Evaluation of Left Ventricular Mechanical Restitution in Closed-Chest Dogs Based on Single-Beat Elastance

Gregory L. Freeman and James T. Colston

The mechanical restitution of the left ventricle of closed-chest dogs was modeled as a monoexponential relation, using peak single-beat elastance as a measure of contractile strength. Data were obtained from nine dogs chronically instrumented with three sets of piezoelectric diameter gauges to assess ventricular volume and high-fidelity manometers to measure pressure. Mechanical restitution curves were obtained during both atrial and ventricular pacing in six dogs. The time constant of mechanical restitution was 64.3±11.4 msec for atrial and 122.2±26.3 msec for ventricular paced runs (p<0.01). These values are smaller than those previously reported from isolated hearts or isolated muscle segments. Although the time of onset of mechanical restitution was longer for atrial than for ventricular runs (255.1±14.3 versus 225.1±9.6 msec, p<0.05), the plateau to which mechanical function rose was not different. During ventricular pacing, fusion beats were noted in four dogs. The magnitude of the mechanical contribution of these fusion beats fell to a nadir at approximately 250 msec, suggesting that intracellular calcium available for crossbridge interaction is dropping during this time. In three additional dogs, the time constant of postextrasystolic restitution was found to vary depending on the preceding extrasystolic interval. Thus, mechanical restitution of the ventricle is a dynamic process that can be assessed using an elastance-based approach in the in situ heart. (Circulation Research 1990;67:1437–1445)

Mechanical restitution governs the return of contractile strength of cardiac muscle after it has been depolarized. An extrastimulus occurring early after a contraction produces a reduced mechanical response; as more and more time elapses before the extrastimulus, mechanical response increases until it reaches a steady-state, plateau level. This phenomenon is one manifestation of the well-described relation of myocardial performance and the interval between contractions (see Reference 1 for review).

In an elegant study of ferret papillary muscle, Weir and Yue2 have shown that time course of mechanical restitution closely follows the time course of availability of intracellular free calcium. In addition, exposure of the muscles to ryanodine led to marked alterations of both the mechanical and calcium responses. These data suggest that assessment of mechanical restitution provides a physiological insight into intracellular calcium handling.

Mechanical restitution has been evaluated in isolated muscle preparations,2-5 isolated supported hearts,6-8 and in intact animals and humans.9,10 Although generally similar results have been found in each of these experimental systems, interpretation of the results from studies in intact hearts is problematic. In an isolated muscle or ventricle, the precontractile muscle length (or chamber volume) can be controlled independently of the stimulation pattern. This is not the case in the intact heart, in which left ventricular (LV) volume depends on diastolic filling time, which is determined by the interval between beats. Because dP/dtmax, the index of contractile performance used in most studies of the intact left ventricle, is sensitive to changes in LV volume,11 assessment of mechanical restitution has been difficult in intact hearts, and this parameter has not been widely applied in clinical situations or in the assessment of pathological conditions.

The purpose of this study was to determine if mechanical restitution of the intact, closed-chest dogs can be quantified using an approach based on the LV elastance construct (see Reference 12 for
review). The underlying rationale is that this may be a tool to improve our assessment of myocardial and ventricular performance in normal and diseased hearts and to evaluate the effects of pharmacological agents. The influence of pacing site on restitution was assessed, as well as the effect of a variable extrasystolic interval on postextrasystolic restitution. Our results indicate the elastance-based approach allows assessment of mechanical restitution and postextrasystolic restitution in intact hearts. The time constant of mechanical restitution for the intact left ventricle is smaller than previously reported values for isolated hearts, and the time constant of postextrasystolic restitution varies, depending on the extrasystolic interval used. In addition, restitution behavior differs for atrial and ventricular pacing sites.

Materials and Methods

All experiments were performed under the conditions described in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (publication No. [NIH] 85-23, revised 1985). Throughout the course of the experiments, all animals were inspected at least once daily by a veterinarian.

Nine mongrel dogs of either sex were used. The instrumentation used is similar to that previously described in detail. In brief, a thoracotomy was performed in the left fifth intercostal space under sterile conditions and halothane anesthesia. A high-fidelity manometer (Konigsberg Instruments, Inc., Pasadena, Calif.) was passed across the cardiac apex into the LV cavity, along with a 1-mm-i.d. polyethylene tube for manometer calibration. Three sets of piezoelectric diameter gauges were placed in the subendocardium of the left ventricle. These were oriented in an orthogonal fashion to represent the anteroposterior (D_{AP}), septal-lateral (D_{SE}), and long-axis (D_{LA}) dimensions of the chamber. Pacing electrodes were sutured to the left atrium and to the apical free wall of the left ventricle, and balloon occluder cuffs were positioned around the inferior vena cava. All leads were tunneled subcutaneously to exit from the base of the neck, and the chest was closed in layers.

After a recovery period of at least 10 days, during which the animals were familiarized with the laboratory, the experiments were performed. On the day of the study, the dogs were brought to the laboratory and positioned in a sling on their right side. Autonomic blockade was produced by the intravenous administration of 2 mg/kg propranolol and 0.2 mg/kg atropine sulfate. The dogs were anesthetized with intravenous droperidol (1.5–3.0 mg/kg) and fentanyl (0.03–0.06 mg/kg) and were intubated. All hemodynamic data were obtained during brief periods of posthyperventilation apnea, a procedure used to assure that respiratory changes in intrathoracic pressure would not influence the parameters being assessed. Signals were recorded on an eight-channel forced-ink oscillograph (Beckman Instruments Inc., Fullerton, Calif.) and were simultaneously converted to digital form using an IBM PC/AT. Data were digitized at a rate of 500 Hz and stored on disk for subsequent processing. The signals recorded were the LV pressure, dP/dt, lead II of the surface electrocardiogram, and the three LV diameters.

In six dogs, heart rate was fixed by atrial pacing at a basic cycle length of 375 msec (160 beats/min). This rate was chosen to be above the upper limit of resting rates generally found in this preparation. To define the baseline end-systolic pressure–volume (P_{es–V_{es}}) relation, caval occlusions were performed. Minimal drops in LV peak systolic pressure of 25 mm Hg were required, and runs with extrasystoles were discarded. After this was complete, the mechanical restitution protocol was begun. The heart was paced with a programmable stimulator (Bloom Instruments, Reading, Pa.). After a train of beats at the basic cycle length (375 msec), a single test pulse was introduced. The initial test pulse interval (TPI) was timed to fall within the absolute refractory period of the atrioventricular node. Subsequently, the TPI was lengthened by 5–10-msec increments until an intrinsic sinus beat occurred before the paced extrastimulus reached the ventricle.

When the atrial protocol was complete, the left ventricle was paced at a basic cycle length of 375 msec. Again, caval occlusions were performed, then single extrastimuli were introduced, beginning in the refractory period of the left ventricle and at increasing intervals until escape beats occurred.

In three additional dogs, we tested to see how introduction of an extrasystole with a fixed interval that followed a priming train would affect mechanical restitution of the subsequent beats, as described by Yue et al. These animals were treated exactly as the first six dogs but were subjected to a different pacing protocol. Mechanical restitution was evaluated by recording postextrasystolic beats with a wide range of TPIs after a fixed extrasystolic interval (ESI) of either 300, 375, or 450 msec. For these runs, the basic cycle length was 375 msec, and only atrial pacing was performed. Vena caval occlusion runs were recorded at the basic cycle length.

Data Analysis

The stored, digitized data were analyzed using algorithms developed in this laboratory. The left ventricle was considered a modified general ellipsoid, and its volume, V_{LV}, was calculated from the three diameters using the equation

\[ V_{LV} = \frac{\pi}{6} (D_{AP} \cdot D_{SE} \cdot D_{LA}) \]

For determination of the P_{es–V_{es}} relations, end-systole was defined using the iterative approach of Kono et al. The end-systolic pressure and volume data were fit to the equation

\[ P_{es} = E_{cs}(V_{es} - V_0) \]
where $E_{es}$ is the slope of the relation and $V_0$ is its volume-axis intercept determined by the least-squares linear regression technique.

The time constant of LV isovolumic relaxation was defined using pressures from the time of peak negative dP/dt until pressure reached a value 5 mm Hg higher than the LV end-diastolic pressure. These data were fit to the equation

$$P = P_0[\exp(-t/\tau)] + P_b$$

where $t$ is time in milliseconds from peak negative dP/dt, $P_b$ is the level to which pressure asymptotically decays, and $P_0$ plus $P_b$ is the initial pressure; $\tau$, the time constant of isovolumic relaxation, was determined by standard nonlinear techniques.

To define the mechanical response of the left ventricle to the test extrastimulus, the peak elastance of each extrasystole was calculated. This was defined as the maximal ratio of LV pressure to corrected LV volume, or the absolute LV volume minus the $V_0$ determined from the caval occlusion run. For each test beat, the single-beat elastance was normalized to the elastance of the preceding control beat and was expressed as a percent.

The mechanical restitution curve was characterized by a monoeXponential function, as described by Burkhoff et al. For this analysis, the normalized single-beat elastance ($SBE_n$) and ESI data were fit to the equation

$$SBE_n = CR_{max}[1 - \exp(-TPI - TPI_0)/TC]$$

where $CR_{max}$ is the plateau value of contractile response, TPI$_0$ is the longest TPI at which no contractile response would occur, and TC is the time constant of mechanical restitution, all determined by standard nonlinear techniques.

Mechanical restitution curves from atrial and ventricular pacing runs were analyzed in six dogs and from the three postextrasystolic runs in three dogs. For the ventricular pacing runs, data from fused beats were excluded from the analysis of the mechanical restitution curve. A beat was defined as fused if its pressure upstroke occurred before full relaxation of the previous beat. To more formally analyze the contractile behavior of these beats, the LV pressure of the last control beat was aligned with the fusion beat and subtracted from it. The remaining LV pressure then was considered to be that generated by the extrasystole. This value was converted to single-beat elastance and normalized to the preceding control beat as described above.

Residuals from each fit were tested to see if they were normally distributed, using the Kolmogorov-Smirnov test of normal distribution. To verify the adequacy of the monoeXponential fit, the normalized root mean square error was calculated. To determine if the data sets from the atrial and ventricular runs for each dog were different, the results of fitting them
separately were compared with the results of combining them, using the “F” test described by Motulsky and Rasnas. Comparisons of the parameters derived from the atrial and ventricular fits were performed using the paired t test. A value of $p<0.05$ was considered significant.

**Results**

**Mechanical Restitution**

Typical analog tracings for a single extrastimulus during an atrial and ventricular run are shown in Figure 1. In Figure 2, beats from different runs with different extrastimulus intervals were plotted on a common time axis to demonstrate the way in which LV pressure increased as a function of TPI. In the bottom panel of Figure 2, it can be seen that during ventricular stimulation, very early extrastimuli led to fusion beats, where the development of increased LV pressure during the period of LV relaxation was seen. In Figure 3, pressure–volume loops from beats following TPIs of different duration are shown. It is clear that in very early beats (top panel), pressure generation is insufficient to open the aortic valve, and no ejection occurs. In later beats (middle and bottom panels), the diastolic filling time is shortened, such that contraction begins at a volume lower than the beats at basic cycle length, and systolic pressure and the amount of ejection are small. These effects are less pronounced as TPI lengthens to the basic cycle length.

Figure 4 shows the technique by which LV pressure from a control beat was subtracted from a fusion beat and the resultant pressure due to the extrasystole.

Figure 5 shows typical mechanical restitution curves from atrial and ventricular pacing in one experiment. In Table 1, the three parameters derived from the analysis of atrial and ventricular mechanical restitution curves are shown. For the atrial runs, an average of 19.8 points was used for each fit (range, 13–36). For these runs, the normalized root mean square error was 0.289±0.23. For the ventricular runs, an average of 13.7 points was used (range, 10–16); this is exclusive of fused beats. The normalized root mean square error was 0.267±0.20 for these runs. The shortest TPI was 276±24 msec for the atrial runs and 250±12 msec for the ventricular runs.

**Figure 2.** *Left ventricular (LV) pressure data from several separate runs superimposed on a common time axis, demonstrating increased mechanical response as a function of extrasystolic interval. Top panel: Data from atrial pacing. Bottom panel: Data from ventricular pacing.*
The longest TPI was 689±200 msec for the atrial runs and 610±151 msec for the ventricular runs.

Analysis of the residuals for each regression showed them to be normally distributed in 20 of 21 cases. For the initial six dogs, comparison of fitting the data separately for atrial and ventricular runs or for combining the data for a single fit showed that a better fit was obtained using separate analyses in every case, with p<0.001 uniformly.

TPI₀, the longest time at which no mechanical response occurred, was longer for the atrial than the ventricular runs in every case. CRₘₐₓ, the maximal mechanical response reached, was not significantly different between atrial and ventricular runs. The time constant of mechanical restitution was smaller for the atrial data in each experiment. For the group, the time constant for the ventricular runs was 45.1±13.6% longer than that for the atrial runs.

Table 2 shows the time constant of LV relaxation data for each dog. These data are from control, noncausal occlusion runs at the basic cycle length during atrial and ventricular runs. During ventricular pacing, τ was longer in each dog and for the group showed a 37±22% increase.

Although mechanical response of fusion beats was not included in the mechanical restitution curves, data from these beats was quantified and demonstrated a pattern of decreasing mechanical response until a nadir was reached. Such a pattern of decreasing single-beat elastance during fusion beats with longer and longer TPIs was seen in four of the six dogs. The data for the descending portion and initial ascending portions of the restitution curves for these dogs are shown in Figure 6. Of interest, the time of the nadir of mechanical response was very similar in these examples—approximately 250 msec in each case.

Postextrasystolic Restitution

Figure 7 shows the postextrasystolic restitution curves resulting from the three ESIs in one dog. Data from these dogs are shown in Table 3. The time constant of restitution of the postextrasystolic beats was faster when the ESI was short in each case. In addition, TPI₀ was proportional to the ESI; with shorter ESI, the earliest mechanical response of the postextrasystolic beats came sooner. Finally, although CRₘₐₓ was less at longer ESIs, this difference was slight. Thus, these data indicate that the heart in the intact circulation can alter both the time constant of restitution and the time of zero mechanical re-

FIGURE 4. Example of a fusion beat from a very early extrasystole produced during a ventricular pacing run. The technique of subtraction of the control beat to yield the pressure due to the extrasystole is shown: the dotted line is the control beat.

FIGURE 3. Pressure–volume loops from three test pulse intervals. Top panel: A very early beat, with no ejection. Middle and bottom panels: Beats with progressively longer test pulse intervals.
response, depending on the stimulus train used before the test pulse intervals of interest.

Discussion

These studies demonstrate that it is possible to quantify the mechanical restitution of the left ventricle in intact closed-chest dogs using an approach based on chamber elastance. They extend the previous work of Burkhoff et al.6,7 and Yue et al.8 on mechanical restitution, in which dP/dt_{max} of isovolumically beating left ventricles was used as a measure of contractile strength. The use of the elastance-based method is critical in intact animals because, as is shown in Figure 3, diastolic filling periods and aortic pressures change substantially during the mechanical restitution protocol. The problem of using dP/dt_{max} to define mechanical restitution was shown in the studies of Anderson et al.9 and Pidgeon et al.17 in which a late descending limb of the curve was found. The load dependency of this phenomenon was demonstrated clearly by Burkhoff et al. (see Figure 8 of Reference 6), who compared isovolumic and ejecting beats in the same hearts. As can be seen in Figure 5 of the present study, the use of the elastance-based analysis eliminated such a descending limb of the restitution curve, allowing quantification of curves similar to those found in isolated muscle segments2–5 or LV chambers.6–8

The general shape of the curves found in this study and in previous studies on isolated hearts6–8 and on isolated tissue2–5 is similar. For this reason, and because the statistical fits to the established monoexponential model were good, we chose this model for our analysis. Two important differences appear to be present between our results and those of previous studies on intact hearts. First, the time constant of mechanical restitution was shorter in our animals. Burkhoff et al.6 showed that the time constant was not dependent on the basic cycle length and averaged 245±21 msec. Yue et al.8 showed an average time constant of 182±44 msec. In both of these studies, canine hearts were stimulated near the bundle of His and presumably had synchronized depolarization via the specialized conduction system.

In a study of isolated ferret muscle, Weir and Yue2 showed a similar monoexponential behavior of me-

![Figure 5. Typical mechanical restitution curves from the atrium (squares) and ventricle (triangles) in one experiment. Raw data are plotted as points, and data predicted by the nonlinear regression coefficients are shown by the lines. ESI, extrasystolic interval.](http://circres.ahajournals.org/)

### Table 1. Data From Mechanical Restitution Curves

<table>
<thead>
<tr>
<th>Dog</th>
<th>Atrial data</th>
<th>Ventricular data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC</td>
<td>TPI₀</td>
</tr>
<tr>
<td>1</td>
<td>82.0(9.8)</td>
<td>256.9(2.0)</td>
</tr>
<tr>
<td>2</td>
<td>74.0(10.2)</td>
<td>264.9(5.2)</td>
</tr>
<tr>
<td>3</td>
<td>66.0(15.2)</td>
<td>235.5(3.3)</td>
</tr>
<tr>
<td>4</td>
<td>43.6(6.0)</td>
<td>281.8(3.8)</td>
</tr>
<tr>
<td>5</td>
<td>65.2(10.0)</td>
<td>238.7(4.1)</td>
</tr>
<tr>
<td>6</td>
<td>54.7(3.6)</td>
<td>252.6(2.2)</td>
</tr>
<tr>
<td>Mean</td>
<td>64.3</td>
<td>255.1</td>
</tr>
<tr>
<td>SD</td>
<td>11.4</td>
<td>14.3</td>
</tr>
<tr>
<td>r Statistic</td>
<td>4.763</td>
<td>3.30</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Notes:**
- TC: time constant of mechanical restitution, in milliseconds; TPI₀, time of zero mechanical response, the extrapolated time-axis intercept of the mechanical restitution curve; CR_{max}, maximal mechanical response of the left ventricle normalized to the steady-state value, expressed as a percent. Numbers in parentheses are asymptotic standard errors of the coefficients.
Table 2. Time Constants of Left Ventricular Relaxation

<table>
<thead>
<tr>
<th>Dog</th>
<th>Atrial (msec)</th>
<th>Ventricular (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26.9</td>
<td>36.3</td>
</tr>
<tr>
<td>2</td>
<td>26.3</td>
<td>40.3</td>
</tr>
<tr>
<td>3</td>
<td>28.0</td>
<td>29.8</td>
</tr>
<tr>
<td>4</td>
<td>30.9</td>
<td>38.6</td>
</tr>
<tr>
<td>5</td>
<td>26.5</td>
<td>35.6</td>
</tr>
<tr>
<td>6</td>
<td>19.0</td>
<td>32.1</td>
</tr>
</tbody>
</table>

Mean: 26.28<br>SD: 3.93

*p* value for atrial and ventricular differences: 0.005

Time constants are for steady-state, control beats at the basic cycle length (375 msec), in milliseconds.

Mechanical restitution, but in that study the time constant was approximately 700 msec. Thus, the time constant of mechanical restitution is smallest in intact, closed-chest dogs, longer in isolated hearts, and longest in isolated muscle preparations, suggesting that the nature of the preparation may influence the kinetics of restitution. Additionally, species-specific differences in muscle behavior and the temperature at which the studies were performed may play a role in such differences.

The second difference we found is the magnitude of the plateau to which contractile response rose when restitution was complete. In the study of Burkhoff et al., CR_{max} was shown to increase as a function of the priming frequency. In that study, the CR_{max} at the same cycle length used in our study (heart rate of 160 beats/min) was 233.0±25.0%, a value roughly twice that we found. In the results from one dog paced with a cycle length of 333 msec, Pidgeon et al. showed that normalized dP/dt_{max} was 140% of control and clearly not yet at a plateau level. In our animals, the plateau value was 114.2±4.2% during atrial pacing and 130.1±17.5% during ventricular pacing. The lower values found in this study are likely a result of the faster time constants of mechanical restitution in our animals, whereby the mechanical response is more nearly returned to its maximal value by the time the basic cycle length has been reached; the heart is functioning closer to its plateau level under baseline conditions. Because the data are normalized to control beats that are nearer the plateau, the relative value of the plateau must be smaller.

Evaluation of postextrasystolic restitution demonstrated that the shape of the curve was similar with different ESl, as has been shown by Yue et al. Of interest, these data demonstrated that in the intact

Figure 6. Data from the fused beats and the initial ascending portion of the mechanical restitution curves for the four dogs in which these were seen. Note the consistency of the nadir of these biphasic curves. ESI, extrasystolic interval.

Figure 7. Raw data (symbols) and predicted data (lines) for postextrasystolic restitution at three different fixed extrasystolic intervals. PESI, postextrasystolic interval; ESI, extrasystolic interval.

Table 3. Data From Postextrasystolic Mechanical Restitution Paced From the Atria

<table>
<thead>
<tr>
<th>ESI (msec)</th>
<th>TC (msec)</th>
<th>TPI (msec)</th>
<th>CR_{max} (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>13.8(5.3)</td>
<td>227.3(6.6)</td>
<td>110.2(2.5)</td>
</tr>
<tr>
<td>2</td>
<td>39.9(2.7)</td>
<td>213.4(1.5)</td>
<td>110.8(1.0)</td>
</tr>
<tr>
<td>3</td>
<td>35.3(4.8)</td>
<td>239.8(2.9)</td>
<td>113.1(1.9)</td>
</tr>
<tr>
<td>375</td>
<td>34.5(3.7)</td>
<td>235.3(2.4)</td>
<td>104.3(1.4)</td>
</tr>
<tr>
<td>2</td>
<td>93.0(11.6)</td>
<td>232.8(3.0)</td>
<td>116.0(3.9)</td>
</tr>
<tr>
<td>3</td>
<td>53.7(8.3)</td>
<td>285.1(2.5)</td>
<td>109.1(3.6)</td>
</tr>
<tr>
<td>450</td>
<td>46.7(5.3)</td>
<td>249.7(2.1)</td>
<td>98.0(2.4)</td>
</tr>
<tr>
<td>1</td>
<td>96.8(13.6)</td>
<td>254.7(3.6)</td>
<td>113.2(4.7)</td>
</tr>
<tr>
<td>3</td>
<td>55.9(10.0)</td>
<td>321.1(4.6)</td>
<td>104.4(4.1)</td>
</tr>
</tbody>
</table>

ESI, extrasystolic interval; TC, time constant of mechanical restitution, in milliseconds; TPI, time of zero mechanical response, the extrapolated time-axis intercept of the mechanical restitution curve; CR_{max}, maximal mechanical response of the left ventricle normalized to the steady-state value, expressed as a percent. Numbers in parentheses are asymptotic standard errors of the coefficients.
heart, the time constant of postextrasystolic restitution differs, depending on the pacing train. When a short ESI was used, the restitution occurred more quickly. In addition, the TPIo for the short ESIs was smaller, indicating that the heart was able to depolarize sooner. Whether this is due to some aspect of intracellular calcium handling or to the duration of the stimulating action potential cannot be answered from our data. The variable nature of TPIo and the time constant of postextrasystolic restitution indicates that the restitution phenomenon is dynamic in the intact heart, adjusting to short-term differences in stimulation pattern.

When the mechanical restitution curves of the atrial and ventricular runs were compared, two differences were found. First, TPIo was longer when the atria were paced. This may reflect the influence of the atrioventricular node, which would block early extrastimuli from reaching the left ventricle. Another possible explanation is that the relative delay in the onset of mechanical restitution results from differences in the action potential duration of beats paced from the atria and ventricles. If the action potential duration of the beats paced from the ventricle was longer, the test diastolic interval may not differ, although the actual extrasystolic interval for the ventricular runs was longer. Because action potential durations were not measured in these experiments, this explanation remains speculative.

The second difference was that the time constant of mechanical restitution was longer for the ventricular paced runs. Prior studies have shown that ventricular pacing causes a rightward shift of the $P_{es}-V_{es}$ relation, with no change in slope. These data have been considered an indication that dyssynchrony has no primary effect on myocardial contractility per se but affects the function of the left ventricle as a pump. Zile and colleagues have shown that ventricular pacing causes a prolongation of the time constant of LV relaxation, indicating that dyssynchrony alters diastolic as well as systolic LV pump performance. Our analysis of LV relaxation (Table 2) confirms these observations and suggests that dyssynchronous relaxation may underlie our results. Early extrastimuli would reach the ventricle when some, but not all, of the wall segments were repolarized sufficiently to generate force. Only after sufficient time had passed for all of the segments to repolarize would the full mechanical response of the left ventricle for that ESI be seen. Thus, direct comparison of data from studies in which atria and ventricles were stimulated may not be valid.

Another observation on the ventricular paced runs was that very early extrastimuli led to fusion beats that appeared during the time of LV relaxation of the control beats (Figures 4 and 6) in four dogs. These data are similar to the findings of Bass, who studied isolated cat papillary muscles, and Hansen et al., who studied cardiac transplant recipients. By subtracting the contribution of the control beat from the fusion beat, the elastance of the fusion beat could be quantified. As shown in Figure 6, the magnitude of these beats decreased to a nadir, which occurred at about 250 msec in each case.

Whereas the data showed a monotonic decline of peak elastance with increasing ESI during fusion beats, the small number of points available and the limited range of elastances over which they covered did not permit formal analysis by either a linear or nonlinear model. The appearance of these beats, however, suggests that during this time of LV relaxation, free ionic calcium is present in the cell, which has yet to be taken up by the sarcoplasmic reticulum and which is still available for crossbridge interaction. As the ESI lengthens, more of this calcium is taken up, and the amount available for crossbridge interaction drops. Consistent with the model of Yue et al., the nadir of the curve would occur when calcium reuptake was greatest and transfer of calcium to the releasable pool was not yet activated. The onset of mechanical restitution would signal the transfer of some calcium to the releasable pool. Thus, the descending limb of mechanical performance found during the time of LV relaxation may reflect the kinetics of calcium reuptake by the sarcoplasmic reticulum, and the mechanical restitution curve may represent the kinetics of transfer to the releasable pool.

The remarkable consistency of the nadir found in these four dogs suggests that the kinetics of these processes may be defined within relatively narrow limits. These observations are, however, complicated by differences in patterns of depolarization that occur during this protocol, and demonstration that more than inferential data on intracellular calcium handling can be obtained from such studies will require further study.

Our results must be interpreted in light of potential experimental weaknesses. First, to determine peak single-beat LV elastance for beats with differing ESI, the $V_0$ for the control $P_{es}-V_{es}$ relation was used. This $V_0$ also was used for analysis of single-beat elastance in the postextrasystolic runs. Although prior studies from this lab have shown that $V_0$ changes with steady-state alterations in heart rate, performing caval occlusions at heart rates corresponding to each ESI is not feasible. Moreover, because in this study the test beat (or in the case of postextrasystolic restitution, both the ESI and the test beat) was transient in nature, it is likely that changes that may occur in steady-state alterations in volume status or pacing rate may be less, or not present. Sugira et al. recently have shown that the effects of changes in ventricular volume, presumably mediated by means of length-dependent activation, occur over a period of dozens of beats. Thus, in the present protocol in which only brief perturbations of pacing frequency and loading conditions occur, such effects would be minimized. For these reasons, we chose to use a common $V_0$ for our definition of single-beat elastance.
A second concern regards the possible effects of curvilinearity of the $P_{es}-V_{se}$ relation on our data, because it was assumed to be linear in this analysis. Formal analysis of the effect of contractility on the linearity of the relation derived in this animal model has been reported by Little et al. They showed that slight but consistent curvilinearity of the relation is present in this model under a variety of contractile states. This may reflect differences in the preparation or in the range of pressures and contractile states testable in the intact animal but suggests that our assumption of linearity is reasonable. Because similar degrees of nonlinearity are present at all contractile states in this preparation, inclusion of a nonlinear model would not substantially alter the restitution behavior and would unnecessarily complicate our analysis.

A final consideration is that these dogs were studied after autonomic blockade and sedation. These interventions do not significantly alter the slope of the $P_{es}-V_{se}$ relation in closed-chest dogs. However, we have not considered the ethics of the experiment.

In summary, the results of this study indicate that the elastance-based approach provides a useful method for assessing LV mechanical restitution. Of note, the time constant of mechanical restitution of the intact left ventricle is substantially smaller than those previously reported for isolated hearts, or muscle segments, and behaves dynamically, depending on the stimulus train used. Also, the restitution behavior was different for atrial and ventricular pacing sites, such that results from studies in which atrial stimulation was used may not be directly comparable to those in which ventricular stimulation was used. The use of elastance-based mechanical restitution may provide new insights into the physiological correlates of intracellular calcium handling in the intact heart.

Acknowledgments

The authors express thanks to Danny Escobedo and Donald Watkins for excellent technical assistance.

References


Key words: cardiac mechanics, force-interval relation, contractility.
Evaluation of left ventricular mechanical restitution in closed-chest dogs based on single-beat elastance.
G L Freeman and J T Colston

Circ Res. 1990;67:1437-1445
doi: 10.1161/01.RES.67.6.1437

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/67/6/1437

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/