Analysis of Isovolumic Relaxation in Failing Hearts by Monoexponential Time Constants Overestimates Lusitropic Change and Load-dependence:

Mechanisms and advantages of alternative logistic fit

Short Title: Load-sensitivity of Relaxation with Heart Failure

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ABSTRACT

Background  Failing hearts display slow relaxation with apparent increased load-sensitivity. However, inaccuracies of monoexponential analysis can contribute to these observations, and different qualitative and quantitative results might be obtained by alternative models. We tested whether pressure relaxation of failing hearts consistently deviates from a mono-exponential waveform leading to overestimations of lusitropic change and load-sensitivity by mono-exponential-derived time constants.

Methods and Results  Fourteen dogs were studied before and after tachycardia-pacing induced heart failure. Relaxation time constants were derived by monoexponential fits ($\tau_E$) with zero or non-zero asymptotes, and by a logistic fit ($\tau_L$). $\tau_L$ assumes non-linear relations between pressure and its first derivative, whereas $\tau_E$ assumes a linear dependence. Load-sensitivity of $\tau$ was tested by comparing beats during vena caval occlusion. $\tau_E$ prolonged by 75-80% with heart failure, three times more than $\tau_L$ (p<0.01). $\tau_E$ displayed marked load-sensitivity in failing hearts, shortening during preload reduction; whereas $\tau_L$ was little changed by the same loading maneuver. Neither $\tau_L$ nor $\tau_E$ varied with preload in control hearts. The discrepancy between $\tau_E$ and $\tau_L$ results was due to non-monoexponential decay reflected by non-linear pressure-dP/dt plots, which was enhanced with heart failure (p<0.01). This non-linearity was reduced by $\beta$-adrenergic stimulation, lowering preload-sensitivity of $\tau_E$ to control levels.

Conclusions  Isovolumic relaxation in failing hearts deviates from a monoexponential waveform, leading to overestimated relaxation delay and increased load-sensitivity of monoexponential time constants. This deviation is under $\beta$-adrenergic modulation. The logistic model improves the fit to real pressure decay in failing hearts, providing more stable measures of relaxation.

Key Words: hemodynamics, diastole, congestive heart failure, relaxation
INTRODUCTION

Left ventricular isovolumic relaxation is prolonged by heart failure, largely the consequence of abnormal calcium handling\(^1,2\) and increased external and internal chamber loading.\(^3,4\) Studies also suggest enhanced sensitivity of relaxation to varied loading as failure worsens.\(^5-7\) For example, Eichhorn et al\(^5\) found that relations between the time-constant of relaxation (\(\tau\)) and end-systolic pressure (ESP) steepened (greater load-dependence) in patients with depressed contractility. Ishizaka et al.\(^6\) subsequently found that the sensitivity of \(\tau\) to load change induced by caval occlusion increased markedly in conscious dogs after tachycardia-induced heart failure. These results may reflect adrenergic down-regulation, since earlier studies had demonstrated that the sensitivity of \(\tau\) to ESP increased with propranolol and declined with isoproterenol.\(^8\)

Another potentially important contributor to these observations, in particular enhanced load-dependence of relaxation, stems from the mathematics used to assess pressure decay. This is most often performed using time constants derived from a monoexponential fit, as employed in each of the prior cited studies. However, the real isovolumic pressure decay does not necessarily follow this waveform,\(^9,10\) and deviations can profoundly influence estimated time constants and qualitative assessments of load-sensitivity when an exponential model is none-the-less employed. This is often treated as a noise in relaxation analysis; however, the potential exists for consistent errors if this deviation is mechanistically linked to adrenergic stimulation or the severity of underlying heart failure. Bi-exponential and polynomial fits\(^11,12\) or pressure-decay half-times\(^13\) do not adequately solve the problem. However, a logistic curve proposed by Matsubara et al\(^14\) appeared advantageous in a study of denervated (isolated) hearts, and might similarly be so in ventricles weakened by heart failure.

The present study tested the hypotheses that: 1) failing hearts display substantial and
consistent deviation from a monoexponential isovolumic pressure decay, leading to greater apparent relaxation delay and preload-sensitivity when the analysis employs monoexponential fits; 2) adrenergic stimulation reduces this deviation and thus apparent load-dependence; and 3) logistic equation analysis of relaxation enhances its stability and minimizes preload-dependence of the derived time constants under baseline and heart failure conditions. Data were obtained in conscious dogs under baseline conditions, and after induction of dilated cardiomyopathy by 4 weeks of tachycardia pacing.\textsuperscript{15-17} Three different monoexponential fits\textsuperscript{18-20} that are slightly different from the perspective of the mathematics used, but have been extensively used both in experimental and clinical studies as “standard”, were tested to obtain universal application of the results.

**METHODS**

**Preparation**

Fourteen adult mongrel dogs (18 to 24 kg) were sedated with sodium thiamylal (15 mg/kg) and anesthetized with halothane (1-2%). The chest was opened by lateral thoracotomy at the 5th intercostal space. A flexible tube was secured within the apical myocardium to facilitate insertion of a micromano-meter catheter (Millar, SPC 350) for pressure measurement. Sono-micrometer crystals were implanted to record internal short-axis dimension and free-wall thickness. A pneumatic cuff occluder placed around the inferior vena cava (IVC) provided a means to alter chamber loading. A screw-in epicardial lead was attached to the right ventricular free wall and connected to a programmable pacemaker (Spectrax, Medtronics) inserted in a subcutaneous pocket for right ventricular tachy-pacing to induce heart failure. In 8 dogs, pacing wires were also secured at the left atrium for constant rate atrial pacing during infusion of adrenergic agents to eliminate
confounding effects from the change in heart rates by adrenergic stimulation and to achieve more physiologic study condition (atrial but not ventricular pacing). Catheters and leads were externalized between the scapulae. The animals were fully recovered from surgery prior to study.

**Protocol**

Hemodynamic data before and after development of pacing-induced heart failure were collected with animals standing quietly in a sling apparatus. Data recordings were performed at steady state and during load reduction by IVC occlusion. On the day following baseline study, right ventricular pacing was initiated at 250 min\(^{-1}\). Studies were repeated at weekly intervals until development of clinical heart failure, characterized by lethargy, anorexia, ascites, and dyspnea. Hemodynamic measurements were made during normal sinus rhythm, with pacing suspended for at least 30 minutes prior to recording. To test the effects of \(\beta\)-adrenergic stimulation on load-sensitivity of various estimates in failing hearts, dobutamine (DOB, 5 \(\mu\)g/kg/min i.v., \(n=5\)) or isoproterenol (ISO, 0.4 \(\mu\)g/kg/min, i.c., \(n=3\)) were administered in 8 dogs after development of heart failure. Heart rate was maintained fixed at 160 min\(^{-1}\) by left atrial pacing before and during drug infusion.

**Relaxation Time Constant Analysis**

Analog signals were digitalized at 500 Hz using custom data acquisition-display software. Signal-averaged data from 5 to 10 sequential steady-state beats measured prior to IVC occlusion were used to obtain end-systolic and end-diastolic ventricular pressures (ESP, EDP), short-axis dimensions (ESD, EDD), and percent fractional shortening (FS). Ventricular contractile state was assessed by the end-systolic pressure-dimension relation (ESPDR).\(^{16,17}\) The first derivative of
pressure (dP/dt) was calculated by a running 5-point weighed local slope:

\[
\frac{dP}{dt_i} = \frac{[(P_{i+1} - P_{i-1}) + (P_{i+2} - P_{i-2})]}{6}.
\]  

(Eq.1)

Time constants of LV isovolumic relaxation were calculated using pressure data from peak negative dP/dt to 2 mmHg above EDP. EDP was defined as the pressure when dP/dt reached a threshold of 10% maximum. Monoexponential time constants were calculated by three methods. The first assumed a zero pressure asymptote (\(T_m\)), and was derived from the negative reciprocal of the linear regression between the natural logarithm of pressure and time.\(^{18}\) The latter two methods assumed a non-zero asymptote, and used the equation:

\[
P(t) = (P_o - P_4)e^{-t/\tau} + P_4
\]

(Eq.2)

where \(P_o\) was the pressure at \(t=0\), and \(P_4\) was the pressure asymptote at \(t = 4\). Two time constants were estimated; one from the inverse slope of the P-dP/dt plot (\(T_D\)),\(^{19}\) and the other by non-linear regression (Marquardt algorithm) to the pressure-time data (\(T_F\)).\(^{20}\)

A fourth time constant was determined from the logistic model proposed by Matsubara et al:\(^{14}\):

\[
P(t) = P_A/(1 + e^{-t/T_L}) + P_4
\]

(Eq.3)

where \(P_4\) is the decay asymptote, and \(P_A\) is an amplitude constant. This equation was also fit by non-linear least squares regression, yielding time constant \(T_L\).

**Analysis of Load-Sensitivity of Relaxation**

Each \(\tau\) estimate was calculated for multiple beats at varying loads during caval occlusion, and the results plot as \(\tau\)-ESP relations. ESP was the point of maximal P/(D-Do) for each beat, where P is pressure, D is dimension, and Do the dimension-axis intercept of the ESPDR. The slope of the \(\tau\)-ESP relations (\(k\)) indexed load-dependence.
To further elucidate the underlying causes of enhanced load-sensitivity of relaxation in heart failure, P-dP/dt relations from measured data and those derived from monoexponential and logistic fits were compared. Model-fit relations were generated by differentiation of Eqs. 2 and 3, yielding:

\[
d\!P/dt = [P(t) - P_4]/\tau = (1/\tau) \cdot P(t) - P_4/\tau
\]  
(Eq. 4)

for the monoexponential model, and

\[
d\!P/dt = [P(t) - P_A] \cdot [P(t) - P_4] / [P_A \cdot T_L] = \alpha P(t)^2 - \alpha (P_A + 2P_4) \cdot P(t) + P_4 (P_A + P_4);
\]  
(Eq. 5)

where \( \alpha = P_A - T_L \), for the logistic model. Thus, as previously noted, the monoexponential model yielded a linear dependence between P and dP/dt, whereas the logistic model yielded a parabolic dependence.

**Statistical Analysis**

Data are presented as mean ± SD. Differences before and after development of heart failure were evaluated by paired t-test. Differences before and after DOB or ISO infusion were also evaluated by paired t-test. Differences in percent changes and load-dependence with heart failure between mono-exponential and logistic tau were evaluated by Dunnett multiple comparisons test. Difference in percent changes after adrenergic stimulation between mono-exponential and logistic tau was also evaluated by Dunnett multiple comparisons test. Goodness of fit for exponential and logistic models to relaxation data was assessed by determining the sum-of-squares difference (SSD) between regression-derived (i.e. Eqs. 4 & 5) and measured dP/dt, and testing for statistical significance of the nonlinear \((P(t)^2)\) term in P-dP/dt relations (multiple linear regression model). To further determine which modeling approach best estimates the relaxation process, Akaike information criterion (AIC) was calculated as \( n \cdot (\log(2\pi \cdot SSD/n)+1)+2(p+2) \), where \( n \)= sample size and \( p \)= number of independent variables. Multivariable regression analysis was performed to test the
association between P$_4$ and EDP using data during load reduction from all the animals. Statistical significance was considered at p < 0.05.

RESULTS

Changes in hemodynamics due to pacing-LV failure

Tachycardia-induced heart failure exhibited marked contractile depression as well as diastolic dysfunction (Table 1). End-systolic elastance declined by 39%, and fractional shortening and dP/dt$_{\text{max}}$ by 50%. End-diastolic pressure rose from 11 to 28 mmHg, accompanied by chamber dilation. These results are exemplified by pressure-dimension loops shown in Fig. 1, and are consistent with previously reported data with this model.

Although all time constants of relaxation were prolonged by heart failure, the quantitative assessment of this change was substantially different between the three monoexponential-based $\tau$ parameters and the logistic-model derived $\tau$ (Table 2). Monoexponential $\tau$s all rose by between 75-85% over baseline, whereas $\tau_L$ increased by only 28% ($p = 0.001, 0.004, 0.0008$ vs. $T_{ln}, T_D,$ and $T_F,$ respectively).

Changes in load-sensitivity of tau due to pacing-LV failure

Figure 2 displays $\tau$-ESP relations at baseline and after development of heart failure from a representative dog. There was minimal change in $\tau$ with preload and ESP reduction under baseline conditions, whereas all monoexponential-derived $\tau$ values ($T_{ln}, T_D,$ and $T_F$) displayed enhanced load-dependence with heart failure. This was not true of $T_L$, which was little load sensitive under both conditions. Table 2 provides the mean slopes ($k$) for the $\tau$-ESP relations from all dogs. $k$
increased consistently, and by nearly a full order of magnitude for $T_D$ and $T_F$ and $T_{ln}$ (the three monoexponential constants), whereas $k$ for $T_L$ was small at baseline and remained so with heart failure ($p=0.002$ versus $k$ for $T_{ln}$, $T_D$ and $T_F$). The results were also identical when we used logarithmic transformed $k$ values assuming a nonlinear distribution of $k$ value with heart failure development. These results indicate that enhanced load-sensitivity of relaxation with heart failure was critically dependent upon the mathematical model used to describe pressure decay.

**Analysis of P-dP/dt relations**

To further probe the basis for disparities between basal relaxation delay and load-dependence of relaxation as indexed by monoexponential versus logistic $\tau$, data were plot as P-dP/dt relations. Figure 3A shows example plots with both types of fit for control and heart failure conditions. At both high (top panels) and reduced (lower panels) preloads, P-dP/dt relations were generally downward convex to the pressure axis, and this non-linearity was consistently enhanced with heart failure. At baseline, the $P(t)^2$ term in the regression (Eq. 5) was statistically significant in only 22% of the P-dP/dt relations. However, with heart failure, the majority (78%) of P-dP/dt relations were nonlinear ($p=0.003$ by $\chi^2$ versus control data). Since these relations are theoretically linear if pressure decay follows a monoexponential form, the increased non-linearity indicated a consistent deviation from a monoexponential pressure decay with heart failure. Since the logistic model assumed a non-linear (parabolic) dependence of $P$ and $dP/dt$, it provided a better data fit at both baseline and heart failure. This was indexed by the sum of squares (SSD) difference between measured and model-predicted $dP/dt$ which was 28% ($p=0.001$) and 62% ($p=0.0007$) higher with the monoexponential than logistic model at baseline and heart failure, respectively. Superiority of the logistic to the monoexponential fit was further confirmed by the results of AIC, which showed
3% (122 vs. 118) and 8% (108 vs. 100) higher with the monoexponential than logistic model at baseline and heart failure, respectively.

Curvilinear P-dP/dt data could explain increased load-sensitivity of monoexponential $\tau$. Fig. 3B displays P-dP/dt data from multiple beats at varying preloads from two dogs (top and lower pair of panels). As noted previously, these data display non-linearity that became more marked with failure. Exponential fits to the data at baseline (high) and reduced load are shown by solid lines. Under control conditions, there was little difference between the fits, since curvilinearity of the P-dP/dt data was minimal. With heart failure, however, there was a flatter slope and lower y-axis intercept in the high load range, and this became steeper with a higher intercept as load declined. Since the negative reciprocal of the slope was $T_D$ (or $T_F$), this corresponded to shortening of the time constant with reduced load as demonstrated in Fig. 2. Similar results were obtained in all hearts.

Another mechanism by which enhanced curvilinearity of P-dP/dt relations increases apparent load-dependence of monoexponential-derived $\tau$ values relates to the lower pressure cutoff (i.e. 2 mm Hg above EDP) used to set the data-range for analysis. When loading is altered, LVEDP also frequently changes thereby influencing this cutoff pressure. Even if the underlying pressure decay data are identical and only this cutoff pressure is changed, monoexponential $\tau$s will vary if the P-dP/dt relation is non-linear. This is demonstrated in Fig. 4, which shows calculated $T_D$ and $T_L$ from the same steady-state data in which only the lower cutoff pressure was varied from 10 to 2 mm Hg above EDP. In failing hearts, lowering the cutoff pressure (as normally accompanies load reduction) yielded marked shortening of $T_D$, whereas there was no significant change in $T_L$. This result is very similar to that previously reported in isolated canine ventricles.14 In the control state, where P-dP/dt relations are more linear, neither parameter was significantly altered by this change.
Increased curvilinearity of P-dP/dt data with heart failure also yielded marked load-dependence of the calculated pressure decay asymptote (P₄). Thus, at resting loads this intercept was often quite negative (mean P₄ for T_D and T_F was -55.6±46 mm Hg), and it rose to -10.2±14.1 mm Hg as loading declined. This is shown by example in Fig. 5A (left panel), which plots P₄ versus EDP in failing hearts from all beats in an example dog. Multivariable regression analysis of similar data from all the animals revealed a significant inverse dependence of P₄ on EDP. In contrast, P₄ derived by the logistic model (Fig 5A, right panel) was generally positive at rest, and displayed a physiologic decline as loading was reduced.

Both P₄ and τ parameters in a monoexponential model are mathematically interdependent, so this apparent load-dependence of P₄ also contributed to the load-dependence of τ. This was tested by redoing the analysis while holding P₄ constant. The value of P₄ was taken as the mean from beats at reduced preload. As shown by example in Fig. 5B, the resulting τ-ESP relations no longer displayed load-sensitivity with heart failure (mean k = 0.14±0.21). It is important to note that this purely mathematical modification trivially altered goodness of fit, as SSD between model and measured P(t) was 2±3 mm Hg with a varying P₄, versus 3±3 mm Hg with a fixed P₄.

P₄ was already constant and assumed equal to zero for T-ln, but this could still enhance T-ln load-sensitivity due to changes in external loading¹⁰,²² and the EDP lower pressure cutoff point. This was tested by offsetting the pressure data for each beat during caval occlusion so that EDP was held constant, without altering the pressure decay waveform itself. This modification also minimized load-dependence of T-ln with heart failure (Fig 5B), similar to that observed under control conditions (k = -0.13±0.19 :control, and -0.09±0.11 :HF, p = 0.67).
Effects of β-adrenergic stimulation on load-sensitivity of τ

To test whether deviation from a mono-exponential pressure decay was modulated by adrenergic activity, we examined τ-ESP relations before and after DOB or ISO in the failing hearts. An example is shown in Fig. 6A. DOB (right panel) reduced the slopes of each monoexponential τ-ESP relation, whereas the T_k-ESP relation was flat before and after DOB. Similar results were obtained in all eight animals (Table 3). The reduced load-sensitivity in monoexponential τ from β-adrenergic stimulation was also associated with a decline in curvilinearity of the P-dP/dt relations. Fig. 6B shows example data with monoexponential and logistic model fits before and after DOB infusion. P-dP/dt relation non-linearity was diminished by β-adrenergic stimulation (p=0.003 by χ^2 for P(t)^2 term in multivariable regression model).

When relaxation data from controls, in which P-dP/dt relations were more linear, was contrasted to heart failure where the relations were more curvilinear, the result was an overestimation of the relaxation delay by monoexponential time constants. Similarly, since β-adrenergic stimulation restored relaxation decay closer to a monoexponential waveform, these same indexes magnified the improvement in relaxation. This is shown in Fig 6C. T_D and T_F shortened by nearly 30 %, whereas T_L declined by only 18 % from DOB/ISO infusion (p=0.0005 and 0.0008, vs T_D and T_F).

DISCUSSION

Monoexponential decay functions are the most commonly employed mathematical fits for the purpose of assessing ventricular relaxation time constants of LV isovolumic pressure decay. The fit can be made by assuming that pressure decays to a zero or a non-zero asymptote.
Deviations of real pressure decay from this idealized waveform have been long appreciated, but their consistency and impact on assessments of lusitropy in heart failure has not been previously tested. The present study demonstrated that this deviation is indeed consistently observed in failing hearts, and that it can be directly linked to the appearance of increased sensitivity of monoexponential-derived $\tau$ values to changes in chamber loading, and that it is under $\beta$-adrenergic control. We also found that an alternative mathematical model based on a logistic equation provides a better data fit both in the time domain $[P(t)]$ and phase-plane domain $(P-dP/dt)$, yielding more stable estimates of relaxation and minimal preload-sensitivity under control and heart failure conditions. These data have important practical implications for the assessment of relaxation in the failing heart.

Load-dependence of relaxation is complex, and despite many studies performed in both isolated muscle and chamber preparations, the exact mechanisms of this dependence remain unclear. These studies have demonstrated that changes in systolic stress or pressure are far more likely to influence relaxation rates than are pure changes in preload (muscle length or chamber volume). However, in the intact heart, preload changes such as induced by caval occlusion are accompanied by changes in end-systolic volumes, stresses, and pressures, blurring this distinction. Despite this, there was generally little change in relaxation rates in control hearts from caval occlusion, independent of the exact mathematical model used to define these rates. This was altered, however, by heart failure, even though the loading intervention remained identical. Previous investigators have interpreted this change to suggest a pathophysiologic enhanced sensitivity of relaxation to chamber load, however, the present analysis suggests that it can be more simply explained based on the increased deviation of real pressure from a monoexponential pattern in the failing heart.
There were several lines of evidence supporting a mathematical rather than physiologic explanation for this behavior. First we found that applying another essentially arbitrary model (logistic equation) to the same pressure data, qualitatively different results were achieved, with the apparent load-dependence in failing hearts nearly disappearing. Secondly, we showed that even if the identical heart failure pressure waveform was curve fit to a monoexponential model, alterations in the lower pressure cut-off point alone (which accompanied loading change) yielded directionally similar changes in relaxation rate. Thus, by taking the same set of pressure curves at varying loads, and simply offsetting the pressures so that EDP was maintained constant, we nearly eliminated apparent load-sensitivity of $T_{ln}$. Third, we found that the monoexponential curve-fit predicted a non-physiologic negative pressure asymptote ($P_4$) that rose as loading declined, whereas the logistic model predicted a smaller more physiologic baseline value that declined with loading. Prior studies directly measuring $P_4$ have reported far smaller values (-7 mm Hg) in normal hearts, although similar data from failing hearts are not available. The increase in $P_4$ with load reduction was non-physiologic, since if anything the asymptote should decline as external constraining forces and possibly elastic recoil are enhanced. Again using a purely mathematical manipulation by maintaining a constant $P_4$ value, the apparent load-variability of the monoexponential time constants was minimized, without compromising quality of fit. The present results in failing hearts are very similar to those previously reported in control isolated blood perfused canine hearts by Matsubara et al. P-dP/dt relations were also nonlinear in these isolated hearts, and the authors demonstrated improved fits to the data using the logistic rather than monoexponential model. The present study puts their analysis in important perspective. While normal contracting hearts display reasonably monoexponential pressure decays, failing hearts do not. This becomes very significant when monoexponential relaxation analysis is used to compare healthy to failing hearts, or study the
effects of agents like dobutamine or isoproterenol that alter this relaxation behavior. The result can be an overestimation of changes in both baseline relaxation rates, and in the load-sensitivity of these rates. The logistic model appears to have important advantages in this regard.

The advantages of the logistic fit may reflect a closer relationship to calcium-crossbridge kinetics, as theoretically suggested by Sakamoto et al., but this is speculative, and the fit remains a somewhat arbitrary mathematical alternative that could also differ from true relaxation physiology. Although the present study arbitrarily set the lower cut-off pressure for defining the relaxation period at 2 mmHg above EDP, as often used in prior studies, this may be lower than the true pressure at which mitral valve opens, especially in heart failure. If a higher cut-off pressure is selected, the segment of pressure analyzed will be reduced, and curvilinear dependence of dP/dt on P less marked in this smaller range, reducing load-dependence. Importantly, this curvilinearity exists throughout relaxation, and not simply after a time when mitral filling starts. Underlying deviation of the monoexponential model from the curvilinear P-dP/dt relations at least indicates that it would be more critical to determine the exact timing of mitral valve opening whenever relaxation is assessed by the monoexponential model. At the same time, pressure at the mitral valve opening is reduced by load reduction, so the effect of P-dP/dt curvilinearity becomes enhanced, contributing to the overestimated load sensitivity of relaxation based on the fitting error. Given that the extent to which actual pressure decay follows curvilinear P-dP/dt relations itself varies with heart condition (heart failure or adrenergic stimulation), the monoexponential model always has the potential to yield erroneous estimates of relaxation change even if purely isovolumic data are chosen.

Several studies have reported enhanced load sensitivity of LV relaxation in heart failure, all using monoexponential models to index LV relaxation, highlighting the importance of load profile as an underlying mechanism. However, the present data raise important cautions to such an
interpretation, since the mechanism appears to reflect more non-monoexponential decay behavior with curvilinear $dP/dt$-$P$ relations, rather physiological load differences. Mechanisms underlying the consistent deviation of relaxation from a monoexponential decay by heart failure such that early rates are slower than later rates remains speculative. The fact that this behavior is restored towards a more uniform rate by $\beta$-adrenergic stimulation suggests an important role of calcium handling, and thus the baseline behavior may reflect reduced sarcoplasmic reticular (SR) function.$^{1,2,32,33}$ There may also have been a component of improved restoring forces. However, restoring forces would also be expected to rise at reduced end-systolic volumes,$^{26,27}$ yet non-linear $P$-$dP/dt$ relations were similarly observed at resting and reduced loads in failure baseline, but not after adrenergic stimulation. This points more towards calcium handling and SR function. Interestingly, recent studies have indicated that phosphorylation of calcium handling and myofilament proteins, such as titin,$^{34}$ myosin binding protein C$^{35}$ and troponin I,$^{36}$ plays important roles in modulating cross-bridge detachment kinetics by complementary but different mechanisms.

**Conclusion**

The logistic model for pressure relaxation analysis was first presented and examined over 15 years ago, yet most parametric fits in current use rely on mono-exponential decay models whether this proves to be a reasonable mathematical fit or not. The current study reinforces our earlier work conducted using human data,$^{37}$ and extends the analysis by showing the importance of adrenergic tone in determining the decay waveshape. While performed in a dog model, this applies to human,$^{37}$ mouse,$^{35,36}$ or other mammals$^{38}$ as well. Investigators should keep the logistic fit in mind when characterizing conditions of heart dysfunction where SR calcium cycling is depressed.

**Disclosures:** None.
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Figure legends

Figure 1. Representative pressure-dimension loops and relations recorded at baseline and after 4 weeks of tachycardia pacing. Dotted lines indicate end-systolic pressure-dimension relations (ESPDR). Pacing induced heart failure was indicated by a reduced ESPDR slope, rightward shift of the PD data with reduced stroke dimension and percent fractional shortening, and marked steepening of the diastolic PD relation.

Figure 2. Example of effect of altering cardiac preload and thus end-systolic pressures on time constants (Tau) of left ventricular pressure relaxation. Data are from one animal. The left hand panel shows relations at control (baseline) and right hand panels after pacing-induced heart failure.

- $T_{ln}$; - $T_F$; - $T_D$; and $\leftrightarrow T_L$

Figure 3. [A] Example of LV pressure versus dP/dt plots at high and reduced preloads under normal and heart failure conditions. Reflecting a reduced contractility with heart failure, pressure changes by caval occlusion are smaller in heart failure than in normal. Measured data are indicated by closed circles, and theoretically calculated dP/dt - P relations based on monoexponential (linear fit) or logistic (parabolic fit) models are shown by solid lines. [B] Two representative P-dP/dt plots (two different dogs) taking data from multiple beats at varying preloads. The two solid lines represent the monoexponential relaxation fits to beats at resting (high) and reduced preloads.

Figure 4. Influence of altering the lower-pressure cutoff point for estimation of relaxation time constant. Results for the logistic constant ($T_L$) and monoexponential constant ($T_D$) are compared. The x-axis indicates three different pressure cutoff points (EDP+2, EDP+5, and EDP+10 mmHg).
defining the range of pressure data extracted for relaxation analysis. EDP is end-diastolic pressure; and HF, heart failure.

Figure 5. [A] Relaxation model derived pressure-decay asymptote ($P_4$) plot versus EDP for each beat in a failing heart during caval occlusion in a typical dog. For monoexponential model fits, $P_4$ was very negative at the baseline (upper) EDP, and rose substantially as EDP declined (mean slope = $-1.21\pm0.7$). In contrast, the logistic model-derived value was small at resting baseline, and declined slightly as loading was reduced (mean slope = $+0.38\pm0.17$). This pattern is more physiologic, whereas the former pattern is more consistent with mathematical model inaccuracies.

[B] Influence of modifications of monoexponential data fits on apparent load-dependence of relaxation with heart failure. Examples of relations (same dog shown in Fig. 2) between $\tau$ derived from modified exponential models and ESP are shown. Open circles are for $T_F$ vs ESP relations in which the $P_4$ asymptote was held constant despite the load change, and closed circles indicate $T_{ln}$ vs ESP relations in which the pressure data for each beat was first vertically displaced to maintain a constant EDP. Either modification effectively eliminated the appearance of enhanced load-sensitivity with heart failure.

Figure 6. [A] An example of tau-endsystolic pressure relations before (left) and after (right) dobutamine infusion in a failing heart. [B] Example of LV pressure versus dP/dt plots at high (closed symbols) and reduced (open symbols) preloads before (circles) and after (triangles) dobutamine infusion. Theoretically calculated dP/dt - P relations based on monoexponential (linear fit) or logistic (parabolic fit) models are shown by solid lines. Under each condition, the logistic model better fit data than the monoexponential model. [C] Changes in each tau before and after $\beta$-
adrenergic stimulation with dobutamine or isoproterenol. Monoexponential tauds overestimated relaxation shortening in response to the β-adrenergic stimulation.
**Table 1. Changes in Hemodynamic data**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Heart Failure</th>
<th>( p ) value vs. baseline</th>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>129 ± 14</td>
<td>157 ± 17</td>
<td>0.0005</td>
</tr>
<tr>
<td>ESP (mmHg)</td>
<td>127 ± 20</td>
<td>104 ± 16</td>
<td>0.02</td>
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<tr>
<td>EDP (mmHg)</td>
<td>10.7 ± 2.7</td>
<td>27.7 ± 7.3</td>
<td>0.002</td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>27.0 ± 5.7</td>
<td>34.7 ± 4.3</td>
<td>0.004</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>36.5 ± 5.1</td>
<td>39.3 ± 4.9</td>
<td>0.007</td>
</tr>
<tr>
<td>FS (%)</td>
<td>25.2 ± 4.6</td>
<td>12.4 ± 3.8</td>
<td>0.0006</td>
</tr>
<tr>
<td>( \frac{dP}{dt_{\text{max}}} ) (mmHg/s)</td>
<td>3368 ± 705</td>
<td>1721 ± 536</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ees (mmHg/mm)</td>
<td>10.3 ± 2.6</td>
<td>6.3 ± 1.4</td>
<td>0.003</td>
</tr>
</tbody>
</table>

HR indicates heart rate; ESP, end-systolic pressure; EDP, end-diastolic pressure; ESD, end-systolic dimension; EDD, end-diastolic dimension; FS, fractional shortening; \( \frac{dP}{dt_{\text{max}}} \), maximum rate of isovolumic pressure rise; and Ees, end-systolic elastance, respectively.
Table 2. Changes in Relaxation Time Constant and Load Sensitivity (k)

<table>
<thead>
<tr>
<th></th>
<th>$T_{ln}$</th>
<th>$T_F$</th>
<th>$T_D$</th>
<th>$T_L$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>26.4±7.5</td>
<td>34.9±9.3</td>
<td>34.7±7.5</td>
<td>18.3±5.5</td>
</tr>
<tr>
<td><strong>Heart Failure</strong></td>
<td>48.8±15.8</td>
<td>61.2±18.9</td>
<td>61.0±15.0</td>
<td>23.5±5.8</td>
</tr>
<tr>
<td><strong>p value vs. baseline</strong></td>
<td>0.00006</td>
<td>0.0002</td>
<td>0.00002</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

**Load sensitivity (k)**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>0.055±0.081</td>
<td>0.117±0.113</td>
<td>0.089±0.119</td>
<td>0.011±0.068</td>
</tr>
<tr>
<td><strong>Heart Failure</strong></td>
<td>0.469±0.386</td>
<td>1.032±0.796</td>
<td>0.945±0.730</td>
<td>0.021±0.090</td>
</tr>
<tr>
<td><strong>p value vs. baseline</strong></td>
<td>0.002</td>
<td>0.001</td>
<td>0.002</td>
<td>0.87</td>
</tr>
</tbody>
</table>
Table 3. Changes in Load Sensitivity ($k$) by β-Adrenergic Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>$p$ value vs. pre</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Tln$ (ms/mmHg)</td>
<td>0.46 ± 0.12</td>
<td>0.10 ± 0.08</td>
<td>0.02</td>
</tr>
<tr>
<td>$TF$ (ms/mmHg)</td>
<td>1.00 ± 0.25</td>
<td>0.23 ± 0.12</td>
<td>0.02</td>
</tr>
<tr>
<td>$TD$ (ms/mmHg)</td>
<td>0.95 ± 0.24</td>
<td>0.24 ± 0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>$TL$ (ms/mmHg)</td>
<td>0.006 ± 0.02</td>
<td>0.014 ± 0.015</td>
<td>0.86</td>
</tr>
</tbody>
</table>
Figure 1

Baseline

Heart Failure

Pressure (mmHg)

Dimension (mm)
Figure 2
Normal  
Heart Failure  
Baseline  
Lowered Preload  

Figure 3
Figure 4
Figure 5

A

Monoexponential Model

![Graph showing EDP (mmHg) vs. P infinite (mmHg)]

B

Logistic Model

![Graph showing EDP (mmHg) vs. P infinite (mmHg)]

ESP (mmHg) 75 95 115

TF with asymptote correction

Tln with EDP correction

TF with asymptote correction

Tln with EDP correction

Figure 5
Figure 6
Analysis of Isovolumic Relaxation in Failing Hearts by Monoexponential Time Constants Overestimates Lusitropic Change and Load-dependence: Mechanisms and Advantages of Alternative Logistic Fit
Hideaki Senzaki and David A. Kass

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