with only minimal compromise to ventricular filling and cardiac output.

■ *Conclusions:* A substantial proportion of measured resting left ventricular diastolic pressure stems from forces extrinsic to the left ventricle rather than from diastolic stiffness in the left ventricle itself. This markedly influences the dependence of cardiac output on filling pressure and has important implications for clinical application of the Starling law.

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The Starling "law of the heart" states that the more the left ventricle fills with blood, the more volume it ejects. This dependence of cardiac output on filling volume was first recognized nearly a century ago (1) and remains at the core of the clinical evaluation and treatment of cardiac disorders. To apply this concept to the individual patient, the clinician must assess left ventricular filling, which is most often estimated using the pressure within the ventricle or the pulmonary capillary wedge pressure. However, these pressures do not solely reflect the blood volume within the left ventricle but are also influenced by extraventricular forces arising from the filling of the right heart and the constraining effects of the pericardium (2–8). Altering these external forces can change left ventricular diastolic pressures, even when left-heart filling volume and, thus, cardiac output are unchanged (9–12).

Previous clinical and animal studies have established that altering extraventricular forces can change left ventricular diastolic pressures (9–12). However, the quantitative importance of external contributions to the resting ventricular diastolic pressure remains controversial. In normal hearts, extraventricular forces are thought to have a small effect (13); in chronically dilated hearts, the influence of these forces is thought to be reduced by simultaneous pericardial enlargement (14, 15). Previous clinical studies probing external forces have been limited by the use of pharmacologic manipulations to alter these forces: These manipulations typically also lower left-heart volumes and arterial pressures, thereby complicating any interpretation of results (8–12, 16). An alternative is to use mechanical interventions that suddenly lower external forces before they change left ventricular filling. For example, Slinker and colleagues (17) inhibited filling of the right heart within a single beat to evaluate ventricular interaction in normal animals. This is not feasible in humans, but an alternative method that can achieve similar effects is rapid obstruction of inferior vena caval inflow using a balloon catheter (18–20). In the first few

 

beats after balloon inflation, right atrial pressures often decrease almost to zero, although blood inflow to the left heart does not immediately diminish. This results in a sudden decrease in left ventricular diastolic pressures with minimal change in filling volumes (20). As obstruction of venous inflow is sustained, filling of the left ventricle eventually decreases. The initial decrease in diastolic pressure, however, principally reflects the withdrawal of extraventricular forces.

We used this maneuver to test the hypothesis that a considerable proportion of resting diastolic filling pressure stems from factors extrinsic to the left heart. We also tested whether this proportion would be diminished by chronic cardiac disease that would be expected to dilate the pericardium. Our results show that 30% to 40% of measured diastolic pressures result from forces external to the left ventricle and that this percentage is only slightly changed by cardiac disease.

## Methods

### Patients

We studied 29 patients. Twelve had normal ventricular function confirmed by echocardiography, ventriculography, or both; an ejection fraction of at least 60%; and end-diastolic pressure of 20 mm Hg or less. All patients had been referred for diagnostic cardiac catheterization to evaluate atypical chest pain. Six patients had chronic idiopathic dilated cardiomyopathy with exertional dyspnea; ejection fraction of 40% or less; chamber dilation (short-axis diastolic dimension ≥6 cm); and a normal coronary angiogram. Five patients presented with dyspnea, pulmonary congestion, or both but had histories of hypertension and ventricular hypertrophy. Lastly, six patients had high-grade proximal coronary stenoses and recent histories of unstable or accelerated angina pectoris. No patients had had a myocardial infarction. The studies were done at the Johns Hopkins Medical Institutions, Baltimore, Maryland ($n$ =19); Veterans General Hospital, Taipei, Taiwan ($n$ = 5); and the Instituto di Coração, São Paolo, Brazil ($n$ = 5). All patients provided informed consent, and the study protocol was approved by the human investigation committee of each institution.

### Procedure

The method used to measure left ventricular pressure and volume with an intracardiac conductance catheter has been previously reported (18–20). Each patient first had standard right- and left-heart catheterization. A multielectrode conductance (volume) catheter was then advanced to the left ventricular apex. A low-amplitude, high-frequency current was applied to electrodes located at the left ventricular base and apex, and resistances were measured at multiple intervening electrodes. This yielded a time-varying signal proportional to intracavitary chamber volume. A micromanometer (PC-330A, Millar, Inc., Houston, Texas) placed within the lumen of the catheter provided a simultaneous high-fidelity measurement of ventricular pressure. A custom-designed, large-balloon occlusion catheter (SP-09168, Cordis, Miami, Florida) was placed in the right atrium. Balloon inflation using 10 to 20 mL carbon dioxide and withdrawal of the catheter toward the proximal inferior vena cava produced rapid reversible decrease of cardiac filling. Pressure-volume data were measured continuously at steady state and immediately after the onset and continuation of inferior vena caval balloon occlusion. Occlusion was sustained for 10 to 15 seconds and then released.

The conductance catheter volume signal was calibrated to the contrast left ventriculogram (single plane, right anterior oblique projection) by matching end-diastolic and end-systolic volumes. Ventriculogram volumes were estimated from the frames of maximal and minimal area, respectively. The corresponding catheter signal volumes were obtained as the averaged volumes during phases of isovolumetric contraction and relaxation.

### Data Analysis

Left ventricular pressure-volume data from five consecutive end-expiratory cardiac cycles were averaged to yield a single pressure–volume loop (plot of instantaneous left ventricular volume on x-axis compared with simultaneous left ventricular pressure on y-axis). From these data, the stable resting diastolic pressure–volume curve (20), end-diastolic and end-systolic volumes, stroke volume and cardiac output, and ejection fraction were measured (19, 20). The isovolumetric relaxation time constant, which indexes the rate of ventricular pressure decay, was also derived from these data (21).

Figure 1 shows an example of the left ventricular pressure-volume data used to assess the relative contributions of the intrinsic (due to properties of the left ventricle itself) and extrinsic components of resting left ventricular diastolic pressure. Figure 1A shows resting pressure–volume loops. During each cardiac cycle, data moved counterclockwise around the loop. Shortly after the obstruction of inferior vena caval inflow, left ventricular diastolic pressures decreased with little change in chamber volumes (Figure 1B). This downward shift of the diastolic pressure–volume relation primarily reflects the sudden decrease in external forces mediated by the extent of right ventricular filling. Continued obstruction of inferior vena caval inflow eventually decreased left ventricular volumes, shifting the pressure–volume loops leftward beat by beat (Figure 1C) and reducing systolic pressures and stroke volume (height and width of loops). This response is the manifestation of the Starling law. Note that after the initial near-parallel decrease of the left ventricular diastolic pressure–volume relation, the remaining diastolic data of subsequent beats occurred along a more or less single curve (Figure 1C). This relation was called the diastolic pressure–volume relation and reflects the intrinsic diastolic properties of the left ventricle.

The initial downward shift of diastolic pressure-volume data was taken as a measure of the contribution of external forces to resting diastolic pressure (Figure 1D). This downward shift was measured as the difference in pressure between initial resting beats and the diastolic pressure–volume relation at a common volume just before atrial contraction. At this point, relaxation of the left ventricle was more than 99% complete as judged by the isovolumetric relaxation time constant, and rapid filling and atrial contraction had minimal influence on diastolic pressures.

### Statistical Analysis

Data are presented as means ± SD. Hemodynamic comparisons between patients with diseased and normal hearts were done using a multiple-comparisons analysis of variance. Data obtained before and after occlusion of the inferior vena cava were compared using a paired Student $t$-test.

## Results

### Clinical and Hemodynamic Characteristics of Patients

Table 1 shows the clinical and major hemodynamic characteristics of the four groups of patients. Mean age was similar among all groups. Left ventricular end-diastolic pressure was significantly higher in each of the groups with disease than in the controls and averaged almost 20 mm Hg. Only patients with dilated cardiomyopathy had increased chamber volumes and decreased ejection fractions. Cardiac output and heart rate were reduced in the group with ischemia, probably because of concomitant β-blocker therapy.

### Contribution of External Forces to Resting Left Ventricular Diastolic Pressure

Figure 2 shows the relation between left ventricular diastolic pressure obtained under resting conditions ($LVP_d$) and the component of this pressure that is caused by forces external to the left ventricle ($\Delta P_d$). Data from

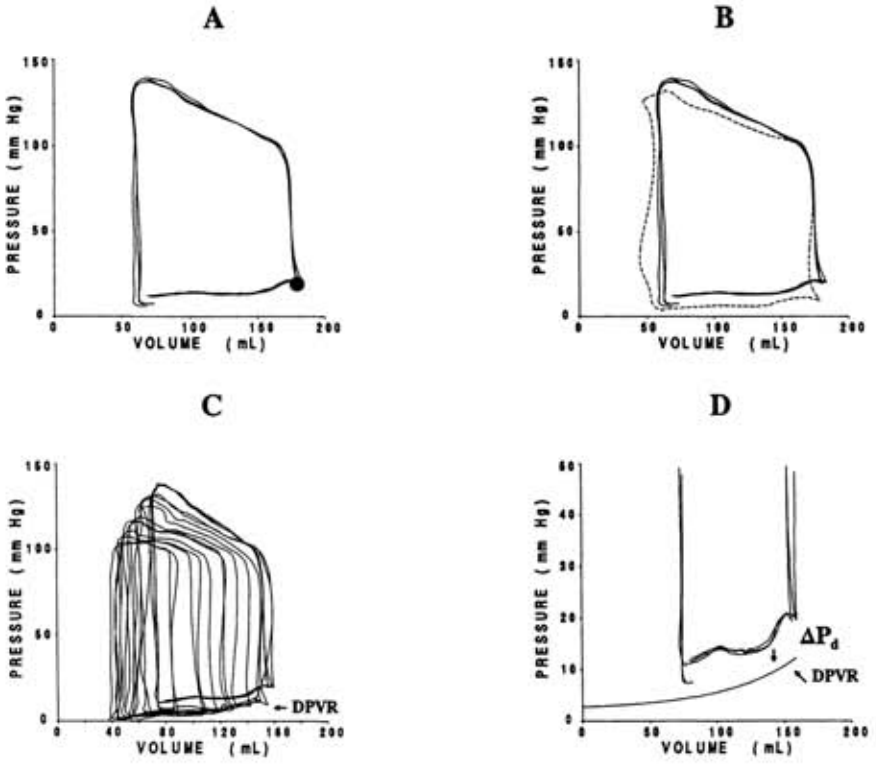


**Figure 1. Measurement of the contribution of external forces to resting left ventricular diastolic pressures.** **A.** Stable resting left ventricular pressure–volume loop. End-diastolic pressure is shown at the lower right corner (•). The diastolic pressure–volume boundary forms the lower side of the loop. **B.** After obstruction of inferior vena caval inflow. Downward shift of the left ventricular diastolic pressure–volume relation is indicated by dashed loop. **C.** With continued obstruction of inferior vena caval inflow. **D.** By subtracting the pressure from the diastolic pressure–volume relation from that at an identical volume on the initial resting pressure–volume loop, this downward shift is quantified ($\Delta P_d$); $\Delta P_d$ reflects the component of initial resting pressure that is not due to filling of the left ventricle per se but that stems from forces extrinsic to the left ventricle. DPVR = diastolic pressure–volume relation.

all groups of patients are combined into a single plot; each group is identified by a different symbol. The correlation between the two pressures was significant. The data were fit by linear regression to yield the following equation: $\Delta P_d = 0.38 \times (LVP_d - 6.1)$ [$r = 0.86$, $P < 0.0001$; standard error of the estimate, 1.6 mm Hg]. Each group of patients fell along a similar relation. This was tested by multivariate regression analysis, which yielded $P > 0.6$ for each comparison between individual group relations and the pooled regression. The x-axis intercept in Figure 2 indicates that at a left ventricular diastolic pressure of approximately 6 mm Hg or less, extraventricular forces contribute only minimally to left ventricular diastolic pressure. The slope of 0.38 indicates that above the initial pressure of 6 mm Hg, only 62% of measured resting pressure is due to the intrinsic properties of the left heart itself.

### Effect of Occlusion of the Inferior Vena Cava on Active Relaxation

If abrupt reduction of filling of the right heart accelerates the relaxation rate of the left ventricle, then left ventricular diastolic pressures might decrease further and contribute to the measure of pressure attributed to external forces. To test this possibility, the time constant of

**Table 1. Clinical and Major Hemodynamic Characteristics of Study Patients***

| Characteristic | Patients | | | |
|---|---|---|---|---|
| | Normal Left Ventricle | Dilated Cardiomyopathy | Hypertensive Cardiomyopathy | Ischemic Heart Disease |
| Age, *y* | 45.2 ± 11.9 | 47.2 ± 11.2 | 53.2 ± 10.0 | 60.5 ± 9 |
| Sex, *n*† | | | | |
| Male | 8 | 4 | 3 | 2 |
| Female | 4 | 2 | 2 | 4 |
| Chief condition, *n*† | | | | |
| Atypical chest pain | 10 | 0 | 3 | 0 |
| Angina pectoris | 0 | 0 | 0 | 6 |
| Dyspnea | 0 | 6 | 0 | 0 |
| Hypertension | 2 | 0 | 2 | 0 |
| Left ventricular end-diastolic pressure, *mm Hg* | 13.6 ± 4.0 | 20.4 ± 6.9‡ | 21.0 ± 10.0‡ | 23.6 ± 5.9‡ |
| Left ventricular end-systolic volume, *mL* | 39.0 ± 15.0 | 153.4 ± 60.0‡ | 55.2 ± 31.2 | 40.5 ± 30.6 |
| Left ventricular end-diastolic volume, *mL* | 116.4 ± 30.4 | 224.2 ± 69.9‡ | 115.2 ± 14.6 | 101.2 ± 42.7 |
| Heart rate, *beats/min* | 78.7 ± 14.8 | 78.5 ± 14.3 | 85.6 ± 10.5 | 58.8 ± 6.2‡ |
| Cardiac output, *L/min* | 6.0 ± 1.5 | 5.5 ± 1.6 | 5.0 ± 1.3 | 3.6 ± 0.5‡ |
| Ejection fraction, % | 67.3 ± 8.0 | 33.0 ± 8.0‡ | 53.7 ± 18.9 | 65.3 ± 13.7 |

* Values expressed as mean ± SD.
† Values refer to number of patients.
‡ $P < 0.05$ compared with group with normal left ventricle.

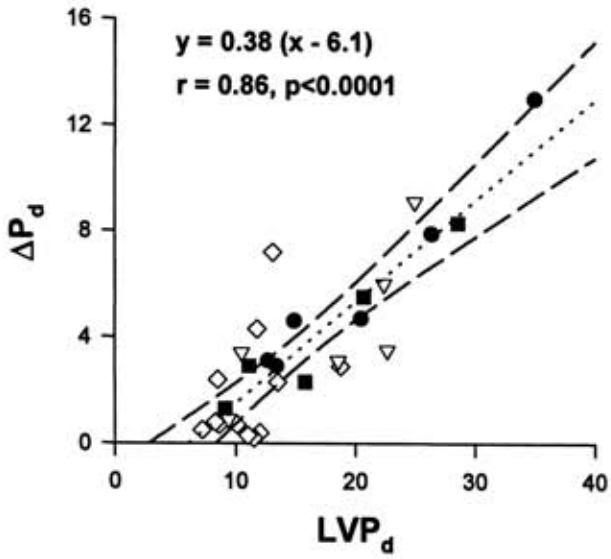


**Figure 2. Relation between initial resting left ventricular diastolic pressure ($LVP_d$) and the component of this pressure that is due to external forces ($\Delta P_d$).** Four groups of patients are shown: patients with normal hearts (◇), those with hypertrophic cardiomyopathy (▽), those with dilated cardiomyopathy (■), and those with ischemic heart disease (●). The data fell along a single relation that was well fit by linear regression. The slope (0.38) indicates that above an initial pressure of 6 mm Hg, 38% of the resting left ventricular diastolic pressure was due to forces external to the left ventricle.

relaxation was measured at resting conditions. This was then compared with the time constant of a cardiac cycle measured after obstruction of the inferior vena cava was initiated but just before left-heart filling or systolic pressure changed (two beats shown in Figure 1B). Mean relaxation times were identical (50.8 ± 13.7 ms and 50.8 ± 16.9 ms, respectively), with minimal change in each patient (SD of the difference was only 6.4 ms). Thus, variable relaxation did not explain the component of left ventricular pressure due to forces external to the left ventricle.

### Relevance of the Contribution of External Forces to the Starling Law

Because the decrease in left ventricular diastolic pressure primarily reflected the removal of extraventricular forces with little change in the filling of the left ventricle, cardiac output should have been only minimally changed according to the Starling law, and it was (Figure 3). With initial obstruction of inferior vena caval inflow, left ventricular diastolic pressure decreased by −19% ± 13%. However, the change in end-diastolic volume was only −3.6% ± 6.7%, and changes in cardiac output were similarly small. However, after extraventricular forces were largely removed, further reductions in ventricular diastolic pressures were only achieved at substantial cost to both filling of the left ventricle and cardiac output. For example, doubling the initial decrease in diastolic pressure (total decrease, −38%) required moving substantially leftward along the diastolic pressure–volume relation (Figure 1C), thus reducing preload and stroke volume (pressure–volume loop width). On average, this resulted in more than a 50% decrease in preload, which in turn resulted in a 60% ± 39% decrease in cardiac output (Figure 3). Thus, an important effect of external contributions to resting left ventricular diastolic pressure is that the dependence between changing the filling pressure and altering cardiac output (the Starling law) is nonuniform and becomes much tighter as chamber diastolic pressures are further reduced.

## Discussion

Our goal was to test the hypothesis that a sizable portion of resting left ventricular diastolic pressures in normal and diseased human hearts is due to factors extrinsic to the left heart. Using a novel mechanical maneuver to rapidly reduce these external forces, we found that nearly 30% to 40% of resting left ventricular measured diastolic pressures (greater than a nominal 6 mm Hg) were not due to properties of the left ventricle itself. Furthermore, left ventricular diastolic pressures could be lowered by 30% to 40% without necessarily changing chamber volume or thus compromising cardiac output according to the mechanism described by the Starling law.

In a 1963 editorial, Braunwald and Ross (22) reflected on the limitations of using left ventricular end-diastolic pressures to diagnose cardiac failure in humans. The authors highlighted several reasons why elevated pressures did not necessarily indicate cardiodepression; these reasons included diastolic dysfunction, variable chamber filling, and external pericardial contributions. The effect of extraventricular forces was later studied by Alderman and Glantz (10), who found that acute hemodynamic manipulations could shift the diastolic pressure–volume curve up or down without changing the passive stiffness of the left ventricle. Many studies followed; the most direct quantifications of extraventricular forces were made in animal experiments, in which the pericardium could sim-

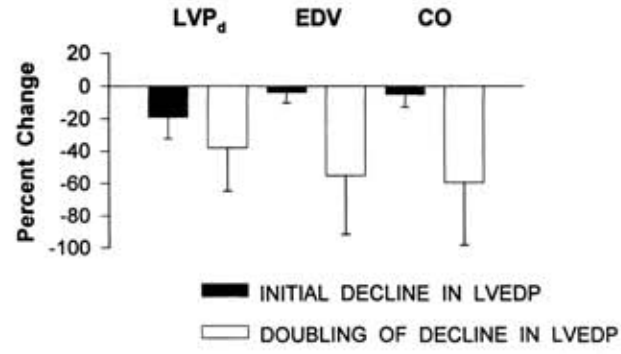


**Figure 3. Implication of external contributions to the resting left ventricular diastolic pressure on clinical application of the Starling Law.** Reducing the resting left ventricular diastolic pressure ($LVP_d$) by 19% was principally achieved by removing the extrinsic forces contributing to this resting pressure. This occurred with almost no change in either left ventricular end-diastolic volume (EDV) or cardiac output (CO). However, after these external forces were removed, there was a much tighter correspondence between changes in $LVP_d$ and EDV and therefore between CO and (according to the Starling law). Lowering $LVP_d$ by an additional 19% (total decrease, −38%) would require a marked reduction in cardiac filling, corresponding to an almost 60% decrease in CO.

ply be removed. When this was done, hearts generated similar cardiac outputs but at reduced diastolic pressures (6, 7, 13, 23).

These studies disagreed, however, about the quantitative importance of external forces to resting left ventricular diastolic pressures. Reported values ranged from almost 0% to nearly 80% (6, 9, 13, 24, 25). The precise volume status was important because euvolemia yielded small effects, and because acute volume loading, which forced the heart against an unyielding pericardial membrane, had a sizable influence (13). Chronic cardiac dilation, however, was accompanied by pericardial enlargement and a decreased influence of extrinsic forces (14, 26, 27). Because most patients with elevated diastolic pressures have chronically enlarged hearts, whether from dilation or increased wall thickness (such as that caused by hypertrophy), this finding suggests that extraventricular forces might be less important in patients with chronic cardiac diseases.

Our results indicate that the proportion of measured left ventricular diastolic pressure that is due to external forces is fairly consistent (between 30% and 40%) after left ventricular diastolic pressure exceeds 6 to 7 mm Hg, regardless of cardiac disease. The finding of a single relation for patients with normal, dilated, hypertrophied, and ischemic hearts suggests a fundamental physiologic dependence between internal and external contributions and resting left ventricular diastolic pressure. The variability of resting left ventricular diastolic pressures shown in Figure 2 largely reflects chronic cardiac changes and presumably concomitant pericardial changes as well. In this respect, it is useful to compare these results with analogous data reported by Applegate and colleagues (23) but measured in anesthetized dogs that had acute volume expansion. The slope of their relation was 0.78, almost twice that observed in our patients, suggesting that chronic adaptations can reduce the influence of extraventricular forces but cannot eliminate them. Both we and Applegate and colleagues found a similar value (approximately 6 mm Hg) for the left ventricular diastolic pressure at which the pressure attributable to external forces decreases to zero.

The right heart and the pericardium are the two major sources for external forces acting on resting left ventricular diastolic pressures. The right heart influences left-heart pressures primarily through shared myocardial fibers in the outer muscle layers and the interventricular septum. The pericardium further couples stresses from one part of the heart to the other. Both forces probably contribute to the observed offset of pressure attributable to external forces. Estimates of direct myocardial interaction have been reported in open-pericardium animal studies (17), showing that an abrupt change in right-heart filling pressure results in one third as much of a decrease in simultaneous left-heart pressure. From the present data, we can estimate a similar ratio using the baseline right atrial pressure to index the right-heart loading change (assuming that balloon occlusion of the inferior vena cava lowered this pressure almost to zero, as shown in Figure 1). This ratio averaged 0.53 (95% CI, 0.44 to 0.62), which is higher than that in open-pericardium animals and possibly reflects the contribution of the pericardium and altered intraventricular interaction.

Our analysis is the first in which a rapid, nonpharmacologic technique was used to alter the filling of the right heart and, thus, the contribution of external forces to resting left ventricular diastolic pressure. It is also the first in which multiple-beat diastolic pressure–volume analysis was used to compare late diastolic pressures before atrial systole with the fully relaxed diastolic pressure–volume relation, both at the same chamber volume. By not obtaining data earlier in diastole, the influences of ongoing relaxation and early rapid filling (27) are minimized. This contrasts with previous clinical studies of the contribution of right-heart filling or extraventricular forces to resting left ventricular diastolic pressures. Generally, low-dose nitrates have been used to vary these forces, and single cardiac cycles have been measured. The data have shown that the left ventricular diastolic pressure–volume relation shifts downward in parallel (4, 8–12), with end-diastolic pressures decreasing by 28% in many instances. However, left-heart end-diastolic volume (9, 10, 12, 16) also decreases 10% to 20% from the nitrates and changes in arterial tone, complicating the analysis.

Our study has several limitations. Although the mechanical method used to assess the component of left ventricular pressure attributable to external forces minimized most of the ambiguities of earlier studies that used drug interventions, this measure of external forces remains indirect. Second, although chronic disease states were evaluated, several factors may have had more acute influences. For example, the precise volume status at the time of the study may have differed from that during the chronic state because patients fasted before catheterization. In addition, studying patients in a supine as opposed to an upright position may have acutely enhanced central vascular volumes, potentially augmenting the component of left ventricular pressure attributed to external forces. However, because most clinical assessments of left ventricular filling pressure are made in supine patients, these measurements are relevant.

A third limitation relates to the conductance catheter method used to measure left ventricular volumes. Although this signal primarily reflects left-heart blood and muscle-wall volume, a portion of the signal stems from right-heart volumes (28). Sudden occlusion of the inferior vena cava could potentially lower the signal even though real left-heart volumes are unchanged. As shown in Figure 3, however, such changes were small at most (−4%) and may have been even smaller in the absence of this artifact. Catheter calibration was done on the basis of contrast ventriculography, and this itself is subject to some error. However, our major findings depended not on this calibration but rather on relative changes in pressure and volume. Last, approximately half of the patients studied who had elevated right- and left-heart filling pressures (mean right atrial pressure $>$ 12 mm Hg) showed minimal or only gradual decreases in right-heart pressures when inferior vena caval inflow was obstructed. In such patients, right-heart unloading is neither large enough nor fast enough to enable meaningful quantification of the component of left ventricular pressure attributable to external forces; thus, these data could not be used. This response is probably caused by the right heart and pulmonary vasculature acting as a large-volume reservoir, buffering the effects of sudden right-heart unloading. This

limitation does not imply that our results are relevant to only a subset of patients but rather that our method was inadequate to quantify external forces in all patients.

In conclusion, we report that extraventricular forces significantly influence measured resting left ventricular pressures in patients with both normal and diseased hearts. This influence is fairly consistent at between 30% to 40% of the resting pressure. When pulmonary capillary wedge pressure is acutely reduced in acute care settings, there is always concern that this may result in decreased cardiac output, as would be predicted by the Starling law. However, current data indicate that a substantial percentage of such increased diastolic pressure is not directly related to distension of the left heart itself. Rather, it depends on forces external to the left ventricle, primarily those influenced by the extent of right-heart filling. The practical implication is that by careful volume reduction (reduced right-heart pressures), a considerable portion of the resting left ventricular diastolic pressure can be lowered without necessarily compromising cardiac output. Future prospective study is needed to directly test this guideline in clinical acute-care settings.

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