Hoffman JIE (1978) Determinants and prediction of transmural myocardial
perfusion. Circulation 58: 381-391
Kirk ES, Hong CR (1964) An experimental and theoretical
analysis of myocardial tissue pressure. Am J Physiol 207: 361-367
Klassen GA, L'Abbate A, Sestier F, Mildenhanger RR (1977)
The determinants of regional myocardial blood flow. In Ath-
erosclerosis, edited by GW Manning; MD Haust. New York,
Plenum Publishing Corporation, pp 697-699
L'Abbate A, Mildenhanger RR, Christie L, McGregor M, Klassen
GA (1974) The role of coronary perfusion pressure and left
ventricular intracavitary pressure as determinants of coronary
blood flow distribution (abstr.) Fed Proc 33: 414
L'Abbate A, Marzilli M, Ballestra AM, Camici P (1978) Myocar-
dial contraction: An additional determinant of transmural flow
distribution. In Primary and Secondary Angina Pectoris, ed-
ted by A Maseri, GA Klassen, M Lesch. New York, Grune &
Stratton, pp 21-28
Ross J Jr, Franklin D (1976) Analysis of regional myocardial
function, dimensions, and wall thickness in characterization of
myocardial ischemia and infarction. Circulation 53 (suppl I):
88-92
Sahbion DC Jr, Gregg DE (1957) Effect of cardiac contraction
on coronary blood flow. Circulation 15: 14-20
Sasayama S, Franklin D, Ross J Jr, Kemper WS, McKown D
(1976) Dynamic changes in left ventricular wall thickness and
their use in analyzing cardiac function in the conscious dog.
Am J Cardiol 38: 870-879
Synder R, Downey JM, Kirk ES (1975) The active and passive
components of extravascular coronary resistance. Cardiovasc
Res 9: 161-166
Theroux P, Ross J Jr, Franklin D, Kemper WS, Sasayama S
(1976) Regional myocardial function in the conscious dog
during acute coronary occlusion and responses to morphine,
propranolol, nitroglycerin, and lidocaine. Circulation 53: 302-
314
Vatner SF, Millard RW, Patrick TA, Heyndrickx GR (1976)
Effects of isoproterenol on regional myocardial function, elec-
trogram, and blood flow in conscious dogs with myocardial
ischemia. J Clin Invest 57: 1261-1271

Time-Dependent Shifts of the Left Ventricular Diastolic Filling Relationship in Conscious Dogs

MARTIN M. LEWINTER, ROBERT ENGLER, AND RICHARD S. PAVELEC

SUMMARY The viscous properties, creep and stress relaxation, have been demonstrated in isolated cardiac muscle preparations but have not been shown to occur in intact, conscious animals. In the present study, time-dependent shifts of the left ventricular (LV) diastolic pressure-dimension and stress-strain relationships consistent with creep and stress relaxation were observed in eight conscious dogs previously instrumented with LV micromanometers and ultrasonic dimension gauges. These changes were seen during recovery from major elevations of systolic and diastolic pressure produced by infusion of saline and phenylephrine. Thus, during recovery, at matched end-diastolic pressures (EDP) between 17 and 21 mm Hg, end-diastolic segment length was increased by an average of 1.6% \( (P < 0.001) \) and minor axis chord length by 2.4% \( (P < 0.01) \). These increases in LV dimensions were accompanied by reductions in diastolic wall thickness. When increases in EDP were limited by caval occlusion, such shifts no longer were apparent. In addition, "rapid" elevation of LV pressures was associated with steeper filling relationships than with "slow" elevation of LV pressures. In beats matched for EDP, systolic pressure, and heart rate, shifts in diastolic LV dimensions during recovery were associated also with increases in stroke volume and percent shortening. In two additional dogs, the presence of an increased end-diastolic volume during recovery was validated by angiographic techniques. We conclude that time-dependent shifts of the LV diastolic filling relationship can be demonstrated after major increases in systolic and diastolic pressure and can significantly influence both the shape of the filling relationship and systolic performance. Circ Res 46:641-653, 1979

TIME-DEPENDENT alterations of the passive length-tension relationship of isolated cardiac muscle have been recognized for many years (Levin and Wyman, 1927; Abbott and Lowry, 1957; Sonnenblick et al., 1966; Little and Wead, 1971; Pinto and Fung, 1973; Pinto and Patitucci, 1977). These have been ascribed to the occurrence of the viscoelastic phenomena, creep and stress relaxation. As a result
of these phenomena, the length-tension relationship exhibits hysteresis during cyclic loading (passive stretch, followed by recovery), such that muscle length is longer for a given tension as the muscle returns to its original length (Levin and Wyman, 1927; Abbott and Lowry, 1957; Little and Wead, 1971; Pinto and Fung, 1973; Pinto and Patitucci, 1977). In addition to passive stretch, increases in active force development also appear to produce time-dependent shifts of the passive length-tension relationship (Sonnenblick et al., 1966).

The occurrence of analogous, time-dependent alterations of the left ventricular diastolic pressure-volume relationship in the intact heart would be of considerable physiological interest with respect to both the assessment of diastolic compliance and, as suggested by Sonnenblick et al. (1966) and Pinto and Patitucci (1977), the possible relationship of these properties to active shortening. Although a number of studies using isolated, supported cardiac preparations (Sonnenblick et al., 1963; Leach and Alexander, 1965; Gilmore et al., 1966; Clancy et al., 1968; Monroe et al., 1968; Janicki and Weber, 1977) have demonstrated time-dependent changes in diastolic pressure-volume relationships, prior attempts to document similar effects in intact, conscious animals have been unsuccessful (Noble et al., 1969; Rankin et al., 1977). We hypothesized that the production of larger changes in left ventricular pressures than employed previously in conscious dogs (Noble et al., 1969; Rankin et al., 1977) might be required to observe time-dependent shifts of the left ventricular diastolic pressure-dimension or pressure-volume relationship. Accordingly, we undertook the present study in previously instrumented conscious dogs in which we sought to determine whether such shifts would be observed after large increases in both left ventricular systolic and diastolic pressure. In addition, we attempted to validate our results with angiographic techniques to determine whether time-dependent shifts were associated with appropriate changes in left ventricular volume. Finally, by selecting hemodynamically matched conditions, we related time-dependent diastolic pressure-dimension shifts to changes in shortening.

**Methods**

**Surgical Technique and Instrumentation**

Eight mongrel dogs, weighing between 24 and 31 kg, were anesthetized with pentobarbital (25 mg/kg, iv) and subjected to a left 5th interspace thoracotomy. The pericardium was incised widely and the heart suspended in a pericardial cradle. Cardiac instrumentation then was carried out as follows (Fig. 1). A fluid-filled length of polyethylene tubing (1.1 mm i.d) and a Konigsberg P-20 micromanometer transducer were inserted side-by-side into the left ventricular cavity through apical stab wounds and secured with purse-string sutures. In six dogs, three ultrasonic dimension gauges (Stegall et al., 1967; Horwitz et al., 1968) then were implanted. Care was taken to position each of them at a site halfway between the atrioventricular valve ring and the left ventricular apex. One gauge measured movement of an anteroposterior endocardial chord across the left ventricular cavity, which approximated a minor axis diameter; one measured a midwall left ventricular anterior segment between 1.0 and 1.5 cm in length, oriented perpendicular to the long axis; and the third measured left ventricular free wall thickness. In one of the six dogs, the chord gauge signal subsequently was technically inadequate, and in two, the wall thickness signal was inadequate. Both the chord and wall thickness gauges later were examined at autopsy to ensure that they did not overlie papillary muscle. In two other dogs, only segment-length gauges were implanted. In these two, cuffed electromagnetic flow probes were implanted about the aortic root. Pacing electrodes then were secured to the left atrial appendages of all dogs and, through a small incision in the neck, a length of polyvinyl tubing was inserted into the superior vena cava from an internal jugular vein. The latter tubing subsequently was used for chronic intravenous access. In six dogs, an inflatable occlusion cuff was positioned about the inferior vena cava. After instrumentation had been completed, the pericardium was left opened widely. All tubing and cables were exteriorized to the posterior surface of the dog's neck, and the chest was closed. In four dogs, lengths of polyethylene tubing with several sideholes near the tip were left in the pleural space and filled with normal saline for subsequent measurement of pleural pressure. The tip of the tubing was positioned posteriorly, as near the spine as possible.

Finally, two dogs were prepared for angiographic studies as follows. The chest was opened and the
pericardium incised as previously described. Pacing electrodes were sutured to the left atrial appendage and catheters left in the pleural space. No further cardiac instrumentation was performed, and the chest was closed with the pericardium left open.

Experimental Protocol

All dogs (except the two used for angiographic studies) were allowed at least 10 days to recover from surgery before studies were begun. All studies were performed in the conscious, unaedated state with the dog lying on its right side. The fluid-filled left ventricular tubing was connected to a Statham P23Db pressure transducer with zero reference level at the dorsal spine. All left ventricular pressures were determined from the micromanometer after it had been matched to the fluid-filled pressure tracing. The micromanometer was checked continuously for drift throughout each study. The electronic first derivative of the micromanometer pressure was obtained using a Hewlett-Packard model 350-12 R-C differentiator, which was calibrated later with a signal of known slope. The ultrasonic dimension gauges were connected to a modified version (Schuessler Assoc.) of the previously described sonomicrometer (Stegall et al., 1967; Horrowitz et al., 1968) and calibrated with a signal of known delay. The pacing electrodes were connected to a constant current Nuclear Chicago model 7150 stimulator. The pleural catheters were flushed with small amounts of normal saline and connected to a second Statham P23Db pressure transducer, also referenced to the dorsal spine, for measurement of pleural pressure. In the two dogs with flow probes, aortic flow was measured with a Biotronex model BL613 sine wave flowmeter. Stroke volume was determined by electronic integration of the flow signal. Techniques for calibration of the flow signal are described below. All data were recorded on a Hewlett-Packard model 7868A or a Brush-Clevite model 2000 multichannel polygraph and on FM magnetic tape.

In the first experimental protocol, which was performed in all dogs, resting recordings of a suitable limb lead electrocardiogram, left ventricular pressures and dP/dt, ultrasonic dimension gauge signals, intrapleural pressure, and aortic flow and its integral (when available) were obtained first. Atrial pacing then was initiated at rates between 125 and 148 beats/min. Atropine sulfate (0.3-0.7 mg) was given to establish one-to-one atrioventricular conduction, and recordings were repeated. In all studies subsequently reported, it was possible to keep heart rate within a 5 beat/min range throughout each study and to use identical heart rates for all studies in each dog. In the two dogs with flow probes, zero flow was assumed to occur during ventricular diastole. The flow signals were calibrated during stable atrial pacing by averaging duplicate indocyanin green dye curves, obtained by injection into the superior vena caval catheter and withdrawal from the left ventricular tubing. Left ventricular systolic and diastolic pressures then were increased by first infusing 0.9% normal saline (250-800 ml) until an end-diastolic pressure of approximately 15 mm Hg was reached. This was followed immediately by an infusion of phenylephrine hydrochloride (19-57 µg/min), using a Harvard infusion pump. The end point for the latter infusion was an end-diastolic pressure of at least 25 mm Hg, which was almost always associated with peak left ventricular systolic pressures in excess of 200 mm Hg. Saline-phenylephrine infusion rates were individualized to raise left ventricular end-diastolic pressure slowly to the desired level over a 14- to 22-minute period of time. To determine whether time-dependent shifts of the diastolic pressure-dimension or stress-strain relationship would be detectable during recovery from saline-phenylephrine infusion, recordings were made continuously as left ventricular pressures were raised and then fell during the recovery phase until end-diastolic pressure had returned to a value no more than 5 mm Hg greater than that present when atrial pacing first was established. This protocol was performed at least once without ß-adrenergic blockade and at least twice with ß-adrenergic blockade (propranolol, 0.5 mg/kg, iv) in each dog, except for one of the dogs with flow probes in which one study with and one study without propranolol were performed. Propranolol was administered immediately after the initial resting tracings were obtained. The dose used has been shown to provide pharmacological levels of ß blockade without producing detectable direct nonspecific myocardial depression (Fitzgerald et al., 1972). Aortic flow was measured only during ß-adrenergic blockade studies using this first protocol, although data from these two dogs, in studies performed without flow measurements, were combined with that obtained from the first six dogs.

In a second protocol performed in six dogs, phenylephrine alone was infused to increase left ventricular pressures rapidly over a 3- to 6-minute period of time, with the end point for the phenylephrine infusion, again, being an end-diastolic pressure of 25 mm Hg. The latter studies all were performed after ß-adrenergic blockade and within 2 days of one of the ß-adrenergic blockade studies using the first protocol. Atropine sulfate and atrial pacing were employed, as in the first protocol, to provide an identical heart rate for both studies.

In a third protocol performed in six dogs (all with ß-adrenergic blockade and atrial pacing), the inferior vena caval cuff was inflated after pacing had been established to reduce left ventricular end-diastolic pressure to a value below 2 mm Hg. Phenylephrine then was infused to increase left ventricular systolic pressure to a value as close as possible to that obtained in the other protocols, but increases in left ventricular end-diastolic pressure were limited to no more than 15 mm Hg by further cuff
inflations as necessary. In this protocol, phenylephrine was infused for 12-18 minutes.

The two dogs prepared for angiographic studies were studied 3 and 4 days after thoracotomy. These dogs were anesthetized, in the supine position, with morphine sulfate (3 mg/kg, iv) and chloralose (90 mg/kg, iv), intubated and ventilated with a Harvard respirator. A 7F pigtail catheter was passed retrograde into the left ventricle from a carotid artery and a 7F Millar micromanometer tip catheter passed into the left ventricle from a femoral artery. The Millar catheter pressure signal was matched to the fluid-filled left ventricular pressure obtained from the pigtail catheter, the latter being connected to a Statham P23Db pressure transducer with zero reference level at the midcitra. The pleural tubing also was connected to a Statham P23Db transducer. Atrial pacing with one-to-one atrioventricular conduction then was established at rates of 124 and 136 beats/min as previously described. At this point, 0.9% normal saline was infused to increase left ventricular end-diastolic pressure to 15-20 mm Hg over a period of 10-15 minutes. When this level of end-diastolic pressure had been reached, anterior and lateral biplane left ventricular angiography was performed at 60 frames/sec by injecting 40-60 ml of radiographic contrast medium at 30 ml/sec through the pigtail catheter. Anterior and lateral plane cine frame markers and left ventricular and pleural pressures were recorded at a paper speed of 200 mm/sec. As soon as angiography was completed, phenylephrine infusion (38 μg/min) was initiated to raise left ventricular end-diastolic pressure to at least 30 mm Hg. When this level of end-diastolic pressure had been reached, the phenylephrine infusion was terminated. Angiography then was repeated when left ventricular end-diastolic pressure had declined to a value similar to that present during the first angiogram. In both instances, angiography was performed with ventilation suspended at end-expiration.

Data Analysis

In the eight conscious dogs, all variables were averaged over 10- to 20-beat periods (at least two respiratory cycles) as left ventricular diastolic pressure was raised and lowered during each of the three previously described protocols. Left ventricular pressures were taken from the micromanometer tracing. End-diastolic pressure was taken at the inflection point of the pressure signal occurring after the a wave of an expanded-scale tracing. If there was no clear-cut inflection point, end-diastolic pressure was taken at the peak of the R wave of the QRS complex. In dogs with pleural catheters, pleural pressure at end-diastole was subtracted from the micromanometer end-diastolic pressure. End-diastolic chord and segment length and wall thickness were measured simultaneously with end-diastolic pressure. End-systolic chord and segment lengths were taken as the nadir of the shortening signals occurring before or simultaneous with peak (-) dP/dt. Percent shortening was calculated as (end-diastolic length - end-systolic length) X 100/ end-diastolic length. Diastolic pressure-dimension relationships during slow filling were determined by measuring pressure and dimension immediately before the a wave of the left ventricular tracing and correcting for intrapleural pressure when available. If no discrete a-wave was present, computer-averaged beats (see below) were used to select pressure and dimension points when the velocity of chord or segment lengthening was zero or as close to zero as possible.

To determine whether time-dependent shifts of the diastolic pressure-dimension relationship were present, all consecutive end-diastolic or slow-filling pressure-dimension points, obtained as diastolic pressure rose and fell, were plotted on graph paper and joined by lines. A shift of the diastolic pressure-dimension relationship during the recovery phase was defined as a lack of intersection of the lines joining saline-phenylephrine points and the lines joining recovery phase points over a range of at least 10 mm Hg of diastolic pressure. In addition, we required that at least five diastolic pressure-dimension data points be available during both saline-phenylephrine infusion and recovery over the range of diastolic pressure at which a shift was present.

Stress-strain calculations were made as follows. Left ventricular wall stress was calculated for a thick-walled ellipsoidal model using the following formula (Burns et al., 1971): Stress = P Ri [(1 - 2Ri^2/L^2)]/h, where P = left ventricular pressure, Ri = internal minor axis radius, L = long axis, and h = measured wall thickness. Since L was not measured directly, it was assumed that Ri/L remained constant as left ventricular pressures were raised and lowered, and an arbitrary value of 0.29 was assigned to this ratio (Dodge et al., 1960). Although Ri/L may well have changed as pressures were varied, the results of the angiographic studies, to be described later, established that at matched end-diastolic pressure, Ri/L was unchanged as pressures were raised and lowered. Therefore, from the standpoint of comparing strain at equivalent stress levels as pressures were raised and lowered, this assumption was felt to be valid. The measured minor axis chord was divided by two to provide Ri. The minor axis chord was normalized using a natural strain definition, ε = lnL/lo, with lo assumed to be the smallest chord measured during a given study. The latter assumption was felt to be valid for the purposes of this study, because we were interested in relative changes in strain at equivalent stress levels as pressures were raised and lowered, rather than absolute values of strain.

To plot left ventricular pressure-chord and pressure-segment lengths, the data recorded on FM magnetic tape were replayed on an oscilloscope and
converted from analog to digital format at 3-msec sampling intervals on an EAI 590 hybrid computer. Data for 10-20 beats then were used to produce an average beat, and the average beat was processed on a Burroughs 6700 digital computer, which printed out pressure and length values for each 3-msec sampling interval over the entire cardiac cycle.

For angiography studies, left ventricular end-diastolic pressure was determined from the micro-manometer and pleural pressure tracings as described previously. End-diastolic angiographic frames were selected by using the anterior-posterior and lateral cineangiographic markers closest to the time of end-diastolic pressure. These frames then were used to calculate end-diastolic volume by the area-length method (Dodge et al., 1960). The paired t-test was used for statistical analysis.

Results

Demonstration of a Time-Dependent Rightward Shift of the Left Ventricular End-Diastolic Pressure-Dimension and Stress-Strain Relationship during Recovery from Saline-Phenylephrine Infusion

An example of tracings obtained at matched levels of end-diastolic pressure during saline-phenylephrine infusion and during recovery, using the first protocol, is shown in Figure 2, and end-diastolic pressure-dimension and wall thickness relationships during an entire study are shown in Figure 3. Note that a rightward shift (i.e., a larger dimension at a given end-diastolic pressure) of the pressure-chord and segment length relationship is evident during recovery from saline-phenylephrine. Correspondingly, end-diastolic wall thickness was reduced when this shift was evident. Similar results were obtained for slow-filling pressure-dimension relationships. In Figure 4, the study presented in Figure 3 is replotted as end-diastolic stress-strain. Once again, a rightward shift was apparent, and results were similar for slow-filling stress-strain relationships. Using this protocol, in which left ventricular pressures were raised slowly, we found rightward shifts were present in a total of 17 of 18 studies carried out in the presence of β-adrenergic blockade. In the dogs in which a shift was not detected in one study, it was present in two other β-adrenergic blockade studies. In a total of 14 studies without β-adrenergic blockade, rightward shifts were present in 12. In two dogs, shifts were not detected on one occasion each. Both of the dogs had at least one other nonblockade study that demonstrated a shift. Of the total of 29 studies in which a rightward shift was present, in seven studies the shift of the diastolic pressure-dimension relationship no longer was apparent when end-diastolic pressure had declined to a value of 11-15 mm Hg and in 17 studies when it had declined to 6-10 mm Hg. In the remaining studies, a shift was present for the entire duration of observation (i.e., until end-diastolic pressure had declined to within 5 mm Hg of the starting value). Of the 24 studies in which measurements were made until shifts no longer were apparent, the time during which a shift was detectable was never longer than 20 minutes. In the remaining five studies, in which a shift was still present when measurements were discontinued because the end-diastolic pressure had declined to a value within 5 mm Hg of the starting end-diastolic pressure, the duration of measurement during recovery from saline-phenylephrine infusion was 25 minutes in one instance and no more than 20 minutes in the other four instances. To provide a quan-

**Figure 2** Dog no. 4, 2/28/78. Representative tracings demonstrating a rightward shift of the diastolic pressure-dimension relationship in single beats matched for left ventricular end-diastolic (LVEDP) minus pleural pressure during saline-phenylephrine infusion (left) and during recovery (right). LVEDP – pleural pressure (mm Hg), 12.5 and 13.0; end-diastole (ED) chord length (mm), 51.0 and 52.9; ED segment length (mm) 9.3 and 9.5; and ED wall thickness (mm), 7.3 and 7.2, respectively. Vertical lines have been drawn at ED for these beats. Horizontal lines indicate ED for dimension signals.
titative estimate of the magnitude of shift of the diastolic pressure-segment, chord and wall thickness relationship, we compared measurements at diastolic pressures differing by no more than 1 mm Hg as this variable was raised and lowered. These results are presented in Table 1. For this analysis, only β-adrenergic blockade studies were used. We selected beats with end-diastolic pressures between 17 and 21 mm Hg (one set of matched beats per study) because rightward shifts were present uniformly over this range of end-diastolic pressure. When more than one study with matched beats in this range of end-diastolic pressure was available for a given dog, the results were averaged. Under these conditions (see Table 1), mean end-diastolic segment length increased from 11.54 ± 2.78 (SD) to 11.73 ± 2.81 mm during recovery from saline-phenylephrine (P < 0.001), an average increase of 1.6%. End-diastolic chord length increased by an average of 2.4%, from 42.1 ± 5.7 to 43.1 ± 5.9 mm (P < 0.01). End-diastolic wall thickness was decreased uniformly by an average of 1.0%, from 11.08 ± 2.74 to 10.97 ± 2.71 mm. The latter measurements were not subjected to statistical analysis because of the small number of dogs. Slow-filling pressure-dimension relationships also are summarized in Table 1, with results similar to those at end-diastole.

In the four dogs in which wall thickness was measured directly, we also compared strain at equivalent levels of diastolic wall stress. For this purpose, beats also were selected between end-diastolic pressures of 17-21 mm Hg as this variable was raised and lowered. Beats within this range of end-diastolic pressure then were matched as closely as possible for wall stress using data from β blockade studies only. As previously, when more than one set of beats were available for a given dog, the results were averaged. By this technique strain always was larger at matched stress when the pressure-dimension relationship was shifted during the recovery phase. Thus, for end-diastole, at an average wall stress of 26.1 g/cm² (range, 22.9-29.7), strain averaged 0.134 (range, 0.123-0.143) during saline-phenylephrine infusion. During recovery, at an average end-diastolic wall stress of 26.2 g/cm² (range, 23.7-29.0), strain averaged 0.159 (range, 0.149-0.173). Results were similar for slow-filling stress-strain relationships. Thus, at an average wall stress of 22.6 g/cm² (range, 20.0-26.5), strain averaged 0.131 (range, 0.121-0.140) during saline-phenye

**Figure 3** Dog no. 5, 3/24/78. End-diastolic pressure-chord, segment and wall thickness relationships throughout an entire study as LV pressures were raised (saline-phenylephrine) and lowered (recovery). Note the shifts of these relationships during the recovery phase.

**Figure 4** Dog no. 5, 3/24/78. Data shown in Figure 3 for LVEDP, and chord and wall thickness are replotted after conversion to end-diastolic stress and strain. As in Figure 3, these relationships are shifted to the right during the recovery phase.
SHIFTS OF THE LEFT VENTRICULAR FILLING RELATIONSHIP/LeWinter et al. 647

TABLE 1  Time-Dependent Shifts of the Left Ventricular Diastolic Pressure-Dimension Relationship: Dimensions at Matched Diastolic Pressures during Saline-Phenylephrine Infusion and Recovery

<table>
<thead>
<tr>
<th>Segment (n = 8)</th>
<th>S-P</th>
<th>R</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mm Hg) ± SD</td>
<td>18.4 ± 1.3</td>
<td>18.4 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>ED segment length (mm)</td>
<td>11.54 ± 2.78</td>
<td>11.73 ± 2.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chord (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>18.4 ± 1.7</td>
<td>18.2 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>ED chord Length (mm)</td>
<td>42.1 ± 5.7</td>
<td>43.1 ± 5.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wall thickness (n = 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>18.3 ± 1.0</td>
<td>18.3 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>ED wall thickness (mm)</td>
<td>11.98 ± 2.7</td>
<td>10.97 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>Slow-filling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segment (n = 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVP (mm)</td>
<td>12.6 ± 1.5</td>
<td>12.7 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Segment length (mm)</td>
<td>11.31 ± 2.90</td>
<td>11.46 ± 2.94</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chord (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVP (mm Hg)</td>
<td>13.7 ± 1.9</td>
<td>13.6 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Chord length (mm)</td>
<td>41.3 ± 6.4</td>
<td>42.2 ± 6.1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Wall thickness (n = 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVP (mm Hg)</td>
<td>13.4 ± 1.3</td>
<td>13.3 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>Wall thickness (mm)</td>
<td>11.12 ± 2.7</td>
<td>11.01 ± 2.7</td>
<td></td>
</tr>
</tbody>
</table>

*P value, paired t-test.

Saline-phenylephrine infusion. During recovery, at an average wall stress of 22.9 g/cm² (range, 20.8-26.8), strain averaged 0.155 (range, 0.148-0.168).

Experiments in which pleural pressure was measured demonstrated that shifts of the diastolic pressure-dimension relationship during recovery from phenylephrine were not an artifact resulting from respiratory differences occurring when diastolic pressure was raised compared to when it declined. That is, a shift still was evident when pleural pressure was subtracted from the measured diastolic pressure to provide an index of true transmural pressure.

Comparison of "Slow" and "Rapid" Elevation of Left Ventricular Pressure

To determine whether the rapidity with which left ventricular pressures were raised would influence the diastolic pressure-dimension relationship, we compared results using the first protocol with those obtained using the second protocol, in which pressures were increased rapidly. Since all of the latter studies were performed with β-adrenergic blockade, we compared them to β-blockade studies using the first protocol, selecting studies performed as close in time as possible (no more than 3 days apart). An example of the difference in end-diastolic pressure-dimension relationships obtained with "rapid" compared to "slow" elevation of left ventricular pressure is shown in Figure 5. These relationships were obtained as pressures were raised. As in this instance, there appeared to be a clear separation between the two types of studies at end-diastolic pressures above the 10-15 mm Hg range, with left ventricular dimensions being larger when pressures were elevated slowly. As previously, results using slow-filling points were similar. To quantify the shift in the end-diastolic pressure-dimension relationship obtained using the two different

![Figure 5](http://circres.ahajournals.org/)

**Figure 5** Dog no. 6. End-diastolic pressure-segment length relationships during "slow" and "rapid" elevation of LV pressures. Note that end-diastolic segment length is longer at end-diastolic pressures greater than 10-15 mm Hg when pressures are raised slowly.
protocols, we compared segment and chord lengths obtained at end-diastolic pressures differing by no more than 1 mm Hg for both the "rapid" and "slow" protocols, in this instance, over a range of end-diastolic pressure between 21 and 24 mm Hg. These results are presented in Table 2. At mean end-diastolic pressures of 22.8 ± 1.5 and 22.7 ± 1.2 mm Hg for "slow" and "rapid" protocols, respectively, mean end-diastolic segment lengths were 12.06 ± 3.09 and 11.93 ± 3.09 mm (P < 0.001). For chord lengths, at mean end-diastolic pressures of 23.0 ± 1.6 ("slow") and 22.8 ± 1.3 ("rapid") mm Hg, end-diastolic chord lengths were 42.8 ± 5.7 and 42.2 ± 5.6 mm (P < 0.001), respectively.

**Influence of Caval Occlusion on Shifts of the Diastolic Pressure-Dimension Relationship**

In studies in which caval occlusion was used to minimize increases in end-diastolic pressure as systolic pressure was raised, shifts in the diastolic pressure-dimension relationship were not demonstrable. The average maximum end-diastolic pressure reached in these studies was 13.7 ± 1.0 mm Hg. An example of an end-diastolic pressure-dimension relationship so obtained is shown in Figure 6 and compared to that obtained when end-diastolic pressure was allowed to increase. It should be emphasized, however, that it was not possible to produce increases in systolic pressure during caval occlusion which were as large as those produced during saline-phenylephrine infusion without caval occlusion. Thus, the average highest peak systolic pressure during caval occlusion studies was 193 ± 10.2 mm Hg compared to 215 ± 11.6 mm Hg without caval occlusion (P < 0.05, unpaired t-test).

**Relationships between Shifts of the Diastolic Pressure-Dimension Relationship and Shortening**

To determine whether the observed shifts in the diastolic pressure-dimension relationship influenced systolic function, we performed several types of data analysis. First, percent shortening was compared for matched data points obtained during the first protocol as pressures were raised and lowered; in this case, end-diastolic pressures differed by no more than 1 mm Hg, peak systolic pressures differed by no more than 5 mm Hg, and end-diastolic dimensions were shifted. This analysis was confined to β-adrenergic blockade studies and was complicated by the fact that there was a general tendency for systolic pressure to decline more rapidly than end-diastolic pressure during recovery from saline-phenylephrine; i.e., for points at matched end-diastolic pressure, systolic pressure tended to be lower during the recovery phase. Nevertheless, it was possible to find at least one set of matched beats for segmental shortening in seven dogs and one for chordal shortening in five dogs. When more than one set was available in a given dog, we selected the one in which peak systolic pressure was most closely matched. As noted previously, heart rate was never more than 5 beats/min different for any data points in each dog. An example of beats used for this analysis is presented in Figure 6. Using this analysis (Table 3) for segmental shortening, at mean end-diastolic pressures of 18.9 ± 4.4 and 19.0 ± 4.8 mm Hg and mean peak systolic pressures of 173 ± 39 and 172 ± 37 mm Hg for saline-phenylephrine and recovery phase, respectively, we found that mean end-diastolic segment length was 11.66 ± 2.77 mm during saline-phenylephrine compared to 11.85 ± 2.75 mm during recovery (P < 0.01), whereas percent shortening was 11.3 ± 2.4 during saline-phenylephrine and 13.1 ± 2.0 during recovery (P < 0.01). Results for chord shortening (five dogs) were as follows for saline-phenylephrine and recovery phase, respectively. End-diastolic pressures were 19.8 ± 8.2 and 19.4 ± 8.5 mm Hg, peak systolic pressures were 159 ± 13 and 158 ± 13 mm Hg, end-diastolic chord lengths were 41.6 ± 6.0 and 42.7 ± 6.0 mm (P < 0.02), and percent shortening was 14.2 ± 4.5 and 16.0 ± 4.7 (P < 0.05). As shown in the example in Figure 6, peak (+) dP/dt was not significantly changed in beats compared in this fashion.

To confirm that the larger end-diastolic dimension during recovery from saline-phenylephrine infusion also was associated with an increase in stroke volume, hemodynamically matched beats obtained in the two dogs with flow probes were compared. It was possible to obtain a total of five such points in these two dogs. In these beats, stroke volume was increased by an average of 10% (range, 6–14) during the recovery phase.

---

**Table 2** Left Ventricular Dimensions at Matched End-Diastolic Pressures during "Slow" and "Rapid" End-Diastolic Pressure Elevation

<table>
<thead>
<tr>
<th></th>
<th>&quot;Slow&quot;</th>
<th>&quot;Rapid&quot;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segments (n = 6)</td>
<td>LVEDP (mm Hg) ± sd</td>
<td>22.8 ± 1.5</td>
<td>22.7 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>ED segment length (mm)</td>
<td>12.06 ± 3.09</td>
<td>11.93 ± 3.09</td>
</tr>
<tr>
<td>Chorda (n = 5)</td>
<td>LVEDP (mm Hg)</td>
<td>23.0 ± 1.6</td>
<td>22.8 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>ED chord length (mm)</td>
<td>42.8 ± 5.7</td>
<td>42.2 ± 5.6</td>
</tr>
</tbody>
</table>

* For definitions, see footnote to Table 1.
* Paired t-test.
SHIFTS OF THE LEFT VENTRICULAR FILLING RELATIONSHIP/Le Winter et al. 649

Figure 6 Dog no. 4. Effect of limiting increases in end-diastolic pressure during phenylephrine infusion by caval occlusion, 3/2/78, (left) compared to a study without caval occlusion, 3/3/78, in which end-diastolic pressure was allowed to rise to 29 mm Hg (right). The shift of the end-diastolic pressure dimension relationship is absent during the caval occlusion study.

The effects on shortening of rightward shifts of the diastolic pressure-dimension relationship also were assessed by constructing pressure-dimension loops for averaged beats at matched end-diastolic pressure obtained as this variable was raised and lowered. Examples of such loops are shown in Figure 8. The loop shown at the bottom of Figure 8 is most representative. In this instance, the rightward shift of the pressure-dimension relationship during the recovery phase was apparent throughout diastole. In addition, the normally linear end-systolic portion of the loop was shifted also but less so than at end-diastole and accounted for greater percent shortening during the recovery phase beat. The loop shown at the top of Figure 8 is similar to that at the bottom, except that the recovery phase loop does not appear shifted at end-systole. In a third pattern, which was present in only two beats so analyzed, the recovery phase diastolic pressure-length relationship appeared shifted only in association with atrial systole.

Angiographic Validation of a Rightward Shift of the Left Ventricular Diastolic Pressure-Volume Relationship

In the two dogs studied angiographically, end-diastolic volume was larger at matched levels of end-diastolic pressure (corrected for pleural pressure) during recovery from saline-phenylephrine infusion. In one, at an end-diastolic pressure of 19 mm Hg, end-diastolic volume was 72 ml during saline-phenylephrine and 81 ml during recovery. In the other, at an end-diastolic pressure of 15 mm Hg, end-diastolic volumes were 86 and 94 ml, respectively. These represent increases in end-diastolic volume of 12.5 and 9.3% during the recovery phase. Further, analysis of the left ventricular angiograms obtained at matched diastolic pressure did not reveal any appreciable change in major:minor axis ratio, indicating that the larger diastolic volume occurring during recovery was not associated with a major shape change.

Discussion

A variety of studies on isolated cardiac muscle preparations have documented and characterized the occurrence of the history-dependent viscoelastic properties, creep and stress relaxation (Levin and Wyman, 1927; Abbott and Lowry, 1957; Sonnenblick et al., 1966; Little and Wead, 1971; Pinto and Fung, 1973; Pinto and Patitucci, 1977). As a result of these properties, the passive length-tension relationship of cardiac muscle manifests hysteresis as the muscle is returned to its original length. Sonnenblick et al. (1966) observed that similar properties could be demonstrated in the papillary muscle after increases in active force generation. As a result, it was proposed that a viscous element in series

Figure 7 Dog no. 2, 1/21/78. Tracings demonstrating enhancement of shortening in association with a rightward shift of the diastolic-pressure dimension relationship. Each series of beats encompasses one respiratory cycle. Saline-phenylephrine infusion is shown at the left and recovery on the right, respectively. Average measurements for each respiratory cycle: heart rate (beats/min), 143 and 140; LVEDP (mm Hg), 13.0 and 13.4; LV systolic pressure (mm Hg), 144 and 145; LVmax dp/dt (mm Hg/sec), 3031 and 2988; ED segment length (mm), 9.50 and 9.79; ES segment length (mm), 8.27 and 8.37; % segment shortening, 13.0 and 14.5; ED chord length (mm), 41.6 and 43.0; ES chord length (mm), 35.0 and 35.7; % chord shortening, 15.9 and 17.0.
with both the contractile-series elastic and parallel elastic elements be included in the classic Hill muscle model. Several studies in open-chest, supported preparations have documented progressive increases in compliance following abrupt increases in systolic force, observations which are consistent with Sonnenblick’s work on the papillary muscle (Sonnenblick et al., 1963; Leach and Alexander, 1965; Gilmore et al., 1966; Clancy et al., 1968; Monroe et al., 1968; Janicki and Weber, 1977). However, attempts to document analogous viscoelastic properties in intact, conscious animals have been unsuccessful previously. Thus, Noble et al. (1969) were unable to document “series viscous” effects after brief infusions of methoxamine in conscious dogs. However, in this study, although increases in diastolic pressures were large, changes in systolic pressure produced by methoxamine apparently were quite modest and “limited by bradycardia” (in the example provided in the paper, systolic pressure increased by only 17 mm Hg). Likewise, Rankin et al. (1977) did not detect shifts in the diastolic left ventricular stress-strain relationship after inflation of aortic occlusion cuffs in conscious dogs. In the latter study, although major increases in systolic pressure occurred, the left ventricular end-diastolic pressure increased by only a small amount (from an average of 9.6 to 14.9 mm Hg). In the present study, we were able to detect rightward shifts of the left ventricular pressure-dimension and stress-strain relationship after large increases in both left ventricular systolic and diastolic pressure. This finding is consistent with the occurrence of both creep and stress relaxation and suggests that the previously cited results obtained in isolated muscles and open-chest supported preparations are not artifacts related to the relatively nonphysiological nature of these preparations. It is also of interest that the quantitative changes in myocardial segment length that we observed in the present study were similar in magnitude to those previously observed in isolated muscle as a result of creep (Pinto and Patitucci, 1977). Our angiographic results would indicate that the larger diastolic volume during recovery from saline-phenylephrine is not associated with a major change in shape of the left ventricle. However, as recently pointed out by Mirsky and Rankin (1979), the possibility that minor shape changes could have influenced our results cannot be completely dismissed.

Although it was not possible in our caval occlusion studies to attain systolic pressures as high as those present in studies in which increases in left ventricular end-diastolic pressure were not limited, the magnitude of systolic and diastolic pressure changes during these studies were quite comparable to those produced during “creep testing” by Rankin et al. (1977). The absence of shifts of the diastolic pressure-dimension relationship in these studies is therefore consistent with the results of the latter investigators. Taken together, our results and those of Noble et al. (1969) and Rankin et al. (1977) suggest that, in conscious animals, increases in pressure that are predominantly diastolic are not sufficient to produce a shift of the diastolic pressure-dimension or stress-strain relationship, but, rather, both systolic and diastolic pressure must be elevated simultaneously. That major elevation of systolic pressure in addition to diastolic pressure apparently is required to observe such a shift is consistent with the presence of a series viscous element, as proposed by Sonnenblick et al. (1966).

Our results have certain implications for the assessment of left ventricular diastolic compliance, particularly if filling relationships are obtained by analyzing multiple cardiac cycles as diastolic pressures are increased. As indicated by our comparisons between “rapid” and “slow” elevation of left ventricular pressures and by the results of caval occlusion studies, both the rate at which left ventricular pressures change and the magnitude of change in diastolic pressure appear to influence significantly diastolic filling relationships. Comparisons between “slow” and “rapid” elevation of left ventricular pressure in particular suggest that creep is an on-going process, occurring as pressures and

### Table 3: Relationship of Shifts of the End-Diastolic Pressure-Dimension to Percent Shortening in Beats with Matched Peak Systolic and End-Diastolic Pressures and Heart Rate

<table>
<thead>
<tr>
<th>Segments (n = 7)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mm Hg) ± SD</td>
<td>18.9 ± 4.4</td>
<td>19.0 ± 4.8</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>173 ± 39</td>
<td>172 ± 37</td>
</tr>
<tr>
<td>ED segment length (mm)</td>
<td>11.66 ± 2.77</td>
<td>11.85 ± 2.75</td>
</tr>
<tr>
<td>%AD</td>
<td>11.3 ± 2.4</td>
<td>13.1 ± 2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chords (n = 5)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mm Hg) ± SD</td>
<td>19.8 ± 8.2</td>
<td>19.4 ± 8.5</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>159 ± 13</td>
<td>158 ± 13</td>
</tr>
<tr>
<td>ED chord length (mm)</td>
<td>41.6 ± 8.0</td>
<td>42.7 ± 6.0</td>
</tr>
<tr>
<td>%AD</td>
<td>14.2 ± 4.5</td>
<td>16.0 ± 4.7</td>
</tr>
</tbody>
</table>

For definitions, see footnote to Table 1.

*S* Paired t-test.

<table>
<thead>
<tr>
<th></th>
<th>S-P</th>
<th>R</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mm Hg) ± SD</td>
<td>18.9 ± 4.4</td>
<td>19.0 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>173 ± 39</td>
<td>172 ± 37</td>
<td>NS</td>
</tr>
<tr>
<td>ED segment length (mm)</td>
<td>11.66 ± 2.77</td>
<td>11.85 ± 2.75</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>%AD</td>
<td>11.3 ± 2.4</td>
<td>13.1 ± 2.0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

| LVEDP (mm Hg) ± SD | 19.8 ± 8.2 | 19.4 ± 8.5 | NS |
| LVSP (mm Hg) | 159 ± 13 | 158 ± 13 | NS |
| ED chord length (mm) | 41.6 ± 8.0 | 42.7 ± 6.0 | <0.02 |
| %AD | 14.2 ± 4.5 | 16.0 ± 4.7 | <0.05 |
Figure 8  Pressure-segment and chord length loops obtained at matched end-diastolic pressure during saline-phenylephrine infusion and during recovery. At top (dog no. 3, 2/4/78), the pressure-segment length loop is shifted to the right throughout diastole, whereas the normally linear end-systolic portion of the loop does not appear shifted. At bottom (dog no. 1, 12/6/77) the pressure-chord length loop also appears shifted at end-systole.
during these beats and that alterations in ventricular afterload cannot explain our shortening results. Therefore, improved shortening in association with a larger diastolic dimension implies either further use of the Frank-Starling mechanism or an increase in inotropic state.

Although an increase in inotropic state as an explanation for our shortening results cannot be excluded, our study design was such that any proposed inotropic mechanism must not be related to heart rate or sympathetic stimulation. Lack of any consistent change in peak (+) dP/dt is not particularly helpful in excluding an inotropic state change, since the latter is known to be influenced by factors other than inotropic state (Mahler et al., 1975) and by the timing of aortic valve opening, a variable which was not available in the present study. A leftward shift of the end-systolic pressure-dimension relationship in association with a rightward shift during diastole might have indicated an increase in inotropic state (Suga et al., 1973; Sagawa et al., 1977), but the latter was not observed. In addition, the end-systolic relationship may be somewhat preload-sensitive (Suga et al., 1977). One possible inotropic mechanism that might be considered is that of aortic pressure-induced homeometric autoregulation, the Anrep effect (Anrep, 1912; Sarroff et al., 1960; Clancy et al., 1968; Monroe et al., 1968; Vatner et al., 1974; Elzinga et al., 1977). Although the mechanism of this apparent increase in inotropic state occurring immediately after abrupt increases in systolic pressure remains unclear, it does not appear to be related to changes in heart rate or sympathetic stimulation (Gilmore et al., 1966; Clancy et al., 1968; Monroe et al., 1968; Monroe et al., 1972), features which would be consistent with our results. However, the fact that the Anrep effect has been shown to be dissipated in about 30 seconds in a preparation very similar to our own (Vatner et al., 1974) argues strongly against this effect playing a role in our results.

Studies by Monroe et al. (1972) suggest that the mechanism of the Anrep effect may relate to recovery from subendocardial ischemia occurring after large increases in systolic pressure. In light of these results, ischemia occurring as systolic pressure was raised and resolving as pressures were lowered also must be considered as a possible explanation for the improvement in shortening that we observed during the recovery phase. However, as described by Monroe et al. (1972), ischemia in association with the Anrep effect was very transient and occurred immediately after abrupt increases in systolic pressure. This description would not fit well with the manner in which pressures were raised during our studies. Additionally, based on the likelihood of an increased ventricular afterload in recovery phase beats that were used for shortening comparisons, it would be anticipated that myocardial oxygen demands would have been larger at a time when shortening was enhanced. Thus, although ischemia cannot be excluded, it would seem an unlikely explanation for our shortening results.

Although our model does not allow definitive identification of the mechanism of enhanced shortening observed in association with time-dependent shifts of the diastolic filling relationship, it would appear that the resulting larger end-diastolic dimension (consistent with the occurrence of creep) confers a previously unappreciated advantage on the acutely-stressed left ventricle from the standpoint of systolic performance. Whether these observations have physiological relevance is uncertain. The fact that rather large elevations in systolic and diastolic pressure were required to produce a rightward shift would suggest that the phenomenon is not important under physiological conditions. Additionally, since the pericardium was left open in our dogs and there is evidence that the normal pericardium is a restraining factor for diastolic filling at high levels of diastolic pressure (Glantz et al., 1978; Shirato et al., 1978), it is entirely possible that an intact pericardium might inhibit the occurrence of rightward shifts at the levels of diastolic pressure reached in our experiments. On the other hand, like other soft tissues, the pericardium itself would be expected to possess similar viscoelastic properties and be capable of undergoing creep and stress relaxation. As a result, the normal pericardium might be able to accommodate the larger diastolic volumes associated with a time-dependent rightward shift of the pressure-dimension relationship.

There are two pathological situations in which rightward shifts of the left ventricular diastolic pressure-dimension relationship are known to occur, both of which may be associated with major elevations in left ventricular diastolic pressure. One is the setting of early myocardial infarction (Forrester et al., 1972; Theroux et al., 1977). It has been suggested that, in this instance, the compliance relationship is shifted to the right because of stress relaxation in ischemic, noncontracting myocardium as a result of continued contraction of adjacent normal myocardium (Forrester et al., 1972). Similar shifts also occur during chronic volume overload (Gault et al., 1970; McCullagh et al., 1972). Indeed, Sonnenblick et al. (1966) and Pinto and Pattitucci (1977) suggested that creep might occur during chronic volume overload and may represent a useful adaptation whereby the left ventricle could dilate without excessive increases in diastolic pressure. Our results suggest that creep might also contribute to maintenance of systolic function in chronic volume overload. Whether creep and/or stress relaxation actually occur on a chronic basis and are significant factors in the adaptation of the left ventricle to volume overload and, in addition, to what extent an intact pericardium modifies these properties constitute areas for future investigative efforts.
Acknowledgments

We are indebted to Dr. James W. Covell for his help in the preparation of this manuscript. The secretarial skills of Ana Gil and Susan Connolly, and the technical support of Frank Trousdale are deeply appreciated.

References

Anrep GV (1912) On the part played by the surarenals in the normal vascular reactions of the body. J Physiol (Lond) 45: 307–317
Time-dependent shifts of the left ventricular diastolic filling relationship in conscious dogs.
M M LeWinter, R Engler and R S Pavelec

*Circ Res.* 1979;45:641-653
doi: 10.1161/01.RES.45.5.641

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/45/5/641.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org/subscriptions/