Correction for Preload in Assessment of Myocardial Contractility in Aortic and Mitral Valve Disease

Application of the Concept of Systolic Myocardial Stiffness

Israel Mirsky, PhD, William J. Corin, MD, Tomoyuki Murakami, MD, Joerg Grimm, PhD, Otto M. Hess, MD, and Hans P. Krayenbuehl, MD

With single-beat analysis, the new concept of systolic myocardial stiffness is applied to provide a new approach for the assessment of myocardial contractility in aortic and mitral valve disease. Seventy patients underwent diagnostic right and left heart catheterization. Twenty-six patients had aortic stenosis, 18 had aortic insufficiency, and 26 had mitral regurgitation. Patients with aortic stenosis were divided into two groups on the basis of left ventricular mass index <172 g/m² (AS1) and mass index 172 g/m² (AS2). The mitral regurgitation patients were divided into those in normal sinus rhythm (MR1) and those in atrial fibrillation (MR2). Nine patients without significant coronary or cardiovascular disease served as controls. Thirteen patients with aortic stenosis and eight with aortic insufficiency were evaluated (average, approximately 18 months) after successful aortic valve replacement. With simultaneous left ventricular pressure and cineangiographic methods, myocardial contractility was assessed by the conventional ejection fraction–afterload relation (uncorrected for preload) and by two new methods that permit the correction of the ejection fraction for preload. Assessments of the contractile state by these two new methods differed from those by the conventional method in 20–40% of the cases studied. Contractile state improved postoperatively in aortic stenosis and aortic insufficiency even in patients with preoperative depressed contractile states. In patients with mitral regurgitation, there was considerable heterogeneity of contractile function preoperatively. Severe left ventricular hypertrophy in aortic stenosis was not a marker for postoperative outcome since contractility was normal postoperatively in AS1 and AS2 in equal numbers. This study demonstrates that preload correction is important in a preoperative assessment of contractility in aortic and mitral valve disease but that it is less important postoperatively, presumably because of reductions in the preload. (Circulation 1988;78:68–80)

Continuing efforts to develop more reliable methods for assessing ventricular and myocardial contractility have met with only moderate success. Currently, the two approaches most frequently used are based on the force-velocity concept and the concept of the end-systolic pressure-volume relation. Since the ejection fraction is affected by preload and afterload and since the slope of the end-systolic pressure-volume relation (ESPVR) is affected by cavity size, inspection of the inotropic state must account for these factors in the setting of aortic and mitral valve disease.

In a recent study, a new concept of end-systolic myocardial stiffness was introduced in an attempt to address some of the problems associated with current methods for assessing ventricular and myocardial contractility. With this concept, it is possible to develop the entire ESPVR and hence the entire ejection fraction–afterload relation from a single-beat analysis. Furthermore, the ejection fraction may be corrected for preload. This single-beat analysis thus alleviates the need to vary preload and afterload by various drug interventions.
Assuming that the end-systolic myocardial stiffness (max E_s) is independent of load in left ventricular (LV) hypertrophy induced by a pressure or volume overload and that V_0 (volume at zero stress) is not markedly affected by loading conditions, the objectives of this study were 1) to develop the entire ESPVR and ejection fraction–afterload (EF-σ) relations based on hemodynamic and angiographic data obtained from patients with aortic stenosis (AS), aortic insufficiency (AI), and mitral regurgitation (MR); 2) to compare assessments of myocardial contractility based on current conventional methods (uncorrected for preload) with those based on the new concept (preload correction); and 3) to assess the contractile state after aortic valve replacement in patients with AS and AI.

**Patients and Methods**

**Terminology**

Confusion still persists in the literature with regard to definitions of terms used in cardiac mechanics. It is appropriate therefore to define in a precise manner some of these terms (see Table of Abbreviations).

**Patients**

Seventy patients underwent diagnostic right and left heart catheterization. Twenty-six patients (age, 52 ± 12 years; 18 men and eight women) had AS with a mean systolic pressure gradient of 40 and 105 mm Hg and had no or only mild aortic regurgitation (regurgitant fraction <0.0). Eighteen patients (age, 44 ± 10 years; 14 men and four women) had AI (regurgitant fraction >0.50 and had no or only minimal systolic pressure gradient <20 mm Hg). Twenty-six patients (age, 57 ± 10 years; 22 men and four women) had chronic MR and were clinically symptomatic at the time of catheterization. Nine patients (age, 42 ± 12 years) evaluated for symptoms of chest pain but who were found to be without significant coronary artery or cardiovascular disease served as controls. Valsalva maneuvers were not performed by patients during LV cineangiography.

Patients with AS were divided into two groups on the basis of LV mass index (LVM1), which was determined by the method of Rackley et al. The classification (AS1: LVM1<172 g/m², n=10; AS2: LVM1≥172 g/m², n=16) was based on a cutoff value of 172 g/m² since this represented approximately double the value observed in control subjects. The MR patients were divided since 17 were in normal sinus rhythm (MR1) and since nine were in atrial fibrillation (MR2). Six patients in the AS1, seven in the AS2, and eight in the AI group were also evaluated for a mean of 18.3 months, range of 14–25 months; mean of 18.1 months, range of 12–23 months; and mean of 19 months, range of 16–26 months, respectively, after successful aortic valve replacement.

**Table of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>E_s</td>
<td>Stress difference (σ, g/cm²), total stress difference, σ = σ_a - σ_r, is the difference of the circumferential (σ_a) and radial (σ_r) stress components, which are averaged throughout the entire cross section.</td>
</tr>
<tr>
<td>e_s</td>
<td>Strain difference (e, dimensionless), associated strain difference, e = e_a - e_r, is the difference of the midwall circumferential (e_a) and radial (e_r) strain components at the equator of an ellipsoid, which is the assumed geometry for the left ventricle.</td>
</tr>
<tr>
<td>E</td>
<td>Average systolic myocardial stiffness (E_s, g/cm²), E_s = σ/(E/K_m), where E = (2/3)(2 + D_m/L_m)^2, and D_m is the midwall major axis.</td>
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<table>
<thead>
<tr>
<th>Analysis</th>
<th>Description</th>
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<tbody>
<tr>
<td>EF</td>
<td>End diastolic volume (EDV), ( V_{ed} ).</td>
</tr>
<tr>
<td>ESV</td>
<td>Minimum LV systolic volume (Figure 1), ( V_{es} ).</td>
</tr>
<tr>
<td>EF &amp; ESV</td>
<td>LV end-systolic volume (ml) (Figure 1), ( V_{es} ).</td>
</tr>
<tr>
<td>EF &amp; ESV</td>
<td>Ejection fraction at end ejection, EF (%), 100 \times (EDV - ESV)/EDV.</td>
</tr>
<tr>
<td>EF &amp; ESV</td>
<td>Ejection fraction at end systole, EF_s (%), 100 \times (V_{ed} - V_{es})/V_{ed}.</td>
</tr>
<tr>
<td>EF &amp; ESV</td>
<td>Ejection fraction at end systole corrected for control mean values of preload and afterload, EF.</td>
</tr>
<tr>
<td>EF &amp; ESV</td>
<td>Ejection fraction at end systole corrected for control mean preload and operating afterload for valve disease and control patients, respectively, EF_p, EF_{sp}.</td>
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</table>

Medications given to patients before catheterization included digoxin, furosemide, thiazides, nitrates, prazosin, and captopril.

**Cardiac Catheterization**

Informed consent was obtained from all patients. Patients were asked by letter for consent to undergo recatheterization. Premedication consisted of 10 mg chloral hydrate given orally 1 hour before the procedure. Biplane contrast left ventriculography was performed in the right anterior oblique (RAO) (30°) and left anterior oblique (LAO) (60°) projections with the patient supine, with 35-mm film at a rate of 50 frames/sec.

LV pressure was measured simultaneously with cineangiography by a Millar 7F micromanometer-angio catheter (Houston, Texas) introduced transseptally into the left ventricle of patients with aortic and mitral valve disease and by the retrograde route in control patients. Aortic pressure was measured by means of a fluid-filled 8F pigtail catheter intro-
duced from the femoral artery. All pressures were recorded at a paper speed of 250 mm/sec (VR12 or VR16, Electronics for Medicine, White Plains, New York) with the ECG, LV pressure, dP/dt, aortic pressure, and cineangiographic time markers simultaneously inscribed.\textsuperscript{11,12} Regurgitant fraction was quantified by the angiographic Fick method, and regurgitant volume was determined as the product of stroke volume and regurgitant fraction.

**Data Analysis**

Data were selected from beats during simultaneous LV micromanometry and cineangiography. Extrasystolic and postextrasystolic beats were excluded, and in general, the first beat providing adequate opacification was analyzed. In the nine MR2 patients, two or three beats were analyzed and the results averaged.

LV volumes for the entire cardiac cycle were calculated from biplane frame-by-frame analysis with the area-length method\textsuperscript{13} or from RAO monoplane analysis. The LV long axis was the longest measured axis from either the RAO or LAO views. The short axis was calculated as the geometric mean of the derived short axes in the RAO and LAO views: short axis (D) = (D\textsubscript{RAO}D\textsubscript{LAO})\textsuperscript{1/2}. The dimension and volume data were smoothed with a five-point moving average formula.\textsuperscript{14}

LV pressure tracings were digitized for the entire cardiac cycle with an electronic digitizer (Numonics, Montgomeryville, Pennsylvania) interfaced with a Digital PDP 11/34 (Marlboro, Massachusetts), with LV pressure measurements every 5 msec.\textsuperscript{11,12} Pressure and volume data were matched at every 20-msec interval with the digital time indicated on each angiographic frame and the corresponding time marks on the pressure recordings.

End diastole was defined as the cineangiographic frame occurring immediately before the upstroke of the simultaneously inscribed dP/dt. End ejection

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Plot of stress difference-volume (\(\sigma - V\)) loops for control, aortic stenosis (AS), aortic insufficiency (AI), and mitral regurgitation (MR) patients. Generally the volume at time of maximum systolic stiffness (\(V_{es}\)) occurred 20 msec before time of minimum end-systolic volume (ESV) in AS and AI. However, in MR, \(V_{es}\) occurred 20–60 msec (average, ~40 msec) before ESV. \(\sigma_{es}\), stress difference at time of \(V_{es}\); \(V_{om}\), left ventricular volume at zero systolic stress.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Plots of estimation of zero stress volume \(V_{om}\) from systolic stress-volume relations. Stress difference-volume (\(\sigma - V\)) and circumferential stress-volume (\(\sigma_{\theta} - V\)) data are curve-fitted from peak stress to the first minimum volume point in the form \(\sigma = A - B, V_{om}\). \(V_{om}\) is thus evaluated from the equation \(A - B, V_{om}=0\) for both \(\sigma =0\) and \(\sigma_{\theta} =0\), and an average value is used. Plots displayed are representative of patients from control; preoperative aortic stenosis (AS2); preoperative aortic insufficiency (AI); preoperative mitral regurgitation (MR1). Generally, values for \(V_{om}\) obtained by the two methods were in close agreement.}
\end{figure}
was defined at the time of minimum LV volume, and end systole at the time of max $E_{es}$. Hence, the ejection fraction at end ejection (EF) and ejection fraction at end systole ($E_{es}$) were defined by the relations $EF = 100 \times (EDV - ESV)/EDV$, and $E_{es} = 100 \times (V_{ed} - V_{es})/V_{ed}$, where $EDV = V_{ed}$ is the end-diastolic volume, $ESV = \text{minimum LV volume}$, and $V_{es} = \text{LV volume at the time of max } E_{es}$. Manipulation of the above equations indicates that EF and $E_{es}$ are related by $100 - E_{es}/V_{es}/ESV$.

**Statistical Analysis**

Statistical and regression analyses were performed on a Hewlett-Packard HP-97 computer (Palo Alto, California). Results are expressed as mean±SEM. A one-way analysis of variance was used to determine whether there were differences between the control group and pressure-overload groups ($C$ vs. $AS1_{pre}$ vs. $AS2_{pre}$) and between the control group and volume-overload groups ($C$ vs. $AI_{pre}$ vs. $MR1_{pre}$ vs. $MR2_{pre}$) for each parameter. The significance of the difference between groups was tested with Bonferroni’s simultaneous multiple comparisons method. Paired $t$ tests were used to determine whether differences existed between the preoperative and postoperative values for each parameter.

**Theoretical Considerations**

Expressions for average stress difference, preload, and afterload. The average stress difference is given by

$$\sigma = \sigma_0 - \sigma_c = 1.36 \times \frac{\text{PLD}/2h(L + D + 2h) + P/2}{(1)}$$

where $\sigma_0$ is the global average circumferential stress (based on an equilibrium of forces in the circumferential direction), and $\sigma_c$ is the global average radial stress, $P$ is the LV pressure, and $L$, $D$, and $h$ are, respectively, the long axis, short axis, and LV wall thickness. Note that the units of stress are in g/cm$^2$ and that $P$ is in millimeters of mercury.

Preload is defined as the global average circumferential stress at end diastole and is given by

$$\sigma_{ed} = 1.36 \times P_{ed} \frac{\text{LD}/2h(L + D + 2h)}{\text{P/2}}$$

where the subscript “ed” denotes the end-diastolic state.

In this study, afterload is defined as the global average circumferential stress at end systole

$$\sigma_{es} = 1.36 \times P_{es} \frac{\text{LD}/2h(L + D + 2h)}{\text{P/2}}$$

where the subscript “es” denotes the end-systolic state. For comparative purposes, two other forms of afterload have been evaluated, namely, peak
systolic circumferential stress ($\sigma_p$) and integrated mean circumferential stress ($\sigma_{es}$) obtained during the ejection period from (dP/dt)$_{max}$ to minimum systolic volume.

**End-systolic stress-strain and pressure-volume relations.** In earlier studies in the normal conscious dog, it was demonstrated that end-systolic stiffness ($E_{av,es}$) is independent of preload and afterload. Furthermore, the end-systolic stress-strain relations were shown to be linear and given by

$$\sigma_{es} = K_m \max E_{av} \times (e_{es,es})$$

(4)

where $(e_{es,es}) = \log(D_{max}/D_{mm})$. In this study, therefore, it is assumed that the linear relation is valid in aortic and mitral valve disease. The parameter max $E_{av}$ (slope of the linear stress-strain relation) is analogous to $E_{max}$ based on the Suga-Sagawa maximum ventricular elastance concept.

Methods for evaluating $V_{sm}$ (Figure 2) and $D_{mm}$, the volume and midwall minor diameter at zero stress, and ESPVR are outlined in Appendix 1. The resulting equation for ESPVR is

$$P_{es} = (\gamma K_m/G) \max E_{av} \times \log (V_{es}/V_{sm})$$

(5)

where $\gamma$ is a curve-fitting parameter, and $G$ is a geometric factor.

**Ejection fraction–afterload relation at constant preload.** Manipulation of Equation 5 and the relations $E_{es} = 100 \times (V_{es}^2 + V_{es}/V_{es})$ and $\sigma_{es} = \sigma_{es} - 1.36 \times (P_{es}/2)$ = $(G - 0.68P_{es})$ results in the complex relation between $E_{es}$ and $\sigma_{es}$

$$(\gamma K_m \max E_{av}) \log \left[ (100 - \max E_{es})V_{es}/(V_{sm} \times 100) \right]$$

$$= G\sigma_{es}/(G - 0.68)$$

(6)

Details for the derivation of this relation are given in Appendix 2.

**Diastolic stress-volume relation.** To estimate the end-diastolic volume ($V_{ed}$) for a given $\sigma_{ed}$, diastolic stress-volume ($\sigma_{ed} - V_{ed}$) data from minimum pressure to end-diastolic pressure were curve-fitted in the form

$$\sigma_{ed} = A_{d} + B_{d} V_{d}$$

(7)

where $A_d$, $B_d$, and $\delta$ are curve-fitting parameters determined by a nonlinear regression analysis and $\sigma_{ed} = 1.36 \times P \times [D_{L}(2h)/L + D + 2h])$. Generally, however, $V_{ed}$ for a given preload could be obtained directly by interpolation of the smoothed LV diastolic volume and stress data.

**Evaluation and normalization of maximum ventricular elastance.** Because the end-systolic pressure-volume relation is nonlinear, the slopes vary with the end-systolic pressure. Therefore, $E_{max}$ in this study is a theoretically derived parameter defined as the absolute maximum slope of this relation and occurs at zero systolic pressure ($P_{es} = 0$):

$$E_{max} = (dP_{es}/dV_{es}) = (\gamma K_m/G) \max E_{av}$$

(8)

Normalizations of $E_{max}$ to cavity size and LV mass were obtained in the form $V_{sm} E_{max}$, and $V_{w} E_{max}$, where $V_w = LV$ wall volume.

**Results**

**Clinical Data**

There were no age differences in the groups of patients with AS and AI compared with controls; however, both groups of patients with MR were significantly older (MR1 vs. C, $p<0.025$; MR2 vs. C, $p<0.05$).
TABLE 2. Myocardial Preload and Afterload Parameters

<table>
<thead>
<tr>
<th>Patient group</th>
<th>$\sigma_{ad}$ (g/cm²)</th>
<th>$\sigma_{at}$ (g/cm²)</th>
<th>$\sigma_p$ (g/cm²)</th>
<th>$\sigma_m$ (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28 ± 2</td>
<td>146 ± 12</td>
<td>250 ± 11</td>
<td>201 ± 8</td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS1 pre (n = 10)</td>
<td>42 ± 6</td>
<td>183 ± 11</td>
<td>335 ± 11*</td>
<td>259 ± 10†</td>
</tr>
<tr>
<td>post (n = 6)</td>
<td>39 ± 5</td>
<td>149 ± 19</td>
<td>252 ± 25‡</td>
<td>200 ± 21</td>
</tr>
<tr>
<td>AS2 pre (n = 17)</td>
<td>57 ± 6*</td>
<td>172 ± 17</td>
<td>329 ± 14*</td>
<td>253 ± 12*</td>
</tr>
<tr>
<td>post (n = 17)</td>
<td>52 ± 6</td>
<td>183 ± 27</td>
<td>271 ± 17‡</td>
<td>231 ± 20</td>
</tr>
<tr>
<td>AI pre (n = 18)</td>
<td>54 ± 6†</td>
<td>218 ± 9*</td>
<td>312 ± 8*</td>
<td>257 ± 6*</td>
</tr>
<tr>
<td>post (n = 8)</td>
<td>33 ± 5§</td>
<td>166 ± 20†</td>
<td>283 ± 17‖</td>
<td>225 ± 14‖</td>
</tr>
<tr>
<td>MR1 pre (n = 17)</td>
<td>74 ± 8‖</td>
<td>179 ± 15</td>
<td>319 ± 6‖</td>
<td>248 ± 8‖</td>
</tr>
<tr>
<td>MR2 pre (n = 9)</td>
<td>48 ± 4</td>
<td>170 ± 15</td>
<td>299 ± 12‖</td>
<td>231 ± 11</td>
</tr>
</tbody>
</table>

All values are mean ± SEM.

$\sigma_{ad}$, circumferential end-diastolic stress (preload); $\sigma_{at}$, circumferential end-systolic stress (afterload); $\sigma_p$, peak circumferential systolic stress; $\sigma_m$, integrated mean circumferential ejection stress; AS, aortic stenosis groups; AI, aortic insufficiency group; MR, mitral regurgitation groups.

*p < 0.005, †p < 0.025 vs. Control; ‡p < 0.05, §p < 0.005, ‖p < 0.025 pre vs. post (paired t test).

C, p<0.005). Furthermore, patients in group MR2 were significantly older than those in MR1 (p<0.05). Mitral valve prolapse was the cause of MR in 15 patients, and ruptured chordae were responsible in nine patients; the remaining cases were due to rheumatic heart disease and endocarditis.

Preoperative Hemodynamic Data (Table 1)

The heart rate did not differ between controls and patients with AS, AI, or MR. There were significant increases in end-diastolic pressure compared with controls, in AS1 (p<0.05), AS2 (p<0.005), AI (p<0.05), and MR1 (p<0.005). No significant increase was observed in MR2. Peak systolic pressure was increased in both AS1 and AS2 (p<0.005) compared with controls; however, no differences were observed for the volume-overload groups (AI, MR1, and MR2).

Preoperative Angiographic Data (Table 1)

All groups except AS1 had larger LV end-diastolic and end-systolic volume indexes compared with controls (p<0.005). As expected, the LV mass index was larger in all groups compared with controls (p<0.005).

EF was lower in AS2 (p<0.025), AI (p<0.05), and MR2 (p<0.05) compared with controls. On the other hand, no differences were observed in AS1 and MR1.

Postoperative Hemodynamic and Angiographic Data (Table 1)

There were no significant alterations in heart rate after surgery in either the AS or AI groups. In the AS1 group, significant alterations occurred in peak systolic pressure (p<0.005), end-diastolic (p<0.005) and end-systolic (p<0.025) volume indexes, and LV mass index (p<0.005) after surgery (before vs. after). However, no significant changes occurred in the end-diastolic pressure and EF. On the other hand, significant changes after surgery occurred in the AS2 group with these parameters (EDP, EF, p<0.05) in addition to the other parameters. Postoperatively in the AI group, changes after surgery occurred only in the end-diastolic and end-systolic volume and mass indexes.

Figure 4. Plots of assessment of myocardial contractility in aortic insufficiency (AI) and in mitral regurgitation (MR) based on conventional and new methods. Explanation is similar to that given in Figure 3. Panel A: Conventional method assessing normal contractility in 13 of 17 AI, 11 of 17 MR1, and 4 of 9 MR2 patients compared with 6 of 17 AI, 4 of 17 MR1, and 1 of 9 MR2 patients based on Method B and 13 of 17 AI, 8 of 17 MR1, and 4 of 9 MR2 patients based on Method C. Note the marked discrepancies in assessment of contractility by Methods A and C compared with Method B.
4A) if

However, myocardial contractility

was

significantly

higher

in

AS2

(p<0.005), AI

(p<0.025),

and

MR1

(p<0.005) but

not

in AS1 and MR2 when compared with controls. The various afterload parameters \(\sigma_{ad}, \sigma_p,\) and \(\sigma_m\) were uniformly higher in all groups compared with controls; however, the relative statistical differences varied. No significant differences were observed in AS1, AS2, MR1, and MR2 for \(\sigma_{ad}\) except for AI (p<0.005). This contrasted with \(\sigma_p\) in which statistical differences were significantly higher (p<0.005) in all groups compared with controls and with \(\sigma_m\) where differences were significantly higher in all groups except MR2.

Postoperatively, \(\sigma_{ad}\), end-systolic stress (\(\sigma_{gh}\)), and \(\sigma_m\) were unaltered in both AS groups but were significantly reduced in AI (\(\sigma_{ad}, p<0.005; \sigma_{gh}, p<0.05; \sigma_m, p<0.025\). However, \(\sigma_p\) was significantly reduced in AS and AI (AS1, AS2, p<0.05; AI, p<0.025).

**Normality Criteria for Assessment of Myocardial Contractility (Figures 3 and 4)**

Current methods for assessing myocardial contractility are based on EF or fiber shortening–afterload relations. In this study, a statistically significant ejection fraction and afterload relation for the control group was obtained for the afterload \(\sigma_{ad}\) only. EF = 77.5 - 0.089\(\sigma_{ad}\) (r = 0.742, p < 0.025), where control mean EF = 64.6 ± 4.3%. Thus, on the basis of the conventional approach (Method A), myocardial contractility was normal (Figures 3A and 4A)

\[
EF \geq (77.5 - 0.089\sigma_{ad}) - 2 \, \text{SD}
\]

for any given afterload (\(\sigma_{ad}\)).

Two methods (Methods B and C) were used for the normality criterion based on the present concept and are outlined in Appendix 3. In Method B, normality was assessed when EF \(\geq 57.7\%\) (Figures 3B and 4B), where EF is the ejection fraction evaluated at control mean levels of preload and afterload (\(\sigma_{ad} = 27.6 \, \text{g/cm}^2, \sigma_{gh} = 146 \, \text{g/cm}^2\)). Method C is similar to one proposed by Wisenbaugh\(^8\) and yields the normality criterion EF \(\geq 78.5 - 0.177 \, \sigma_{ad}\). The ejection fraction EF is evaluated at control mean preload and at operating afterload with Equation 6.

**Preoperative and Postoperative End-Systolic Parameters (Table 3)**

\(V_{le}\) preoperatively was significantly higher in all groups compared with controls (AS1, p<0.05; AS2, AI, MR1, and MR2, p<0.005) and was significantly reduced after surgery (paired t test) in AS1 (p<0.005) and AS2 (p<0.025) but not in AI. Max \(E_{av}\) was significantly higher in AS (p<0.005) and returned to near normal limits postoperatively, whereas in the volume overload groups (AI and MR), stiffness was within normal limits both preoperatively and postoperatively. Ejection fraction corrected for preload and afterload (EF\(_c\)) did not differ significantly in AS1 and AI groups compared with controls both preoperatively and postoperatively; however, EF\(_c\) was significantly depressed in AS2, MR1, and MR2.
E_max was within normal limits in AS both preoperatively and postoperatively and was significantly lower preoperatively compared with controls, in AI and MR (p<0.005), but returned to near normal values postoperatively in AI. When E_max was normalized to V_0m or to V_w, the differences varied. Values of V_0m E_max were within normal limits in the AI and MR groups only, and V_w E_max was normal only in the AI group, both preoperatively and postoperatively.

Discussion
Numerous attempts to assess myocardial contractility on the basis of the ejection fraction–afterload relation have met with only mild success mainly because of the inability to correct for preload. Similarly, the lack of success to assess ventricular contractility on the basis of the ventricular elastance concept stems from the difficulty to develop appropriate normalization parameters for E_max.

This study was designed to address these questions, which are now discussed in more detail.

Entire Ejection Fraction–Afterload and Ejection Fraction–Preload Relations
The complex relation that exists between EF_es, σ_ah, and σ_ed has been demonstrated in Appendix 2. In Figure 5, the EF_es versus σ_ed (at constant afterload) and EF_es versus σ_ah relations (at constant preload) are displayed over the physiological ranges of σ_ed and σ_ah. It is observed that the preload effect on the ejection fraction is more marked at the higher levels of afterload. Thus, such relations may be

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** Plots of control ejection fraction vs. preload and afterload relation. Panel A: Control ejection fraction vs. preload relations at constant afterloads. Normality of contractile state is based on the criterion that EF = control mean EF – 2 SD. Note marked effect of preload at higher afterloads. Panel B: Control ejection fraction vs. afterload relations at constant preloads. Solid curve represents relation at control mean preload=27.6 g/cm². Range of control curve corresponds to control mean σ_ah=2 SD (74≤σ_ah≤218 g/cm²). Alternative assessment of contractility is given in terms of area under EF, vs. σ_ah curve (at control preload, throughout the control curve range of afterload). Specifically, contractile state for a given patient is considered normal if this area is greater than or equal to the shaded area in Figure 5B (see text for explanation).

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Plot of percent error in ejection fraction (EF) vs. percent error in zero stress-volume (V_0m) for six patients with aortic insufficiency. Large errors in V_0m induce correspondingly smaller errors in EF, and errors in V_0m of 27%, 13%, 27%, 22%, 35%, and 43% in patients 1–6, respectively, would be required to alter assessments of contractile state. *,**, two patients having similar error curves.
helpful to better understand the results of pump performance after various drug interventions or after aortic or mitral valve replacement. For example, drugs that cause large reductions in afterload may concomitantly cause significant reductions in preload, thus resulting in a depression or no alteration of pump performance.

Comparison of Methods for Assessing Myocardial Contractility

Assessments of myocardial contractility based on the three methods are displayed in Figure 3 for the pressure overload groups AS1pre and AS2pre and in Figure 4 for the volume overload groups AI, MR1, and MR2. Overall, there were marked discrepancies between all three methods (Method A vs. Method B, 41%; Method A vs. Method C, 22%; and Method B vs. Method C, 23%). However, when comparing the two present Methods B and C, marked differences were particularly noticeable in the AI group. The discrepancies between the various methods could be due to several factors including errors induced in \( V_{om} \) by invalid extrapolations (Figure 2C), assessments of the contractile state (Methods A and C) taking place at afterload levels outside the range of the control group, and assumptions of linearity of the ejection fraction–afterload relations (Methods A and C) throughout wide ranges of afterload contrasting with the nonlinear relations (Figure 5B) observed in Method B.

Figure 6 displays the errors induced in \( E_F \) resulting from errors in \( V_{om} \) for patients in the AI group where the greatest discrepancies occurred between the Methods B and C. Large errors in \( V_{om} \) result in correspondingly smaller errors in \( E_F \). The results of Method B, however, are supported in part by the studies of Wisenbaugh et al.\(^\text{19}\) who observed that contractile function was more depressed in MR than in AI patients.

Contractile State in Aortic Stenosis and Aortic Insufficiency After Aortic Valve Surgery

We now address the question of postoperative contractile state in AS and AI patients.

Many studies have shown that pump function is generally restored to within normal limits in AS patients who have undergone aortic valve replacement. This was the case in the present studies (Table 1). However, postoperative contractile state was not assessed in these earlier studies. In this study, postoperative assessments of the contractile state by conventional and present methods were in good agreement. Method A versus Methods B and C demonstrated normal contractility postoperatively (Figure 7) in most patients in the AS and AI groups. One possible explanation for this closer agreement between the three methods is the fact that reduction of preload postoperatively resulted in minimal effects of preload in the assessment of the contractile state. It is worthy of note that group statistics can often be misleading as evidenced by the results that normal contractile states were present in a number of patients of the AS2 and AI groups postoperatively. Moreover, severe LV hypertrophy in AS, while indicative of depressed contractility preoperatively, is not necessarily a marker for depression of the contractile state postoperatively. As seen in Figure 7, normality occurred in equal numbers in the AS1 and AS2 groups.

Figure 8 displays the preoperative and postoperative contractile states (as assessed by \( E_F \) vs. \( \sigma_{0th} \) relations at operating preload levels) for representative patients of the AS1, AS2, and AI groups. In both AS1 and AS2 groups (Figures 8A and 8B), the contractile states were improved postoperatively from preoperative abnormal levels. On the other hand, in the AI group (Figure 8C), the contractile states remained within normal limits preoperatively and postoperatively.

End-Systolic Pressure-Volume Relations

The present studies indicate that the ESPVR, as given by Equation 5, are nonlinear although in controls and in patients with AS they appear to be linear throughout wide ranges of end-systolic pressure (Figure 9A). However, in patients with AI and MR, this is clearly not the case (Figure 9B).

**Figure 7.** Plot of preoperative and postoperative contractile states in aortic stenosis (AS) and aortic insufficiency (AI). Contractile state is classified as normal if \( E_F \) (at control mean preload and control mean afterload levels) \( \geq \) control mean \( E_F \) – 2 SD. On a group basis, contractile state is unchanged postoperatively and near normal levels in AS1 and AI but markedly improved in AS2. It does appear, however, that postoperative contractile state in AS is independent of severity of left ventricular hypertrophy since normality was present in equal numbers in AS1 and AS2 groups.
Suga and Sagawa,2 in one of their earlier studies, have demonstrated linearity of the ESPVR throughout wide pressure ranges, but more recent studies20,21 display marked nonlinearity at higher levels of end-systolic volume. The assumption of linearity in clinical and animal studies has often led to nonphysiological negative values for \( V_0 \). On the other hand, the present approach yielded positive values for \( V_{0m} \) in all cases studied.

The clinical utility of \( E_{\text{max}} \) based on the Suga-Sagawa concept must now be questioned and may no longer be considered constant because of the nonlinearity of the ESPVR as evidenced by the results displayed in Figure 9. The AS2 patient (Figure 9A), whose preoperative and postoperative contractile states were abnormal, had a preoperative value of \( E_{\text{max}} = 19.2 \), which was higher than the control value (\( E_{\text{max}} = 9.3 \)). This contrasted with AI and MR1 preoperative patients (Figure 9B) having normal contractile states and low \( E_{\text{max}} \) values of 2.6 and 2.7, respectively. While it is true that \( E_{\text{max}} \) in the present study has been obtained theoretically, the above results would not be altered qualitatively by errors induced in \( V_{0m} \). Furthermore, if future studies demonstrate nonlinearity of the end-systolic stress-strain relation, the slope of this relation at zero stress might have clinical value.

**Size and LV Weight Dependence of \( E_{\text{max}} \)**

In studies with normal dog hearts, Bogen et al22 and Belcher et al26 demonstrated significant inverse relations between \( E_{\text{max}} \) and body weight or LV weight. Results in this regard were varied in the present studies. While no significant relation existed between \( E_{\text{max}} \) and \( V_w \) in the combined AS groups, a significant inverse relation was observed in MR patients, but only a borderline significant relation was observed in AI patients. However, the relation between \( E_{\text{max}} \) and \( V_{0m} \) was significant with all groups and suggests that \( V_{0m} \) rather than \( V_w \) may be a more appropriate normalization parameter for \( E_{\text{max}} \). This possibility will now be examined in more detail.

**Normalization of \( E_{\text{max}} \)**

Based on suggestions in the articles by Sagawa5 and Suga et al,6 we examined the two normalized parameters \( V_w \), \( E_{\text{max}} \) and \( V_{0m} \), \( E_{\text{max}} \) in relation to the contractility parameter \( EF_s \). In an attempt to explore these parameters as candidates for assessment of contractility, we conducted studies in which the effects of pressure-volume relations were examined (Figure 8).

**Figure 8. Plots of preoperative and postoperative \( EF_s \) vs. \( \sigma_{\text{tot}} \) relations in aortic stenosis (AS) and aortic insufficiency (AI).**

Preoperatively, contractile state relations in AS1, AS2, and AI patients at operating levels are mildly depressed but return to normal postoperatively. Solid curves, control relations at specified pre-load levels.
ing myocardial contractility, we adopted the normality criteria:

\[ V_w \, E_{max} \leq \text{control mean} - 2 \, SD = 1,780 \, \text{mm Hg} \]
\[ V_{0m} \, E_{max} \leq \text{control mean} - 2 \, SD = 382 \, \text{mm Hg} \]

The results shown in Figures 10 and 11 indicate that, in AS (Figure 10) and to a lesser extent in AI and MR patients (Figure 11), neither parameter is useful in assessing the myocardial contractile state. These results are in part consistent with those obtained by Nakamura et al.\(^{27}\) who concluded that in pressure overload hypertrophy, \( V_d \, E_{max} (V_d = V_0) \) is sensitive to the degree of hypertrophy. Suga et al.\(^{28}\) extended their investigations to normalize \( E_{max} \) and suggested that it was necessary to examine the effects of changes in \( V_0 \) and \( V_w \) as well as the ratio \( V_0/V_w \). It would appear, however, that relations rather than simple normalized parameters are needed for a reliable assessment of the contractile state.

**Limitations of the Analysis**

There are several limitations to the present analyses, and these must be addressed.

1) The load independence of \( E_{cat} \) has yet to be validated in LV hypertrophy. Unpublished studies conducted in the laboratory of Dr. S. Vatner demonstrate the linearity of the end-systolic stress-strain relations in perinephritic hypertension. However, results are as yet unavailable in MR and AI groups. If future studies demonstrate nonlinearity of these stress-strain relations, multiple-beat analyses will be required, and the analyses described in Appendices 1 and 2 will need modification.

2) Estimation of the parameter \( V_{0m} \) is subject to error. While this did not appear to be critical in the analysis of the AS and MR patients, it may present problems in patients with AI. Therefore, more caution should be exercised in the analysis and interpretation of results from such patients. On the other hand, the qualitative results obtained in the present study are similar to those obtained in AS and AI groups in the studies by Wisenbaugh et al.\(^{29}\) who used two differently loaded beats in their analyses.

3) Future studies are required to examine first-order (viscous) and second-order (inertial) effects.\(^{30,31}\) This will require the measurement of volumes at more frequent intervals than those used in the present study.

4) In all three methods, comparisons of the contractile states were made at a single level of afterload. We therefore used Method B to examine the \( E_{fes} \) versus \( \sigma_{ef} \) relations throughout wider ranges of afterload. In particular, we defined normality of the contractile state if

\[ A = \int_{74}^{218} (E_{fes})_{27.6} \, \text{d}_{\sigma_{ef}} \geq \text{shaded area in Figure 5B} \]

where \( A \) is area, the range \( 74 \leq \sigma_{ef} \leq 218 \, \text{g/cm}^2 \) corresponds to the control mean \( \sigma_{ef} \pm 2 \, \text{SD} = 146 \pm 36 \, \text{g/cm}^2 \), and \( (E_{fes})_{27.6} \) signifies that ejection fraction \( E_{fes} \) was evaluated at control mean preload \( (\sigma_{ed} = 27.6 \, \text{g/cm}^2) \). The results obtained from this
analysis were in agreement with those obtained from a single point comparison (Figures 3B, 4B, and 7).

In summary, the concept of maximum systolic myocardial stiffness permits the development of the entire ejection fraction–afterload relation and demonstrates the importance of correcting for preload in an assessment of myocardial contractility in aortic and mitral valve disease.

Finally, the assumptions made in these analyses need experimental validation, and an assessment of the reliability and sensitivity of the methods presented here will require the preoperative and postoperative study of larger numbers of patients.

Appendix 1

Estimation of Zero Stress Midwall Minor Diameter D0m and Evaluation of the End-Systolic Pressure-Volume Relation

An approximate method for estimating zero stress volume, V0m (hence D0m), was obtained by curve-fitting the stress-volume (σ–V, σa–V) data in late systole from peak stress to the first minimum volume point in the form

$$\sigma, \sigma_a = A_c - B_c \ V^{-\alpha_c}$$

where A_c, B_c, and \(\alpha_c\) are curve-fitting parameters, \(\sigma\) is the total stress difference, and \(\sigma_a\) is average circumferential stress. V0m was thus obtained by extrapolation of these curve fits to zero stress with the result

$$A_c - B_c \ V^{\alpha_c} = 0$$

The resulting value for V0m was taken as the average of the two values obtained from these curve fits.

Midwall diameter-volume (Dm vs. V) and V/P versus V relations in late systole were obtained in the form

$$D_m = A_m \ V^\gamma; \ V/P = G = \alpha + \beta V$$

where A_m, \(\gamma\), \(\alpha\), and \(\beta\) are curve-fitting parameters.

By definition (see “Patients and Methods”), the maximum systolic myocardial stiffness is expressed as

$$\max E_{av} = \sigma_{es}/K_m(\varepsilon_{es})$$

$$= \sigma_{es}/K_m \log (D_{ne}/D_{0m})$$

where K_m = [(2/3)(2 + D_m^2/L_m^2)]_av, L_m is the midwall major axis, and subscript “es” denotes the end-systolic state. From Equation 1.3, we obtain

$$D_{ne}/D_{0m} = A_m \ V_{ed}/A_m \ V_{0m} = (V_{es}/V_{0m})^\gamma$$

$$= \log (D_{ne}/D_{0m}) = \gamma \log (V_{es}/V_{0m})$$

Hence

$$E_{es}/G = (K_m/G) \ max E_{av} \log (D_{ne}/D_{0m})$$

$$= (\gamma K_m/G) \ max E_{av} \log (V_{es}/V_{0m})$$

Appendix 2

Ejection Fraction–Afterload Relation at Constant Preload

In the animal studies,7 end-systolic stiffness (Eav)es was shown to be independent of the end-systolic stress difference (\(\sigma_{es}\)). However, it is also independent of the end-systolic circumferential stress (\(\sigma_{es}\)) (I. Mirsky et al., unpublished results). For comparison, we have used \(\sigma_{es}\) as the definition of afterload in this study rather than \(\sigma_{es}\) to be consistent with the definition used by Colan et al.17 Note also that (Eav)es = max Eav in the present study since only a single-beat analysis was used.

The relation (Eav vs. \(\sigma_{es}\)) is determined from the following equations:

$$P_{es} = (\gamma K_m/G) \ max E_{av} \log (V_{es}/V_{0m})$$

$$100 \times V_{es} = (100 - E_{es}) \ V_{ed}$$

$$\sigma_{es} = \sigma_{af} = \sigma_{es} - 1.36 \ (P_{es}/2)$$

$$= GF_{es} - 1.36 \ (P_{es})/2$$

$$= (G - 0.68) \ P_{es}$$

where the various parameters have been previously defined.

Elimination of P_{es} and V_{es} from these equations yields the complex relation between E_{es} and \(\sigma_{af}\), namely,

$$\max (E_{av} \log ((100 - E_{es}) \ V_{ed}/(V_{0m} \times 100)) = G \sigma_{af}/(G - 0.68)$$

where V_{ed} is the diastolic volume corresponding to the control mean preload and is obtained from the relation

$$\sigma_d = A_d + B_d \ V_d^\delta$$

Appendix 3

Criteria for Normality of the Contractile State Based on the Concept of End-Systolic Stiffness

Two methods are used for the assessment of myocardial contractility and are outlined here.

Method B. Normality based on the ejection fraction (E_{es}) evaluated at control mean preload and control mean afterload. Equation 2.4 is used to evaluate the ejection fraction E_{es} for each patient at the control mean value of afterload \(\sigma_{af} = 146\ g/cm^2\) and at a value of V_{ed} corresponding to the control mean preload \(\sigma_{ed} = 27.6\ g/cm^2\). Now at \(\sigma_{ed} = 27.6\ g/cm^2\) and \(\sigma_{af} = 146\ g/cm^2\), control mean ± SD for E_{es} = 63.7 ± 3%, and normality of myocardial contractility is assessed when E_{es} = control mean E_{es} ± 2 SD = 63.7 ± (2 × 3) = 57.7%.

Method C. Normality based on ejection fraction evaluated at control mean preload and operating afterload. This method is similar to that proposed by Wisenbaugh.18 With Equation 2.4, the ejection fraction E_{es} for each control patient is evaluated at a value of V_{ed} corresponding to the control mean preload \(\sigma_{ed} = 27.6\ g/cm^2\) and at the operating value of afterload (\(\sigma_{af}\)). A linear regression analysis is conducted for (E_{es}) versus operating \(\sigma_{af}\) (Figures 3C and 4C) with the result E_{es} = 27.6 = (E_{es})_{27.6} = 88.9 - 0.177\sigma_{af} (r = 0.90) and control mean ± SD for (E_{es})_{27.6} = 64.5 ± 5.2%. Hence normality is assessed when
EF_p ≥ EF_{cp} - 2 SD
= 88.9 - 0.177 σ_{atf} - 2(5.2)
= 78.5 - 0.177 σ_{atf} (evaluated at operating afterload)

where EF_p is ejection fraction corrected for control mean preload and operating afterload and is evaluated from Equation 2.4 for each patient with valvular disease.

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