Myocardial relaxation: effects of preload on the time course of isovolumetric relaxation

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ABSTRACT We studied the effect of an isolated increase in preload on isovolumetric relaxation in the intact dog heart and isometric relaxation in isolated cardiac muscle (dog and rat) preparations. In eight anesthetized dogs, 8 to 12 ml of blood was infused into the left ventricle during a single diastole. The exponential time constant (T) of isovolumetric relaxation was measured in single-beat experiments in which the left ventricular systolic pressure increased (112 ± 2 to 128 ± 3 mm Hg; p < .05, n = 62). In a second series of experiments, left ventricular systolic pressure was held constant (109 ± 2 to 107 ± 2 mm Hg; p = NS, n = 23) by simultaneous ventricular infusion and aortic unloading. In the first protocol, T increased from 28.0 ± 0.4 to 30.7 ± 0.4 msec (p < .05), whereas in the second protocol (constant systolic pressure) there was no change in T. The time course of isometric relaxation was also studied in six rat left ventricular papillary muscles and four dog right ventricular trabecular muscles. Preload was varied from 30% to 100% of the peak of the isometric length-tension curve in each muscle. Over this wide range of preload, the isometric force decline recordings were superimposable as long as the comparisons were made at equal levels of total load. Thus an isolated increase in preload does not influence the time course of isovolumetric relaxation.

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THE TIME COURSE of left ventricular isovolumetric pressure decline is determined by a series of interacting factors, including loading conditions, the inactivation rate of individual fibers, and the degree of fiber inhomogeneity within the wall of the ventricle.1 These factors are continuously modulated by autonomic tone and metabolic events, and for these reasons it is difficult to interpret some of the reported changes in left ventricular isovolumetric relaxation rate. For example, angina pectoris is associated with an apparent stiffening of the left ventricular chamber, which is widely thought to be caused by impaired or slowed myocardial relaxation.2 Because ischemia also produces changes in several of the factors that may independently influence the time course of left ventricular relaxation, Raff and Glantz3 reasoned that changes in relaxation “could have been due to the changes in the load the heart faces rather than any direct effect on the relaxing system.” These investigators then went on to assess whether an increase in left ventricular preload could be responsible for an increase in the time constant of left ventricular isovolumetric pressure decline (T). They found that volume loading slows T in the intact dog heart and, on the basis of a multivariate analysis, concluded that this effect was a reflection of the dependence of relaxation on both left ventricular end-diastolic pressure and aortic systolic pressure. In conscious dogs, however, Karriner et al.4 found that primary changes in afterload produced changes in T, but volume infusion did not produce such changes. We also found that modest changes in left ventricular preload did not influence T, but when volume loading was sufficient to produce an increase in aortic pressure, T increased.5 To date, there are no published studies that define the effects of an isolated increase in left ventricular preload on isovolumetric relaxation. Accordingly, we designed the present series of experiments to assess the effect of a pure increase in preload on isovolumetric relaxation in the intact dog heart and isometric relaxation in isolated cardiac muscle preparations.

Methods

Intact dog studies. Eight adult mongrel dogs were premedicated with morphine (5 mg/kg) and anesthetized with chloralose
(80 to 100 mg/kg); anesthesia was maintained with intermittent administration of morphine. The animals were ventilated to maintain physiologic blood gases. A median sternotomy was performed, the pericardium was opened, and the heart was suspended in a pericardial cradle. A bipolar electrode was attached to the right atrium, the sinus node was crushed, and the heart was paced at a constant rate of 120 beats/min. A micromanometer (Millar Mikrotip) was calibrated to mercury at 37°C and introduced into the left ventricle from the right carotid artery. In two dogs endocardial sonomicrometer crystals were positioned in the minor (anteroposterior) axis to measure left ventricular dimension during the preload interventions.

A large-bore cannula was inserted into the apex of the left ventricle and sutured into place with heavy silk suture. This cannula was used to deliver an 8 to 12 ml aliquot of blood (37°C) directly into the left ventricle during a single diastole, thus producing an acute (single-beat) increase in left ventricular preload. A second large-bore cannula was inserted into the arch of the aorta from the left carotid artery. This cannula was used for the rapid evacuation of blood from the central aorta, thus producing an acute (single-beat) reduction in afterload. Both the left ventricular and aortic cannulas were attached to large-bore syringes that were operated manually. With practice, the operators could produce a single-beat increase in preload that was associated with an increase in afterload (infusion into the left ventricle only) or a single-beat increase in preload with constant afterload; this latter condition could be obtained by abrupt systolic unloading of the preload beat (withdrawal of aortic blood in the preloaded cardiac cycle; figure 1). These single-beat interventions are similar to those we have used in previous studies.5–6 Comparison of data from a control beat (immediately preceding the intervention beat) with data from the preload beat does not allow sufficient time for neurohumoral or reflex changes to influence the results.

To was calculated from time-expanded recordings of left ventricular pressure; pressure records were digitized at 5 msec intervals beginning 10 msec after peak negative dP/dt began returning monophasically toward zero and terminating at an isovolumetric pressure (P) of 15 mm Hg. The coordinates were fit by a monoexponential equation, \( P = P_e^{-t/T} + P_o \), where \( P_e \) is left ventricular pressure at 10 msec after peak negative dP/dt and \( P_o \) is the baseline pressure toward which the monoequivalent decay. It is the quantity \( ln (P - P_o) \) that bears a near-linear relationship to time (t). Because \( P_o \) is largely influenced by intrathoracic or intrapericardial pressure (both of which were atmospheric in our open-chest preparation), we assumed that \( P_o \) was equal to zero. These methods are essentially the same as those used in previous studies from our laboratory.

Sixty-two paired beats (control and preload increment) were obtained, and a paired t test was used to assess changes in T; in this series, identified as protocol A, systolic pressure was permitted to increase. In a second series (n = 23), left ventricular systolic pressure was held constant in the preload beats (protocol B) and again the control data were compared with intervention data with a paired t test. Data are presented as mean ± SD.

Isolated muscle studies. Right ventricular trabeculae located under the tricuspid valve from mongrel dogs and left ventricular papillary and trabecular carnea muscles from Charles River CD rats were removed and mounted vertically in a chamber containing Krebs-Henseleit solution at 28°C and oxygenated with 95% O₂ and 5% CO₂. Muscles were stimulated at a rate of 12/min by parallel platinum electrodes delivering 5 msec pulses at voltages 10% greater than the minimum necessary to produce a maximum mechanical response. The spring clip on the tendon end of the muscle was connected to the lever arm of a low-inertia direct current motor (General Scanning G100PD); the lower clip was attached to a semiconductor strain-gauge transducer (Kistler-Morse DSC-3) immersed in the bath.

Either the length or tension of the preparation could be controlled by means of an electronic servosystem controlled by a digital computer (Data General Nova 2). Muscle contractions were recorded by sampling length and force at a rate of 2 kHz. Quantitation error was less than 5 μm for length and 20 mg for force. All contractions were viewed on a CRT display screen and recorded on disk for future analysis.

After a 60 min equilibration period, muscles were gradually lengthened to the peak of the isometric length-tension curve (\( L_{max} \)) by means of an automatic computer routine. This routine was repeated five times and, after a consistent \( L_{max} \) was determined, the muscles contracted in a physiologically sequenced manner in which the loading conditions of the intact heart are simulated (i.e., isometric contraction is followed by shortening of the muscle and isometric relaxation precedes lengthening).8 Loading conditions were adjusted so that the muscle preparations contracted over a wide range of preload (preload was varied from 30% to 100% of resting tension at \( L_{max} \)); comparisons were made at constant total load. Six rat left ventricular papillary muscles and four right ventricular trabecular muscles from the dog were studied and, except as noted, the experiments were carried out at 28°C. For each muscle, the force records were plotted on the same axes and the time course of isometric force decay was directly compared.

Results

Intact dog studies. The results of both preload interventions are presented in table 1. In protocol A (62 paired beats), the abrupt increase in left ventricular preload caused an increase in maximum positive dP/dt and systolic pressure; this intervention was associated with a small but statistically significant (p < .05) increase in T. Left ventricular anterior-posterior dimension was measured (sonomicrometer) in two dogs. End-diastolic dimension increased from an average of 40.5 ± 1.3 mm in the control beats to 43.6 ± 1.5 mm in the preloaded beats (p < .05, n = 13). An example of this intervention is shown in figure 2. In protocol B (23 paired beats), the preload increment caused an increase in maximum positive dP/dt, but in this group...
systolic pressure was held constant; this preload increment was not associated with a change in T.

**Isolated muscle studies.** The effect of varying preload (at constant total load) in the dog trabecular muscle is shown in figure 3; note that total load is the sum of preload and afterload. In the panel on the left, lengthening at preload force occurs after isometric relaxation; in the panel on the right, end-systolic length is maintained at minimum muscle length and force is allowed to dissipate to a minimal value. In both types of experiments, the time course of isometric relaxation was clearly superimposable with different preloads. This was a consistent finding in all dog trabecular muscle experiments at temperatures of 28°, 33°, and 37° C.

Similar results were obtained with the rat papillary muscle. In figure 4, the effects of varying preload (at two levels of total load) are shown. In this example, two preload levels at each of two levels of total load demonstrate that as long as the comparisons were made at equal levels of total load, superimposed force decline records were present over the differing levels of preload. This was a consistent finding in all six rat papillary muscle experiments.

**FIGURE 2.** Recording of left ventricular (LV) pressure and diameter during an abrupt increase in LV end-diastolic volume. Pressure was recorded at low (micromanometer) and high (fluid-filled catheter) gain; anteroposterior diameter was measured with endocardial sonomicromanometers. Ten milliliters of warm (37° C) blood was rapidly infused into the ventricle during the diastolic interval indicated by the arrows (inject). Left ventricular end-diastolic pressure (LVEDP) increased from 3.7 to 5.8 mm Hg and end-diastolic diameter increased from 42 to 45 mm; systolic pressure increased from 123 to 138 mm Hg and the end-systolic length increased from 37 to 38 mm. T increased from 28 to 31 msec.
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Discussion

An increase in preload provides a more optimal overlap of actin and myosin filaments, which can be translated into increased developed force or systolic pressure by way of an increased number of cross-bridges. Under conditions in which increased preload causes an increase in developed force, the time course of relaxation is prolonged. The data reported herein, however, indicate that as long as systolic load (or total load) remains constant, the time course of isovolumetric relaxation in the intact dog heart (and time course of isometric relaxation in isolated muscle studies) is not influenced by acute changes in preload. Thus, when the more optimal myofibril overlap, produced by an abrupt increase in preload, is not translated into a higher developed force, the time course of relaxation is not altered. This conclusion is consistent with previous observations indicating that volume loading in dogs produces an increase in T only when aortic pressure or systolic load increases. A complete interpretation of these previous results has been hampered by reflex changes and physiologic adjustments that occur during volume infusion in the intact dog; the single-beat intact heart interventions and the isolated muscle studies used in the present study avoids the effects of these changes.

To confirm that the volume infusion resulted in a change in left ventricular dimension as well as pressure, left ventricular chamber dimension was measured in two dogs. The observed 3 mm increase in left ventricular chamber diameter corresponds to an 8 ml increase in ventricular volume (spherical model). This 25% increase in chamber volume was associated with a relatively small (2 mm Hg) increase in left ventricular end-diastolic pressure presumably because our experimental preparation (open chest, open pericardium) and method of volume infusion (single-beat left ventricular injection) minimized extrinsic constraints and provided a relatively flat diastolic pressure-volume curve.

In the intact heart, isovolumetric pressure decline is not perfectly exponential nor does it always decline toward zero. In part for these reasons there has been lack of agreement as to the optimal method for determining T. Fortunately, most of these methods provide

![Graph showing shortening and tension over time for different preload conditions.]
similar results. A short-term increase in systolic pressure produced by aortic cross-clamping (i.e., variably afterloaded and single isovolumetric beats) is associated with a substantial prolongation of T. Even smaller, more physiologic increases in systolic pressure are, in most studies, associated with a small increase in T. Thus, in contrast to the preload independence of T, systolic loading conditions do influence the time course of left ventricular isovolumetric relaxation. For this reason, it would seem that T should be normalized or corrected for systolic pressure or load if it is to be a useful index of relaxation.

Isolated muscle relaxation data may likewise be difficult to interpret. One reason for this is that most isolated muscle experiments are performed at low temperatures, where contraction and relaxation are prolonged and isometric relaxation is not exponential. In part for this reason, several indexes of relaxation have been developed (i.e., the time for tension to fall from peak to 50% of peak tension, the maximum rate of tension decline, etc.). In our present studies we did not assume an exponential force decay nor did we evaluate relaxation with a single index or a specified load or point in time. Rather, we examined the time course of force decline throughout the entire period of isometric relaxation and found that it is independent of changes in preload. Other experiments performed in our laboratory indicate that the maximum rate of isometric tension decline is directly related to end-systolic length and total load, but it is independent of preload.

In summary, an isolated change in preload does not effect a change in the time constant of left ventricular isovolumetric pressure decline, nor does it influence the time course of isometric relaxation in isolated heart muscles. Our findings provide an improved basis for the interpretation of hemodynamic data in clinical and experimental studies of relaxation. For example, abnormal myocardial relaxation can prolong the time course of left ventricular isovolumetric pressure decay and thus influence diastolic pressure-volume relationships and preload; however, primary changes in preload do not affect isovolumetric relaxation rate.

References
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