Time-Dependent Increase in Left Ventricular Contractility Following Acute Volume Loading in the Dog

Wilbur Y.W. Lew

Acute volume alterations were produced in eight anesthetized dogs to determine if the contractility of the left ventricle is partially volume-dependent. Pressures were measured in the left ventricle with a micromanometer and regional ventricular function was measured with sonomicrometers implanted in the midwall of the anterior, lateral, and posterior left ventricle. Regional end-systolic pressure-length relations (ESPLR) were determined with transient venae cavae occlusions. The ESPLR data were fitted to a quadratic equation, then end-systolic lengths were compared at matched end-systolic pressures at multiple time periods after the acute load alterations. Bilateral vagotomy, carotid sinus denervation, and stellate ganglion denervation were performed to prevent reflex alterations in contractility. The heart was paced at a constant rate. In seven animals, dextran was infused intravenously over $77 \pm 23$ seconds ($\pm$SD) to increase left ventricular end-diastolic pressure from $5 \pm 2$ to $13 \pm 3$ mm Hg and peak pressures from $113 \pm 11$ to $147 \pm 18$ mm Hg. The end-diastolic lengths increased $14 \pm 6\%$ in the anterior, $9 \pm 2\%$ in the lateral, and $12 \pm 4\%$ in the posterior segments. The ESPLR was measured immediately ($77 \pm 23$ seconds), early ($3 \pm 1$ minutes), and late ($10 \pm 2$ minutes) after initiation of the volume load. In all three regions, there was a significant time-dependent leftward shift in the ESPLR. From 1 to 10 minutes after the volume load, the regional end-systolic lengths decreased by a mean of $4-6\%$ when compared at a matched end-systolic pressure of $96 \pm 10$ mm Hg, and decreased by $7-9\%$ when compared at a matched pressure of $139 \pm 20$ mm Hg. The end-systolic lengths immediately after the volume load were not significantly different from the control value (compared at a matched end-systolic pressure) but were significantly shorter 10 minutes after the volume load. The leftward shift of the ESPLR represented a true increase in contractility and not merely a recovery from a transient myocardial depression. A similar leftward shift in the ESPLR occurred in four animals after release of a partial venae cavae occlusion, producing an acute volume load without acute hemodilution. Acute volume loads in four animals treated with propranolol also produced a leftward shift in the ESPLR, ruling out the possibility that a time-dependent increase in circulating catecholamines was responsible for the alterations in contractility. In five animals, the ESPLR shifted to the right after a transient (1-2 minutes) decrease in venous return. The end-diastolic pressure-volume relation did not shift after volume alterations in any of the protocols, ruling out significant viscoelastic effects. It is concluded that in the intact, ejecting ventricle, an abrupt increase in volume is accompanied by a time-dependent increase in contractility. The time course for this load-induced alteration in contractility is similar to the time course for length-dependent activation effects previously reported in isolated cardiac muscles studies. Interventions that alter left ventricular volume therefore induce concomitant alterations in the ventricular contractility. (Circulation Research 1988;63:635–647)
lated muscle studies that contractility is in part dependent on the length of the cardiac muscle. This phenomenon, termed length-dependent activation, has been demonstrated with two basic approaches. First, the shape of the steady-state length-tension relation is significantly dependent on the degree of inotropic stimulation, suggesting that these two factors (muscle length and contractility) are interrelated.\textsuperscript{1-8} The second approach demonstrates length-dependent activation effects more directly. When the resting cardiac muscle length is abruptly increased, the peak tension increases immediately, followed by a time-dependent increase in contractility (i.e., a further increase in peak tension) over several minutes as the muscle reaches a new steady state.\textsuperscript{1,3-9,11,13-15} As a result, the steady-state length-tension relation is significantly steeper than the instantaneous length-tension relation. Conversely, if the resting length of a cardiac muscle is suddenly decreased, the peak tension falls immediately, then continues to decrease over several minutes to a new steady state.

Although length-dependent activation is an established property of isolated cardiac muscle, it is unclear if a similar phenomenon occurs under more physiological circumstances. Accordingly, the purpose of the current study was to determine the magnitude and significance of length-dependent activation effects in the intact, ejecting ventricle. This study demonstrates that acute volume alterations within a physiological range in the intact ventricle are accompanied by time-dependent alterations in contractility. The time course of these volume-dependent alterations in left ventricular contractility is similar to the time course of length-dependent activation effects observed in isolated cardiac muscles.\textsuperscript{1,3,9,11,13-15}

Materials and Methods

Instrumentation

Eight adult mongrel dogs were anesthetized with sodium pentobarbital (25 mg/kg i.v.), intubated, and ventilated with a Harvard respirator (South Natick, Massachusetts). A femoral vein and a femoral artery were cannulated. Arterial blood gases were measured throughout the experiment, and the arterial pH was maintained between 7.35 and 7.45 with adjustments of the respirator and/or with sodium bicarbonate administered intravenously. The animal’s core temperature was monitored with a rectal thermometer and maintained with a table heater. The level of anesthesia was evaluated throughout the experiment, and additional doses of anesthetic were administered as needed.

The heart was exposed with a midline sternotomy and bilateral thoracotomy at the fifth intercostal space. The pericardium was opened widely and used to support the heart in a pericardial cradle. A Konigsberg P-20 micromanometer (Pasadena, California) was inserted into the left ventricle through an apical stab wound and secured with a purse-string suture. A 7F 100 cm fluid-filled pigtail catheter, attached to a Statham P23 DB transducer (Spectramed, Oxnard, California), was inserted into a femoral artery and advanced retrograde into the left ventricle. A zero reference was established at the level of the right atrium. The pigtail catheter was used to calibrate the left ventricular micromanometer, and then was withdrawn into the ascending aorta above the aortic valve to measure central aortic pressure. An electronic derivative of the left ventricular micromanometer signal was obtained to monitor the left ventricular dP/dt. The differentiator had a 3-dB drop in frequency response at 80 Hz with a phase shift of 90°.

Regional ventricular function was measured with ultrasonic segment length gauges, composed of two piezoelectric crystals (2 mm in diameter). The two crystals were inserted through stab wounds in the epicardium and placed approximately 1 cm apart. The segment gauges were oriented in the circumferential direction and placed at a midwall depth through the use of previously described techniques.\textsuperscript{16} Ultrasonic segment gauges were implanted in the anterior, lateral, and posterior walls of the left ventricle. The gauges were connected to a sonomicrometer amplifier box and calibrated with a signal of known duration.

The following instrumentation was performed to manipulate venous return. The azygous vein was ligated and both superior and inferior vena cavae were isolated. Inflatable balloon occlusion cuffs were placed around the vena cavae and used to produce steady-state decreases in venous return. Strips of umbilical tape were placed around the vena cavae. Traction was applied to the tapes to acutely decrease venous return. A large bore (16F) Bardic arterial cannula (model 1858, USCI, Billerica, Massachusetts), connected to Bentley blood formulation Tygon tubing (3¥ in. i.d.), was inserted into a femoral vein. The Tygon tubing was placed through an American Optical roller pump, then into a large reservoir of prewarmed 0.9% dextran in saline. The roller pump was used for rapid infusions of dextran to acutely increase venous return.

Limb leads for an electrocardiogram were placed. The electrocardiogram was processed through a biotachometer to measure heart rate. The descending aorta was gradually occluded to measure reflex changes in heart rate produced by baroreceptor activation. To eliminate potential reflex alterations in contractility, the cardiac reflex pathways were interrupted with bilateral vagotomy, carotid sinus denervation, and denervation of the stellate ganglion. The adequacy of denervation was documented by demonstrating that a repeat occlusion of the descending aorta did not produce any reflex change in heart rate. Pacing wires were sutured to the right or left atrial appendage and attached to an electronic stimulator. The sinus node was crushed.
with a Pean clamp and the heart was paced at a constant rate.

The electrocardiogram, left ventricular pressure and dP/dt, central aortic pressure, and segment length signals (from the anterior, lateral, and posterior midwalls of the left ventricle) were recorded on an eight-channel forced-ink recorder (Brush-Clevite model 2000, Gould, Cerritos, California) at a paper speed of 200 mm/sec and on FM tape for subsequent analysis.

Protocols

In all protocols, regional contractility was assessed by examining changes in the end-systolic pressure-length relation (ESPLR) (see "Data Analysis" below). The ESPLR was obtained by applying traction to the umbilical tapes around the superior and inferior venae cavae to abruptly decrease venous return and decrease end-systolic pressure. After a wide range of pressures were obtained (typically over 8–15 cardiac cycles), the umbilical tapes were released and the ventricular volume allowed to return to the baseline state. In all cases, the ESPLR was evaluated as end-systolic pressure fell and with respirations suspended at end-expiration.

Protocol 1 examined the time-dependent effects of acute volume loading on regional contractility in seven animals. Control measurements were obtained during a steady state. A rapid intravenous infusion of dextran was performed over 1–2 minutes until regional end-diastolic lengths increased by ≥5%. The ESPLR was determined by transient venae cavae occlusions immediately (within 2 minutes), early (2–4 minutes), and late (8–10 minutes) after initiation of the volume infusion. These time periods were chosen because in preliminary studies a time-dependent leftward shift in the ESPLR occurred over a 10-minute period after an acute volume infusion, with much of the shift occurring within the first 3–5 minutes.

Protocol 2 examined the effects of an acute volume load produced without acute hemodilution. In four animals, the occlusion cuffs around the inferior and/or superior venae cavae were partially inflated (after the initial volume load of protocol 1) for 5–10 minutes, then released abruptly. This produced an increase in venous return without hemodilution. As with protocol 1, the ESPLR was determined immediately, early, and late after release of the partial venae cavae occlusion.

Protocol 3 examined the effects of an acute decrease in load on regional contractility. In five animals, a control ESPLR was obtained, then the venae cavae were partially occluded for 1–2 minutes, then released. After the ventricular volume returned toward the control value, the ESPLR was measured to determine if there had been a decrease in regional contractility following this transient (1–2 minute) decrease in load.

Protocol 4 examined the possibility that acute volume loads induced an increase in circulating catecholamines, which were responsible for the time-dependent increase in contractility. Four animals were given isoproterenol (0.01 mg i.v.) to increase left ventricular systolic pressure and peak positive dP/dt. The animals then were treated with propranolol (0.4 mg/kg i.v.) and rechallenged with an identical dose of isoproterenol. If the pressor response was not abolished, additional doses of propranolol were given. After adequate β-blockade, an acute volume infusion was performed as outlined in protocol 1, with the ESPLR determined immediately, early, and late after initiation of the volume load.

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

**Figure 1.** This original tracing shows left ventricular (LV) pressure at low and high gain, LV dP/dt, and three segment length signals from anterior, lateral, and posterior LV midwalls. Control beat is shown in first panel. Dextran was infused over 1 minute to increase LV pressure from 102/15 to 158/13 mm Hg. The second through fourth panels show beats at 1, 3.5, and 9 minutes after initiation of volume load. From 1–9 minutes after volume load peak systolic LV pressure increased by 30 mm Hg; there was a progressive increase in the LV peak positive dP/dt and a time-dependent decrease in regional end-systolic lengths, despite an increase in end-systolic pressures. Thus, acute volume loading produced a time-dependent increase in contractility. See text for further discussion.
Figure 2. Representative pressure-length loops (obtained from data digitized at 5-msec intervals) are shown for a control period, then immediately (40 seconds), early (2 minutes), and late (10 minutes) after an acute volume load increased left ventricular pressure from 145/6 to 167/16 mm Hg. For the sake of clarity, only four pressure-length loops from each time period are shown. Note that end-systolic pressure-length relation (ESPLR) immediately (solid lines) after volume load does not differ from control pressure-length loop (open circles). However, there is a significant time-dependent leftward shift in ESPLR early (dotted lines), and late (dashed lines) after acute volume load.

Data Analysis

All data were recorded on FM tape. Subsequent tape playback was used for analog-to-digital conversion of data at 5-msec intervals using customized computer software. For each cardiac cycle, end diastole was defined by the trough of the left ventricular pressure waveform after atrial systole. When this was not readily apparent, end diastole was timed by the peak of the R wave on the electrocardiogram.

End systole was timed by measuring the ratio of left ventricular pressure to regional segment lengths throughout the cardiac cycle (at 5-msec intervals). End systole was taken as the time of maximum pressure-length ratio. In the majority of cases, this ratio reached a maximum value simultaneously in all three segments (anterior, lateral, and posterior left ventricle). In a few cases, the maximum pressure-length ratio occurred at different times in the three segments but usually within 5–10 msec of each other. In these cases, the time interval between the three segments was used to define end systole and to determine the end-systolic left ventricular pressure and the simultaneous three end-systolic segment lengths.

In three animals, the timing of the maximum pressure-length ratio shifted from end systole to early systole at low ventricular volumes (i.e., during the last few beats of the ESPLR determination). This occurred because of subtle changes in the left ventricular pressure waveform and segment signals. As ventricular volumes decreased (during the ESPLR determination), the systolic pressure changed from upsloping to flat or downsloping, resulting in an earlier peak in left ventricular systolic pressure at low volumes. At low ventricular volumes, most of the segment shortening occurred during isovolumic and early systole. This combination (an early peak in left ventricular pressure and early systolic segment shortening) resulted in an early occurrence of maximum pressure-length ratio at low volumes. In these cases (in approximately 16% of the beats), the algorithm for defining end systole was based on the left ventricular dP/dt. In the beats in which the maximum pressure-length ratio occurred at end systole (i.e., the initial beats of the ESPLR determination), the time difference between the maximum pressure-length ratio and the onset of a negative left ventricular dP/dt (the onset of a negative deflection before peak negative dP/dt) was measured and averaged. This time interval did not vary significantly as ventricular pressures fell over several beats. This time interval, along with the left ventricular dP/dt, were used to time end systole in beats in which the maximum pressure-length ratio occurred during early systole. The results of this study were not affected even if the beats with end systole defined by this alternative algorithm are excluded from the analysis.

In all animals, the ESPLR was determined by progressively lowering the end-systolic pressure over several cardiac cycles. To measure time-dependent shifts in the ESPLR, end-systolic lengths were compared at matched end-systolic pressures. For each animal in which there was ESPLR data available from all time periods, the range of end-systolic pressures was determined. In Figure 3A, for example, there was data at all time periods with end-systolic pressures in the range of 100–140 mm Hg. The end-systolic lengths then were measured at three matched end-systolic pressures, chosen as the maximum, minimum, and midpoint values of this range (e.g., 100, 120, and 140 mm Hg in Figure 3A). To provide data at precisely the same matched end-systolic pressure, the data were fitted to a second order polynomial (the ESPLR was not linear). The quadratic equations were solved to
determine the end-systolic lengths at the three matched end-systolic pressures (low, mid, and high) at all time periods. The quadratic equations were used to interpolate data to the same matched end-systolic pressures. Data were not extrapolated beyond the range of measured data. In order to compare shifts in the ESPLR among different regions and different animals, all end-systolic lengths were normalized to (divided by) the end-systolic length at the low end-systolic pressure from the initial ESPLR determination of each protocol.

The end-diastolic pressure-length data from all the runs in each protocol were plotted to determine if the shift in regional contractility after acute volume loads was also accompanied by changes in a global index of contractility. To estimate time-dependent shifts in this relation, the peak positive dP/dt data were compared at a single, matched end-diastolic length. For each animal, the range of anterior end-diastolic lengths was determined from the initial ESPLR determination after the volume load. The midpoint value of this range was arbitrarily chosen as the anterior end-diastolic length used for comparisons. The beat from each time period with an anterior end-diastolic length closest to this midpoint value was used to compare time-dependent changes in peak positive dP/dt.

Statistical Analysis

Changes in the ESPLR as a function of time after each intervention was evaluated by a repeated measure analysis of variance using Tukey’s test for comparing mean values. In all cases, p≤0.05 was used to indicate statistical significance. Throughout the text and in the tables, are values mean±SD. The only exceptions are in Figures 4 and 7, where the mean values are presented with standard error bars.

Results

The heart was paced at a rate of 99±8 beats/min (± SD) and did not change in any animal with any of the acute volume alterations. A mean of 10±3 data points was used for each regional ESPLR.

Protocol 1: Acute Volume Load

In seven animals, dextran was infused over 77±23 seconds (range 40–110 seconds) to increase left ventricular end-diastolic pressure (LVEDP) from 4.7±2.1 to 12.6±3.3 mm Hg and peak left ventricular pressure from 112.6±11.0 to 146.9±17.5 mm Hg. The acute volume load increased the end-diastolic pressures 13.7±5.6% in the anterior segment, 8.5±2.2% in the lateral segment, and 11.7±4.5% in the posterior segment. The ESPLR were determined immediately (77±23 seconds), early (3.3±0.8 minutes), and late (10.4±2.5 minutes) after initiation of the volume infusion.

An original tracing is shown in Figure 1. In this example, dextran was infused over 1 minute to increase left ventricular pressure from 102/5 (control) to 158/13 mm Hg (1 minute). The LVEDP dropped slightly from 1–3.5 minutes after the volume load (from 13 to 11 mm Hg), yet peak systolic pressure remained constant as peak positive dP/dt increased. The LVEDP remained constant between 3.5 and 9 minutes, yet peak systolic pressure increased 30 mm Hg, peak positive dP/dt increased nearly 50%, and regional end-diastolic segment lengths decreased, despite a higher end-diastolic pressure. Thus there was a time-dependent increase in contractility after the acute volume load.
The effect of acute volume loading on the ESPLR is shown in another example in Figure 2. After a control pressure-segment length loop, dextran was infused over 40 seconds to increase left ventricular pressure from 145/6 to 167/16 mm Hg. The ESPLR was determined immediately (40 seconds), early (2 minutes), and late (10 minutes) after the volume infusion. The acute volume load produced a progressive time-dependent leftward shift in the ESPLR.

Figure 3 displays the end-systolic (Panel A) and end-diastolic (Panel B) data from another animal. An intravenous infusion of dextran over 80 seconds increased the left ventricular pressure from 97/6 to 140/18 mm Hg. In this example, the ESPLR 80 seconds after the infusion was not different from the control beat (open circle), but there was a progressive time-dependent leftward shift in the ESPLR (Panel A), indicating an increase in contractility. In contrast, there was no time-dependent change in the end-diastolic pressure-length relation (Panel B). In this example, the acute volume load had been performed after treatment with propranolol (see protocol 4 below).

Figure 4 displays the group data for protocol 1. The ESPLR data are presented as mean ± SEM for three time periods; immediately, early, and late (approximately 1, 3, and 10 minutes, respectively) after the acute volume infusion. The regional segment length data are normalized to the end-systolic length 1 minute after the volume load at the low left ventricular end-systolic pressure. For each individual animal, the normalized end-systolic lengths were compared for different time periods at the same three matched end-systolic pressures. However, these three matched end-systolic pressures varied among different animals (explaining the vertical standard error bars). There was a leftward shift in ESPLR between 1 and 3 minutes, which was significant in the anterior segment at all pressures. This shift was significant in the lateral and posterior walls.

### TABLE 1. Normalized Regional End-Systolic Lengths Before and After Volume Loading

<table>
<thead>
<tr>
<th></th>
<th>Anterior</th>
<th>Lateral</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.00±0</td>
<td>1.00±0</td>
<td>1.00±0</td>
</tr>
<tr>
<td>1 minute</td>
<td>1.00±0.03</td>
<td>1.01±0.02</td>
<td>1.01±0.02</td>
</tr>
<tr>
<td>3 minutes</td>
<td>0.97±0.07</td>
<td>0.99±0.02</td>
<td>0.98±0.02</td>
</tr>
<tr>
<td>10 minutes</td>
<td>0.95±0.07*</td>
<td>0.98±0.02†</td>
<td>0.96±0.02†</td>
</tr>
</tbody>
</table>

Regional end-systolic segment lengths, normalized to the control value, obtained at 1, 3, and 10 minutes after acute volume load in seven animals. All end-systolic lengths were determined at the end-systolic pressure of the control period, which was 102±8 mm Hg. There were no significant differences between regions. All values are mean ± SD.

* p<0.05 vs. control.
† p<0.05 vs. 1 minute.
segments at the mid and high, but not at the low end-systolic pressure. At 1 minute, the ESPLR was significantly flatter for the anterior than either the lateral or posterior segments. There was a significant leftward shift in the ESPLR between 1 and 10 minutes in all three regions (anterior, lateral, and posterior walls) at all pressures.

Table 1 shows regional end-systolic lengths normalized to the control value, before and after volume loading. All end-systolic lengths were determined at the matched end-systolic pressure of the control beat. The end-systolic length 1 minute after the acute volume load was not significantly different from the end-systolic length during the control period. However, the end-systolic length was significantly shorter 10 minutes after the acute volume load, as compared with the control period or the 1 minute value. These findings were similar for all three regions.

The time-dependent increase in regional contractility after acute volume loading was accompanied by a time-dependent increase in global indexes of contractility. Figure 5 displays the effects of acute volume loading on the relation between left ventricular peak positive dP/dt and anterior end-diastolic length in the same animal before (Panel A) and after (Panel B) treatment with propranolol. There was a direct relation between peak positive dP/dt and the anterior end-diastolic length. There was a progressive, time-dependent, upward shift in this entire relation after an acute volume load, indicating a time-dependent increase in contractility. Although propranolol reduced peak positive dP/dt, there was a similar upward shift in peak positive dP/dt at any matched end-diastolic length (of approximately 50%) from early to late after the volume load, both before (Panel A) and after (Panel B) propranolol. The data of Figure 5 was taken from the same animal as Figure 3. Thus, data in Figure 5B can be compared directly with the data in Figure 3.

The left ventricular peak positive dP/dt was compared at a matched anterior end-diastolic length for each animal, using a midrange length for all comparisons. Immediately (1 minute) after the acute volume load, the left ventricular peak positive dP/dt was 2,464 ± 534 mm Hg/sec at the midrange anterior end-diastolic length. At a matched length, there was a significant increase in peak positive dP/dt to 2,904 ± 602 mm Hg/sec early (3 minutes) and to 3,919 ± 958 mm Hg/sec late (10 minutes) after the volume load. The left ventricular peak positive dP/dt increased by 19 ± 15% between 1 and 3 minutes, and by 61 ± 33% between 1 and 10 minutes after the volume load when compared at this matched anterior end-diastolic length.

Protocol 2: Acute Release of Venae Cavae Occlusions

In four animals, acute volume loading was produced by partially occluding the venae cavae for 5–10 minutes, then abruptly releasing the occlusion. The regional ESPLR was measured immediately (0.6 ± 0.1 minute), early (3.1 ± 1.3 minutes), and late (7.5 ± 2.5 minutes) after release of the partial venae cavae occlusions. The results are shown in Table 2. As with protocol 1, there was a progressive time-dependent leftward shift in the ESPLR in all three regions. The end-systolic lengths early and late after the acute volume load were significantly shorter than the end-systolic length immediately after the volume load.
Protocol 4: Acute Volume Load After β-Blockade

Acute volume loading increased the LVEDP from 7.2 ± 1.6 to 19.4 ± 5.2 mm Hg and peak left ventricular pressure from 105.3 ± 14.2 to 129.8 ± 6.6 mm Hg. After acute volume loading, the end-diastolic lengths increased 11.2 ± 4.3% in the anterior segment, 7.4 ± 1.5% in the lateral segment, and 9.1 ± 3.8% in the posterior segment.

The typical responses to an acute volume load after β-blockade are shown in Figures 3 and 5B, which were discussed above. With protocol 1, an acute volume load after β-blockade produced a progressive, time-dependent leftward shift in the ESPLR and an upward shift in the left ventricular peak positive dP/dt.

The group data for protocol 4 are shown in Table 3. The regional ESPLR was measured immediately (1.0 ± 0.2 minute), early (4.8 ± 1.8 minutes), and late (9.3 ± 2.9 minutes) after initiation of acute volume loading. There was a significant leftward shift in the ESPLR (decreased end-systolic length at a matched end-systolic pressure) in the anterior segment between 1 and 5 minutes after the acute volume load. The ESPLR was shifted significantly to the left in all three regions between 1 and 9 minutes after the volume load.

Discussion

The major finding of this study is that acute increases in load produce time-dependent increases in contractility in the intact, ejecting left ventricle. Conversely, acute decreases in load produce time-dependent decreases in contractility. The time course for these alterations in contractility is similar to the time course for length-dependent activation effects, which have been observed after acute length changes in isolated cardiac muscles. 1, 3-9, 11-13-15

The loads applied in this study were within a physiological range. Left ventricular end-diastolic pressure increased from 5 to 13 mm Hg and regional end-diastolic segment lengths increased by 8-14%. If the heart is modeled as a sphere, a 10% increase in end-diastolic segment length would correspond.
Acute volume loads produced a time-dependent increase in global contractility. Left ventricular peak positive dP/dt increased by 61% between 1 and 10 minutes after volume loading, when compared with a matched anterior end-diastolic length.

Load-induced, time-dependent changes in contractility are an intrinsic property of the intact left ventricle and are not due to neural or humoral factors. Although acute volume loads could stimulate cardiac and extracardiac mechanoreceptors and baroreceptors, the cardiac vagal and sympathetic reflex pathways and pathways of the carotid and aortic arch receptors were interrupted by bilateral vagotomy, stellate ganglion denervation, and carotid sinus denervation. In addition, the heart was paced at a constant rate after denervation. A load-induced increase in circulating catecholamines was not important since time-dependent increases in contractility also occurred in animals treated with propranolol (protocol 4). It is possible that an increase in arterial pressure after volume loads may cause withdrawal of sympathetic tone in the peripheral circulation, which alters arterial impedance. Thus, a comparison of end-systolic lengths at matched end-systolic pressures may not reflect matched afterload conditions. However, arterial impedance does not influence the slope of the end-systolic pressure-volume relation, and minimally affects the volume intercept. In addition, wall stress probably provides a better index to ventricular afterload than arterial impedance. Therefore, reflex vasodilation of peripheral arterioles and alterations in arterial impedance do not explain time-dependent changes in contractility after acute volume loads.

The rapid infusion of large volumes of dextran may have produced an experimental artifact by producing an acute hemodilution and initial myocardial depression. However, the time-dependent leftward shift in ESPLR after acute volume loads represented a true increase in ventricular contractility, and not merely a recovery of contractility after an initial myocardial depression. The end-systolic lengths immediately after the acute volume load were not significantly different from the control value (at the same matched end-systolic pressure), whereas late after the loads, there was a significant decrease in end-systolic lengths as compared with the control values. Furthermore, time-dependent increases in contractility also occurred when acute volume loads were produced without hemodilution (by abrupt release of a partial venae cavae occlusion, protocol 2). An experimental artifact such as a transient decrease in myocardial contractility also does not explain the rightward shift in ESPLR after a transient mild decrease in load (protocol 3) since coronary perfusion pressures were maintained well within the autoregulatory range.

Acute volume loads may produce two other effects that should be considered, a time-dependent change in viscoelasticity and the Anrep effect. A time-dependent rightward shift in the end-diastolic pressure-length or pressure-chord relation occurs in the intact ventricle after very large loads (e.g., an increase in left ventricular end-diastolic pressure to
Figure 7. Group data for five animals from protocol 3 are shown. Format is similar to Figure 4, where end-systolic pressure-length relations (ESPLR) are shown for all three regions (anterior, lateral, and posterior), with the same three matched end-systolic pressures. Data are normalized to end-systolic values at lowest end-systolic pressure during control period. Each data point represents group mean value with standard error bars. After a transient decrease in load, there was a significant rightward shift in ESPLR for all three regions. LVESP, left ventricular end-systolic pressure.

≥25 mm Hg or an increase in peak systolic pressure to ≥200 mm Hg) but not with modest increases in pressure. In the current study, acute volume loads did not alter the end-diastolic pressure-length relation. It is not surprising that viscoelastic effects did not occur, since the increase in left ventricular pressures was modest (end-diastolic pressure increased from 5 to 13 mm Hg and peak systolic pressure increased from 113 to 147 mm Hg). If viscoelastic effects had occurred, the rightward shift of the entire pressure-length loop may tend to mask any leftward shift in ESPLR. Interestingly, LeWinter et al20 found a greater rightward shift in the end-diastolic than end-systolic pressure-length relations after large volume and pressure loads. Diameter and segment shortening increased after the development of viscoelastic effects (when compared at matched end-diastolic and peak systolic pressures). In retrospect, these results could be explained by a rightward shift in the entire pressure-length loop due to viscoelastic effects, which partially masked a leftward shift in the ESPLR due to a load-induced, time-dependent increase in contractility.

The Anrep effect is an apparent increase in inotropic state after abrupt increases in systolic pressure. The increase in contractility with acute volume loads in the present study may have been caused by the increase in systolic loads (Anrep effect), rather than the increase in end-diastolic volume and segment lengths (length-dependent activation effects). However, there are several lines of evidence against this mechanism. First, large increases in peak systolic pressure (typically 60–150 mm Hg) applied abruptly (over a few seconds) are required to demonstrate the Anrep effect. In the present study, peak systolic pressures increased only 30 mm Hg, and this occurred over several minutes after an initial increase in end-diastolic pressure and length. Second, the increase in contractility with the Anrep effect occurs primarily over the first 60 seconds after an acute systolic load, with most of the effect fully expressed by 3 minutes. In the present study and in studies of length-dependent activation, contractility increased over a 10–15 minute period. Third, and most importantly, the Anrep effect may not represent a true increase in contractility, but rather a recovery in function after a transient subendocardial ischemia induced by the acute volume load. In the present study, there was no initial decrease in contractility (rightward shift in the ESPLR from control) after acute volume loading and the leftward shift in ESPLR from control indicated a true increase in contractility.

A few comments should be made regarding the method used to assess contractility in this study. Several investigators have used the ESPLR to
describe regional contractility \(^{25-28}\) and have described this relation as linear. \(^{26-28}\) In the current study, the ESPLR was not linear, but best fitted to a quadratic equation. This is not entirely surprising since the end-systolic pressure-volume relation is linear and segment length is not linearly related to volume. The quadratic equations provided data over a wide and continuous range of end-systolic pressures. The quadratic equations were used only to interpolate data between actual data points. Data were not extrapolated to end-systolic pressures beyond the range of actual measurements.

Because the ESPLR was not linear, it was difficult to compare either the slope or intercept of the ESPLR. Accordingly, the ESPLR data were used in a more restrictive sense. End-systolic lengths were compared at three matched end-systolic pressures, with the pressures chosen to represent the entire range over which actual data had been obtained. A decrease in end-systolic length at a matched end-systolic pressure indicated an increase in contractility. Conversely, an increase in end-systolic length at a matched pressure indicated a decrease in contractility. This method circumvented the need to define the precise shape of the ESPLR and obviated the need to attach any significance to changes in slope (or in coefficients of a polynomial equation) or intercept. Finally, to avoid problems with hysteresis, all ESPLR data were obtained during a progressive decrease in end-systolic pressure and time comparisons were made over the same range of pressures. These precautions were necessary since the shape of the ESPLR depends on the level of end-systolic pressure and differs if measured with increasing as compared with decreasing end-systolic pressures. \(^{25,29}\)

The present study indicates that acute volume loads in the intact left ventricle produce a time-dependent increase in contractility, analogous to the length-dependent activation observed in isolated cardiac muscles after abrupt lengthening. \(^{1,2,9-11,13-15}\) Although length-dependent activation effects have been established for isolated cardiac muscle preparations, \(^{1-12}\) evidence of this phenomenon in the intact heart has been limited. Suga and Sagawa \(^{10}\) qualitatively noted that a step increase in end-diastolic volume in isolated, supported hearts produced an instantaneous increase in peak ventricular pressures, followed by a slower further increase in peak pressure until steady-state was reached. Tucci et al. \(^{31}\) found a time-dependent increase in peak developed pressure in isolated left ventricles after abrupt volume expansion. However, the physiological significance of this study is uncertain, since the peak developed pressure of their isolated left ventricular preparation was only 14 mm Hg during the control period and 50 mm Hg initially after acute volume expansion. \(^{31}\) The time-dependent increase in developed pressure after volume expansion may have represented a time-dependent recovery from myocardial depression. Recently, Burkoff et al. \(^{32}\) found that the shape of the end-systolic pressure-volume relation in isolated, supported hearts, was influenced by the degree of inotropic stimulation. Thus, ventricular contractility may depend in part on the volume, analogous to isolated cardiac muscle studies, which demonstrate that the shape of the length-tension relation depends on the degree of inotropic stimulation. \(^{1-8}\)

The precise mechanisms of length-dependent activation are not completely understood, but likely involve length-dependent alterations in excitation-contraction coupling. \(^{33,34}\) Length-dependent alterations in the action potential duration occur and may influence the amount of calcium release and peak tension development. \(^{11}\) However, the action potential duration increases within 3–5 minutes, whereas the peak tension increases over 10–12

### Table 3. Normalized Regional End-Systolic Pressure-Length Measurements With Acute Volume Loading After Propranolol

<table>
<thead>
<tr>
<th>End-systolic pressure (mm Hg)</th>
<th>Low</th>
<th>Mid</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior end-systolic lengths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 minute</td>
<td>0.97±0.02*</td>
<td>0.99±0.03*</td>
<td>0.97±0.02*</td>
</tr>
<tr>
<td>5 minutes</td>
<td>0.95±0.04*</td>
<td>0.99±0.03*</td>
<td>0.93±0.02*</td>
</tr>
<tr>
<td>9 minutes</td>
<td>1.00±0.00*</td>
<td>1.00±0.00*</td>
<td>1.00±0.00*</td>
</tr>
<tr>
<td>Lateral end-systolic lengths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 minute</td>
<td>0.98±0.02*</td>
<td>0.99±0.03*</td>
<td>0.97±0.02*</td>
</tr>
<tr>
<td>5 minutes</td>
<td>0.99±0.01</td>
<td>0.99±0.02</td>
<td>0.98±0.01</td>
</tr>
<tr>
<td>9 minutes</td>
<td>0.98±0.02*</td>
<td>1.00±0.00*</td>
<td>1.00±0.00*</td>
</tr>
<tr>
<td>Posterior end-systolic lengths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 minute</td>
<td>1.00±0.00</td>
<td>1.03±0.01</td>
<td>1.04±0.01</td>
</tr>
<tr>
<td>5 minutes</td>
<td>0.97±0.02*</td>
<td>0.99±0.01</td>
<td>0.97±0.02*</td>
</tr>
<tr>
<td>9 minutes</td>
<td>0.98±0.01</td>
<td>0.99±0.01</td>
<td>0.97±0.01</td>
</tr>
</tbody>
</table>

Regional end-systolic lengths in four animals treated with propranolol at 1, 5, and 9 minutes after an acute volume load (protocol 4). All regional lengths were normalized to the 1 minute end-systolic length at the low end-systolic pressure. At 1 minute, the increase in end-systolic length with increasing end-systolic pressures was significantly greater for the anterior than lateral or posterior segments. Values are mean ± SD. *p<0.05 vs. 1 minute at the same end-systolic pressure.
minutes after abrupt length changes. The magnitude of the change in action potential duration is also insufficient to fully explain the tension changes with length-dependent activation. Calcium-triggered calcium release from the sarcoplasmic reticulum is greater at longer sarcomere lengths than at shorter lengths, indicating a length-dependence relation in the effectiveness of calcium release. Transsarcolemmal calcium influx also is greater at longer muscle lengths than at shorter muscle lengths. The role of these calcium fluxes is unclear. Some studies have found attenuation of length-dependent activation effects with verapamil. However, others have used verapamil and manganese to inhibit transsarcolemmal calcium fluxes and did not observe any alteration in the slow changes in tension after abrupt changes in muscle length.

The sensitivity of cardiac muscles to calcium is length-dependent. This could be due to an increased affinity of troponin for calcium and/or an increased effect of calcium bound to troponin at longer muscle lengths. The calcium transient, using aequorin to estimate intracellular free calcium, is also length-dependent. After an abrupt increase in muscle length, the calcium transient is initially unchanged, despite an initial increase in peak tension. The calcium transient then increases progressively, with a time course that parallels the slow increase in peak tension. The calcium transient represents a balance between processes that increase intracellular calcium (e.g., entry of calcium across surface membranes and calcium release from the sarcoplasmic reticulum) and processes that reduce intracellular calcium (e.g., calcium binding to troponin, reuptake of calcium by the sarcoplasmic reticulum, and active pumping of calcium out of the cell). The lack of an initial change in the calcium transient may indicate that calcium release and calcium binding are initially unchanged after the change in muscle length. However, in view of the previously cited studies, it is also possible that an increase in calcium release occurs immediately with increased muscle length, but due to the increase in calcium binding to troponin, there is no net change in the calcium transient. The subsequent parallel increase in the calcium transient and in peak tension suggests that alterations in calcium kinetics are associated with length-dependent activation effects, in particular with the slow changes in tension after abrupt changes in muscle length. However, it is difficult to establish a cause and effect relation. Furthermore, it is difficult to establish the relative importance of changes in calcium release, calcium binding to troponin, and calcium reuptake with regard to the changes in calcium transient after acute muscle length changes.

In summary, our study demonstrates that in the intact, ejecting ventricle under physiological conditions, an acute increase in load produces a significant time-dependent increase in regional and global contractility. Conversely, an acute decrease in load produces a decrease in contractility. These changes occur independently of the method of acute volume loading (i.e., with rapid volume infusions or with acute release of a partial venal caval occlusion) and independently of reflex neural and humoral changes. The time course of these changes in contractility are consistent with the phenomenon of length-dependent activation, which has been described in isolated cardiac muscles. Therefore, any intervention that alters ventricular volume will induce a concomitant time-dependent alteration in ventricular contractility. These time-dependent changes must be taken into consideration when evaluating left ventricular function after load changes.

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