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Mechanisms for Left Ventricular Systolic Dysfunction in Aortic Regurgitation: Importance for Predicting the Functional Response to Aortic Valve Replacement

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To test the hypothesis that the combined use of the time-varying elastance concept and conventional circumferential stress-shortening relations would elucidate differential mechanisms for left ventricular systolic dysfunction in severe, chronic aortic regurgitation and therefore predict the functional responses to aortic valve replacement, 31 control patients and 37 patients with aortic regurgitation were studied. The studies included micromanometer left ventricular pressure determinations, biplane contrast cineangiograms under control conditions and radionuclide angiograms under control conditions and during methoxamine or nitroprusside infusions with right atrial pacing.

The patients with aortic regurgitation were classified into three groups: Group I had normal E_{max} and stress-shortening relations, Group II had abnormal E_{max} but normal stress-shortening relations and Group III had abnormal E_{max} and stress-shortening relations. The left ventricular end-diastolic and end-systolic volumes showed a progressive increase and the ejection fraction showed a progressive decrease from Group I to III; these values differed from those in the control patients ($p < 0.001$). In Group I, there was a decrease in left ventricular volumes ($p < 0.05$) but no significant change in ejection fraction (61 ± 7% versus 63 ± 4%) after aortic valve replacement. In contrast, in Group II, reduction in left ventricular volumes ($p < 0.01$) was associated with an increase in ejection fraction from 50 ± 8% to 64 ± 11% ($p < 0.01$). Finally, in Group III, reduction in left ventricular volumes ($p < 0.05$) was associated with a further decrement in ejection fraction from 35 ± 13% to 30 ± 13%.

Group I patients had compensated adequately for chronic volume overload. However, Group II had left ventricular dysfunction that was associated with an increase in the left ventricular volume/mass ratio compared with that in the control patients and Group I ($p < 0.05$ for both), suggesting inadequate hypertrophy and assumption of spherical geometry. Finally, irreversible myocardial dysfunction had supervened in Group III.

In conclusion, a combined analysis of left ventricular chamber performance using the time-varying elastance concept and myocardial performance using conventional circumferential stress-shortening relations provides complementary information that elucidates differential mechanisms for left ventricular systolic dysfunction and therefore predicts the functional response to aortic valve replacement.

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It has been suggested that patients with severe, chronic aortic regurgitation follow a predictable and potentially identifiable hemodynamic course, which is characterized by progressive left ventricular dilation and dysfunction (1). Initially, compensated left ventricular hypertrophy is followed by progressive left ventricular dilation with impaired performance, presumably without irreversible myocardial dysfunction and then, late in this hemodynamic course, irreversible myocardial dysfunction supervenes. If the mechanism for left ventricular systolic dysfunction, occurring before irreversible myocardial dysfunction, could be elucidated, then hemodynamic data might emerge to explain the favorable effects of aortic valve replacement on left ventricular systolic performance observed in some patients with aortic regurgitation and left ventricular dysfunction.

Clinical, noninvasive and invasive descriptors have been proposed to guide the referral of patients with aortic regurgitation for aortic valve replacement (2–18). Indexes that indicate a markedly enlarged left ventricle with impaired performance have, in general, predicted a poor functional response to aortic valve replacement (9–12,15–17). This is presumably because these indexes identify patients in

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whom irreversible myocardial dysfunction has supervened (7,19,20). Individual patients with aortic regurgitation who fulfill these criteria may have a good response to aortic valve replacement (7). However, these indexes of left ventricular size and performance have been unable to elucidate mechanisms for left ventricular systolic dysfunction. This may be due to their variable load dependence (21–23) and their potential for errors in the assessment of left ventricular size and performance (24).

Accordingly, we hypothesized that a more complex hemodynamic approach, which employed the time-varying elastance concept to evaluate left ventricular chamber performance and conventional stress-shortening relations to assess myocardial performance, would elucidate differential mechanisms for left ventricular systolic dysfunction in patients with aortic regurgitation and thus would predict the functional response to aortic valve replacement.

Methods

Study patients. *Control group.* The study groups consisted of 31 control patients who were referred for cardiac catheterization to evaluate an atypical chest pain syndrome and 37 patients with severe, chronic aortic regurgitation. Time-varying elastance (E_{max}) data have been previously reported (25) for 25 of the control patients, who are used here to establish normal limits for E_{max}. Also, 10 of these 25 control patients and 6 additional control patients had one or more biplane contrast cineangiograms performed to calculate normal values for conventional stress-shortening relations. The control group comprised 25 men and 6 women with an age range of 33 to 71 years (mean ± SD 52 ± 10). The patients had a normal physical examination, electrocardiogram (ECG) and chest radiograph and at cardiac catheterization they had normal left ventricular pressure, volume, ejection fraction and mass (26).

Aortic regurgitation group. The patients with aortic regurgitation consisted of 32 men and 5 women with an age range of 23 to 78 years (mean 55 ± 16). They were drawn from a larger group of 51 consecutive patients who were referred for cardiac catheterization to establish the hemodynamic significance of their valvular heart disease. Fourteen of these 51 patients were not included in this investigation because of concomitant aortic stenosis (n = 2) or coronary artery disease (n = 4), technical difficulties with data acquisition (n = 5) or patient refusal (n = 3). The 37 patients were in clinical class I to IV by New York Heart Association criteria (27), had an aortic pulse pressure/systolic pressure ratio of ≥ 0.50 (28); an ECG demonstrating left ventricular hypertrophy by Romhilt and Estes criteria (29) in 23 patients; a chest radiograph showing cardiomegaly, that is, a cardiothoracic ratio of 0.50 or more, in 18 patients; and angiographic 3+ or 4+ aortic regurgitation. Administration of all diuretics, beta-adrenergic and calcium-channel blocking and vasoactive medications were stopped 24 to 48 h before cardiac catheterization and nitrates were stopped 12 h before cardiac catheterization. All patients gave written, informed consent for this investigation on forms approved by the Human Studies Committees at the University of Michigan or Veterans Affairs Medical Centers, Ann Arbor, Michigan.

Protocol. After a diagnostic right and left heart catheterization documented baseline intracardiac pressures, cardiac output and normal coronary anatomy, the protocol was initiated. It consisted of the simultaneous recording of micromanometer left ventricular pressure, biplane contrast cineangiogram under control conditions and radionuclide angiogram under control conditions and during methoxamine or nitroprusside infusion with heart rate held constant by right atrial pacing. The methoxamine infusion was adjusted to achieve a variable increase in left ventricular pressure of 30 to 50 mm Hg, and the nitroprusside infusion was adjusted to achieve a variable decrease in pressure of 20 to 40 mm Hg. A stable hemodynamic condition was considered present when the left ventricular systolic pressure varied by ≤10 mm Hg. The radionuclide angiogram was performed 20 to 25 min after the cineangiogram and was used to obtain multiple pressure-volume data acquisitions (n = 4 to 8) to calculate statistically reliable E_{max} values.

Twenty-seven of the 37 patients with aortic regurgitation underwent aortic valve replacement on the basis of the available clinical, noninvasive and cardiac catheterization data. The decision whether to perform aortic valve replacement was not influenced by the investigational data. Twenty-three of these 27 patients had a follow-up evaluation of their clinical status and left ventricular size and performance by radionuclide angiography 3 to 6 months after aortic valve replacement. In the remaining four patients there was one perioperative death, and three patients refused to return for repeat radionuclide angiograms.

Hemodynamics. After completion of the diagnostic cardiac catheterization, a bipolar pacing catheter was placed in the right atrium to maintain a constant heart rate throughout the protocol. A precalibrated micromanometer catheter (VPC-780C, VPC-784D or VPC-784A, Millar Instruments) was positioned to measure left ventricular pressure; and a pigtail catheter was placed in the left ventricle for biplane contrast cineangiography. The hemodynamic recordings were obtained using an Electronics for Medicine VR-12 or Micor physiologic recorder at 100 mm/s paper speed. These recordings included an ECG lead, micromanometer left ventricular pressure (50 and 200 mm Hg scales) and aortic pressure (200 mm Hg scale), and the first derivative of left ventricular pressure (dP/dt). These hemodynamics with cine frame markers were recorded simultaneously with the biplane contrast cineangiogram. They were also recorded for 10 to 20 cardiac cycles at the beginning, middle and end of each radionuclide acquisition. An average left ventricular pressure waveform was then obtained to match with the corresponding radionuclide left ventricular volume data for each loading condition.

The left ventricular pressure waveforms were hand digi-

tized with use of a Calcomp 9100 inductance digitizing surface (resolution 0.02 mm) interfaced to an IBM XT, beginning at the peak of the R wave of the simultaneously recorded ECG (30–35). This program yields instantaneous left ventricular pressure and the first derivative of pressure, dP/dt, at 200 Hz. Interpolation of the left ventricular pressure data was performed to guarantee isochronicity of the pressure values with the middle of each cineangiographic frame pair and with the midpoint of each radionuclide frame.

Biplane contrast cineangiography. This was performed in the 30° right anterior oblique and 60° left anterior oblique projections after the injection of 36 to 50 ml of Renografin-76 at 60 frames/s (16.7 ms sampling frequency). One of the first three beats after contrast injection, which did not follow a ventricular ectopic beat, was used for volume analysis (36). Left ventricular volumes were calculated frame by frame using a sonic digitizer (Science Accessories) mounted on a Vanguard XR-35 cine projector and interfaced to an IBM XT. The long axes were measured in both projections from the apex to the junction of the aortic and mitral valve planes. Using these long axes and the digitized silhouettes, a modified Simpson's rule algorithm was used to calculate left ventricular volumes frame by frame, as previously validated in this laboratory (37). Left ventricular end-diastolic volume (EDV) was defined as the maximal ventricular volume occurring before the increase of the simultaneous recorded dP/dt signal, and end-systolic volume (ESV) was defined as minimal ventricular volume. The left ventricular ejection fraction (EF) was then calculated as: EF = [(EDV − ESV)/EDV] × 100.

Left ventricular midwall circumferential stress (σ_θ) was used to quantitate the integrated contribution of left ventricular pressure, chamber geometry and wall thickness to myocardial fiber loading. Left ventricular end-diastolic wall thickness was determined by the digitized average dimension between the epicardial and endocardial surfaces of the anterior free wall over the middle one third of the long axis in the 30° right anterior oblique projection (34). Left ventricular mass was calculated with use of the approach of Rackley et al. (38). Frame by frame estimates of left ventricular wall thickness were obtained by using the iterative approach of Hugenholtz et al. (39). With use of the corresponding digitized left ventricular pressure, the long axes and minor dimensions, and the estimated wall thickness, frame by frame midwall circumferential stress (σ_θ) was calculated using the equation of Mirsky (40) as: $\sigma_\theta = (Pb/h)(1-h/2b-b^2/2a^2)$ for a thick-walled ellipsoid of revolution. In this equation, P is the instantaneous left ventricular pressure, h is the estimated wall thickness and a and b are the midwall semimajor and semiminor axes, respectively.

Radionuclide angiography. Gated equilibrium radionuclide angiograms were obtained after in vivo red blood cell labeling with 30 mCi of technetium-99m for 30 ms frames throughout the cardiac cycle for 250 cardiac cycles. During the midportion of each radionuclide acquisition, a 2 ml blood sample was drawn. The blood samples were later counted for 2 min, and the time delay between acquisition and counting of the blood samples was recorded. At the end of the protocol, measurements were made for each patient to determine the distance from the gamma scintillation camera in the left anterior oblique projection to the center of the left ventricle for attenuation correction. Attenuation-corrected radionuclide left ventricular volumes were then calculated frame by frame using background subtracted, hand-drawn region of interest count data, decay-corrected blood sample counts and attenuation correction, as previously validated in this laboratory (32,41).

The radionuclide left ventricular ejection fraction (EF) was calculated as: EF = [(EDC−ESC)/EDC] × 100, where EDC represents end-diastolic counts and ESC represents end-systolic counts from the radionuclide time-activity curve. We also calculated left ventricular regurgitant index. Right ventricular stroke counts were obtained using a modification of the method described by Maddahi et al. (42). We have used this method to calculate right ventricular (RV) volumes for comparison with those obtained from biplane contrast cineangiography (43) and to calculate right ventricular volumes and ejection fraction in patients with right ventricular infarction (44). We calculated left ventricular (LV) regurgitant index (RI) as: RI = (LVEDC−LVESC)/(RVEDC−RVESC).

Calculation of the left ventricular time-varying elastance and conventional stress-shortening relations. The corresponding micromanometer left ventricular pressure and radionuclide volume for each loading condition were plotted to generate multiple pressure-volume loops in each patient. Then, isochronal, instantaneous pressure-volume data points from each loading condition were subjected to linear regression analysis to obtain the maximal slope (E_{max}) and extrapolated volume-axis intercept (V_0). E_{max} has been proposed as a relatively load-independent index of contractility (45–47). This is probably valid when E_{max} is measured in the same heart after pharmacologic interventions, which either positively or negatively affect contractility (35–45). However, when E_{max} is calculated in different hearts, it may be affected by several influences in addition to contractility (48–53). Accordingly, in this investigation E_{max} was corrected for heart size (25,30,33,54,55), and the corrected E_{max} was used to represent net left ventricular systolic performance.

Conventional midwall circumferential stress-shortening relations were calculated as an independent measure of myocardial performance (56–60). Because the extent and velocity of shortening of either isolated muscle or an intact heart follow predictable pathways, which depend on both the load that the myocardial fibers must carry during shortening and contractility, they have an inverse relation with load. Therefore, by relating operational circumferential stress (σ_θ) at end-systole to the extent of shortening (ejection fraction [EF]), normal myocardial performance was established in the control patients and the effects of severe, chronic aortic regurgitation on myocardial performance

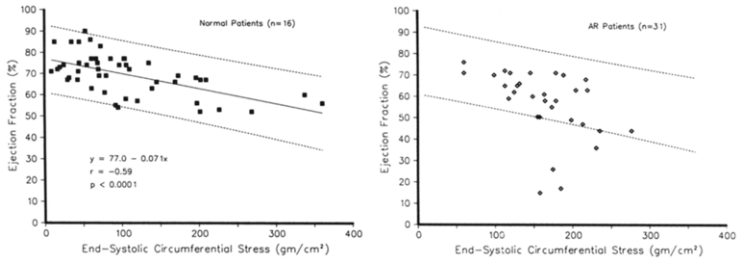

Figure 1. Left panel. The relation between cineangiographic left ventricular end-systolic circumferential stress (**abscissa**) and ejection fraction (**ordinate**) for the 16 control patients. The individual data points, regression line (**solid line**), regression equation, correlation coefficient and 95% confidence intervals (**dotted lines**) are shown. **Right panel.** The relation between cineangiographic left ventricular end-systolic circumferential stress (**abscissa**) and ejection fraction (**ordinate**) for the 31 patients with severe, chronic aortic regurgitation (AR). The 95% confidence intervals for the control patients are shown to establish normal limits for this relation. Note that only 4 (13%) of the 31 patients who had adequate biplane cineangiograms to calculate this relation have abnormal values.

were established by plotting the stress-shortening values in each patient with aortic regurgitation relative to these normal limits.

Surgical technique. Twenty-seven patients underwent aortic valve replacement. After a median sternotomy, each patient was placed on cardiopulmonary bypass, cooled to a systemic temperature of 28°C; myocardial preservation was achieved by the instillation of hypothermic, hyperkalemic cardioplegia by way of the coronary ostia to maintain a myocardial temperature of 10° to 15°C. This was supplemented with topical hypothermia. Twenty-six patients received a mechanical valve and only one patient received a bioprosthetic valve. The average pump time in these patients was 105 ± 67 min and the average aortic cross-clamp time was 74 ± 40 min.

Statistical analysis. All data are represented as mean values ± 1 standard deviation. Comparisons of continuous variables were made between the control patients and patients with aortic regurgitation using nonpaired *t* tests. Differences between the ability of various indexes to detect the presence of abnormal left ventricular systolic performance were identified using McNemar's test (61). A least squares linear regression analysis was used in the control patients to obtain 95% confidence intervals for the conventional circumferential stress-shortening relations.

The patients with aortic regurgitation were subgrouped according to the normalcy of their preoperative E_{max} and conventional stress-shortening relations. Accordingly, because no patient had an abnormal stress-shortening value in the absence of an abnormal E_{max}, Group I had normal E_{max} and stress-shortening relations, Group II had abnormal E_{max} but normal stress-shortening relations, and Group III had abnormal E_{max} and stress-shortening relations. Then, comparisons with the control patients were performed using an analysis of variance. When a significant F statistic was obtained, multiple range tests were employed to identify specific differences. Within the group, comparisons of the pre- and postoperative data were performed using paired *t* tests. A probability value of ≤ 0.05 was used to determine whether a significant difference was present.

Results

Baseline hemodynamic data (Table 1). The baseline hemodynamic data in the control patients and patients with aortic regurgitation did not differ, including average heart rate, left ventricular (+)dP/dtmax, stress at end-diastole ($\sigma_d$ed) and volume-axis intercept (V_0) values. However, in the patients with aortic regurgitation, left ventricular pressures were higher ($p < 0.01$ for both), volumes were larger ($p < 0.001$ for both), ejection fraction was lower ($p < 0.001$), mass and wall stress at end systole ($\sigma_s$es) were greater ($p < 0.001$ for both), and maximal slope of the pressure-volume relation, (E_{max}), was lower ($p < 0.001$) in comparison with values in the control patients; the regurgitant index averaged 2.61 ± 1.55.

Normal limits of left ventricular systolic performance. The relation between cineangiographic left ventricular mid-wall circumferential stress (σ_s) at end-systole and ejection fraction (EF) in the control patients was used to establish normal conventional stress-shortening relations for our laboratory (Fig. 1). Also shown in Figure 1 are the stress-shortening values for each of the 31 patients with aortic regurgitation who had adequate biplane cineangiograms. Only 4 (13%) of

Table 1. Baseline Hemodynamic in 31 Control Subjects and 37 Patients With Aortic Regurgitation

	HR (beats/min)	LVP (mm Hg)	LVEDP (mm Hg)	(+dP/dt$_{max}$) (mm Hg/s)	EDV (ml)	ESV (ml)	EF (%)	LV mass (g)	$\sigma_d$cd (g/cm^2)	$\sigma_d$es (g/cm^2)	E_{max} (mm Hg/ml)	V_0 (ml)
Control (n = 31)	82 ± 9 (SD)	179 ± 22	11 ± 4	1316 ± 325	106 ± 39	42 ± 20	62 ± 10	158 ± 60	401 ± 139	961 ± 88	5.01 ± 1.52	22 ± 18
AR (n = 37)	79 ± 10	151 ± 38*	18 ± 10*	1233 ± 298	325 ± 202†	175 ± 146†	50 ± 12*	299 ± 111†	521 ± 311	170 ± 55†	1.87 ± 1.42†	19 ± 186

*p < 0.01; †p < 0.001. dP/dt max = first derivative of left ventricular pressure; EDV = end-diastolic volume; EF = ejection fraction; E_{max} = maximal slope of pressure-volume relation; ESV = end-systolic volume; HR = heart rate; LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; LVP = left ventricular systolic pressure; $\sigma_d$cd and $\sigma_d$es = end-diastolic and end-systolic wall stress, respectively. V_0 = extrapolated volume-axis intercept.

Figure 2. Average radionuclide left ventricular end-diastolic volume (EDV) (**left panel**), end-systolic volume (ESV) (**middle panel**) and ejection fraction (EF) (**right panel**) are compared between the control subjects (Ctrl) and the patients with aortic regurgitation subdivided into Groups I, II, and III. The **bars** represent mean values + 1 SD. **Right panel,** *p < 0.05 versus control subjects and Group I. **p < 0.001 versus control subjects; + p < 0.001 versus Group I. **Middle panel,** *p < 0.05 versus control subjects and Groups I and II; **p < 0.01 versus control subjects; + p < 0.001 versus control subjects and Group I. **Right panel,** *p < 0.01 versus control subjects and Group I, **p < 0.001 versus control subjects, + p < 0.05 versus Group II; ++ = p < 0.01 versus Group I.

the 31 patients with aortic regurgitation had an abnormal stress-shortening relation.

Stratification of patients with aortic regurgitation into subgroups based on E_{max} and conventional stress-shortening relations (Table 2). The preoperative hemodynamics in the three subgroups of patients with aortic regurgitation are shown in Table 2 and are compared with the control patients in Figures 2 to 5. The mean heart rate in Group III (abnormal E_{max} and σ_d-EF relations) was higher than that in Groups I (normal E_{max} and σ_d-EF relations) and II (abnormal E_{max}, normal σ_d-EF relations) ($p < 0.05$ for both). The mean left

Figure 3. Cineangiographic left ventricular (LV) mass (**left panel**) and radionuclide left ventricular end-diastolic volume:cineangiographic left ventricular mass ratios (**right panel**) are compared between the control patients (Ctrl) and the patients with aortic regurgitation subdivided into Groups I, II and III. The **bars** represent the mean +1 standard deviation. **Left panel,** *p < 0.05 versus control subjects and Group I, **p < 0.01 versus control subjects, + p < 0.01 versus Group I; ++ p < 0.001 versus control subjects. **Right panel,** *p < 0.05 versus control subjects, + p < 0.05 versus Group I; ++ p < 0.001 versus Group I.

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Table 2. Preoperative Hemodynamics in Three Subgroups of Patients With Aortic Regurgitation

	HR (beats/min)	LVP (mm Hg)	LVEDP (mm Hg)	$(+)dP/dt_{max}$ (mm Hg/s)	EDV (ml)	ESV (ml)	EF (%)	LV mass (g)	$\sigma_c ed$ (g/cm²)	$\sigma_c es$ (g/cm²)	E_{max} (mm Hg/ml)	V_0 (ml)
Group I (n = 11)	74 ± 9	157 ± 35	17 ± 11	1372 ± 385	177 ± 49	69 ± 22	61 ± 8	209 ± 37	48 ± 17	155 ± 55	3.50 ± 1.40	35 ± 26
Group II (n = 16)	77 ± 8	149 ± 34	17 ± 9	1176 ± 227	360 ± 102[*]	184 ± 108[†]	50 ± 9[‡§]	314 ± 92[‖¶]	52 ± 25	176 ± 59	1.33 ± 0.47[‡]	44 ± 72
Group III (n = 4)	92 ± 15[*‖]	123 ± 5	37 ± 10	1043 ± 93	669 ± 245[*‖]	477 ± 166[*‖]	30 ± 10[*‖]	458 ± 126[*‖]	79 ± 20	187 ± 31	0.26 ± 0.14[*‖]	−102 ± 592

A = $p < 0.05$; B = $p < 0.01$; C = $p < 0.001$ vs. Group I; D = $p < 0.05$; E = $p < 0.01$ vs. Group II; Group I = normal E_{max} and o-EF; Group II = abnormal E_{max} but normal o-EF; Group III = abnormal E_{max} and o-EF. Abbreviations as in Table 1.

ventricular pressures, $(+)dP/dt_{max}$, $\sigma_c ed$ and $\sigma_c es$ and V_0 values did not differ among the three groups.

Left-ventricular end-diastolic and end-systolic volumes in the control patients averaged 106 ± 39 and 42 ± 20 ml, respectively, and they demonstrated a progressive increase from Group I to III patients with aortic regurgitation. The ejection fraction averaged 62 ± 10% in the control patients and, in contrast, showed a progressive decrease from Group I to III (Fig. 2). Similarly, left ventricular mass averaged 158 ± 60 g in the control patients and increased progressively from Group I to III (Fig. 3). To determine whether the increase in left ventricular mass was appropriate for the increase in volume in the patients with aortic regurgitation, the radionuclide left ventricular volume/cineangiographic mass ratio was calculated for each group. The volume/mass ratio averaged 0.80 ± 0.46 ml/g in the control patients (Fig. 3); the ratio was 0.81 ± 0.16 ml/g in Group I, and it did not differ from that of the control patients. However, there was an increase in the volume/mass ratio in Groups II and III, averaging 1.24 ± 0.59 ml/g ($p < 0.05$ vs. control and $p < 0.001$ vs. Group I) and 1.55 ± 0.59 ml/g ($p < 0.05$ vs. Group I), respectively.

The cineangiographic left ventricular end-diastolic stress ($\sigma_c ed$) averaged 40 ± 19 g/cm² in the control patients; it increased in the patients with aortic regurgitation from Group I to III (Table 2). The $\sigma_c ed$ in Groups I and II was not different from that in the control patients despite a significant increase in end-diastolic volume, but it was increased in Group III ($p < 0.05$ versus control and Group I) (Fig. 4). In contrast, the cineangiographic left ventricular end-systolic stress ($\sigma_c es$) averaged 96 ± 58 g/cm² in the control patients, and it was increased in all three groups of patients with aortic regurgitation ($p < 0.05$ to $p < 0.001$). Notably, despite the significant increase in $\sigma_c es$ in Group I ($p < 0.05$ vs. control), the ejection fraction did not differ from that in the control patients (Fig. 4). In contrast, despite a minimal further increase in $\sigma_c es$ in Group II, there was a reduction in ejection fraction to 50 ± 9% ($p < 0.001$ vs. control and $p < 0.01$ vs. Group I). Finally, in Group III little further increase in $\sigma_c es$ was observed, but a further reduction in ejection fraction to 30 ± 10% was noted ($p < 0.05$ to $p < 0.01$ vs. control and Groups I and II).

The average E_{max} value in Group I was 4.78 ± 1.56 mm Hg/ml after correction for heart size and it did not differ from that in the control patients. In contrast, E_{max} averaged 2.76 ± 1.07 mm Hg/ml in Group II and 0.84 ± 0.41 mm Hg/ml in Group III; these corrected E_{max} values differed from that in the control patients ($p < 0.001$ for both) (Fig. 5).

Clinical response to aortic valve replacement. In the 24 patients with aortic regurgitation who had aortic valve replacement, 2 were asymptomatic and 12 were in class II, 7 in class III and 3 in class IV before surgery. One patient died in the perioperative period. After aortic valve replacement, 17 were asymptomatic and 5 were in class II and only 1 was in class III; no patient was in class IV. Thus, the average

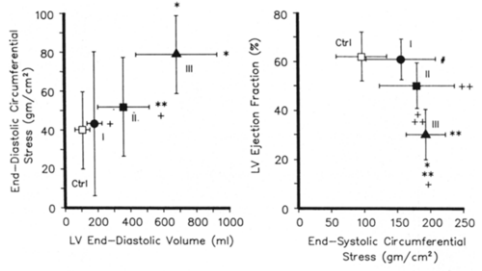


Figure 4. Left panel. The cineangiographic left ventricular end-diastolic circumferential stresses (**ordinate**) are plotted against the corresponding radionuclide left ventricular (LV) end-diastolic volume (**abscissa**) for the control patients (Ctrl) and the patients with aortic regurgitation subdivided into Groups I, II and III. **Right panel.** In a similar format the radionuclide left ventricular (LV) ejection fraction (**ordinate**) is plotted against the corresponding cineangiographic left ventricular end-systolic circumferential stress (**abscissa**). **Left panel.** *p < 0.05 versus control subjects and Group I; **p < 0.001 versus Group I; + p < 0.001 versus control subjects. **Right panel.** *p < 0.05 versus Group II, **p < 0.01 versus control subjects; + p < 0.01 versus Group I; + + p < 0.001 versus control subjects; # p < 0.05 versus control subjects.

clinical functional class improved from 2.4 ± 0.8 to 1.3 ± 0.6 (p < 0.001).

Left ventricular size and performance response to aortic valve replacement. For the 23 patients with aortic regurgitation who survived to have a postoperative radionuclide angiogram, left ventricular end-diastolic volume decreased from 343 ± 229 to 213 ± 141 ml (p < 0.001) and end-systolic volume decreased from 183 ± 157 to 106 ± 112 ml (p < 0.001). In contrast, ejection fraction increased from 50 ± 10 to 57 ± 14% (p < 0.05). The regurgitant index decreased after aortic valve replacement from 2.93 ± 1.77 to 1.25 ± 0.42 (p < 0.001).

When the left ventricular size and performance responses to aortic valve replacement were examined in the three subgroups of patients with aortic regurgitation, a more clear picture emerged. In Group I there was a reduction in end-diastolic volume from 183 ± 45 to 131 ± 33 ml and end-systolic volume from 69 ± 21 to 49 ± 12 ml (p < 0.05). There was no significant change in ejection fraction (61 ± 7 versus 63 ± 4%). Group II patients also had a reduction in end-diastolic volume from 356 ± 145 to 218 ± 106 ml (p < 0.01) and end-systolic volume from 180 ± 88 to 84 ± 55 ml (p < 0.01). However, there was an increase in ejection fraction from 50 ± 8 to 64 ± 11% (p < 0.01). Consequently, the ejection fraction in Groups I and II did not differ after aortic valve replacement. Finally, in Group III, there was a reduction in end-diastolic volume from 860 ± 42 to 551 ± 54 ml and end-systolic volume from 560 ± 93 to 392 ± 112 ml (p < 0.05). In contrast with Groups I and II, Group III had a further decrement in ejection fraction from 35 ± 13 to 30 ± 13%.

To illustrate further the differences in the left ventricular volume and ejection fraction responses to aortic valve

Figure 5. The E_{max} values corrected for heart size are compared between the control patients (Ctrl) and the patients with aortic regurgitation subdivided into Groups I, II and III. The bars represent the mean values +1 SD. *p < 0.01 versus Group I, + p < 0.001 versus control subjects and Group I; + p < 0.001 versus control subjects and Groups I and II.

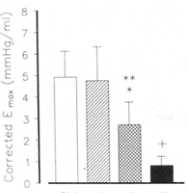
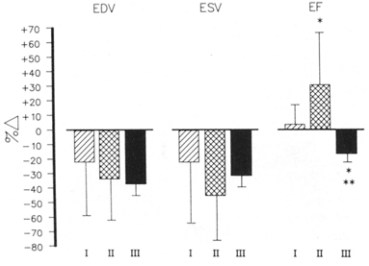


Figure 6. Postoperative percent changes (%Δ) in radionuclide left ventricular end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF) are shown as percent change from their corresponding preoperative values. There was a comparable reduction in left ventricular end-diastolic volume in all three subgroups of patients with aortic regurgitation but a greater reduction in end-systolic volume in Group II, which resulted in a proportionately greater increase in ejection fraction in Group II as compared with Groups I and III. *p < 0.05 versus Group I; **p < 0.01 versus Group II.



replacement, the percent changes for volumes and ejection fraction in each subgroup are shown in Figure 6. In all three patients groups there was a comparable percent reduction in end-diastolic volume ranging from −21% to −36% and end-systolic volume from −22% to −45%, with the greatest reduction in end-systolic volume in Group II. Because of these relative percent changes in volumes, the ejection fraction responses differed. Group I had an increase of 4% and Group II had an increase of 31% ($p < 0.05$ vs. Group I) compared with a 16% reduction in Group III ($p < 0.05$ vs. Group I and $p < 0.01$ vs. Group II).

Discussion

Left-ventricular dilation and dysfunction in chronic aortic regurgitation. The hemodynamic history of severe, chronic aortic regurgitation is characterized by left ventricular dilation and dysfunction (1). The initial phase of this hemodynamic course is characterized by eccentric left ventricular hypertrophy to adapt to the chronic volume overload. This is followed by left ventricular systolic dysfunction, which presumably occurs in the absence of myocardial dysfunction. This hemodynamic course is completed when irreversible myocardial dysfunction supervenes. The extent of left ventricular dilation and dysfunction observed in patients with aortic regurgitation reflects the complex interaction between the chronic volume overload and the adaptive mechanisms employed to compensate for the resultant hemodynamic perturbation including preload augmentation, eccentric hypertrophy, configurational changes and alterations in contractility. Commonly employed noninvasive indexes of left ventricular size and performance identify patients who do poorly after aortic valve replacement (6,7,9,10,12–17,20). These patients have persistent left ventricular dysfunction and symptoms of congestive heart failure after aortic valve replacement, presumably resulting from irreversible myocardial dysfunction before aortic valve replacement (19,20). However, noninvasive indexes have been unable to elucidate the mechanisms for left ventricular systolic dysfunction in patients with aortic regurgitation due, in part, to their variable load dependence (21–23) and the potential errors associated with assessing left ventricular size and performance in patients with aortic regurgitation (24).

Importance of E_{max} in aortic regurgitation. The data in the present investigation clearly demonstrate that patients with aortic regurgitation have distinctly different mechanisms for left ventricular systolic dysfunction. This was due to the fact that the slope of the pressure-volume relation (E_{max}) identified a greater proportion of patients with aortic regurgitation who had abnormal left-ventricular systolic performance (24 [65%] of 37 patients) than did an ejection fraction (EF) of <45% (12 [32%] of 37 patients; $p < 0.05$ vs. E_{max}); a $(+)dP/dt_{max}$ of <1,000 mm Hg/s (1 [3%] of 37 patients; $p < 0.01$ vs. E_{max}) or abnormal stress-shortening relations (4 [13%] of 31 patients; $p < 0.01$ vs. E_{max}). Thus, an abnormal E_{max} occurred frequently in the presence of preserved myocardial performance. Consequently, three subgroups of patients with aortic regurgitation were characterized who had distinctly different preoperative hemodynamic characteristics and left ventricular size and performance responses to aortic valve replacement.

Compensated left ventricular volume overload. Group I had adequately compensated for their volume overload. This was manifest by an increase in left ventricular volumes and a compensatory increase in mass, so that the volume/mass ratio remained comparable with that in the control patients. This suggests that eccentric hypertrophy was adequate and that the left ventricle had maintained a normal elliptical shape (62,63). The hypothesis for eccentric hypertrophy proposed by Grossman et al. (64) suggests that an increase in volume stimulates replication of sarcomeres in series to maintain a normal end-diastolic stress. Because of an associated increase in end-systolic stress, this is followed by replication of sarcomeres in parallel to, presumably, return end-systolic stress to normal. We observed that the preoperative end-diastolic stress ($\sigma_e$ed) in Group I was similar to that in the control patients, but, despite a similar preoperative ejection fraction, end-systolic stress ($\sigma_e$es) was greater in Group I than in the control patients. This has also been observed by others (1,62,65–68).

Gould et al. (62) suggested that the persistent increase in end-systolic stress in patients with aortic regurgitation may be explained by a consideration of left ventricular shape and, consequently, myocardial fiber orientation. If the ventricle maintains a normal elliptic shape, end-systolic stress will increase to a greater extent than if it assumes a spherical shape. Consequently, end-systolic stress can be carried by a greater proportion of myocardial fibers oriented in the equatorial plane, which implies that circumferential wall stress (σ_θ) per cross-sectional area may actually be normal. Finally, the corrected E_{max} was no different from that of the control patients. Group I therefore had no significant change in their ejection fraction after aortic valve replacement, which suggests that this hemodynamic subgroup of patients with aortic regurgitation may not have needed aortic valve replacement. This supports the suggestion of Rahimtoola (8) that not all patients with chronic, severe aortic regurgitation need surgery, especially if they are asymptomatic.

Left ventricular systolic dysfunction. Our data also suggest that aortic valve replacement results in an excellent left ventricular size and performance response in those patients with aortic regurgitation who have an abnormal E_{max} but preserved myocardial performance (Group II). This group is therefore a particularly interesting subgroup of patients with aortic regurgitation in whom the possible mechanisms for a reduction in E_{max} in the absence of myocardial dysfunction, as evidenced by preserved stress-shortening relations, is of particular importance. These patients demonstrated an increase in left ventricular volume/mass ratio compared with that of patients in the control group and Group I. Other investigators (62,63) have suggested that an increased vol-

ume/mass ratio in patients with aortic regurgitation reflects inadequate eccentric hypertrophy and have demonstrated a configurational change in the ventricle from ellipsoid to spherical geometry. Despite evidence for sphericalization of the left ventricle, end-diastolic stress remained no different from that in patients in the control group and Group I despite a further increase in end-diastolic volume. However, end-systolic stress increased only slightly beyond that of Group I patients, but the ejection fraction decreased significantly compared with that in patients in the control group and Group I. These observations may be explained by the assumption of spherical geometry. The equation for circumferential stress suggests that an increase in stress will be less in a spherical than in an elliptic ventricle. Moreover, in a spherical ventricle fewer myocardial fibers will be oriented in the equatorial plane. There will therefore be fewer myocardial fibers per cross-sectional area appropriately oriented to carry the increase in end-systolic circumferential stress. Consequently, the ventricle is placed at an operational disadvantage and cannot maintain left ventricular systolic performance.

Myocardial dysfunction. Our data also confirm that, after the development of myocardial dysfunction (Group III), the functional response to aortic valve replacement is poor. Despite modest reductions in left ventricular volumes, there was a further decrement in ejection fraction postoperatively in Group III. The marked reduction in preoperative ejection fraction was associated with depressed conventional stress-shortening relations in these patients and their response to aortic valve replacement is consistent with previous hemodynamic data (19,20). These data suggest that it is important to identify patients with abnormal left ventricular systolic performance before the development of irreversible myocardial dysfunction and thus to intervene with aortic valve replacement when these patients are in Group II.

Potential limitations. There are three potential limitations to the approaches used in this investigation to assess left ventricular chamber and myocardial performance. First, loading conditions were altered pharmacologically to calculate E_{max} with reflexes intact. As in previous investigations from this laboratory (30–35), right atrial pacing was performed to eliminate the influence of alterations in heart rate on this relation (69). Moreover, we have previously reported (34) that the modest alterations in loading conditions used in this investigation do not alter isovolumic indexes of contractility. These data are consistent with the observations reported from intact animals that suggest that greater changes in loading conditions than the modest changes performed in this investigation are necessary to produce reflex sympathetic effects on contractility (70,71). Therefore, there was probably little effect of intact autonomic reflexes on the calculation of E_{max} in this investigation.

Second, we assumed that E_{max} was linear. Several investigations (49–52,72) have demonstrated that E_{max} or E_{cs} may not be linear under all circumstances. At the extremes of load, the relation may have a saturation effect (72) or be concave toward the volume axis (49). Moreover, others (50,52) have demonstrated that there may be contractile, dependent curvilinearity. Little et al. (52,73), however, showed that, within the operational range of pressure and volume, this relation can be assumed to be linear. Consequently, because several investigations in animals and humans have demonstrated linearity (30–35,45–48,52,69,73), we considered it reasonable to assume linearity within the operational range of pressure and volume for E_{max} in our patients.

Finally, we did not use a preload correction for the conventional end-systolic stress-shortening relation in this investigation. Although the preload effect on ejection fraction is modest in the normal ventricle (58), this may not be true in chronic volume overload (59,60). Employing the systolic myocardial stiffness concept, Mirsky et al. (60) demonstrated that correcting ejection fraction for differences in preload, defined as end-diastolic stress, and relating it to operational afterload did not identify more patients with abnormal myocardial performance than did the use of conventional stress-shortening relation. Importantly, Groups I and II had left ventricular end-diastolic stress values that were similar to those in the control patients, suggesting that preload may have been unchanged in these patients. Consequently, because we used operational afterload, it is unlikely that a preload correction would have altered significantly our subgrouping of patients with aortic regurgitation.

Clinical implications. An analysis of left ventricular systolic performance using the time-varying elastance concept and myocardial performance using conventional end-systolic stress-shortening relations provide complementary information that identify differential mechanisms for left ventricular systolic dysfunction in patients with severe, chronic aortic regurgitation. Moreover, it would appear that the preferred response of left ventricular size and performance to aortic valve replacement occurs in patients with aortic regurgitation in whom E_{max} is abnormal because of inadequate left ventricular hypertrophy and the assumption of spherical geometry in the presence of preserved myocardial performance. This combined hemodynamic assessment may therefore be useful in those mildly symptomatic or asymptomatic patients with chronic, severe aortic regurgitation in whom the decision for aortic valve replacement is most difficult.

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