Left Ventricular Diastolic Capacity in Man

ATHAN P. FLESSAS, M.D., AND THOMAS J. RYAN, M.D.

SUMMARY Plasma volume expansion with 500 ml of low-molecular-weight dextran was used in 27 patients (nine normal subjects, 13 patients with ischemic heart disease, four with aortic stenosis and one with cardiomyopathy) to increase left ventricular end-diastolic pressure (LVEDP) from a control value of 12.4 ± 7.0 mm Hg (mean ± SD) to 23.3 ± 7.0 mm Hg and end-diastolic volume (EDV) from 84.0 ± 23.8 ml/m² to 97.6 ± 22.9 ml/m². EDV-LVEDP curves constructed for 12 patients from multiple angiograms at progressively increasing LVEDPs during plasma volume expansion showed an initial part where EDV increased in parallel with LVEDP and a final steep or perpendicular part where EDV increased minimally or not at all as LVEDP exceeded 20 mm Hg. Exponential equations were used to fit diastolic volume-pressure data obtained with catheter-tip manometers in seven patients: the exponential constant, k, was 0.012–0.044 ml⁻¹ and was inversely related to EDV (Spearman's rank correlation coefficient = -1). For comparable EDV, there were no differences in k values between normal subjects and patients with a variety of heart diseases.

STUDIES of the hemodynamic responses in acutely induced hypervolemia have shown the ability of the human heart to augment its stroke volume. The ventricles, even during normovolemia and in the supine position, maintain some capacity to enlarge beyond their normal operative end-diastolic volume (EDV) and thus augment stroke output by the Frank-Starling mechanism. In the present study, we quantitated this left ventricular (LV) diastolic reserve by measuring ventricular volumes during plasma volume expansion induced by infusion of low-molecular-weight dextran. We also investigated LV systolic function and diastolic volume-pressure relationships over a wide range of diastolic pressures.

Methods

Twenty-seven patients undergoing diagnostic cardiac catheterization participated in this study. Thirteen patients had ischemic heart disease, four aortic stenosis and one congestive cardiomyopathy; nine patients with atypical chest pain had no discernible heart disease and were considered normal. Five of the ischemic heart disease patients had ECG evidence of old myocardial infarction. All patients gave informed consent.

Cardiac catheterization was performed in the fasting state, after premedication with 10 mg of oral diazepam. After coronary arteriography by the Sones technique, a #8 angiographic catheter (Gensini in 20 patients and Millar microtip catheter pressure transducer PC-481 in seven) was advanced into the left ventricle, and a #8 Cournand catheter was positioned in
the pulmonary artery. After a resting left cineventriculogram was performed, 20 minutes were allowed for dissipation of the effects of the contrast medium, and plasma volume expansion was started by manually pumping low-molecular-weight dextran, 15 ml/min, into the pulmonary artery. In 12 patients, two to four sequential left cineventriculograms were performed during plasma volume expansion at progressively higher LV end-diastolic pressures (LVEDPs). In 15 patients, only one left cineventriculogram was obtained after 500 ml of low-molecular-weight dextran had been infused. Catheter-tip manometers were used in three patients of the former group and four of the latter, making possible the study of the entire diastolic volume-pressure curve over a wide range of diastolic pressures in seven patients. In nine additional patients, volume-pressure curves were constructed from three to five end-diastolic volume-pressure measurements obtained by fluid-filled catheter.

Single-plane left cineventriculograms were filmed at 64 frames/sec and recorded on 35-mm film with the patient positioned in a 30° right anterior oblique projection and breathing quietly. Thirty milliliters of meglumine and sodium diatrizoate were used in three sequential ECG-triggered diastolic injections (10 ml each) through a Siemens power injector. When fluid-filled catheters were used, they were connected by three-way stopcock to both the power injector and pressure transducer (P23Db) to shorten the time lag between pressure and volume measurements. During ventriculography, the cine pulse signals (for synchronization of volume-pressure measurements) and the respiratory movements were recorded together with the ECG at a paper speed of 200 mm/sec. Rotation of the patient, height of the x-ray table and image intensifier, and x-ray settings were kept the same for repeated left cineventriculograms. EDV was measured from the synchronized frame corresponding to the peak of the R wave in the ECG; end-diastolic volume (ESV) was derived from the smallest angiographic silhouette during cardiac contraction. Ejection fraction (EF) was calculated as (EDV−ESV)/EDV. LV volumes and mass were measured by the method of Kennedy et al. In five patients, ESV could not be determined owing to poor visualization of the end-systolic frames. When fluid-filled catheters were used, EDV in the three opacified beats and LVEDP in the last recorded respiratory cycle were averaged. With catheter-tip manometers, volumes were measured frame by frame, beginning at the frame corresponding to the lowest pressure in early diastole (the nadir of diastolic pressure) and ending with the end-diastolic frame at the peak of the ECG R wave; all frames with inadequate opacification of the left ventricular cavity were omitted. Heart rate (HR) was calculated from the average cardiac cycle length of the opacified beats during cineventriculography. In five patients, HR data could not be retrieved as the recording paper was inadvertently cut for the pressure measurements. LV systolic pressure (LVSP) immediately preceding ventriculography was measured in only 12 patients. LV volume-pressure data were analyzed by fitting to a first-order exponential function: P = be\(^{-kt}\), where P = pressure in mm Hg, b = data constant

### Table 1. Hemodynamic and Volumetric Data

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>LVEDP (mm Hg)</th>
<th>EDV (ml/m²)</th>
<th>ESV (ml/m²)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n  R  E</td>
<td></td>
<td>n  R  E</td>
<td>n  R  E</td>
<td>n  R  E</td>
</tr>
<tr>
<td>Entire group</td>
<td>22 69.6 76.7†</td>
<td>27 12.4 23.3*</td>
<td>27 84.0 97.6*</td>
<td>22 38.5 42.9*</td>
<td>22 56.6 59.6*</td>
</tr>
<tr>
<td></td>
<td>± 12.7 14.1</td>
<td>± 7.0 7.0</td>
<td>± 23.8 22.9</td>
<td>± 18.4 18.8</td>
<td>± 12.1 12.2</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>6 79.7 88.5‡</td>
<td>9 10.4 22.6*</td>
<td>9 76.3 92.2*</td>
<td>6 30.0 35.0§</td>
<td>6 61.4 64.1†</td>
</tr>
<tr>
<td></td>
<td>± 12.8 9.1</td>
<td>± 4.4 5.3</td>
<td>± 15.7 18.5</td>
<td>± 12.6 15.4</td>
<td>± 12.1 9.5</td>
</tr>
<tr>
<td>Ischemic heart disease, no myocardial infarction</td>
<td>8 63.9 70.5§</td>
<td>8 9.2 19.3*</td>
<td>8 74.4 89.1*</td>
<td>8 27.8 32.8§</td>
<td>8 62.3 63.4</td>
</tr>
<tr>
<td></td>
<td>± 11.4 15.0</td>
<td>± 2.3 4.2</td>
<td>± 18.7 17.7</td>
<td>± 9.9 11.2</td>
<td>± 7.6 7.7</td>
</tr>
<tr>
<td>Ischemic heart disease, old myocardial infarction</td>
<td>4 67.0 76.0 5 17.4 28.2†</td>
<td>5 94.0 103.8§</td>
<td>5 57.8 61.4</td>
<td>5 40.3 43.6§</td>
<td>4 8.2 7.7</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>3 70.3 70.0 4 17.7 27.7§</td>
<td>4 86.7 95.8†</td>
<td>2 51.7 55.0</td>
<td>2 60.0 61.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± 18.0 9.5</td>
<td>± 11.6 7.3</td>
<td>± 12.3 11.0</td>
<td>± 27.3 27.1</td>
<td>± 11.3 11.3</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1 69.0 72.0 1 16.0 23.0</td>
<td>1 169 180</td>
<td>1 83 86 1 51</td>
<td>52.2</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD.

* p < 0.001.
† p < 0.01.
‡ p < 0.02.
§ p < 0.05.

Abbreviations: HR = heart rate; LVEDP = left ventricular end-diastolic pressure; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; n = number of subjects in whom paired observations were made; R = rest; E = plasma volume expansion.
(pressure intercept) in mm Hg, \( V = \) volume in ml, and \( k = \) constant of the exponential function in ml\(^2\). Similar analysis was done after volumes were expressed as ml/m\(^2\).

Eight other patients who were not subjected to plasma volume expansion are also included in this study. These patients underwent resting cineventriculography with catheter-tip manometers in a similar fashion to the other patients. These patients were included to compare exponential curves derived from volume-pressure data at rest with exponential curves derived from a wider range of diastolic volume-pressure values after plasma volume expansion.

One patient developed shortness of breath within 3–4 minutes of ventriculography after plasma volume expansion. Symptoms responded promptly to sublingual nitroglycerin and i.v. furosemide.

**Statistics**

The control values and values after plasma volume expansion were compared by paired \( t \) test. Groups were compared by analysis of variance with the UCLA BMDP statistical package. The relationship between \( k \) and EDV and \( k \) and ventricular mass was determined by Spearman’s rank-correlation test and was expressed as Spearman’s rank-correlation coefficient (\( r_s \)). Data are presented as mean \( \pm \) SD.

**Results**

For the entire group of 27 patients, plasma volume expansion increased LVEDP by 10.9 \( \pm \) 4.9 mm Hg, EDV by 13.7 \( \pm \) 7.1 ml/m\(^2\), ESV by 4.5 \( \pm \) 4.6 ml/m\(^2\), and EF by 3%. LVSP increased from 136.8 \( \pm \) 28 to 151.2 \( \pm \) 26.6 mm Hg (\( p < 0.02 \)) and HR increased by 6.8 \( \pm \) 7.9 beats/min. All these changes were statistically significant. There were no differences between groups in any of the hemodynamic or volumetric values at rest or after plasma volume expansion.

LV mass could be measured in only 13 patients: in five normals (range 44–177 g/m\(^2\)), in five ischemic heart disease patients (range 105–120 g/m\(^2\)) and in three patients with aortic stenosis (range 138–191 g/m\(^2\)).

**Diastolic Volume-Pressure Relationships**

Figure 1, an example of the primary data from which diastolic volume-pressure analysis was subsequently done, shows the study of a normal patient who had a left cineventriculogram at rest and three cineventriculograms at progressively higher EDPs during plasma volume expansion. Pressures were recorded by catheter-tip manometer. Respiratory variations in diastolic pressure are evident. Volume-pressure data from early diastole — between the nadir of diastolic pressure and the onset of diastasis — atrial systole and end-diastole, were superimposable with volume-pressure data obtained from the diastasis (fig. 2). Figure 3 shows volume-pressure curves constructed from data derived from the entire diastole by catheter-tip manometer in seven patients. Panels 1, 2, 4 and 5 are data from normal subjects; panel 3 shows data from a patient with aortic stenosis, panel 6 from a patient with old myocardial infarction and panel 7 from a patient with cardiomyopathy. In five patients, diastolic volume reached a limit, beyond which it did not enlarge despite further elevation of diastolic pressure. In one patient no limit was evident for diastolic pressure rising to 25 mm Hg. In another patient, a wide scatter of the data, caused mostly by respiratory variations in pressure, obscured the actual limit.

Diastolic volume-pressure curves were also constructed from end-diastolic volume-pressure data alone in 12 patients subjected to multiple left cineventriculograms at progressively increasing LVEDPs during plasma volume expansion (fig. 4). The pressures were recorded by fluid-filled catheters in nine patients and catheter-tip manometers in three. In three of the five patients who had large body surface areas, LVEDP did not exceed 20 mm Hg and the EDV/m\(^2\) = LVEDP relationship remained linear. In nine pa-
patients, LVEDP exceeded 20 mm Hg and the EDV/m²-LVEDP curve had a final steep or perpendicular part.

The constant k of the exponential equation for the volume-pressure data in figure 3 was 0.012–0.044 ml⁻¹. It was inversely related to both resting EDV ($r_s = -1.00$) and maximal EDV after plasma volume expansion ($r_s = -1.00$). When volumes were expressed as ml/m² body surface area, k was larger (0.02–0.07 ml⁻¹), but still dependent on EDV/m² ($r_s = -0.93$). The exponential constant k obtained from volume-pressure data of the entire diastole of a single ventriculogram in eight patients not subjected to plasma volume expansion correlated with EDV ($r_s = -0.90$) and was remarkably similar to the exponential constants obtained from a wider range of volume-pressure data during plasma volume expansion (fig. 5). Exponential constants derived from three to five volume-pressure points, using fluid-filled catheters, correlated moderately with EDV ($r_s = -0.70$). The relation of k to left ventricular mass in five normal subjects and three ischemic heart disease patients with normal ventricular contraction and no evidence of old myocardial infarction showed a good correlation ($r_s = -0.90$). Figure 6 depicts the relation between resting EDV and k for normal subjects and patients with heart disease. Patients with heart disease and EDV less than 200 ml have k values that are not different from those of normal subjects with similar EDV.

**Discussion**

A summary of the diastolic filling and volume-pressure relations in normal subjects is presented in figure 7. The left ventricle can enlarge its end-systolic size by 60 ml/m². Three-fourths of this diastolic

**FIGURE 2.** Volume-pressure data from the patient presented in the last panel of figure 3. Filled circles represent data from early diastole (between the nadir of diastolic pressure and the onset of diastasis), open squares data from diastasis, filled triangles atrial systole and closed squares end-diastole. The curve has been smoothed by averaging pressure for equal volumes, but the original data show similar superimposition.

**FIGURE 3.** Volume-pressure data in seven patients subjected to plasma volume expansion. Pressure was measured by catheter-tip monometer. The abscissa shows diastolic volume (ml) not divided by body surface area; the ordinate shows diastolic pressure (mm Hg).
capacity is used in the resting state and supine position and 16 ml/m² remain as “diastolic reserve.” Increasing diastolic reserve by plasma volume expansion will also increase end-systolic volume by 5 ml/m² because of a concomitant increase in systolic pressure. Therefore, the net diastolic reserve is only 11 ml/m². This finding agrees with the results of Schnabel and co-workers, who reported a 10-ml/m² increase in stroke volume in normal subjects subjected to prolonged dextran infusion. Patients undergoing cardiac catheterization might not be normovolemic. They are fasting overnight, receive no fluids for at least 12 hours and are inactive or confined to hospital beds before the procedure. The LV diastolic reserve may well be smaller than 11 ml/m². Vatner and Boettcher showed that in conscious reclining dogs with low physiologic heart rates, maximal tolerable saline infusion did not increase stroke volume, although it elevated left atrial pressure by 15 mm Hg and accelerated HR from 62 to 155 beats/min. Three mechanisms, alone or in combination, may limit left ventricular diastolic reserve: inherent sarcomere resistance to elongation beyond its optimal diastolic length; external constraints by the pericardium; right ventricular loading and coronary perfusion pressure; and acceleration of HR.

Russell and co-workers infused low-molecular-weight dextran in patients with LV power failure and observed no further increase in stroke index as LV filling pressure was increased to more than 20–24 mm Hg; in fact, cardiac index decreased in some patients. Our results also indicate that at about this level of filling pressures, the left ventricle reaches the limit of its

**Figure 4.** Sequential changes in end-diastolic volume (EDV) with progressively increasing left ventricular end-diastolic pressures (LVEDP) during plasma volume expansion. Patients are subdivided in groups of small body surface area (BSA) (top), average body surface area (middle), and large body surface area (bottom). EDV/m² (ml) = end-diastolic volume in milliliters per square meter of BSA. Open circles indicate normal subjects, filled circles ischemic heart disease with no evidence of previous myocardial infarction, filled squares old myocardial infarction, and filled triangles aortic stenosis.

**Figure 5.** Relation between resting end-diastolic volume (EDV, in ml), and exponential constant (k, in ml²). Closed circles indicate k derived from the entire diastolic volume-pressure curve in seven patients subjected to plasma volume expansion. Data were obtained by catheter-tip manometer. Open circles indicate k derived from the entire diastolic volume-pressure curve of patients who were not subjected to plasma volume expansion, but underwent resting ventriculography with catheter-tip manometers. Open triangles indicate k derived from only three to five volume-pressure measurements obtained by fluid-filled catheter.
distensibility. However, we found that diastolic pressures as high as 40 mm Hg had no adverse effect on LV systolic performance.

Noble et al., described a nonlinear volume-pressure relationship in animals and the present study confirms a similar behavior in the human heart. Most of the increase in EDV takes place with only modest elevations in diastolic pressure; therefore, most of the gain in stroke volume after plasma volume expansion can be achieved at relatively low pressures. Within this range, volume-pressure relationships remain more or less linear. Similar observations were made by McCullagh and co-workers, who used a linear fit in dogs for diastolic pressures of 5–23 mm Hg. However, to describe the entire diastolic volume-pressure behavior, some form of curvilinear fit is more appropriate. Exponential equations have been used to fit volume-pressure data in man, and the exponential constant k of this equation is considered a modulus or coefficient of volume compliance. Evidence from animal studies summarized by Mirkys indicates that the exponential constant k is dependent on LV wall volume. Our findings in man, that k is dependent on LV mass and EDV, are consistent with these animal studies and suggest caution in using k to compare compliance in different groups of patients. Indeed, for comparable EDVs, we found no difference in k between normal subjects and patients with various heart diseases.

With one exception, studies of the hemodynamic responses to acute hypervolemia have not shown significant acceleration of HR. Schnabel and co-workers reported a mean HR increase of 7.3 ± 10.5 beats/min (± SD) (p < 0.02) in normal subjects, but not in patients with mitral stenosis. Differences in HR response between the present and previous studies may reflect
different levels of LVEDP elevation after plasma volume expansion. Sanghvi and co-workers\textsuperscript{12} raised LVEDP in normal patients to \(18.4 \pm 3.2\) mm Hg with no change in heart rate, whereas in the normal subjects of the present study, LVEDP was elevated to \(22.6 \pm 6.3\) mm Hg and HR increased by 8.8 beats/min. Thus, high LV filling pressures may trigger receptors at the junction of the left atrium and the pulmonary veins\textsuperscript{20} and result in reflex tachycardia.

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