**Left Ventricular Stiffness Associated with Chronic Pressure and Volume Overloads in Man**

*By William Grossman, Lambert P. McLaurin, and Miltiadis A. Stefadouros*

**ABSTRACT**

The relative effects of chronic pressure overload and chronic volume overload on left ventricular diastolic chamber stiffness were examined using a combined hemodynamic and ultrasonic technique in 27 patients. The slope of the left ventricular pressure-diameter relation in late diastole was measured and found to be steep in the groups with pressure or volume overload (9.0 ± 1.8 mm Hg/mm for pressure overload, 5.6 ± 0.9 mm Hg/mm for volume overload) compared with a control group (2.2 ± 0.2 mm Hg/mm). When this slope was normalized for either pressure or diameter, chamber stiffness remained high in the pressure-overloaded ventricles but was only slightly increased in the volume-overloaded ventricles compared with control. Ventricular wall thickness was much greater in pressure-overloaded ventricles (15.6 ± 1.0 mm) than in normal (9.0 ± 0.4 mm) ventricles but only slightly increased in volume-overloaded ventricles (10.6 ± 0.9 mm).

The large increases in both effective and normalized diastolic stiffness indexes associated with chronic pressure overload suggest an increase in intrinsic left ventricular chamber stiffness, possibly related to an increase in wall thickness. In contrast, chronic volume overload results in only slight increases in normalized diastolic stiffness indexes and wall thickness. It is suggested that differences in the pattern of hypertrophy, which result in a significant disparity in ventricular wall thickness between the two conditions, best account for the observed differences in diastolic left ventricular chamber stiffness.

**KEY WORDS**

left ventricular compliance  
left ventricular wall thickness  
left ventricular diastolic stiffness  
pressure-diameter relations  
hypertrophy  
ultrasonic technique

Both pressure and volume overload of the left ventricle may lead to major elevations of left ventricular end-diastolic pressure. Although the increased stiffness (decreased compliance) resulting from left ventricular hypertrophy is thought to play an important role in the generation of the elevated filling pressures seen with pressure overload (1-4), the role of altered stiffness in patients with volume overload is less certain. Dodge and his co-workers (1, 5) have pointed out that left ventricles subjected to a chronic volume overload frequently exhibit large volumes at normal filling pressures, suggesting a decrease in stiffness. However, in a recent study of experimentally induced chronic volume overload, McCullagh et al. (6) concluded that a chronic volume overload results in a progressive increase in left ventricular diastolic stiffness.

To clarify this problem, we examined the nature and the magnitude of diastolic stiffness abnormalities in patients with a chronic left ventricular volume overload and compared the left ventricular stiffness associated with pressure and volume overloads in man.

**Methods**

Twenty-seven patients undergoing complete right and left heart catheterization for diagnostic purposes formed the study population. Included were 6 patients with chronic pressure overload (5 with valvular aortic stenosis and 1 with hypertrophic subaortic stenosis) and 15 patients with chronic volume overload (5 with mitral regurgitation, 7 with aortic regurgitation, 2 with mixed mitral and aortic regurgitation, and 1 with mitral and aortic regurgitation, and 1 with ventricular septal defect). Six patients with chest pain but with normal coronary arteries served as controls. All patients were in sinus rhythm. The diagnostic and hemodynamic data for each patient are detailed in Table 1.

Catheterization was carried out in the fasting state following the administration of diazepam (5-10 mg, im). Brachial arteriography and retrograde left heart catheterization were performed with standard no. 8 French catheters in 14 patients and with high-fidelity micromanome-
### Hemodynamic Data and Stiffness Indexes

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#### Pressure Overload

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**CI** = cardiac index, **h₀** = posterior wall thickness at end-diastole, **LVEDP** = left ventricular end-diastolic pressure, **LVEDVI** = left ventricular end-diastolic volume index, **S** = ΔP/AD (see text for details), **F** = average pressure during interval of measurement, **EDD** = end-diastolic left ventricular diameter, **AS** = aortic stenosis, **IHSS** = idiopathic hypertrophic subaortic stenosis, **MR** = mitral regurgitation, **AR** = aortic regurgitation, **VSD** =ventricular septal defect, and **CP, NC** = chest pain but with normal coronary arteries.

* Left ventricular pressure was measured with a micromanometer-tipped catheter; all other pressures were measured with standard fluid-filled catheters.

† Compared to control.

GROSSMAN, McLAURIN, STEFADOUROS

Circulation Research Vol. 38, November 1971
ter-tipped catheters (Millar Mikro-tip) in 13 patients. The Millar catheter system was calibrated externally against a mercury reference and matched for end-diastolic and peak systolic left ventricular pressures against a simultaneously determined lumen pressure before and after each measurement; base-line drift of this system has not been a problem in our experience. All pressure measurements were made relative to atmospheric pressure and averaged over at least five beats without correction for intrathoracic pressure. In this regard, our study is comparable to others in closed-chest subjects (1-3, 6, 7). All pressures were recorded on an Electronics-for-Medicine DR-12 recorder. Cardiac output was determined by the Fick method and indexed for body surface area in all patients. In the only patient with ventricular septal defect, the cardiac index reported in Table 1 represents systemic blood flow inotropic. Left ventricular cineangiography was performed in each study, and patients with angiographic evidence of regional abnormalities of contraction were excluded.

Immediately following the determination of cardiac output but prior to angiography, the electrocardiogram, (ECG), left ventricular pressure, and ultrasonically determined left ventricular septal and posterior wall motion in the plane of the mitral valve (recorded with a SmithKline Ekoline 20-A ultrasonoscope interfaced with the Electronics-for-Medicine recorder) were simultaneously recorded on a strip chart as previously described (8-10). Differentiation of the posterior wall endocardium from the epicardium was aided by suddenly damping the intensity of the ultrasonic beam in all cases and by injecting indocyanine green dye into the left ventricular chamber whenever possible. High-quality recordings with clean delineation of posterior wall and septal endocardial surfaces were obtained in approximately 70% of the studies carried out in our laboratory (8, 9); only patients for whom such high-quality recordings were obtained are included in this report.

THEORETICAL CONSIDERATIONS AND CALCULATIONS

We must emphasize that we use the term left ventricular diastolic stiffness to mean the elastic behavior of the entire left ventricular chamber, not the specific elastic properties of the materials of which that chamber is constructed. This approach is essentially a hydraulic one; it does not attempt to define the material properties of the heart wall. Thus, we are viewing left ventricular chamber stiffness as the resistance encountered by a bolus of blood entering the left ventricle in diastole. As such, it is a composite function of many factors, including the material properties of the heart wall, wall thickness, pericardial properties, completeness of ventricular relaxation, and residual volume from the preceding systolic effort.

A combined hemodynamic and ultrasonic technique in the analysis of left ventricular diastolic stiffness has been used previously in this laboratory (8, 9). Basically, the slope of the late diastolic pressure-diameter relation at the time of left atrial systole was measured in each patient as illustrated in Figure 1. This slope, \( \Delta P/\Delta D \), was used as a measure of effective left ventricular stiffness.

![Figure 1](https://example.com/figure1.png)

*Strip chart showing simultaneously recorded echocardiogram, left ventricular pressure (LVP), and electrocardiogram (ECG). The actual record (left) is shown in traced form (right) where the technique of experimental measurement is indicated. Distances between the endocardial surfaces of the left ventricular septum and the posterior wall (PW) are shown as lines AB and CD at the onset and the peak of left atrial systole, respectively. Measurement of the corresponding pressures, \( P_s \) and \( P_d \), allowed calculation of \( \Delta P/\Delta D \), as discussed in detail in the text. End-diastolic wall thickness, \( h_{eD} \), was measured as the distance between the endocardial and the epicardial surface of the posterior wall.*

*Circulation Research, Vol. 35, November 1974*
GROSSMAN, McLAURIN, STEFADOUROS

The diameter at which it is measured. If $S$ is related to the average pressure $P$ during the interval of measurement $P = (P_1 + P_2)/2$, we can define the pressure-normalized stiffness as $S/P$. Similarly, $S$ can be normalized for left ventricular chamber size by dividing by end-diastolic diameter, EDD, as $S/EDD$. The rationale for normalizing by pressure or diameter can be summarized as follows. Animal experiments (7, 11) as well as certain human studies (2) suggest that diastolic pressure-geometry relations are exponential. Thus, if the pressure-diameter relation can be expressed in the form $P = ae^{KP}$, then $dP/dD$ (which represents the instantaneous value of $AP/AD$) can be obtained by differentiation:

$$dP/dD = KP \quad (1a)$$

or

$$(dP/dD)/P = K. \quad (1b)$$

Eq. 1b states that for an exponential left ventricular pressure-diameter plot the pressure-normalized slope is a constant independent of the portion of the curve from which it is derived. Data of sufficient quality to permit analysis of the entire late diastolic pressure-diameter relation was available for 11 of our patients. The fit to an exponential equation of the form $P = ae^{KP}$ was excellent with a range of correlation coefficients from $r = 0.84$ to $r = 0.96$. This finding supports the rationale for normalization by average pressure. Since ventricular enlargement in response to a chronic volume overload is clearly different from simple movement on a given pressure-diameter plot and may involve a shift of the entire plot to the right, it is possible that calculation of a diameter-normalized stiffness may also be important; this parameter was routinely determined in the present study.

Patients were instructed to maintain normal quiet respiration while recordings were made. When significant respiratory variation in pressures was observed, measurements were made and averaged over an entire respiratory cycle; otherwise, measurements were averaged over five beats. We have previously shown that the standard error of the echocardiographic diameter measurements over five successive beats is approximately 10% (9). Ventricular end-diastolic volumes were calculated from ultrasonically measured end-diastolic diameters in each patient according to the method of Feigenbaum et al. (12), and volumes were indexed for body surface area. Left ventricular posterior wall thickness ($h_p$) was measured echocardiographically as the distance between the endocardial and epicardial surfaces at end-diastole (9, 13, 14) (Fig. 1). End-diastole was chosen as the time of measurement to allow consistency and because $h_p$ measured at end-diastole does not differ significantly from that measured at $P_1$ or $P_2$, as can be seen in Figure 1. This technique for measuring $h_p$ has previously been described by others (13, 14); it reportedly shows excellent correlation with methods for directly measuring wall thickness.

In support of our use of an ultrasonic approach for measuring left ventricular chamber dimensions, it should be pointed out that ultrasonic techniques have been extensively utilized to measure left ventricular dimensions in experimental animals (15-17) and in man (18-23). In animals, Rushmer et al. (15), Hawthorne (16), and Bishop and Horwitz (17) have shown that left ventricular chamber dimensions can be continuously and accurately monitored by implanted ultrasonic transducers. In man, Popp and co-workers (18) have used reflected ultrasound to estimate right and left ventricular chamber size. Pombo et al. (19) have demonstrated an excellent correlation between angiographically and ultrasonically measured left ventricular diameters both at end-diastole ($r = 0.90$) and end-systole ($r = 0.91$). Feigenbaum and co-workers in a cooperative study with Dodge (12) have reported a close correlation between the cube of ultrasonically measured left ventricular diameter and the biplane angiographically determined left ventricular volume at end-diastole ($r = 0.89$) and at end-systole ($r = 0.81$). Similar data have been reported by Murray (20), by Popp and Harrison (21), and, from our own department, by Fortuin et al. (22). In addition to correlations at end-diastole and end-systole, close correlations between angiographically and ultrasonically determined left ventricular dimensions throughout the cardiac cycle have been reported by our group (10) and by others (23). In view of these varied investigations, we feel that it was reasonable to use ultrasonic measurements of left ventricular dimensions in the analyses described in this report.

Data were analyzed by standard statistical methods; Student's $t$-test for unpaired data was used.

**Results**

Table 1 details pertinent clinical and hemodynamic data for all 27 patients. The patients were separated into three groups: those with left ventricular pressure overload, those with volume overload, and the control group (patients with chest pain but with normal coronary arteries).

**HEMODYNAMICS**

The group with pressure overload and the group with volume overload exhibited major elevations in left ventricular end-diastolic pressure ($22.8 \pm 2.8$ mm Hg for pressure overload, $24.3 \pm 3.0$ mm Hg for volume overload) compared with the control group ($11.1 \pm 0.5$ mm Hg, $P < 0.01$ for both groups). As expected, the left ventricular end-diastolic volume index was significantly increased for the group with volume overload ($185 \pm 21$ ml/m$^2$, $P < 0.01$) but not for the group with pressure overload ($94 \pm 14$ ml/m$^2$, NS) compared with the control group ($67 \pm 9$ ml/m$^2$). The cardiac index determined by the Fick method was similar in all groups ($3.2 \pm 0.2$ liters/min m$^-2$) for pressure overload, ($3.0 \pm 0.3$ liters/min m$^-2$ for volume overload, $3.4 \pm 0.3$ liters/min m$^-2$ for the control group). Heart rate was somewhat increased for the groups with volume overload ($92 \pm 5$ beats/min) and pressure overload ($81 \pm 5$ beats/min) compared with the control group ($72 \pm 2$ beats/min, $P < 0.05$ for volume overload, NS for pressure overload). Left ventricular hypertrophy (Estes' criteria [24]) was equally common in the group with pressure overload (5 of 6 patients, 83%)...
Comparison of effective diastolic stiffness, $\Delta P/\Delta D$, in patients with left ventricular pressure overload and volume overload against a control group. Both experimental groups showed increases in $\Delta P/\Delta D$ compared with the control group. Bars and horizontal brackets represent mean values ± SE.

and the group with volume overload (12 of 15 patients, 80%).

**STIFFNESS INDEXES AND WALL THICKNESS**

As can be seen from Table 1, both the group with pressure overload and the group with volume overload showed significant increases in effective diastolic stiffness, S, compared with the control group. Figure 2 also illustrates this finding. However, when these groups were compared using either pressure-normalized ($S/P$) or diameter-normalized ($S/EDD$) stiffness indexes, patients with volume overload showed only a slight and statistically insignificant increase in stiffness compared with control, but those with pressure overload continued to show a significant increase in stiffness (Table 1, Fig. 3).

Posterior wall thickness at end-diastole, $h_p$, was significantly increased in patients with pressure overload ($15.6 \pm 1.0$ mm, $P < 0.01$) but only slightly increased in those with volume overload ($10.6 \pm 0.9$ mm, NS) compared with the control group ($9.0 \pm 0.4$ mm). Changes in posterior wall thickness tended to parallel those in normalized stiffness (Table 1, Fig. 3), suggesting that the increase in chamber stiffness might be a result of an increase in wall thickness rather than some change in the material properties of the left ventricular wall.

With regard to the component measurements utilized in the calculation of $S$, $\Delta P$ was increased equally in the groups with pressure and volume overloads compared with the control group ($13.0 \pm 1.7$ mm Hg, $P < 0.01$, for pressure overload, $13.8 \pm 2.2$ mm Hg, $P < 0.01$, for volume overload, $4.7 \pm 0.9$ mm Hg for control). $\Delta D$ tended to be greatest in the patients with volume overload ($3.1 \pm 0.5$ mm for volume overload, $1.6 \pm 0.2$ mm for pressure overload, $2.1 \pm 0.3$ mm for control), although the differences were not significant.

**Discussion**

This study used a recently developed combined hemodynamic and ultrasonic technique (8–10) to quantitatively assess left ventricular diastolic chamber stiffness in patients with chronic pressure...
and volume overloads. The slope of left ventricular pressure-diameter relations in late diastole was steep in both the group with pressure overload and the group with volume overload compared with the control group, but, when this slope was normalized for either average pressure during the interval of measurement or end-diastolic diameter, only the group with pressure overload retained its comparative stiffness. These findings suggest that chronic pressure overload produces a change in left ventricular pressure-diameter relations indicative of an increase in stiffness of the left ventricular chamber at any level of filling pressure. The left ventricles of patients with chronic volume overload also showed increased stiffness reflected by high values for S, but this effect appeared to be more related to the distention of their ventricles with blood consequent to the volume overload, since the comparative chamber stiffness of these patients was not maintained when S was related to the diameter or the pressure at which it was measured (normalized stiffness). Although this observation applies to the group with volume overload as a whole, it should be emphasized that some of the 15 patients with chronic volume overload had significantly elevated values for normalized chamber stiffness, suggesting that a few of the patients with chronic left ventricular volume overload had shifted to a steeper pressure-diameter relation as had the patients with chronic pressure overload.

One hypothesis that might explain the observations reported in this study is that the differences in normalized diastolic chamber stiffness between patients with chronic left ventricular pressure overload and those with chronic volume overload reflect differences in ventricular wall thickness in the two conditions. Hood et al. (25) have noted that pressure overload produces substantial increases in wall thickness (16.6 ± 1.0 mm) compared with compensated volume overload (9.7 ± 0.5 mm) or a control group (8.5 ± 0.5 mm). Our ultrasonic measurements of wall thickness gave remarkably similar results (15.6 ± 1.0 mm for pressure overload, 10.6 ± 0.9 mm for volume overload, 9.0 ± 0.4 mm for control). Left ventricular hypertrophy by electrocardiographic criteria was present with equal frequency in both groups but was primarily concentric (judging from measurements of wall thickness) only in the group with pressure overload; it is this distinction which appears to best account for the differences in diastolic left ventricular chamber stiffness between the two groups. Previous observations from this laboratory suggesting that wall thickness is a major determinant of left ventricular diastolic chamber stiffness and pressure (9) support this hypothesis. In that study (9), both S and S/P showed excellent linear correlations with wall thickness, h_p, in 24 patients with a variety of cardiac disorders. The good linear correlations suggested that stiffness per unit of wall thickness, (S/P)/h_p, was essentially the same for all of the patients in that study. Similar findings can be noted in Table 1 of the present study, suggesting that the increased chamber stiffness was simply due to a thicker wall in the group with pressure overload without any change in the material properties of the tissue composing that wall.

The effects of chronic volume overloading on left ventricular diastolic chamber stiffness have been previously examined by several investigators (1, 6, 26, 27), who have reached conflicting conclusions. Dodge and co-workers (1) have suggested that volume overload is generally associated with increased compliance (decreased stiffness) in that such patients frequently exhibit large left ventricular volumes over a range of normal filling pressures. Gault et al. (26) have reported on diastolic pressure-radius relations in patients undergoing aortic valve replacement for correction of severe aortic regurgitation. They noted either no change or an increase in stiffness postoperatively, and they discussed possible mechanisms for the "apparent increase in myocardial compliance" associated with the left ventricular dilation of aortic regurgitation prior to corrective surgery. In contrast to these reports, a recent paper by McCullagh et al. (6) on dogs with a chronic volume overload has suggested that this experimentally induced abnormality results in an increased left ventricular diastolic stiffness which appears to be progressive and is at least partially reversible following surgical correction of the volume overload. Their report represents an advance over previous studies in that quantitative measurements of stiffness were made, enabling statistical analysis of the data. Our results are in agreement with those of McCullagh et al. (6) in so far as both studies noted an increase in effective stiffness in association with chronic volume overload. In our studies, however, chronic volume overload was associated with only slight and statistically insignificant increases in the normalized stiffness indexes, suggesting to us that no intrinsic change occurred in the stiffness characteristics of the left ventricular chamber.

In a recent editorial, Levine (28) has emphasized that characterization of left ventricular diastolic properties is a prerequisite to the proper understanding of left ventricular function. Since systolic
LEFT VENTRICULAR STIFFNESS

Ventricular performance is markedly affected by the degree of sarcomere stretch achieved during diastole, changes in either of the two major determinants of diastolic sarcomere stretch, wall tension and stiffness, might influence systolic performance in a very direct manner. The marked increases in left ventricular diastolic stiffness observed in patients with chronic pressure overload probably account for the well-known importance of atrial contraction (3, 4) in these patients, since it is by this mechanism that sufficient tension can be created in the left ventricular wall to produce adequate diastolic sarcomere stretch.

Certain limitations of the present study should be emphasized. First, accurate ultrasonic measurements of left ventricular internal diameter can only be made after careful scanning with the ultrasonic probe has established the plane of the anterior mitral valve leaflet; the transducer is then tipped slightly inferolaterally to identify the septal and posterior wall endocardial surfaces. Identification of both sides of the interventricular septum and distinction between posterior wall endocardial and epicardial surfaces are difficult but necessary prerequisites to obtaining meaningful data. Second, even with accurate measurements of left ventricular internal diameter, it is possible that ventricular filling may occur in a different fashion in volume overload as opposed to pressure overload. Thus, if major-axis lengthening plays a more significant role in either condition than does minor-axis (internal diameter) lengthening, a consistent bias might be introduced by relying on only internal diameter to characterize changes in diastolic geometry. Third, we cannot exclude the possibility that the differences observed in this study were to some extent an expression of diastolic “creep.” As pointed out by McCullagh et al. (6), diastolic creep is one possible mechanism by which volume-overloaded hearts may shift their pressure-length relation to the right. In our patients, left ventricular end-diastolic pressure was nearly identical in the groups with pressure and volume overload (Table 1), making this possibility less likely. Furthermore, the results were substantially the same whether the stiffness ratios were normalized for pressure or diameter, suggesting that the differences observed were related to true changes in chamber stiffness.

In summary, we examined the nature and magnitude of diastolic chamber stiffness abnormalities seen in patients with chronic left ventricular pressure overload and volume overload. Chronic pressure overload was associated with large increases in both normalized chamber stiffness and left ventricular wall thickness compared with control. In contrast, chronic volume overload resulted in only slight and statistically insignificant increases in normalized chamber stiffness and wall thickness. It is suggested that the differences in normalized chamber stiffness reflect differences in left ventricular wall thickness seen in association with pressure and volume overload.

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