Delayed End Ejection Increases Isovolumic Ventricular Relaxation Rate in Isolated Perfused Canine Hearts

Masatsugu Hori, Masafumi Kitakaze, Yoshio Ishida, Masatake Fukunami, Akira Kitabatake, Michitoshi Inoue, Takenobu Kamada, and David T. Yue

We sought to determine the ejection variables that are principally responsible for increases in isovolumic ventricular relaxation rate observed with increases in stroke volume. In nine isolated canine hearts, left ventricular ejection was controlled by patterns specially designed to isolate the ejection parameters most critical to isovolumic relaxation rate. When stroke volume was augmented by increases in end-diastolic volume (EDV) with end-systolic volume (ESV) held constant, isovolumic ventricular relaxation rate was unchanged, as gauged by the time constants of single-exponential fits to decaying pressure. In contrast, when ESV was decreased with EDV held constant, isovolumic relaxation time constants decreased significantly, from approximately 100 to 70 msec (protocol I). The important difference in these two situations might have been that the time of end ejection was delayed in the case with faster isovolumic relaxation. To rule out other parameters that may have influenced isovolumic relaxation, ejection velocity was varied in another protocol (protocol II) by either delays in time of the onset of ejection or advances in end-ejection time, always with constant ESV and EDV. Here isovolumic relaxation was progressively slowed as end ejection occurred earlier, whereas isovolumic relaxation rate was insensitive to changes in the onset of ejection, consistent with the unique importance of end ejection to isovolumic relaxation. In fact, our analysis reveals the remarkable finding that changes in isovolumic relaxation time constant produced by either protocol I or protocol II could be related quantitatively to end ejection by a single curve. Taken together, these results argue strongly that neither extent nor velocity of muscle shortening influences the decay of ventricular pressure; rather, delays in end ejection are uniquely important in hastening isovolumic relaxation. (Circulation Research 1991;68:300-308)

The duration of mechanical activity of cardiac muscle is abbreviated by muscle shortening.1–7 A previous study in the whole heart8 demonstrated that an increase in stroke volume increases isovolumic ventricular relaxation rate, leading to the conclusion that the history of muscle shortening can alter isovolumic ventricular relaxation rate. However, an increase in extent of ejection is always associated with changes in several hemodynamic parameters including the velocity of ejection, the volumes at end diastole and/or end systole, and the timing of ejection. Any one or combinations of these factors may affect isovolumic ventricular relaxation rate.8–13 We have recently begun to focus on the important factors of these parameters and have found that ejection timing seems to be especially influential in determining isovolumic ventricular relaxation rate, in both isolated and in situ canine hearts.14–17 In these previous studies, however, changes in ejection timing have not been dissected definitively from changes in other parameters like the extent or velocity of ventricular ejection.16–17 In addition, it remains unclear whether the times of onset of ejection (Eo) and end of ejection (Ee) both influence isovolumic relaxation.14

Therefore, we used volume servo-controlled, isolated canine hearts to determine the ejection variables that are principally responsible for increased rates of isovolumic ventricular relaxation observed with increases in stroke volume. This experimental design is especially suited to the question at hand.
because ejection could be controlled by patterns specifically designed to isolate the ejection parameters most critical to the isovolumic relaxation process. Using this strategy, we find that delays in Ee time are uniquely important in hastening isovolumic relaxation. Some of these findings have been reported in preliminary form.15

Materials and Methods

Animal Preparation

Nine isolated blood-perfused canine hearts were used in this study. The method of preparation has been previously described.14,18 Briefly, pairs of mongrel dogs weighing 15–25 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg). In the donor dog, the heart was exposed, and a perfusion cannula was introduced into the brachiocephalic artery. This cannula was in turn connected to a carotid artery of the support dog. Coronary venous flow collecting in the right ventricle of the donor dog heart was drained to the jugular vein of the support dog. Blood temperature was kept at 37°C. After administration of heparin (500 units/kg), institution of cross-circulation was followed by ligation of all free vessels from the heart. A thin latex balloon was placed in the left ventricular (LV) cavity with a miniature pressure transducer (model P-7, Konigsberg Instruments, Inc., Pasadena, Calif.). When filled with fluid, this latex balloon was distensible enough to cover a large range of LV volumes, while nicely fitting the LV cavity. A metal tube adaptor connected to the opening of the balloon was fixed at the mitral ring with a purse-string suture, thereby tightly linking the balloon to a hydraulic pump system.

The Servo-Control System of LV Volume

We have previously reported14,18 the components of the hardware system and mechanical setup that enabled servo control of LV volume. This system allowed us to control LV volume as shown in Figure 1 (upper panel). The details of the LV ejection pattern were determined by setting the following parameters through keyboard input: Eo, Ee, the times of onset and end of filling, end-systolic volume (ESV), and end-diastolic volume (EDV). All times were relative to the R wave of the electrocardiogram.

Experimental Protocols

Protocol I: Effect of stroke volume on isovolumic ventricular relaxation rate. In six isolated hearts, LV volume was adjusted so that the LV developed pressure equaled about 100 mm Hg in isovolumic contraction. Thereafter, in this protocol (Figure 1, middle panel), stroke volume was altered either by increasing EDV in four increments with ESV held constant (protocol Ia) or by decreasing ESV in four increments with constant EDV (protocol Ib). Ejection velocity was kept constant throughout. In protocol Ia, Eo moved earlier as EDV increased. In protocol Ib, ESV was progressively decreased with the progressive delay of Ee while EDV was clamped.

The pressure–volume relations of both modes of contraction were monitored and photographed, and LV pressure and volume data were stored in a data recorder (Figures 2–5).

Protocol II: Effect of ejection velocity on isovolumic LV relaxation rate. In six isolated hearts, we clamped both EDV and ESV and varied ejection velocity in two ways. In protocol IIa (Figure 1, bottom panel), Eo was progressively delayed in four increments of 10–30 msec with the time of Ee clamped constant. In protocol IIb, Ee was progressively moved earlier in steps of 10–30 msec with the Eo unchanged.

These experiments were performed with spontaneous heart rates of 125 ± 2 beats/min, and changes in heart rate were less than 2% in each run.

![Figure 1](http://circres.ahajournals.org/DownloadedFrom/...}

![Figure 1](http://circres.ahajournals.org/DownloadedFrom/...}

![Figure 1](http://circres.ahajournals.org/DownloadedFrom/...}
I -(a) an increase in EDV  I -(b) a decrease in ESV

![Graphs showing LV volume and pressure changes](image)

Figure 2. Representative left ventricular (LV) volume curves and LV pressure (LVP) curves in protocol I. Panels A–C: Protocol Ia: Two different contractions with small (pattern a) and large (pattern b) end-diastolic volume (EDV). Panels B and C correspond to pattern a and pattern b in panel A, respectively. Note that the time to the peak in LV pressure is almost the same. Panels D–F: Protocol Ib: Two different contractions with large (pattern a) and small (pattern b) end-systolic volume (ESV). Panels E and F correspond to pattern a and pattern b in panel D, respectively. (See “Materials and Methods” for discussion of protocol I.)

Data Processing

The LV pressure was digitized every 4.2 msec. Isovolumic LV relaxation rate was assessed by the time constant (T) of isovolumic LV pressure decay assuming that this decay is exponential. The onset of the isovolumic relaxation period is defined as the time of minimal dP/dt.9,10,19 and T was calculated with the pressure data from the minimal dP/dt (dP/ dt,min) to 10 mm Hg above the minimal LV pressure by fitting the following equation20:

\[ P = (P_0 - P_s) \exp(-t/T) + P_s \]

where P is pressure, P_0 is pressure at dP/dt,min and P_s is asymptotic pressure. Two methods were used to obtain the two time constants: the semilogarithmic method (T_L) and the exponential method (T_{exp}). The former method assumes that P_s=0, whereas the latter assumes that P_s is variable. T_{exp} was obtained by least-squares linear regression between P and dP/dt, because the negative inverse of the slope of the dP/dt becomes T_{exp} when it is plotted as a function of P.

Statistical comparison was made by repeated-measures analysis of variance in protocols I and II.21 Analysis of covariance was also used in Figure 6. Data were expressed as mean±SEM.

Results

Protocol I: Effect of Stroke Volume on Isovolumic LV Relaxation Rate

Figure 2 shows the differences in LV volume and pressure patterns when Ee is clamped or altered during increased stroke volume. Figure 3 depicts LV pressure–volume relations and time constants of isovolumic LV pressure decay from a single experiment. When stroke volume was increased by an increase in EDV, both T_{exp} and T_L changed minimally; in contrast, when stroke volume was increased by reducing ESV, there were decreases in both T_{exp} and T_L (Figure 3). Table 1 depicts the summary data from seven hearts in which stroke volume was altered in four discrete steps. When ESV and Ee time were kept constant (protocol Ia), neither T_{exp} nor T_L changed significantly, although mean ejection fraction increased from 22.6±3.5% to 34.3±2.9%, and Ee occurred progressively earlier. In contrast, when ESV was decreased by delaying Ee (protocol Ib), both T_{exp} and T_L were significantly decreased (p<0.01), although EDV and Ee were constant. Decreases in peak LV pressure were associated with decreases in T_{exp} and T_L. These results indicate that isovolumic LV relaxation rate is not directly related to a change in the stroke volume but might be determined by end-systolic volume, LV pressure, or Ee.
Protocol II: Effect of Ejection Velocity on Isovolumic LV Relaxation Rate

Figure 4 depicts the differences in LV volume and pressure patterns when ejection velocity was changed. Figure 5 shows LV pressure–volume relations and time constants of isovolumic LV pressure decay when ejection velocity was increased in four increments. When ejection velocity was increased by delaying Eo while holding EDV, ESV, and Ee constant (Figure 5, upper panels), both T-exp and TL changed minimally. The timing of peak LV pressure changed slightly (Figures 4B and 4C). The contrary, an increase in ejection velocity due to earlier Ee was associated with increases in both T-exp and TL (Figure 5, lower panels). The timing of the peak of LV pressure moved earlier when Ee was delayed (Figures 4E and 4F). Table 2 summarizes results of experiments in which ejection velocity was varied. When Eo was progressively delayed from 210±15 to 259±18 msec (protocol IIa), ejection velocity increased from 85.7±13.3 to 183.4±19.0 ml/sec, but neither T-exp nor TL changed significantly. In contrast, both T-exp and TL increased significantly ($p<0.01$) when ejection velocity was increased over a comparable range by advancing Ee. Peak LV pressure did not change in both protocols.

These results indicate that isovolumic LV relaxation rate is not affected directly by the ejection velocity per se but is primarily regulated by Ee.

A Unique Relation Between $T_{\text{exp}}$ and Ee

Figure 6 shows the relations between Ee and isovolumic LV relaxation rate in protocols I and II. In protocol Ib, both ESV and Ee are altered, whereas in protocol IIb, Ee is changed under constant ESV. However, despite the differences in ESV and peak LV pressure in the two protocols, the relations between $T_{\text{exp}}$ and Ee were not significantly different since slopes of linear regression lines of $T_{\text{exp}}$ versus Ee in protocols Ib and IIb were 0.80 and 0.78, respectively. The data of protocols Ia and IIa were not significantly different from the lines of $T_{\text{exp}}$ versus Ee in protocols Ib and IIb. Although peak LV pressure changes corresponded with the changes in $T_{\text{exp}}$ and $T_L$ in protocol Ib, $T_{\text{exp}}$ and $T_L$ were decreased when Ee was delayed, despite no changes in peak LV pressure, suggesting that peak LV pressure has little effect on isovolumic ventricular relaxation rate in ejecting hearts. This analysis suggests that neither LV pressure nor ESV affects isovolumic LV relaxation appreciably but that Ee ultimately regulates isovolumic LV relaxation.

Discussion

The present study demonstrates that the primary factor that speeds isovolumic ventricular relaxation rate during increases in stroke volume is not the altered extent or velocity of ejection but a delayed Ee.

$Ee$: A Unique Determinant of Isovolumic LV Relaxation Rate?

Since ejection timing under constant contractility may be affected markedly by changes in aortic impedance in open chest dogs, we changed aortic impedance by clamping the ascending and descending aorta and showed that Ee affects isovolumic ventricular relaxation rate when peak LV pressure is increased. However, in these experiments, we could not control either the extent and velocity of ejection or LV volume because of the nature of the open-chest dog model. Thus, we could not exclude contributions of these hemodynamic parameters on relaxation.
In the present study, we observed increases in isovolumic ventricular relaxation rate when EDV was held constant, but ESV volume decreased when Ee was delayed (Figure 3, lower panels, and Table 1). Neither EDV nor Eo affected isovolumic ventricular relaxation (Figure 3, upper panels, and Table 1). These results indicated that a decrease in ESV and/or delayed Ee could potentially increase the rate of isovolumic relaxation.

Considering these and earlier data alone, we could already argue that the influence of ESV on Texp must be small relative to that of Ee. Earlier work suggests that an increase in ESV or peak LV pressure is usually observed to increase isovolumic relaxation rate.11.17.18 Yet, in the present study, we show that delayed Ee predominantly increases isovolumic ventricular relaxation rate, despite decreases in ESV (Table 1). Thus, if ESV does have an independent effect on Texp, it must be small relative to that of Ee.

More importantly, Figure 6 provides crucial evidence that an independent effect of ESV on Texp must be very small in absolute terms. We argue as follows: The relation between Texp and Ee in protocol Ib is produced when both Ee and ESV are allowed to vary. In contrast, the relation between Texp and Ee in protocol Ib is measured when Ee changes but ESV is held constant. Since the two relations—one measured when ESV changes, the other determined when ESV is constant—virtually superimpose, the independent contribution of ESV to Texp must be very small.

The present results also argue against an independent role for afterload in determining Texp. Although we demonstrated previously18 that an increase in peak LV pressure correlates with an increase in ventricular relaxation rate, our results here suggest that this is an indirect linkage, probably mediated by changes in Ee. As shown in Tables 1 and 2, peak LV pressure decreases as Texp decreases in protocol Ib, whereas peak LV pressure holds constant or decreases slightly as Texp increases in protocol Ib. These inconsistent trends stand in contrast to the unitary relation between Texp and Ee; the simplest explanation is that changes in peak LV pressure ultimately affect Texp by way of changes in Ee.

From these considerations, our results lead us to place special emphasis on Ee as a determinant of isovolumic ventricular relaxation rate when stroke volume increases. The effects of extent of ejection, ventricular volume (ESV and EDV), and ejection velocity on isovolumic ventricular relaxation rate are economically attributed to a common end pathway, changes in Ee.

Relation to Previous Studies

We have previously reported that an increase in afterload increases isovolumic ventricular relaxation rate,1,8 consistent with observations in papillary muscles.11 At first glance, these results hint that afterload, that is, muscle tension in end systole, is a controlling factor of relaxation rate. However, in

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Table 1. Hemodynamic Parameters and Time Constants of Isovolumic Left Ventricular Pressure Decay in the Augmented Ejection Volume

<table>
<thead>
<tr>
<th>Contraction</th>
<th>Increase in EDV</th>
<th>TLVP (mm Hg)</th>
<th>LVDP (mm Hg)</th>
<th>dp/dt max (mm Hg/sec)</th>
<th>dp/dt min (mm Hg/sec)</th>
<th>dP/dt max (mm Hg/sec)</th>
<th>dP/dt min (mm Hg/sec)</th>
<th>TP (mm Hg)</th>
<th>TP (ms)</th>
<th>Texp (ms)</th>
<th>Ee (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (control)</td>
<td>0</td>
<td>2.4 ± 0.5</td>
<td>3.0 ± 0.6</td>
<td>4.5 ± 0.5</td>
<td>3.0 ± 0.6</td>
<td>3.0 ± 0.6</td>
<td>2.4 ± 0.5</td>
<td>1.2 ± 0.1</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>2 (control)</td>
<td>0</td>
<td>3.0 ± 0.5</td>
<td>3.6 ± 0.6</td>
<td>4.0 ± 0.5</td>
<td>3.0 ± 0.6</td>
<td>3.0 ± 0.6</td>
<td>3.0 ± 0.5</td>
<td>1.2 ± 0.1</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>3 (control)</td>
<td>0</td>
<td>3.6 ± 0.5</td>
<td>4.2 ± 0.6</td>
<td>4.5 ± 0.5</td>
<td>3.6 ± 0.6</td>
<td>3.6 ± 0.6</td>
<td>3.6 ± 0.5</td>
<td>1.2 ± 0.1</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>4 (control)</td>
<td>0</td>
<td>4.2 ± 0.5</td>
<td>4.8 ± 0.6</td>
<td>4.5 ± 0.5</td>
<td>4.2 ± 0.6</td>
<td>4.2 ± 0.6</td>
<td>4.2 ± 0.5</td>
<td>1.2 ± 0.1</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. n, number of data; TLVP, peak LV pressure; LVDP, left ventricular end-diastolic pressure; ESV, end-systolic volume; EDV, end-diastolic volume; Texp, time constant of isovolumic ventricular pressure decay obtained by the exponential method and by the semilogarithmic method, respectively (see Materials and Methods). * NS, not significant.

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Honi et al: Delayed End Ejection and Isovolumic LV Relaxation

 Delayed Ejection and Isovolumic LV Relaxation

Patterns (a) and (b) illustrate the delay of onset of ejection (Eo) and advance of end-ejection (Ee), respectively.

**FIGURE 4.** Representative left ventricular (LV) volume curves and LV pressure (LVP) curves in protocol II. Panels A–C: Protocol IIa: Two different contractions with the early onset of ejection (pattern a) and delayed onset of ejection (pattern b). Panels B and C correspond to pattern a and pattern b in panel A, respectively. Panels D–F: Protocol IIb: Two different contractions with delayed end ejection (pattern a) and early end ejection (pattern b). Panels E and F correspond to pattern a and pattern b in panel D, respectively. (See "Materials and Methods" for discussion of protocol II.)

Ejecting hearts, an increase in peak LV pressure can slow isovolumic ventricular relaxation, indicating that some other potent regulatory factor of isovolumic relaxation rate is involved during ventricular ejection and supersedes the effect of ventricular load or volume per se. One such potent regulatory factor appears to be Ee. In this vein, understanding the special role of Ee points up many consistencies with earlier work and may help to resolve some discrepant findings regarding the mechanical determinants of isovolumic ventricular relaxation rate. In the report of Frederiksen et al., isovolumic relaxation rate was not affected when stroke volume was increased by increasing end-diastolic pressure, keeping peak LV

**FIGURE 5.** Graphs showing representative left ventricular pressure-volume relations (left panels) and time constants (Texp and TL) during an increase in ejection velocity (right panels, contractions 1–4) in protocol II. When onset of ejection (Eo) was delayed, neither Texp nor TL changed (Figures 4A–4C). In contrast, both Texp and TL increased when end-ejection time (Ee) became earlier with an increase in ejection velocity (Figures 4D–4F). (See "Materials and Methods" for discussion of protocol II.)
TABLE 2. Hemodynamic Parameters and Time Constants of Isovolumic Left Ventricular Pressure Decay in the Enhanced Velocity of Ejection

<table>
<thead>
<tr>
<th>Contraction</th>
<th>n</th>
<th>PLVP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>dP/dt\text{max} (mm Hg sec)</th>
<th>dP/dt\text{min} (mm Hg sec)</th>
<th>Po (mm Hg)</th>
<th>Eo (msec)</th>
<th>Ee (msec)</th>
<th>Vel (m/sec)</th>
<th>T\text{exp} (msec)</th>
<th>T\text{i} (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay of Eo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (control)</td>
<td>7</td>
<td>105.0±5.8</td>
<td>3.6±0.6</td>
<td>1,130±40</td>
<td>−1,080±70</td>
<td>48.9±1.7</td>
<td>210±15</td>
<td>290±21</td>
<td>85.7±13.3</td>
<td>66.4±3.9</td>
<td>39.0±1.1</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>104.1±4.3</td>
<td>4.7±0.3</td>
<td>1,130±110</td>
<td>−1,130±110</td>
<td>51.8±2.0</td>
<td>226±16</td>
<td>290±21</td>
<td>93.1±9.9</td>
<td>57.5±11.4</td>
<td>41.4±2.0</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>99.9±3.0</td>
<td>4.5±0.2</td>
<td>1,140±30</td>
<td>−1,110±70</td>
<td>52.1±2.9</td>
<td>243±17</td>
<td>290±21</td>
<td>125.7±13.8</td>
<td>66.4±3.7</td>
<td>40.6±2.6</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>100.9±4.1</td>
<td>4.7±0.3</td>
<td>1,140±70</td>
<td>−1,070±70</td>
<td>54.1±3.0</td>
<td>259±18</td>
<td>290±21</td>
<td>183.4±19.0</td>
<td>69.2±2.5</td>
<td>42.3±2.6</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>Advance of Ee</td>
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<tr>
<td>1 (control)</td>
<td>7</td>
<td>107.4±1.9</td>
<td>3.4±0.6</td>
<td>1,130±50</td>
<td>−1,040±50</td>
<td>52.6±2.0</td>
<td>209±6</td>
<td>297±10</td>
<td>66.8±6.3</td>
<td>64.9±3.4</td>
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<tr>
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<td>7</td>
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<td>3.4±0.5</td>
<td>1,140±60</td>
<td>−1,000±50</td>
<td>50.9±2.1</td>
<td>209±6</td>
<td>278±9</td>
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<tr>
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<td>102.5±3.0</td>
<td>3.5±0.5</td>
<td>1,150±60</td>
<td>−970±60</td>
<td>48.0±1.9</td>
<td>209±6</td>
<td>259±8</td>
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<tr>
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<td>4.1±0.6</td>
<td>1,160±60</td>
<td>−960±60</td>
<td>46.9±1.7</td>
<td>209±6</td>
<td>239±7</td>
<td>191.9±19.6</td>
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<td>p</td>
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<td>NS</td>
<td>&lt;0.05</td>
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<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM, n, number of data; PLVP, peak left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; dP/dt\text{max} and dP/dt\text{min}, maximal and minimal dP/dt, respectively; Po, left ventricular pressure at dP/dt\text{min}, Eo and Ee, time of onset and end of ejection, respectively; Vel, velocity of ejection; T\text{exp} and T\text{i}, time constants of isovolumic left ventricular pressure decay obtained by the exponential method and by the semilogarithmic method, respectively (see "Materials and Methods"); NS, not significant. EDV and ESV in protocol Ia were 18.3±0.7 and 12.6±0.8 ml, respectively. EDV and ESV in protocol Ib were 17.6±0.6 and 11.7±0.6 ml, respectively.

Pressure constant. This protocol was similar to our protocol Ia.

Weiss et al.\(^5\) indicate the important role of ejection velocity on isovolumic ventricular relaxation. They reported that isovolumic LV relaxation rate is increased by augmented stroke volume with constant EDV, in agreement with results of our protocol Ib. Paradoxically, they also observed that isovolumic relaxation rate is increased when EDV is increased, keeping ESV unchanged. This seems, at first, to be incompatible with our results in protocol Ia, in which only EDV was changed without a change in Ee. However, in the experiments of Weiss et al.,\(^5\) peak LV pressure increased significantly when the stroke volume increased, presumably with a change in Ee.\(^4\) In contrast, in our protocol Ia, peak LV pressure was not altered significantly because Ee was held constant. Thus, an increase in peak LV pressure in Weiss et al.\(^5\) may have resulted from an earlier Ee. If this is indeed the case, our results are compatible with theirs.

The results of Suga and Yamakoshi\(^8\) seem to be identical with our results. When they increased stroke volume by an increase in EDV, with both Eo and ESV clamped, isovolumic relaxation was speeded. In this situation, Ee may have been delayed to keep the ejection velocity constant. Thus, delayed Ee may have ultimately resulted in increasing relaxation rate.

Potential Subcellular Mechanisms

Despite numerous studies regarding the interaction of relaxation and contraction history, there is no consensus regarding the mechanisms underlying the observed phenomena. The most popular class of explanations focuses on changes in active state\(^2\) or its modern analogue, Ca\(^{2+}\) handling. We argue, however, that there are serious inconsistencies between this type of theory and experimental data. First, during the isometric relaxation phase of mammalian cardiac muscle, intracellular Ca\(^{2+}\) concentration has long decreased to nearly end-diastolic levels.\(^22\) Thus, changes in the rate of decline of intracellular Ca\(^{2+}\) concentration should have little effect on the time course of relaxation. Second, muscle shortening during the contraction phase of muscle has been proposed to decrease the affinity of troponin C for Ca\(^{2+}\).\(^23,27\) The main effect of shortening during the contraction phase would be to reduce the residual amount of calcium bound to troponin C during the relaxation phase. This in itself would not change the...
rate at which calcium dissociates from troponin C, especially at constant ESV.

One is left, by exclusion, with the idea that the history of contraction somehow affects the nature of crossbridge cycling\(^{28,29}\) during the relaxation phase. Although our ventricular finding of the special role of Ee limits the theories that might derive from this line of reasoning, our work by no means provides direct evidence for any such model. Nonetheless, in the spirit of a new working hypothesis, we sketch the following scheme because it fits so naturally and economically with our own ventricular data, as well as with observations made at the muscle and biochemical levels.

During contraction, myosin heads attached to actin may be found at a variety of distances, X, from their unstretched displacements. For simplicity, consider all attached myosin heads to reside at an average distance X \(<X>\). During isometric contraction, \(<X>\) tends toward some steady-state position. With active shortening, however, heads are swept toward the zero position so that \(<X>\) decreases. If intracellular Ca\(^{2+}\) concentration is still high enough after cessation of shortening to enable further, unimpeded cycling of crossbridges, then \(<X>\) will recover to its isometric, steady-state position. However, if shortening persists beyond the period when intracellular Ca\(^{2+}\) concentration is high, recovery from shortening-induced reduction in \(<X>\) will be incomplete because cycling of crossbridges, required for a return to steady state, will be hampered. Since the detachment rate for myosin heads is proposed to be much higher for \(<X>\) less than the isometric steady-state value,\(^{28,29}\) shortening that persists into a period where cycling is restricted (i.e., delayed Ee) will result in a faster rate of relaxation. Shortening that terminates while cycling is still unrestriced (early Ee) will allow \(<X>\) to return to its isometric, steady-state position, so that relaxation will proceed according to a slower rate constant. Such a proposal not only explains our own results but is entirely consistent with the features of Ca\(^{2+}\) handling raised at the beginning of this section.

**Limitations of the Present Study**

The isolated servo-controlled heart that we used in the present study is effective in the search for the major determinant of relaxation rate during ejection because we can control all variables during ejection and observe the pure effect of Ee on relaxation rate. However, we should consider the differences between the contractions in the in vivo and isolated servo-controlled hearts. The LV pressure–volume loops in the servo-controlled hearts are comparable with those in the in vivo hearts,\(^{14–18}\) and if the left ventricle in the present study just happens to contract and eject according to such a pattern observed in the in vivo hearts, the pressure response would be the same. However, this argument does not necessarily lead to the idea that LV contractions in the present study are realized in the in vivo hearts. The reasons for this are as follows: 1) the contractile states in the isolated heart preparations are low, as is indicated by the low dP/dt\(_{max}\) (Tables 1 and 2), 2) although the ejection speed is a function of time in the in vivo hearts due to time-varying changes in afterload, we set the ejection speed constant in the present study, and 3) our experimental model is free from the neurohumoral control of the in vivo animals. Furthermore, we observed the responses of the relaxation rate under relatively small values of EDV and ESV. This relatively small stroke volume may change the quantitative relations between Ee and relaxation rate. However, it is not likely that this relation is abolished, because the important roles of ejection timing are also observed in the relatively large EDV and ESV.\(^{14–17}\) Taken together, our results contribute to the understanding of the ventricular relaxation process, although further investigations are necessary to extend our findings to the physiological controlling mechanisms of relaxation rate in the in vivo hearts.

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