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EVALUATION OF THE TIME CONSTANT AS AN INDEX OF ISOVOLUMIC VENTRICULAR RELAXATION IN THE NORMAL CAT

A Thesis

Presented for the

Master of Science

Degree

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A. Lynelle Golden

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ABSTRACT

Ventricular relaxation is of considerable importance to the overall performance of the heart. Because relaxation cannot be measured directly in the intact heart, clinicians and physiologists are dependent upon indirect indices of relaxation. The time constant of isovolumic pressure decline (T) is currently the most frequently used index of ventricular relaxation.

The time constant describes the rate of left ventricular pressure (LVP) decline, and has been calculated either by fitting the LVP data to one of two monoexponential models or determined directly from the left ventricular pressure recording. The time constant Texp is derived by fitting LVP to the function: $P = Ae^{bt} + Pb$, where Texp $= -1/b$ and Pb is a variable pressure asymptote. The time constant Tln is calculated from a simplification of the above model. The asymptote Pb is assumed to be equal to zero, and the function is linearized using a logarithmic transformation so that: $\ln P = \ln Po + bt$, with Tln $= -1/b$. A third time constant $T\frac{1}{2}$ is determined directly from the pressure-time data as the time required for the pressure at the beginning of isovolumic relaxation to decline by one-half.

Although the time constant has been used frequently as an index of relaxation, the appropriateness of the methods used to estimate T is controversial. It is not clear whether the values of Tln, Texp, and $T\frac{1}{2}$ are affected by changes in other hemodynamic conditions, or whether the three estimates of T provide equivalent information regarding relaxation.

The present study was designed to define the limitations of the three estimates of T. The effects of independent increases in preload, afterload, contractility, and heart rate on the values of Tln, Texp, and $T_{\frac{1}{2}}$ were evaluated using normal cats anesthetized with isoflurane. In addition, the appropriateness of the mathematical models used to calculate Tln and Texp were assessed by comparing how well each of the models predicted actual LVP decline.

The values of Tln, Texp, and $T_{\frac{1}{2}}$ were unaffected by changes in heart rate, inotropic state, and afterload. The index Texp also proved to be independent of preload, but the values of Tln and $T_{\frac{1}{2}}$ both increased as preload was increased. Whereas the values of Tln and $T_{\frac{1}{2}}$ were consistently related across all hemodynamic conditions, Texp was not consistently related to either Tln or $T_{\frac{1}{2}}$ due to variability in the values of Texp.

These results indicate that $T_{\frac{1}{2}}$ and Tln provide similar information regarding relaxation, but both indices must be interpreted carefully in experiments in which preload is changed. Although the mathematical model used to calculate Texp is somewhat better statistically than the model used to calculate Tln, the complexity of the model used to calculate Texp introduces variability which may confound attempts to measure small changes in ventricular relaxation. On the basis of these results, it is recommended that $T_{\frac{1}{2}}$ may be the most practical and reliable method of determining a time constant in experiments in which preload is constant.

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CHAPTER I

INTRODUCTION

A. STATEMENT OF THE PROBLEM

Since the primary abnormality in many cardiovascular diseases is impaired diastolic function, reliable indices of ventricular relaxation are essential to characterize the physiology and to improve the clinician's ability to detect and treat heart disease. The time constant (T) describes the time course of isovolumic pressure decline, and is widely accepted as an index of ventricular relaxation. The fact that isovolumic pressure decline may be approximated by an exponential function is the basis for the use of a time constant to describe ventricular relaxation. Several different methods have been used to calculate T and these are described in Appendix A. The time constant Tln is calculated from a semilogarithmic transformation of the pressure-time data and has been used most frequently to describe ventricular relaxation. The semilogarithmic method has been criticized on the basis that it is a poor representation of actual ventricular pressure decline because the method requires the assumption that left ventricular pressure approaches a zero pressure asymptote. The time constant Texp, which has been proposed as an alternative to Tln, is calculated by fitting the pressure-time data to a variable asymptote, exponential model. The model is complex, and it is unclear whether Texp represents a better empirical index of relaxation than Tln. The relaxation

half-time ($T_{\frac{1}{2}}$) is an estimate of T derived directly from the pressure data which may prove to be a valuable index of relaxation since no curve fitting procedures are required. Currently, the appropriateness of the methods used to estimate T remains controversial.

The time constant is an indirect measure of ventricular relaxation which must be interpreted in the context of changes in other determinants of myocardial function including preload, afterload, contractility, and heart rate. It is important, therefore, to understand how the value of T is affected by changes in these factors. The effects of changes in loading conditions, contractility, and heart rate on Tln have been evaluated in a number of studies, and although the effects of changes in heart rate and inotropy have been characterized fairly well, the effects of changes in loading conditions remain controversial. There are no studies which have reported the effects of other hemodynamic factors on $T_{\frac{1}{2}}$, and relatively few studies which have assessed the effects of hemodynamic conditions on Texp. Although the time constant has been used routinely as an index of relaxation, the dependence of Tln, Texp, and $T_{\frac{1}{2}}$ on other determinants of cardiovascular function has not been completely described, and the limitations of the three estimates of T have not been defined. The present study addresses the following questions:

1. Do changes in other hemodynamic conditions produce changes in the values of Tln, Texp, or $T_{\frac{1}{2}}$ which may not reflect changes in ventricular relaxation?

2. Do the mathematical models used to estimate Tln and Texp predict actual ventricular pressure decline equally well?

3. Does fitting either of the mathematical models produce errors in estimating T?

4. Do Tln, Texp, and $T_{\frac{1}{2}}$ provide equivalent information regarding relaxation under a variety of hemodynamic conditions?

B. LITERATURE REVIEW

1. Concepts of Myocardial Relaxation

Diastole has traditionally been misconceived as a period of quiescence during which the ventricles passively fill with blood. The recognition that abnormalities in relaxation and filling often precede systolic dysfunction (1-4), has led to the reassessment of the functional significance of diastole and a growing interest by clinicians and physiologists in this phase of the cardiac cycle.

Functionally, ventricular filling is the event of primary importance during diastole since the heart must fill with blood in order to operate as a pump. Furthermore, the Frank-Starling relationship dictates that systolic performance is determined, in part, by the end-diastolic volume (sarcomere length) (5). Left ventricular filling is a dynamic process which is dependent upon myocardial relaxation and affected by a number of viscoelastic and inertial properties intrinsic and extrinsic to the ventricle (4). During the rapid filling phase the rate of filling is determined primarily by the completeness of myocardial relaxation and the

atrioventricular pressure difference, whereas compliance properties become most important during the later stages of filling (4). Therefore, since much of the ventricular volume is contributed during the early filling phase, especially at rapid heart rates, myocardial relaxation is of considerable importance to the overall performance of the heart (6, 7).

Relaxation is a complex process by which the myocardium returns to its precontractile tension and length (2, 8). The decline in active myocardial tension requires the dissociation of actin and myosin crossbridges and the return of contractile proteins to their resting configuration. These processes are, in turn, dependent upon the active removal of calcium by the sarcoplasmic reticulum and cell membrane (2, 4, 9). Since both the detachment of crossbridges and the removal of calcium require ATP, myocardial relaxation is an active process (2, 4, 9). In fact, the energy required for calcium sequestration by the sarcoplasmic reticulum may account for 6 to 15% of the total energy expenditure of the mammalian heart (10). The energy dependence of relaxation dictates that the process should also be variable, and relaxation is modified by a number of metabolic and mechanical factors (1-3).

Brutsaert and associates have reviewed many of the studies designed to elucidate the primary determinants of myocardial relaxation and have proposed a conceptual framework for understanding the variability of the process (1-3, 11). They hypothesized that relaxation is controlled by an interaction of inactivation, load dependence, and inhomogeneity, which they described as a "triple

control mechanism" (3). Within this context, inactivation describes the collection of processes which result in the decline in active tension as described earlier. The load is the external force which opposes the generation of active tension, and inhomogeneity refers to spatial and temporal differences in the degree of inactivation and distribution of load.

The load faced by the intact heart is variable, and Brutsaert and others catagorized various loading factors according to the time during the cardiac cycle at which they are applied. Loads such as preload and afterload which exist prior to the development of tension or that occur during the initial two-thirds of contraction are defined as contraction loads. Those loads applied during the last third of ejection or during relaxation are defined as relaxation loads. Relaxation loads in the intact heart include systolic chamber deformation (external restoring forces) and various hemodynamic loads such as arterial impedance, coronary filling, and wall stress during rapid filling (1, 8).

The distinction between relaxation loading and contraction loading is important to the proposed concept of relaxation control (1-3, 11). Strictly defined, the load dependence of relaxation describes the phenomenon by which increased relaxation loads promote an earlier onset of relaxation (1-3). Contraction loading has the opposite effect of delaying the onset of relaxation. These concepts were based upon the results of load clamp experiments using cat papillary muscles performing afterloaded isotonic contractions (12-14). In these experiments an abrupt increase in load near peak

shortening promoted an earlier onset of lengthening, whereas an increase in afterload had the opposite effect. Similar results have been reported by other investigators for both cat (15) and rat (16) papillary muscle. In these experiments the relaxation sequence was not physiological since isotonic lengthening preceded isometric tension decline. The load dependence of relaxation was also verified in contractions which model the isometric-isotonic relaxation sequence of the intact heart (17). In these experiments a small increase in load at the beginning of isotonic relaxation resulted in a more rapid rate of lengthening. Brutsaert and others hypothesized that the primary importance of the load dependence of relaxation is the facilitation of ventricular filling (1-3).

The effects of various loads on the onset of relaxation was explained in terms of the interaction between the degree of inactivation (calcium availability) and the existing load (1-3). It was proposed that the phenomenon of load dependence, or the earlier onset of relaxation with relaxation loading, reflects an advanced stage of inactivation where the availability of calcium has decreased to a critical level. The onset of relaxation is accelerated because the load exceeds the ability of the myofibrils to generate tension. In contrast, during the initial two-thirds of contraction, when calcium availability is high, the myofibrils are able to readjust to an increase in load by increasing the number of active sites, and the onset of relaxation is delayed (1-3). To understand the interaction of load and inactivation it is important to remember that the

concentration of calcium in the area of the myofibrils begins to decline early in systole prior to the development of peak tension (2).

The theory that the degree of inactivation determined the effects of various loading conditions was extrapolated from observations that the sensitivity of mammalian myocardium to both contraction and relaxation loading was reduced when the reuptake of calcium was supressed by caffeine (18-19), tetanic stimulation (18) and hypoxia (19). These studies are the basis for the hypothesis that load dependence requires the presence of calcium sequestering membranes (2). Additional support for this hypothesis is provided by the insensitivity of myocardium from animals with poorly developed sarcoplasmic reticulum including frogs (18) and immature rats (20) to relaxation loading. In addition, single cardiac cells from rat heart have been converted from load sensitive to load independent by elimination of the sarcoplasmic reticulum (21). Hence both the degree of inactivation and loading conditions appear to be important determinants of myocardial relaxation.

The third important determinant of myocardial relaxation according to Brutsaert and associates is the nonuniform distribution of load and inactivation (1, 3, 11). They suggested that nonuniformity enhances load dependent relaxation. Shortening of myofibrils in some areas of the heart constitutes an increase in load on other fibers in more advanced stages of inactivation and thereby promotes early relaxation of these fibers. This theory is supported by the results of a study in which hypoxic rat trabecular muscles

were made to contract in series with normal muscles (22). A premature onset of lengthening was observed in the hypoxic muscle as a result of the longer duration of contraction in the normal muscle. The potential importance of nonuniformity is easily appreciated in cardiovascular diseases such as ischemic heart disease which are characterized by regional inhomogeneities (1). It has been proposed that nonuniformity is also an important factor in the normal heart due to inherent regional differences in dimensions and fiber orientation, and the asynchrony of electrical activity (11). The control of relaxation by load and inactivation may, therefore, be modified by the spatial and temporal nonuniformity of these factors.

It should be noted that although isolated muscle studies provide support for Brutsaert's explanation of the effects of various loading conditions on the timing of the onset of relaxation, there is some discrepancy regarding the effects of these loads on the subsequent rate of tension decline. Parmley and Sonnenblick reported a decrease in the rate of isometric tension decline following an increase in afterload in isotonic, afterloaded contractions (15). In contrast, a linear increase in the maximum rate of tension decline with an increase in total load (afterload + preload) was observed in studies using physiologically sequenced contractions in rat trabeculae carnae (23) and blood perfused canine papillary muscles (24). Brutsaert and others suggested that a delay in the onset of relaxation may be followed by either a more rapid or a slower rate of tension decline depending upon the state of inactivation at the beginning of relaxation (1). Therefore, it appears that a given change in loading

conditions may expedite the onset of relaxation, but then delay the subsequent rate of tension decline. Additional studies in isolated muscle are necessary to clarify this apparent discrepancy. It seems clear that relaxation in isolated muscle is influenced by both loading conditions and biochemical factors which affect inactivation. Moreover, the "triple control" concept may provide a basis for understanding relaxation in both the normal and diseased heart (1-3, 11).

2. Measurement of Relaxation of the Intact Heart

Description of Indices

Characterization of relaxation in the intact heart is difficult due to the inherent complexity of the heart, as compared to isolated muscle, and the impossibility of measuring relaxation directly. A number of indices have been developed based on the measurement of ventricular volumes, dimensions, or pressures to indirectly describe relaxation in the intact heart (1). Pressure derived indices are used most frequently to measure relaxation in the intact heart (25), due, perhaps, to the relative ease with which left ventricular pressure (LVP) is measured.

In addition to their convenience, indices derived from isovolumic pressure decline are also justified on theoretical grounds. The law of La Place describes the relationship between wall tension and ventricular pressure: Tension = Pressure (radius/wall thickness). Since the chamber radius and wall thickness are assumed to be constant during isovolumic relaxation, a decrease in pressure

should reflect a proportionate decline in wall tension (26). Pressure derived indices of isovolumic relaxation include the maximal rate of ventricular pressure decline (dP/dt min) and the time constant of isovolumic pressure decline (27-29). These indices are analogous to the maximum rate of tension decline (-dF/dt max) and the relaxation half-time ($t_{\frac{1}{2}}$) which have been used to measure relaxation in isolated myocardium (22, 23). The time constant is the most widely accepted of these two pressure derived indices since T describes relaxation throughout the isovolumic relaxation period instead of at a single instant, and because dP/dt min is dependent on the timing of aortic valve closure (26).

The use of T as an index of relaxation in the intact heart was originally justified by the observation that pressure decline in an isolated canine preparation was exponential (26). The time constant is defined as the time required for the pressure at dP/dt min to fall by 1/e, where e is the base of natural logarithms. Under ideal isovolumic conditions this means that pressure would fall to 36.8% of the original pressure in 1T and that relaxation would be 97% completed by 3.5 T (26). The exponential relationship between pressure and time, stated in another way, means that the rate of change in pressure at a given time is proportional to the pressure already reached, and T is the negative inverse of the constant relative rate of decrease. Weiss and associates (26) suggested that T might be an index of the inactivation process since T was decreased by catecholamines which are believed to enhance the reuptake of calcium by the sarcoplasmic reticulum (30). It should be appreciated

that the description of isovolumic pressure decline as exponential was originally made in an isolated heart with nonfunctional valves. The description of ventricular pressure decline as exponential is an approximation in the working heart (26, 31). Deviation of the pressure-time relationship from an exponential function has been described by several investigators (29, 32). Nevertheless, the deviation appears to be minor and the monoexponential function is generally regarded as sufficiently adequate to justify the use of a time constant as an index of isovolumic relaxation (29, 32-35).

The time constant Tln is calculated from a semilogarithmic transformation of the pressure-time data (see Appendix A) and has been the most frequently used method of calculating T (26). Several alternative methods of calculating T have been proposed on the basis of a number of practical and theoretical considerations. A complete description of these methods including a sample LVP recording (Figure 10) and graphic presentations of two of the mathematical models (Figure 11) is presented in Appendix A.

The semilogarithmic method is based on the assumption that the asymptote, or the transmural pressure that the ventricle would approach if isovolumic relaxation were to continue infinitely, is equal to zero. This assumption has been challenged on the basis of two points. First, zero reference pressure is not necessarily equal to zero transmural pressure, and respiratory shifts in the LVP curve may introduce error into the calculation of T (36, 32-34). Secondly, it has been argued that if the end-systolic volume is very small and filling is prevented, then isovolumic relaxation will proceed to a

negative transmural pressure due to restoring forces in the myocardial wall (32). The semilogarithmic method has also been criticized on the grounds that the logarithmic function is inherently nonlinear and may produce mathematical error when different levels of pressures are used to calculate T (34, 37). The variable asymptote, exponential model (33), the derivative method (36), and the relaxation half-time have been proposed as alternatives to the semilogarithmic method to obviate these problems.

The derivative method (TD) has been used to calculate a time constant in several studies (38-40). The sensitivity of the measurement of the derivative of the LVP curve to electronic noise limits the use of this method (37). Furthermore, Tln has been determined to be statistically superior to TD as a measure of LVP decline (37).

Although $T_{\frac{1}{2}}$ has been used infrequently as an index of relaxation in the intact heart, it has been used to describe relaxation in isolated muscle studies (15). In addition, a recent study indicated that $T_{\frac{1}{2}}$ was well correlated with Tln (32). The relaxation half-time, $T_{\frac{1}{2}}$, is calculated directly from the pressure-time data, and may prove to be a valuable method of determining a time constant since it circumvents the need for curve fitting procedures (41).

The use of Texp as an alternative to Tln was first proposed by Thompson and associates (33). In a series of studies using normal human patients (33) and patients with a variety of cardiovascular diseases (34), Thompson and others compared the semilogarithmic and variable asymptote, exponential methods to determine whether the

assumption of a zero asymptote contributed error to the calculation of T. The two methods were compared with regard to the calculated values of T and the statistical fit between measured pressures and the pressure decline predicted by the respective models. Statistical comparisons were made using the chi-square statistic for goodness of fit and the ratio of the residual sums of squares to the total sums of squares (RSS/TSS). The ratio RSS/TSS describes the variability in the data which is not accounted for by the model (33). The results of the study indicated that the variable asymptote model (Texp) was statistically superior to the zero asymptote semilogarithmic model (Tln) in 90% of the heart beats tested (33).

Plots of the natural log of pressure against time illustrated that the lack of fit in the semilogarithmic model was due to a systematic downward curvature of the measured pressures from the predicted linear model at lower pressure levels. The asymptote estimated by the exponential model was consistently negative, and the value of Texp was consistently greater than Tln for the same beats. Moreover, both the ratio of Texp and Tln and the lack of fit of the semilogarithmic model were inversely related to the value of the asymptote. Thompson and others concluded that Tln is an unreliable estimate of the time constant because Tln underestimates Texp when the asymptote is negative and the asymptote is negative under a variety of hemodynamic conditions (33, 34). The relationship between Tln and Texp was evaluated by other investigators using anesthetized dogs (37). The results were consistent with those of Thompson et al

in that the value of Texp was consistently greater than Tln, and the statistical fit was superior for the variable asymptote model in 98% of the beats analyzed.

Thompson and associates noted that even though the ratio of Texp and Tln was related to the value of the asymptote, the difference between these estimates of T was not altogether explained by this relationship (33). It was proposed that the value of Tln is determined, in part, by the level to which pressure declines due to artifacts of the logarithmic function (33). In order to test this hypothesis, values of Tln were compared with values of T calculated from a zero asymptote exponential model using nonlinear regression rather than a semilogarithmic transformation. It was determined that Tln also underestimated values of T estimated by the zero asymptote, exponential model and that the ratio of the two values of T was related to the lowest value of pressure included in the analysis (34). It was concluded that the logarithmic transformation as well as the assumption of a zero asymptote contributes error to the calculation of a time constant.

Martin and associates used a different approach to determine the significance of mathematical artifacts contributed by the semilogarithmic transformation (37). In an experiment using anesthetized dogs, the LVP curves following interventions which changed left ventricular end-diastolic pressure (LVEDP) were translated so that pre- and post-intervention time constants were calculated from similar values of pressures at the lower end of the curve. Pressure curves were translated by adding or subtracting the

difference between LVEDP before and after the intervention from all of the post-intervention pressures used in the analysis. The results demonstrated that values of Tln increased with upward translation of pressures and decreased with downward translation. Martin et al attributed the dependence of values of Tln upon the levels of pressure analyzed to the nonlinearity of the logarithmic function. Values of the natural log of pressure become increasingly negative as values of pressure approach zero (37). Therefore, the observed lack of fit of the semilogarithmic model at low pressures may be partially due to artifacts which result from the use of logarithms.

The hypothesis that left ventricular pressure might actually decline to negative levels in the absence of filling was confirmed using an open chest canine preparation (32). Filling was prevented, in this experiment, by occlusion of the mitral valve for single cardiac cycles. The lowest LVP for these nonfilling beats was used as an empirical estimate of the asymptote and was found to be consistently negative. The time constant TE was computed for nonfilling beats for pressures between dp/dt min and the measured asymptote and compared with values of Texp* and Tln calculated for the same beats using pressures between dP/dt min and the atrio-ventricular pressure crossover. The index Texp* is analogous to Texp except that a semilogarithmic transformation was used to linearize the variable asymptote, exponential function. This transformation was also used to calculate TE (see Appendix A). The results of the study were consistent with previous studies with respect to the relationship between Texp and Tln (33, 34, 37). The

unique aspect of the study was the comparison of TE with both Tln and Texp*. The best-fit estimate of the asymptote proved to be significantly more negative than the actual measured value, and Texp* was significantly larger than TE. Furthermore, the value of Tln, though consistently smaller, was not significantly different from TE. Therefore, if TE is considered to represent the true rate of isovolumic pressure decline, Tln was a better estimate of the time constant than Texp* (32).

The finding that Tln was a better estimate of the true rate of pressure decline than Texp* was attributed to a combination of two errors. First, actual pressure decline is more rapid than the rate of decline predicted by a monoexponential function. And, secondly, forcing the function to a zero asymptote estimates a more rapid rate of pressure decline than that predicted using a variable asymptote model. The overall result of these errors is that the rate of pressure decline predicted by the semilogarithmic model is closer to the actual rate of pressure decline. Therefore, it was concluded that Tln is a useful index of relaxation in spite of the errors inherent in the assumption of a zero asymptote (32). It should be noted, however, that this study does not address the problems associated with the nonlinearity of the logarithmic function.

Although it has been established that the semilogarithmic method may produce errors in the calculation of T due to the assumption of a zero pressure asymptote and mathematical artifacts of the logarithmic function, the variable asymptote model is also controversial. Much of the controversy may be attributed to different interpretations of

the significance of the asymptote. Several investigators have demonstrated that the asymptote may be affected by the accuracy of the zero reference pressure and baseline shifts due to respiration (32, 33, 36). The asymptote has been interpreted simply as a correction for respiration dependent shifts in intrathoracic pressure, and several investigators have assumed that the asymptote was equal to zero when open-chest preparations were used (25, 38, 42). Since variations in the asymptote may also occur with changes in other factors such as the inotropic state and heart rate (33, 37), others have suggested that variations in Texp are not meaningful unless changes in the asymptote are considered simultaneously (37). Unfortunately, interpretation of changes in the asymptote are problematic since the variable has no clear physiological correlate (33, 37) and may not be independent of changes in Texp (37). Therefore, although the exponential model with a variable asymptote is well founded on theoretical and statistical grounds, there is no consensus as to whether Texp is an empirically better index of relaxation than Tln.

Evaluation of Factors Which Affect the Time Constant

In order to more completely characterize T as an index of isovolumic relaxation and provide an empirical basis by which the methods of calculation can be distinguished, it is important to understand how values of Texp and Tln are affected by changes in other hemodynamic conditions. The effects of variables which reflect loading conditions or changes in myocardial calcium flux are of

particular interest given the current concept of the regulation of myocardial relaxation (1-3, 11). Also, the fact that pressure decline may be affected by a number of interacting factors (3) warrants an understanding of how values of T are affected by hemodynamic factors such as heart rate which are not clearly related to the process of myocardial relaxation.

The effects of changes in heart rate on Tln have been described by a number of investigators. Weiss and associates (26) observed a significant decrease in Tln with an increase in heart rate from 110 to 130 beats per minute (bpm) in an isolated, isovolumic heart preparation, but additional increases in rate between 130 and 160 bpm had no additional effect on the value of Tln. A decrease in Tln was observed for the isolated working heart when heart rate was abruptly increased by 70 bpm but not for smaller changes in rate (29). Similar results were reported for studies using conscious (43) and anesthetized dogs (40) in which large abrupt increases in heart rate were required to produce small, though significant, decreases in Tln. In another study heart rate was increased incrementally between 86 and 132 bpm in normal humans and although the maximal increase in rate produced a significant (23%) decrease in Tln, the overall relationship between Tln and heart rate was not significant (33). In general, the results of these studies established that large increases in heart rate were necessary to produce relatively small changes in Tln under a variety of conditions. Therefore, Tln appears to be only nominally dependent on heart rate. Karliner and associates (43) proposed that the decrease in Tln with abrupt

increases in rate might be related to the positive inotropic effect of increased heart rate (Bowditch effect) which is mediated by changes in calcium transport. The fact that four out of six studies (29, 33, 40, 43) reported significant increases in contractility (dP/dt max) concurrent with increases in heart rate lends some support to this hypothesis. The effect of changes in heart rate on Tln, Texp, and other hemodynamic parameters is presented in table 1.

There are few papers which have reported the effects of heart rate on Texp. In a series of articles, Thompson and others reported that Texp was inversely related and the asymptote directly related to heart rate in normal humans (33), and in human patients with coronary artery disease (CAD) or hypertrophic cardiomyopathy (HCM) (33, 35). In normal humans a maximal, 53%, increase in heart rate promoted a 38% decrease in Texp and a 64% increase in the asymptote (33). A comparable increase in heart rate in patients with CAD and in patients with HCM produced changes in Texp and the asymptote of smaller magnitude, but the changes were significant and consistent with those observed for normal patients (33, 35). Changes in Texp with heart rate could not be consistently related to changes in other hemodynamic parameters (33). The fact that Texp changed incrementally with changes in heart rate, whereas Tln did not (33), suggests that Texp may be more sensitive to changes in heart rate than Tln.

The effects of various inotropic agents including catecholamines, calcium chloride, and acetylstrophanthidin (ACS) on Tln have also been evaluated (see Table 2). Even though relaxation

Table 1. REPORTED CHANGES IN RELAXATION INDICES AND HEMODYNAMIC VARIABLES WITH PACING

Reference	HR % change[a]	Tln % change	Texp % change	Pb % change	EDP change (mmHg)	LVPSP % change	dP/dt max % change
26	+45%	-8%	-	-	-	NSC	-
29	+42%	NSC	-	-	NSC	NSC	+39%
43	+64%	-18%	-	-	-5.2 mmHg	NSC	+10%
33	+53%	-22%	-38%	+64%	-3.4 mmHg	-	+27%
40	+167%	-30%	-	-	-3.3 mmHg	-	+16%
35	+63%	-	-38%	+64%	-	-	-

[a] % change is equal to the % change of reported means

Table 2. REPORTED CHANGES IN RELAXATION INDICES AND HEMODYNAMIC VARIABLES WITH CHANGES IN INOTROPIC STATE

Reference	Drug	dP/dt max % change[a]	Tln % change	Texp % change	Pb % change	LVPSP % change	EDP change (mmHg)	HR % change
26	ACS[b]	-	NSC	-	-	+19%	-	NSC
29	ACS	+45%	-27%	-	-	NSC	-	NSC
26	$CaCl_2$[c]	-	NSC	-	-	+49%	-	NSC
43	$CaCl_2$	+25%	-15%	-	-	NSC	NSC	NSC
40	$CaCl_2$	+53%	-26%	-	-	-	NSC	-29%
26	NE[d]	-	-29%	-	-	+46%	-	NSC
29	NE	+28%	-19%	-	-	NSC	NSC	NSC
43	IP[e]	+37%	-26%	-	-	NSC	-5.4 mmHg	+22%
40	IP	+169%	-45%	-	-	-	NSC	+48%
44	IP	+57%	-17%	-	-	-	-2.3 mmHg	NSC
37	IP	+38%	-19%	NSC	NSC	NSC	-1.4 mmHg	NSC
29	Propr[f]	-19%	+36%	-	-	NSC	+8 mmHg	NSC
40	Propr	-42%	NSC	-	-	-	NSC	NSC
44	Propr	-28%	+10%	-	-	-	+1.1 mmHg	NSC
35	Propr	-19%	-	NSC	NSC	NSC	NSC	NSC
37	Propr	-39%	+60%	NSC	NSC	NSC	+8 mmHg	NSC

[a]% change is equal to the % change of reported means
[b]ACS is acetylstrophanthidin
[c]$CaCl_2$ is calcium chloride
[d]NE is norepinephrine
[e]IP is isoproterenol
[f]Propr is propranolol

can be modified independently of contractility (15), the relationship between the two processes is of interest since both are clearly affected by calcium fluxes. The effects of catecholamines on Tln and Texp are of particular interest given that they reportedly increase the rate of tension decline in isolated myocardium (15, 23, 24) and given the hypothesis that catecholamines augment relaxation by facilitating calcium uptake by the sarcoplasmic reticulum (30).

Decreases in Tln produced by norepinephrine and isoproterenol have been reported for studies using isolated hearts (26, 29) and conscious (43) and anesthetized dogs (40, 44). These changes were consistently associated with significant increases in the maximal rate of LVP rise (dP/dt max). Dosages of propranolol sufficient to produce significant reductions in dP/dt max have been shown to significantly increase Tln in both isolated (29) and intact (44, 37) canine preparations. In contrast, in a single study the increase in Tln with propranolol was not significant despite a comparable reduction in dP/dt max (40).

The effects of propranolol on the value of Texp have been described in anesthetized dogs (37) and in human patients with HCM (35). In both studies propranolol failed to produce consistent changes in Texp or the asymptote in spite of significant decreases in dP/dt max. Isoproterenol, which produced a significant decrease in Tln, had no effect on Texp or the asymptote in anesthetized dogs (37). The results of these studies indicate that beta stimulation and blockade may have a more significant effect on Tln than on Texp.

The effects of calcium chloride and the cardiac glycoside ACS have been reported for Tln but not for Texp. Calcium chloride administration increased dP/dt max and decreased Tln in conscious and anesthetized dogs (40, 43), and ACS had similar effects in the canine isolated, working heart (29). In the study using conscious dogs beta-blockade prior to calcium administration did not change the results which suggests that the effects of calcium on Tln were not mediated through changes in autonomic tone. Calcium chloride and ACS did not significantly affect the value of Tln in an isolated, isovolumic heart preparation (26). It is possible that changes in loading conditions, reflected by the increase in LVPSP, may have obscured the effects of increased contractility in this study. Although increases in the rate of tension decline with calcium chloride have also been reported for isolated muscle (23, 24), the mechanism by which calcium might augment relaxation has not been defined (43).

Based on a study using an isolated canine heart, Frederiksen and associates originally concluded that Tln was independent of afterload (29). No changes in Tln were observed in this experiment as left ventricular peak systolic pressure (LVPSP) was increased in 25 mmHg increments from 85 to 185 mmHg. In contrast, the results of studies done in more intact preparations have generally indicated that Tln increases when afterload increases. Karliner and others observed a 47% increase in Tln concurrent with a 46% increase in LVPSP following phenylephrine infusion in conscious dogs (43). A similar change in Tln was reported with phenylephrine administration in anesthetized

dogs (40). Gaasch and associates (44) observed increases in Tln of 16 and 42% with successive increases in LVPSP of 12 and 24%, respectively, following methoxamine infusion. In the same study Tln was significantly decreased with a 34% decrease in LVPSP elicited by nitroprusside but not with a 26% decrease in LVPSP produced by the same drug. Because the end-systolic length (ESL) was decreased by methoxamine and increased in the one experiment in which nitroprusside produced a decrease in Tln, it was concluded that changes in Tln as a result of changes in afterload were related directly to ESL (44).

Significant changes in Tln have also been reported following acute changes in afterload. Aortic constriction prior to the opening of the aortic value resulted in a significant increase in LVPSP and Tln (44, 45), whereas rapid withdrawal of blood from the aorta during diastole significantly decreased both LVPSP and Tln (44). These changes in Tln were again associated with changes in ESL. The fact that acute and steady state changes in afterload had the same effect on Tln was used as evidence that the effects of afterload were not due to sympathetic reflexes (44, 45). The results of studies evaluating the effects of afterload on T are summarized in Table 3. With the exception of the experiment conducted in the isolated heart preparation, the effects of changes in afterload in the intact heart are consistent with the view that relaxation is significantly affected by changes in loading conditions. It should be appreciated that the changes in afterload produced in most of these studies were associated with concurrent changes in preload (LVEDP). It is

Table 3. REPORTED CHANGES IN RELAXATION INDICES AND HEMODYNAMIC PARAMETERS WITH CHANGES IN AFTERLOAD

Reference	LVPSP % change[a]	Tln % change	Texp % change	Pb % change	EDP change (mmHg)	dP/dt max % change	HR % change	ESL % change
29	+126%	NSC	-	-	+8.4 mmHg	+27%	NSC	-
43	+46%	+47%	-	-	+13 mmHg	NSC	NSC	+21%
44	-26%	NSC	-	-	-1.3 mmHg	-14%	NSC	NSC
44	-34%	-19%	-	-	-1.4 mmHg	-13%	NSC	-6%
44	+12%	+16%	-	-	NSC	NSC	NSC	NSC
44	+24%	+42%	-	-	+1.8 mmHg	NSC	NSC	+13%
45	+22%	+35%	-	-	-	NSC	NSC	+12%
40	-[b]	+49%	-	-	+18.8 mmHg	+38%	-31%	-

[a]% change is equal to the % change of reported means

[b]Mean aortic pressure increased by 66%

possible, therefore, that changes in Tln in these studies may reflect the effects of changes in preload as well as afterload.

Studies evaluating the effects of preload changes on Tln have yielded conflicting results (Table 4). Incremental increases in LVEDP between 7 and 22 mmHg in an isolated, isovolumic heart preparation produced no significant increase in Tln (26). Similarly, no significant changes in Tln were observed for comparable increases in LVEDP in an isolated, working heart preparation as cardiac input was gradually increased (29). No significant changes in Tln were also reported for conscious (43) and anesthetized dogs (40) in which LVEDP was significantly increased by volume loading. In contrast, Raff and Glantz observed significant increases in Tln following volume loading in anesthetized dogs with either a closed-chest, open-chest or open-pericardium (38). In this study LVEDP was increased sequentially in 5 mmHg increments up to 20 mmHg above baseline, and Tln increased linearly with LVEDP up to 60% above baseline with the maximum increase in preload. Gaasch and others (44) observed a significant increase in Tln following volume expansion only with relatively large increases in LVEDP concurrent with increases in LVPSP, dP/dt max, and ESL. In a second study from the same laboratory, an in situ canine heart preparation was used to determine the effects of single beat increases in preload with and without increases in total load (afterload + preload) (42). Preload was increased by infusion of blood into the left ventricle prior to opening of the aortic valve. For beats in which total load was held constant blood was withdrawn from the aorta during systole. The

Table 4. REPORTED CHANGES IN RELAXATION INDICES AND HEMODYNAMIC VARIABLES WITH CHANGES IN PRELOAD

Reference	EDP change (mmHg)	Tln % change[a]	Texp % change	Pb % change	LVPSP % change	dP/dt max % change	HR % change	ESL % change
26	+15 mmHg	NSC	-	-	+63%	-	NSC	NSC
29	+6 mmHg	NSC	-	-	NSC	NSC	NSC	-
43	+8 mmHg	NSC	-	-	NSC	NSC	NSC	NSC
38[b]	+20 mmHg	+60%	-	-	-	-	-	-
44	+1.7 mmHg	NSC	-	-	NSC	NSC	NSC	NSC
44	+7.6 mmHg	+27%	-	-	+21%	+34%	NSC	+13%
40	+15 mmHg	NSC	-	-	-[c]	+22%	+51%	-
37	-2 mmHg	-17%	NSC	NSC	-12%	+12%	NSC	-

[a]% change is equal to the % change of reported means

[b]Actual changes in HR LVPSP and dP/dt max were not reported, but all three were reported to have increased significantly

[c]Mean aortic pressure increased 22%

results indicated that acute increases in preload promoted an increase in Tln only when total load was also increased. When total load was held constant by reducing afterload Tln was unaffected. These data were interpreted to mean that increased preload has a significant effect on Tln only when the increase in preload is translated into an increase in systolic load (developed tension). Gaasch and associates suggested that afterload is the primary determinant of Tln rather than preload (42). This hypothesis may explain why an increase in Tln has been observed in some studies (38, 44), but not in others (43, 44). Nevertheless, no increase in Tln was observed in a single study where a concurrent increase in dP/dt max and aortic pressure would suggest that afterload was also increased (40). Therefore, the effects of changes in preload on Tln remain controversial.

Martin and others designed a study to determine whether the nonlinearity of the logarithmic function might explain some of the inconsistency with respect to the effects of preload on Tln (37). In this experiment the effects of incremental decreases in LVEDP produced by nitroprusside were evaluated before and after translation of post-intervention LVP curves. Since curve translation matched the lowest values of LVP used in the calculation of Tln before and after changes in preload, the process removed any artifacts introduced by the semilogarithmic transformation (37). Decreases in Tln with decreases in preload continued to be significant even after curve translation, but the apparent effect was attenuated. The decrease in the value of Tln was 9% following curve translation compared with an

apparent decrease of 17% before translation. Hence, the nonlinearity of the logarithmic transformation may have an important effect on the results of studies evaluating changes in loading conditions when LVEDP is changed significantly (37). Nevertheless, the effects of preload changes on Tln could not be attributed solely to the mathematical artifacts of the semilogarithmic transformation (37).

There is a paucity of data regarding the effects of changes in loading conditions on Texp. In a study using anesthetized dogs, simultaneous changes in afterload and preload elicited by angiotensin and nitroprusside had no consistent effect on either Texp or the asymptote (37). In this study Texp exhibited some tendency to increase with successive increases in LVEDP and LVPSP produced by angiotensin, and to decrease with opposite changes in these parameters elicited by nitroprusside, but the observed changes in Texp and the asymptote were neither dose dependent or homogeneous. These observations are consistent with the observation by Thompson and others that Texp was not related directly to changes in loading conditions in human patients with HCM (35). There are too few studies on which to base firm conclusions regarding the effects of loading conditions on Texp. The available data suggest that Texp may be less sensitive to loading conditions than Tln.

In summary, Tln appears to be minimally dependent on heart rate and significantly affected by agents that alter inotropy. The effects of changes in afterload and preload on Tln are more controversial, which is due, in part, to the difficulty of assessing the effects of either preload or afterload independently under steady

state conditions. Loading conditions do appear to have an important effect on Tln in intact preparations particularly when both preload and afterload are altered simultaneously. It is important to note that there were apparent differences in the effects of both loading conditions and inotropic agents on Tln when they were assessed in isolated hearts rather than more intact preparations. The type of preparation, therefore, may affect the sensitivity of Tln to various hemodynamic factors (7, 38, 44, 45).

The effects of changes in various hemodynamic factors on Texp are poorly defined, but Texp appears to be more dependent on heart rate and less sensitive to changes in inotropy and loading conditions than Tln. These apparent differences between Tln and Texp are important because they indicate that the conclusions regarding the effects of certain mechanical or pharmacologic interventions on relaxation may depend on the method used to calculate T (33).

C. OBJECTIVES FOR THE STUDY

Because the method by which the time constant is derived may affect the results of studies using T as a measurement of relaxation, a more complete characterization of the limitations of the methods used to calculate the index is warranted. In addition, given that the experimental preparation may affect the sensitivity of the estimates of T to various hemodynamic conditions it is necessary to examine the respective time constants under the same experimental conditions in order to make valid comparisons between them. In this study the time constants Tln, Texp, and $T_{\frac{1}{2}}$ were evaluated using

normal cats anesthetized with isoflurane and interventions which mimic the changes in afterload, preload, heart rate, and contractility encountered under clinical conditions. The objectives of the study were:

I. To reexamine the models used to calculate Texp and Tln with respect to how accurately the models predict actual pressure decline by comparing the ratio of the residual sum of squares to the total sum of squares (RSS/TSS).

II. To evaluate and compare the effects of changes in afterload, preload, heart rate, and inotropic state on the values of Tln, $T_{\frac{1}{2}}$, and Texp, to determine whether these estimates of a time constant are affected by hemodynamic factors which may not directly reflect changes in ventricular relaxation.

III. To compare values of the three time constants under a variety of hemodynamic conditions using linear regression analysis and the correlation coefficient to determine whether they are consistently related.

CHAPTER II

MATERIALS AND METHODS

A. ANIMALS AND INSTRUMENTATION

Normal cats (2.2-4.6 kg) of either sex were premedicated with oxymorphone (0.045 mg/kg im) and anesthetized with isoflurane. Animals were maintained in a stable surgical plane of anesthesia throughout the experiment using isoflurane and oxygen at a flow rate of 2-3 L/min. Respiration was spontaneous and regular in all animals. A circulating warm water blanket (K-Pad, American Hospital Supply, Norcross, GA) was used to maintain body temperature.

A carotid artery and jugular vein were isolated through a single incision made lateral to the trachea. A micromanometer (Model PC-330, Millar Instruments, Houston, Texas) was zeroed at atmospheric pressure, calibrated to mercury, and introduced into the left ventricle via the carotid artery. A bipolar pacing catheter (Bard USCI, Billerica MA) was positioned in the right atrium via the jugular vein.

The micromanometer was connected to a universal amplifier (Model 13-4615-68, Gould Inc., Cleveland, Ohio) via a transducer control unit (Model TC-100, Millar Instruments, Houston, Texas). The derivative of left ventricular pressure (dp/dt) was derived by electronic differentiation of the pressure signal using a differentiator amplifier (Model 13-4615-71, Gould Inc., Cleveland, Ohio). Left ventricular pressure, dP/dt, and the ECG were monitored

continuously on a video monitor (Model V-1000, Gould Inc., Cleveland, Ohio). Data were recorded at paper speeds of 25 and 250 mm/sec on an electrostatic recorder (Model ES1000, Gould Inc., Cleveland, Ohio).

Atrial pacing was accomplished using a square wave stimulator (Model S48, Grass Electronics, Quincy, MA) connected in series with an stimulus isolation unit (Model SIU5, Grass Electronics, Quincy, MA) and a constant current unit (Model CCUIA, Grass Electronics, Quincy, MA). Hearts were paced using a current of 0.04 milliamperes at a duration of 3.5 milliseconds (ms). Drugs and fluids were infused into the cephalic vein at a constant rate using a syringe pump (Model 341, Sage Instruments, Cambridge, MA).

B. PROTOCOL

Preload was increased by volume loading with a 1:1 mixture of isotonic saline and blood maintained at 37° C. The mixture was infused at a constant rate of 8 mls/min to produce successive steady state increases in LVEDP of approximately 3 mm Hg and 6 mm Hg. Actual volumes infused ranged between 10 and 40 ml (mean 20 $\pm$ 2.6 ml) for the initial increase, and between 23 and 56 ml (mean 35 $\pm$ 5.3 ml) for the larger increase. Volume loading did not produce significant changes in body temperature or hematocrit. When volume loading preceded a second intervention, LVEDP was returned to the baseline level by slowly withdrawing blood from the jugular vein.

Afterload was increased by the infusion of the alpha-adrenergic agonist phenylephrine (Withrop Breon, New York, NY) at a rate of approximately 0.001 mg/kg/min. The dosage of the drug was titrated

to successively increase LVPSP by 14% (0.0009-0.003 mg/kg total dosage) and 26% (0.0013-0.005 mg/kg total dosage).

Calcium chloride (Upjohn, Kalamazoo, MI) was used to augment contractility. The drug was given as a slow bolus (2.5-3 mg/kg) followed by an infusion of approximately 2.5 mg/kg/min. Total dosages of calcium chloride were adequate to produce successive increases in dP/dt max of 12% (4-19 mg/kg) and 24% (12-40 mg/kg).

Heart rate was increased in increments of approximately 16 bpm above the lowest paced rate. The effects of increasing heart rate were determined for rates in the same ranges in all animals. The four ranges and the mean rate $\pm$ SEM for each range were: 155-175 bpm (166 $\pm$ 2.4), 176-190 bpm (182 $\pm$ 1.5), 195-200 bpm (197 $\pm$ 0.8) and 205-220 bpm (213 $\pm$ 1.6).

Each animal was used for several interventions, and the order of the interventions was randomized. Data were recorded for the basal state and during steady state changes in hemodynamic conditions. Variables were allowed to return to baseline between separate experiments. The heart was paced at a constant rate approximately 20 bpm above the unpaced rate for each animal during the afterload, preload and contractility experiments. Each intervention was completed in seven to ten different animals.

C. DETERMINATION OF TIME CONSTANTS

The high gain LVP recordings were enlarged to produce copies for which 1 mm on the vertical scale was equivalent to 0.4 mmHg, and 1 mm on the horizontal scale was equivalent to 3.3 ms. The pressure

tracings were digitized at 4 ms intervals between dP/dt min and a pressure 2 mmHg above the LVEDP using a digitizing tablet interfaced with a computer (Carl Zeiss Inc., West Germany). Each heart beat was digitized twice and the mean pressures were used to calculate Texp and Tln. The LVEDP was determined as the pressure at the peak of the R wave of the QRS complex. An example of a LVP tracing used for calculation of Tln, Texp, and $T_{\frac{1}{2}}$ is shown in Figure 11, Appendix A.

The time constants Tln and Texp were calculated by fitting the pressure-time data to the functions given in Appendix A using SAS® linear and nonlinear regression programs, respectively. The multivariate secant (DUD) iterative method (46) was used to fit the nonlinear model, whereas the least-squares method was used to fit the linear model (47). The relaxation half-time was calculated directly from the enlarged pressure recordings as the time required for the pressure at dP/dt min to decline by one-half. Each value of the time constant was calculated as the mean value for three heart beats for a given set of hemodynamic conditions.

D. STATISTICAL METHODS

The statistical fit of the two mathematical models used to calculate Tln and Texp was evaluated by comparing the respective ratios of the residual sums of squares to the total sums of squares (RSS/TSS). Least-squares, multiple linear regression was used to fit a quadratic term to the semilogarithmic model to examine the model for systematic departures from linearity (47). The effects of increasing preload, afterload, heart rate, and contractility were

assessed using a SAS® (GLM) repeated measures analysis of variance. When the overall treatment effect was significant, a profile transformation (GLM®) was used to determine which adjacent treatment levels were significantly different (48). Least-squares, linear regression and the correlation coefficient were used to examine the relationships between values of Tln, Texp, and $T_{\frac{1}{2}}$ (47). All variables are expressed as the mean $\pm$ SEM. Differences were considered significant at the 0.05 level.

CHAPTER III

RESULTS

A. EFFECTS OF PACING

Time constants and hemodynamic parameters were compared at four levels of heart rate using seven animals. The results are shown in Table 5. The heart rate was increased in increments of 16 bpm (10-22 bpm) beginning at an initial rate (Heart Rate I) of 20 bpm above the nonpaced rate for each animal. The initial rate was in a range from 155 to 175 bpm, and the maximal rate (Heart Rate IV) was between 205 and 220 bpm. The initial increase in heart rate from 166 $\pm$ 2.4 bpm (mean $\pm$ SEM) to 182 $\pm$ 1.5 bpm had no significant effect on any of the hemodynamic variables measured. An additional increase in heart rate from 182 $\pm$ 1.5 bpm to 197 $\pm$ .8 bpm decreased LVPSP significantly from 82 $\pm$ 2.2 mmHg to 79 $\pm$ 1.9 mmHg and dP/dt min from 1800 $\pm$ 86 mmHg/s to 1686 $\pm$ 85 mmHg/s. The last incremental increase in heart rate up to 213 $\pm$ 1.6 bpm produced additional decreases in LVPSP and dP/dt min of 5% and 7%, respectively, and a significant decrease in dP/dt max from 2223 $\pm$ 176 mmHg/s to 2102 $\pm$ 179 mmHg/s. No significant changes in LVEDP were observed as heart rate was increased. It should be noted that the changes in LVPSP, dP/dt max, and dP/dt min, though significant, were rather small. In fact, changes in these parameters were less than 10% in the majority of cats studied.

The time constants Tln and Texp and the asymptote (Pb) were not related to heart rate. The index $T_{\frac{1}{2}}$ was significantly related to

Table 5. THE RESPONSE OF RELAXATION INDICES AND HEMODYNAMIC VARIABLES TO PACING[a]

	Heart Rate I	Heart Rate II	Heart Rate III	Heart Rate IV
$T_{\frac{1}{2}}$[b], ms	18.6 ± 1.1	18.9 ± 1.3	19.4 ± 1.2	20.1 ± 1.4
Tln, ms	24.5 ± 1.6	24.8 ± 1.7	25.7 ± 1.6	25.8 ± 2.0
Texp, ms	27.0 ± 1.9	28.1 ± 2.8	29.2 ± 4.6	32.2 ± 4.8
Pb, mmHg	-1.4 ± 2.0	-2.2 ± 1.8	-2.9 ± 4.1	-4.9 ± 4.1
Heart Rate, bpm	166 ± 2.4	182 ± 1.5[c]	197 ± .8[d]	213 + 1.6[e]
LVPSP, mmHg	84 ± 2.6	82 ± 2.2	79 ± 1.9[f]	75 + 2.0[g]
LVEDP, mmHg	6.2 ± 1.9	5.7 ± 1.9	5.9 ± 1.9	5.9 + 1.8
dP/dt max, mmHg/s	2257 ± 190	2269 ± 193	2223 ± 176	2102 ± 179[h]
dP/dt min, mmHg/s	1794 ± 81	1800 ± 86	1686 ± 85[i]	1560 ± 93[j]

[a] Values are mean ± SEM, n = 7

[b] When all heart rates were considered, $T_{\frac{1}{2}}$ was significantly related to heart rate (P = .0435), but individual contrasts were not significant.

[c] P = .0001 Heart Rate II vs Heart Rate I

[d] P = .0001 Heart Rate III vs Heart Rate II

[e] P = .0001 Heart Rate IV vs Heart Rate III

[f] P = .0007 Heart Rate III vs Heart Rate II

[g] P = .0027 Heart Rate IV vs Heart Rate III

[h] P = .0177 Heart Rate IV vs Heart Rate III

[i] P = .0004 Heart Rate III vs Heart Rate II

[j] P = .0333 Heart Rate IV vs Heart Rate III

heart rate when all heart rates were considered (P = 0.0435), but the value of $T\frac{1}{2}$ was not significantly increased between any pair of rates. The value of $T\frac{1}{2}$ was increased by 5-20% between the lowest and highest paced rate in five cats, and was decreased or unchanged in two cats. A consistent increase in $T\frac{1}{2}$ with each successive increase in heart rate was observed in only three animals. Therefore, although increases in $T\frac{1}{2}$ were associated with increases in heart rate, the relationship was not consistent. The relationship of the values of $T\frac{1}{2}$, Texp, Tln, and Pb, respectively, with heart rate are presented for each animal in Figure 1. Notice that the changes in Texp, Tln, and Pb are not consistent for successive increases in heart rate for each cat or across heart rates between cats.

B. EFFECTS OF CALCIUM CHLORIDE

Calcium chloride was infused to increase contractility in 7 cats and the results are given in Table 6. The initial dosage (Calcium I) was sufficient to increase dP/dt max by an average of 12% (10-14%) above the control. The enhanced inotropic state was accompanied by small, significant mean increases in LVPSP and dP/dt min of 3% and 4%, respectively. Continued infusion of calcium chloride (Calcium II) produced a subsequent increase in dP/dt max of 11% (8-16%), an increase in LVPSP from 83 $\pm$ 4.4 mmHg to 87 $\pm$ 5.3 mmHg, and an increase in dP/dt min from 1748 $\pm$ 129 mmHg/s to 1874 $\pm$ 141 mmHg/s. Neither increase in contractility produced a concurrent change in LVEDP. The heart was paced at a constant rate for each animal.

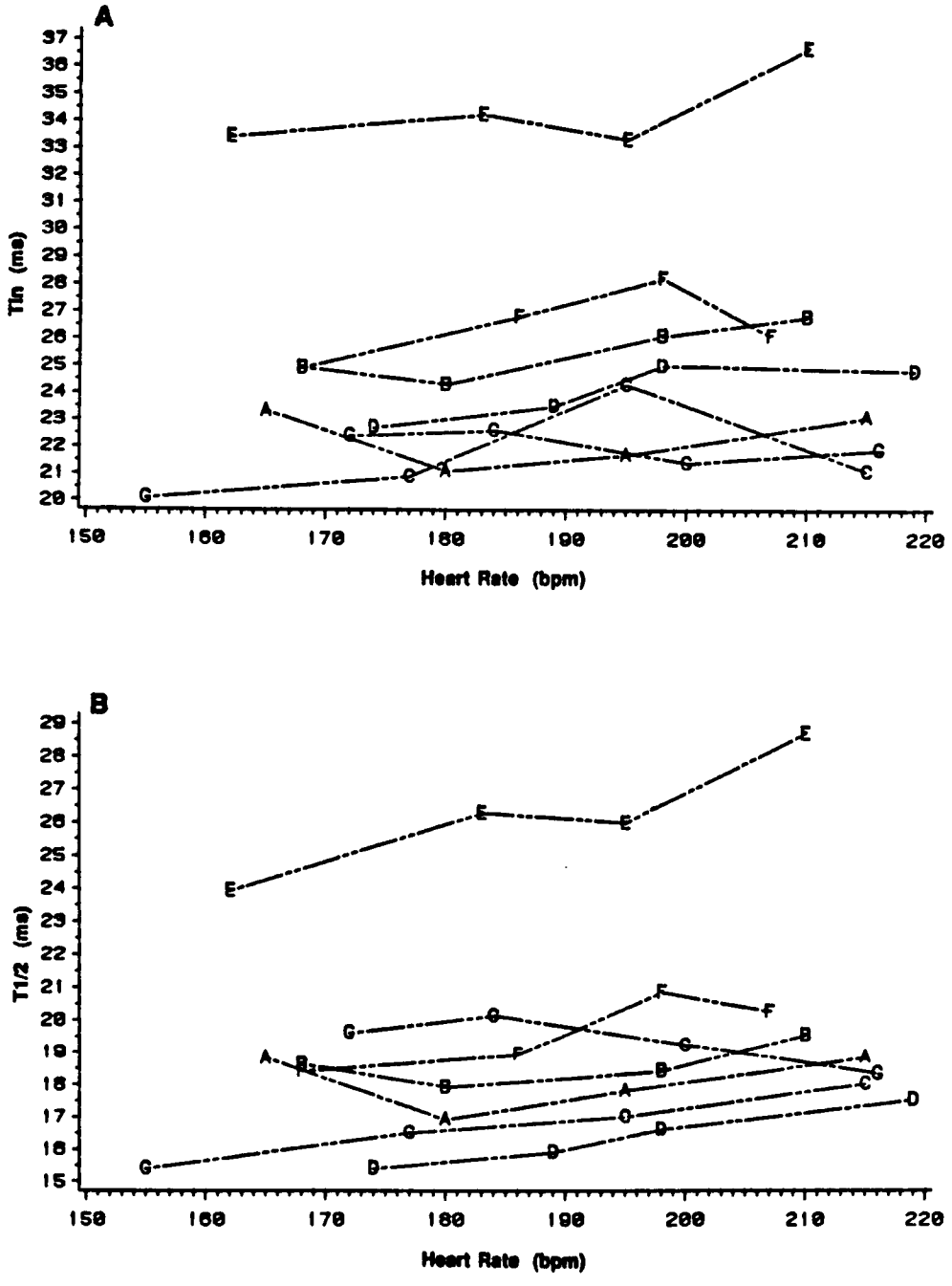
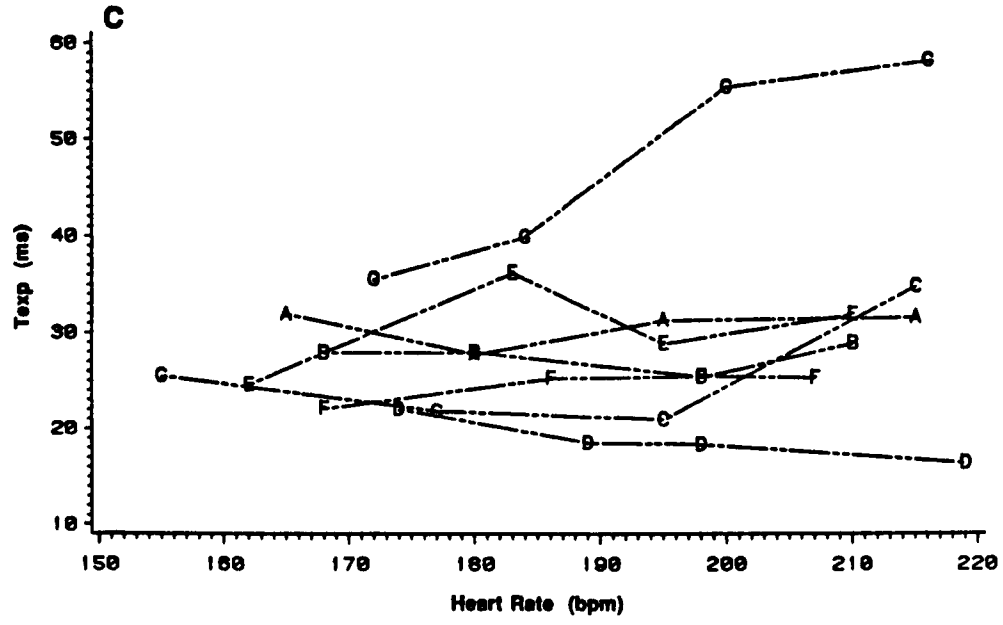


Figure 1. The Effect of Increasing Heart Rate on the Values of Relaxation Indices for Individual Cats. Each symbol represents a single cat. Plots illustrate the changes in Tln (A), $T_{\frac{1}{2}}$ (B), Texp (C), and Pb (D) with three successive increases in heart rate. Only the relationship between heart rate and $T_{\frac{1}{2}}$ was significant.



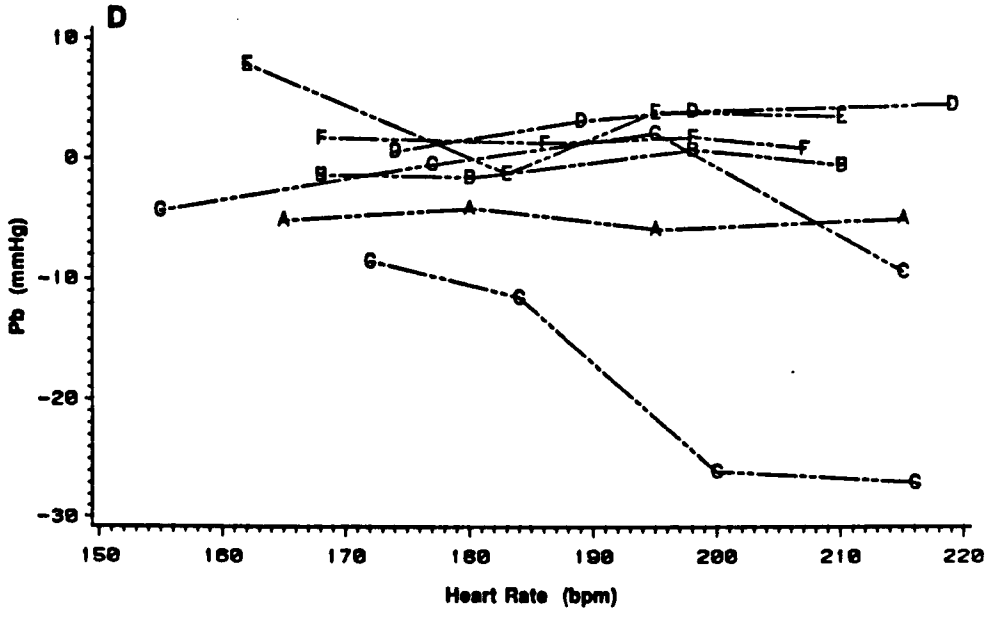


Figure 1 (continued)

Table 6. THE RESPONSE OF RELAXATION INDICES AND HEMODYNAMIC VARIABLES TO CALCIUM CHLORIDE[a]

	Control	Calcium I	Calcium II
$T_{\frac{1}{2}}$, ms	20 ± 1.1	19.3 ± 1.2	19.7 ± 1.4
Tln, ms	25.9 ± 2.0	26.6 ± 2.0	25.7 ± 2.0
Texp, ms	30 ± 1.7	28.6 ± 2.0	30.3 ± 2.3
Pb, mmHg	-2.5 ± .9	-1.5 ± 1.0	-3.0 ± .7
Heart Rate, bpm	151 ± 2.5	151 ± 2.5	151 ± 2.5
LVPSP, mmHg	81 ± 4.2	83 ± 4.4[b]	87 ± 5.3[c]
LVEDP, mmHg	4.6 ± 1.0	4.4 ± .9	4.0 ± .9
dP/dt max, mmHg/s	2051 ± 163	2291 ± 189[d]	2542 ± 211[e]
dP/dt min, mmHg/s	1674 ± 111	1748 ± 129	1874 ± 141[f]

[a] Values are mean ± SEM, n = 7

[b] P = .0353 Calcium I vs Control

[c] P = .0465 Calcium II vs Calcium I

[d] P = .0002 Calcium I vs Control

[e] P = .0002 Calcium II vs Calcium I

[f] P = .0471 Calcium II vs Calcium I

Calcium infusion had no significant effect on either of the three time constants or Pb. There were inconsistent changes in all four relaxation indices with increases in dP/dt max for individual cats (Figure 2).

C. EFFECTS OF PHENYLEPHRINE

Two sequential increases in afterload were produced by infusing phenylephrine in 10 cats (Table 7). The first infusion (Phenylephrine I) increased LVPSP by an average of 14% (11-19%) and the second infusion (Phenylephrine II) promoted an additional increase in LVPSP of 11% (6-18%) above the increase achieved with the initial dosage. With the initial increase in afterload, there was a significant increase in dP/dt max from 2328 $\pm$ 166 mmHg/s to 2568 $\pm$ 187 mmHg/s, and a significant increase in dP/dt min from 1724 $\pm$ 138 mmHg/s to 2032 $\pm$ 152 mmHg/s. Similarly, the second infusion of phenylephrine produced significant increases in dP/dt max and dP/dt min of 6% and 10%, respectively. Only the second increase in afterload was associated with a significant increase in LVEDP. The increase in LVEDP was 1.0 $\pm$ .13 mmHg between phenylephrine I and II. Since there was no increase in LVEDP with phenylephrine I, the initial increase in LVPSP represents a relatively pure increase in afterload.

Incremental changes in afterload did not produce uniform changes in any of the estimates of T or Pb. Figure 3 illustrates that the values of the relaxation indices were decreased with increasing LVPSP

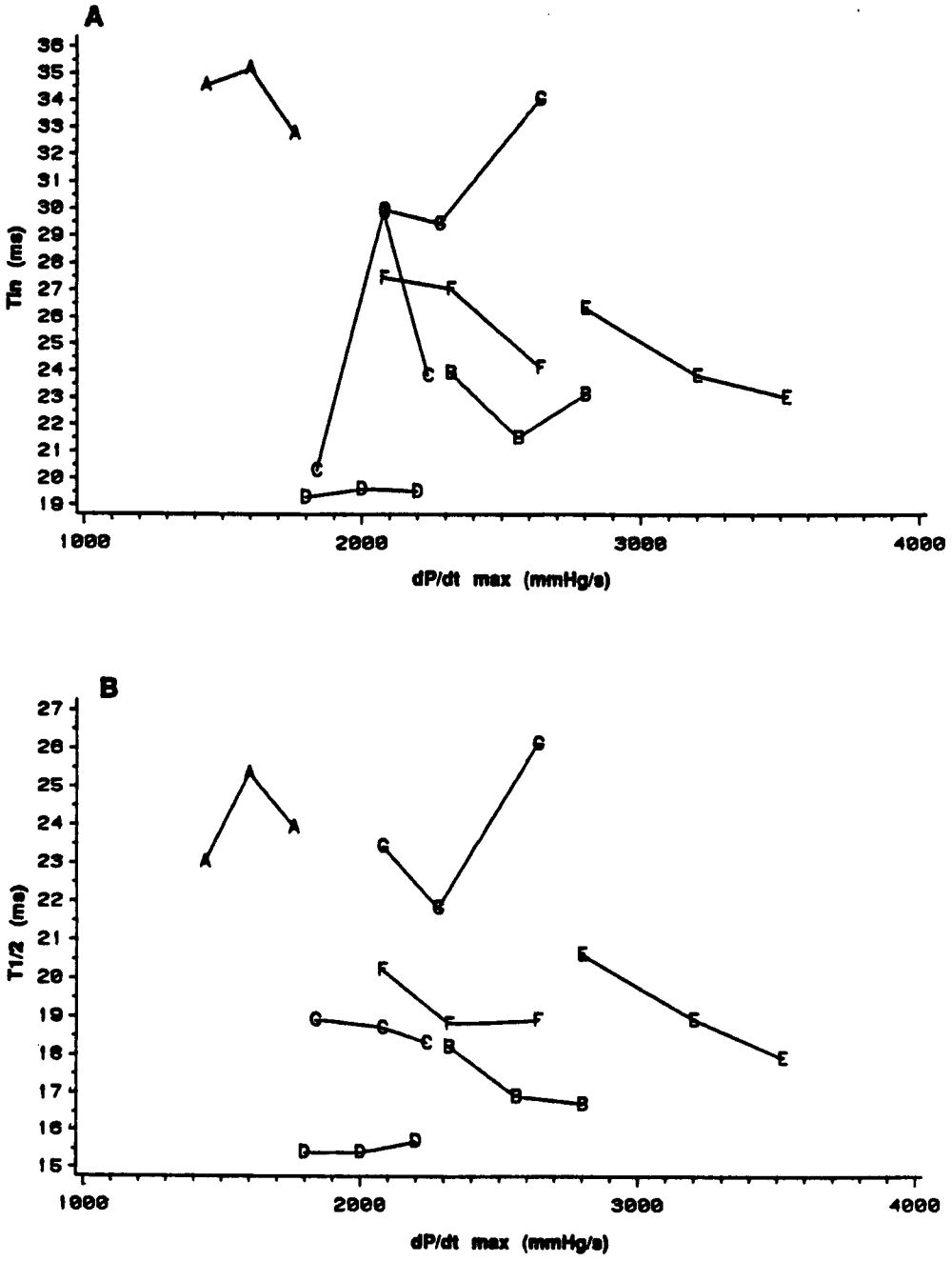
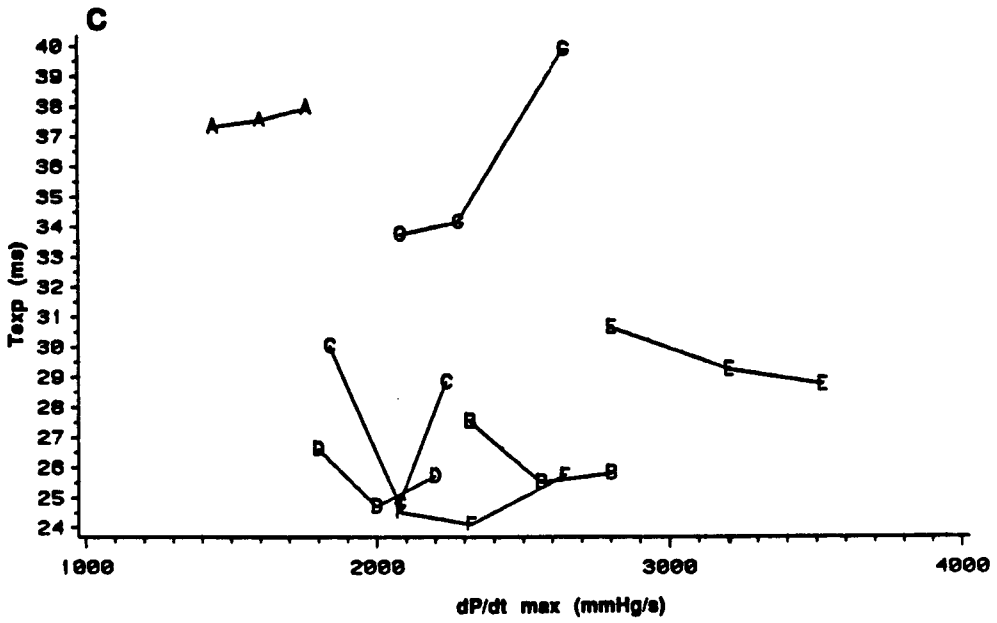


Figure 2. The Effect of Calcium Chloride Infusion on the Values of Relaxation Indices for Individual Cats. Each symbol represents a single cat. Plots show the changes in Tln (A), $T_{\frac{1}{2}}$ (B), Texp (C), and Pb (D) following two successive increases in dP/dt max. None of the relationships between relaxation indices and dP/dt max were significant.



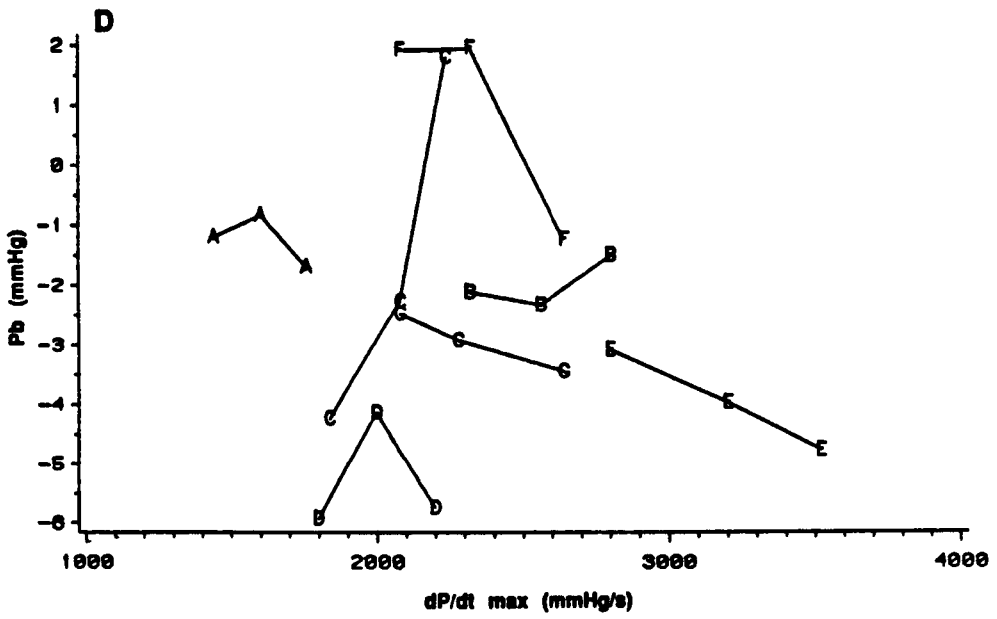


Figure 2 (continued)

Table 7. THE RESPONSE OF RELAXATION INDICES AND HEMODYNAMIC VARIABLES TO PHENYLEPHRINE[a]

	Control	Phenylephrine I	Phenylephrine II
$T_{\frac{1}{2}}$, ms	19.7 ± 1.3	18.6 ± 1.3	18.6 ± 1.3
Tln, ms	25.2 ± 1.7	23.6 ± 1.6	24.1 ± 1.4
Texp, ms	28.4 ± 2.5	27.4 ± 2.8	27.0 ± 2.2
Pb, mmHg	-2.1 ± 1.2	-2.6 ± 1.3	-2.6 ± 1.1
Heart Rate, bpm	154 ± 5.1	154 ± 5.1	154 ± 5.1
LVPSP, mmHg	82 ± 4.1	94 ± 4.8[b]	104 ± 6.0[c]
LVEDP, mmHg	4.2 ± .7	5.4 ± 1.1	6.1 ± 1.1[d]
dP/dt max, mmHg/s	2328 ± 166	2568 ± 187[e]	2756 ± 244[f]
dP/dt min, mmHg/s	1724 ± 138	2032 ± 152[b]	2240 ± 180[g]

[a] Values are mean + SEM, n = 10
[b] P = .0001 Phenylephrine I vs Control
[c] P = .0001 Phenylephrine II vs Phenylephrine I
[d] P = .0091 Phenyleprine II vs Phenylephrine I
[e] P = .0251 Phenylephrine I vs Control
[f] P = .0317 Phenylephrine II vs Phenylephrine I
[g] P = .0111 Phenylephrine II vs Phenylephrine I

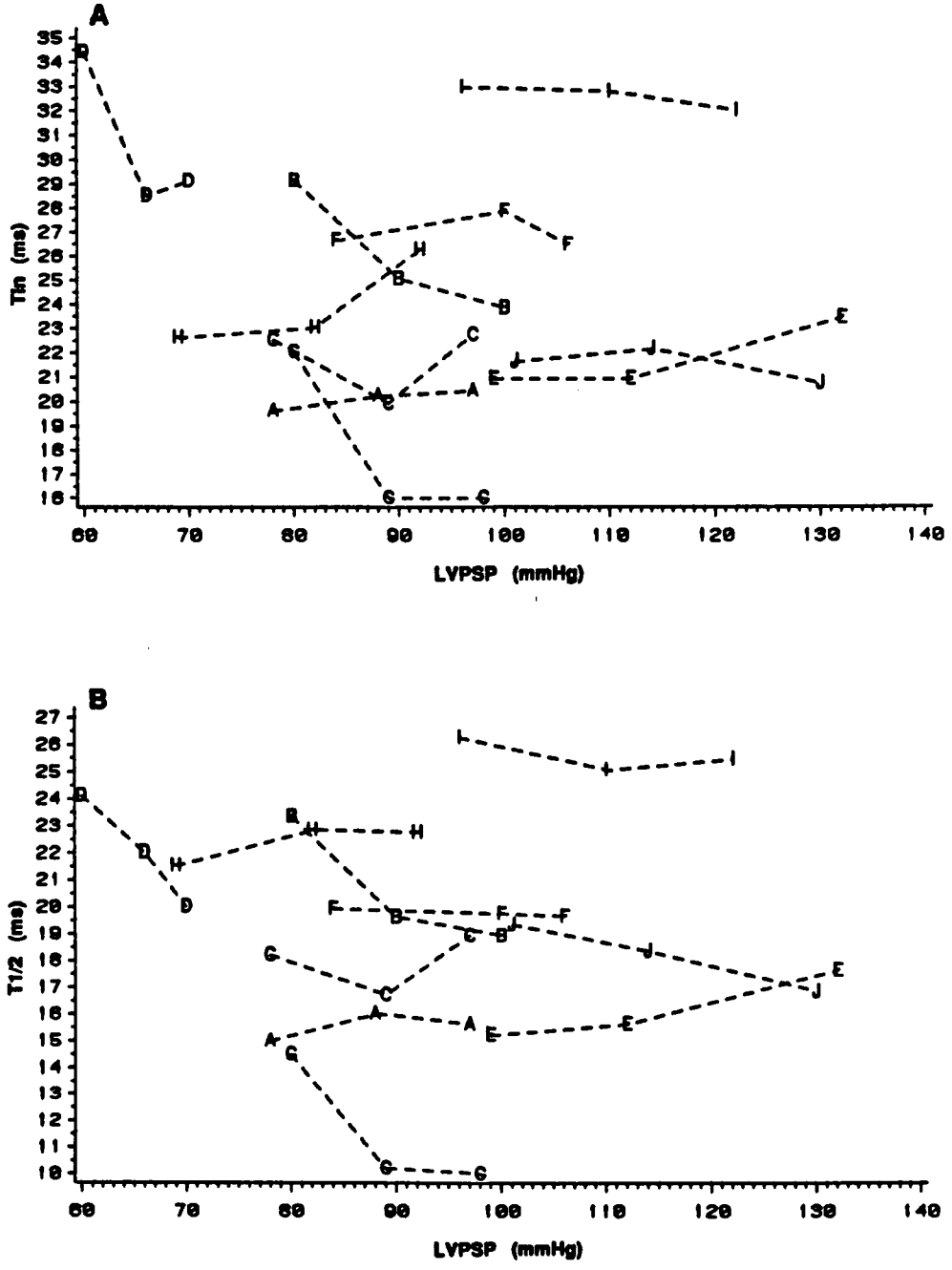
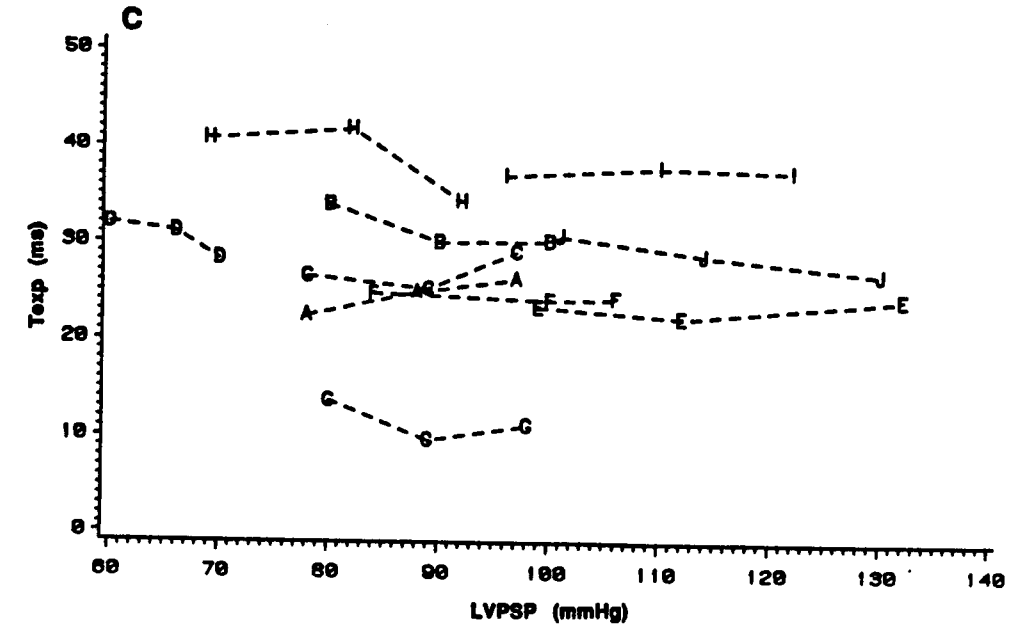


Figure 3. The Effect of Phenylephrine Infusion on the Values of Relaxation Indices for Individual Cats. Each symbol represents a single cat. Plots show the changes in Tln (A), $T_{\frac{1}{2}}$ (B), Texp (C), and Pb (D) following two successive increases in LVPSP. None of the relationships between relaxation indices and dP/dt max were significant.



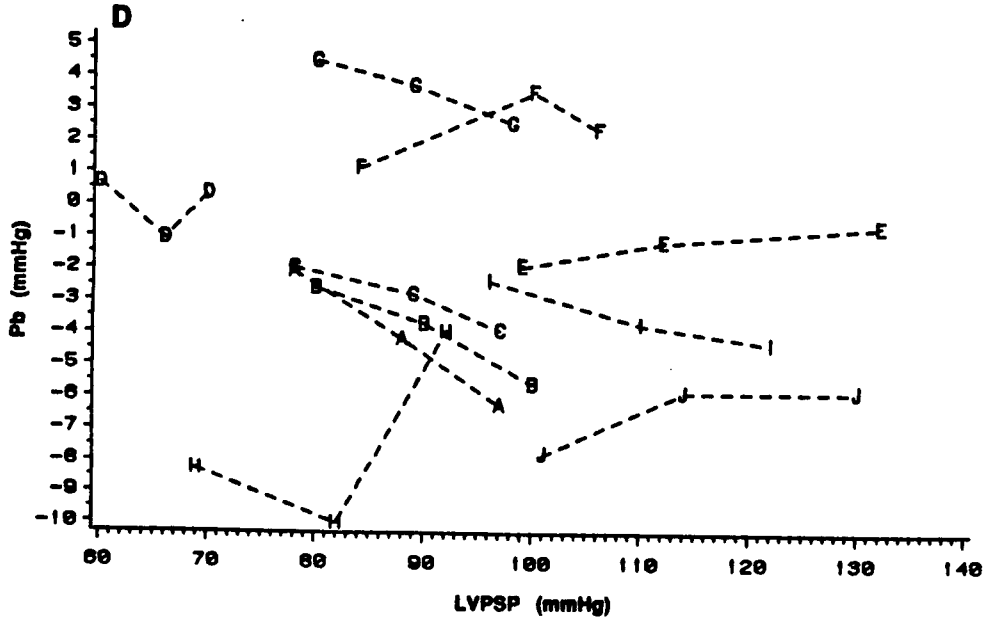


Figure 3 (continued)

in some animals and increased or unchanged in others. Moreover, the response to different levels of afterload were not consistent in individual animals.

D. EFFECTS OF VOLUME LOADING

Seven cats were volume loaded to produce two successive increases in preload. The results are shown in Table 8. The primary increase in blood volume (Volume Load I) elicited an increase in LVEDP of 2.8 $\pm$ .16 mmHg accompanied by a small, significant increase in LVPSP of 5%. The second infusion of fluid (Volume Load II) produced an additional 2.9 $\pm$ .29 mmHg elevation in LVEDP, but no significant change in LVPSP. Volume loading did not produce observable changes in any other hemodynamic parameter. Heart rate was held constant in all animals by atrial pacing. Therefore, Volume Load II represented a pure increase in preload.

Changes in preload were not associated with significant changes in either Texp or Pb. In contrast, Tln increased significantly with each increase in LVEDP. Volume Load I produced an increase in Tln from 26.3 $\pm$ 2.9 ms to 28.6 $\pm$ 3.0 ms, and the second volume increment resulted in an additional rise in Tln up to 30.7 $\pm$ 2.7 ms. The index $T_{\frac{1}{2}}$ was also related significantly to preload. The mean value of $T_{\frac{1}{2}}$ increased from 19.1 $\pm$ 1.9 ms to 20.0 $\pm$ 1.7 ms with the initial increase in LVEDP and increased further up to 21.3 $\pm$ 1.7 ms with the second volume load, but only the increase between volume load I and volume load II was significant. The response of the relaxation indices to changes in LVEDP are presented in Figure 4 for each

Table 8. THE RESPONSE OF RELAXATION INDICES AND HEMODYNAMIC VARIABLES TO VOLUME LOADING[a]

	Control	Volume Load I	Volume Load II
$T_{\frac{1}{2}}$, ms	19.1 ± 1.9	20.0 ± 1.7	21.3 ± 1.7[b]
Tln, ms	26.3 ± 2.9	28.6 ± 3.0[c]	30.7 ± 2.7[d]
Texp, ms	30.1 ± 2.8	30.2 ± 1.8	29.9 ± 2.0
Pb, mmHg	-2.8 ± .6	-1.4 ± .4	0 ± .6
Heart Rate, bpm	150 ± 6	150 ± 6	150 ± 6
Peak LVP, mmHg	79 ± 4.4	83 ± 4.5[e]	85 ± 4.0
LVEDP, mmHg	3.9 ± .9	6.7 ± .8[f]	9.6 ± 1.0[g]
dP/dt max, mmHg/s	2011 ± 124	2068 ± 115	2114 ± 126
dP/dt min, mmHg/s	1726 ± 142	1766 ± 116	1771 ± 117

[a]Values are mean ± SEM, n = 7

[b] P = .0032 Volume Load II vs Volume Load I

[c] P = .0056 Volume Load I vs Control

[d] P = .0052 Volume Load II vs Volume Load I

[e] P = .0016 Volume Load I vs Control

[f] P = .0001 Volume Load I vs Control

[g] P = .0001 Volume Load II vs Volume Load I

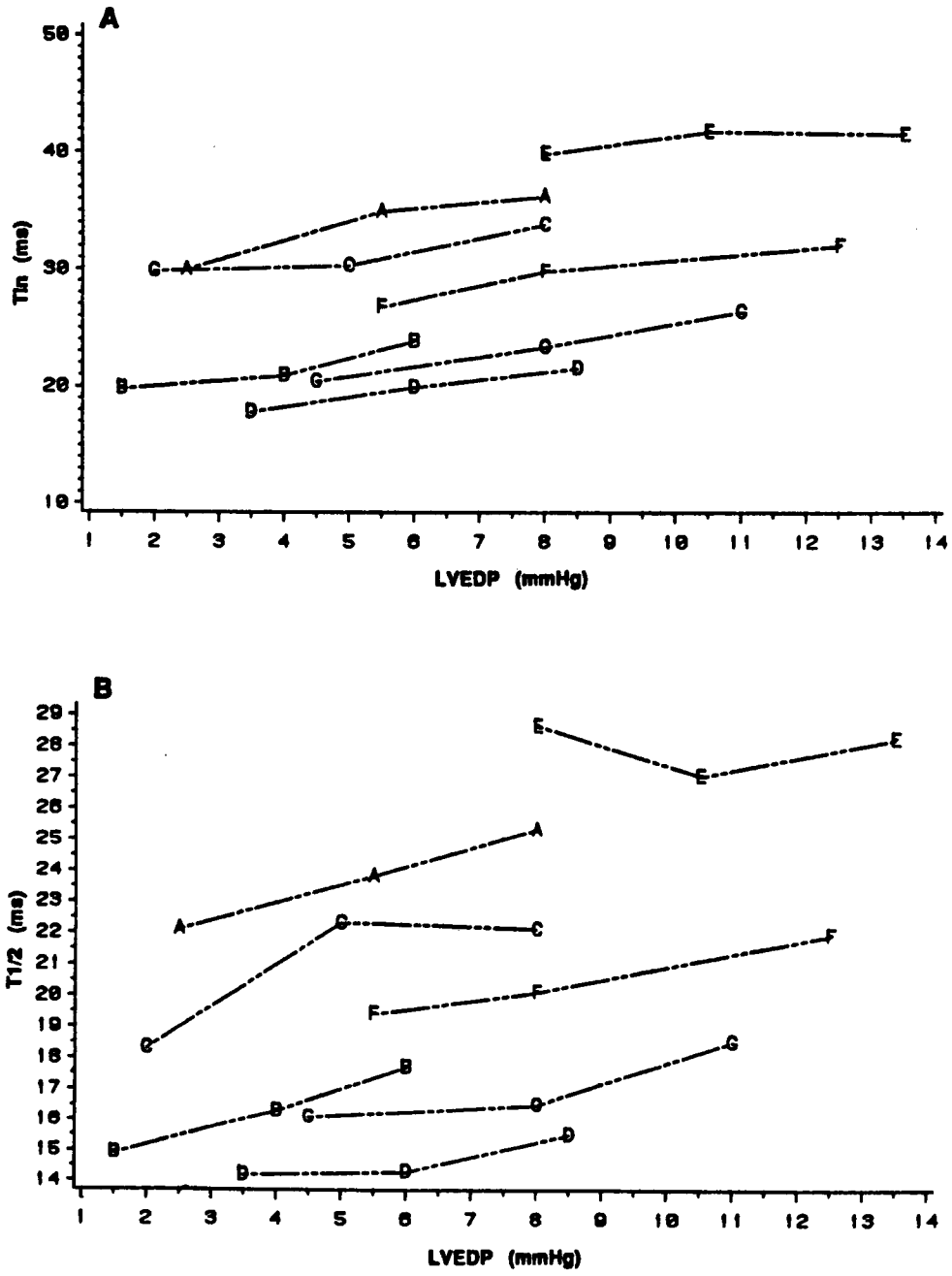
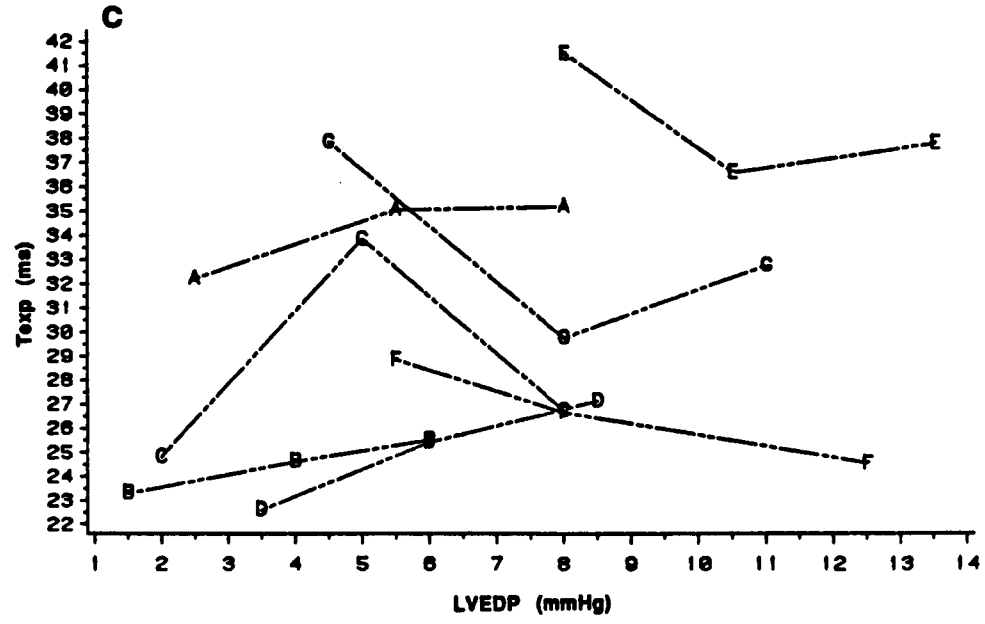


Figure 4. The Effect of Volume Loading on the Values of Relaxation Indices for Individual Cats. Each symbol represents a single cat. Plots show the changes in Tln (A), $T\frac{1}{2}$ (B), Texp (C), and Pb (D) following two successive increases in LVEDP. Volume loading significantly prolonged both Tln and $T\frac{1}{2}$, but had no consistent effect on Texp or Pb.



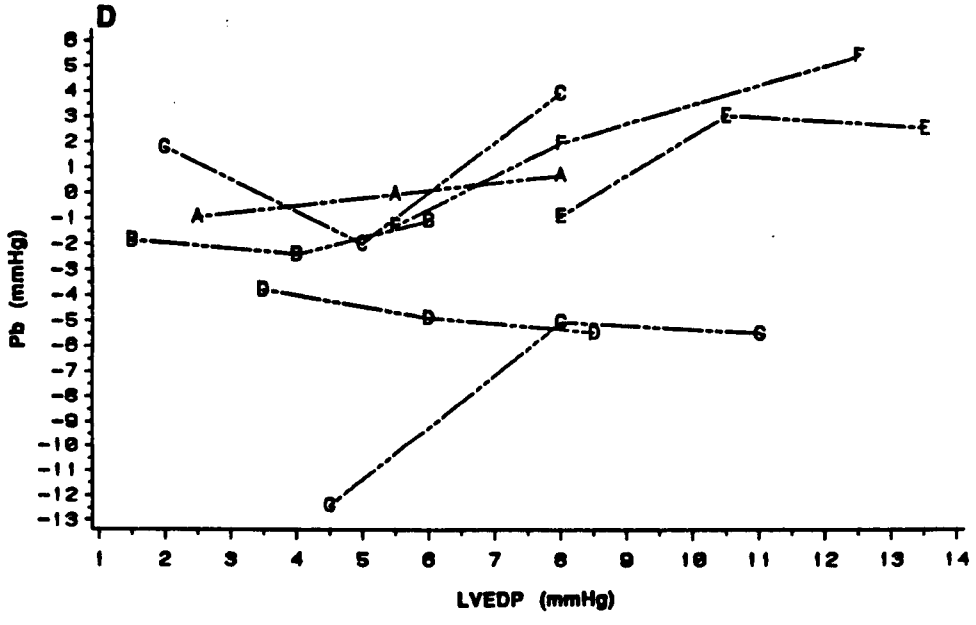


Figure 4 (continued)

individual cat. The value of Tln in individual cats increased by 1% to 16% with the primary increase in LVEDP. In one animal the value of Tln was unchanged following the second increase in LVEDP and increased by 4% to 30% in the other six animals. With the first volume load, $T_{\frac{1}{2}}$ decreased by 5% in one cat and was increased by 1% to 22% in six animals. The second increase in LVEDP produced no change in $T_{\frac{1}{2}}$ for one animal and increased $T_{\frac{1}{2}}$ by 4% to 12% in six animals. Although Texp increased successively with each increase in LVEDP in two animals, the relationship of both Texp and Pb with LVEDP was generally inconsistent. Therefore, Texp and Pb were not significantly affected by changes in preload, whereas Tln and $T_{\frac{1}{2}}$ both increased as LVEDP was increased.

E. RELATIONSHIPS BETWEEN THE TIME CONSTANTS

Three hundred heart beats from eleven cats across all levels of preload, afterload, heart rate and contractility were used to examine the relationships between values of Tln, Texp, and $T_{\frac{1}{2}}$, and to compare the statistical fit of the models used to calculate Tln and Texp. The ratio RSS/TSS, expressed as a percentage, was used to compare the semilogarithmic (Tln) and variable asymptote, exponential (Texp) models with respect to how well the models fit actual pressure decline. The RSS/TSS describes the amount of variability in the data not explained by the model, therefore, the lower the RSS/TSS the better the statistical fit. The RSS/TSS was smaller for the variable asymptote model in 93% of the 300 heart beats analyzed. The distribution of the RSS/TSS for the two models is illustrated for all

levels of each treatment in Figure 5. The range of the RSS/TSS for the model used to calculate Texp was from 0.001% and 0.876%, whereas the RSS/TSS ranged between .011% and 5.6% for the semilogarithmic model. On the average, RSS/TSS for the semilogarithmic model was twice as large as for the variable asymptote model in a given heart beat. The small values of RSS/TSS for both of the models indicates that both models successfully predicted LVP decline. Nevertheless, the statistical fit was better for the variable asymptote model across all levels of preload, afterload, contractility, and heart rate.

To determine whether the lack of fit in the semilogarithmic model was systematic the variable time was squared (t^2) and added to the semilogarithmic model to test for curvature. The quadratic term was significant in 181 of the 300 beats analyzed. In 81% of those 181 beats the term t^2 had a negative coefficient indicating significant downward curvature of the natural log of pressure vs time relationship. In the beats with significant downward curvature the asymptote was less than zero. In the remaining 34 beats the coefficient of t^2 was positive (indicating significant upward curvature), Pb was positive, and Tln was greater than Texp. Therefore, in 60% of the beats tested the relationship between the natural log of pressure and time was curvilinear and the direction of curvature could be related to the value of the asymptote. These results confirm that Tln is derived from a poorer mathematical model than Texp and that the lack of fit of the semilogarithmic model is due, in part, to the assumption that the asymptote is zero.

Figure 5. Comparison of the Statistical Fit of the Models Used to Calculate Texp and Tln for All Hemodynamic Conditions. Graphs show the distribution of the RSS/TSS for the variable asymptote, exponential model (A) and the semilogarithmic model (B) for the same 300 heart beats. Observations are grouped by hemodynamic intervention and treatment level. Abbreviations are as follows VC, volume load control; V1, volume load I; V2, volume load II; PC, phenylephrine control; P1, phenylephrine I; P2, phenylephrine II; CC, calcium control; C1, calcium I; C2, calcium II; HR1-HR4, heart rate I - heart rate IV. Both models predicted actual LVP decline successfully, but the agreement between predicted LVP and actual LVP was better for the variable asymptote, exponential model for all hemodynamic conditions.

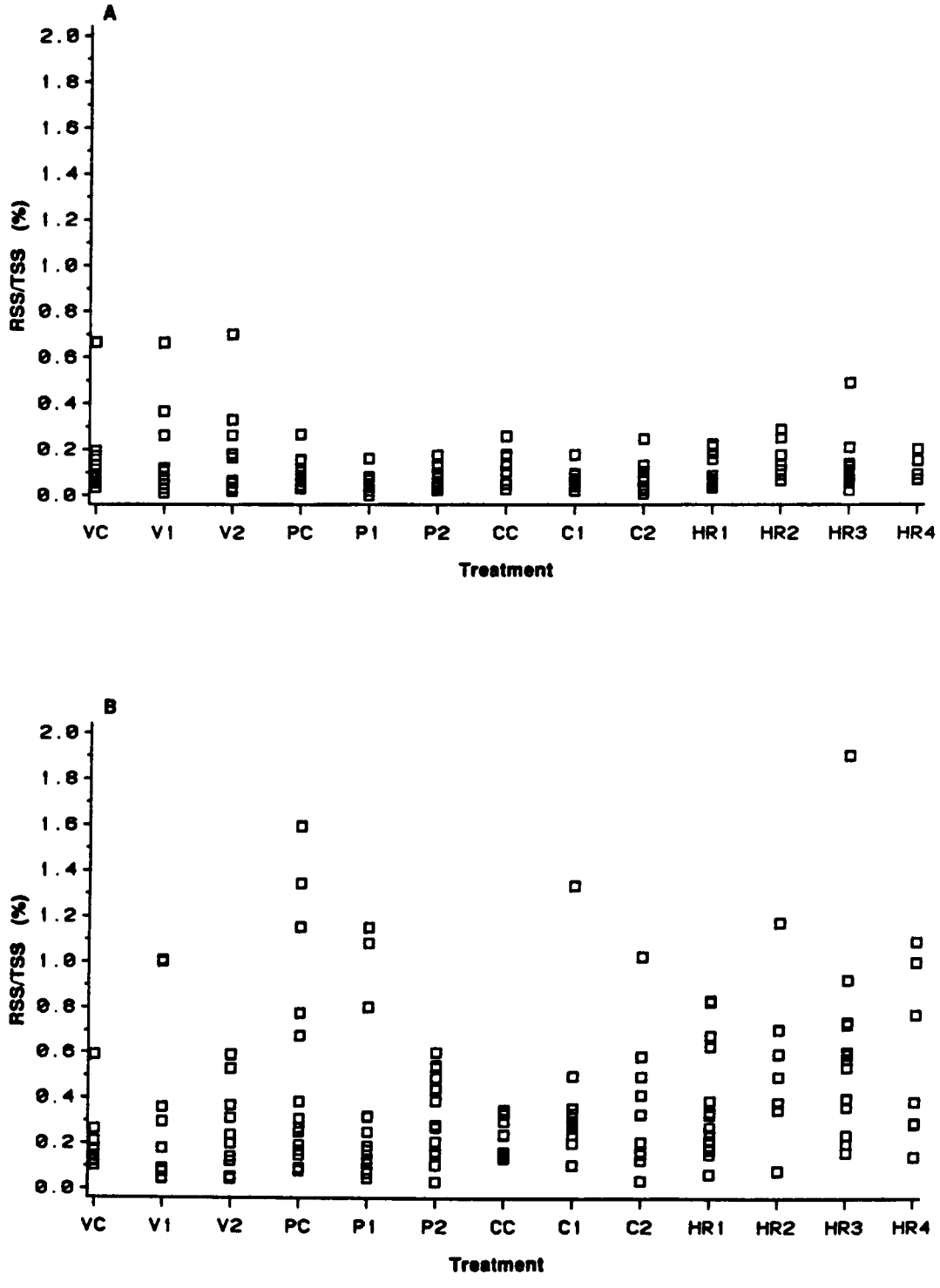

A
RSS/TSS (%)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
VC V1 V2 PC P1 P2 CC C1 C2 HR1 HR2 HR3 HR4
Treatment
B
RSS/TSS (%)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
VC V1 V2 PC P1 P2 CC C1 C2 HR1 HR2 HR3 HR4
Treatment

Figure 5

The value of Texp was greater than the value of Tln in 67% of the heart beats tested. The relationship between Texp and Tln is presented in Figure 6. The regression of Tln on Texp was significant (r^2 = .3807) and indicated that Tln was generally less than Texp. The regression was significantly different from the line of identity (p = .0001). In all 202 heartbeats where Texp was greater than Tln Pb was less than zero. Moreover, the ratio Texp/Tln was significantly related to the value of Pb (Figure 7). The regression of Texp/Tln on Pb was significant (r^2 = .9399) and illustrated that the ratio Texp/Tln increased as Pb became more negative. Therefore, the ratio of the two estimates of the time constant Tln and Texp was related to the value of the asymptote.

The relationship of both Tln and Texp with $T_{\frac{1}{2}}$ is shown in Figure 8. Note that $T_{\frac{1}{2}}$ describes the time required for the pressure at dP/dt min to decline by $\frac{1}{2}$ not $1/e$, and therefore $T_{\frac{1}{2}}$ theoretically should be less than both Texp and Tln by a factor of $2/e$, or approximately 0.74. Both the regression of $T_{\frac{1}{2}}$ on Tln and the regression of $T_{\frac{1}{2}}$ on Texp were significant, but the slope of each of the regression lines was significantly different (p = .0001) from the slope of the line describing the theoretical relationship. Note that $T_{\frac{1}{2}}$ was more closely related to Tln (r^2 = .8022) than Texp (r^2 = .6499). Therefore, although Tln is derived from a model with a poorer statistical fit than Texp, Tln is a better predictor of $T_{\frac{1}{2}}$ which is derived from the actual pressure-time data.

To determine whether the respective relaxation indices were related consistently under a variety of hemodynamic conditions

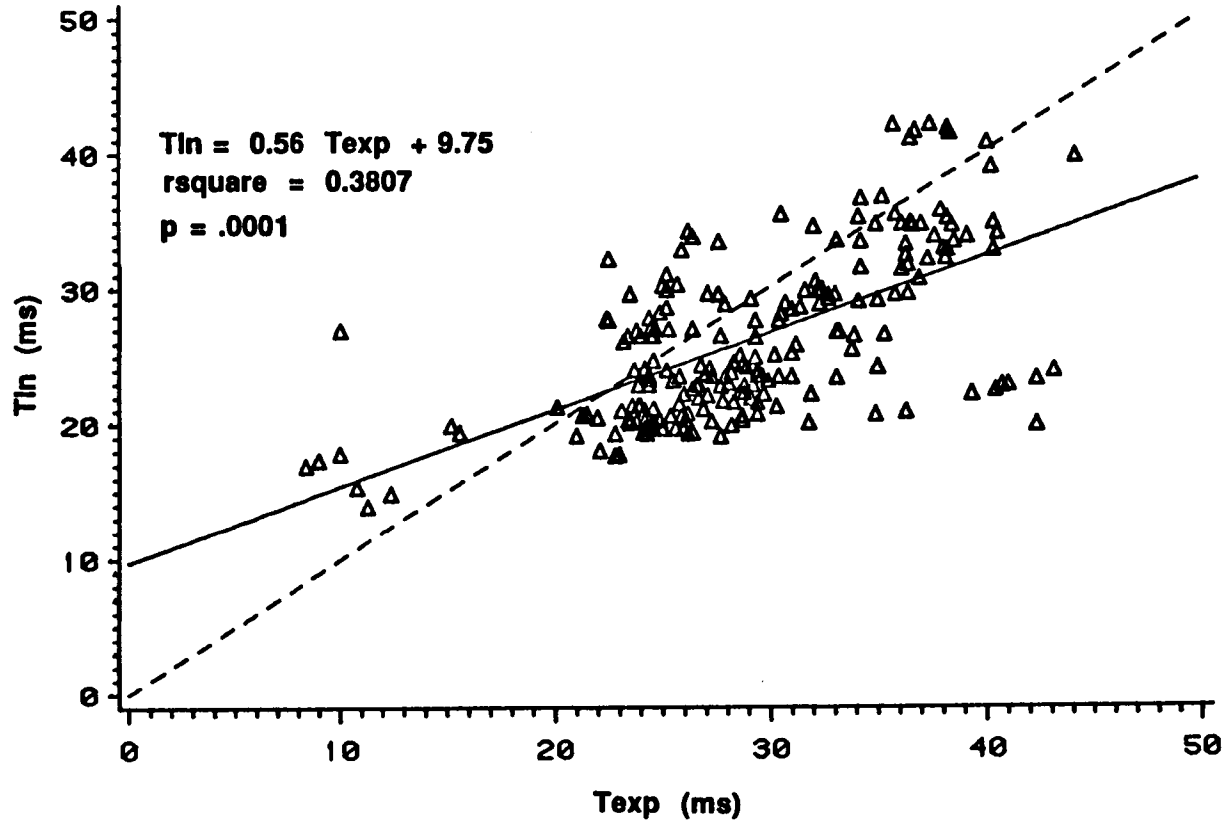


Figure 6. Relationship Between Texp and Tln. Scatter plot and linear regression analysis between 216 values of Texp and Tln calculated from the same 216 heart beats across all levels of preload, afterload, and contractility. Note that the relationship between Texp and Tln was not significant for the heart rate data, and these data were omitted from the analysis. The solid line is the regression line, and the broken line is the line of identity. The slopes are significantly different (p = .0001). See text for discussion.

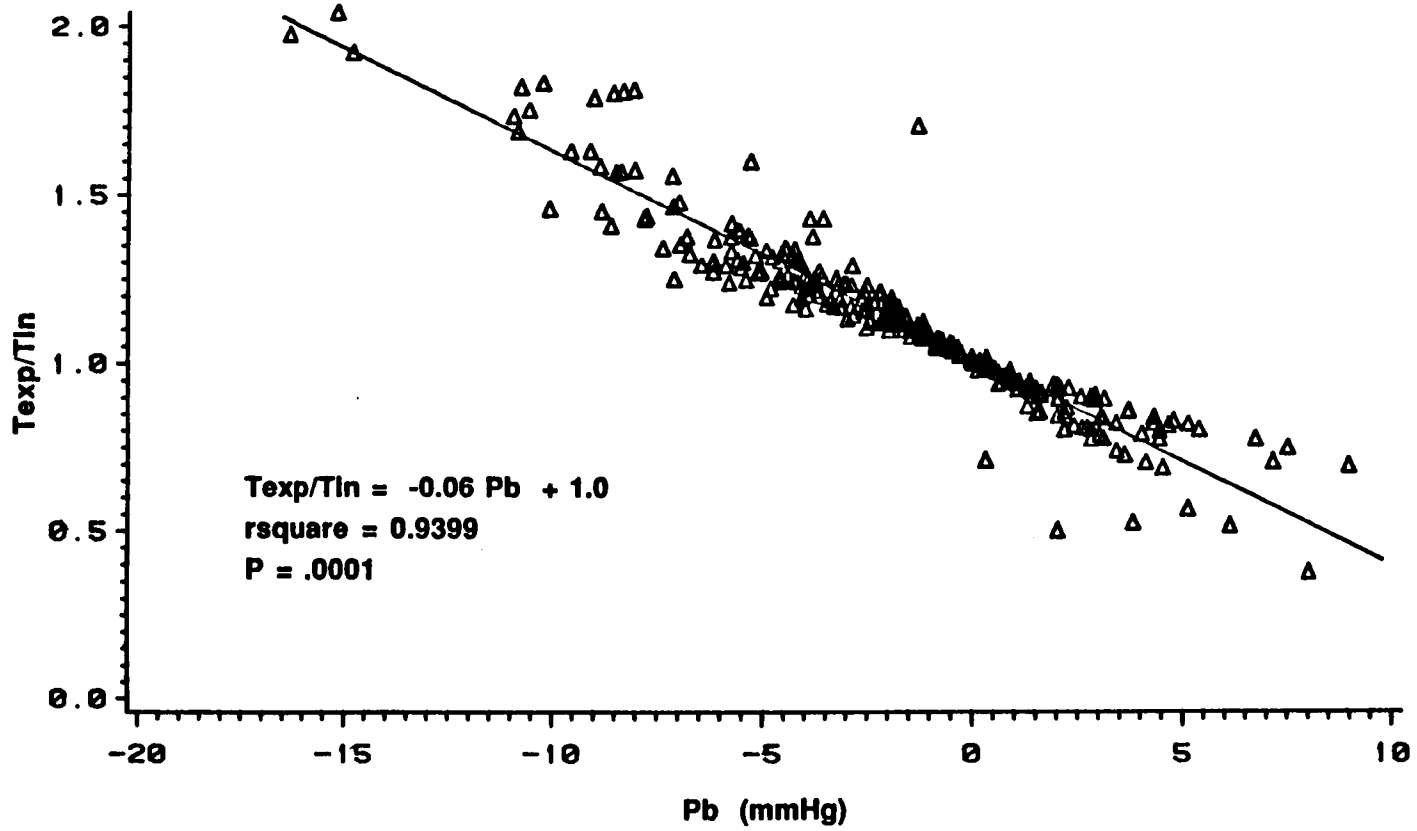
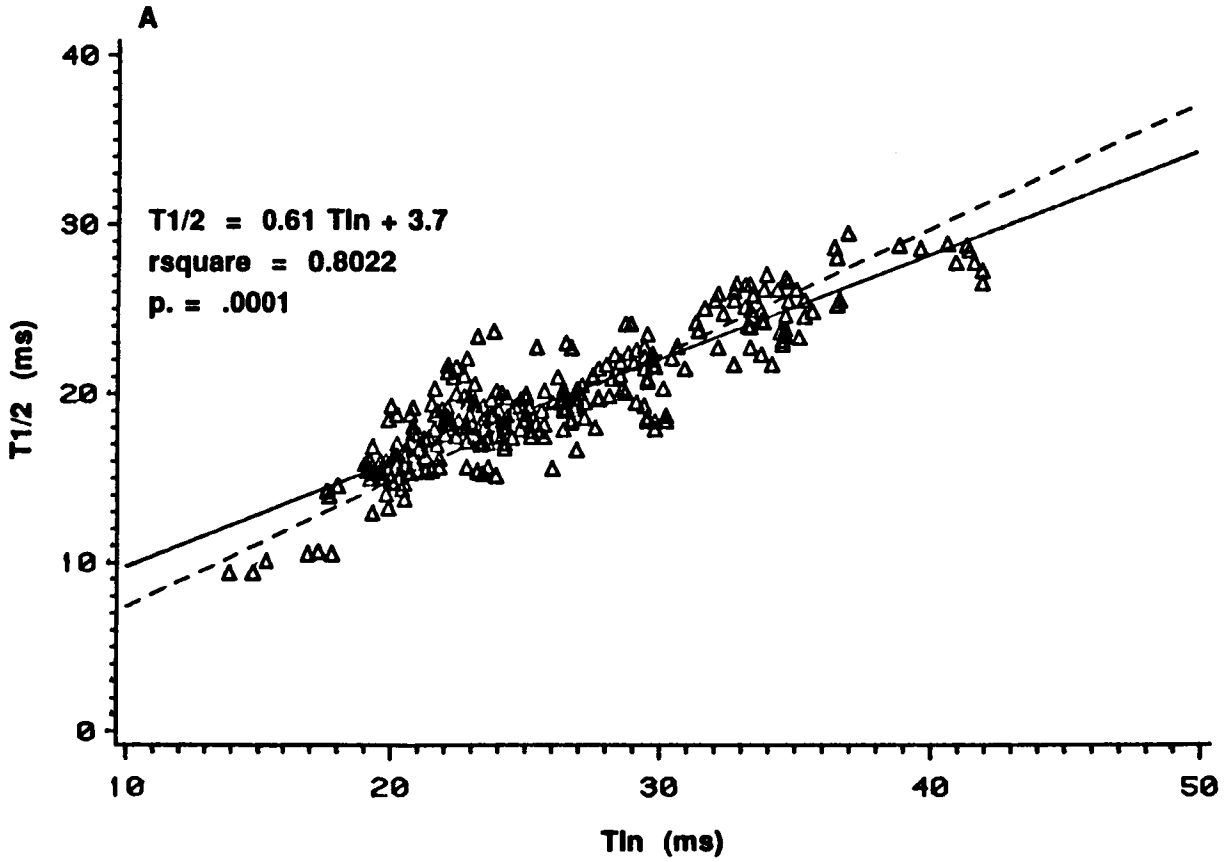
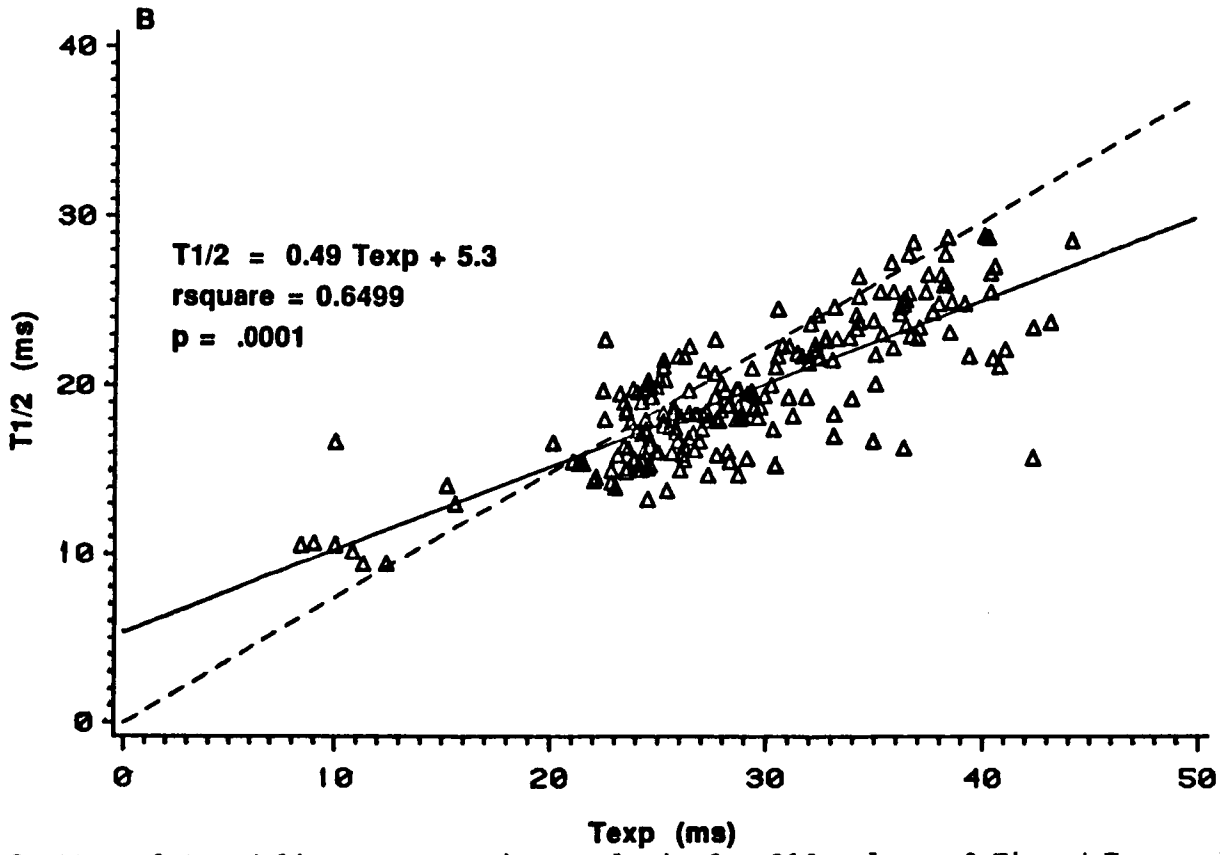


Figure 7. Relationshp Between Texp/Tln and the value of Pb. Scatter plot and linear regression analysis for 300 heart beats across all levels of preload, afterload, heart rate, and contractility. The solid line is the regression line. Note that the ratio Texp/Tln increases as the value of Pb becomes more negative.



(A) Scatter plot and linear regression analysis for 300 values of $T_{\frac{1}{2}}$ and Tln calculated for 300 heart beats across all levels of preload, afterload, contractility, and heart rate. The solid line is the actual regression line, and the broken line is the regression line for the relationship: $T_{\frac{1}{2}}$ = 0.74 Tln. The slopes are significantly different (p = .0001). See text for discussion.

Figure 8. Relationship of $T_{\frac{1}{2}}$ with Tln and Texp.



(B) Scatter plot and linear regression analysis for 216 values of $T_{\frac{1}{2}}$ and Texp calculated for 216 heart beats across all levels of preload, afterload, and contractility. Note that the relationship between $T_{\frac{1}{2}}$ and Texp was not significant for the heart rate data, and these data were omitted from the analysis. The solid line is the actual regression line, and the broken line is the regression line for the relationship: $T_{\frac{1}{2}}$ = 0.74 Texp. The slopes are significantly different (p = .0001). See text for discussion.

Figure 8 (continued)

correlation coefficients (r) were calculated for each pair of indices at each treatment level for all interventions. The results are presented in Table 9. The time constants Tln and $T_{\frac{1}{2}}$ were significantly related ($p = .0001$) across all hemodynamic conditions. The correlation coefficient ranged between 0.794 and 0.986. The closeness of the relationship improved as LVEDP and LVPSP were increased, but did not change consistently as dP/dt max and heart rate were increased. The correlation was highest at higher levels of LVEDP. The correlation coefficient for Texp and $T_{\frac{1}{2}}$ ranged from -0.003 to 0.927. The relationship between the two indices was significant for the preload, afterload, and inotropy data, but nonsignificant at all but one treatment level for the heart rate data. Similarly, the correlation coefficient for Texp and Tln ranged from -0.353 to .820 and was not significant for the heart rate data. The poor correlation of Texp with $T_{\frac{1}{2}}$ and Tln was not related to changes in heart rate. The poor relationship of Texp with both Tln and $T_{\frac{1}{2}}$ for the heart rate data is explained by the fact that there were several heart beats for which the value of Texp was smaller than the value of either Tln or $T_{\frac{1}{2}}$. Additionally, there were several instances where large changes in Texp were not paralleled by comparable changes in the values of Tln and $T_{\frac{1}{2}}$. For example, in one instance Texp increased by 15 ms, whereas Tln and $T_{\frac{1}{2}}$ both changed by less than 2 ms between the same pair of heart beats. Therefore, the inconsistency of the relationships of Texp with the other time constants was, in part, due to unexplained variability in the values of Texp.

Table 9. CORRELATIONS BETWEEN RELAXATION INDICES FOR ALL HEMODYNAMIC CONDITIONS

Hemodynamic Condition	Tln with $T_{\frac{1}{2}}$ r	P	Texp with $T_{\frac{1}{2}}$ r	P	Texp with Tln r	P	Texp with Pb r	P
Phenylephrine Control	.860	(.0001)	.776	(.0001)	.439	(.0152)	-.718	(.0001)
Phenylephrine I	.880	(.0001)	.920	(.0001)	.644	(.0001)	-.775	(.0001)
Phenylephrine II	.920	(.0001)	.909	(.0001)	.764	(.0001)	-.634	(.0002)
Calcium Chloride Control	.888	(.0001)	.724	(.0002)	.665	(.001)	-.105	NS
Calcium Chloride I	.955	(.0001)	.898	(.0001)	.810	(.0001)	-.137	NS
Calcium Chloride II	.896	(.0001)	.927	(.0001)	.765	(.0001)	-.237	NS
Preload Control	.956	(.0001)	.700	(.0004)	.578	(.006)	-.364	NS
Volume Load I	.971	(.0001)	.836	(.0001)	.820	(.0001)	.304	NS
Volume Load II	.986	(.0001)	.648	(.0015)	.609	(.0034)	-.155	NS
Heart Rate I	.862	(.0001)	.221	NS	-.209	NS	-.744	(.0001)
Heart Rate II	.867	(.0001)	.672	(.0008)	.366	NS	-.827	(.0001)
Heart Rate III	.794	(.0001)	.193	NS	-.353	NS	-.962	(.0001)
Heart Rate IV	.935	(.0001)	-.003	NS	-.240	NS	-.945	(.0001)

When all data were considered, there was a significant linear relationship (r^2 = .488) between Texp and the asymptote. The scatter plot (Figure 9) indicates that Texp and Pb were inversely related. Nevertheless, inspection of the correlation coefficients (Table 9) reveals that the relationship of Texp and Pb was not consistent for all the data. The correlation coefficient ranged from -0.945 to 0.304 and was nonsignificant for both the inotropy and preload data. The relationship between the indices was closest for the heart rate data where large values of Texp were associated with highly negative values of Pb. The lack of a significant relationship for the preload and inotropy data is explained by the fact that Pb varied within a fairly narrow range while values of Texp were spread over a wide range with the result that values of Texp between 20 and 40 ms were associated with approximately the same values of Pb.

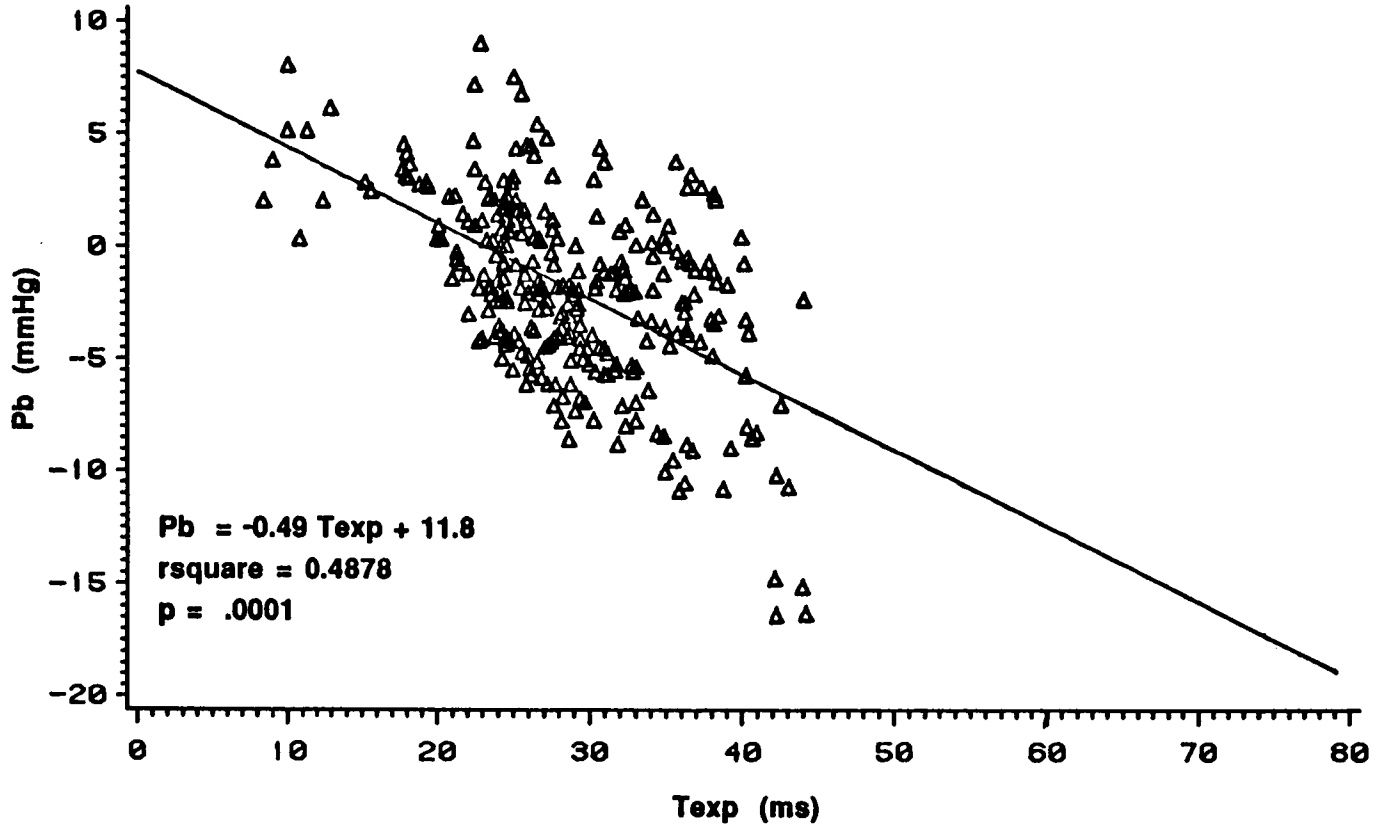


Figure 9. Relationship Between Texp and Pb. Scatter plot and linear regression analysis for 300 heart beats across all levels of preload, afterload, heart rate, and contractility. The solid line is the regression line. See text for discussion.

CHAPTER IV

DISCUSSION

The time constants Tln and Texp have been compared in several studies. Some investigators have recommended that Texp be used instead of Tln because of the statistical superiority of the variable asymptote, exponential model (33, 34). Other investigators have concluded that the choice of a time constant is not critical as long as the same method is used consistently throughout an experiment (32). The use of different methods of calculating a time constant may make comparisons between experiments difficult if the values of the respective time constants respond differently to changes in hemodynamic conditions. This study was designed to define the limitations of Tln, Texp, and $T\frac{1}{2}$ as estimates of a time constant with respect to the effects of changes in hemodynamic conditions on the values of T and possible errors introduced by the use of mathematical models.

The finding in this study that the statistical fit of the variable asymptote, exponential model was, in most cases, superior to the fit of the semilogarithmic model is consistent with the results of previous comparisons between Texp and Tln (33, 34, 37). Both Thompson and associates (33, 34) and Martin et al (37) observed consistent downward curvature of the natural log of pressure vs time relationship and values of Texp which were consistently larger than values of Tln. In the present study the natural log of pressure vs time relationship exhibited significant curvature in greater than 50%

of the heart beats analyzed, but in a significant number of those beats, the direction of curvature was upward, the asymptote was positive, and Tln was greater than Texp. The lack of fit of the semilogarithmic model was not as uniform as has been reported previously, but the direction of curvature and the ratio of Texp to Tln were consistently related to the value of the asymptote. These results support the claim that estimating the asymptote results in a statistically better model of isovolumic pressure decline.

The values of Tln, Texp, and $T\frac{1}{2}$ were not affected by changes in heart rate, inotropic state, or afterload. Both Texp and Pb were also unaffected by changes in preload, whereas the values of Tln and $T\frac{1}{2}$ both increased significantly as LVEDP was increased.

Previous studies assessing the effects of preload on Tln have yielded variable results. Significant increases in Tln were reported for dogs following volume loading (38), and a decrease in Tln was observed following a small decrease in LVEDP produced by nitroprusside (37). In contrast, other investigators have reported no changes in Tln with significant increases in LVEDP (26, 29, 40, 43). It has been hypothesized that afterload rather than preload is a determinant of Tln, and therefore that an increase in preload has no effect on Tln unless there is a subsequent increase in systolic load (44). The increase in Tln observed in the current study with a small increase in LVEDP (2.8 mmHg) and no simultaneous change in LVPSP is incongruous with the aforementioned hypothesis. The results indicate that preload is a primary determinant of Tln.

The majority of studies which have evaluated the effects of afterload on Tln have indicated that Tln changes directly with changes in LVPSP or mean aortic pressure. Significant increases in Tln have been reported in dogs following steady state increases in LVPSP produced by both phenylephrine (40, 43) and methoxamine (44). Similarly, decreases in Tln have been observed with decreases in LVPSP produced by nitroprusside (44). Some researchers have associated the increases in Tln with afterload to increases in ESL. The results of the present study indicate that Tln is not significantly affected by changes in afterload. Although ESL was not measured, the changes in LVPSP were of the same magnitude as those for which concurrent changes in ESL and Tln were previously observed (44). Neither the initial pure increase in LVPSP or the more profound increase in afterload with a concurrent increase in LVEDP produced significant changes in Tln. These results conflict with the theory that afterload is a primary determinant of Tln.

The lack of a relationship between loading conditions and either Texp or Pb observed in this study are consistent with the finding by Martin et al (37) that simultaneous changes in afterload and preload produced by either nitroprusside or angiotensin had no uniform effects on Texp and Pb. Note that the results of the present study also indicate that relatively pure changes in either preload or afterload have no significant effect on Texp and Pb.

The effects of pacing in this study are consonant with the conclusion by other investigators that Tln is relatively independent of changes in heart rate (26, 29, 33, 40, 43). The results of

earlier studies have indicated that significant decreases in Tln occur only with large, abrupt increases in heart rate. It should be noted that the large increases in heart rate in these studies were often associated with significant decreases in LVEDP such that Tln may have decreased because of changes in preload rather than heart rate. Incremental increases in heart rate in the present study were associated with small changes in LVPSP and dP/dt max, but not with changes in LVEDP or Tln.

The observation that Texp and Pb were not affected by changes in heart rate is in conflict with the results of a study by Thompson and associates in which Texp decreased and the asymptote increased as heart rate was elevated (33, 35). The reason for the discrepancy is unclear, but it should be noted that the study by Thompson et al was done in human patients undergoing cardiac catheterization for suspected coronary artery disease. Although a group of these patients was subsequently classified as normal, it is possible that Texp may have been atypically affected by increases in heart rate in these patients.

No relationship was found between Tln and inotropic state. This finding is consistent with the results of an experiment in which an enhanced inotropic state produced by calcium chloride in an isolated canine heart had no effect on Tln (26). In contrast, significant decreases in Tln have been observed with calcium chloride administration in conscious and anesthetized dogs (40, 43). The maximal increase in dP/dt max produced in the present study was comparable to the increase reported for the experiment using

conscious dogs (43). Although increases in dP/dt max in the current study were associated with small increases in LVPSP, changes in LVPSP do not obscure the interpretation of the results since Tln was found to be independent of afterload. Although the effects of calcium chloride administration have not been reported for Texp or Pb, the results of this study are consistent with an earlier finding that these parameters were not changed by increases in inotropic state (dP/dt max) produced by isoproterenol in anesthetized dogs (37).

The reasons for the differences noted between this study and earlier studies with regard to the effects of changes in afterload and inotropic state on Tln are unclear. Although no attempt was made to control autonomic tone, there is no indication that any of the results were confounded by autonomic reflexes. In fact, each intervention was free of profound changes in any hemodynamic variable which might have interfered with interpretation of the results. It has been suggested previously that the type of experimental preparation may have an effect on the dependence of Tln on various factors (7, 38, 44, 45). Attempts were made in the current study to maintain conditions within a physiologic range. Although the cats were anesthetized, the anesthetic isoflurane has only moderate cardiovascular effects (49). The indication that the hemodynamic determinants of T may vary in different experimental preparations requires that the experimental conditions be considered when interpreting changes in the time constant in a particular study.

The hemodynamic determinants of $T_{\frac{1}{2}}$ have not previously been characterized. The results of this study indicate that $T_{\frac{1}{2}}$, like Tln,

is independent of changes in heart rate, inotropic state and afterload but significantly affected by changes in preload. The results indicate that $T_{\frac{1}{2}}$ and Tln yield different information than Texp when preload (LVEDP) is changed appreciably. It is tempting to conclude that the preload dependence of Tln and $T_{\frac{1}{2}}$ reflects the effects of loading conditions on relaxation. Unfortunately, such conclusions are speculative, especially since these indices are independent of afterload which should have effects on relaxation similar to preload. Therefore, changes in Tln or $T_{\frac{1}{2}}$ must be interpreted cautiously in experiments in which preload is altered significantly.

The time constants Tln and $T_{\frac{1}{2}}$ were uniformly related across all hemodynamic conditions, which indicates that the indices provide essentially the same information concerning relaxation. In contrast, the relationship of Texp with Tln and $T_{\frac{1}{2}}$, respectively, was variable and nonsignificant for the heart rate data. Moreover, the variability in these relationships was, for the most part, due to relatively large random changes in the values of Texp with respect to Tln and $T_{\frac{1}{2}}$. In general, the values of Texp varied over a greater range (9-66 ms) than either Tln (14-41.4 ms) or $T_{\frac{1}{2}}$ (9.4 to 28.7 ms) despite the fact that Texp was not changed consistently by any intervention. This variability may reflect the complexity of fitting the nonlinear model.

The relationship between Texp and the asymptote was also variable. There was a significant inverse relationship between Texp and Pb for the afterload and heart rate data, but the relationship

was not significant for the preload and inotropy data. It is not clear how the two variables should be related. Thompson and associates (33) suggested that Texp was independent of Pb, but they also noted that Texp and Pb changed in opposite directions as heart rate was increased. The problem of interpreting changes in the asymptote has been discussed by other investigators (37). The lack of uniformity in the relationship between Texp and Pb suggests that Pb should not be interpreted simply as a correction for shifts in intrathoracic pressure with respiration as has been suggested by some investigators (25, 38, 42), but the appropriate interpretation of changes in the asymptote remains unclear.

Unfortunately, there is no accurate measure of relaxation in the intact heart with which to compare the time constant. In general, indices of relaxation should be based on known physiologic properties and mathematical models should be statistically valid representations of physiological behavior (41). Moreover, changes in relaxation indices should be predictable across a wide spectrum of hemodynamic conditions.

All three of the time constants Tln, $T_{\frac{1}{2}}$, and Texp describe isovolumic pressure decline reasonably well and are independent of changes in heart rate afterload and inotropic state. Statistically, Texp is a better index than Tln since the variable asymptote, exponential model describes actual pressure decline more accurately than the semilogarithmic model. The index Texp also offers the advantage of being independent of preload, whereas changes in preload must be considered in the interpretation of changes in either Tln or

$T_{\frac{1}{2}}$. Despite these advantages, the large random changes observed for Texp seem to be the result of fitting the complex nonlinear model, and variability in Texp could confound attempts to measure small changes in relaxation using this index.

The time constant $T_{\frac{1}{2}}$ was highly correlated with Tln and was also significantly related to Texp in the absence of large random changes in Texp. In addition, $T_{\frac{1}{2}}$ is derived directly from the pressure tracing and is therefore free from the errors associated with fitting a model. Therefore, although the preload dependence of $T_{\frac{1}{2}}$ must be appreciated, the relaxation half-time is recommended as the most practical and reliable method of determining the time constant of isovolumic relaxation.

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APPENDICES

APPENDIX A

METHODS OF CALCULATING T

I. Semilogarithmic Method (26)

Based upon a monoexponential model for which the asymptote is zero: $P(t) = Poe^{bt}$ where Po = pressure at dP/dt min, t = time after dP/dt min and P(t) = pressure at time t

Since the asymptote is assumed to be zero the function is linearized to yield: $\ln(Pt) = \ln(Po) + bt$

The variable b is estimated from the linear regression of ln (pressure) against time and $T\ln = -1/b$

II. Exponential Method (33)

Based upon a monoexponential model for which the asymptote is variable:

$P(t) = ae^{bt} + Pb$ where Pb = asymptote and a is an estimate of (Po - Pb)

The variables b and Pb are estimated from the nonlinear regression of pressure against time and $Texp = -1/b$

III. Derivative Method (36)

Based on the monoexponential model with variable asymptote:

$$P(t) = Poe^{-t/T} + Pb \text{ where } T = -1/b$$

The equation is differentiated to yield:

$$dP/dt = -1/T\ Poe^{-t/T}$$

And by substitution of the equation for P(t) yields the linear function:

$$dP/dt = -1/T_D\ P(t) + Pb/T_D$$

The variables T_D and Pb are estimated from the linear regression of dP/dt against pressure.

IV. Relaxation Half-time (41)

The relaxation half-time, $T_{\frac{1}{2}}$, is calculated directly from the pressure time tracing as the time required for the pressure at dP/dt min to decline by one half. The value of $T_{\frac{1}{2}}$ should by definition be less than the value of Texp and Tln which estimate the time required for the pressure at dP/dt min to decline by a value of 1/e, where e is the base of natural logarithms.

V. A variation of the variable asymptote exponential model (32):

$$\ln [P(t) - Pb] = \ln (Po - Pb) - t/T$$

Yellin et al used this method to compare the time constant TE calculated using empirical measures of Pb determined for nonfilling beats with Texp* for which Pb was a variable estimated by least squares regression. Note that Texp* approximates Texp, but is not equivalent since logarithms are used in the calculations.

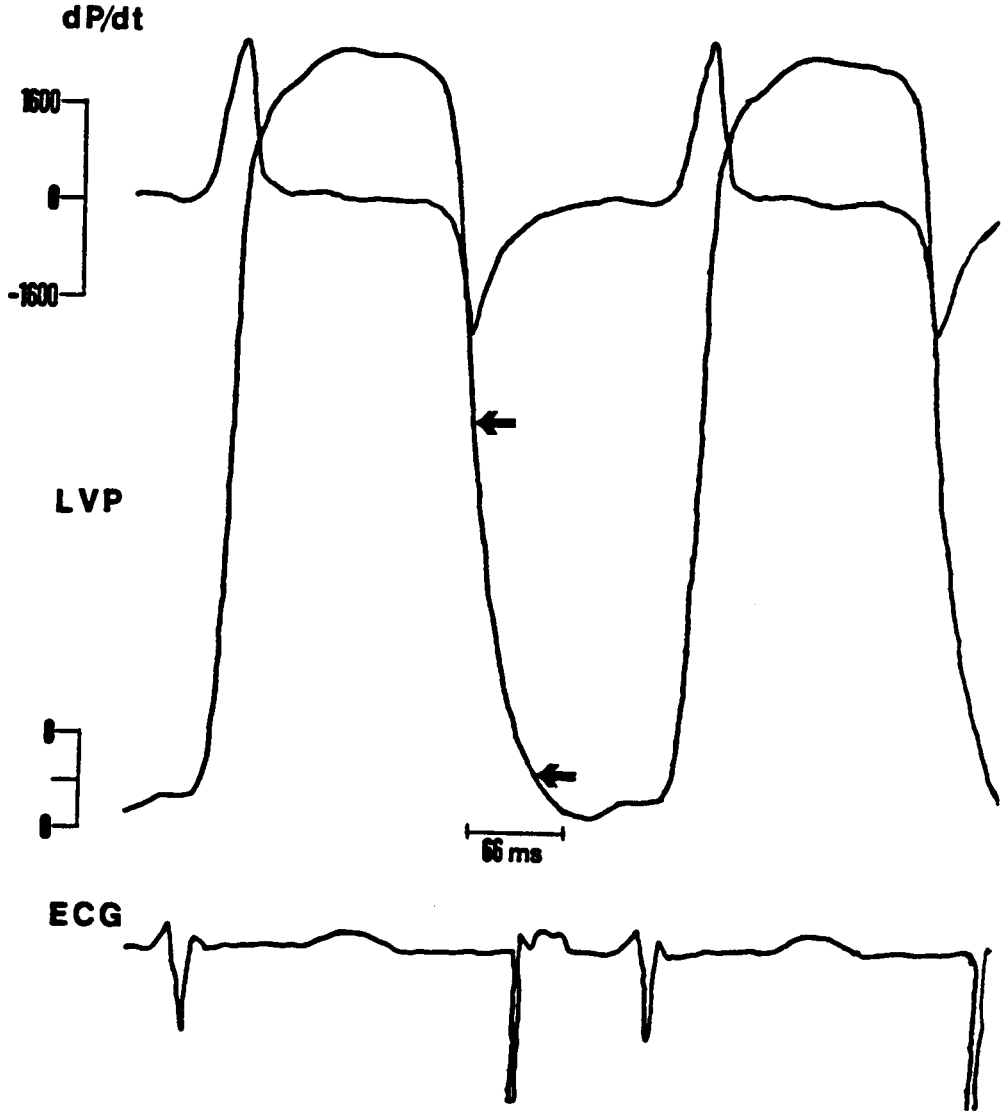

Figure 10. Recording of Left Ventricular Pressure (LVP) and the Pressure Derivative (dP/dt). The time constant is determined from LVP decline during isovolumic relaxation using one of several methods described in the text. In the present study, Tln and Texp were calculated using the pressure-time data between dP/dt min and a pressure 2 mm Hg above the LVEDP (between arrows). Pressures were digitized at 4 ms intervals. The time constant $T_{\frac{1}{2}}$ was determined directly from the pressure tracing as the time required for the LVP at dP/dt min to decline by one-half.

Figure 11. Graphs of the Mathematical Models Used to Calculate Tln and Texp. The graphs are comparisons of measured and predicted pressures for the variable asymptote, exponential model (A), and the semilogarithmic model (B) for the same heart beat. The solid line is the regression line, and the dots represent measured pressures.

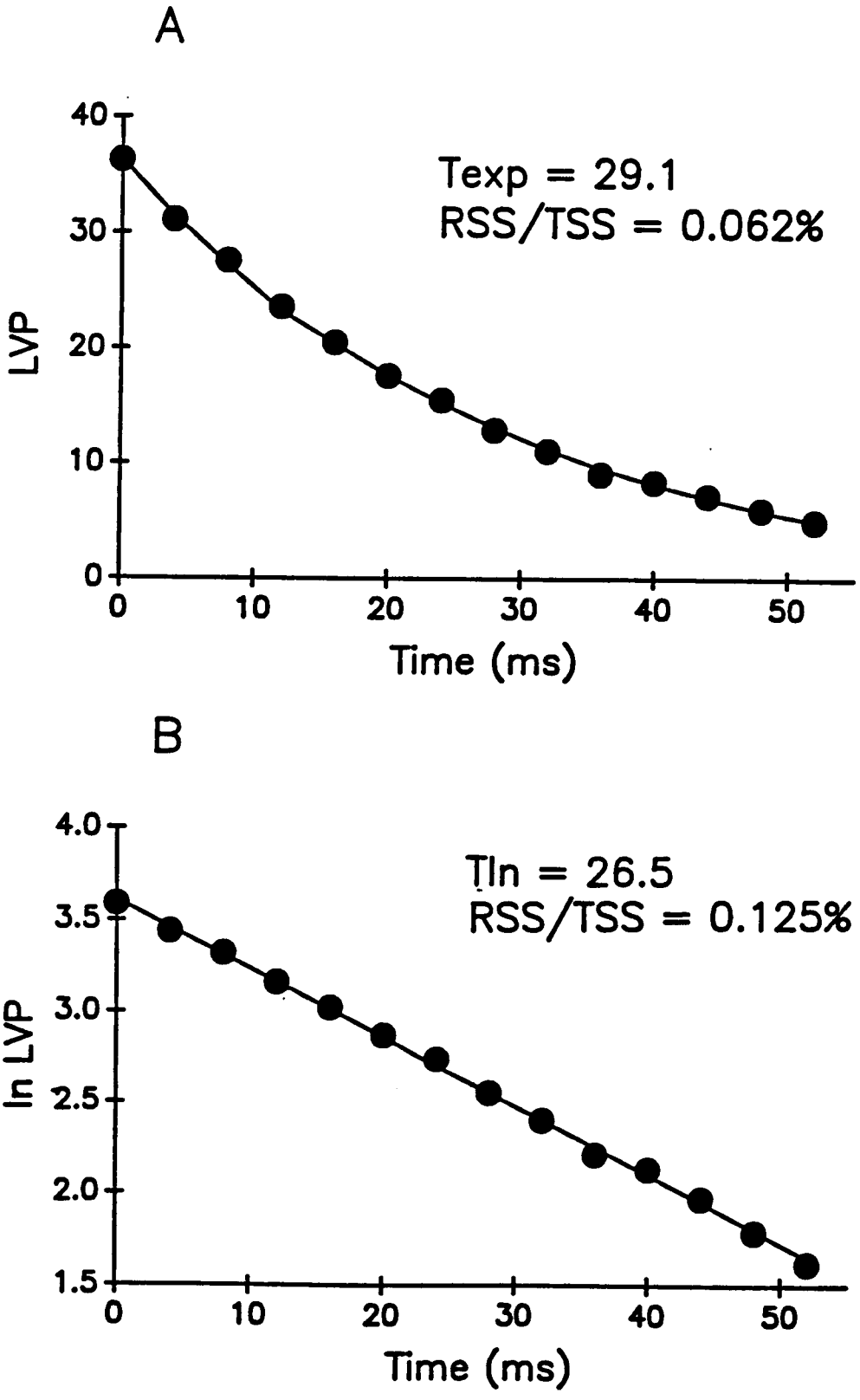
A
40
30
20
10
0
LVP
Texp = 29.1
RSS/TSS = 0.062%
0
10
20
30
40
50
Time (ms)
B
4.0
3.5
3.0
2.5
2.0
1.5
ln LVP
Tln = 26.5
RSS/TSS = 0.125%
0
10
20
30
40
50
Time (ms)

Figure 11

VITA

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Lynelle is a member of the American Physiological Society, and the American Heart Association. She began working on a Ph.D. in the Comparative and Experimental Medicine Program at the University of Tennessee College of Veterinary Medicine in January 1988.