Evidence of Incomplete Left Ventricular Relaxation in the Dog

PREDICTION FROM THE TIME CONSTANT FOR ISOVOLUMIC PRESSURE FALL

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ABSTRACT Although it has been proposed that incomplete relaxation explains certain increases in left ventricular end diastolic pressure relative to volume, there has been no clear demonstration that incomplete relaxation occurs in the intact working ventricle. To identify incomplete relaxation, left ventricular pressure-dimension relationships were studied in 10 canine right heart bypass preparations during ventricular pacing. The fully relaxed, exponential diastolic pressure-dimension line for each ventricle was first determined from pressure and dimension values at the end of prolonged diastoles after interruption of pacing. For 167 beats during pacing under widely varying hemodynamic conditions, diastolic pressure-dimension values encountered this line defining the fully relaxed state during the filling period indicating that relaxation was complete before end diastole. The time constant for isovolumic exponential pressure fall (T) was determined for all beats. For this exponential function, if no diastolic filling occurred, 97% of pressure fall would be complete by $3.5 T$ after maximal negative dp/dt . For the 167 beats the fully relaxed pressure-dimension line was always encountered before $3.5 T$.

With very rapid pacing rates (170–200 beats/min) and/or with pharmacologic prolongation of relaxation, incomplete relaxation occurred as evidenced by the fact that the line defining the fully relaxed state was never reached during diastole ($n = 15$). This evidence of incomplete relaxation occurred only when the subsequent

beat began before $3.5 T$ but did not always occur under these conditions. Thus, an increase in end diastolic pressure relative to diastolic volume may result from incomplete relaxation under conditions of sufficiently rapid heart rate or sufficiently prolonged ventricular relaxation. Incomplete relaxation does not occur when the next beat begins more than $3.5 T$ after maximum negative dp/dt .

INTRODUCTION

Relaxation of cardiac muscle is the process of return to the resting state after contraction. For the intact working left ventricle, relaxation begins toward the end of the ejection period and continues through the isovolumic period and perhaps into the filling period after mitral valve opening. Although incomplete relaxation clearly can occur in an isovolumic ventricle (1), for incomplete relaxation to occur in the working left ventricle relaxation would need to continue throughout the period of diastolic filling. Evidence of continued relaxation during filling has been suggested (2, 3) but not clearly demonstrated. Recently, some investigators (4) have suggested that it is not possible for incomplete relaxation to occur in the working heart. Therefore, we examined the time period after mitral valve opening looking for evidence that relaxation continued to influence the left ventricular pressure-dimension relationship.

Using the canine right heart bypass preparation, the fully relaxed, left ventricular diastolic-pressure-dimension line was determined for each heart during prolonged diastolic periods brought about by interruption of pacing. For paced beats we assumed that relaxation was complete when this fully relaxed pressure-dimension line was encountered during the filling period. This

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time of encounter was related to the time constant for isovolumic pressure fall (T)¹ (5) previously determined for that beat. Because under isovolumic conditions pressure fall should be essentially complete by 3.5 T after maximum negative dp/dt , we anticipated that the time of encounter of pressure-dimension values with the fully relaxed pressure-dimension line should occur before 3.5 T after maximal negative dp/dt . Incomplete relaxation should occur only if the next beat begins before this time and should be identified by a failure of pressure-dimension values to encounter the fully relaxed line at any time during diastole.

METHODS

The right heart bypass preparation has been described in detail elsewhere (6). Briefly, mongrel dogs weighing 20–30 kg were anesthetized with thiamylal, 20 mg/kg, and alpha chloralose, 30 mg/kg, and ventilated with a volume ventilator. The heart was exposed through a median sternotomy. Venous blood from the cannulated venae cavae was diverted to a reservoir where it was warmed to 37°C, oxygenated, and returned to the pulmonary artery by a calibrated, occlusive roller pump. The isolated right heart received coronary venous flow, which was drained to the venous reservoir. Cardiac input was changed by changing the pump output. Aortic pressure was controlled by adjusting the height of an overflow reservoir in the line leading from the cannulated thoracic aorta, or by varying the resistance in this line with a screw clamp. The innominate and the left subclavian arteries were ligated within 2 cm of the aortic arch.

Left ventricular pressure (LVP) and left atrial pressure were measured with Millar catheter tip micromanometers (Millar Instruments, Inc., Houston, Tex.) (7), each inserted into its respective chamber through a small plastic adapter. Each adapter was sewn in place with a purse-string suture. The micromanometers were calibrated at 37°C against a mercury column. Base-line drift was detected by removing the catheters and exposing the tips to zero pressure at 37°C several times during each experiment. In the event of drift, the catheters were rebalanced as necessary before being replaced. Aortic pressure was measured with a Statham P23Db strain gauge (Statham Instruments, Inc., Oxnard, Calif.) via a 50-cm 8F fluid-filled catheter in the aortic arch. The ventricular and atrial and aortic pressure signals were amplified by Honeywell Accudata 143 amplifiers (Honeywell Information Systems, Inc., Waltham, Mass.) and recorded on a 1858 Visicorder (Honeywell Information Systems, Inc.) at 400 mm/s paper speed. The LVP signal was differentiated electronically with a Honeywell Accudata 132 differentiator (Honeywell Information Systems, Inc.), which was calibrated by supplying a triangular wave form of known slope to the differentiating circuit. Right ventricular pacing was established with electrodes sewn to the right ventricular free wall after the sino-atrial node was crushed.

LVP after the time of maximum negative dp/dt , and before the time at which the ventricular pressure equaled left atrial pressure (assumed to be the time of mitral valve opening) (8) was digitized with a Hewlett-Packard 8964A Digitizer (Hewlett-Packard Co., Palo Alto, Calif.) with a hand-held planimeter as previously described (5). Pressure and time co-

ordinates were digitized at 4.0-ms intervals along this portion of the curve and were plotted on-line as $(\ln P, t)$. In some beats dp/dt after maximal negative dp/dt was constant at or near its minimal value for 10–20 ms, and thereafter increased toward zero continuously. In these beats digitization of the ventricular pressure curve was begun at the point where the dp/dt began increasing continuously toward zero. The plotted $(\ln P, t)$ coordinates were fitted by the least squares method to the function $\ln P = At + B$, $P = e^{(At+B)}$. P is the pressure at any time, t , after the curve becomes exponential; A , a negative constant, is the slope of $\ln P$ vs. t ; and B is the $\ln$ of the highest pressure on the exponential portion of the curve. The average correlation coefficient for the fitted curves of over 200 examined beats was 0.995 and the lowest correlation coefficient was 0.990. Constants for the fitted curves were reproducible to within 2% on repeat digitization. The time constant, T , equals $1/-A$ and is the time required for P at any point on the exponential portion of the curve to fall to $1/e^{\text{th}}$ of that P . Under isovolumic conditions pressure would fall to 36.8% by 1 T , 13.5% by 2 T , 10.0% by 2.3 T , 5.0% by 3 T , and 3.0% by 3.5 T .

Pulse-transit ultrasonic dimension transducers were used to measure ventricular dimension in the minor semiaxis plane (9). 5-mega Hz piezo-electric crystals were positioned via blind needle puncture on the anterior and posterior endocardial surface. The position was confirmed at the conclusion of the study. Ultrasonic impulses were delivered as described by Stegall et al. (10). The transducers were calibrated by direct measurement of the distance between the transducers in saline at the beginning and end of each study. The frequency response of the system was flat to beyond 60 Hz with the minimum change in distance resolved to 0.5 mm.

To obtain the fully relaxed diastolic pressure-dimension relationship, simultaneous LVP and dimension were obtained at the end of prolonged diastolic periods. These prolonged periods were brought about by interruption of ventricular pacing after sinus node crush. Values were obtained for all hearts between 5 and 30 mm Hg diastolic pressure by modifying cardiac input before interruption (Fig. 1). No value was used

FIGURE 1 Record showing LVP, left atrial pressure, and left ventricular dimension in a beat immediately before interruption of pacing and during a prolonged diastolic period. During the prolonged diastole, LVP and left ventricular dimension values were obtained as shown by the vertical lines on the trace at the far right. During and after the beat shown, pressure and dimension values are marked at intervals related to T , beginning at 0 T (or the time of maximal negative dp/dt), which is the beginning of the exponential pressure fall. These types of data were generally obtained on beats without interruption.

¹ Abbreviations used in this paper: LVEDP, left ventricular end diastolic pressure; LVP, left ventricular pressure; T , time constant for isovolumic exponential pressure fall.

that occurred less than 5 T after maximal negative dP/dt of the preinterruption beat. At least 30 values were obtained for each heart from 5 to 10 individual prolonged diastoles at varying cardiac input. The fully relaxed pressure-dimension relationship for each heart was taken as the least squares best fit between $\ln$ pressure and dimension for these values. The correlation coefficient, r , was >0.90 for all hearts studied. In only two hearts was $r < 0.95$. The position of the fully relaxed line was confirmed after beats evaluated for the time-course of relaxation were obtained (Fig. 2).

To assess the time of apparent completion of relaxation, pressure and dimension values were obtained at intervals of 0.25 T from the time of maximal negative dP/dt to the time of onset of the next beat in each of the 182 beats studied (Fig. 1) during ventricular pacing. These values were plotted along with the fully relaxed pressure-dimension line. Where the lines appeared to encounter one another (Fig. 3) a time of crossing was estimated by linear interpolation between values separated by 0.25 T on both sides of the fully relaxed line. Crossing occurred in all beats described as showing complete relaxation. Where the lines did not appear to cross further pressure-dimension values were obtained at 4.0 ms intervals or less at the time these lines were most closely approximated. These detailed data confirmed that the lines in fact did not cross and, therefore, that relaxation was not complete at any time during this diastole (Fig. 4).

Five right heart bypass preparations were subjected to

FIGURE 2 Fully relaxed late diastolic pressure-dimension relationship for a single heart. Points during prolonged diastoles of many interrupt periods as shown in Fig. 1 are plotted together. Points at various positions were obtained by varying the loading conditions before interruption. Points plotted as an exponential relationship and fit by the method of least squares.

FIGURE 3 Complete relaxation: pressure and dimension values for single beats during diastole, and the onset of subsequent systole beginning at maximal negative dP/dt (0 T) along with the fully relaxed diastolic pressure-dimension line for this heart. In panel A the fully relaxed line is encountered by 3.5 T after maximal negative dP/dt , indicating completion of relaxation. In panel B from the same heart under identical conditions except for an increase in heart rate from 130 to 150/min, relaxation is still complete because the fully relaxed line is encountered by 3.0 T. The next beat began at 3.7 T after maximal negative dP/dt (time of LVEDP).

three experimental hemodynamic runs in varying sequence. The sequence of changes in the independent variable (heart rate, cardiac input, or peak LVP) in each run was randomized while the other variables were held constant (11). Studies in which heart rate and/or cardiac input were varied were

FIGURE 4 Incomplete relaxation: pressure and dimension values for single beats during diastole and the onset of subsequent systole beginning at maximal negative dP/dt (0 T) along with the fully relaxed diastolic pressure-dimension line for these hearts. In panel A are shown data from the same heart as in Fig. 3 at a faster heart rate of 170/min. Here the fully relaxed line is never encountered during diastole. The time of onset of the next beat was 2.7 T after maximal negative dP/dt . In panel B are data from another heart after 10.0 mg of propranolol to prolong relaxation. Again the fully relaxed line is not encountered at any point during diastole and the next beat begins at 2.5 T after maximal negative dP/dt .

performed at the same specific heart rates and cardiac inputs in all preparations. Heart rate was varied in increments of 10/min between 120 and 170/min with a constant stroke volume of 20 ml. Cardiac input was varied in 500-ml increments between 1.5 and 3.5 liters/min. Studies in which peak LVP was varied were performed at the lowest obtainable peak LVP and at peak LVP's $\approx$ 25, 50, and 75 mm Hg above this pressure. Relaxation was prolonged by addition of 2.0–10.0 mg of propranolol to the reservoir. In these runs heart rate was increased from 120 to 170 to 200 beats/min at a constant cardiac input of 1.5 liters/min and peak LVP of 125 mm Hg.

Statistical analysis was performed with the Student's *t* test for paired or unpaired data as appropriate or by an analysis of variance. Within the analysis, group means were compared using the Scheffé-multiple range test (12). Except as noted, $\pm$ indicates SE.

RESULTS

Complete relaxation. In 167 beats from 10 hearts, pressure-dimension values encountered the fully relaxed line before 3.5 T after maximal negative dP/dt (Fig. 3). This evidence of complete relaxation was present under widely varying hemodynamic conditions with heart rates from 120 to 170/min, cardiac input from 1.5 to 3.5 liters/min, and peak LVP from 80 to 180 mm Hg. In five hearts in which complete hemodynamic data were obtained, changes in heart rate and peak LVP had no significant effect on the time of encounter (Table I). With increases in cardiac output there was a tendency for the time of encounter to come earlier. This trend was statistically significant ($P < 0.05$) at the highest cardiac output. This dependency on cardiac output at high outputs is discussed below. For 134 of the 167 beats the fully relaxed line was reached >2.3 T after maximal negative dP/dt . For these beats the time of mitral valve opening was 1.96 ± 0.10 T. At 2.3 T, 90% of

pressure fall would be complete if ventricular relaxation were entirely isovolumic. The time of encounter in these 134 beats was 2.85 ± 0.33 (SD) T with no encounter occurring after 3.5 T. Values for T in these beats varied from 19 to 81 ms (40 ± 9 ms). With a four-fold range for T the encounter time occurred between 2.3 and 3.5 T.

Beats from hearts under severe hemodynamic stress as a result of high cardiac output, high peak LVP, or depressed contractile function and thus large end systolic volumes, had relatively large volumes at the onset of filling. The left ventricular end diastolic pressure for these 33 beats was >25 mm Hg. In such beats the time of encounter occurred <2.3 T after maximal negative dP/dt , range 0.37–2.22 T (mean 1.67 ± 0.09 T $n = 33$). These beats were identified by the fact that the time of encounter calculated from (a) the time of maximal negative dP/dt , (b) T, and (c) the fully relaxed line, assuming no diastolic filling, was <2.3 T.

Thus, all beats with a left ventricular end diastolic pressure (LVEDP) of the next beat occurring more than 3.5 T after maximal negative dP/dt had relaxed completely. Relaxation appeared to influence diastolic pressure-dimension relationships under most conditions for 2.3–3.5 T after maximal negative dP/dt . As a result of higher early diastolic volumes and a higher position on the fully relaxed curve, hearts under severe hemodynamic stress had earlier time of encounter. By 3.5 T, relaxation no longer influenced diastolic pressure-dimension values.

Incomplete relaxation. Pressure-dimension points did not encounter the fully relaxed line at any point during diastole in 15 beats in 5 hearts during rapid pacing (Fig. 4) at rates from 170 to 200/min and after

TABLE I
Crossover Times and Time of Mitral Valve Opening (*T*'s after Maximal Negative dP/dt) in Five Hearts under Varying Hemodynamic Conditions

Variable heart rate, constant peak LVP (125 mm Hg), and stroke volume (20 ml)				Variable cardiac input, constant peak LVP (125 mm Hg), and constant heart rate (150/min)				Variable peak LVP, constant heart rate (150/min), and cardiac input (3.0 liters/min)			
Heart rate	T	Mitral valve opening	Crossover time	Cardiac input	T	Mitral valve opening	Crossover time	Peak LVP	T	Mitral valve opening	Crossover time
beats/min	ms	T's	T's	liters/min	ms	T's	T's	mm Hg above 83 $\pm$ 5 mm Hg	ms	T's	T's
120	45 $\pm$ 0.2	1.82 $\pm$ 0.22	2.84 $\pm$ 0.26	1.5	41 $\pm$ 0.1	1.90 $\pm$ 0.20	2.80 $\pm$ 0.08	0	44 $\pm$ 0.5	1.95 $\pm$ 0.18	2.60 $\pm$ 0.05
130	37 $\pm$ 0.5	1.95 $\pm$ 0.33	2.93 $\pm$ 0.29	2.0	43 $\pm$ 0.01	1.87 $\pm$ 0.22	2.74 $\pm$ 0.08	25	41 $\pm$ 0.3	2.02 $\pm$ 0.21	2.74 $\pm$ 0.09
140	37 $\pm$ 0.4	1.98 $\pm$ 0.30	2.77 $\pm$ 0.25	2.5	40 $\pm$ 0.2	1.95 $\pm$ 0.30	2.68 $\pm$ 0.11	50	42 $\pm$ 0.3	1.95 $\pm$ 0.23	2.90 $\pm$ 0.12
150	38 $\pm$ 0.4	1.88 $\pm$ 0.27	2.99 $\pm$ 0.27	3.0	41 $\pm$ 0.2	2.05 $\pm$ 0.32	2.66 $\pm$ 0.08	75	42 $\pm$ 0.3	1.72 $\pm$ 0.20	2.70 $\pm$ 0.20
160	37 $\pm$ 0.4*	1.85 $\pm$ 0.30	2.71 $\pm$ 0.18	3.5	40 $\pm$ 0.3	1.90 $\pm$ 0.25	2.56 $\pm$ 0.04†				
170	35 $\pm$ 0.3*	1.81 $\pm$ 0.27	2.71 $\pm$ 0.26								

* $P < 0.05$ vs. 120 beats/min.

† $P < 0.05$ vs. 1.5 liters/min.

prolongation of relaxation with propranolol. This evidence of incomplete relaxation occurred only when the time of LVEDP of the next beat was <3.5 T after maximal negative dP/dt . All beats in which LVEDP occurred before 3.5 T did not demonstrate incomplete relaxation because some beats with LVEDP occurring before 3.5 T were beats with early time of encounter as described above.

As seen in the representative beat illustrated in Fig. 4A, LVEDP was significantly elevated in beats with no crossover as a result of the incomplete relaxation. In this beat LVEDP was 24 mm Hg. If encounter had occurred by 2.7 T, LVEDP for this beat would have been 9.5 mm Hg. Thus, incomplete relaxation can be hemodynamically significant in the working canine ventricle and occurs only when the onset of the next beat occurs at <3.5 T.

DISCUSSION

Previous studies emphasizing the relaxation characteristics of isolated cardiac muscle and the intact left ventricle have concentrated on the effects of variations in relaxation as reflected in the time-course of tension and pressure fall during isometric or isovolumic periods. In studies of isolated muscle it has only been recently recognized that the classic afterloaded muscle is not physiologically sequenced during relaxation (13). Recent studies have attempted to "physiologically load" isolated cardiac muscle such that isometric relaxation precedes isotonic lengthening (13, 14). These studies have concentrated on the time-course of tension fall during the isometric phase and have placed little emphasis on the time-course of isotonic lengthening or effects of lengthening during the period of tension fall. Detailed analysis of such models has recently been called into question because of the injury to the muscle at their attachments (15). These injured ends might well have profound effects on behavior of muscle after tension fall. Therefore, the present study was undertaken in the intact left ventricle where one is likely looking at physiological events with greater similarity to the intact heart.

The emphasis of this study has been an attempt to examine whether relaxation influences the time-course of diastolic filling of the intact left ventricle in a predictable and quantitative fashion. The results of the study suggest strongly that such a predictable quantitative effect is present.

The definition of relaxation used in the study is essential to the understanding of this interrelationship. We have defined relaxation as the return of the heart to the state that existed before the initiation of contraction. Full relaxation was assumed to exist at the end of prolonged diastoles induced by interruption of pacing. Thus, by definition, if there were no electrical

activation of the ventricle and no initiation of contractile activity, relaxation would be complete.

By considering relaxation in this fashion, we have found that the time-course can be indexed by T (5). The present study shows that the time-course of the effects of relaxation on the diastolic filling period after the mitral valve opens and the ventricle begins to expand during the phase of diastolic filling can also be predicted from T. Some (16) have described early diastolic viscous behavior and have variably accounted for this on the basis of either passive viscous elements or residual activity during relaxation of contraction. If early diastolic viscous effects had significant effects on the time-course of relaxation this would be expected to be manifested in beats with the largest early diastolic filling where viscous effects would be maximal. However, even in 8 beats where almost 50% of filling occurred between 2 and 3 T, the times of encounter (3.2 ± 0.2 T SD) were not significantly different from the other beats with presumably less viscous effects. Hence, early viscous effects do not appear to significantly alter the effects of relaxation on diastolic filling. The fact that the time constant derived from isovolumic data does predict the time-course of the effects of relaxation on diastolic filling supports the use of the time constant as an index of the process of relaxation itself. In the canine left ventricle functioning under usual hemodynamic and contractile conditions large variations in the time constant for relaxation from 19 to 81 ms were associated with an apparent completion of the effect of relaxation on the time-course of diastolic filling at a predictable time between 2.3 and 3.5 time constants after maximum negative dP/dt .

With this approach we were able to detect the presence of incomplete relaxation by a failure of pressure-dimension values to approximate or encounter the fully relaxed diastolic pressure-dimension line at any time during diastole. Such evidence of incomplete relaxation occurred only when the subsequent beat occurred at <3.5 T. In these studies T was prolonged by the administration of propranolol. Karliner and associates (17) have recently reported studies in the intact animal showing no change in T with propranolol. This inconsistency may reflect model related factors discussed in detail elsewhere (18).

In our study, hearts were paced from a ventricular location to eliminate the atrial contraction. This simplified the system by eliminating possible viscous effects thought by some (16) to be present during atrial systole. Diastolic values for pressure-dimension after the time of encounter approximates the line representing the truly relaxed diastolic state until the time of the left ventricular end diastolic pressure of the next beat as shown in Fig. 3.

In contrast to the conclusions of others (4), the present study seems to demonstrate quite clearly that in-

complete relaxation between beats does occur in the intact beating heart under conditions of sufficiently long relaxation and sufficiently rapid heart rate. In view of these data it would appear that an elevation in LVEDP or alterations in the LVP-volume or dimension relationship at end diastole cannot be ascribed to incomplete relaxation if the next beat begins more than 3.5 T after maximal negative dP/dt . Despite the previous lack of evidence that incomplete relaxation can occur, incomplete relaxation has been suggested as the mechanism for elevation of end diastolic pressure during angina pectoris in man (19–22), and relief of incomplete relaxation has been suggested as a mechanism for the fall in LVP relative to volume after the administration of vasodilating agents to patients (23) with congestive heart failure. Other factors that influence relaxation, and therefore may relate to the presence or absence of incomplete relaxation, have been recently reviewed (20).

Even if the next beat begins before 3.5 T this does not necessarily imply the presence of incomplete relaxation. As demonstrated herein, if the left ventricle has a large end systolic volume, the fully relaxed curve appears to be encountered well before 3.5 T as a result of the relatively high fully relaxed pressure for the large end systolic volume. We suspect that other alterations of left ventricular mechanics that would lead to a stiffer, fully relaxed, diastolic pressure-dimension line and consequently higher, fully relaxed pressures would lead to an encounter that was earlier than 2.3 T. To demonstrate incomplete relaxation by the criteria presented here one would need to know pressure-dimension points throughout the period of diastole where incomplete relaxation is suspected, and one would need to define the fully relaxed diastolic pressure-dimension relationship for that heart at the particular period of time.

The early time of encounter of beats with large end-systolic volumes compared to normal beats is compatible with a model in which the actively relaxing elements are functionally in parallel with the passive diastolic elements. With the onset of relaxation the systolic load is gradually transferred back to the passive element with a time-course for transfer that is determined by the stiffness of the passive element. Hence, larger systolic loads cause the load to be borne solely by the passive element earlier than with lighter loads. If the actively relaxing elements were in series with the passive elements, no load transfer occurs so that larger systolic loads might be expected to result in delayed rather than early completion of relaxation. Although Rankin and associates (16) suggest the presence of an important parallel viscous element during early diastole, there is no attempt to identify effects of possible active relaxing elements within their system.

The present studies are limited by the fact that left

ventricular dimension was measured in only one location. Thus, we are of course unable to detect shape changes in the left ventricle in diastole under these conditions. These studies would be aided by knowledge of multiple dimensional changes within the ventricle during this critical period of time and by knowledge of the actual time sequence of flow across the mitral valve and through the aortic valve. By obtaining such information one could examine the exact time sequence of events relating to diastolic shape change and to actual filling during the isovolumic and filling periods.

Thus, ventricular relaxation continues past the isovolumic period into the diastolic filling period. Ventricular relaxation influences the time-course of changes in LVP and dimension during the diastolic filling period. This time-course is predictable from T. Ventricular relaxation does not continue to influence the pressure-dimension relationship during the diastolic filling period beyond 3.5 T after maximal negative dP/dt . After 3.5 T diastolic events cannot be explained by factors relating to ventricular relaxation. Incomplete relaxation can be demonstrated when relaxation is sufficiently long and when the next beat occurs before 3.5 T. The time at which relaxation no longer influences the pressure-dimension relationship can be defined precisely only with knowledge of the fully relaxed diastolic pressure-dimension relationship.

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