Nonuniform Course of Left Ventricular Pressure Fall and Its Regulation by Load and Contractile State

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**Background** Effects of systolic left ventricular pressure (LVP) on rates of pressure fall remain incompletely understood. This study analyzed phase-plane dP/dt versus LVP plots to differentiate between accelerating and decelerating effects and to investigate the variability in reported load effects on rates of LVP fall.

**Methods and Results** Abrupt aortic occlusions were performed by inflating a balloon positioned in the ascending aorta of anesthetized open-chest dogs (n=17). The occlusions resulted in clamp elevations of systolic LVP. In protocol A, the elevations of systolic LVP induced by total aortic occlusions were timed at early, mid, and late ejection. The magnitude of the elevations was 36.0±3.6 mm Hg for early, 11.6±0.6 mm Hg for mid, and negligible for late occlusions. The course of LVP fall appeared to be more complex than previously appreciated. Pressure fall might be subdivided in an initial accelerative phase, an intermediate decelerative phase, and a terminal decelerative phase. The initial phase accelerated with mid and late occlusions. The intermediate phase slowed down with early and to a lesser extent with mid occlusions. The terminal phase was never affected by aortic clamp occlusions. In protocol B, early elevations of systolic LVP were obtained with multiple graded aortic occlusions. The effects of matched LVP elevations of 12 mm Hg on rate of LVP fall were evaluated with the time constant of LVP fall (τ) and showed an interanimal variability ranging from acceleration and a 20% decrease in τ to deceleration and a 35% increase in τ. Changes in τ were moderately correlated with commonly used indexes of contractility (peak +dP/dt, r=−.78; regional fractional shortening, r=−.63). These changes in τ showed a close correlation with the systolic LVP of the test beat, expressed as a percentage of the peak isovolumetric LVP, obtained with total aortic occlusion (r=−.984). This suggested that the contraction-relaxation coupling should be analyzed in terms of peak force development rather than contraction velocity or ejection fraction.

**Conclusions** LVP fall could be subdivided into an initial accelerative phase, an intermediate decelerative phase, and a terminal decelerative phase. Effects of elevations in systolic LVP on rate of LVP fall could be predicted by knowing peak isovolumetric LVP. Nonuniformity of LVP fall and adequate interpretation of load effects should be taken into account when clinical situations or pharmacological interventions are considered. In congestive heart failure, slow LVP fall could mainly reflect working conditions close to isovolumetric rather than relaxation disturbances. (*Circulation*, 1994;90:2481-2491.)

**Key Words** contractility • inotropic agents • diastole • ventricles • myocardium • pressure

Diastolic heart failure results from the interplay between impaired myocardial relaxation, decreased chamber compliance, and inappropriate reduction of filling duration.1 Indexes of myocardial relaxation are often used for early detection of cardiac dysfunction, to evaluate the natural history of a disease state, or to assess therapeutic effects. A correct interpretation supposes a thorough insight into how changes in load interfere with these indexes. Left ventricular pressure (LVP) fall is the in vivo manifestation of isometric relaxation. It has a time course that is close to monoeponential and that would be the rather direct expression of cardiac muscle inactivation.2 When systolic LVP increases, the peak rate of pressure fall (peak –dP/dt) becomes more negative,3 reflecting faster initial LVP fall. It is widely accepted that the same intervention increases the time constant of isovolumetric relaxation, τ,4,5 reflecting a slower course of subsequent LVP fall. This nonuniform response of LVP fall has been known for years. It is still difficult, however, to relate this nonuniform response of the rate of LVP fall to underlying mechanisms or to afterload effects in isolated cardiac muscle. In the isonomic-isometric relaxation sequence,7 force decay of isolated cardiac muscle is exponential, and its rate increases with increasing afterload. With afterload >80% of peak isometric force, force decay deviates from a single exponential and becomes slower. In the isometric-isometric relaxation sequence,7 the relation between the peak rate of force decay and afterload is similar and was described as curvilinear.

In conditions of elevated blood pressure, the systolic pressure waveform of the left ventricle is altered by aortic impedance and by reflected waves.9 The effects of systolic pressure waveform on rate of LVP fall were previously evaluated with abrupt clamp elevations of systolic LVP. Changes in the systolic pressure waveform with increasing load toward end ejection slowed LVP fall,9,10,11 while other studies showed that late pressure elevations could accelerate LVP fall.12,13 It also remains difficult to link effects of late ejection elevations in load...
to underlying mechanisms and to data obtained with late load clamps on afterloaded twitches of isolated cardiac muscle. When the isolated cardiac muscle was allowed to yield before force decline (isotonic-isometric relaxation sequence), force decline was accelerated with a late load clamp, and relaxation prematurely terminated.\textsuperscript{14} When force decline occurred at minimum systolic muscle length (isometric-isometric, physiologic relaxation sequence), force decline slowed even with very late load clamps.\textsuperscript{15}

The present study analyzed, in the intact canine heart, the effects of abrupt clamp occlusions of the ascending aorta on timing and course of LVP fall. Acute, beat-to-beat elevations of systolic LVP were selected to exclude effects of preload and long-term load history and to prevent changes in contractility induced by neurohumoral reflexes. The goals of the study were to differentiate between accelerating and decelerating effects on LVP fall, to clarify the variability in reported load effects on relaxation, and to relate the observations to underlying cross-bridge mechanisms. The results indicated that initial, intermediate, and terminal LVP fall responded differently to clamp occlusions and that the response of relaxation to elevations of systolic LVP depended primarily on peak isovolumetric LVP, obtained with total aortic occlusion.

**Methods**

**Experimental Preparation**

Mongrel dogs (n=17; weight, 15 to 34 kg) were premedicated with a subcutaneous injection of morphine (2.5 mg/kg) and anesthetized with an intravenous injection of a solution containing 5.5-diallylbarbituric acid (50 mg/kg), urethane (200 mg/kg), and 2-imidazolodione (200 mg/kg). The trachea was intubated, and ventilation was instituted (Harvard Apparatus). A 0.9% saline solution was administered through the femoral vein to compensate for perioperative fluid losses. The femoral artery was cannulated to obtain samples for blood gas analysis and to monitor arterial pressure. A median sternotomy and left lateral fourth interspace thoracotomy were performed. The pericardium was excised and the heart suspended in a pericardial cradle. A high-fidelity micromanometer (KONIGSBERG) was inserted through an aortic stab wound into the left ventricular cavity, positioned at the midventricular level, and secured in place with a purse-string suture. A fluid-filled pigtail catheter was advanced retrogradely into the left ventricle through the left femoral artery and was connected to a conventional transducer (Druck). Left atrial pressures were measured with a polyvinyl tube inserted into the left atrium through an incision in the left atrial appendage. The manometers were calibrated against a mercury column before the experiment. The zero was set at the level of the right atrium. The LVP waveform from the micromanometer and fluid-filled catheters were matched. An electronic derivative of the high-fidelity LVP was recorded to measure dP/dt. The right atrial appendage was electronically paced. A limb lead ECG (DII) was recorded throughout (frequency response, 0.05 to 100 Hz, –3 dB). Regional ventricular function was measured with ultrasonic segment length gauges implanted in the circumferential direction of apical and basal left ventricular anterior midwall and connected to a sonomicrometer amplifier system (TRITON). Clamp elevations of systolic pressure were produced by inflating a saline solution into a rubber balloon securely tied on the tip of a Silastic tube 20 in long. A rigid tube with a large lumen (0.2 in) was selected for minimizing resistance to flow. The left subclavian artery was dissected, tied off before the first branch, and cut. The Silastic tube was introduced through the left subclavian artery and advanced to the ascending aorta 1 in above the aortic valve. The position of the balloon was checked manually and with two-dimensional echocardiography (Toshiba SSH140A) after a test inflation. The balloon-tipped tube was tied to a custom-made power pump described in Fig 1. The isolated cardiac muscle data (shown in Fig 9) were obtained in papillary muscle of the right ventricle of a cat (temperature, 29°C; [Ca\textsuperscript{2+}], 2.5 mmol/L; length, 10 mm; cross-section, 0.8 mm²; ratio resting/total load, 8.3%).

**Experimental Protocol**

The intra-aortic balloon was inflated with saline to produce clamp occlusions within one cardiac cycle (test beat). Each test beat was compared with the preceding cardiac cycle (control beat). After a test beat, the intra-aortic balloon was rapidly deflated and the animal was allowed to stabilize before another intervention.

**Protocol A**

In pilot experiments (n=5), total aortic occlusions were performed at intervals of 10 milliseconds, resulting in elevations of systolic LVP timed throughout ejection. We observed a gradual transition in the effects from early to late ejection, which could be summarized by describing the effects of LVP elevations at three different timings, referred to as early, mid, and late (n=17). Early LVP elevations were induced by occlusions, which were completed before aortic valve opening and resulted in isovolumetric nonejecting beats. Mid ejection LVP elevations were induced at 71.3±0.4% of the interval from end diastole to peak –dP/dt. In four dogs with central aortic pressure recording, this corresponded to 55% to 60% of left ventricular ejection duration. Late ejection LVP elevations were induced at 85.4±0.8% of the interval from end diastole to peak –dP/dt, or 88% to 92% of left ventricular ejection duration.

**Protocol B**

Graded aortic obstructions, obtained by varying the amount of fluid injected into the balloon, were induced before aortic valve opening to obtain graded and early elevations of systolic LVP ranging from 2 mm Hg up to isovolumetric beats. The entire range of LVP elevations from 2 mm Hg up to isovolumetric were obtained. Two aspects were examined: (1) the interanimal variation of effects of LVP elevations with a matched amplitude. Interventions that induced a 12 mm Hg elevation of LVP were selected. The magnitude of 12 mm Hg was a compromise. Smaller elevations in systolic LVP resulted in effects that were too limited, and larger elevations in systolic
systolic segment length.17  

**Data Analysis**

Recordings were made with respiration suspended at end expiration. Parameters were converted on-line to digital data (Atcodas, Data-Q) with a sampling rate of 500 Hz. End diastole was defined as the trough in the LVP tracing after atrial contraction. If this corresponded to the R wave on the ECG, the R wave was used for timing purposes. Sometimes the Q wave or the rising limb of the ECG was preferred. Time intervals were measured from end diastole to peak $-dP/dt$, to mitral valve opening, and to minimum systolic segment lengths. The timing of mitral valve opening was determined by transposing the peak of the v wave from the left atrial pressure tracing onto the high-fidelity LVP tracing. The timing of a clamp elevation of systolic LVP was measured as the time interval from end diastole to the peak positive value of $dP/dt$ corresponding to this elevation. The course of LVP fall was analyzed with peak $-dP/dt$; the time constant of isovolumetric LVP fall, $\tau$; and the duration of isovolumetric relaxation. The duration of isovolumetric relaxation was estimated as the time interval from peak $-dP/dt$ to mitral valve opening. $\tau$ was calculated as the negative inverse slope of the relation of $dP/dt$ versus LVP, assuming a variable asymptote and using data from peak $-dP/dt$ to 5 mm Hg above the mitral valve opening pressure.16 The course of LVP fall was further characterized by the description of phase-plane plots of $dP/dt$ versus LVP, in which the test beat was superimposed on the preceding control beat. The description of the phase-plane plots was supported by two measurements. Initial slope or slope of initial LVP fall (second$^{-1}$) was computed by use of data between the onset of LVP fall and peak $-dP/dt$. The first data points from peak systolic LVP to the point at which $dP/dt$ exceeded −150 mm Hg/s and the last two data points before peak $-dP/dt$ (ie, 4 milliseconds) were excluded, since these extremities of the tracing as a rule deviated from linear. Intermediate slope or slope of intermediate LVP fall (second$^{-1}$) was computed so as to describe the linear segment of the tracing between peak $-dP/dt$ and mitral valve opening. The first two to five data points (ie, 4 to 10 milliseconds) after peak $-dP/dt$ were excluded, because the tracing was not yet linear.

Segment lengths were measured at end diastole and mitral valve opening. Minimum segment length was measured as the minimum length preceding or coinciding with peak $-dP/dt$. Segment length changes were expressed as a percentage of end-diastolic segment length. Negative values indicate segment shortening, and positive values indicate segment lengthening. Fractional shortening was calculated as the percent segment length change from end diastole to minimum segment length. Early segment reextension measured the extent of segment lengthening before mitral valve opening and was calculated as the percent segment length change from minimum segment length to segment length at mitral valve opening. Early segment reextension was divided into reextension during initial LVP fall (initial reextension) and reextension during intermediate LVP fall (intermediate reextension). Temporal nonuniformity index was calculated as the base-to-apex ratio of time to minimum segment length. Regional nonuniformity index was calculated as the base-to-apex ratio of segment length at mitral opening divided by minimum systolic segment length.17

Group data were presented as mean±SEM. A two-tailed paired t test was used to compare test with control, and $P<.05$ indicated statistical significance. Correlations were performed with a linear regression analysis and the computation of the regression coefficient, $r$.  

**Results**

Protocol A analyzed the effects of systolic elevations of LVP at different time points during ejection. The ascending aorta was abruptly and totally occluded. Protocol A is illustrated in Fig 2, and the data are summarized in Tables 1 and 2.

Early occlusions (Fig 2, left) induced nonejecting isovolumetric beats and elevated systolic LVP by 36.0±3.6 mm Hg. Compared with control, time to peak $-dP/dt$ decreased (Table 1). Pressure fall was slower, with a decreased absolute value of peak $-dP/dt$ and an increased $\tau$. The isovolumic relaxation time became longer due to increased extent and slower course of LVP fall. The opening of the mitral valve was delayed as a consequence of slower LVP fall. On the plot of $dP/dt$ versus LVP (Fig 2, lower left), LVP fall of the test beat (dashed line) started at the right of control. Its initial course was slightly more gradual, more convergent toward control. The slope of this initial LVP fall was decreased (Table 1, initial slope) corresponding to a more gradual initial acceleration. After peak $-dP/dt$, during intermediate LVP fall, the test tracing was shifted upward and followed a more horizontal course. The intermediate slope became less negative (Table 1, intermediate slope). These changes corresponded to slowed intermediate LVP fall.

Mid occlusions (Fig 2, middle) increased peak LVP by 11.6±0.6 mm Hg. Peak $-dP/dt$ occurred earlier. LVP fall underwent complex changes. Peak $-dP/dt$ could be increased as in the example of Fig 2, unchanged, or decreased. $r$ always increased. The complex course of LVP fall is better appreciated on the lower panel: LVP fall of the test beat started to the right of control with a steep, almost vertical segment, divergent from control. Initial slope increased accordingly in all dogs. This fast initial acceleration of LVP fall soon evolved into a slower intermediate decelerative phase of LVP fall, manifesting as an upward shift and a more horizontal course of the tracing after peak $-dP/dt$. The intermediate slope decreased in absolute values and became less negative.

Late occlusions (Fig 2, right) did not increase peak LVP. Time to peak $-dP/dt$ was decreased. LVP fall accelerated with an increase in absolute value of peak $-dP/dt$ and a decreased $\tau$. In the lower right panel of Fig 2, LVP fall of the test beat started with an almost vertical, divergent course and joined the control curve soon after peak $-dP/dt$. Initial slope increased, and intermediate slope remained unchanged. No decelerative effect was observed, and this intervention resulted selectively in a faster acceleration, which was limited, however, to initial LVP fall.

Of note, terminal LVP fall at the left end of the tracings in the lower panels of Fig 2 remained unaffected by all these interventions. The tracings were superimposed on control or were slightly shifted to the right, to higher pressures, with no measurable changes in slope.

The midwall circumferential segment lengths (Table 2) shortened in control circumstances by a mean of 11% and showed some degree of early segment reextension, presumably related to torsional left ventricular shape changes. Early occlusions decreased fractional segment shortening. Early segment reextension was decreased.
Fig 2. Graphs showing total aortic clamp occlusion with pressure elevation timed during early, mid, and late ejection. Time course of left ventricular pressure (LVP, mm Hg) is displayed in the upper panels and its first derivative (dP/dt, mm Hg/s) in the middle panels. The lower panels are phase-plane plots of dP/dt vs LVP. On such a plot, the cardiac cycle is read clockwise from the left, pressure rise being displayed above the zero line and pressure fall below the zero line. In each panel, a test beat (dashed lines) was superimposed on the preceding control beat (solid lines). Compared with control, the early elevation of systolic LVP (left panels) had a magnitude of 55 mm Hg. Peak -dP/dt was premature. In the lower panel, initial LVP fall (on the right of the tracing) was slightly more gradual, convergent toward control, and peak -dP/dt was decreased. LVP fall after peak -dP/dt (to the left of peak -dP/dt) was projected above control and followed a more horizontal course. These changes reflected an overall slowing of LVP fall. The mid elevation of systolic LVP (middle panels) increased systolic LVP by 11 mm Hg. Peak -dP/dt was premature. In the lower panel, initial LVP fall was steeper, divergent from control, and peak -dP/dt was increased. LVP fall after peak -dP/dt evolved toward a linear portion of the curve, which was projected above control and followed a more horizontal course. These changes reflected faster initial LVP fall, followed by a transition toward slower intermediate LVP fall. The late elevation in systolic LVP (right panels) was of limited magnitude, if not just a shape change during initial LVP fall. Peak -dP/dt was premature. In the lower panel, initial LVP fall was steeper, divergent from control, and peak -dP/dt was increased. LVP fall after peak -dP/dt joined the control tracing. These changes reflected faster initial LVP fall with unchanged intermediate LVP fall. Of note, terminal LVP fall at the left end of the tracing remained unaffected by these interventions.

Table 1. Protocol A: Aortic Occlusions at Different Timings: Hemodynamic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Early Occlusion</th>
<th>Mid Occlusion</th>
<th>Late Occlusion</th>
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<tr>
<td></td>
<td>Control</td>
<td>Test</td>
<td>P</td>
</tr>
<tr>
<td>End-diastolic LVP, mm Hg</td>
<td>5.9±0.4</td>
<td>6.0±0.4</td>
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<td>Systolic LVP, mm Hg</td>
<td>118±2</td>
<td>155±4 *</td>
<td>*</td>
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<td>Time to peak -dP/dt, ms</td>
<td>258±4</td>
<td>249±7 *</td>
<td>*</td>
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<tr>
<td>Isovolumic relaxation time, ms</td>
<td>73±4</td>
<td>117±7 *</td>
<td>*</td>
</tr>
<tr>
<td>Peak -dP/dt, mm Hg/s</td>
<td>-2125±125</td>
<td>-1579±104 *</td>
<td>*</td>
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<td>Time constant, (\tau), ms</td>
<td>41±2</td>
<td>233±71 *</td>
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<td>Phase-plane analysis</td>
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<td>Initial slope, s^{-1}</td>
<td>66±4</td>
<td>48±3 *</td>
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<tr>
<td>Intermediate slope, s^{-1}</td>
<td>-24±3</td>
<td>-6±2 *</td>
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LVP indicates left ventricular pressure. Data are presented as mean±SEM. *P<.05.
intermediate reextension. Calculated indexes of nonuniformity between basal and apical segments were not affected, suggesting that basal and apical segments responded similarly to clamp occlusions. Fig. 3 illustrates the effects of a late occlusion on the apical segment. Compared with control, early segment reextension before mitral valve opening was markedly reduced, and the segment remained almost isometric during LVP fall. A small degree of segment reextension, indicated by the arrows, could be noticed during initial LVP fall. This limited segment reextension during fast initial LVP fall averaged 0.84% of end-diastolic length for mid occlusions and 0.92% for late occlusions.

Protocol B analyzed the effects of graded aortic obstructions, inducing graded and early elevations of systolic LVP. The elevations ranged from 2 mm Hg up to peak isovolumetric systolic LVP. A first step in the analysis was to compare matched 12 mm Hg elevations of systolic LVP in different animals. Time to peak $-\Delta P/\Delta t$ increased from 258±4 to 267±5 milliseconds. The initial slope of LVP fall decreased slightly, from 64±4 to 54±3 second$^{-1}$, reflecting slower initial LVP fall. Isovolumic relaxation time, peak $-\Delta P/\Delta t$, $\tau$, and intermediate slope of LVP fall remained, as a mean, unchanged. When individual data were examined, however, it appeared that a 12 mm Hg LVP elevation induced effects on rate of LVP fall that were highly reproducible for a given animal but that showed an important interanimal variability, ranging from acceleration and a 20% decrease in $\tau$ to deceleration and a

![Fig 3. Protocol A. Pressure and segment length tracings with a late elevation in systolic left ventricular pressure (LVP). A total aortic occlusion resulting in a small and late elevation of systolic LVP is illustrated with an LVP time course (upper left), a segment length time course (lower left), and an LVP–segment length plot (right). Systolic LVP abruptly increases by 5 mm Hg during terminal ejection. Early segment length reextension was decreased compared with control, and this particular segment remained almost isometric during LVP fall. During initial LVP fall, however, there was a small dimensional increase, indicated by the arrows. This increase corresponded to 0.85% of end-diastolic segment length. We speculated that this increase during initial LVP fall was the manifestation of cross-bridge backrotation.](http://circ.ahajournals.org/abstract)
TABLE 3. Protocol B: Effect of a 12 mm Hg Elevation in Systolic LVP on Myocardial Relaxation

<table>
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<tr>
<th>Animal</th>
<th>Heart Rate, bpm</th>
<th>Time to Peak (-dP/dt, \text{ms})</th>
<th>Systolic LVP, Control Beat, mm Hg</th>
<th>Systolic LVP, Test Beat, mm Hg</th>
<th>Isovolumetric LVP, mm Hg</th>
<th>Time Constant, (\tau), Control Beat, ms</th>
<th>Time Constant, (\tau), Test Beat, ms</th>
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LVP indicates left ventricular pressure; bpm, beats per minute.

35% increase in \(\tau\). The data displayed in Table 3 allow evaluation of the interanimal variability of the effects on \(\tau\) of paced heart rate and hemodynamic data. The isovolumetric systolic LVP mentioned in Table 3 was obtained by total aortic occlusion, as illustrated in Fig 2, left. This variability is further illustrated in Fig 4. In the upper right panel, the 12 mm Hg systolic LVP elevations induced a convergent, more gradual course of initial LVP fall, a decrease in absolute value of peak \(-dP/dt\), and a projection of intermediate LVP fall above control.

Fig 4. Graphs showing variability in the effects of a 12 mm Hg elevation of systolic left ventricular pressure (LVP). Time course of LVP (mm Hg) is displayed in the left panels and regional segment length (SL, mm) in the middle panels. The right panels are plots of dP/dt versus LVP. In each panel, a test beat (dashed lines) was superimposed on the preceding control beat (solid lines). The upper panels display data of an animal (dog 8) with a limited intrinsic contractile state. Segmental shortening was reduced compared with control. Upper right, initial pressure fall was more gradual, peak \(-dP/dt\) was decreased, and intermediate LVP fall projected above baseline. The 12 mm Hg elevation of systolic LVP therefore slowed LVP fall. The lower panels display data of an animal (dog 17) with a high intrinsic contractile state. Segmental shortening was hardly affected. Lower right, initial LVP fall paralleled control, peak \(-dP/dt\) was increased, and intermediate LVP fall was slightly steeper and projected below control. A 12 mm Hg elevation of systolic LVP therefore accelerated LVP fall.
The ratio of \( \tau \) of the test beat divided by \( \tau \) of the control beat (\( r_{\text{test}}/r_{\text{control}} \)) was plotted against peak \( +dP/dt \) (left, mm Hg/s) and systolic shortening (right, %). A value of 1, indicated by the dashed horizontal line, corresponded to an unchanged \( \tau \). The dots projected below the dashed line corresponded to shorter \( \tau \) and faster pressure fall. The dots projected above the dashed line corresponded to longer \( \tau \) and slower pressure fall.

\( \tau \) went from 47 (control) to 53 milliseconds (test). LVP fall slowed during both its initial and its intermediate phases. As shown in the lower right panel, the 12 mm Hg LVP elevation induced a less convergent, almost parallel course of initial LVP fall, an increase in absolute value of peak \(-dP/dt\), and a projection of intermediate LVP fall below control. \( \tau \) went from 36 (control) to 31 milliseconds (test). LVP fall accelerated accordingly. If we look at the segment length data of Fig 4, middle panels, minimum systolic segment length increased in the upper panel, where LVP slowed, but was almost unchanged in the lower panel, where LVP fall accelerated. This observation led to the hypothesis that changes in \( \tau \) induced by 12 mm Hg LVP elevations could be related to the contractile state of the animal. In Fig 5, changes in \( \tau \) were presented as the ratio of the value of \( \tau \) in the test beat divided by the value of \( \tau \) in the control beat (\( r_{\text{test}}/r_{\text{control}} \)). A value smaller than 1 indicated decreased \( \tau \) and accelerated LVP fall. A value larger than 1 indicated increased \( \tau \) and slower LVP fall. The ratio was plotted against control values of peak \(+dP/dt\) and systolic segmental shortening (apical segment), two commonly used indexes of contractility.

The next step in the analysis of protocol B was to compute the effects on \( \tau \) of multiple graded elevations of peak LVP ranging from 2 mm Hg up to peak isovolumetric LVP elevation. In Fig 7 (upper panel), the ratio \( \tau_{\text{test}}/\tau_{\text{control}} \) was plotted against the corresponding elevation of systolic LVP. Such a plot typically resulted in a J-shaped curve. Data from two representative animals were displayed. In dog 15 (solid circles, left curve), peak isovolumetric LVP elevation was 22 mm Hg, and the ratio \( \tau_{\text{test}}/\tau_{\text{control}} \) stayed above 1.0, indicating that \( \tau \) increased over the entire range of elevations of LVP. The 12 mm Hg pressure elevation induced a ratio \( \tau_{\text{test}}/\tau_{\text{control}} \) of 1.23. In dog 17 (open circles, right curve), peak isovolumetric LVP elevation was 55 mm Hg. A decrease in the ratio \( \tau_{\text{test}}/\tau_{\text{control}} \) was observed until an LVP elevation of 27 mm Hg, and the 12 mm Hg pressure elevation induced a ratio \( \tau_{\text{test}}/\tau_{\text{control}} \) of 0.86. With pressure elevations >27 mm Hg, \( \tau_{\text{test}}/\tau_{\text{control}} \) increased. The response of the duration of systole to elevations of systolic LVP was evaluated with the time interval from end diastole to peak \(-dP/dt\). This response was somehow related to the response of the ratio \( \tau_{\text{test}}/\tau_{\text{control}} \) (Fig 6, lower panel). In dog 15 (solid circles), the time to peak \(-dP/dt\) became longer with small pressure elevations, corresponding to the horizontal portion of the J-shaped curve, where changes in \( \tau \) were limited. In the vertical portion of the J-shaped curve, where \( \tau \) started to increase exponentially, the prolongation of the time to peak \(-dP/dt\) became less pronounced and evolved into abbreviation. In dog 17 (open circles), the parallelism was even more striking. The horizontal leg of the
Fig 7. Graphs showing effects of multiple graded systolic pressure elevations on the time constant, \( \tau \), and on the time interval from end diastole to peak \(-dP/dt\). Top, Ratio of \( \tau \) of the test beat divided by \( \tau \) of the control beat (\( \tau_{test}/\tau_{control} \)) as a function of the corresponding elevation of systolic left ventricular pressure (LVP elevation, mm Hg). The plots were J-shaped. LVP elevations ranged from 2 mm Hg up to isovolumetric in multiple steps. Data from two animals were shown. In dog 15 (solid circles, left curve) with the limited intrinsic contractile state, peak isovolumetric LVP elevation reached 22 mm Hg, and no decrease in the ratio \( \tau_{test}/\tau_{control} \) was observed. In dog 17 (open circles, right curve) with the high intrinsic contractile state, peak isovolumetric LVP elevation reached 55 mm Hg, and a decrease in the ratio \( \tau_{test}/\tau_{control} \) (this means an acceleration of LVP fall) was observed up to an LVP elevation of 27 mm Hg. Bottom, Changes in the time interval from end diastole to peak \(-dP/dt\) (milliseconds). In dog 15 (solid circles), time to peak \(-dP/dt\) became longer with smaller pressure elevations that induced limited changes in \( \tau \). When \( \tau \) started to increase exponentially, the prolongation became less important and evolved into abbreviation. In dog 17 (open circles), time to peak \(-dP/dt\) became progressively longer with greater pressure elevations up to 27 mm Hg. Above 27 mm Hg, and with pressure elevations inducing increasingly slower LVP fall, the increase of the time to peak \(-dP/dt\) became less important and disappeared close to isovolumetric.

J-shaped curve corresponded to both an increase in the time to peak \(-dP/dt\) and an acceleration of LVP fall evidenced by a ratio \( \tau_{test}/\tau_{control} < 1 \). The vertical leg of the J-shaped curve corresponded to less increase in the time to peak \(-dP/dt\) and to a deceleration of LVP fall.

Fig 8 repeated the baseline data of Fig 7 (solid symbols in all panels) and showed, in addition, data obtained after an inotropic intervention (open symbols). In the upper left panel (circles), intravenous administration of calcium chloride (0.2 mg·kg\(^{-1}\)·min\(^{-1}\), \( n = 4 \)) shifted the curve downward and to the right. After calcium chloride, a given elevation of systolic LVP induced a smaller increase in \( \tau \). In the lower left panel (squares), intravenous administration of propranolol (1 mg/kg, \( n = 3 \)) shifted the curve upward and to the left. After propranolol, a given elevation of systolic LVP induced a greater increase in \( \tau \).

The right panel of Fig 8 displays the four separate curves as a function of the systolic LVP of the test beat, expressed as a percentage of the peak isovolumetric LVP. The result of this normalization was a merger of the four curves. These curves were obtained in two different animals at baseline, under calcium infusion, and after administration of propranolol. The ratio \( \tau_{test}/\tau_{control} \) obtained with multiple elevations of systolic LVP and plotted as a function of the normalized systolic pressure of the test beat therefore appeared to be unique, albeit with some scatter. Pressure elevations of different magnitudes but leading to a similar LVP of the test beat (expressed in percentage of peak isometric LVP) induced similar effects on \( \tau \). The dashed horizontal line separating increased from decreased rate of relaxation was crossed at the same level as in Fig 6, namely, 81% to 84% of peak isovolumetric pressure. With increasing afterload, isometric relaxation accelerated until 81% to 84% of peak isovolumetric LVP and decelerated beyond this load level.

**Discussion**

**Nonuniform Course of LVP Fall**

The course of LVP fall appeared more complex and nonuniform than previously appreciated. Three consecutive phases of LVP fall were identified, which were subjected to different regulations by load. The initial accelerative phase of LVP fall started at the onset of LVP fall, before aortic valve opening, and was measured with the initial slope of the plot of \( dP/dt \) versus LVP.
The intermediate decelerative phase started after peak $-\frac{dP}{dt}$ and was measured with the intermediate slope. The terminal phase corresponded to late LVP fall slightly before, at, and after mitral valve opening. The proposed subdivision of LVP fall positioned peak $-\frac{dP}{dt}$ at the transition between initial and intermediate LVP fall, at a moment when the first phase merged with the second. This view was supported by group data on mid occlusions (Table 1). With mid occlusions, the initial slope increased and the intermediate slope decreased in absolute values (became less negative). Peak $-\frac{dP}{dt}$ was, as a mean, unchanged and could either increase or decrease, depending on the relative effects of the intervention on initial acceleration and on intermediate deceleration of pressure fall. This particular position of peak $-\frac{dP}{dt}$ may explain in part its well-known lack of reliability as an index of myocardial relaxation.

**Regulation of Initial Pressure Fall**

The first initial phase of LVP fall, which started before aortic valve closure, accelerated with mid and late occlusions. Accelerated LVP fall with late ejection load was explained by load-dependent muscle yielding, cross-bridge disruption, and premature termination of relaxation.\textsuperscript{13,18} A previous study\textsuperscript{11} analyzing effects of late occlusions could not find increased segment yielding (early segment reextension) in the anterior or posterior left ventricular wall. Analysis of segmental behavior during pressure fall in the present study did not reveal increased segment yielding in the basal or the apical left ventricle. We might speculate that acceleration of initial LVP fall with mid and late occlusions would instead be explained by backrotation of cross-bridges with no yielding or disruption. Cross-bridge formation manifests as increased muscle stiffness or resistance to stretch, although not directly as increased active force development. Force development occurs as the attached head undergoes a rotation about a flexible joint between segments S1 and S2 of myosin.\textsuperscript{19} Backrotation might then imply loss of force without loss of resistance to stretch. The experimental data supported the backrotation, the loss of force, and the persistent resistance to stretch (Table 1, Fig 3). Cross-bridge backrotation might have occurred during initial LVP fall. In isolated cardiac muscle, motion of attached cross-bridges is confined to near 0.80% (twitch) to 1.02% (tetanus) of total muscle length.\textsuperscript{18} During initial pressure fall, segment length increased by a mean of 0.85% of end-diastolic length with mid occlusions and by 0.93% with late occlusions. Apical and basal segments responded similarly. The loss of force, which was the consequence of backrotation, presumably corresponded to the accelerated initial phase of pressure fall. Altered viscous properties, possibly due to persistent resistance to stretch of the non-force-generating cross-bridges, manifested as the decreased early segment reextension during LVP fall. This particular regulation can affect timing of LVP fall and value of peak $-\frac{dP}{dt}$.

**Regulation of Intermediate Pressure Fall and $\tau$**

The magnitude of the elevation of peak LVP after total aortic occlusions decreased progressively from early to late, and so did the slowing of intermediate LVP fall. In previous studies, the rate of LVP fall had been related to systolic pressure,\textsuperscript{4,5} stroke volume,\textsuperscript{20} systolic volume,\textsuperscript{4} and the timing of the elevation in systolic LVP.\textsuperscript{10,11} The slowing of LVP fall with early pressure elevations was attributed to recruitment of additional cross-bridges, cooperative activity, decreased cycling rate, and slower inactivation.\textsuperscript{19,21} With mid ejection pressure elevations, additional cross-bridge formation would not have been predominant, since the intervention was timed after the calcium transient had returned almost to baseline.\textsuperscript{22} It was suggested that mid ejection pressure elevations induced an imbalance between load and number of interacting cross-bridges, increasing the stress on individual cross-bridges and delaying cross-bridge inactivation.\textsuperscript{11} This proposed mechanism might also be operative with early occlusions, in which the ventricle faced excessive afterload from aortic valve opening on, which induced extreme slowing of LVP fall (see below). With late ejection aortic occlusions, systolic LVP did not increase, and intermediate pressure fall, evaluated by its slope (Table 1), remained unchanged. $\tau$, however, decreased solely because of a slightly faster pressure fall at and immediately after peak $-\frac{dP}{dt}$ and unrelated to the slope of intermediate pressure fall.

**Regulation of Terminal Pressure Fall**

Terminal LVP fall, including pressure fall during initial rapid filling, remained unaffected by clamp occlusions. This finding reinforces the view that changes in early left ventricular filling are not related to changes in LVP fall. Courtois et al.\textsuperscript{23} for instance, found no correlation between changes in $\tau$ before mitral valve opening and changes in peak early diastolic transmitral pressure gradient and left ventricular filling after mitral valve opening. The independent regulation of late LVP fall was analyzed in isolated cardiac muscle,\textsuperscript{24} in which late force decline was shown to be independent of timing and of short-term load history. Late force decline of isolated cardiac muscle was mainly a function of instantaneous active force and was slightly modulated by instantaneous muscle length.

**LVP Fall and Contractility**

A beat-to-beat elevation of systolic LVP with a magnitude of 12 mm Hg induced variable effects on $\tau$, ranging from a 20% decrease to a 35% increase. Changes in $\tau$ were inversely related to contractility, as evaluated by peak +$\frac{dP}{dt}$ or regional fractional shortening (Fig 5). This observation is in agreement with the concept that relaxation is part of systole\textsuperscript{10} and that inotropy and relaxation are intimately related.\textsuperscript{25} This issue was recently addressed in two clinical studies. Eichhorn et al.\textsuperscript{26} published data in patients with congestive heart failure. A linear relation was found between $\tau$ and systolic LVP: when systolic pressure decreased during nitroprusside infusion, $\tau$ decreased. The slope of this relation was flat when contractility was normal. The slope became steeper and increasingly dependent on load when contractility was impaired. This steeper slope reflected the more pronounced slowing of pressure fall observed in conditions of severely impaired contractility. In another study, in transplant recipients, Paulus et al.\textsuperscript{27} indicated that myocardial relaxation showed variable responses to exercise, ranging from acceleration to a marked deceleration. The deceleration of relaxation in transplant recipients was attributed mainly to greater
use of left ventricular preload reserve. According to the present study and the analysis of the published data of the transplant study, an impaired contractile response to exercise, observed in some transplant recipients, could have resulted in working conditions close to isovolumetric, hence to slower relaxation, and then to secondary dilatation of the left ventricle.

**LVP Fall and Peak Isovolumetric Pressure**

To clarify the mechanisms underlying the observed contraction-relaxation coupling, the effects of a 12 mm Hg pressure elevation on τ were related to the systolic LVP of the test beat, expressed as a percentage of peak isovolumetric LVP (Fig 6). This presentation is similar to describing an afterloaded isotonic muscle twitch as a percentage of peak isometric force. This linear relation was almost predictive \((r=.984)\) of the effect of an elevation of systolic LVP with a magnitude of 12 mm Hg on the rate of pressure fall. When multiple graded elevations of systolic LVP were considered (Fig 8), the plot relating \(\tau_{test}/\tau_{control}\) to the elevation of systolic LVP was J-shaped. In a previous study, limited, however, to elevations of \(\leq 20\) mm Hg, we described a linear relation, which corresponded to the horizontal leg of the J-shaped curve.\(^{11}\) Both the horizontal and the vertical positions of the J-shaped curve on the graph depended on the magnitude of peak isovolumetic LVP elevation and could be altered by inotropic interventions such as intravenous calcium infusion and administration of propranolol. A similar elevation of systolic LVP will induce less slowing of pressure fall after a positive inotropic intervention and more slowing after a negative inotropic intervention. This may explain why, in a recent experimental study,\(^{28}\) LVP elevations induced by phenylephrine slowed left ventricular relaxation only after congestive heart failure induced by rapid pacing and not in control animals. Changes in left ventricular relaxation, such as induced by phenylephrine, could turn out to become valuable indexes of contractility and inotropic reserve. These changes evaluated by the isovolumic relaxation time could prove to be useful in noninvasive echocardiographic examination of cardiac function. The right panel of Fig 8 displays the same four curves as in the left panels as a function of the systolic LVP of the test beat, expressed as percentage of peak isovolumetric LVP. The result of this normalization was a merger of the four curves. The ratio \(\tau_{test}/\tau_{control}\) obtained with multiple elevations of systolic LVP and plotted as a function of the normalized systolic pressure of the test beat therefore appeared to be unique. Elevations in systolic LVP reaching a similar percentage of peak isovolumetric LVP had similar effects on τ regardless of the animal, the inotropic state, and to a certain extent the magnitude of the elevation. Both in Fig 6 and in Fig 8, the intercept of the relation with the dashed horizontal line, corresponding to an unchanged τ, was situated at 81% to 84% of peak isovolumetric pressure. If the test beat remained below 81% to 84% of peak isovolumetric LVP, pressure fell accelerated. If the test beat exceeded 81% to 84% of peak isovolumetric LVP, pressure fall slowed.

**From Muscle to Heart: Load Dependence**

The data showed for the first time that relaxation response to afterload of the intact left ventricle was identical to that of a load-dependent\(^{19}\) isolated cardiac muscle such as described by Parmley and Sonnenblick\(^{7}\) for the isotonic-isometric relaxation sequence and by Wiegener and Bing\(^{8}\) for the isometric-isotonic relaxation sequence. This similarity is illustrated by Fig 9. The upper panel shows LVP tracings, and the lower panel shows afterloaded twitches of cat papillary muscle with a physiological relaxation sequence. Both in the isolated cardiac muscle and in the intact left ventricle, it was observed that load increments up to 81% to 84% of isovolumetric load delayed the onset and accelerated the rate of isometric relaxation. Beyond 85% of isovolumetric load, onset of relaxation became premature, and rate of relaxation decreased. This presentation did not take into account our observations after small elevations in LVP in dogs with limited isovolumetric LVP, such as dog 15 in Fig 7. Under these conditions, both time to peak −dp/dt and τ could increase, but the increase in time to peak −dp/dt was mainly the consequence of slowed initial LVP fall rather than of prolonged contraction duration. Of note, LVP tracing 3 exceeded the contour of the isovolumetric beat during early LVP fall. This observation, previously reported in isolated cardiac muscle, was described as suprasystometric force.\(^{29}\)

The idea that the history of contraction would affect the nature of cross-bridge cycling during relaxation was sug-
gested by Hori et al. They attributed earlier onset and slower rate of LVP fall, observed with increasing load, to less active shortening, less cross-bridge cycling, and position of the attached myosin heads closer to the steady-state isometric position. The relation revealed by the present study is more complex and biphasic. We might speculate that the balance between the number of cross-bridges and the load to be carried would affect the nature of cross-bridge cycling during relaxation rather than the extent of shortening. The delayed onset and increased rate of LVP fall observed when the actual systolic LVP was much smaller than peak isovolumetric could be the manifestation of compensating cross-bridge recruitment with no changes in the stress on the individual cross-bridge and hence no change in the position of the attached myosin head. The earlier onset and decreased rate of LVP fall observed when the actual systolic LVP exceeded 81% to 84% of peak isovolumetric afterload could be explained by insufficient calcium availability and insufficient recruitment of cross-bridges. The stress on individual cross-bridges would then increase. Early onset and slower rate of pressure fall observed with LVP elevations close to isovolumetric would then be explained by mechanisms similar to those with mid aortic occlusions (see above). This speculation is in accordance with the timing of the calcium transient in isolated cardiac muscle, which is almost over at peak isometric force.

Limitations of the Study

This study was performed in anesthetized open-chest animals, in which contractility might have been impaired. Only changes of \( \tau \) in response to elevations of systolic LVP were analyzed, and the present data do not explain baseline values of \( \tau \). The analyzed beat-to-beat changes in systolic LVP were not identical to prolonged elevations in systolic LVP induced by volume loading or methoxamine infusion, in which the Frank-Starling compensation and neurohumoral readjustments add to the complexity of the regulation of myocardial relaxation.

Acknowledgments

This work was supported by The Belgian Program on Interuniversity Pools of Attraction Initiated by the Belgian State, Prime Minister’s Office, Science Policy Programming, the foundation Bekales, and from the Junta Nacional de Investigação Científica e Tecnológica (J.N.I.C.T. Programa CIENCIA), Portugal. Dr Leita-Moreira was funded by Research Fellowships from the J.N.I.C.T. and by the University of Porto, Portugal. Dr Gillebert was funded by an Investigator Grant of the Belgian National Foundation for Scientific Research. The authors sincerely thank the reviewers for their thorough but constructive comments. They acknowledge the valuable advice of Stanislas U. Sys, MD, PhD, in the interpretation of the data. They express their gratitude to Annie Van Weert, Willy Delnay, and Marc Demolder for technical assistance and animal care.

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Nonuniform course of left ventricular pressure fall and its regulation by load and contractile state.
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Circulation. 1994;90:2481-2491
doi: 10.1161/01.CIR.90.5.2481

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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