Myocardial Relaxation

III. Reoxygenation Mechanics in the Intact Dog Heart

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SUMMARY Reoxygenation of hypoxic isolated cardiac muscle results in prolonged duration of contraction—relaxation. To determine whether similar mechanical changes occur in the intact left ventricle (LV), and especially to assess the influence of prolonged relaxation on LV diastolic stiffness, we examined LV pressure transients (micromanometer) and changes in myocardial segment length (ultrasonic transit time) during reoxygenation in 22 anesthetized dogs following 15 minutes of hypoxia (Paco₂ = 21 ± 2 mm Hg). The time constant (T) of LV isovolumic exponential pressure decline was used as an index of myocardial relaxation; LV end-diastolic stiffness was assessed from stiffness constants derived from multiple coordinates of end-diastolic pressure and segment length (volume loading). During reoxygenation, after LV systolic pressure and segment length measurements had returned to control levels, relaxation was prolonged; T increased from a control of 32 ± 2 to 44 ± 3 msec at 5 minutes of reoxygenation (P < 0.01). Prolonged relaxation resulted in a consistent increase in LV early-diastolic stiffness. Furthermore, calculated values for LV end-diastolic stiffness increased during reoxygenation when the next beat began less than 3.5 T after maximum negative dP/dt; this condition was present more frequently at a heart rate of 150 beats/min than at 120 beats/min. Thus, rapid correction of acute hypoxia in the dog results in prolonged LV relaxation; prolonged relaxation can influence LV end-diastolic stiffness when relaxation is sufficiently slow and/or when diastole is sufficiently short. Circ Res 49:633-639, 1981

REOXYGENATION of hypoxic cardiac muscle results in a substantial lengthening of the duration of contraction-relaxation. This tension prolongation phenomenon was discovered initially during the reoxygenation of hypoxic isolated cardiac muscles (Bing et al., 1968; Tyberg et al., 1970; Bing et al., 1971), but a similar phenomenon also occurs on reperfusion of ischemic segments in the intact heart (Bing et al., 1971; Gaasch and Bing, 1979). Other studies have shown that, in the isovolumic dog heart preparation, recovery from hypoxia or ischemia is associated with an elevation in left ventricular (LV) diastolic pressure (Weisfeldt et al., 1974); the rate of LV pressure decline was not measured in these experiments, nor was LV diastolic compliance measured directly. The present studies were designed to examine the effects of reoxygenation (rapid correction of acute hypoxia) on the mechanical behavior of the LV in the anesthetized dog. Our studies document the presence of prolonged LV relaxation during recovery from hypoxia; data from these studies also lend support to the concept that prolonged relaxation can influence LV diastolic pressure and even LV end-diastolic pressure—length relations.

Methods

Twenty-two adult mongrel dogs weighing 20–25 kg were anesthetized with intravenous sodium pentobarbital (25 mg/kg). Respiration was supported with a Harvard respirator and cuffed endotracheal tube. Inspired gas concentrations were delivered from cylinders containing calibrated gas mixtures and administered through a Quantiflex anesthesia machine. A median sternotomy was performed, the heart was suspended in a pericardial cradle, and after sinus rhythm had been abolished by crushing the sinoatrial node, the heart was paced from the right atrium at a constant rate of 120 or 150 beats/min. Systemic arterial pressure was measured with a fluid-filled catheter placed in the thoracic aorta via a femoral arteriotomy (Statham transducer model P23Db). High fidelity LV pressure recordings were obtained by advancing a micromanometer (Millar, mikro-tip) through a plastic cannula inserted in the apex of the LV; this allowed us to remove the micromanometer for periodic calibration. Intramyocardial temperature was measured with a thermistor in the LV free wall, and the micromanometer was calibrated at the measured temperature. Ultrasonic piezoelectric crystals (Park Electronics), positioned perpendicular to the long axis of the LV and midway between the apex and...
base, were used for continuous measurement of myocardial segment length. They were separated by a distance of approximately 1 cm and were placed in the inner one-third of the LV free wall through small stab incisions. At the end of each study, the crystals were carefully dissected free, their intramyocardial position verified, and calibration performed.

The ECG was monitored continuously, and all data were derived from paced beats with normal QRS complexes. Measurements were recorded simultaneously on photographic (Electronics for Medicine) and magnetic tape (Hewlett Packard 3513-14-20) recorders. LV pressure was recorded at full scale and at high gain for accurate determination of both peak LV pressure and LV diastolic pressures. The tape recordings were replayed in one-quarter speed to produce a time-expanded record for measurement of LV pressure during isovolumic relaxation.

LV systolic pressure and an index of the duration of systole (t_{sys}) were measured; t_{sys} was defined as the time from end diastole to the time of maximum negative dP/dt. At a constant heart rate of 120 beats/min, the sum of t_{sys} plus the time from maximum negative dP/dt to end diastole (t_{dias}) equals 500 msec. As will be seen, t_{sys} was found to be increased during recovery from hypoxia; the extent or duration of this increase, termed the "time of systolic prolongation" (t_{sys}), was measured as the difference between the control t_{sys} and the reoxygenation t_{sys}. LV end-diastolic pressure and two early-diastolic pressures were measured. The earliest of these two pressures (DP_{1}) was defined as the "lowest early-diastolic pressure in the control state" (LDPC); this point is identified as LDPC in Figure 4. Throughout each study, measurements of DP_{1} were made at a constant interval prior to end diastole. The second early-diastolic pressure (DP_{2}) was measured at a time after DP_{1}, which equaled t_{sys}. Thus, DP_{2} (since it was measured at a fixed time relative to end diastole) may be influenced by the duration of systole and the time course of isovolumic pressure decline; since DP_{2} was corrected for the change in the duration of systole, changes in DP_{2} primarily reflect alterations in the time course of relaxation.

The time constant (T) of isovolumic LV pressure decline was used as an index of myocardial relaxation (Weiss et al., 1976). LV pressure was measured at 5-msec intervals beginning at the time of maximum negative dP/dt and terminating at a point prior to mitral valve opening; this point was defined at an isovolumic pressure of 10 mm above end-diastolic pressure. To calculate T, the pressure and time coordinates were fit (least squares) by a straight line (P = kL + b), and length at an end-diastolic pressure of 5 mm Hg during control was assigned a value of 100%. Other length coordinates were then expressed as a percent of that value (normalized length), and the data were replotted as

\[ \ln P = \ln P_0 + At \]

where P is pressure, \( \ln P_0 \) is the pressure at t = 0, and A is a negative number. The slope of the \( \ln P \) vs. t relation is represented by A (a negative number) and the time constant (T in msec) is equal to the negative inverse of A. In this example, control pressure coordinates are shown as the circles, and data obtained during correction of acute hypoxia are shown by the squares. The relaxation time constant (T) lengthened from a control value of 34 to 45 msec during reoxygenation.

\[ T = \frac{1}{A} \]

Figure 1 LV isovolumic pressure (P) is plotted against time (t) after maximum negative dP/dt. The slope of the \( \ln P \) vs. t relation is represented by A (a negative number) and the time constant (T in msec) is equal to the negative inverse of A. In this example, control pressure coordinates are shown as the circles, and data obtained during correction of acute hypoxia are shown by the squares. The relaxation time constant (T) lengthened from a control value of 34 to 45 msec during reoxygenation.
pressure vs. normalized segment length. This allowed comparison of data among animals in which heart size and crystal separation varied. The slope (k) of the end-diastolic pressure-normalized segment length line was used as an index of end-diastolic stiffness.

Experimental Protocol

In six dogs (series 1), control measurements of LV pressure, myocardial segment length, and arterial blood gases were made; the inspired gas mixture during this control period was 50% oxygen and 50% nitrogen. Arterial hypoxemia was then produced by changing the inspired gas to a mixture consisting of 5% oxygen and 95% nitrogen. Arterial blood gas measurements were made after 5 minutes and again between 10 and 12 minutes of exposure to the hypoxic gas mixture; LV pressure and segment length recordings were made after 15 minutes of hypoxia, and the PaO₂ then was restored to near physiological levels (reoxygenation). To rapidly restore a physiological PaO₂, the gas mixture was changed initially to 100% oxygen for 2 minutes, and then to 50% oxygen-50% nitrogen for the remainder of each experiment. Arterial PaO₂ was measured after 2 minutes of reoxygenation and again between 15 and 30 minutes of reoxygenation. LV pressure and segment length were recorded at 2, 5, 10, 15, and 30 minutes of reoxygenation.

In four dogs anesthetized with chloralose-urethane, we evaluated the influence of β-adrenergic receptor blockade (propranolol, 0.15 mg/kg) on the hypoxia-reoxygenation sequence. The protocol in these four experiments was otherwise the same as that outlined for the series 1 studies.

The gas mixtures, the duration of hypoxia, and the reoxygenation protocol were based on a series of pilot studies which identified a 15-minute period of hypoxia not only as technically feasible, but as a period which was associated with reproducible prolongation of the duration of systole and of the time constant of LV pressure decline. Higher levels of inspired oxygen or shorter periods of hypoxia produced less marked changes in the LV pressure transients; more severe hypoxemia caused an unstable hemodynamic state which was commonly associated with atrial or ventricular arrhythmias.

In 12 additional dogs (series 2), we followed a protocol that was similar to the one in series 1, except that several coordinates of end-diastolic pressure-segment length relations were measured (volume expansion, see above) during the control period and again between 5 and 15 minutes of reoxygenation. The series 2 experiments were performed to evaluate potential changes in LV end-diastolic chamber stiffness during reoxygenation. As in series 1, pressure and length data were obtained during the control period, after 15 minutes of hypoxia, and at 2, 5, 15, and 30 minutes of reoxygenation; the 10-minute recording was not made because the volume expansion protocol was underway at this time. The period between 5 and 15 minutes of reoxygenation was selected for the volume expansion because (based on our observations in series 1) the hemodynamic conditions were stable during this period. Studies in series 2 were carried out at constant heart rate of 120 beats/min (n = 8) or 150 beats/min (n = 6). Unless otherwise stated, the results are presented for the studies performed at a heart rate of 120 beats/min.

Throughout each experiment, variations in myocardial temperature were less than 1°C. Only one study was performed in a single dog, since it is not known whether serial (hypoxia-reoxygenation) studies produce the same response. All data are presented as the mean ± SEM. Values during hypoxia and throughout the period of reoxygenation were compared to control values and to each other using analysis of variance and a Duncan’s test to locate the variance. When only a single comparison was made, as in the comparison of control and reoxygenation stiffness constants (k), a paired t-test was used.

Results

The time course of changes in LV pressure transients during hypoxia and reoxygenation is shown in Figure 2; these data from 14 experiments are presented as the average ± SEM.

Changes during Hypoxia

After 10 to 12 minutes of hypoxia, the arterial PaO₂ averaged 21 ± 2 mm Hg. LV systolic pressure increased from 113 ± 4 mm Hg during the control period to 130 ± 5 mm Hg during hypoxia (P < 0.01); LV end-diastolic pressure increased from 2.6 ± 0.2 to 5.2 ± 0.6 mm Hg (P < 0.01). LV maximum positive dP/dt increased from 2105 ± 138 to 3980 ± 380 mm Hg/sec (P < 0.01); the small change in maximum negative dP/dt (1919 ± 100 to 2103 ± 136 mm Hg/sec) was not statistically significant. Normalized end-diastolic segment length increased to 1.06 (the prehypoxic control = 1.00; P < 0.05), but there was no significant change in end-systolic length (0.87 to 0.88); fractional shortening increased from 13 to 17% (P < 0.01). T, the time constant of isovolumic pressure decline, shortened from 34 ± 2 to 27 ± 3 msec, but this change did not achieve statistical significance.

In the four studies with propranolol, there were only minimal changes in LV systolic pressure and positive dP/dt during hypoxia (from an average of 112 to 116 mm Hg and 1131 to 1501 mm Hg/sec). Likewise, there was little change in maximum negative dP/dt (1868 to 1845 mm Hg/sec) or in T (30 to 34 msec).

Time Course of Changes during Reoxygenation

After 2 minutes of reoxygenation, the arterial PaO₂ was 158 ± 24 mm Hg; all values thereafter ranged
FIGURE 1 The time course of changes in LV pressure transients during hypoxia and reoxygenation in 14 dogs. Relative to control values, the relaxation time constant (T) was significantly prolonged during reoxygenation (5-15 minutes); other LV pressure transients and measured segment lengths were not significantly different from control during this period. Note that n = 6 at 10 minutes and n = 14 at all other times.

from 100 to 160 mm Hg. LV systolic pressure returned to control values by 5 minutes of reoxygenation and was stable thereafter (P > 0.05 for all reoxygenation vs. control). LV end-diastolic pressure also returned to control levels during the reoxygenation period. At 5 minutes, the average end-diastolic pressure was 3.2 ± 0.2 mm Hg (P > 0.05 vs. control); there was no significant change in end-diastolic pressure thereafter. Although there was a tendency for maximum positive dP/dt and maximum negative dP/dt to be reduced slightly during reoxygenation, these changes were not statistically significant; at 5 minutes of reoxygenation, maximum positive dP/dt was 1834 ± 159 mm Hg/sec and maximum negative dP/dt was 1735 ± 116 mm Hg/sec (both P > 0.05 vs. control). Myocardial segment length likewise returned to control during the early reoxygenation period and remained stable thereafter. At 5 minutes, end-diastolic and end-systolic lengths (1.02 ± 0.12 and 0.89 ± 0.25, respectively) were not significantly different from control lengths.

In the dogs that were paced at 120 beats/min (series 1 and 2, n = 14), T increased to 38 ± 3 msec at 2 minutes (P > 0.05 vs. control of 34 ± 2 msec), and reached a peak of 44 ± 3 msec at 5 minutes (P < 0.01). There was a tendency for T to decline between 5 and 15 minutes (41 ± 2 msec at 15 minutes), but this small difference (5-minute vs. 15-minute values) was not statistically significant. T had returned nearly to control at 30 minutes of reoxygenation (37 ± 2 msec, P > 0.05 vs. control). When series 1 experiments (n = 6) were examined separately and the changes at 5, 10, and 15 minutes of reoxygenation were compared, there was no significant difference among the three values; the average values for T at 5, 10, and 15 minutes were 39 ± 3, 39 ± 2, and 37 ± 3 msec, respectively. Control T in series 1 was 32 ± 2 msec.

In the four dogs treated with propranolol, there was no qualitative difference in the reoxygenation response. LV systolic pressure remained constant (107 to 110 mm Hg) between 5 and 15 minutes of reoxygenation; similarly, LV positive and negative dP/dt remained stable. T increased in all four dogs (from a prehypoxic control of 30 msec) to an average of 38 msec at 10 minutes.

Duration of Systole and Diastole

After 5 minutes of reoxygenation, the index of the duration of systole (t<sub>a</sub>) was 279 ± 10 msec; this was significantly longer (P < 0.01) than the control measurement of 245 ± 7 msec. These data are presented graphically in Figure 3. The systolic ejection period increased from an average control value of 184 ± 5 to 201 ± 6 msec during reoxygenation. The duration of diastole (t<sub>d</sub>) decreased from a control of 253 ± 9 to 216 ± 7 msec during reoxygenation (P < 0.01).

The t<sub>d</sub>:T ratio at 5 minutes of reoxygenation (4.7 ± 0.7) was significantly less than the control ratio (7.7 ± 0.4). Thus, whereas prolonged relaxation might be expected to influence early-diastolic pressure, under the circumstances of these studies (heart rate = 120), prolonged relaxation alone would not be expected to influence end-diastolic pressure (since t<sub>d</sub>:T was greater than 3.5, see Methods above). In contrast, when the heart rate was maintained at 150 beats/min, the ratio of t<sub>d</sub>:T declined to 3.1 ± 0.6 during reoxygenation (see Table 1)

Early-Diastolic Pressure

The earliest of the two measured diastolic pressures (DP<sub>1</sub>) increased from a control of 0.3 ± 0.2 to 4.7 ± 0.7 mm Hg at 5 minutes of reoxygenation (P < 0.01). The second diastolic pressure (DP<sub>2</sub>) increased from 0.9 ± 0.2 to 2.1 ± 0.3 mm Hg (P < 0.01). These data are presented graphically in Figure 4.

End-Diastolic Pressure-Segment Length Relations

In 14 experiments, several coordinates of end-diastolic pressure and segment length were obtained (volume loading) during the control period
and again between 5 and 15 minutes of reoxygenation. The length data were normalized, the end-diastolic pressure-length coordinates were fitted by a linear function, and values for the LV stiffness constant (k) were found. The data are presented in Table 1 and an example of a single experiment is shown in Figure 5.

At a constant heart rate of 120 beats/min, the LV end-diastolic stiffness constants (k) during reoxygenation were not statistically different (P > 0.05) from the control values. Likewise, there was no significant change in the pressure intercepts (b) when the reoxygenation values were compared to control values (—35 ± 7 and —32 ± 3, respectively; P > 0.05). In five of the six experiments carried out at a heart rate of 150 beats/min, the end-diastolic stiffness constant increased during reoxygenation (Table 1); there was no change in the pressure intercept during reoxygenation (—26 ± 6 and —28 ± 7, respectively; P > 0.05). When these data are separated into experiments in which $t_{\text{Hi}}$ was less than 3.5, the importance of this ratio becomes apparent (Fig. 6). The end-diastolic stiffness constant uniformly increased (>0.1 units) during reoxygenation when values for $t_{\text{Hi}}$ were less than 3.5. In contrast, when values for $t_{\text{Hi}}$ remained above 3.5, changes in the stiffness constant were variable and small by comparison (range, +0.06 to −0.10).

Discussion

In isolated cardiac muscle, brief periods of hypoxia are associated with a decline in developed

![Figure 3](image-url)

**Figure 3.** The duration of systole ($t_{\text{sy}}$) at 5 minutes of reoxygenation is shown relative to the $t_{\text{sy}}$ from the control period. In the diagram on the left, the time of systolic prolongation ($t_{\text{sp}}$) represents the increment in the duration of systole. On the right, $t_{\text{sy}}$ during reoxygenation was significantly longer ($P < 0.01$) than control measurement.

![Figure 4](image-url)

**Figure 4.** LV diastolic pressure measurements during the control period and at 5 minutes of reoxygenation. Early-diastolic pressures were measured at the time of the lowest diastolic pressure in the control state (LDPc), and at a time after LDPc that equals $t_{\text{sp}}$ (where $t_{\text{sp}}$ equals the time of systolic prolongation). These two early-diastolic pressures are referred to as DPc and DPc in the text. During reoxygenation, both of these early-diastolic pressures were significantly greater (both $P < 0.01$) than the control pressures. The small increase in end-diastolic (ED) pressure was not statistically significant.

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**Abbreviations:** T = relaxation time constant (msec); $t_{\text{Hi}}$ = time from maximum negative dp/dt to end diastole (msec); k = end-diastolic stiffness constant; C = prehypoxic control; R = reoxygenation; HR = heart rate (beats/min).
to more rapid relaxation. In the intact animal, hypoxia is a potent central nervous system stress which leads to a release of catecholamines (Hammill et al., 1979). It is likely that catecholamine release resulted in an augmented LV contractile state and a tendency toward more rapid LV relaxation in our experiments; these effects were attenuated by the administration of propranolol. It appears that, during the brief exposure to hypoxia, the contribution of catecholamines overrode the direct depressant effect of hypoxia on the myocardium.

The rapid restoration of a physiological arterial Po2 (after 15 minutes of hypoxia) resulted in the prompt return of LV systolic pressure, positive dP/dt, and fiber length to control levels; however, both the duration of systole and the relaxation time constant were significantly prolonged during reoxygenation. Because the change in relaxation was present at a time when LV systolic pressure and fiber length had returned to control levels, we conclude that the slowed relaxation (T\textsubscript{T}) was a direct result of the hypoxia-reoxygenation sequence and was not caused by acute alterations in LV loading conditions or other hemodynamic factors (Karliner et al., 1977; Gaasch et al., 1980; Brutsaert et al., 1980).

The prolonged relaxation observed in our intact working LV is analogous to that observed in isolated cardiac muscle. Bing et al. (1968, 1971) and Tyberg et al. (1970) initially described the phenomenon of myocardial tension prolongation during recovery from hypoxia in isolated cardiac muscle. Bing, however, extended his observations to regional ischemia in the dog heart and found that regional tension prolongation occurred on reperfusion of ischemic segments (produced by transient coronary ligation). Weisfeldt et al. (1974) used an isolated dog heart preparation, and also found that reperfusion following global ischemia and reoxygenation following hypoxia were associated with a failure of the LV to fully relax (as determined by changes in diastolic pressure during interruption of rapid pacing). Although the hypoxia-reoxygenation sequence differs in many important respects from the ischemia-reperfusion sequence (Hearse, 1977), both are associated with a transient abnormality in myocardial relaxation. Clinically the ischemia-reperfusion sequence occurs not only with angina pectoris, but also during the course of coronary bypass surgery, with relief of coronary artery spasm, and following elective ischemic cardiac arrest during open heart surgery. The hypoxia-reoxygenation sequence may also occur clinically following respiratory arrest, pulmonary embolism, or even repeatedly in patients with sleep apnea syndromes. The potential deleterious results of reperfusion or reoxygenation in these situations remains to be defined.

The mechanisms responsible for prolonged contraction-relaxation (following correction of hypoxia) are not completely defined. However, Bing et al. (1976) found that blockers of mitochondrial respiration abolished the tension prolongation phenomenon in isolated heart muscle. Similarly, segmental tension prolongation, which occurs with reperfusion of ischemic segments of the intact heart, can be blocked by the local administration of potassium cyanide (Gaasch and Bing, 1979). In contrast, when electron transport is uncoupled from ATP production, abnormal relaxation during reoxygenation is not prevented. These observations suggest that the tension prolongation and slowed relaxation which occur with the ischemia-reperfu-
sion or the hypoxia-reoxygenation sequence are related to the restoration of oxygen and/or to a process linked to electron transport, but not to ATP production.

A major goal of our present experiments was to examine the effect of prolonged myocardial relaxation on LV diastolic events. LV pressures, measured in early diastole, showed small but significant increases during reoxygenation, and although a contribution of viscous and inertial factors cannot be excluded with certainty, our data and those of others (Weisfeldt et al., 1978; Pouleur et al., 1979) support the idea that variable myocardial relaxation acts as an important determinant of early-diastolic pressure. As will be seen, prolonged or slowed myocardial relaxation can also influence calculated values for LV end-diastolic stiffness. If relaxation is incomplete at end diastole, then end-diastolic stiffness constants do not represent the passive properties of the muscle.

The conditions under which abnormal relaxation may directly influence end-diastolic pressure include either a prolonged relaxation (\(t^1\)) and/or an abbreviated diastole (\(t^\text{max}\)). Weisfeldt et al. (1978) have suggested that a critical relation exists between these two factors. In studies in which LV relaxation was slowed or heart rate increased (under conditions in which the next systole begins less than 3.5 T after the previous peak negative dP/dt), they demonstrated that the end-diastolic pressure-dimension coordinate of the LV was shifted upward and to the left of that in the fully relaxed ventricle. Heart rate was held constant throughout each of our studies and the increase in the duration of LV contraction-relaxation (\(t^1\)) and an abbreviated diastole (\(t^\text{max}\)) resulted in a decrease in the duration of diastole (\(t^\text{calc}\)). In every experiment, reoxygenation was associated with decreased values for the ratio of \(t^\text{calc}:T\); in many experiments this ratio fell to less than 3.5, indicating that the processes of relaxation might be incomplete at the onset of the next beat. As expected, incomplete relaxation at end diastole was more frequent at faster heart rates, but our most consistent finding was a transient increase in LV end-diastolic stiffness when end diastole occurred before 3.5 T after peak negative dP/dt (Fig. 6). These data complement those of Weisfeldt et al. (1979) in that they support the hypothesis that the process of myocardial relaxation can influence LV end-diastolic chamber stiffness if diastole is sufficiently short and/or relaxation is sufficiently prolonged.

This transient state of incomplete relaxation at end diastole should be distinguished from myocardial contracture which is largely an irreversible process that follows severe depletion of myocardial energy stores (Hearse et al., 1977; Gaasch et al., 1978). The development of contracture could result in a failure of the ventricle to fully relax irrespective of the heart rate or the ratio of \(t^\text{calc}:T\). Similarly, under conditions of intracellular calcium overload, calculated values for muscle stiffness might be increased by virtue of saturated calcium binding mechanisms. Again, the ventricle might not fully relax even after long periods of diastole. It appears, therefore, that several mechanisms can result in a failure of the ventricle to fully relax prior to the next beat and that further research in this area is needed.

Nonetheless, the results of the present studies indicate that rapid correction of acute hypoxia in the dog results in prolonged LV contraction—relaxation, an abbreviation of the duration of diastole, and an increase in LV early-diastolic pressures. Furthermore, prolonged relaxation can influence calculated values for end-diastolic stiffness if relaxation is sufficiently slow and/or diastole is sufficiently short.

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