Contraction-relaxation coupling: determination of the onset of diastole

STEVEN B. SOLOMON,¹ SRĐJAN D. NIKOLIC,² ROBERT W. M. FRATER,¹ AND EDWARD L. YELLIN¹

¹Department of Cardiothoracic Surgery and the Department of Biophysics and Physiology, Albert Einstein College of Medicine, Bronx, New York 10461; ²Department of Cardiovascular and Thoracic Surgery, Research Institute of the Palo Alto Medical Foundation, Stanford University School of Medicine, Palo Alto, California 94306

Solomon, Steven B., Srdjan D. Nikolic, Robert W. M. Frater, and Edward L. Yellin. Contraction-relaxation coupling: determination of the onset of diastole. Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H23–H27, 1999.—Left ventricular relaxation is dependent on afterload conditions during systole. An abrupt increase in afterload while the ventricle is actively contracting prolongs the duration of systole. An increase in afterload during ventricular relaxation shortens the duration of systole. Therefore, we hypothesized that the point during systole when an abrupt increase in afterload had no effect on the duration of systole represented the onset of ventricular relaxation. To determine when this point occurs, we performed aortic occlusions progressively throughout the duration of systole in six dogs. We determined the change in systolic time (t sys) after an intervention normalized to t sys of a control beat (t sys/C sys) as a function of systolic occlusion time as a percentage of total systolic time (t sys/C sys/r), where t sys is the duration from time of left ventricular end-diastolic pressure to the time of minimum first derivative of left ventricular pressure. Our results show the onset of left ventricular relaxation during normal ejection occurs at 34 ± 3% of systolic time and 16% after the onset of ejection. Thus the beginning of relaxation occurs soon after the beginning of ejection, suggesting that relaxation is modulated by variable loading conditions during ejection, significantly before what has been conventionally assumed to be the beginning of ventricular relaxation.

delayed afterload; left ventricular relaxation

THERE HAS BEEN INCREASING interest in impaired left ventricular relaxation as a precursor to early heart failure or as a possible cause of diastolic failure (7, 22). Investigators (1, 4, 6, 12) have pointed to left ventricular relaxation as the link between activation during contraction and inactivation during relaxation and to loading conditions as a major determinant of relaxation. Several studies (3, 10, 16, 24) have investigated the role of preload and afterload on isovolumic relaxation. Specifically, the dependence of relaxation on afterload conditions has been investigated by transiently changing afterload at various times during systole in isolated muscle, isolated heart, and intact heart preparation (1, 3, 5, 10, 16, 21, 24).

Muscle twitch experiments in isolated muscle showed that an increase in afterload early in systole both delays the onset and slows down the rate of relaxation, whereas an increase in afterload late in systole abbreviates contraction time and increases the rate of relaxation (5). In isolated heart studies, interventions designed to increase afterload immediately after aortic valve opening increased the duration of systole, whereas an increase in afterload late during ejection decreased the duration of systole (1, 24). In an intact heart study, afterload was changed by inflating a balloon catheter to occlude the aorta (10). The aortic occlusion resulted in a decrease in the rate of relaxation when the balloon was inflated during the first one-third of the ejection and an increase in the rate of relaxation when the balloon was inflated during the last one-third of the ejection. Thus all physiological studies on the effects of afterload dependence on the duration of systole and the rate of relaxation showed two important findings (1, 5, 10, 24). First, an increase in afterload while the muscle or the ventricle was actively contracting prolonged the duration of systole and slowed relaxation. Second, an increase in afterload during muscular or ventricular relaxation shortened the duration of systole and increased the rate of relaxation.

The dependence of the duration of systole and the rate of relaxation on loading conditions has been described to changes in the recruitment of cross bridges (6), cooperative cross-bridge activity (2, 11, 23), cross-bridge cycling rate (23), and changes in cross-bridge inactivation (17). The increase in systolic time and slowing of the rate of relaxation with afterloads imposed during early ejection were attributed to an increase in cross-bridge recruitment, a cooperative activity of cross-bridge formation resulting in further cross-bridge formation, a decreased rate of cross-bridge attachment/detachment cycling, and a slower inactivation of cross-bridge formation due to changes in calcium handling (6, 23). The shortening of systole and increased rate of relaxation with increased afterload has been related to an inability of cross bridges to sustain increasing load while the rate of detachment was greater than the rate of attachment, resulting in cross-bridge disruption and increasing the rate of relaxation (13, 25).

According to these mechanisms, it is obvious that there must be a transition point during systole when load ceases to sustain the cross bridges and starts opposing their formation (i.e., there must be a transition point between what is conventionally called contraction and relaxation). However, it is not clear when this
transition point occurs during the cardiac cycle and when left ventricular relaxation actually begins. If the beginning of relaxation is close to the beginning of isovolumic relaxation, the loading condition of the left ventricle, which is not changing dimensions, may be a major determinant of the relaxation. If the relaxation starts earlier during ventricular ejection, the loading conditions of the rapidly contracting ventricle may become the prevailing determinant of relaxation. These two situations are dramatically different in terms of the mechanisms that govern their contraction-relaxation sequences and cross-bridge dynamics, and these differences may be significant in our understanding of the physiological and pathophysiological determinants of left ventricular function.

Therefore, the present study was designed to test the working hypothesis that the point during systole when an abrupt increase in afterload has no effect on the duration of systole represents the onset of relaxation in the intact left ventricle. To determine this point when the left ventricle begins to relax, we changed the afterload in six open-chest dogs by progressively occluding the aorta throughout systole. Surprisingly, the data show that the onset of left ventricular relaxation during normal ejection occurs very early in systole, after only ~16% of ejection is completed.

METHODS

Surgical preparation. Six mongrel dogs (wt 21–28 kg) were anesthetized with fentanyl citrate (10 µg/kg iv), intubated, and mechanically ventilated with 100% oxygen. Anesthesia was maintained by administration of fentanyl citrate (30 µg) and pancuronium bromide (4 mg) every 20 min or as needed. The dogs were placed in the supine position, and a median sternotomy was performed. The pericardium was opened wide to create a pericardial cradle. Arterial blood gases and pH were monitored and maintained in the normal range by ventilator adjustment, administration of sodium bicarbonate, or both.

Instrumentation. To measure left atrial and left ventricular pressures, two 5-Fr micromanometers (Millar Instruments) were inserted, one into the left atrium via a small branch of a left pulmonary vein and the other into the left ventricle via the apex (Fig. 1). Before the experiment, the micromanometers were warmed to 37°C overnight to achieve a steady state. The micromanometers were zeroed, and they were calibrated against a mercury manometer before being inserted into the dog. An ultrasonic flow transducer (Transonic System) was placed around the ascending aorta to measure aortic flow. An electromagnetic flow probe was placed on the mitral orifice according to a previously published procedure (15). Pressures and flows were recorded at high gain on an oscillographic recorder (VR-12, Electronics for Medicine) at a speed of 100 mm/s. The data were also recorded on CODAS (DATAQ Instruments), a computer-based real-time data acquisition system at 200 samples/s · channel ·1, which is the standard rate of data acquisition of physiological waveforms in dogs.

Aortic occluder. An occluder was placed around the aorta to abruptly increase the afterload of the ventricular chamber. The aortic occluder is a free-moving right-angle clamp, carefully placed around the aorta to avoid constriction (Fig. 1). The edges of the clamp are covered with soft plastic to minimize trauma to the aorta on occlusion. One side of the clamp is fixed in place, whereas the other is attached to a control cable welded to the core of the solenoids. The solenoids are adjusted to ensure that the stroke will occlude the aorta and are positioned on an adjustable platform near the open-chest area.

Protocol. The aorta was occluded progressively throughout the duration of systole. These aortic occlusions were performed before ejection, resulting in an isovolumic contraction, and subsequent occlusions were performed progressively throughout the duration of systole. Before each occlusion, a hemodynamic steady state was achieved and the respirator was turned off to avoid respiratory variations in the hemodynamic measurements and to control artifacts that might interfere with the signal. We recorded hemodynamic measurements for several control beats, and an aortic occlusion was performed. The aortic occlusion was triggered on the R-wave from a lead II electrocardiogram. After the aortic occlusion, ~20 beats were allowed for the hemodynamic and flow signals to return to steady state before another occlusion was performed.

Data analysis. The oscillographic records were digitized (Science Accessories) by manually tracing the pressure curve and calculating the change in slope to determine the rate of relaxation from the time constant of left ventricular pressure decline. The CODAS data could not be used for this purpose because each waveform was recorded on a separate channel. The CODAS data were calibrated and analyzed using Asystant (Asyst Software Technologies) to measure the pressure and the timing of events. Systolic time was determined by taking the first derivative of left ventricular pressure (dP/dt) and measuring the interval from the onset of mechanical contraction to the minimum of dP/dt (dP/dtmin). Linear regression analysis using the least squares method was applied to the occlusion data. The data were evaluated using two statistical packages, Primer of Biostatistics (Stan-

Fig. 1. Cross section of the left heart instrumented with the aortic clamp, left atrial pressure (LAP) and left ventricular pressure (LVP) micromanometers, and mitral flow (MF) transducer.
ton Glantz, McGraw-Hill) and Statpak (Northwest Analyti-
cal). Statistical significance was determined by a paired
t-test. Differences were considered significant when \( P < 0.05 \).
Data are means \( \pm SD \). The results of the digitized data were
then plotted using SigmaPlot (Jandel Scientific).

RESULTS

To determine the effect of abrupt increases in afterload throughout the duration of systole, the data were divided
into three groups: late systolic occlusion, early systolic occlusion, and isovolumic contraction (Table 1). Late sys-
tolic occlusion was an intervention that caused the time to
dP/dt \( \text{min} \) to decrease compared with a control systole;
early systolic occlusion increased time to dP/dt compared
with a control systole. An isovolumic contraction was
defined as an occlusion performed before systolic con-
traction.

Figure 2 illustrates the effect of a late aortic occlusion,
an early aortic occlusion, and an isovolumic occlusion on
left ventricular pressure and the rate of change of left ventricular pressure with respect to time
dP/dt) compared with a control beat. The duration of
systole (systolic time) was defined as the interval from
the onset of mechanical contraction to the minimum of
dP/dt (systolic time of a control beat, \( t_{\text{sys,c}} \)). In normal
control beats, the beginning of ejection was calculated
to occur at 23.4 \pm 2.5\% of systolic time and the end of
ejection occurred at 90.8 \pm 3.3\% of systolic time. During
a late aortic occlusion, peak left ventricular pressure is
unchanged but relaxation is accelerated (51.1 \pm 14.5
vs. 61.5 \pm 15.8 ms, \( P < 0.05 \)) and systolic time is
decreased. During an early aortic occlusion, peak left
ventricular pressure increases, relaxation is slowed
(60.7 \pm 18.9 vs. 54.4 \pm 12.2 ms, \( P < 0.002 \)), and systolic
time is slightly increased. During an isovolumic occlusion,
the peak left ventricular pressure increases
(greater than that seen during early aortic occlusion),
relaxation is slowed (72.3 \pm 29.6 vs. 57.9 \pm 19.3 ms,
\( P < 0.002 \)), and systolic time is significantly increased.

The systolic time of an intervention (time of left
ventricular end-diastolic pressure to time of dP/dP \( \text{min} \))
was normalized to a control beat \( t_{\text{sys,c}}/t_{\text{sys,c}} \) to eliminate
the differences caused by heart rate. The normalized
systolic time was plotted against the occlusion time expressed as a percentage of the systolic time of a
control beat \( t_{\text{occ}}/t_{\text{sys,c}} \) (Fig. 3). The scatterplot shows the
results obtained from varied systolic aortic occlusions
followed by normal mitral filling. The intersection of
the regression line and the isosystolic timeline (horizon-
tal line) represents the instant during systole when an
intervention does not affect the duration of systole. The
plot shows that the onset of left ventricular relaxation
during a normal beat occurs after the first one-third of
systolic time (34 \pm 3\%) measured from the onset of
mechanical contraction (Fig. 3).

DISCUSSION

The effect of afterload on the rate of relaxation and
other various determinants of filling has been investi-
gated extensively (3, 8, 9, 10, 20, 21). Isolated muscle
experiments showed that the onset of relaxation occurred earlier with smaller loads when shortening was
the greatest (3, 21). In an intact heart, abruptly increas-
ing afterload during early systole resulted in a delay in
the onset of relaxation and a decreased rate of relax-
ation (8, 10). Increasing afterload late in systole re-
sulted in an increase in the rate of relaxation (8, 10, 20).
All of these results are consistent with the findings in
this study and can be understood within the context of
the cross-bridge theory of muscle contraction (14).

An early increase in systolic load increases the
myocardial sensitivity to free calcium, thereby increas-
ing the recruitment of cross bridges and increasing the
duration of systole, in part, by slowing the rate of
relaxation. A late increase in systolic load does not
increase myocardial sensitivity to calcium, resulting in
a decrease in cross-bridge formation. The cross bridges
cannot maintain the increased load, resulting in an
increase in the rate of relaxation and a subsequent
decrease in the duration of systole.

The data plotted in Fig. 3 show the effect of varied
systolic interventions on the duration of systole. The
data points, which intersect the isosystolic time line,
neither increase or decrease the duration of systole.
These data support our hypothesis that there is a point
in the intact heart when increases in afterload do not
affect the duration of systole. We speculate that this
intersection suggests a point when the sarcomere cross-
bridge cycling (the attachment and detachment of cross
bridges) is in equilibrium just before the onset of
relaxation. It is surprising that the onset of relaxation
occurs this soon after the onset of ejection (34\% of
systolic time, after \( \sim 16\% \) of ejection). These results also

Table 1. Summary of the hemodynamic effects of isovolumic, early systolic, and late systolic occlusions

<table>
<thead>
<tr>
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<th>Late Systolic Occlusion</th>
<th>Early Systolic Occlusion</th>
<th>Isovolumic Occlusion</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Intervention</td>
<td>Baseline</td>
</tr>
<tr>
<td>( t_{\text{cyc}} ), ms</td>
<td>458 ± 18</td>
<td>454 ± 120</td>
<td>470 ± 117</td>
</tr>
<tr>
<td>( t_{\text{occ}} ), ms</td>
<td>271 ± 26</td>
<td>266 ± 23</td>
<td>285 ± 19</td>
</tr>
<tr>
<td>( LVP_{\text{oc}} ), mmHg</td>
<td>12.4 ± 5.6</td>
<td>12.1 ± 6.4</td>
<td>9.4 ± 4.5</td>
</tr>
<tr>
<td>( SV ), ml</td>
<td>25.5 ± 6.4</td>
<td>19.2 ± 6.4‡</td>
<td>21.7 ± 6.3</td>
</tr>
<tr>
<td>( \tau_{\text{r}} ), ms</td>
<td>61.5 ± 15.8</td>
<td>51.1 ± 14.5*</td>
<td>54.4 ± 12.2</td>
</tr>
<tr>
<td>( t_{\text{DF}} ), ms</td>
<td>191 ± 61</td>
<td>182 ± 53</td>
<td>196 ± 34</td>
</tr>
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</table>

Values are means ± SE. \( t_{\text{cyc}} \), Cycle length; \( t_{\text{occ}} \), time of atrioventricular crossover; \( LVP_{\text{oc}} \), left ventricular pressure at atrioventricular crossover; \( SV \), stroke volume; \( \tau_{\text{r}} \), rate of isovolumic pressure decay; \( t_{\text{DF}} \), diastolic filling time; *\( P < 0.05 \), ‡ \( P < 0.002 \), † \( P < 0.0001 \) vs. baseline value.
show that a significant portion of relaxation is influenced by variable systolic loading and length before the isovolumic relaxation phase. If true, these results are not consistent with the physiologically loaded isolated muscle model of left ventricular relaxation, which assumes isometric relaxation (3). This study agrees with the findings of Gillebert and co-workers (9, 18) that during abrupt aortic occlusions using balloon inflation in dogs, the transition from contraction to relaxation occurs when 81 to 84% of peak isovolumic pressure is reached. When this value for the transition from contraction to relaxation is converted into the equivalent timing of a normal beat, the results are similar to those found in this study. Our results are also consistent with previous work (19) that suggested inertial forces due to left ventricular outflow were responsible for the continuing increase in aortic pressure even after the onset of relaxation. The pressure gradient from left ventricle to the aorta remains positive even after the onset of relaxation during acceleration and becomes negative shortly after deceleration begins. Therefore, it is the aortic outflow-left ventricular pressure gradient that determines acceleration with the fall of left ventricular pressure being the primary determinant of the rate of deceleration.

Aside from the obvious (and inevitable) drawbacks of an open-chest animal model, the study is limited by the application of the aortic occluder. The aortic occluder closes the aortic orifice in 12 ms. This abrupt occlusion

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**Fig. 2.** Control beat (A) compared with the effect of a late aortic occlusion (B), an early aortic occlusion (C), and an isovolumic occlusion (D) on LVP and systolic time (t_{sys}). The duration of systole (systolic time of a control beat, t_{sys,c}) was defined as the interval from the onset of mechanical contraction to minimum first derivative of LVP (dP/dt). t_{sys,i}, Systolic time of an intervention; t_{occ}, time of occlusion; AoF, aortic flow.

**Fig. 3.** Onset of relaxation as a percentage of systolic time. Plot shows the systolic time of an intervention normalized to a control beat (t_{sys,i}/t_{sys,c}) vs. systolic occlusion time as a percentage of total systolic time (t_{occ}/t_{sys,c}).
of the aortic valve may change the dynamics of the valve or the ventricle. This effect was minimized by placing the aortic occluder a sufficient distance from the aortic valve to avoid interfering with valve function and the ventricle. Another limitation was the electromagnetic flow transducer on the mitral valve. This mitral transducer fixes the mitral annulus. We did not consider this to be a significant limitation because the possible influence of the mitral transducer had a constant effect throughout the study.

In summary, our study shows that the onset of relaxation occurs soon after the beginning of ejection (after ~16% of ejection). This result shows that relaxation is modulated by variable loading conditions during ejection significantly before what has been conventionally assumed to be the beginning of ventricular relaxation.

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Address for reprint requests and other correspondence: S. Solomon, NIH, Critical Care Medicine Dept., 10 Center Dr., Rm. 7D43, Bethesda, MD 20892 (E-mail: ssolomon@cc.nih.gov).

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