Dissociation of End Systole From End Ejection in Patients With Long-term Mitral Regurgitation

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To determine whether left ventricular (LV) end systole and end ejection uncouple in patients with long-term mitral regurgitation, 59 patients (22 control patients with atypical chest pain, 21 patients with aortic regurgitation, and 16 patients with mitral regurgitation) were studied with micromanometer LV catheters and radionuclide angiograms. End systole was defined as the time of occurrence (Tmax) of the maximum time-varying elastance (Emax), and end ejection was defined as the time of occurrence of minimum ventricular volume (minV) and zero systolic flow as approximated by the aortic dicrotic notch (Aodi). The temporal relation between end systole and end ejection in the control patients was Tmax (331±42 [SD] msec), minV (336±36 msec), and then, zero systolic flow (355±37 msec). This temporal relation was maintained in the patients with aortic regurgitation. In contrast, in the patients with mitral regurgitation, the temporal relation was Tmax (266±49 msec), zero systolic flow (310±37 msec, p<0.01 vs. Tmax), and then, minV (355±37 msec, p<0.001 vs. Tmax and p<0.01 vs. Aodi). Additionally, the average Tmax occurred earlier in the patients with mitral regurgitation than in the control patients and patients with aortic regurgitation (p<0.01, for both), whereas the average time to minimum ventricular volume was similar in all three patient groups. Moreover, the average time to zero systolic flow also occurred earlier in the patients with mitral regurgitation than in the control patients (p<0.01) and patients with aortic regurgitation (p<0.05). Because of the dissociation of end systole from minimum ventricular volume in the patients with mitral regurgitation, the end-ejection pressure-volume relations calculated at minimum ventricular volume did not correlate (r=-0.09), whereas those calculated at zero systolic flow did correlate (r=0.88) with the Emax slope values. We conclude that end ejection, defined as minimum ventricular volume, dissociates from end systole in patients with mitral regurgitation because of the shortened time to LV end systole in association with preservation of the time to LV end ejection due to the low impedance to ejection presented by the left atrium. Therefore, pressure-volume relations calculated at minimum ventricular volume might not be useful for assessing LV chamber performance in some patients with mitral regurgitation. (Circulation 1990;81:1277–1286)

Various definitions of left ventricular (LV) end systole and end ejection have been used interchangeably to assess LV performance based on the assumption that the timing of these systolic events is nearly coincident. Berko et al have recently demonstrated in an animal model of acute mitral regurgitation that indices of LV performance calculated at end systole and end ejection might not respond in a comparable manner. It has also been proposed that uncoupling of end systole from end ejection might occur in patients with long-term mitral regurgitation because LV ejection into the low-impedance left atrium continues beyond end systole. Whether uncoupling of end systole from end ejection does indeed occur, whether this is mechanistically due to prolongation of ejection in patients with long-term mitral regurgitation, and whether uncoupling, if it does occur, affects the relation between pressure-volume relations calculated at various definitions of end systole and end...
ejection have not, however, been elucidated in humans.

To establish whether uncoupling of end systole from end ejection occurs in patients with long-term mitral regurgitation, a reasonable conceptual framework within which the time of occurrence of end systole can be established is a prerequisite. The time-varying elastance concept has been proposed as a relatively load-independent index of LV contractility, which has been calculated in an excited, supported left ventricle,6-8 various animal preparations,9,10 and humans.5,11-15 It characterizes LV chamber elastance by a maximal slope (Emax), an unstressed volume (V0), and a time of occurrence of Emax (Tmax). Accordingly, we used the time-varying elastance concept to establish the time of LV end systole to determine whether or not LV end systole and end ejection temporally uncouple in patients with long-term mitral regurgitation.

Methods

Patients

The study population consisted of 59 patients who were referred for a diagnostic cardiac catheterization. There were 22 control patients who had an atypical chest pain syndrome but no definable cardiac pathology on physical examination, electrocardiogram, chest radiography, or echocardiogram. There were also 37 patients with long-term LV volume overload, 21 patients with aortic regurgitation, and 16 patients with mitral regurgitation. Each of these patients with LV volume overload had a physical examination consistent with moderate-to-severe aortic or mitral regurgitation; an electrocardiogram, which demonstrated normal sinus rhythm and LV hypertrophy by Estes criteria16 in 19 of the 21 patients with aortic regurgitation and 12 of the 16 patients with mitral regurgitation; and an echocardiogram demonstrating an increase in LV end-diastolic dimension to 6.0 cm or more.17 All patients with aortic and mitral regurgitation were clinically stable at the time of cardiac catheterization. In the patients with aortic regurgitation, nine were class I or II and 12 were class III or IV, whereas in the patients with mitral regurgitation, 11 were class I or II and five were class III or IV, all by New York Heart Association criteria.18 All patients gave written informed consent for participation in this research protocol on forms approved by the human studies committees of the University of Michigan or Veterans Administration Medical Centers.

Protocol

For the purposes of this protocol, all β-adrenergic receptor blocking, calcium channel blocking, and vasodilating agents were stopped 24-48 hours before cardiac catheterization, and all nitrate preparations were stopped 12 hours before cardiac catheterization. A standard right and left heart catheterization documented normal coronary anatomy in all patients; normal left ventricular size, performance, and wall motion in the control patients; and 3+ or 4+ angio-

graphic aortic or mitral regurgitation in the patients with LV volume overload. Each patient then entered the protocol, which consisted of the acquisition of simultaneous micromanometer LV pressures and radionuclide angiograms under control conditions and during steady-state infusions of methoxamine or nitroprusside. The methoxamine infusion was adjusted to increase LV pressure by approximately 50 mm Hg, and the nitroprusside infusion was adjusted to decrease LV pressure by approximately 30 mm Hg as compared with the control LV pressure.

Hemodynamics

A bipolar right atrial pacing catheter was placed through the right femoral vein to maintain a constant heart rate throughout the protocol. Using the right femoral artery, a micromanometer catheter (VPC-780C or VPC-784D; Millar Instruments, Houston, Texas) was positioned to record LV pressure with the distal sensor and central aortic pressure with the proximal sensor. Two electrocardiographic leads, micromanometer LV pressures (50 and 200 mm Hg scales) and central aortic pressure (200 mm Hg scale), and the first derivative of LV pressure (dP/dt) were simultaneously recorded using an Electronics for Medicine VR-12 (PPG Biomedical Systems, Pleasantville, New York) or a Micor (Siemens, Solna, Sweden) physiological recorder at 100 mm/sec paper speed. These hemodynamic measurements were recorded for 10–20 cardiac cycles at the beginning, middle, and end of each radionuclide acquisition as previously described from this laboratory.19-21

The LV pressure waveforms were averaged, and then, the average LV pressure waveforms were hand-digitized with a Calcomp 9100 inductance digitizing surface interfaced to an IBM-PC using a program developed in this laboratory.15 This program provides instantaneous LV pressure and dP/dt at a variable sampling frequency (200 Hz in this investigation) beginning at the peak of the R wave of the simulta-

neously recorded electrocardiogram. The hand-

digitized LV pressure data were interpolated, if necessary, so that they would coincide with the midpoint of each radionuclide frame to guarantee isochronicity of the LV pressure and volume data.

Radionuclide Angiography

Gated equilibrium radionuclide angiograms were acquired after in vivo red blood cell labeling with 30 mCi technetium 99m. The gamma scintillation camera was positioned in the left anterior obliquity that best separated the right and left ventricles in the plane of the interventricular septum (usually 45°). The radionuclide images were acquired into 30-msec frames throughout the cardiac cycle for 500 cardiac cycles. A 2-ml blood sample was drawn at the mid-

point of each radionuclide acquisition, and it was later counted on the collimator for 2 minutes. The time delay between drawing and counting the blood samples was recorded and used for decay correction.
of the blood sample counts. Finally, the distance from the gamma scintillation camera in the left anterior oblique projection to the center of the left ventricle was determined at the completion of the protocol using a simple geometric technique previously validated in this laboratory.\textsuperscript{22,23}

The radionuclide images acquired during each loading condition were processed using hand-drawn regions-of-interest to obtain frame-by-frame LV counts.\textsuperscript{21} After background subtraction and smoothing, the LV counts from each image were standardized to the frame duration, number of cardiac cycles processed, and decay-corrected blood sample counts. These standardized LV counts were then attenuation-corrected as previously described by this laboratory.\textsuperscript{22,23} Briefly, attenuation correction was performed using $u^{\text{rad}}$, where $u$ represents the linear attenuation coefficient of 0.15 cm\(^{-1}\) for the 140 keV photon of technetium 99m, and $d$ represents the calculated distance from the gamma scintillation camera in the left anterior oblique projection to the center of the left ventricle.

This radionuclide LV volume technique has been extensively evaluated in this laboratory.\textsuperscript{19–23} Although several radionuclide methods have been developed for calculating LV volumes,\textsuperscript{24–31} count-based methods with attenuation correction have produced the most accurate estimates of LV volume.\textsuperscript{22,23,30,32,33} Moreover, the accuracy of the frame-by-frame radionuclide LV volumes that are obtained with the methodology described for this investigation and are particularly important for the calculation of LV chamber elastance and other pressure-volume relations has been previously demonstrated in comparison with the volumes obtained from biplane contrast cineangiography in humans.\textsuperscript{21}

\textbf{Definitions and Calculations}

The definition of end systole used in this investigation was the time at which a measure of LV contractility was maximal.\textsuperscript{4} The time-varying elastance concept, which is characterized by a maximum slope $(E_{\text{max}})$, an extrapolated volume-axis intercept $(V_0)$, and a time of occurrence of $E_{\text{max}}$ $(T_{\text{max}})$, was used as an index of LV contractility. To calculate the maximum time-varying elastance, the corresponding micromanometer LV pressure and radionuclide LV volume data points were plotted for each loading condition to obtain pressure-volume loops. Isochronal pressure-volume data points from each loading condition were then subjected to linear regression analysis beginning at the peak of the R wave and continuing every 30 msec for 20 sequential frames.\textsuperscript{20,21} The slope of these linear relations increased progressively throughout systole until the maximum LV chamber elastance $(E_{\text{max}})$ was achieved. The time from the peak of the R wave to $E_{\text{max}}$ $(T_{\text{max}})$ was used in this investigation as a representative measure of the time of end systole.\textsuperscript{4,6–8,15}

The definitions of end ejection used in this investigation were 1) the time from the peak of the R wave to the first frame on the radionuclide LV time-activity curve to demonstrate minimum ventricular volume and 2) the time from the peak of the R wave to zero systolic flow as approximated by the aortic dicrotic notch.\textsuperscript{34} The aortic dicrotic notch was clearly defined in the control patients and patients with mitral regurgitation, but in the patients with aortic regurgitation, a clear dicrotic notch could not be defined in six patients. Consequently, tangential lines were drawn on the central aortic pressure tracing to demarcate the early rapid decline from peak aortic pressure, which occurred before peak $(-)$-dP/dt, and a second slower decline in the aortic pressure tracing, which occurred after peak$(−)$-dP/dt. The intersection of these two lines was used to approximate the time of zero systolic flow in these six patients. In two patients with aortic regurgitation and one with mitral regurgitation, no aortic pressure tracing was available because of a malfunction of the pressure transducer.

Using these two definitions of end ejection, pressure-volume relations were calculated as previously described from this laboratory.\textsuperscript{15,19,20} Briefly, the corresponding LV pressures and radionuclide minimum ventricular volumes from the three loading conditions were plotted and subjected to linear regression analysis to obtain a slope (minPV). Also, the aortic dicrotic notch pressures and corresponding LV volumes from the radionuclide time-activity curve were plotted for the three loading conditions and subjected to linear regression analysis to obtain a slope (AodiPV).

\textbf{Statistical Analysis}

The hemodynamic data acquired during baseline conditions in the control patients and patients with aortic and mitral regurgitation were compared using an analysis of variance (ANOVA). Additionally, the times to end systole and end ejection, defined as minimum ventricular volume and zero systolic flow, were compared between and within the three patient groups with ANOVA. When a significant $F$ statistic was obtained, $t$ tests with a Bonferroni correction were used to identify differences. Additionally, the minPV and AodiPV relations were compared with the $E_{\text{max}}$ slope values by linear regression analysis to obtain correlation coefficients $(r)$. A probability value of 0.05 or less was considered significant.

\textbf{Results}

\textbf{Hemodynamic Data}

The hemodynamic data acquired during baseline conditions in the control patients and patients with aortic and mitral regurgitation are shown in Table 1. The mean heart rates, LV peak systolic and end-diastolic pressures, and $(+)$-dP/dtmax values did not differ significantly between these patient groups. In contrast, the patients with aortic regurgitation had mean LV end-diastolic and end-systolic volumes of $347±316$ and $187±235$ ml ($179±154$ and $95±114$ ml/m\(^2\)$), and the patients with mitral regurgitation had mean LV end-diastolic and end-systolic volumes of $257±67$ and $112±48$ ml (135±36 and 59±25 ml/m\(^2\))}, which were all larger than the values of $97±32$ and
Representative examples of the time of occurrence of these systolic events in a control patient and patients with long-term aortic or mitral regurgitation are shown in Figure 1. As shown in Figure 2 (left panel), T\text{max} averaged 331±42 msec, whereas the time to minV and Aodi averaged 356±36 and 355±23 msec, respectively, in the control patients. Similarly, in the patients with aortic regurgitation, T\text{max} averaged 321±51 msec, whereas the time to minV and Aodi averaged 318±57 and 357±63 msec, respectively. The time of occurrence of these definitions of end ejection did not differ significantly from T\text{max} in these two patient groups. In contrast, in the patients with mitral regurgitation, T\text{max} occurred earlier than both measures of end ejection. T\text{max} averaged 266±49 msec, whereas the time to minV averaged 355±37 msec (\textit{p}<0.001 vs. T\text{max}), and the time to Aodi averaged 310±37 msec (\textit{p}<0.01 vs. T\text{max}). Also, the time to minV occurred later than the time to Aodi (\textit{p}<0.01) in the patients with mitral regurgitation.

As shown in Figure 2 (right panel), the average T\text{max} occurred earlier in the patients with mitral regurgitation as compared with the control patients and patients with aortic regurgitation (\textit{p}<0.01, for both comparisons). In contrast, the timing of end ejection as defined by the time to minV did not differ significantly between the three patient groups. Similar to T\text{max}, the time to zero systolic flow (Aodi) occurred earlier in the patients with mitral regurgitation as compared with the control patients (\textit{p}<0.01) and the patients with aortic regurgitation (\textit{p}<0.05).

Relation Between End-Systolic and End-Ejection Pressure-Volume Relations

To establish whether uncoupling had a detrimental effect on the relation between pressure-volume relations calculated at end systole and end ejection, the slopes of the pressure-volume relations generated at minV and Aodi were compared with the E\text{max} slope values. When all three patient groups were combined, the end-ejection pressure-volume relations at minV correlated with the E\text{max} slope values (r=0.84) (Figure 3), and the end-ejection pressure-volume relations at Aodi also correlated with the E\text{max} slope values (r=0.86) (Figure 4).

Despite the significant group correlation for the end-ejection pressure-volume relations obtained at minimum ventricular volume and zero systolic flow with

### Table 1. Baseline Hemodynamic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (beats/min)</th>
<th>LVP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>(+)-dP/dt\text{max} (mm Hg/sec)</th>
<th>EDV (ml)</th>
<th>ESV (ml)</th>
<th>EF (%)</th>
<th>E\text{max} (mm Hg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>80±10</td>
<td>134±27</td>
<td>11±5</td>
<td>1,307±410</td>
<td>97±32</td>
<td>38±19</td>
<td>62±11</td>
<td>5.38±1.34</td>
</tr>
<tr>
<td>AR</td>
<td>76±11</td>
<td>142±17</td>
<td>12±5</td>
<td>1,189±218</td>
<td>374±316*</td>
<td>187±235*</td>
<td>53±12†</td>
<td>1.96±1.58*</td>
</tr>
<tr>
<td>MR</td>
<td>80±10</td>
<td>125±15</td>
<td>15±7</td>
<td>1,221±257</td>
<td>257±67*</td>
<td>112±48*</td>
<td>57±11</td>
<td>1.27±0.97*</td>
</tr>
</tbody>
</table>

Values are mean±SD. HR, heart rate; LVP, left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; (+)-dP/dt\text{max}, maximum rate of change of left ventricular pressure; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; E\text{max}, maximum time-varying elastance; Control, patients with no definable cardiac pathology (\textit{n}=22); AR, patients with aortic regurgitation (\textit{n}=16).  
*\textit{p}<0.001, †\textit{p}<0.05 vs. control.

38±19 ml (54±17 and 21±11 ml/m²) in the control patients (\textit{p}<0.001, for all comparisons). The LV ejection fraction in the control patients averaged 62±11%; in the patients with aortic and mitral regurgitation, it averaged 53±12% and 57±11%, respectively. Although the mean LV ejection fraction in the patients with aortic regurgitation was less than in the control patients (\textit{p}<0.05), the mean ejection fractions did not differ significantly between the control patients and patients with mitral regurgitation.

**Left Ventricular Chamber Elastance**

In contrast to the mean isovolumic and ejection phase indices, the maximum time-varying elastance values in the patients with LV volume overload differed significantly from the values in the control patients. The E\text{max} slopes averaged 5.38±1.34 mm Hg/ml with a range of 2.99–7.46 mm Hg/ml in the control patients. In the patients with aortic regurgitation, the average was 1.96±1.58 mm Hg/ml with a range of 0.18–6.04 mm Hg/ml (\textit{p}<0.001 vs. control patients); in the patients with mitral regurgitation, the average was 1.27±0.97 mm Hg/ml with a range of 0.40–3.36 mm Hg/ml (\textit{p}<0.001 vs. control patients).

When the E\text{max} slope values were calculated with the indexed LV volumes, they increased in proportion to body surface area (BSA) and continued to differ significantly. The E\text{max} slope values averaged 9.61±2.19 mm Hg/ml/m² in the control patients. In the patients with aortic regurgitation, the average was 3.72±3.14 mm Hg/ml/m² (\textit{p}<0.001 vs. control patients); in the patients with mitral regurgitation, the average was 2.38±1.75 mm Hg/ml/m² (\textit{p}<0.001 vs. control patients). The coefficients of variation for the E\text{max} slopes in each patient group were similar whether or not the E\text{max} slopes were calculated with indexed LV volumes, suggesting that indexing of LV volumes does not reduce the range of E\text{max} slopes, at least in these patient groups.

**Comparison of Time to End Systole and End Ejection**

The time of occurrence of end systole, as defined by T\text{max}, and end ejection, as defined by minimum ventricular volume (minV), and zero systolic flow, as approximated by the aortic diastolic notch (Aodi), were compared within and among the patient groups.
the $E_{\text{max}}$ slope values, this was not the case when these relations were compared in the individual patient groups. The end-ejection pressure-volume relations at minimum ventricular volume and zero systolic flow continued to correlate with the $E_{\text{max}}$ slope values in the control patients ($r=0.69$ and $0.63$, respectively) and the patients with aortic regurgitation ($r=0.84$ and $0.96$, respectively). In contrast, in the patients with mitral regurgitation, the end-ejection pressure-volume relations at zero systolic flow continued to correlate with the $E_{\text{max}}$ slope values ($r=0.88$); however, the relations at minimum ventricular volume demonstrated no correlation with the $E_{\text{max}}$ slope values ($r=-0.09$). This was because the pressure-volume relations at minimum ventricular volume were nonphysiological in some patients with mitral regurgitation (Figure 3).
There were three patients with mitral regurgitation who had negative pressure-volume relations at minV and two patients who had pressure-volume relations at minV near zero despite $E_{\text{max}}$ slope values greater than 1.00 mm Hg/ml. When hemodynamic variables in these five patients were compared with those in the remaining 11 patients with mitral regurgitation, no differences were found between the mean LV and aortic pressures, LV end-diastolic volumes, isovolumic indices, or LV ejection fractions. In contrast, the average LV end-systolic volume was smaller in these five patients ($85 \pm 19$ vs. $124 \pm 52$ ml, $p<0.05$). Although the timing of occurrence of these systolic events did not differ significantly between these two groups of patients with mitral regurgitation, there was a tendency for greater uncoupling of end systole from end ejection to occur in these five patients ($114 \pm 78$ vs. $72 \pm 47$ msec).

**Discussion**

The data in the present investigation indicate that the time to end systole, defined as $T_{\text{max}}$, and to end ejection, defined as minimum ventricular volume and zero systolic flow as approximated by the aortic dicrotic notch, do not uncouple in patients with aortic regurgitation, and they maintain a temporal relation that is comparable with that in control patients with atypical chest pain but no definable cardiac pathology at cardiac catheterization. In contrast, in patients with mitral regurgitation, end systole uncouples from end ejection. The uncoupling of the time to minimum ventricular volume from end systole did not, however, seem to be related to a prolongation of ejection because the average time to
minimum ventricular volume did not differ between the control patients and the patients with aortic and mitral regurgitation. In contrast, end systole occurred significantly earlier in the patients with mitral regurgitation as compared with end systole in the control patients and patients with aortic regurgitation. Similarly, zero systolic flow occurred earlier. This suggests that the time to zero systolic flow tracked end systole more closely than did the time to minimum ventricular volume in our patients with mitral regurgitation. As a result, the pressure-volume relations calculated at zero systolic flow correlated with the $E_{\text{max}}$ slope values in all patient groups, whereas the pressure-volume relations calculated at minimum ventricular volume correlated with the $E_{\text{max}}$ slope values only in the control patients and patients with mitral regurgitation and not in the patients with mitral regurgitation because of the calculation of some nonphysiological slope values, which might be related, in part, to the extent of uncoupling.

Sagawa\textsuperscript{4} has remarked that the temporal relation between end systole and various definitions of end ejection is coincidental. As generally believed and as demonstrated in the present study, end systole occurred at or before minimum ventricular volume with zero systolic flow as approximated by the aortic dicrotic notch soon after minimum ventricular volume. They all occurred within an average of $20\pm38$ msec of each other in our control patients. A similar temporal relation was noted in the patients with aortic regurgitation, except zero systolic flow was somewhat more delayed, probably because of the difficulty with defining the exact timing of the aortic dicrotic notch in a few ($n=6$) of our patients with aortic regurgitation. Nevertheless, even in the patients with aortic regurgitation, end systole and the two definitions of end ejection were tightly coupled to within $34\pm55$ msec of each other. Consequently, the relations between end-ejection pressure-volume relations and the $E_{\text{max}}$ slope values in the control patients and patients with aortic regurgitation were maintained, which is consistent with previous reports.\textsuperscript{5,15}

It has been suggested that end systole and end ejection might become uncoupled in patients with long-term mitral regurgitation.\textsuperscript{2,4,5} The data in the present investigation demonstrate a clear temporal dissociation between these systolic events in patients with long-term mitral regurgitation. In contrast to control patients and patients with aortic regurgitation, zero systolic flow followed end systole, whereas the time to minimum ventricular volume was delayed beyond zero systolic flow and $T_{\text{max}}$ by an average of $86\pm60$ msec in our patients with mitral regurgitation. Thus, as previously shown in an animal model of acute mitral regurgitation,\textsuperscript{1} the data in the present investigation demonstrated that an ejection phase index, for example, left ventricular ejection fraction, can be preserved although end-systolic indices of LV contractility are, on average, reduced in patients with long-term mitral regurgitation.

The time of occurrence of the maximum time-varying elastance has been shown to be relatively independent of loading conditions, whereas the time to end ejection, particularly minimum ventricular volume, can be significantly affected by loading conditions.\textsuperscript{4,8,35–37} Maughan\textsuperscript{et al}\textsuperscript{38} have reported that right ventricular ejection into the low-impedance pulmonary circulation can be prolonged beyond end systole as defined by the maximum right ventricular chamber elastance. Brown and Ditchez\textsuperscript{39} have made similar observations in the human right ventricle. Furthermore, Remington and Huggins\textsuperscript{40} have suggested that the end of LV ejection might not be a clear indication of the end of active muscle contraction, and Nishioka\textsuperscript{et al}\textsuperscript{30} and Suga\textsuperscript{and} Nishiura\textsuperscript{37} have demonstrated that end ejection can variably dissociate from end systole depending on the loading conditions presented to the LV, that is, the time to end ejection will progressively exceed the time to end systole as arterial resistance is reduced. Therefore, a dissociation of end ejection from end systole can theoretically occur under the appropriate set of loading conditions.

The mechanism proposed for the dissociation of LV end systole from end ejection in mitral regurgitation has been the continued ejection of blood into the low-impedance left atrium beyond the end of active contraction. Braunwald,\textsuperscript{41} in a canine model of acute mitral regurgitation, demonstrated a continuation of regurgitant flow into the left atrium into LV protodiastole. Similar observations have been made in studies of LV systolic ejection patterns in humans.\textsuperscript{42–44} Others have suggested that ejection of blood into the left atrium in mitral regurgitation is not prolonged because the regurgitant blood flow is nearly complete by the time of zero systolic flow as approximated by the aortic dicrotic notch.\textsuperscript{3,1,15,46} An examination of the timing of systolic events in our patients with mitral regurgitation demonstrates that minimum ventricular volume does indeed occur well after both end systole and zero systolic flow, suggesting that regurgitant flow does continue into protodiastole as shown by Braunwald.\textsuperscript{41} If one examines the timing of these systolic events between patient groups, however, the time to minimum ventricular volume is similar in all patient groups, whereas end systole is achieved more rapidly in patients with mitral regurgitation than in control patients or in patients with aortic regurgitation.

The mechanism for the more rapid achievement of end systole in patients with mitral regurgitation is unclear. Sagawa\textsuperscript{47} has suggested that the time to maximum LV chamber elastance is determined almost entirely by the LV contractile state, whereas the loading conditions presented to the LV have only a minor influence on $T_{\text{max}}$. It is possible, therefore, that the difference in the timing of these systolic events might be related to depressed LV contractility, as reflected in the lower mean $E_{\text{max}}$ slope value observed in our patients with mitral regurgitation. Not all patients with mitral regurgitation included in
this investigation, however, had reduced LV chamber elastance. In the patients with long-term mitral regurgitation and preserved LV chamber elastance, dissociation of end systole from minimum ventricular volume was also noted. Moreover, in the patients with aortic regurgitation and reduced $E_{\text{max}}$ slope values, dissociation of end systole from minimum ventricular volume did not occur. Alternatively, the favorable loading conditions presented to the LV by the long-term low impedance to ejection presented by the left atrium might have allowed end systole to occur more rapidly while preserving the time to minimum ventricular volume during all loading conditions, similar to the observations made for the right ventricle.\textsuperscript{38,39} Thus, the reduced LV chamber elastance, the favorable loading conditions presented to the LV throughout ejection at all levels of afterload, or both might have accelerated the time to end systole while preserving the time to end ejection in our patients with long-term mitral regurgitation.

The radionuclide sampling frequency, the definition of end systole, and the methods of altering LV loading conditions, should be considered as potential limitations of this investigation. The use of a 30-msec sampling frequency might have minimized our ability to discriminate between the timing of these systolic events because they are usually tightly coupled. Importantly, the time to end systole and minimum ventricular volume were essentially comparable in our control patients and patients with aortic regurgitation. Nevertheless, in some patients with aortic regurgitation, $E_{\text{max}}$ occurred slightly after minimum ventricular volume. This might be because of the fact that we chose the first frame on which minimum ventricular volume occurred despite having two and, occasionally, three frames at minimum ventricular volume on the radionuclide time-activity curves in some of these patients. This was done to provide consistency to the definition of the time of occurrence of this systolic event. Moreover, despite this sampling frequency, the time to end systole and minimum ventricular volume clearly differed by an average of 86±60 msec in our patients with long-term mitral regurgitation, suggesting that the significant differences, or lack thereof, observed in the timing of systolic events in this investigation were probably not obscured by the sampling frequency.

Second, we defined end systole as the time of occurrence of the maximum LV chamber elastance, which was obtained by subjecting isochronal pressure-volume data points to linear regression analysis to obtain $E_{\text{max}}$ slope values and, therefore, $T_{\text{max}}$. In a previous investigation,\textsuperscript{21} the average $E_{\text{max}}$ slope value obtained by radionuclide angiography occurred approximately 18 msec after that calculated with biplane cineangiography, but these slope values correlated and the mean $E_{\text{max}}$ slope values were comparable.\textsuperscript{21} This suggests the possibility that differences in the time to end systole and end ejection might have been greater if the higher temporal and spatial resolution of biplane contrast cineangio-

phy had been used. Also, although $E_{\text{max}}$ slope values differ from the end-systolic pressure-volume relations ($E_{\text{es}}$), they are independent of preload, afterload is incorporated into the calculation, and they are relatively time independent. In contrast, the time to the maximal pressure-volume ratio on each pressure-volume loop and, consequently, the $E_{\text{es}}$ slope values are affected by loading conditions.\textsuperscript{15,48,49} To avoid this confounding influence, we chose to use the maximum LV chamber elastance to define end systole in this investigation.

Finally, the methods of altering the loading conditions presented to the left ventricle and their effect on LV contractility when reflexes are left intact should be considered. As in previous investigations from this laboratory,\textsuperscript{15,19–21} right atrial pacing was performed to eliminate the influence of alterations in heart rate on LV contractility.\textsuperscript{6} We altered loading conditions to calculate $E_{\text{max}}$ and, consequently, $T_{\text{max}}$ with methoxamine and nitroprusside infusions. We have previously reported that these alterations in LV loading conditions do not alter isovolumic indices of LV contractility.\textsuperscript{15,21} These data are consistent with previous observations\textsuperscript{50} that demonstrated a greater change in loading conditions than that performed in this study is necessary to produce a reflex sympathetetic effect on LV contractility. Therefore, there was probably little effect of intact autonomic reflexes on the generation of the maximum LV chamber elastance or the time to this systolic event in our patients.

We conclude that the timing and temporal relation between end systole and end ejection defined as minimum ventricular volume and zero systolic flow are similar in control patients and patients with long-term aortic regurgitation. In contrast, uncoupling of the time to minimum ventricular volume from end systole does occur in patients with long-term mitral regurgitation, and it seems that this might be because of a more rapid achievement of end systole, whereas end ejection is preserved because of the low impedance to ejection provided by the left atrium in these patients. Consequently, pressure-volume relations generated at minimum ventricular volume should be used cautiously in patients with mitral regurgitation because of the calculation of some nonphysiological values, which might be related, in part, to the extent of uncoupling.

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**KEY WORDS** • left ventricle • elastance • end ejection • aortic regurgitation • mitral regurgitation
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