Left Ventricular Diastolic Dysfunction Limits
Use of Maximum Systolic Elastance as an
Index of Contractile Function

Michael R. Zile, MD; Gerald Izzi, MD; and William H. Gaasch, MD

We tested the hypothesis that maximum systolic elastance (E_{\text{max}}) fails to detect a decline in left ventricular (LV) contractile function when diastolic dysfunction is present. Canine hearts were studied in an isolated blood-perfused heart apparatus (isovolumic LV); contractile dysfunction was produced by 60 or 90 minutes of global ischemia, followed by 90 minutes of reperfusion. Nine normal hearts underwent 60 minutes of ischemia, and five underwent 90 minutes of ischemia. After the ischemia–reperfusion sequence, developed pressure, pressure–volume area, and myocardial ATP level were significantly less than those at baseline in all 14 hearts. In the group undergoing 60 minutes of ischemia, LV diastolic pressure did not increase, whereas E_{\text{max}} decreased from 5.2±2.5 to 2.9±1.4 mm Hg/ml (p<0.05). In the group undergoing 90 minutes of ischemia, diastolic pressure increased (from 10±2 to 37±20 mm Hg, p<0.05), and E_{\text{max}} did not change significantly (from 5.1±4.3 to 4.3±2.5 mm Hg/ml). A second series of experiments was performed in 13 hearts with pressure–overload hypertrophy (aortic-band model with echocardiography and catheterization studies before the ischemia–reperfusion protocol). Five had evidence for pump failure, whereas eight remained compensated. After 60 minutes of ischemia and 90 minutes of reperfusion, developed pressure, pressure–volume area, and myocardial ATP level were significantly less than those at baseline in all 13 hearts. In the group with compensated LV hypertrophy, LV diastolic pressure did not change, whereas E_{\text{max}} decreased from 6.9±3.0 to 3.1±2.3 mm Hg/ml (p<0.05). In the group with pump failure, diastolic pressure increased (from 12±3 to 34±19 mm Hg, p<0.05), and E_{\text{max}} did not significantly change (from 3.8±1.3 to 3.7±1.6 mm Hg/ml). Thus, all hearts exhibited ischemic injury and contractile dysfunction. When diastolic distensibility did not change (i.e., diastolic pressure did not increase), E_{\text{max}} decreased. However, when diastolic distensibility decreased, E_{\text{max}} did not change. These data indicate that E_{\text{max}} (which is based on measurements of total pressure) fails to reflect contractile dysfunction when LV diastolic pressures are elevated. Function indexes based on developed pressure are preferable when changes in diastolic distensibility complicate changes in systolic function. (Circulation 1991;83:674–680)

Left ventricular (LV) contractile function can be assessed by measuring the ventricle’s ability to generate pressure and to shorten. Thus, in an ejecting heart with constant preload, a decrease in stroke work (the product of developed pressure and stroke volume) indicates a decline in contractile function.\(^1\)\(^2\) In an isovolumic preparation, when end-diastolic volume is constant, a decrease in developed pressure reflects a decrease in contractile function.\(^3\)\(^–\)\(^6\) In contrast to these analyses based on developed pressure, some indexes of contractile function are based on the measurement of total pressure (the sum of developed pressure and end-diastolic pressure). Maximum systolic elastance (E_{\text{max}}) is one such index. To date, essentially all of the published experimental and clinical studies using E_{\text{max}} were performed under conditions in which changes in LV diastolic pressures were minimal.\(^6\)\(^–\)\(^8\) In such studies, changes in total pressure were not substantially different from changes in developed pressure. However, if E_{\text{max}} was used in a clinical or experimental setting in which a significant decrease in LV diastolic distensibility were to occur, changes in total pressure would possibly be much smaller than changes in developed pressure. Thus, an index of contractile function based on total

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pressure may not detect a decline in contractile function when end-diastolic pressure increases.

While studying the mechanical and metabolic effects of LV ischemia followed by reperfusion,3-5 we observed that total systolic pressure did not decrease in hearts with ischemic contracture; this was the case despite the presence of significant myocardial injury and a marked decline in developed pressure. In contrast, hearts without contracture demonstrated a comparable decline in total pressure and developed pressure. Based on these observations, we speculated that indexes of contractile function based on measurements of total systolic pressure (e.g., Emax) may be limited when LV diastolic pressure was increased. Therefore, we measured Emax during interventions that would uniformly depress systolic function but cause a decrease in LV diastolic distensibility in some hearts and not in others. Thus, we tested the hypothesis that Emax fails to detect a decline in contractile function when LV diastolic distensibility is decreased.

Methods

Myocardial injury was produced by prolonged global ischemia followed by reperfusion. Fourteen normal hearts and 13 hearts with pressure–overload hypertrophy were studied in an isolated blood-perfused apparatus. Two levels of injury were produced: 1) injury limited to a decrease in systolic contractile function with no change in LV diastolic pressure or 2) injury with a decrease in contractile function and an increase in diastolic pressure. Under these conditions, Emax was evaluated as an index of contractile function.

Isolated Heart Apparatus

The isolated blood-perfused dog heart preparation used in these experiments has been described in detail.3-5 Briefly, the heart from the experimental dog was placed on cardiopulmonary bypass, then removed and placed in the isolated heart chamber; hearts were perfused at a constant pressure of 100 mm Hg. The coronary venous blood from the experimental isolated heart was extracted from the right heart and returned to the femoral vein of the support dog. A balloon was placed in the LV through the mitral annulus, and the preparation was allowed to equilibrate for 30 minutes before starting the experiment. All studies were performed at 37°C.

LV systolic and diastolic pressures were measured with a Statham P23Db pressure transducer (Gould–Statham, Oxnard, Calif.) during incremental additions of saline to the ventricular balloon until a systolic pressure of approximately 100 mm Hg was obtained. The volume associated with a systolic pressure of 100 mm Hg was assigned a value of 100% (V100), and all other volumes were related to the 100% volume. The mean V100 value for all hearts was 25±5 ml; this value includes the volume of the plastic mitral annulus stent (the stent–balloon mount displaced 4 ml).19 LV pressures were measured throughout a range of 5 volumes from V20 to V100. At each volume, data from six stable beats were averaged. The entire sequence of incremental balloon inflations from V20 to V100 was accomplished between 5 and 10 minutes. During each experimental state, this sequence of balloon inflations was performed in duplicate. Variance between data from the two sets of balloon inflations was minimal.

Model of Left Ventricular Hypertrophy

The aortic-band model of pressure–overload hypertrophy and the hemodynamic measurements used to study this model have been described in detail.5,20 In 8-week-old puppies, a nonconstricting band was placed around the aorta approximately 2 cm above the aortic valve. After banding, the animals were allowed to "grow into" supravalvular aortic stenosis. Twelve months after aortic banding, the animals underwent cardiac catheterization and echocardiography5,20 to define the functional state of the LV.

Eight animals exhibited normal fractional shortening and normal LV end-diastolic pressure; this group was designated LVH-compensated. Five animals had reduced shortening and increased LV end-diastolic pressure; this group was designated LVH-failure. Complete hemodynamic data from these dogs, including LV stress–shortening relations and myocardial blood flow measurements, were the subject of a previous report.20 These hypertrophic hearts were selected because the ischemia–reperfusion intervention produced ischemic contracture in the LVH-failure group but not in the LVH-compensated group.5 Similarly, normal hearts developed ischemic contracture after 90 minutes but not after 60 minutes of ischemia.3,4 Metabolic data from these four groups of dogs, including coronary blood flow, myocardial oxygen consumption, and lactate extraction measurements were included in previous reports.3-5

Experimental Protocol

Data from four experimental groups were analyzed: 1) nine normal hearts with 60 minutes of ischemia (normal 60IA), 2) five normal hearts with 90 minutes of ischemia (normal 90IA), 3) eight LVH-compensated hearts with 60 minutes of ischemia (LVH-compensated 60IA), and 4) five LVH-failure hearts with 60 minutes of ischemia (LVH-failure 60IA). After baseline measurements of systolic pressure, diastolic pressure, and tissue ATP level were obtained, ischemic arrest was initiated by cross-clamping the coronary arterial perfusion line. After the ischemic period, the hearts were reperfused for 90 minutes, and repeated measurements were obtained.

Measurements and Data Analysis

Three methods were used to detect a change in LV contractile function: 1) developed pressure (total systolic pressure minus end-diastolic pressure), 2) the pressure–volume area, and 3) Emax. Because these studies were performed with isovolumic contractions, external stroke work was zero. Thus, instead of relating stroke work to end-diastolic volume as a
measure of function, the relation between end-diastolic volume and total mechanical energy (or work), which was measured as the pressure–volume area, was used.7 In each heart, five isovolumic contractions were obtained by incrementally filling the LV balloon throughout a range of volumes from V20 to V100. The five systolic pressure–volume coordinates produced by these contractions were fit by a linear equation with least-squares analysis. The slope of this total systolic pressure–volume relation represents Emax and the volume at 0 mm Hg LV pressure represents V0. (The total systolic pressure–volume line represents the upper border of the pressure–volume area.) Similarly, the diastolic pressure–volume coordinates were used to evaluate changes in diastolic distensibility. (The diastolic pressure–volume line represents the lower border of the pressure–volume areas.) The pressure–volume area at V100 was calculated as the area encompassed by the systolic and diastolic pressure–volume lines and the isovolumic pressure trajectory at V100. Pressure–volume area was measured in mm Hg/ml/beat/100 g LV and was expressed as J/beat/100 g LV (1.0 mm Hg/ml is equivalent to 0.000133 J).

Developed pressure, pressure–volume area, and Emax were measured in the baseline state and after 90 minutes of reperfusion; in each heart, all data were obtained throughout the same range of volumes.

Tissue ATP level was measured at baseline and after reperfusion by use of spectrophotometric analysis of the neutralized perchloric acid supernatant.21,22 Depletion of ATP was used as a metabolic marker of posts ischemic dysfunction.

Data in the text and tables are presented as the mean±SD; data in the figures are presented as mean±SEM. Differences in LV developed pressure, pressure–volume area, ATP level, and LV diastolic pressure produced by the ischemia–reperfusion sequence within a single group were analyzed with analysis of variance and a Newman–Keuls multiple sample comparison. Differences in the slope (Emax) and intercept (V0) of the systolic pressure–volume relation were analyzed with analysis of covariance. Differences in data between groups were analyzed with an unpaired Student’s t test. Differences were considered significant at a probability level less than 0.05.

All animals received humane care in compliance with principles formulated by the National Society for Medical Research and by the National Academy of Sciences.

Results

Normal Hearts

Eight normal hearts were subjected to 60 minutes of ischemia and 90 minutes of reperfusion (normal 60IA) (Table 1 and Figure 1); five normal hearts were subjected to 90 minutes of ischemia (normal 90IA) (Table 1 and Figure 1). As shown in Table 1, baseline values in these two groups did not differ significantly. In addition, there were no differences in the LV volume at V100 (26±11 in normal 60IA versus 25±10 ml in normal 90IA) or LV mass (105±27 in normal 60IA versus 110±21 g in normal 90IA).

In the normal 60IA hearts, ischemia–reperfusion caused a significant decrease in total systolic pressure, developed pressure, pressure–volume area, tissue ATP level, and Emax. Diastolic function as evidenced by the overlapping diastolic pressure–volume curves and diastolic pressure at V100 did not change. In the normal 90IA hearts, ischemia–reperfusion resulted in no change in total systolic pressure and no change in Emax. However, LV diastolic pressure markedly increased, and the entire diastolic pressure–volume relation shifted upward. Thus, developed pressure and pressure–volume area measured at V100

FIGURE 1. Plots of effect of ischemia–reperfusion on left ventricular (LV) systolic and diastolic pressure–volume relations in normal hearts. Left panel: Results from normal hearts subjected to 60 minutes of ischemia (NORMAL 60 min IA) followed by 90 minutes of reperfusion. ●, baseline data; □, reperfusion data. LV total systolic pressure–volume data are plotted on the upper portion of the panel; LV diastolic pressure–volume data are plotted on the lower portion. Ischemia–reperfusion caused total systolic pressure, developed pressure (total pressure minus diastolic pressure), and the slope of the total systolic pressure–volume relation to decrease (Emax decreased from 5.2±2.5 to 2.9±1.4 mm Hg/ml, p<0.05); diastolic pressures did not change. Right panel: Results from normal hearts subjected to 90 minutes of ischemia (NORMAL 90 min IA) followed by 90 minutes of reperfusion. Diastolic pressures increased, and developed pressures decreased. Total systolic pressure decreased slightly but not significantly; likewise, the slope of the total systolic pressure–volume relation was not significantly different from baseline (Emax 5.1±4.3 before versus 4.3±2.5 mm Hg/ml after ischemia–reperfusion).
significant decrease. In addition, tissue ATP levels significantly decreased.

**Pressure–Overload Hypertrophy Hearts**

Results in the hypertrophied hearts were similar to the results in the normal hearts. Eight LVH-compensated 60IA hearts (Table 2 and Figure 2) and five LVH-failure 60IA hearts (Table 2 and Figure 2) were subjected to 60 minutes of ischemia and 90 minutes of reperfusion. Both the LV volume at V100 and LV mass were smaller in LVH-compensated hearts compared with LVH-failure hearts (18±9 versus 28±10 ml and 144±33 versus 178±22 g, respectively).

In the LVH-compensated 60IA hearts, ischemia–reperfusion caused a decrease in total pressure, developed pressure, pressure–volume area, ATP level, and E\(_{\text{max}}\), with no change in diastolic pressure. In the LVH-failure 60IA hearts, ischemia–reperfusion resulted in no change in total pressure or E\(_{\text{max}}\).

However, diastolic pressures were significantly increased, and developed pressure, pressure–volume area, and tissue ATP level were significantly reduced.

**Linear Fit and V\(_0\) Intercept**

In each of the 27 dogs studied, total systolic pressure–volume data were well fit by a linear function. The correlation coefficients uniformly exceeded 0.91. There were no differences in the correlation coefficients between groups either at baseline or reperfusion. V\(_0\) was 2.0±0.5 ml for the study population as a whole. There were no differences in V\(_0\) between or within the groups at baseline or reperfusion.

**Discussion**

The purpose of this study was to determine whether the presence of LV diastolic dysfunction limits the use of E\(_{\text{max}}\) as an index of contractile (systolic) function. Myocardial injury was produced.

![Figure 2](https://circ.ahajournals.org/)

**Table 1. Effects of Ischemia–Reperfusion in Normal Hearts**

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<th>Normal 60IA</th>
<th>Normal 90IA</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Reflow</td>
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<tr>
<td>Total systolic</td>
<td>108±8</td>
<td>66±8*</td>
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<tr>
<td>pressure (mm Hg)</td>
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<tr>
<td>End-diastolic</td>
<td>9±2</td>
<td>12±5</td>
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<tr>
<td>pressure (mm Hg)</td>
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<td></td>
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<tr>
<td>Developed pressure (mm Hg)</td>
<td>99±8</td>
<td>54±9*</td>
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<tr>
<td>Pressure–volume area (J/beat/100 g LV)</td>
<td>0.147±0.021</td>
<td>0.073±0.008*</td>
</tr>
<tr>
<td>Maximum elastance (mm Hg/ml)</td>
<td>5.2±2.5</td>
<td>2.9±1.4*</td>
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<tr>
<td>V(_0) (ml)</td>
<td>2.0±0.7</td>
<td>2.5±1.9</td>
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<tr>
<td>ATP (mg/ml/g LV)</td>
<td>18±1.1</td>
<td>10±1.1*</td>
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</table>

Data are mean±SD.
Left ventricular pressures and pressure–volume area were obtained at V100.
Normal 60IA, normal hearts subjected to 60 minutes of ischemia; normal 90IA, normal hearts subjected to 90 minutes of ischemia.

*p<0.05 vs. baseline.
by subjecting normal and hypertrophic hearts to an ischemia–reperfusion sequence. Two patterns of myocardial injury were produced: 1) a decrease in contractile function with no change in diastolic distensibility (no change in diastolic pressure) or 2) a decrease in contractile function and the development of ischemic contracture (that is, increased diastolic pressure). The principal finding of this study was that $E_{\text{max}}$ failed to detect a decrease in contractile function when diastolic pressure increased.

In each of the four groups of hearts, the ischemia–reperfusion sequence produced significant myocardial injury. This injury resulted in a decline in developed pressure, a decrease in the pressure–volume area, and a reduction in myocardial ATP levels. In two groups of hearts, diastolic distensibility remained constant, and diastolic pressure did not increase. In these hearts, all measured indexes of contractile function decreased concordantly; a decrease in $E_{\text{max}}$ paralleled the decrease in developed pressure, pressure–volume area, and ATP levels. These findings (using zero-flow ischemia) were similar to those reported by others in which low-flow ischemia caused a decrease in the slope of the end-systolic pressure–volume relation. By contrast, two groups of hearts in the current study exhibited a decrease in contractile function and a decrease in diastolic distensibility. In these groups, the decrease in developed pressure, pressure–volume area, and ATP levels was not associated with a significant change in $E_{\text{max}}$. These data suggest that the presence of diastolic dysfunction limits the ability of $E_{\text{max}}$ to detect a change in contractile function.

Early experiments on isolated cardiac muscle strips demonstrated that active tension (in an isometric contraction) could be altered either by a change in initial muscle length (preload) or a change in inotropic state. With this length–active tension relation, Sonnenblick showed that at constant preload, an increase in inotropic state resulted in an increase in the extent and rate of force development. Thus, developed (active) force was basic not only to the length–tension relation but also to the force–velocity relation; force was expressed as developed force.

As these principles apply to the present experiments, LV volume is analogous to muscle length, and developed pressure is analogous to developed (active) force. Because LV volume and LV mass were constant in our isovolumic preparation, changes in wall stress during the experiments were principally determined by changes in LV pressure. Thus, the relation between LV volume and developed pressure is analogous to the length–active tension relation in isolated muscles. By this analysis, contractile function decreased in all four groups in this study.

The Starling relation also provides the basis for constructing ventricular function curves relating stroke work to end-diastolic volume. In early studies of cardiac physiology, ventricular function was quantified by examining the curvilinear relation between stroke work and end-diastolic pressure. Suggestions that there was a linear relation between stroke work and end-diastolic volume have been confirmed by Glower et al., and this relation has been used to evaluate changes in contractile function. With concepts developed by Sagawa et al., the total mechanical energy (or “work”) produced by the ventricle can be assessed by measuring the pressure–volume area. This area is analogous to stroke work. In the present study, the relation between pressure–volume area and LV volume was used as an index of contractile function; for any given LV volume, a decrease in pressure–volume area indicates a decrease in function. A decrease in pressure–volume area and, thus, a decrease in contractile function occurred in all four groups.

Sagawa et al developed $E_{\text{max}}$ as an index of contractile function that was not based on measure-

<table>
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<th>Table 2. Effects of Ischemia–Reperfusion in Hypertrophic Hearts</th>
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<tr>
<td><strong>LVH-compensated 60IA</strong></td>
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<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>Total systolic pressure (mm Hg)</td>
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<td>End-diastolic pressure (mm Hg)</td>
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<td>Developed pressure (mm Hg)</td>
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<td>Pressure–volume area (J/beat/100 g LV)</td>
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<td>$V_0$ (ml)</td>
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<td>ATP (mg/ml/g LV)</td>
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Data are mean±SD.

Left ventricular pressures and pressure–volume area were obtained at $V_{op}$.
LVH-compensated, hearts with compensated left ventricular hypertrophy subjected to 60 minutes of ischemia; LVH-failure, hypertrophic hearts with evidence of pump failure subjected to 60 minutes of ischemia.

*p<0.05 vs. the baseline value.
mements of isovolumic or ejection phase indexes; instead, the LV was represented by a model having the property of time-varying elastance. At a given inotropic state, the relation between end-systolic pressure and end-systolic volume was unique and linear; changes in inotropic state caused changes in the slope of the relation. Of particular relevance to the present study, end-systolic pressure was taken as total pressure, not as developed pressure.

Recent investigations indicate a number of limitations in the use of $E_{\text{max}}$ as a contractile index. Some have shown that the slope of the end-systolic pressure–volume relation was dependent on the method used to alter pressure or volume.\textsuperscript{10,16,17} In addition, the end-systolic pressure–volume relation appears to be curvilinear at higher levels of pressure and volume\textsuperscript{6,10} and curvilinear at lower values of pressure and volume.\textsuperscript{11} Moreover, Burkhoff et al\textsuperscript{b} and Kass et al\textsuperscript{d} demonstrated that the linearity or curvilinearity of the end-systolic pressure–volume relation was dependent on the contractile function itself. These investigators suggested that, in an isolated isovolumic canine ventricle, when the slope of the end-systolic pressure–volume relation was between 3.4 and 7.8 mm Hg/ml, the data from this relation were fit better by a linear equation than by a nonlinear equation. In the present study, $E_{\text{max}}$ in all four groups both before and after reperfusion fell within this range. Our measurements were made at an average volume of 25±5 ml. Therefore, data from previous studies and the high linear correlation coefficients in the present study indicate that a linear fit was appropriate for the data from the current study.

Despite its limitations, the end-systolic pressure–volume relation continues to be useful in measuring acute changes in contractile function in many clinical and experimental settings. Data from this study emphasize that a complete characterization of LV contractile function requires measurements of systolic and diastolic properties. It should also be recognized that our conclusions are based on data from isovolumic contractions. Whether the results of this study also apply to ejecting hearts remains uncertain and should be the subject of further studies. Nonetheless, our results underline a potential limitation in the use of $E_{\text{max}}$ and emphasize the importance of using developed pressure or force in the assessment of contractile function. In many clinical situations such as hypertension, aortic stenosis, and coronary heart disease, LV passive stiffness may increase with little or no apparent change in contractile function.\textsuperscript{28} In such a setting, indexes based on developed pressure or stress may be more reliable than those based on total pressure or stress.

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