Relation of Left Ventricular Filling Dynamics to Alterations in Load and Compliance in Patients With and Without Pressure-Overload Hypertrophy

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A large atrial contribution to left ventricular (LV) filling (%A) in patients with LV hypertrophy has been assumed by some to indicate abnormal LV compliance. We tested this assumption by examining the influence of short- and long-term changes in load on compliance and filling dynamics using nitroprusside to decrease load in 11 patients with severe aortic stenosis (AS) and ergonovine to increase load in nine normal subjects. LV angiographic volume was analyzed frame-by-frame simultaneous with micromanometer pressure recordings. Operative LV chamber compliance (dV/dP) and a time constant for isovolumic relaxation rate were computed using three-constant exponential equations fit to the data. Compared with normal subjects, resting left ventricular end-diastolic pressure was increased and dV/dP was reduced in AS, but %A was not different. %A was inversely related to left ventricular end-diastolic pressure (r = -0.48, p = 0.02) and positively correlated with dV/dP (r = 0.90, p < 0.001) within the AS group. Nitroprusside infusion reduced LV peak systolic pressure by 11%, end-diastolic pressure by 38%, and end-diastolic volume by 12% (p = 0.004 for each) and tended to increase dV/dP by 26% (p = 0.23). These alterations in load resulted in a 21% decrease (16 ml) in the early filling volume (p < 0.05) and variable increases (mean, +7 ml; p = NS) in the late atrial filling volume and in the percent atrial contribution to ventricular filling (26±19% to 35±25% for the AS group, p = NS) that were related to changes in compliance. Changes in filling dynamics with load augmentation by ergonovine in normal subjects were characterized by a 25% increase in early filling (p = 0.03) and a 37% decrease in late atrial filling (p = 0.01), with a 49% decrease (p = 0.04) in operative compliance. In conclusion, load-induced decreases in compliance in normal subjects result in increased early filling and reduced late atrial filling; in aortic stenosis, %A was inversely related to left ventricular end-diastolic pressure and positively correlated with dV/dP; and the positive correlation between operative compliance and %A is opposite to the stated assumption. (Circulation 1990;81:101-106)

Although diastolic dysfunction may have important clinical consequences, it is difficult to measure with precision, even under the most rigorous conditions. Recently, many investigators have purported to detect diastolic dysfunction by studies of left ventricular filling dynamics using contrast angiography, radionuclide angiography, or Doppler transmural flow recordings. Having observed the ratio of late (atrial)-to-early filling velocity to be higher than normal in the elderly, diabetics, hypertensives, and patients with coronary artery disease, it has been assumed by some that a high atrial-to-early filling ratio indicates abnormal ventricular compliance, because clinical evidence of diastolic dysfunction often is found among patients in these groups.

Recently, it has been recognized, however, that the atrial-to-early filling ratio may be affected by alterations in ventricular filling pressures. Despite these findings, the hypothesis that an augmented atrial contribution to left ventricular (LV) filling indicates impaired compliance has not been fully tested. We tested this assumption by examining the influence on ventricular filling dynamics of both long-term changes in compliance associated with pressure-overload hypertrophy and short-term changes in compliance produced by pharmacologic load intervention.
Methods

Subjects

Patients with aortic stenosis (AS) undergoing diagnostic catheterization who gave informed consent to a load-intervention protocol approved by the joint UK/VA Institutional Review Board were included in the study if they had isolated AS with aortic valve area 1.2 cm² or less by the Gorlin equation and no more than 1+ aortic insufficiency, no history of myocardial infarction or segmental wall motion abnormalities on angiography, left ventriculograms adequate for edge detection recorded simultaneously with LV micromanometer pressure recordings, and normal sinus rhythm. Between January 1985 and December 1988, 11 such patients 19–70 years old were identified and comprise the AS group. The mean aortic valve area for the AS group was 0.74±0.19 cm². Coronary arteriograms were normal in all of these patients.

A second group was comprised of nine “normal” subjects 39–61 years old who were catheterized to evaluate chest pain syndromes that were not typical of angina and who were found to have normal coronary arteries, normal LV function as defined by an angiographic ejection fraction of 0.60 or more, LV angiographic wall thickness of less than 1.1 cm, and no evidence of valvular heart disease or history of hypertension. β-Adrenergic blockade was not used for the protocol, although one of the nine normals was on long-term β-blocking therapy.

Procedure

Patients were premedicated with oral diazepam 5–10 mg. Right heart catheterization was performed in all patients in the AS group. Left heart catheterization was performed retrograde via femoral or brachial artery using an 8F micromanometer catheter with a pigtail configuration. LV pressure was recorded simultaneously with injection of 39–54 ml meglumine diatrizoate into the LV during biplane cine angiography (30° right anterior oblique and 60° left anterior oblique).

In each patient, angiography was performed twice: once with and once without pharmacologic afterload manipulation. In all patients in the AS group, load was reduced by infusing sodium nitroprusside beginning at 0.25 μg/kg/min and increasing the dose by 0.25 μg/kg/min every 3 minutes to decrease aortic systolic pressure (SP) by 20–40% but to no less than 90 mm Hg. Aortic pressure was measured by a micromanometer catheter placed in the proximal aorta in four patients and by a well-flushed fluid catheter in the remaining patients. No patient developed chest pain during nitroprusside infusion. In the normal group, load was altered by ergonovine 0.35 mg in three divided intravenous doses. Ergonovine was preferred to nitroprusside in the normal group because it allowed us to rule out coronary spasm as a cause of the chest pain; furthermore, load augmentation in the normal group and load reduction in the AS group allowed us to examine filling dynamics over a more closely matched range of loading conditions. None of the patients developed spasm in response to ergonovine. A 15–20 minute interval separated the first and second ventriculograms to allow the hemodynamic effects of the contrast agent to dissipate. During this time, neither the patient nor the imaging equipment was moved. Patients were instructed not to perform a Valsalva maneuver during inspiration held for the ventriculogram. Immediately after the second contrast cineangiogram, a radiographic grid positioned at midchest was imaged biplane to provide corrections for magnification.

During the early period of study, the baseline cine was performed before the nitroprusside infusion and second cine. However, we soon learned that it was easier to reduce load with nitroprusside before rather than after the first contrast injection. Subsequently, the nitroprusside cine was performed first; the drug was then discontinued, and the second cine was performed 15–20 minutes later. This allowed for a greater difference in load between the two cines because the volume loading effect of contrast further elevated pressures above baseline. There were no complications.

Precise synchronization between pressure and cine was achievable with a cine frame marker, which records a mark for each film exposure (60/sec) simultaneous with the pressure recording and exposes every 100th frame with a diode simultaneous with an accentuated mark on the pressure recording.

Analysis of Catheterization Data

LV silhouettes for each frame of the first well-opacified beat of each LV cine not preceded by an ectopic beat were digitized using a hand-held cursor. LV wall thickness was measured at the middle third of the anterior wall in the right anterior oblique view for the end-diastolic frame. Correction factors for ventricular measurements were derived from the grids positioned at the center of the ventricle. LV volume was computed using the area-length method and a regression equation.11 Because the silhouette borders in the left anterior oblique view were sometimes unclear over the spine and diaphragm and segmental dysynchrony was absent, volumes were computed from the single-plane right oblique view. LV mass was computed using wall thickness measured at end diastole.12 LV pressure for the corresponding cardiac cycle was digitized using the midportion of the QRS complex as a reference point for end diastole.

LV volume and pressure were computer-plotted frame by frame. We previously have shown the intraobserver and interobserver variability of our volume measurements to be approximately 5%.13 To make the volume-time waveform analysis as objective as possible, the data were fit to 9–11th-order polynomial equations with a Marquardt curve-fitting program. Differentiation of this equation at each frame with respect to time (dV/dT) yields instantaneous flow rate. End-diastolic volume (EDV) was located as the maximum volume
and end-systolic volume (ESV) as the minimum volume where the equation \( \frac{dV}{dt} = 0 \). The onset of the A wave was defined as the inflection point where \( \frac{dV}{dt} \) reached a nadir during filling as shown in Figure 1. The stroke volume (SV) was computed as the difference between EDV and ESV. The percent of atrial contribution to ventricular filling was computed as \( \%A = \frac{A}{SV} \times 100\% \). End-diastolic operative compliance was computed according to Gaasch et al\(^{14,15} \) with the exception that the stiffness parameter \( k \) was computed by curve-fitting the diastolic pressure (DP) volume data to the three-constant model \( P = a + b e^{kVd} \) as described by Hess et al\(^{15} \): \( \frac{dV}{dP} = \frac{1}{k(1/EDV)(1/(EDP-a))} \) where EDP is end-diastolic pressure. This is illustrated in Figure 2. The relaxation time constant \( T \) was also determined by curve-fitting a three-constant exponential model \( P = C + Be^{-t/T} \) to the pressure-time data from peak \(-dP/\) dt to a pressure 5 mm Hg above LVEDP.\(^{16} \) To further assess the possibility that decreases in aortic pressure during nitroprusside infusion might have induced ischemic diastolic dysfunction by reducing the myocardial oxygen supply-to-demand ratio, the DP and SP–time index ratio (DPTI:SPTI) was computed from the digitized aortic and LV pressure tracings.\(^{17} \)

Values are given as mean±SD. Comparisons were made using unpaired (AS versus normal) or paired (before versus after drug infusion) t tests. Correlations for \( \%A \) versus LVEDP and compliance were evaluated using a linear model model (\( \%A = \text{constant} + \text{LVEDP} \) or \( \%A = \text{constant} + \frac{dV}{dP} \)) with a statistics program.\(^{18} \)

**Results**

Patients with hypertrophy due to AS had a higher mean LVEDP than normal subjects and a mean end-diastolic operative compliance, \( \frac{dV}{dP} \), that was depressed compared with normal (Table 1). The stiffness constant, \( k \), was not different between groups (\( k = 0.021\pm 0.014 \) for AS vs. 0.023±0.021 for normal subjects). LV mass was 166±36 g/M² vs. 99±17 in normal subjects (\( p < 0.05 \)). Mean values for EDV and ESV did not significantly differ from normal in AS, although values for ESV varied widely in the AS group. Likewise, the early filling volume (E), the atrial filling volume (A), and the \( \%A \) did not significantly differ from normal in AS. However, marked differences in filling patterns existed within the AS group. As illustrated in Figure 3, larger atrial contributions (\( \%A \)) to LV filling were observed for patients with both lower values for LVEDP and higher values for \( \frac{dV}{dP} \) such that significant correlations were present within the AS group both for \( \%A \) versus LVEDP (\( r = -0.48, p = 0.02 \)) and for \( \%A \) versus \( \frac{dV}{dP} \) (\( r = 0.90, p < 0.001 \)). In five patients of the AS group, \( \frac{dV}{dP} \) was below the normal range (0.016–0.078 mm Hg), and \( \%A \) was below the normal range (17–54%) in four of these five. Conversely, operative compliance and \( \%A \) were both above the normal range in two patients in the AS group. The time constant for isovolumic relaxation \( T \) was not prolonged versus normal in our group of patients with AS (Table 1).

As shown in Table 1, nitroprusside infusion in patients with AS produced an 11% reduction (−23 mm Hg) in the mean value of LV peak SP, a 38% reduction (−10 mm Hg) in mean EDP, a 12% reduction (−23 ml) in mean EDV (\( p \leq 0.004 \) for each), and a 26% increase (+0.007) in mean \( \frac{dV}{dP} \) that was not statistically significant (\( p = 0.23 \)). These changes were associated with a 21% decrease (−16 ml) in the volume of the early filling wave (\( p = 0.04 \)) and a 30% increase (+7 ml) in the volume of the late atrial filling wave (\( p = \text{NS} \)). A nitroprusside-induced decrease in early filling and reciprocal increase in late atrial filling with improved operative compliance is illustrated by patient 5 (Figure 4). Although neither mean increase in the A wave volume nor \( \%A \) was significant for the AS group due to the heterogeneous response to nitroprusside, there was a strong direct relation between \( \%A \) and \( \frac{dV}{dP} \) within this group (\( r = 0.90, p < 0.001 \)). This also was true when...
%A was examined as a function of compliance without normalizing for volume \((r=0.89, p<0.001\) for %A vs. \(dV/dP\)). The reduction in early filling and increase in late filling with nitroprusside could not be explained by an effect of either altered load or ischemia on isovolumic relaxation rate because the mean values for neither the time constant \(T\) (Table 1) nor ratio of DPTI:SPTI (0.55±0.13 to 0.57±0.18) were altered by reducing load.

Among normal subjects, load augmentation with ergonovine produced a 26% increase (+30 mm Hg) in the mean value of LV peak SP, a 71% increase (+10 mm Hg) in mean EDP, and a 14% increase (+21 ml) in mean EDV (\(p=0.01\) for each), and a 49% decrease (−0.025) in mean \(dV/dP\) (\(p=0.03\)). As in the AS group, the change in filling pattern was not attributable to a significant change in isovolumic relaxation rate (Table 1).

The significant influence of \(dV/dP\) on the atrial contribution to ventricular filling for both groups combined is illustrated in Figure 5. This demonstrates that the size of the atrial filling wave increases with increasing compliance.

**Discussion**

We examined the assumption that a large atrial contribution to LV filling indicates abnormal ventricular chamber compliance. Our findings do not support this assumption. To the contrary, we found that the relative size of the atrial filling volume (%A) in AS increases with increasing end-diastolic operative compliance estimated as \(dV/dP\). Conversely, end-diastolic operative compliance was below the normal range in five AS patients (before load reduction), and atrial filling waves were below the normal range in four of these five. Likewise, short-term alterations in filling pressure and operative compliance produced changes in filling dynamics such that %A increased in response to both decreasing LVEDP and increasing compliance.

Our findings are consistent with the results of some recent studies that examined the effect of filling pressures on filling dynamics. Choo and coworkers found that a short-term decrease in the mean filling pressure has little influence on late atrial filling but markedly diminishes early filling as measured by transmitral Doppler.\(^9\) This is probably due to a decrease in mitral valve opening pressure as indicated by the experimental results of Ishida et al.\(^8\) The importance of mitral opening pressure was also demonstrated by the study of Murakami et al.,\(^7\) who observed decreases in early peak filling rates with decreases in mitral opening pressure after successful valve replacement in patients with AS who had

**FIGURE 3.** Plots of pressure (■) and volume (□) plotted frame by frame in a patient with aortic stenosis in whom the volume A wave was small (patient 5, left panel) and another patient with aortic stenosis in whom the volume of the A wave was large (patient 6, right panel). Note that LVEDP is greater and operative compliance (\(dV/dP\)) reduced in the patient with the small volume A wave compared with the patient with the large volume A wave.
congestive heart failure before surgery. A decrease in early filling associated with short- or long-term load reduction is partly offset by an increase in late atrial filling, the extent of which is affected by operative LV compliance. A normal or increased compliance presumably permits an augmentation of atrial filling when early filling is reduced. Conversely, when early filling is augmented by a high mean left atrial pressure (i.e., in congestive failure) or high mitral valve opening pressure (i.e., large v wave), the operative compliance will tend to be reduced and the already-distended LV resists further filling during atrial systole. This hypothesis is supported by our data showing an inverse relation between %A and LVEDP and by the data of Ambrose et al.19 Recently, Drinkovic et al20 also reported that the Doppler A:E ratio tended to be reduced in stiffer ventricles of patients with ischemia or pressure-overload hypertrophy.

Why some patients with AS have markedly accentuated volume A waves compared with normal is not so intuitive from our study. It is possible that atrial hypertrophy develops in patients who have AS and are not in congestive failure at rest due to an increase in LVEDP with exercise.21 At rest, the ventricle then returns to a relatively flat portion of the passive-pressure volume curve, early filling is limited by a mitral opening pressure that is normal or low, and ventricular filling is augmented by the hypertrophied left atrium. There was no evidence to indicate that the diminished early filling (E wave) and reciprocally increased atrial filling in these patients is explained by impaired relaxation that was not significantly prolonged in our patients (including the one illustrated on the right in Figure 3) or in the patients of Murakami et al7 who had moderate hypertrophy. Even in patients with prolonged isovolumic relaxation constants, it is unlikely that marked changes in filling dynamics can be explained by changes in T on the order of magnitude that have been reported (approximately 25 msec in the patients of Murakami et al7 who had severe hypertrophy and failure) unless the diastolic filling period (on the order of 400 msec at normal heart rates) is markedly abbreviated due to tachycardia. A low resting left atrial pressure and hypertrophied left atrium may at least in part account for abnormal filling dynamics observed in other hypertrophy states in which compliance is reputed to be abnormal.3-6 Whatever the mechanism, although a large atrial filling volume does not indicate abnormal LV compliance, it may, nevertheless, when extreme be a marker of some altered diastolic property. The relation of filling rates to relaxation and filling pressures requires further study because therapeutic interventions directed at improving relaxation could conceivably be exerting their effect on filling dynamics through an undesirable effect on left atrial pressure.10 It is also important to note that the ratio of early to late filling should not be used as a sole index of diastolic dysfunction.

Several limitations in our study may be noteworthy. First, β-adrenergic blockade was not used. Thus, alterations in the mean cardiac cycle length of 63 msec in AS

**Figure 4.** Plots of pressure (■) and volume (□) plotted frame by frame in patient 5 (aortic stenosis) in whom operative compliance was abnormal before nitroprusside infusion (left panel) and normal after nitroprusside (right panel). Note that the volume of the A wave increases with an increase in operative compliance and a decrease in end-diastolic pressure.

**Figure 5.** Plot of relation between percent atrial (%A) contribution to left ventricular filling and operative compliance, dV/dP, among patients with aortic stenosis before (○) and after nitroprusside (●), and dV/dP among normal subjects before (□) and after ergonovine (■). %A increases with increasing operative compliance.
patients and 61 msec in normal subjects were observed with load alterations due to autonomic reflexes. This may have had some small effect on filling dynamics that we cannot quantitate. Second, shifts in the DP-volume curve with load manipulation\textsuperscript{22} complicate the assessment of diastolic function, particularly because we used different drugs for the two groups that may have different effects on the position of the pressure-volume curve. Also, because atrial pressure and total filling volume also were affected by our load interventions, the observed changes in filling dynamics may also be affected by these variables and not just compliance. Third, ventricular compliance is very difficult to quantify even with sophisticated indexes of compliance, no single one of which can completely describe diastolic properties of the ventricle.\textsuperscript{1,2} However, LV EDP and dV/dP are relatively simple indices that probably do reflect changes in operative compliance at different loads. Fourth, limitations exist for all currently used methods of assessing ventricular volumes and filling dynamics, including angiography, but the reproducibility for calculating volume in our angiography laboratory is reasonably good,\textsuperscript{13} and any errors in our volume determinations probably do not critically affect our conclusions.

Finally, one could question the relevance of our study of filling dynamics using angiographic volumes to Doppler studies of filling velocities; however, it has been demonstrated that alterations in filling dynamics are comparably reflected by filling velocities and filling volumes\textsuperscript{20} and that filling dynamics measured by contrast\textsuperscript{23} and radionuclide\textsuperscript{24} angiography correlate with Doppler measures. Also, it is not the usefulness of Doppler in the assessment of filling dynamics that we have challenged but rather the concept that “abnormal” filling dynamics, characterized by an augmented atrial filling wave, indicate abnormal LV compliance. Our data clearly indicate that the %A or E/A ratio cannot be used as an index of LV compliance.

References


Key Words: diastolic • hypertension • ventricular function • stenoses
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