Kinetics of Restitution of Left Ventricular Relaxation

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Although the kinetics of cardiac systolic force restitution have been well described, the restitution kinetics of left ventricular relaxation have not been examined. To define relaxation restitution behavior, we studied seven dogs chronically instrumented with left ventricular high-fidelity micromanometers and piezoelectric dimension crystals. After a priming period at a basic cycle length of 375 msec, test extrastimuli were introduced after a range of extrasystolic intervals (ESIs). Relaxation behavior of control and extrasystolic beats was characterized by the time constant of isovolumic relaxation, $\tau$. Relaxation restitution can be described by two concatenated monoeponential curves, an early phase described by a rapid time constant and a late phase described by a slower time constant ($TC_1$, 36.21±7.90 msec; $TC_2$, 75.94±10.65 msec; $p<0.05$). The first phase of relaxation restitution parallels systolic force restitution over the same range and displays faster recovery ($TC_1$, 58.93±10.01 msec, $p<0.05$). Postextrasystolic restitution of test pulses after beats at fixed ESIs depends on the initial ESI. Relaxation recovery of postextrasystolic beats proceeds faster with smaller initial ESIs ($TC_1$ for ESI of 300 msec, 13.27±4.05 msec; $TC_1$ for ESI of 450 msec, 72.85±21.72 msec; $p<0.0001$). The monoeponential pattern of restitution was seen with model-independent descriptors of relaxation as well as with $\tau$. (Circulation Research 1992;70:29–38)

The force–interval relation describes differences in contractile response of cardiac muscle resulting from variation of the rate and rhythm of stimulation. This relation has two distinct aspects, mechanical restitution and postextrasystolic potentiation.1 Mechanical restitution is the time-dependent process by which the ability of the muscle to contract returns after a stimulation. Postextrasystolic potentiation describes the way in which the contractile strength of a beat at a fixed time after an extrasystole depends on the interval preceding the extrasystole. Both of these phenomena have been described by monoeponential functions relating mechanical response to the extrasystolic interval,1 and both ultimately reach a steady-state plateau when contractile performance is independent of further changes in the extrasystolic interval. The force–interval relation is a basic property of myocardium and has been studied in intact animals2,3 as well as in isolated hearts4–6 and isolated muscle preparations.7–10

Weir and Yue10 have shown that the time constants of mechanical restitution and postextrasystolic potentiation are very similar and that contractile response has a linear correlation with intracellular Ca$^{2+}$ concentration. Their studies with ryanodine, an inhibitor of the sarcoplasmic reticulum (SR) Ca$^{2+}$ release channel, have defined an essential role for the SR in the force–interval relation. These investigators concluded that the relation is a physiological expression of the availability of intracellular Ca$^{2+}$, which is dependent on the SR. A phenomenological model of Ca$^{2+}$ flux among the SR, myoplasm, and extracellular space has been proposed to describe the kinetics of the force–interval relation.6,10

Despite the large body of work performed delineating cardiac systolic restitution, very little has been done to define the pattern by which the heart's ability to relax rapidly returns after a stimulus, a phenomenon we term relaxation restitution. Relaxation, like myocardial contraction, is an energy-requiring process. Myocardial crossbridge separation and sarcomere force decay are dependent on active Ca$^{2+}$ uptake by the SR and resultant dissociation of Ca$^{2+}$ from troponin C. Although sarcolemmal Na$^+$-Ca$^{2+}$ exchange participates in determining intracellular Ca$^{2+}$ levels, it is a low-affinity transport system and probably does not play a major role during isovolumic relaxation (see Reference 11 for review).
Because myocardial relaxation depends on the SR, we hypothesized that the ability of the left ventricle to relax should also display time-dependent recovery. The purpose of this study was to determine whether this was the case and, if so, how it could be best described. Our results indicate that the restitution of isovolumic relaxation follows a specific pattern that can be fit by two monoeponential functions, one with a rapid and one with a slow time constant. Thus, in a fashion similar to other aspects of mechanical performance, relaxation behavior of the myocardium is dependent on the stimulus interval and demonstrates time-dependent restitution.

Materials and Methods

All animal studies were performed in accordance with guidelines described in the “Guide for Care and Use of Laboratory Animals” (DHHS publication No. [NIH] 85-23, revised 1985). Seven healthy mongrel dogs of either sex were surgically instrumented for long-term physiological monitoring as previously described by this laboratory.12,13 After premedication with xylazine and pentobarbital, endotracheal intubation was performed under general anesthesia with 1–2% halothane. Under sterile conditions, a left thoracotomy was performed. Fluid-filled polyvinyl 16-gauge catheters were placed in the descending aorta and the left atrium. A high-fidelity micromanometer (Konisberg Instruments, Inc., Pasadena, Calif.) and a 1.1 mm i.d. fluid-filled catheter for micromanometer calibration were implanted across the left ventricular apex and held in place with a purse-string suture. Three sets of piezoelectric crystals were implanted in the endocardium of the left ventricle along the anterior-posterior, septal-lateral, and long axis diameters to allow for continuous measurement of these dimensions. Pacing electrodes were sutured to the epicardium of the left atrium and the free wall of the left ventricle. Balloon occluder cuffs were placed around the inferior vena cava. After the chest was closed in multiple layers, all wires and tubes were tunneled subcutaneously to exit from the back of the neck. The animals were allowed to recover a minimum of 2 weeks before experimentation.

All experiments were performed with the animal lying in a sling on its right side. The dogs were anesthetized with a combination of thiopental sodium (25–30 mg/kg), droperidol (1.5–3.0 mg/kg), and fentanyl (0.03–0.06 mg/kg). Once anesthetized, respiration was supported with endotracheal intubation and mechanical ventilation with room air. Pharmacological autonomic blockade was produced by the administration of intravenous atropine (0.1 mg/kg; maximum dose, 2 mg) and hexamethonium (20–25 mg/kg). All experimental hemodynamic data were collected during 10–15-second periods of posthyperventilation apnea to avoid respiratory variation in intrathoracic pressure. Analog tracings were recorded on an eight-channel forced-ink oscillograph (Beckman Instruments Inc., Palo Alto, Calif.) at a paper speed of 25 mm/sec. The following signals were recorded: left ventricular pressure, the first derivative of the left ventricular pressure with respect to time (dP/dt), electrocardiogram, aortic pressure, and the three left ventricular dimensions. These signals were also simultaneously converted to digital form at a sampling rate of 500 Hz by using an IBM-PC and stored on floppy disks.

For these protocols the atra were paced at a basic cycle length of 375 msec (160 beats per minute), a rate above the ambient heart rate in the animals. After a hemodynamic steady state was achieved, data were collected during rapid caval occlusions to acutely alter left ventricular pressures and volumes. Runs that did not display at least a 20 mm Hg drop in peak systolic left ventricular pressure were discarded. After caval occlusions were performed, mechanical restitution was assessed. After an initial train of beats at the basic cycle length, a single test atrial extra-stimulus was introduced using a programmable stimulator (Bloom Instruments, Reading, Pa.). The initial extrasystolic interval (ESI) was timed to be within the absolute refractory period of the atrioventricular node. The ESI was subsequently increased at 20-msec intervals with the resultant production of extrasystoles with progressively increasing EISIs. The process was terminated when an intrinsic sinus beat captured the ventricle before the paced beat.

As an extension of this protocol, we studied the effect of varying ESI on postextrasystolic restitution.8 The test stimulus was introduced after an initial extrasystole at fixed EISIs of either 300 or 450 msec. With each separate ESI, postextrasystolic restitution was evaluated. The postextrasystolic interval (PESI) was increased by 20-msec increments until the PESI was long enough for conduction of an intrinsic sinus beat. Thus, postextrasystolic restitution data were available from runs with ESIs fixed at 300, 375, and 450 msec.

Data Analysis

The digitized data were analyzed using computer software developed in our laboratory. The left ventricular chamber was assumed to be an ellipsoid, and left ventricular volume (V_LV) was calculated from the three orthogonal dimensions using the equation

$$V_{LV} = \pi/6 \times (D_{AP} \times D_{SL} \times D_{LA})$$

where D_{AP} is the anterior-posterior diameter of the left ventricle, D_{SL} is the septal-lateral diameter, and D_{LA} is the long axis diameter. For the caval occlusion runs, end systole was defined as occurring at the upper left corner of the left ventricular pressure-volume loop, and the end-systolic pressure-volume (P_s-V_e) relation was determined using the iterative approach of Kono et al.14 The data were fitted to the equation

$$P_s = E \times (V - V_0)$$
by least-squares linear regression technique, where $E_{\text{max}}$ is the slope of the relation and $V_0$ is its volume intercept.

For the mechanical restitution experiments, end systole was considered to occur at the point of maximal time-varying elastance ($E_{\text{max}}$) for the beat, as previously described by Suga et al (see Reference 15 for review). This was defined as the maximal ratio of left ventricular pressure to corrected left ventricular volume (the absolute volume minus the $V_0$, determined from the caval occlusions). End diastole was defined as occurring at the peak of the QRS complex. For analysis purposes, dP/dt was calculated from the instantaneous left ventricular pressure by using a running five-point linear fit. The period of isovolumic relaxation was defined as occurring between the time of peak negative dP/dt to the time when pressure had fallen to 5 mm Hg above the end-diastolic pressure for that beat.

For each mechanical restitution run several parameters were determined for both the test extrasystole (the beat after either the ESI or PESI, depending on the run) and the control beat (defined as the last beat occurring at the basic cycle length before the test extrasystole). The time constant of isovolumic relaxation, $\tau$, was determined by nonlinear regression analysis of the pressure and time data during isovolumic relaxation by using a monoexponential function of the form

$$P_{LV}=(P_0-P_b)\times \exp\left(-\frac{t}{\tau}\right)+P_b$$

where $P_{LV}$ is left ventricular pressure, $P_0$ is an estimate of the pressure at peak negative dP/dt, $t$ is the time (in milliseconds), $\tau$ is the time constant of relaxation, and $P_b$ is the floating pressure asymptote as $t$ approaches infinity. The computer algorithm used the method described by Hartley.\(^\text{16}\) $R_{\text{avg}}$, the average rate of pressure fall during isovolumic relaxation, was defined as the total pressure fall during this period divided by its duration (in milliseconds). $E_{\text{max}}$ for each beat was determined as described above. Each of these parameters was normalized to the value from its matched control beat and expressed as a percent.

The time interval from end-diastolic pressure to $E_{\text{max}}$ was defined as $T_{\text{max}}$ (time to maximal elastance). The time of the isovolumic relaxation period was defined as $T_r$. The time from the beat starting pressure to the end of isovolumic relaxation was defined as total time ($T_t$) for the beat. To determine relative contributions of relaxation time, the ratios $T_{\text{max}}/T_r$ and $T_t/T_r$ were determined. These ratios were normalized to the control values and expressed as a percent.

All monoexponential function analysis and restitution time constant derivations were performed according to standard nonlinear techniques. The forms of the equations themselves are noted in the text.

**Statistical Analysis**

Comparisons between time constants of the first and second phases of relaxation restitution as well as comparisons between the time constants of systolic force recovery and relaxation recovery were made using the paired $t$ test. A value of $p<0.05$ was considered significant. Comparisons between the time constants of postextrasystolic restitution were made using repeated-measures analysis of variance and least-squares means. A value of $p<0.025$ was considered significant.

**Results**

**Relaxation Restitution of Single Extrasystoles**

Analog tracings from a typical run at a basic cycle length of 375 msec are shown in Figure 1. There is no respiratory variation in intrathoracic pressures or diameters. Figure 2 is a composite of the ventricular pressure data during isovolumic relaxation from several beats with different ESIs from one experiment. With decreasing ESIs, the beats become smaller, left ventricular pressure appears to drop more slowly, and the relative time of isovolumic relaxation increases progressively. This is better appreciated if the time of isovolumic relaxation ($T_r$) is compared with the time of systole ($T_{\text{max}}$) and with the total time of the beat ($T_t$). Figure 3 shows raw data plots of normalized $T_{\text{max}}/T_r$ and normalized $T_t/T_r$ as a function of ESI. Note that there is a progressive increase in the relaxation time relative to both $T_{\text{max}}$ and $T_t$ as ESI is shortened.

Figure 4 (top panel) shows the group data relating normalized $\tau$ to ESI. Note that normalized $\tau$ decreases monotonically from small ESIs until the basic cycle length and then displays a gradual increase thereafter. A logarithmic transformation of these data is plotted in the inset, showing that the transformed data fall on two lines. These lines have good correlation coefficients ($r=0.975$ and 0.914) with a break point near the basic cycle length of 375 msec. From these observations, we concluded that the restitution of $\tau$ can be divided into two phases and that each phase can be described by a monoexponential equation.

To more fully characterize this behavior we fit the data from the early phase (up to the basic cycle length) to the equation

$$\tau_0=(K_0-K_a)\times \exp\left(\frac{(ESI_0-ESI)}{TC_1}\right)+K_a \quad (1)$$

where $\tau_0$ is normalized $\tau$, $ESI_0$ is the smallest ESI that produces a mechanical response ("initial" ESI), $K_0$ is an estimate of normalized $\tau$ at ESI$_b$, $K_a$ is the plateau asymptote during the first phase of restitution, and $TC_1$ is the time constant of the first phase of isovolumic diastolic restitution. The second (late) phase of restitution can be described by the equation

$$\tau_0=K_b \times (1-\exp\left(\frac{(ESI_0-ESI)}{TC_2}\right)) \quad (2)$$

where $K_b$ is the plateau, or asymptote, and $TC_2$ is the time constant of the second phase of restitution.

The first column in Table 1 displays $K_a$, $K_b$, $TC_1$, and $TC_2$ calculated for the group data along with the asymptotic standard errors for each parameter. Figure
4 (bottom panel) displays the data points and their respective nonlinear regressions. It is clear that the early phase of restitution decays toward an asymptote value of approximately 100% normalized \( \tau \) (\( K_r \), 102.22±20.32), indicating complete recovery of relaxation at the basic cycle length. With ESIs longer than the basic cycle length, normalized \( \tau \) rises toward an asymptote of approximately 130% (\( K_r \), 133.86±6.06). The second phase of restitution proceeds much more slowly than the first phase, with \( T_C_2 \) approximately 3.5 times greater than \( T_C_1 \).

Individual data sets from each animal displayed the same pattern of relaxation behavior. Because of the smaller number of observations for each ESI, however, individual data sets had inherently less descriptor power when fitted to the above monoeponential equations. This was especially true for the early phase of restitution, since there were very few data points at the asymptote value. To improve descriptor power of individual data sets, \( K_r \) was assumed to be 102.2% normalized \( \tau \), as predicted by the group data. This is physiologically predictable, since normalized relaxation must approach 100% at the basic cycle length. Data from individual dogs analyzed in this manner are presented in Table 2. Mean values and standard errors for each parameter are also listed. The mean values for \( T_C_1 \), \( T_C_2 \), and \( K_r \) obtained are similar to those obtained with group analysis, but the disparity between \( T_C_2 \) and \( T_C_1 \) is less (\( T_C_2 \) approximately two times greater than \( T_C_1 \), \( p<0.05 \)).

Because \( \tau \) is a model-dependent descriptor of the speed of left ventricular relaxation and may be subject to limitations of the model, we also chose to examine a relaxation parameter that is model independent, \( R_{avg} \). This variable is the ratio of the total drop in pressure during isovolumic relaxation to the time of isovolumic relaxation (i.e., an average rate of pressure fall during isovolumic relaxation). Figure 5 (left panel) displays normalized \( R_{avg} \) as a function of ESI for the group. The data reveal a monoeponential increase in \( R_{avg} \) from smaller ESIs until the basic cycle length and a gradual nonlinear decrease thereafter. Because a long \( \tau \) reflects a small \( R_{avg} \) this result parallels that described above. If the data are inverted, they can be described by the same monoeponential equations described above for \( \tau \). The same relation is seen for normalized \( dP/dt_{min} \) (Figure 5 [right panel]), and inversion of the data again pro-
roduces a curve similar to those seen for \( \tau \) and \( 1/R_{\text{avg}} \). Table 1 lists the parameters for the first and second phases of restitution for the three different descriptors of relaxation. Regardless of which is used, a similar pattern of restitution behavior is seen.

**Relaxation Restitution of Postextrasystoles**

Table 3 lists the restitution parameters of postextrasystolic beats for three different extrasystolic intervals: 300, 375, and 450 msec. Values for the group as well as individual data (calculated as described above) are presented. With longer ESI the time constants for both phases of restitution increase, and the second phase asymptotes tend to decrease. There are statistically significant differences between TC\(_1\) with ESIs of 300 and 450 msec (\( p<0.0001 \)) as well as between ESIs of 375 and 450 msec (\( p<0.002 \)). Although TC\(_1\) between 300 and 375 msec tended to be different, the difference failed to reach statistical significance (\( p<0.03 \)). This is probably due to the fact that two animals displayed very rapid recovery of the first phase so that at an ESI of 300 msec, normalized \( \tau \) already reached baseline values at PES\(_{L0}\). Thus, first phase time constants could not be calculated, yielding a smaller sample size at 300 msec and reducing statistical power. TC\(_2\) is significantly different for all three ESIs. Group data for postextrasystolic restitution at each ESI along with the curves determined from nonlinear regression analysis are shown in Figure 6. Note that in addition to prolongation of the time constants with increasing ESI, the transition between the first and second phases of restitution occurs earlier with lower ESIs and that the entire curve appears to be shifted to the right with increasing ESI.

**Systolic Mechanical Restitution**

As previously reported, restitution of mechanical contractile response can be described by an elastance-based construct.\(^3\) The restitution curve obtained is approximated by a monoexponential function of the form

\[
\text{SBE}_n = CR_{\text{max}} \times \left(1 - \exp\left([\text{ESI}_0 - \text{ESI}] / TC \right)\right) \tag{3}
\]

where \( \text{SBE}_n \) is normalized single beat elastance, \( CR_{\text{max}} \) is the maximal (plateau) value of contractile response, and TC\(_1\) is the time constant of systolic force restitution. Normalized elastance refers to the ratio of \( E_{\text{max}} \) for the extrasystolic beat to \( E_{\text{max}} \) for the control beat and is a measure of myocardial contractile response. Figure 7 displays normalized elastance and normalized \( \tau \) as a function of ESI in a single animal, along with respective nonlinear regression curves and time constants. Note that relaxation recovers faster than force generation (TC\(_1\) is approximately 2.3 times greater than TC\(_1\) of relaxation). Table 4 displays systolic restitution time constants for individual animals. There is a statistically significant difference between TC\(_1\) and TC\(_2\) (listed in Table 2) with \( p<0.05 \).

**Discussion**

The results of these studies demonstrate that left ventricular relaxation in closed-chest dogs follows a pattern of restitution that can be accurately defined mathematically. The restitution of relaxation in the intact dog occurs in two phases as shown in Figures 4–6. As shown in Figure 7, the increase in relaxation rate seen from short ESIs until the basic cycle length parallels the increase in systolic mechanical response during the same period. We propose that this relaxation restitution behavior can be modeled as a monoexponential and that it is consistent with available models of intracellular calcium handling.

Numerous previous studies have indicated that a major determinant of myocardial relaxation is the reuptake of intracellular calcium by the SR (see References 17 and 18 for review), which results in dissociation of calcium from troponin C. In consid-
Figures 4. Top panel: Group data for normalized time constant of isovolumic relaxation (τ) (±SEM) plotted as a function of extrasystolic interval (ESI). The inset shows a logarithmic transform indicating that the data fall along two lines with a break point at the basic cycle length and can be described by two concatenated monoexponential functions. Bottom panel: The same data points plotted with nonlinear regression curves derived using Equations 1 and 2 in the text. The time constants (TC) for the first and second phases of restitution are listed.

Regarding aspects of the force–interval relation, Yue et al.6,10 have proposed a phenomenological model in which the SR is compartmentalized into an uptake (SR_u) and release (SR_r) pool. In this construct calcium taken up after a contraction by the SR is not immediately available to the contractile machinery but must first be transferred to a release pool, a process that occurs in a time-dependent fashion. This transfer process is represented by K2 in Figure 8, which illustrates the model. As shown by Weir and Yue,10 if K2 proceeds according to first-order kinetics, a monoexponential time course of both mechanical restitution and postextrasystolic potentiation will occur. This model also assumes that transsarcolemmal calcium movement via separate mechanisms (including voltage-dependent Ca^{2+} influx)19 proceeds in a rate-independent fashion and does not produce a net effect on beat-to-beat regulation of intracellular calcium.

It should be stressed that the calcium behavior predicted by this model does not necessarily mean that ions are physically moving from one site in the
SR to another. The kinetics could be related to some time-dependent enzyme behavior or other governing mechanism of calcium uptake and release. Nonetheless, the model does predict how mechanical performance can be related to intracellular calcium fluxes in the myocardium.

Direct evaluations of cardiac SR support this model. Studies with ryanodine indicate that SR calcium uptake and sequesteration capacity are not unlimited but that they display saturation. Also, studies of calcium transport by isolated SR vesicles demonstrate that in the appropriate medium these will reach a plateau level of calcium accumulation (see Reference 21 for review). If this is the case, lower calcium concentration within SRU will produce faster SR calcium uptake, reflected in faster rates of cardiac relaxation. On the other hand, if enough time elapses so that the calcium level in the SRU nears its accumulation capacity, slower rates of calcium uptake and cardiac relaxation would occur.

This outline can provide a basis for understanding the early phase of the relaxation restitution curve. When the ESI is short there is less transfer of calcium between the SRU and SRE compartments; the higher calcium concentration in the SRU compartment would result in more limited SR uptake during relaxation and slower rates of relaxation. Concomitantly, less calcium is available for release to the myofilaments, resulting in a smaller mechanical response. As previously demonstrated with systolic mechanical restitution, the monoexponential nature of this relation suggests that calcium transfer between these pools follows first-order kinetics. Moreover, our results suggest that in the steady state (at the basic cycle length) SR uptake of calcium proceeds to near the saturation plateau. If this were not the case, relaxation rate should not be markedly affected by differences in extrasystolic intervals.

Another contributing factor to interval-dependent differences in myocardial relaxation could be substrate level regulation of the SR Ca\(^{2+}\)-ATPase pump. Both ATP concentration and the concentration of intracellular calcium have been shown to regulate this pump. The lower levels of free intracellular calcium present after short ESIs could downregulate the SR pump and reduce SR calcium

### Table 1. Restitution Parameters Obtained Using Nonlinear Regression for Three Different Descriptors of Relaxation

<table>
<thead>
<tr>
<th>Relaxation parameters</th>
<th>(\tau)</th>
<th>(1/R_{avg})</th>
<th>(1/(dP/dt_{min}))</th>
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<tbody>
<tr>
<td>(K_s)</td>
<td>102.22</td>
<td>87.07 (11.26)</td>
<td>89.68 (14.57)</td>
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<tr>
<td>(TC_1)</td>
<td>30.17</td>
<td>35.49 (3.80)</td>
<td>33.21 (4.33)</td>
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<tr>
<td>(K_b)</td>
<td>133.86</td>
<td>105.84 (1.52)</td>
<td>117.24 (2.44)</td>
</tr>
<tr>
<td>(TC_2)</td>
<td>104.86</td>
<td>75.06 (8.61)</td>
<td>87.49 (9.47)</td>
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</tbody>
</table>

Values in parentheses are asymptotic standard errors. \(\tau\), time constant of relaxation; \(R_{avg}\); average rate of relaxation; \(dP/dt_{min}\), minimum value of the first derivative of left ventricular pressure; \(K_s\), plateau asymptote for first phase of restitution; \(TC_1\), time constant of the first phase of isovolumic diastolic restitution; \(K_b\), plateau asymptote for the second phase of restitution; \(TC_2\), time constant of the second phase of isovolumic diastolic restitution.

### Table 2. Restitution Parameters From Individual Dogs

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>(TC_1)</th>
<th>(K_b)</th>
<th>(TC_2)</th>
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<tbody>
<tr>
<td>1</td>
<td>38.65</td>
<td>130.23</td>
<td>100.84</td>
</tr>
<tr>
<td>2</td>
<td>56.49</td>
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<td>51.91</td>
</tr>
<tr>
<td>3</td>
<td>51.82</td>
<td>86.65</td>
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</tr>
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<td>57.42</td>
<td>147.40</td>
<td>87.00</td>
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<tr>
<td>5</td>
<td>31.07</td>
<td>144.56</td>
<td>110.91</td>
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<td>6</td>
<td>8.08</td>
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<td>7</td>
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<td>Mean</td>
<td>36.21</td>
<td>126.63</td>
<td>75.94*</td>
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<tr>
<td>SEM</td>
<td>7.90</td>
<td>8.14</td>
<td>10.65</td>
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</table>

\(TC_1\), time constant of the first phase of isovolumic diastolic restitution; \(K_b\), plateau asymptote for the second phase of restitution; \(TC_2\), time constant of the second phase of isovolumic diastolic restitution.

\(p<0.05\) compared with \(TC_1\).

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**Figure 5.** Group data for normalized average rate of pressure fall during isovolumic relaxation (\(R_{avg}\)) (left panel) and normalized \(dP/dt_{min}\) (right panel) as a function of extrasystolic interval (ESI) (values are \(\pm \)SEM). Inversion of the data yields a qualitatively similar relation of these two model-independent relaxation parameters as seen with normalized time constant of isovolumic relaxation, \(\tau\).
The uptake of myocardial substrate was increased by this stimulation pattern, with resultant diastolic distribution of calcium. The imbalance of calcium distribution produced by this stimulation pattern, and in particular the reduction of SR\textsubscript{a} during the postextrasystolic beat, will be of smaller magnitude as the ESI is increased toward the basic cycle length and reversed as it exceeds the basic cycle length. This would be reflected in slowed restitution of postextrasystolic relaxation as the ESI becomes longer. In addition, the same mechanism would dictate that systolic mechanical restitution of postextrasystolic beats would proceed more rapidly with smaller ESIs, a result we have previously demonstrated.\textsuperscript{3}

The model does not explain the second phase of relaxation restitution, and the determinants of this behavior are less clear. A likely mechanism is that this phase of relaxation restitution results from load-induced effects on relaxation. Prior studies have demonstrated that contraction loading prolongs $\tau$,\textsuperscript{24,25} In addition, higher load during relaxation (relaxation loading) shortens $\tau$.\textsuperscript{26} In evaluating a pres-

### Table 3. Restitution Parameters for Postextrasystolic Beats at Three Different Extrasystolic Intervals

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>ESI=300 msec</th>
<th>ESI=375 msec</th>
<th>ESI=450 msec</th>
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<td>TC\textsubscript{2}</td>
<td>TC\textsubscript{1}</td>
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<tr>
<td>SEM</td>
<td>4.05</td>
<td>10.48</td>
<td>7.13</td>
</tr>
</tbody>
</table>

Note that two animals did not display an early restitution phase at ESI=300 msec (see text). ESI, extrasystolic interval; TC\textsubscript{1} and TC\textsubscript{2}, time constants of the first and second phases of isovolumic diastolic restitution, respectively.

$^p<0.0001$ compared with TC\textsubscript{2} at ESI=300 msec.

$p<0.002$ compared with TC\textsubscript{1} at ESI=375 msec.

$s<0.0001$ compared with TC\textsubscript{2} at ESI=300 msec and $p<0.025$ compared with TC\textsubscript{2} at ESI=375 msec.
TABLE 4. Systolic Restitution Parameters for Individual Dogs

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>TC_s</th>
<th>CR_max</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>88.09</td>
<td>116.02</td>
</tr>
<tr>
<td>2</td>
<td>72.34</td>
<td>122.60</td>
</tr>
<tr>
<td>3</td>
<td>49.04</td>
<td>105.69</td>
</tr>
<tr>
<td>4</td>
<td>56.05</td>
<td>106.50</td>
</tr>
<tr>
<td>5</td>
<td>91.94</td>
<td>138.04</td>
</tr>
<tr>
<td>6</td>
<td>20.07</td>
<td>99.98</td>
</tr>
<tr>
<td>7</td>
<td>35.86</td>
<td>104.98</td>
</tr>
<tr>
<td>Mean</td>
<td>58.93*</td>
<td>113.40</td>
</tr>
<tr>
<td>SEM</td>
<td>10.01</td>
<td>5.02</td>
</tr>
</tbody>
</table>

TC_s, time constant of systolic restitution; CR_max, maximal value of contractile response.

*p < 0.05 compared with TC_1 of relaxation restitution (listed in Table 2).

sure–volume loop from a beat with an ESI longer than the basic cycle length (Figure 9), it can be seen that the load during the early phase of contraction is increased in the extrasystole compared with control: there is higher left ventricular volume and consequently higher wall stress (contraction load is higher in this beat, an effect that would prolong relaxation). In addition, left ventricular volume is lower during isovolumic relaxation in this beat (relaxation load is lower in this beat, an effect that would also prolong relaxation). Thus, in the extrasystole with a long ESI, loading conditions favor a slower rate of relaxation, or a longer \( \tau \). These effects would be greater with progressive increases in ESI beyond the basic cycle length and are consistent with the slow rise in \( \tau \) seen at high ESIs during the second phase of relaxation restitution.

The pattern of relaxation restitution we found was observed regardless of the parameter used to define isovolumic relaxation. The results obtained using \( \tau \), a model-dependent parameter, were similar to those obtained using \( R_{WS} \) or \( dP/dt_{min} \), which are model independent. This suggests that results were not altered by the analytical approach used to describe relaxation. Previous studies from this laboratory have demonstrated that indexes of left ventricular relaxation have significantly more variability than other hemodynamic parameters.\(^{27}\) Despite this variability the biphasic pattern of relaxation restitution was seen in all of the animals, indicating it reflects an important control mechanism.

In summary, our results demonstrate that as with cardiac contraction, cardiac relaxation follows a pattern of restitution. A model of compartmental Ca\(^{2+}\) flux proposed previously\(^{6,10}\) predicts early relaxation restitution behavior; late phase restitution may be accounted for by changes in loading conditions. Studies of relaxation restitution may be a useful tool to delineate alterations in cardiac performance in pathological states such as ischemia or heart failure as well as in response to pharmacological agents. Separation of systolic and diastolic restitution behavior may yield insights in disease states that preferentially produce either systolic or diastolic dysfunction. Further studies are needed to determine the precise cellular mechanisms underlying the restitution behavior of relaxation and to investigate alterations in this behavior caused by cardiac disease.

References


FIGURE 8. Compartmental model of calcium transport, after Weir and Yue.\(^{10}\) There are three compartments: the sarcoplasm (S), the sarcoplasmic reticulum uptake pool (U), and the sarcoplasmic reticulum release pool (R). The transsarcolemmal flux of Ca\(^{2+}\) is assumed to be in a steady state. Ca\(^{2+}\) transport between the three pools is modeled by monoexponential functions with separate time constants (K1, K2, and K3) occurring at specific periods during the cardiac cycle.

FIGURE 9. Pressure-volume loops from an extrasystolic beat longer than the basic cycle length (extrasystolic interval, 544 msec; dashed lines) and a control beat at 375 msec (solid line). Total load is higher at early ejection and lower at the start of relaxation for the extrasystolic beat compared with the control beat (see text).


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