Left Ventricular Relaxation in Patients with Left Ventricular Hypertrophy Secondary to Aortic Valve Disease

Peter Eichhorn, M.D., Joerg Grimm, Ph.D., Rosemarie Koch, Lab. Tech., Otto Hess, M.D., John Carroll, M.D., and Hans P. Krayenbuehl, M.D.

SUMMARY We studied 58 patients with aortic valve disease (AVD). Twenty-three patients had aortic stenosis (AS), 17 aortic insufficiency (AI) and 18 combined lesion (AS + AI). In these 58 patients and in 10 control subjects, left ventricular (LV) high-fidelity pressure and single-beam echocardiographic measurements were carried out simultaneously. Relaxation was assessed from peak negative dP/dt (index of left-heart relaxation) and peak negative dS/dt (index of myocardial relaxation, S = meridional wall stress). Peak negative dP/dt was 1793, 1645 and 1373 mm Hg/sec in AS, AS + AI and AI, respectively, and did not differ from the value in control subjects (1589 mm Hg/sec). LV peak systolic pressure was higher in AS (212 mm Hg, p < 0.01), AS + AI (190 mm Hg, p < 0.01) and AI (144 mm Hg, p < 0.02) than in control subjects (116 mm Hg). In contrast, peak negative dS/dt was increased in AS (14055 · 10 dyne/cm²/sec, p < 0.001), in AS + AI (144710 dyne/cm²/sec, p < 0.001) and in AI (1355· 10 dyne/cm²/sec, p < 0.02) compared with control subjects (900· 10 dyne/cm²/sec). LV Speak was 131· 10 dyn/cm² in controls and was increased (p < 0.01) in all three groups with AVD (261, 257 and 212· 10 dyn/cm², respectively). Linear regression analysis between peak negative dS/dt and Speak yielded significant correlations in controls (r = 0.84), in 27 patients with AVD and normal LV systolic function (r = 0.79) and 31 patients with AVD and depressed LV systolic function (r = 0.79). Slopes and intercepts of these three regressions did not differ significantly. In 33 patients with AVD (12 AS, 11 AS + AI, 10 AI) in whom the early relaxation phase (A + to mitral valve opening) could be determined from combined echocardiographic measurements the time constant of LV pressure decay (T) was calculated from the regression plot of negative dP/dt vs LV pressure. T, which was also considered an index of chamber relaxation, was increased in AS (67 msec, p < 0.01), in AS + AI (68 msec, p < 0.01) and in AI (56 msec, p < 0.05) compared with control subjects (41 msec). T was similar in 20 patients with depressed and 13 with normal LV systolic function. T did not correlate with Speak but did correlate with LV angiographic mass (p < 0.01, r = 0.40).

We conclude that in LV hypertrophy secondary to AVD, the speed of left-heart relaxation is impaired, but the peak rate of myocardial relaxation is unaltered. Abnormalities of LV systolic function have no direct bearing on relaxation, and the extent of LV hypertrophy appears to be a determinant of left-heart relaxation.

The speed of left ventricular relaxation has been investigated at rest in patients with coronary artery disease1,2 and after induction of acute ischemia.3 Only a few reports deal with the relaxation process in the hypertrophied myocardium. Studying cat papillary muscles hypertrophied from chronic pressure overload, Parmley and Sonnenblick7 found an increased time constant of isometric tension decline after an afterloaded contraction. Increased duration and reduced velocity of relaxation were reported in isovolumically contracting hypertrophied left hearts of rats whose abdominal aorta had been coarcted for 3 months.8 In patients with hypertrophic cardiomyopathy, an increased time constant of isovolumic left ventricular pressure decay (assessed from the quotient Fpeak negative dP/dt/peak negative dP/dt)9 and a prolonged time interval from the point of minimal left ventricular cavity dimensions to mitral valve opening (MVO)10 have been described. Delayed MVO was also observed in patients with aortic stenosis before as well as after aortic valve replacement.10,11 Although these investigations suggest impaired relaxation in hypertrophy, the analyses in humans with hypertrophy5-11 appear to be incomplete because they do not take into account the size and the wall thickness of the left ventricle, which can be markedly abnormal in patients with hypertrophy.

We studied left ventricular relaxation in patients with secondary hypertrophy from aortic valve disease using both peak rate of decay of left ventricular pressure (peak negative dP/dt) and of meridional wall stress (peak negative dS/dt) as indexes of relaxation. We also investigated the relationship of these indexes of relaxation to systolic function and, in a subgroup of patients with hypertrophy, determined the time constant of left ventricular pressure decay during the early relaxation phase.12

Material and Methods

Patients

Fifty-eight patients (47 males and 11 females) with aortic valve disease underwent diagnostic right- and left-heart catheterization, single-beam echocardiography and biplane right (RAO) and left anterior (LAO) oblique cineangiography. Premedication consisted of 10 mg of oral Librium. After the diagnostic part of the investigation, a Millar #7F micromanometer-tip angiographic catheter was introduced trans-
septally into the left ventricle. Informed consent was obtained for this study. The hemodynamic data characterizing the three types of aortic valve disease are presented in Table 1. Twenty-three patients had aortic stenosis (AS) defined as an aortic mean systolic pressure gradient (MSPG) ≥ 20 mm Hg and an aortic regurgitation fraction (fao) < 0.20 by thermoculmination. Eighteen patients had both aortic stenosis and aortic insufficiency (AS + AI) (MSPG ≥ 20 mm Hg, fao ≥ 0.20) and 17 had AI (MSPG < 20 mm Hg, fao ≥ 0.20). Selective coronary arteriography was performed in 47 patients and excluded coronary artery disease in 44. Two patients had a 50% stenosis of the left anterior descending coronary artery and one patient had a 50% stenosis of the circumflex artery. The left ventricular cineangiogram showed no localized wall motion abnormality in these patients. The 11 other patients (nine males and two females), all of whom were younger than 38 years old, did not undergo coronary arteriography. All patients were in sinus rhythm and the duration of the QRS did not exceed 0.11 second. Thirty-four of the 58 patients were taking maintenance doses of digitalis at the time of catheterization.

Ten patients (five males and five females) with minimal or no heart disease who were investigated by the same techniques served as controls. The diagnoses were functional systolic murmur in four patients and small aorti atrial defect, minimal infundibular pulmonic stenosis, dilated ascending aorta, atypical chest pain, minimal mitral insufficiency and slight mitral valve prolapse without reflux in one patient each.

**Measures of Systolic Function**

The first derivative (dP/dt) and the instantaneous quotient ([dP/dt]/P) of left ventricular pressure were obtained from the high-fidelity left ventricular pressure curves recorded at a paper speed of 200 or 250 mm/sec on an oscillograph (Electronics for Medicine DR-16 or VR-12). The peak measured velocity of contractile element shortening (Vpm) was calculated as previously reported. Normal Vpm in our laboratory is 1.14–1.96 muscle lengths (ML)/sec. The second index of systolic function was the ejection fraction (EF), derived from the biplane RAO and LAO cineangiograms using the area-length method for volumetric calculations. Extrasystolic and postextrasystolic beats were excluded from the analysis. In the control subjects, EF was 0.62–0.83, but we considered an EF ≥ 0.57 as normal because in a larger control group of 20 patients with atypical chest pain or functional murmur (mean age 38 years) studied by conventional pressure measurements and biplane cineangiography EF ranged from 0.57–0.83 (mean 0.68).

Left ventricular end-diastolic wall thickness was determined from the middle third of the anterior portion of the RAO silhouette in 31 patients and from the posterolateral portion of the LAO silhouette in 22 patients. There was an excellent correlation (r = 0.91) between LAO wall thickness (y) and RAO wall thickness (x) (y = 0.983x + 0.069; see 0.11 cm; n = 20). Wall thickness was determined in 15 patients from a second cineangiogram filmed in the anteroposterior projection. Left ventricular muscle mass was calculated as the volume of the muscle shell distributed evenly around the RAO end-diastolic volume × 1.05 (specific gravity).

**Indexes of Left Ventricular Relaxation**

The echocardiograms were obtained with an Ekoline 20A echocardiograph (Smith-Kline Instruments) interfaced to the Electronics for Medicine DR-16 recorder or with an echocardiograph Electronics for Medicine V-3280 interfaced to the VR-12 oscillograph. The recordings were made with a 2.25-MHz, ¾- or ½-inch diameter transducer (intermediate collimation) with the patients in the anteroposterior or slight right anterior decubitus position. The left ventricular high-fidelity pressure tracings and the echocardiograms were recorded together with the conventional aortic pressure tracing, a peripheral lead of the ECG and the external phonocardiogram at a paper speed of 100 mm/sec (fig. 1). All recordings were made before injection of contrast dye. Peak negative

| Table 1. Hemodynamic Data Characterizing Aortic Valve Disease |
|---|---|---|---|
| Age (years) | MSPG (mm Hg) | fao | AVA (cm²) |
| 1. Controls (n = 10) | 31 (19-51) | 69 < 0.01 (21-70) | 0.66 (0.10-0.19) |
| 2. AS (n = 23) | 52 p (2 vs 1) = 0.01 (21-120) | 0.16 n = 6 |
| 3. AS + AI (n = 18) | 48 p (3 vs 1) = 0.01 (24-65) | 0.42 (21-126) |
| | p (3 vs 2) NS | 1.24 (0.20-0.68) |
| 4. AI (n = 17) | 42 p (4 vs 1) < 0.02 (18-69) | 0.58 (6-18) |
| | p (4 vs 2) < 0.05 n = 4 |
| | p (4 vs 3) NS |

Mean values are shown, with ranges in parentheses.

Abbreviations: AVA = aortic valve area; AS = aortic stenosis; AI = aortic insufficiency; fao = aortic regurgitation fraction; MSPG = mean systolic pressure gradient across the aortic valves.
endocardial border of the septum and the endo- and epicardial borders of the posterior wall, were digitized by hand with an electronic digitizer (Numonics) interfaced to a PDP-11 computer equipped with a printer-plotter (Versatec). The resolution of the digitizer was 0.25 mm and the paper speed 100 mm/sec; we thus obtained 400 coordinates/sec. All variables were printed out by computer 130 times per cardiac cycle. From the digitized data, the following instantaneous measurements were derived and presented as computer plots (fig. 2) and as numerical tables: left ventricular internal diameter (D), posterior wall thickness (h), intraventricular pressure (P) and dP/dt, meridional wall stress (S) \( ^{14} \) (calculated as \( P \cdot D/4h \cdot [1 + h/D] \)) and dS/dt. In each patient a cardiac cycle whose end-diastolic pressure corresponded to the arithmetic mean of the highest and the lowest end-diastolic pressures of a respiratory swing was digitized by two observers. The data used in an individual patient represent the average of the two observers. The mean percent error ([first observer - second observer] \* 100/average of both observers) between the two observers evaluated in 32 instances was 1.2 ± 0.9% (± sd) for D at end-diastole, 6.1 ± 5.9% for h at end-diastole, 6.6 ± 4.8% for Speak and 11.6 ± 8.3% for peak negative dS/dt. Similarly, variation of these variables between two beats (32 pairs) with end-diastolic pressures as close as possible (average difference 2.9 ± 2.0 mm Hg) was evaluated by one observer and amounted to 3.9 ± 4.1% for D at end-diastole, 9.5 ± 7.8% for h at end-diastole, 13.5 ± 10.7% for Speak and 17.2 ± 13.4% for peak negative dS/dt.

Another index of relaxation is the time constant (T) of the exponential pressure decay after peak negative

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**Figure 1.** Single-beam echocardiogram, left ventricular high-fidelity (LVP) and conventional aortic pressure (AoP) tracing, first derivative of LVP (dP/dt), external phonocardiogram (PCG) and ECG of a 51-year-old patient with pure aortic stenosis (AS) (aortic valve area 0.65 cm\(^2\)). The heavy echo within the left ventricular cavity posterior to the left endocardial border of the interventricular septum (IVS) stems from the transseptal Brockenbrough catheter. PW = posterior wall of the left ventricle.

dP/dt and peak negative dS/dt were determined by computer. 16 For this purpose, the left ventricular pressure curve and the echocardiogram obtained just below the mitral valve, including the left ventricular

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**Figure 2.** Computer plots obtained after digitization of the echo-pressure curves in figure 1. (upper left) The traced contours of the left endocardial border of the interventricular septum (SEPT) and of the endocardial and epicardial (EPIC) border of the posterior wall of the left ventricle. (lower left) The traced left ventricular (LV) pressure curve. (upper right) The LV dimension. (lower right) The computed meridional wall stress (mer. strs) throughout the cardiac cycle. The end-diastolic pressure, the first vibrations of the aortic component of the second heart sound (A\(_2\)) and the echocardiographic mitral valve opening are marked.
Table 2. Pressure-derived Systolic and Angiographic Data

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<th>BSA (m²)</th>
<th>HR (beats/min)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>peak dP/dt (mm Hg/sec)</th>
<th>Vpm (ML/sec)</th>
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<td>1. Controls</td>
<td>1.72 ± 0.17</td>
<td>71 ± 13</td>
<td>116 ± 11</td>
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<td>(1.52–2.03)</td>
<td>(49–96)</td>
<td>(102–132)</td>
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| n = 10
| 2. AS         | 1.73 ± 0.12 | 75 ± 15      | 212 ± 38     | 18 ± 8        | 1864 ± 496             | 1.36 ± 0.39 | 127 ± 31     |
|                | (1.48–1.95) | (50–104)     | (152–284)    | (7–38)        | (975–3108)             | (0.69–2.17) | (78–220)     |
| 23
| 3. AS + AI    | 1.75 ± 0.17 | 74 ± 13      | 190 ± 33     | 20 ± 8        | 1570 ± 333             | 1.19 ± 0.31 | 176 ± 64     |
|                | (1.39–1.98) | (58–104)     | (150–265)    | (5–35)        | (1011–2200)            | (0.56–1.82) | (92–317)     |
| n = 18
| 4. AI         | 1.77 ± 0.14 | 73 ± 13      | 144 ± 22     | 15 ± 8        | 1300 ± 282             | 1.27 ± 0.26 | 243 ± 50     |
|                | (1.48–1.94) | (53–108)     | (109–190)    | (5–32)        | (975–2050)             | (0.73–1.81) | (1.69–359)   |

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Values are mean ± SD. Ranges are given in parentheses.

Abbreviations: AI = aortic insufficiency; AS = aortic stenosis; BSA = body surface area; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; HR = heart rate; LMMI = left ventricular muscle mass; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular end-systolic pressure; peak dP/dt = maximal rate of rise of left ventricular pressure; Vpm = peak measured velocity of shortening of the contractile elements; ML = muscle lengths.

dP/dt up to mitral valve opening.12, 17, 18 Although the calculation of T would at first glance only make sense in subjects with an isovolumic relaxation period and therefore would apply solely to our controls and the patients with pure AS, we extended the estimation of T also to the patients with aortic regurgitation because the delay in pressure decay due to blood influx into the left ventricle after A2 is counteracted by the acceleration effect of force or elongation on the relaxing muscle.19 Assuming that the acceleration effect compensates for the effect of influx, an increased T (reduced rate of pressure decay) in the presence of aortic regurgitation is likely to represent a true reduction of the speed of relaxation.

In 33 patients with aortic valve disease (12 AS, 11 AS + AI, 10 AI) and in the 10 controls, A2 and echocardiographic MVO were clearly visible. The time interval between A2 and MVO represents the early relaxation phase (ERP), the pressure decay used to calculate T. ERP was measured in four or five heart cycles and the average value (ERP) was added to the time at A2 marked on the tabulated printout of the pressure cycle chosen for analysis. All negative dP/dt and P values falling within ERP were used to calculate T except those at or before peak negative dP/dt. In patients in whom peak negative dP/dt occurred before A2, the calculation of T was begun at A2. T was determined using the technique originally suggested by Murgo and Craig and described by Weisfeldt et al.12 that allows the calculation of T when only intracavitary pressure rather than transmural pressure is measured or when there are baseline shifts in the pressure record (fig. 3).

Statistical Analysis

For intergroup comparisons, the SPSS program ONEWAY was used. If the analysis of variance was significant, p values were obtained by the least-significant-difference (LSD) procedure; otherwise, the Scheffe procedure was applied. For the interpatient comparison of correlation coefficients of linear regression analyses (negative dP/dt vs P), the Wilcoxon rank-sum test was used. Slopes and intercepts of regression lines were compared by covariance regression analysis.21

Results

Hemodynamic Data and Indexes of Systolic Function (table 2)

Left ventricular peak systolic and end-diastolic pressure, end-diastolic volume index and muscle mass index were significantly greater in all three groups with aortic valve disease than in the control group. End-systolic volume index was increased significantly only in patients with AS + AI and AI. Heart rate did not differ between the four groups. Vpm and biplane EF were significantly reduced in the three groups with aortic valve disease except EF in the patients with AS. Thirty-one patients had depressed Vpm (< 1.14 ML/sec) or EF (< 0.57) (10 AS, nine AS + AI, 12 AI). In 27 patients with aortic valve disease, both systolic contractile indexes were normal.

Indexes of Left Ventricular Relaxation (table 3)

Peak negative dP/dt did not differ significantly between the three groups with aortic valve disease and the control subjects. In contrast, peak negative dS/dt was significantly increased in all three groups with aortic valve disease. Peak systolic meridional wall stress was also significantly increased in AS, AS + AI and AI. In the control subjects and in the two subgroups of the patients with aortic valve disease and either normal (n = 27) or depressed (n = 31) left ventricular systolic function, there were significant linear
correlations between peak negative dS/dt and peak systolic stress (fig. 4) ($r = 0.84, 0.79$ and $0.79$, respectively). The slopes and the intercepts of the three linear regressions did not differ significantly. Thus, peak negative dS/dt was related to peak systolic stress regardless of the level of systolic function.

Peak negative dS/dt occurred before peak negative dP/dt and $A_2$ in all four groups (table 4). The time interval between peak negative dS/dt and peak negative dP/dt was somewhat longer in the patients with aortic valve disease than in the control subjects (NS). Peak negative dP/dt occurred at or within a few msec of the first vibrations of $A_2$. No statistical differences between the four groups were observed.

The early relaxation phase (table 3) was slightly and insignificantly longer in the patients with aortic valve disease than in the controls. T was significantly greater in all three groups with aortic valve disease than in the control group.

The correlation coefficients of the individual regressions of negative dP/dt vs P during the ERP that served for the determination of T were higher in the control subjects than in the three groups with aortic valve disease (table 3). The lower correlation coefficients in the patients with aortic valve disease (fig. 5) occurred because the relationship of negative dP/dt vs P showed often a biphasic slope with an early flat portion and a steeper portion toward MVO. To test whether the faster left ventricular pressure fall before MVO might have been related to the aortic reflux — even though a progressively faster decrease appeared unlikely because, theoretically, the acceleration effect must cease as soon as it overcompensates the delaying effect on pressure decay due to blood influx after $A_2$ — the $r$ values of patients with AS in whom no aor-

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Determination of the time constant of isovolumic pressure decay (T) from the linear regression between negative dP/dt and left ventricular pressure (LVP). The data are from a control subject whose average early relaxation phase (ERP) was 65 msec, during which nine pairs of data points were obtained. The formula for the least-squares regression was $\frac{dP}{dt} = \frac{1}{T} (P - P_b)$, which derives from the general formula of exponential pressure decay $P = P_o \cdot e^{-t/T} + P_b$, where $P_b$ is an additional pressure different from zero reference level for P (as with baseline shifts). From the slope (A) of the least squares regression, T was calculated as $1/A$. Curve shifts with respect to the baseline do not influence the determination of T. When the pressure curve is shifted upward by the amount $P_b$ from the lowest (dashed) curve position to the highest (dashed-dotted) curve, the regression line (triangles) is displaced to the right (open circles) by the amount $P_b$. The slope of the regression line, and hence T, remain the same. The traditional method of estimating $T^2.18$, where T is determined from the inverse slope of the plot lnP vs time, would have elicited different values of T for the four curves. The longest T would have been obtained from the curve with the largest upward shift (dotted-dashed curve) and the shortest from the lowest (dashed) curve.
Table 3. Relaxation Data

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<th>Peak neg dP/dt (mm Hg/sec)</th>
<th>S_{peak} (dyn ⋅ cm^2)</th>
<th>Peak neg dS/dt (dyn ⋅ cm^2/sec)</th>
<th>ERP (msec)</th>
<th>T (msec)</th>
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<tr>
<td>1. Controls</td>
<td>1589 ± 267 (1289–2137)</td>
<td>131 ± 50 (81–223)</td>
<td>900 ± 421 (488–1600)</td>
<td>53 ± 17 (28–78)</td>
<td>41 ± 12 (24–61)</td>
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<td>2. AS</td>
<td>1793 ± 430 (821–2581)</td>
<td>261 ± 88 (146–463)</td>
<td>1415 ± 572 (763–2983)</td>
<td>68 ± 19 (39–101)</td>
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<td>3. AS + AI</td>
<td>1645 ± 407 (1296–3007)</td>
<td>257 ± 86 (127–444)</td>
<td>1467 ± 447 (833–2353)</td>
<td>74 ± 26 (50–124)</td>
<td>68 ± 17 (43–100)</td>
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<td>4. AI</td>
<td>1273 ± 233 (928–1890)</td>
<td>212 ± 68 (118–391)</td>
<td>1355 ± 458 (648–2505)</td>
<td>79 ± 34 (41–136)</td>
<td>56 ± 11 (38–71)</td>
<td>0.975 ± 0.016 (0.942–0.993)</td>
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Values are mean ± sd. Ranges are given in parentheses.

Abbreviations: ERP = early relaxation phase; peak neg dP/dt = maximal rate of decay of left ventricular pressure; peak neg dS/dt = maximal rate of decay of left ventricular meridional wall stress; r = correlation coefficient of individual regressions of negative dP/dt vs P during ERP; S_{peak} = peak systolic meridional wall stress; T = time constant of left ventricular pressure decay during ERP. Other abbreviations as in table 2.

tic reflux was detectable (pure AS, n = 9) were compared with those of the controls. In pure AS, r = 0.972 ± 0.022 (p < 0.05 vs controls, r = 0.988 ± 0.009). In the other patients with aortic valve disease (n = 24; three AS with minimal reflux, 11 AS + AI, 10 AI) who had minimal-to-severe aortic reflux, r = 0.969 ± 0.019 (p < 0.002 vs controls). Thus, the biphasic slope is probably inherent to the relaxation of the hypertrophied left ventricle in aortic valve disease.

When the 33 patients with aortic valve disease in whom T was determined were further divided into a group with normal (n = 13) and a group with depressed (n = 20) left ventricular systolic function, T did not differ significantly (65 ± 21 and 63 ± 15 msec, respectively). Linear regression analysis in the 10 control patients and the 33 patients with aortic valve disease yielded no significant correlation between T and ERP. T and left ventricular muscle mass index correlated significantly (p < 0.01, r = 0.40). T did not correlate with left ventricular peak systolic stress.

Discussion

Left ventricular relaxation was assessed by peak negative dP/dt, peak negative dS/dt, ERP and T.

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Linear regression between peak rate of decay of wall stress (peak negative dS/dt) and left ventricular peak systolic stress in the control (C) subjects (dots), in the patients with aortic valve disease and normal (N) systolic function (open triangles, dashed regression line) and patients with aortic valve disease and depressed (D) systolic function (asterisks, dashed-dotted regression line). The slopes and the intercepts of these regression lines did not differ significantly.
Peak negative dP/dt was not significantly different in the three groups of patients with aortic valve disease or in the controls. However, peak negative dP/dt does not reflect exclusively the inherent speed of relaxation of the left ventricle, but is also influenced by the peak systolic pressure, the end-systolic fiber length and the heart rate. If these determinants of peak negative dP/dt, which have been evaluated in acute studies in experimental animals, are operative in patients with chronic left ventricular pressure and volume overload the following arguments appear to be pertinent: In all three groups of aortic valve disease, left ventricular peak systolic pressure was increased and end-systolic volume index, which might be taken as a measure of end-systolic fiber length, was increased in AS + AI and in AI. Heart rate did not differ. Thus, in the patients with aortic valve disease the determinants of peak negative dP/dt were altered as to produce a higher-than-normal peak negative dP/dt. However, this was not observed (fig. 6) and therefore a relative depression of peak negative dP/dt and hence an impaired speed of left ventricular relaxation appeared to be present in the three groups of aortic valve disease. The determinants of peak negative dS/dt have to

![Linear regression between negative dP/dt and left ventricular pressure (LVP) during the early relaxation phase (interval A, to mitral valve opening [MVO]) in four patients. The best fit was found in the control subject (upper left). In the three patients with aortic valve disease — one with pure aortic stenosis (AS) (upper right), one with AS and small aortic insufficiency (AI) (lower left) and one with AI (lower right) — the slope was biphasic, with an early flat portion and a steeper portion toward MVO. The most marked change in slope toward MVO occurred in the patient with AI. Despite the faster slope in the second part of the regression line in the three patients with aortic valve disease, which would tend to shorten T, T was longer than in the control subject. Thus, a true increase of T does exist in aortic valve disease. fao = aortic regurgitation fraction; A, = aortic component of the second heart sound; T = time constant of left ventricular pressure decay.](http://circ.ahajournals.org/doi/10.1161/01.CIR.109.3.1401)
Figure 6. Relationship between peak negative dP/dt and left ventricular peak systolic pressure (LVSP) (left) and between peak negative dS/dt and peak systolic stress (right). Despite a significant increase of LVSP in all three groups with aortic valve disease, peak negative dP/dt did not differ significantly from that in the control group. This indicates a relative depression of peak negative dP/dt and, hence, impaired relaxation of the left-heart chamber. In contrast, the increased peak systolic stress in the three groups with aortic valve disease was associated with an increased peak negative dS/dt. Thus, left ventricular myocardial relaxation appears to be unaltered. Peak negative dP/dt = peak rate of decay of left ventricular pressure; peak neg dS/dt = peak rate of decay of left ventricular meridional wall stress; C = control group; AS = aortic stenosis; AS + AI = combined aortic valve lesion; AI = aortic insufficiency.

our knowledge not been defined in the ejecting left ventricle of the experimental animal. In analogy to the increase of peak negative dP/dt consequent to an increase in left ventricular peak systolic pressure,22-24 an increase in peak negative dS/dt at an increased peak systolic stress would be expected. In fact, significantly increased values of peak negative dS/dt in AS, AS + AI and AI were associated with commensurately increased values of peak systolic stress (fig 6). Moreover, the relationship between peak negative dS/dt and peak wall stress was similar in patients with normal and those with depressed left ventricular systolic function (fig. 4). Thus, based on peak negative dS/dt, relaxation was unaltered in secondary hypertrophy from aortic valve disease and peak negative dS/dt seems to be determined by peak stress regardless of the actual level of systolic function.

The conclusions as to the presence or absence of relaxation disturbances one derives from the relationship between peak negative dP/dt and P on one hand and from the relationship between peak negative dS/dt and peak stress on the other appear at first glance to be contradictory. However, peak negative dP/dt is related primarily to the speed of relaxation of the left-heart chamber, whereas peak negative dS/dt might reflect more closely the speed of left ventricular myocardial relaxation. Because in normal subjects28 and in patients with hypertrophy,11 shortening of the left ventricular diameter and thickening of the wall progress until A₂ or sometimes until MVO, the rate of decay of muscle stress does not parallel the rate of pressure decline, and hence, the latter may be modulated such that peak negative dS/dt increases, while peak negative dP/dt does not change. Thus, in hypertrophied states, relaxation dynamics of the chamber could be abnormal despite normal relaxation of the myocardial fibers. We recognize that the calculation of meridional wall stress does not take into account left ventricular geometry, as the long ventricular axis was not determined. However, no method allows two-dimensional images of the left ventricular cavity to be recorded fast enough to determine the events of relaxation. Two-dimensional echocardiography has an image rate of 30 frames/sec and standard cineangiography 50 frames/sec; in the present study, the simultaneous echo-pressure measurements were digitized at a rate of 400 coordinates/sec. Nevertheless, single-beam echocardiography is not ideal for determining meridional wall stress because we have no proof that left ventricular diameter and wall thickness are measured strictly at the same myocardial location throughout the cardiac cycle. We also assume that with respect to the long ventricular axis, the echocardiographic measuring site was at the same height. However, the tips of the mitral valve may not be at the same cross-sectional level in a normal and an elongated left ventricle. Finally, we had to assume that the myocardial properties at the site of measurement are representative of the entire left ventricle.

The early relaxation phase was somewhat longer in the patients with aortic valve disease than in the control subjects (NS). Gibson et al.10 and Hanrath et al.11 reported an increased time interval between minimal cavity dimension and the onset of mitral valve opening in patients with secondary hypertrophy from aortic stenosis or arterial hypertension. This specific time interval is shorter than the true ERP, and direct comparison with the true ERP is complicated because there is no consistent relationship between A₂ and minimal cavity dimension in various forms of left ven-
tricular disease. Hence, our finding of an insignificant prolongation of the ERP may not be at variance with the observations of Gibson et al. 10 and Hanrath et al. 11

The time constant of left ventricular pressure decay during the ERP was significantly increased in all three groups of aortic valve disease. Because T is independent of peak systolic pressure, stroke volume and fiber shortening velocity, 18 the increased T in aortic valve disease seems to indicate an intrinsic depression of the speed of relaxation of the left-heart chamber in these patients. T was similarly increased in patients with and without depression of left ventricular systolic function. Thus, the level of systolic function has no direct bearing on the intrinsic speed of left ventricular relaxation. In contrast, T and left ventricular muscle mass correlated significantly, although the correlation coefficient was low. Therefore, hypertrophy of the ventricle by itself, regardless of the systolic performance, might be considered a determinant of the speed of left ventricular pressure decay.

The plots of negative dP/dt vs left ventricular pressure from which T was determined elicited the highest correlation coefficients in the control subjects. In the patients with aortic valve disease, an early flat and thereafter a steeper slope was present. Thus, in the hypertrophied left ventricle there is no absolutely true exponential pressure decay during the early relaxation phase. Similar observations have been made by Rousseau et al. 2 in patients with coronary artery disease. In the absence of a true exponential decay of the left ventricular pressure, the number of data points included in the calculation of T is important. Because with ongoing relaxation the plot of negative dP/dt vs left ventricular pressure becomes steeper (fig. 5), including data points beyond the MVO that is likely to occur when data points are used down to the level of end-diastolic left ventricular pressure 19, 20 leads to a too short T. Conversely, the use of a fixed time interval (80 msec) 2 would lead to an erroneously long T when the effective early relaxation phase exceeded the assumed time interval. Therefore, we believe that the calculation of T requires determination of the exact time of MVO.

The duration of ERP did not correlate significantly with T. This implies that a valid assessment of the time course of left ventricular pressure decay from the noninvasive determination of the ERP is precluded.

In conclusion, the unchanged peak rate of left ventricular pressure decay at an increased peak systolic pressure and the increased time constant of pressure decay during the early relaxation phase indicate an impaired speed of left-heart relaxation in patients with secondary hypertrophy from aortic valve disease. The magnitude of the time constant was related to left ventricular hypertrophy as estimated from the angiographic muscle mass, but did not differ between patients with normal and those with depressed left ventricular systolic function. In contrast to left-heart relaxation, myocardial relaxation appears to be unaltered because peak rate of decay of left ventricular wall stress was increased in accordance with the increased peak systolic stress.

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The Relationship Between the Strength of the Human Heart Beat and the Interval Between Beats


SUMMARY In 15 patients undergoing cardiac catheterization and pacing tests, the left ventricular (LV) pressure and its maximum rate of rise (LV dP/dt max) were measured with catheter-tip manometers. Atrial or ventricular pacing at a single steady frequency (the priming frequency) was followed by a test pulse at a varying interval (test pulse interval). In 14 subjects in whom it was examined, the contractile response after the test pulse increased with test pulse interval to reach a maximum plateau value — the optimum contractile response (OCR). In five cases, further prolongation of the test pulse interval decreased the contractile response. The optimum test pulse interval occurred at 800–900 msec. An increase in the priming frequency before the introduction of the test pulse caused a progressive increase in OCR, in contrast to the minor effects on LV dP/dt max of the control beats. Similar results were recorded in four other patients in whom contractile response was assessed from the rate of rise of right ventricular pressure. These results indicate that with tachycardia, the interval between beats is insufficient to allow maximum contractile performance (presumed to be activated by calcium ions) to develop. The true effect of increasing heart rate is only revealed by the relationship between OCR and the preceding frequency of contraction.

RECENT STUDIES in isolated muscle and in intact animal hearts have given insight into the mechanisms relating contractile behavior, electrical events in the cell membrane and the interval between beats.1-8 These studies have demonstrated dependence of contractile force of a beat upon the interval preceding it and the force, action-potential duration, and timing of the beats leading up to that interval. These findings have been interpreted in terms of calcium fluxes into and within the cell. The concept has arisen of an intracellular calcium store whose contents are discharged to activate the contractile proteins on each depolarization. This store takes a finite time to refill, and thereafter loses calcium by leakage if depolarization is delayed; thus, an optimum interval between beats exists. The store is filled from two sources: calcium released from the contractile proteins on the previous beat and calcium entering the cell during the depolarization phase of previous action potentials. Thus, there is also dependence upon the force and frequency of preceding beats.

Interval-strength relationships in animal preparations can be explained by such a model, and we wished to establish whether it was also applicable in man. We therefore examined the relationship between an index of contractile force and beat-to-beat interval in conscious human subjects with and without coronary artery disease.

Methods

Patients

Each patient gave informed consent before the study, which had been approved by the Ethical Committee of the Brompton Hospital. Subjects were studied during the course of diagnostic cardiac catheterization, without premedication. We did not make the decision to perform cardiac catheterization. Clinical and catheterization findings for the patients in whom we studied mechanical performance of the left ventricle are listed in Table I. Eight of these (group A) had no significant hemodynamic abnormality; seven
Left ventricular relaxation in patients with left ventricular hypertrophy secondary to aortic valve disease.

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