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

Mechanisms and Advantages of Alternative Logistic Fit

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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 monoexponential waveform, leading to overestimations of lusitropic change and load sensitivity by monoexponential-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 nonzero asymptotes and by a logistic fit ($\tau_L$). $\tau_L$ assumes nonlinear 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% to 80% with heart failure, 3 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 nonmonoexponential decay reflected by nonlinear pressure-time derivative of pressure plots, which was enhanced with heart failure ($P<0.01$). This nonlinearity 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. (Circ Heart Fail. 2010;3:268-276.)

Key Words: hemodynamics | diastole | congestive heart failure | relaxation

Left ventricular isovolumic relaxation is prolonged by heart failure (HF), largely as the consequence of abnormal calcium handling and increased external and internal chamber loading. Studies also have suggested enhanced sensitivity of relaxation to varied loading as failure worsens. For example, Eichhorn et al found that relations between the time constant of relaxation ($\tau$) and end-systolic pressure (ESP) steepened (greater load dependence) in patients with depressed contractility. Ishizuka et al subsequently found that the sensitivity of $\tau$ to load change induced by caval occlusion increased markedly in conscious dogs after tachycardia-induced HF. These results may reflect adrenergic downregulation because earlier studies had shown that the sensitivity of $\tau$ to ESP increased with propranolol and decreased with isoproterenol.

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Another potentially important contributor to these observations, 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 used in each of the prior cited studies. However, the real isovolumic pressure decay does not necessarily follow this waveform, and deviations can profoundly influence estimated time constants and qualitative assessments of load sensitivity when an exponential model is nonetheless used. This deviation often is treated as a noise in relaxation analysis, but the potential exists for consistent errors if it is mechanistically linked to adrenergic stimulation or the severity of underlying HF. Biexponential and polyno-
mial fits\textsuperscript{11,12} or pressure decay halftimes\textsuperscript{13} do not adequately solve the problem. However, a logistic curve proposed by Matsubara et al\textsuperscript{14} seemed advantageous in a study of denervated (isolated) hearts and might similarly be so in ventricles weakened by HF.

This 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 uses 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 HF 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 thiamyal (15 mg/kg) and anesthetized with halothane (1 to 2%). The chest was opened by lateral thoracotomy at the fifth intercostal space. A flexible tube was secured within the apical myocardium to facilitate insertion of a micromanometer catheter (SPC 350) for pressure measurement. Sonomicrometer crystals were implanted to record internal short-axis dimension and free-wall thickness. A pneumatic cuff occluder placed around the inferior vena cava 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) inserted in a subcutaneous pocket for right ventricular tachycardia pacing to induce HF. In 8 dogs, pacing wires also were 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 a more physiological study condition (atrial but not ventricular pacing). Catheters and leads were externalized between the scapulae. The animals were fully recovered from surgery before study.

Protocol

Hemodynamic data before and after development of pacing-induced HF were collected with animals standing quietly in a sling apparatus. Data recordings were performed at steady state and during load reduction by inferior vena cava occlusion. On the day after baseline study, right ventricular pacing was initiated at 250 min\textsuperscript{-1}. Studies were repeated at weekly intervals to develop clinical HF, characterized by lethargy, anorexia, ascites, and dyspnea. Hemodynamic measurements were made during normal sinus rhythm, with pacing suspended for at least 30 minutes before recording. To test the effects of β-adrenergic stimulation on load sensitivity of various τ estimates in failing hearts, dobutamine (DOB, 5 µg·kg\textsuperscript{-1}·min\textsuperscript{-1} IV, n=5) or isoproterenol (0.4 µg·kg\textsuperscript{-1}·min IC, n=3) was administered in 8 dogs after development of HF. Heart rate was maintained fixed at 160 min\textsuperscript{-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 before inferior vena cava occlusion were used to obtain ESP and end-diastolic pressure (EDP), short-axis dimensions (end-systolic and end-diastolic dimensions), and percent fractional shortening. Ventricular contractile state was assessed by the ESP-dimension relation.\textsuperscript{16,17} The first derivative of pressure (dP/dt) was calculated by a running 5-point-weighted local slope as follows:

\[ \text{dP/dt} = \frac{1}{6} \left( (P_{t+1} - P_{t-1}) + (P_{t+2} - P_{t-2}) \right) \]

Time constants of left ventricular (LV) isovolumic relaxation were calculated using pressure data from peak negative dP/dt to 2 mm Hg above EDP. EDP was defined as the pressure when dP/dt reached a threshold of 10% maximum. Monoexponential time constants were calculated by 3 methods. The first assumed a zero-pressure asymptote (T\textsubscript{L}), and was derived from the negative reciprocal of the linear regression between the natural logarithm of pressure and time.\textsuperscript{18} The latter 2 methods assumed a nonzero asymptote and used the following equation:

\[ P(t) = P_0 e^{-t/T_L} + P_A \]

where \( P_0 \) was the pressure at \( t=0 \), and \( P_A \) was the pressure asymptote at \( t=\infty \). Two time constants were estimated as follows: one from the inverse slope of the P-dP/dt plot (T\textsubscript{L})\textsuperscript{19} and the other by nonlinear regression (Marquardt algorithm) to the pressure-time data (T\textsubscript{L}).\textsuperscript{20}

A fourth time constant was determined from the logistic model proposed by Matsubara et al\textsuperscript{14} as follows:

\[ P(t) = \frac{P_A}{(1 + e^{T_L t})} + P_0 \]

where \( P_0 \) was the decay asymptote, and \( P_A \) was an amplitude constant. This equation also was fit by nonlinear least squares regression, yielding time constant T\textsubscript{L}.

Analysis of Load Sensitivity of Relaxation

Each τ estimate was calculated for multiple beats at varying loads during caval occlusion, and the results plot as τ-ESP relations. ESP was the point of maximal P(D-D\textsubscript{0}) for each beat, where P is pressure, D is dimension, and Do the dimension-axis intercept of the ESP-dimension relation. The slope of the τ-ESP relations (k) indexed load dependence.

To further elucidate the underlying causes of enhanced load sensitivity of relaxation in HF, P-dP/dt relations from measured data and those derived from monoeponential and logistic fits were compared. Model-fit relations were generated by differentiation of Equations 2 and 3, yielding the following equations:

\[ \frac{dP}{dt} = \frac{P(t) - P_A}{\tau} \]

for the monoexponential model and

\[ \frac{dP}{dt} = \frac{P(t) - P_A}{\tau} \cdot \left( \frac{P_A}{T_L} - P_0 \right) \]

\[ \alpha = \frac{P_A}{T_L} - P_0 \]

for the logistic model. The portion of \( \alpha = P_A - T_L \) 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 HF were evaluated by paired t test. Differences before and after DOB or isoproterenol infusion also were evaluated by paired t test. Differences in percent changes and load dependence with HF between monoexponential and logistic τ were evaluated by Dunnett multiple comparisons test. Difference in percent changes after adrenergic stimulation between monoexponential and logistic τ also was evaluated by Dunnett multiple comparisons test. Goodness of fit for exponential and logistic models to relaxation data were assessed by determining the
sum-of-squares difference between regression-derived (ie, Equations 4 and 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 was calculated as \(n\times(\log(2\pi\times\text{sum-of-squares difference/n})\) and remains so with HF (Figure 2). Tachycardia-induced HF exhibited marked contractile depression and diastolic dysfunction (Table 1). End-diastolic dimension decreased by 39% and fractional shortening and dP/dt_max increased by 50%. EDP increased from 11 to 28 mm Hg, accompanied by chamber dilation. These results are exemplified by pressure-dimension loops shown in Figure 1 and are consistent with previously reported data with this model.16,21

Although all time constants of relaxation were prolonged by HF, the quantitative assessment of this change was substantially different among the 3 monoexponential-based \(\tau\) parameters and the logistic model-derived \(\tau\) (Table 2). Monoexponential \(\tau\) all increased by between 75% and 85% over baseline, whereas \(\tau_\ln\) increased by only 28% (\(P=0.001, 0.004, 0.0008\) versus \(T_{in}, T_{D},\) and \(T_F\), respectively).

### Results

#### Changes in Hemodynamics Due to Pacing LV Failure

Tachycardia-induced HF exhibited marked contractile depression and diastolic dysfunction (Table 1). End-diastolic dimension decreased by 39% and fractional shortening and dP/dt_max increased by 50%. EDP increased from 11 to 28 mm Hg, accompanied by chamber dilation. These results are exemplified by pressure-dimension loops shown in Figure 1 and are consistent with previously reported data with this model.16,21

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#### Changes in Load Sensitivity of \(\tau\) Due to Pacing LV Failure

Figure 2 displays \(\tau\)-ESP relations at baseline and after development of HF from a representative dog. There was minimal change in \(\tau\) with preload and ESP reduction under baseline conditions, whereas all monoexponential-derived \(\tau\) values (\(T_{in}, T_{D},\) and \(T_F\)) displayed enhanced load dependence with HF. This was not true for \(T_L\), which was little load sensitive under both conditions. Table 2 provides the mean slopes (k) for the \(\tau\)-ESP relations from all dogs. The k increased consistently and by nearly a full order of magnitude for \(T_D, T_F,\) and \(T_{in}\) (the 3 monoexponential constants), whereas k for \(T_L\) was small at baseline and remained so with HF (\(P=0.002\) versus k for \(T_{in}, T_D,\) and \(T_F\)). The results were also identical when we used logarithmic-transformed k values, assuming no nonlinear distribution of k value with HF development. These results indicate that enhanced load sensitivity of relaxation with

### Table 1. Changes in Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Heart Failure</th>
<th>(P) vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>129±14</td>
<td>157±17</td>
<td>0.0005</td>
</tr>
<tr>
<td>ESP, mm Hg</td>
<td>127±20</td>
<td>104±16</td>
<td>0.02</td>
</tr>
<tr>
<td>EDP, mm Hg</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>dP/dt_max, mm Hg/s</td>
<td>3368±705</td>
<td>1721±536</td>
<td>0.0001</td>
</tr>
<tr>
<td>EES, mm Hg/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; ESD, end-systolic dimension; EDD, end-diastolic dimension; FS, fractional shortening; dP/dt_max, maximum rate of isovolumic pressure rise; and EES, end-systolic elastance.

Parameters and the logistic model-derived \(\tau\) (Table 2). Monoexponential \(\tau\) all increased by between 75% and 85% over baseline, whereas \(\tau_\ln\) increased by only 28% (\(P=0.001, 0.004, 0.0008\) versus \(T_{in}, T_{D},\) and \(T_F\), respectively).

### Table 2. Changes in Relaxation Time Constant and Load Sensitivity (k)

<table>
<thead>
<tr>
<th></th>
<th>(T_{in})</th>
<th>(T_F)</th>
<th>(T_D)</th>
<th>(T_L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\tau, \text{ms})</td>
<td>Baseline</td>
<td>26.4±7.5</td>
<td>34.9±9.3</td>
<td>34.7±7.5</td>
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<tr>
<td>Heart failure</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>(P) vs baseline</td>
<td>0.00006</td>
<td>0.0002</td>
<td>0.00002</td>
<td>0.00002</td>
</tr>
<tr>
<td>Load sensitivity (k), mm/Hg</td>
<td>Baseline</td>
<td>0.055±0.081</td>
<td>0.117±0.113</td>
<td>0.089±0.119</td>
</tr>
<tr>
<td>Heart failure</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>(P) vs baseline</td>
<td>0.002</td>
<td>0.001</td>
<td>0.002</td>
<td>0.87</td>
</tr>
</tbody>
</table>

HR indicates heart rate; ESD, end-systolic dimension; EDD, end-diastolic dimension; FS, fractional shortening; dP/dt_max, maximum rate of isovolumic pressure rise; and EES, end-systolic elastance.

### Figure 1

Representative pressure-dimension loops and relations recorded at baseline and after 4 weeks of tachycardia pacing. Dotted lines indicate ESP dimension relations. Pacing-induced HF was indicated by a reduced ESP dimension relation slope, rightward shift of the pressure-dimension data with reduced stroke dimension, and percent fractional shortening and marked steepening of the diastolic pressure-dimension relation.

### Figure 2

Example of effect of altering cardiac preload and thus ESPs on time constants (\(\tau\)) of LV pressure relaxation. Data are from 1 animal. Relations are shown at control (baseline) and after pacing-induced HF. ● indicates \(T_{in}, \square, T_F, \Delta, T_D,\) and \(\nabla, T_L\).
HF was critically dependent on 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 plotted as \( P \)-dP/dt relations. Figure 3A shows example plots with both types of fit for control and HF conditions. At both high (top panel) and reduced (bottom panel) preloads, \( P \)-dP/dt relations were generally downward convex to the pressure axis, and this nonlinearity was consistently enhanced with HF. At baseline, the \( P(t)^2 \) term in the regression (Equation 5) was statistically significant in only 22% of the \( P \)-dP/dt relations. However, with HF, the majority (78%) of \( P \)-dP/dt relations were nonlinear (\( P = 0.003 \) by \( \chi^2 \) versus control data). Because these relations are theoretically linear if pressure decay follows a monoexponential form, the increased nonlinearity indicated a consistent deviation from a monoexponential pressure decay with HF. Because the logistic model assumed a nonlinear (parabolic) dependence of \( P \) and dP/dt, it provided a better data fit at both baseline and HF. This was indexed by the sum-of-squares difference between measured and model-predicted dP/dt, which was 28% (\( P = 0.001 \)) and 62% (\( P = 0.0007 \)) higher with the monoexponential model than with the logistic model at baseline and HF, respectively.

Curvilinear \( P \)-dP/dt data could explain increased load sensitivity of monoexponential \( \tau \). Figure 3B displays \( P \)-dP/dt data from multiple beats at varying preloads from 2 dogs (top and bottom panels). As noted previously, these data display nonlinearity 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 because curvilinearity of the \( P \)-dP/dt data was minimal. With HF, 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 decreased. Because the negative reciprocal of the slope was \( T_D \) (or \( T_F \)), this corresponded to shortening of the time constant with reduced load as shown in Figure 2. Similar results were obtained in all hearts studied.

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 point (ie, 2 mm Hg above EDP) used to set the data range for analysis. When loading is altered, LV EDP 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 nonlinear as depicted in Figure 4, which shows calculated \( T_D \) and \( T_F \) 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

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**Figure 3.** A, Example of LV pressure versus dP/dt plots at high and reduced preloads under normal and HF conditions. Reflecting a reduced contractility with HF, pressure changes by caval occlusion are smaller in HF than in normal. Measured data are indicated by closed circles, and theoretically calculated P-dP/dt relations based on monoexponential (linear fit) or logistic (parabolic fit) models are shown by solid lines. B, Two representative P-dP/dt plots (2 different dogs), taking data from multiple beats at varying preloads. The 2 solid lines represent the monoexponential relaxation fits to beats at resting (high) and reduced preloads.
shortening of TD, whereas there was no significant change in TL. 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 HF also yielded marked load dependence of the calculated pressure decay asymptote (P4). Thus, at resting loads, this intercept often was quite negative (mean P4 for TD and TF, −55.6±46 mm Hg), and it increased to −10.2±14.1 mm Hg as loading decreased. This is shown by an example in Figure 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 (Figure 5A, right panel) was generally positive at rest and displayed a physiological decrease because loading was reduced.

Both P4 and τ parameters in a monoexponential model are mathematically interdependent; hence, 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. As shown by an example in Figure 5B, the resulting τ-ESP relations no longer displayed load sensitivity with HF (mean k, 0.14±0.21). It is important to note that this purely mathematical modification trivially altered goodness of fit because the sum-of-squares difference between model and measured P(t) was 23 mm Hg with a varying P4 versus 33 mm Hg with a fixed P4.

P4 was already constant and assumed equal to 0 for Tln, but this could still enhance Tln load sensitivity because of 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 Tln with HF (Figure 5B), similar to that observed under control conditions (control k, 0.13±0.19; HF k, 0.09±0.11; P=0.67).

Effects of β-Adrenergic Stimulation on Load Sensitivity of τ

To test whether deviation from a monoexponential pressure decay was modulated by adrenergic activity, we examined τ-ESP relations before and after DOB or isoproterenol in the

![Figure 4](http://circheartfailure.ahajournals.org/)

**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 3 different pressure cutoff points (EDP +2, EDP +5, and EDP +10 mm Hg), defining the range of pressure data extracted for relaxation analysis.

![Figure 5](http://circheartfailure.ahajournals.org/)

**Figure 5.** A, Relaxation model-derived pressure-decay asymptote (P4) plot versus EDP for each beat in a failing heart during caval occlusion in a typical dog. For monoexponential model fits, P4 was very negative at the baseline (upper) EDP and increased substantially as EDP decreased (mean slope, −1.21±0.7). In contrast, the logistic model-derived value was small at resting baseline and decreased slightly as loading was reduced (mean slope, 0.38±0.17). This pattern is more physiological, 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 HF. Examples of relations (same dog shown in Figure 2) between τ derived from modified exponential models and ESP are shown. Open circles indicate T_F versus ESP relations in which the P4 asymptote was held constant despite the load change, and closed circles indicate T_L versus ESP relations in which the pressure data for each beat were first vertically displaced to maintain a constant EDP. Either modification effectively eliminated the appearance of enhanced load sensitivity with HF.
failing hearts. An example is shown in Figure 6A. DOB (right panel) reduced the slopes of each monoexponential τ-ESP relation, whereas the T_L-ESP relation was flat before and after DOB. Similar results were obtained in all 8 animals (Table 3). The reduced load sensitivity in monoexponential τ from β-adrenergic stimulation also was associated with a decline in curvilinearity of the P-dP/dt relations. Figure 6B shows example data with monoexponential and logistic model fits before and after DOB infusion. P-dP/dt relation nonlinearity was diminished by β-adrenergic stimulation (P=0.003 by χ² 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 HF in which the relations were more curvilinear, the result was an overestimation of the relaxation delay by monoexponential time constants. Similarly, because β-adrenergic stimulation restored relaxation decay closer to a monoexponential waveform, these same indexes magnified the improvement in relaxation (see Figure 6C). T_D and T_F shortened by approximately 30%, whereas T_L decreased by only 18% from DOB or isoproterenol. Monoexponential τs overestimated relaxation shortening in response to the β-adrenergic stimulation.

Table 3. Changes in Load Sensitivity (k) by β-Adrenergic Stimulation

<table>
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<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>P vs Prebaseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_L, ms/mm Hg</td>
<td>0.46±0.12</td>
<td>0.10±0.08</td>
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</tr>
<tr>
<td>T_F, ms/mm Hg</td>
<td>1.00±0.25</td>
<td>0.23±0.12</td>
<td>0.02</td>
</tr>
<tr>
<td>T_D, ms/mm Hg</td>
<td>0.95±0.24</td>
<td>0.24±0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>T_L, ms/mm Hg</td>
<td>0.006±0.02</td>
<td>0.014±0.015</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Discussion

Monoexponential decay functions are the most commonly used 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 nonzero asymptote. Deviations of real pressure decay from this idealized waveform have been long appreciated, but their consistency and impact on assessments of lusitropy in HF has not been previously tested. This study showed that this deviation is indeed consistently observed in failing hearts, that it can be directly linked to the appearance of increased sensitivity of monoexponential-derived τ values to changes in chamber loading, and that it is under β-adrenergic control. We also found that an alternative mathematical model based on a logistic equation provides a better data fit in both the time domain [P(t)] and the phase-plane domain (P-dP/dt), yielding more stable estimates.
of relaxation and minimal preload sensitivity under control and HF 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 shown 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 HF, although the loading intervention remained identical. Previous investigators have interpreted this change to suggest a pathophysiologically enhanced sensitivity of relaxation to chamber load; however, this 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 physiological explanation for this behavior. First, we found that when 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. Second, we showed that even if the identical HF pressure waveform was curve fit to a monoexponential model, alterations in the lower pressure cutoff 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 Tn. Third, we found that the monoexponential curve fit predicted a nonphysiologic negative pressure asymptote (P4) that increased as loading decreased, whereas the logistic model predicted a smaller, more physiological baseline value that decreased with loading. Prior studies that directly measured P4 have reported far smaller values (−7 mm Hg) in normal hearts, although similar data from failing hearts are not available. The increase in P4 with load reduction was nonphysiologic because if anything, the asymptote should decrease as external constraining forces and possibly elastic recoil are enhanced.

Again, using a purely mathematical manipulation by maintaining a constant P4 value, we found 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.14 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. This study puts their analysis in important perspective. Although normally contracting hearts display reasonably monoexponential pressure decays, failing hearts do not. This becomes very significant when monoexponential relaxation analysis is used to compare healthy hearts with failing hearts or to study the effects of agents such as DOB or isoproterenol that alter this relaxation behavior. The result can be an overestimation of changes in both baseline relaxation rates and load sensitivity of these rates. The logistic model seems 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.28 but this is speculative, and the fit remains a somewhat arbitrary mathematical alternative that could also differ from true relaxation physiology. Although this study arbitrarily set the lower cutoff pressure for defining the relaxation period at 2 mm Hg above EDP, as often used in prior studies, this may be lower than the true pressure at which the mitral valve opens, especially in HF. If a higher cutoff 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; hence, 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 (HF 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 HF using monoexponential models to index LV relaxation, highlighting the importance of load profile as an underlying mechanism. However, the present data increase important cautions to such an interpretation because the mechanism seems to reflect more nonmonoexponential decay behavior with curvilinear P-dP/dt relations than physiological load differences. Mechanisms underlying the consistent deviation of relaxation from a monoexponential decay by HF such that early rates are slower than later rates remain speculative. The fact that this behavior is restored toward a more uniform rate by β-adrenergic stimulation suggests an important role of calcium handling; thus, the baseline behavior may reflect reduced sarcoplasmic reticular function. There also may have been a component of improved restoring forces. However, restoring forces would be expected to increase at reduced end-systolic volumes yet nonlinear P-dP/dt relations were similarly observed at resting and reduced loads in failure baseline but not after adrenergic stimulation. This points more toward calcium handling and sarcoplasmic reticular function. Interestingly, recent studies...
have indicated that phosphorylation of calcium handling and myofilament proteins, such as titin, myosin-binding protein C, and troponin I plays an important role in modulating cross-bridge detachment kinetics by complementary but different mechanisms.

Conclusion
The logistic model for pressure relaxation analysis was first presented and examined more than 15 years ago, yet most parametric fits in current use rely on monoeponential decay models whether they prove to be a reasonable mathematical fit or not. This study reinforces our earlier work conducted using human data and extends the analysis by showing the importance of adrenergic tone in determining the decay waveform. Although performed in a dog model, this applies to human, mouse, or other mammals as well. Investigators should keep the logistic fit in mind when characterizing conditions of heart dysfunction in which sarcoplasmic reticular calcium cycling is depressed.

Disclosures
None.

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**CLINICAL PERSPECTIVE**

Abnormal ventricular relaxation is a common feature of cardiac failure syndromes and may play an important role in limiting ventricular performance and generating clinical symptoms. However, like many aspects of ventricular mechanics, its quantitation has presented challenges. The traditional time constant of pressure decay is based on fitting pressure data to a monoexponential decay function and is generally considered the gold standard used in experimental and clinical studies. This decay model is more a convenience rather than based on first principles of muscle mechanics; thus, it is important to assess the accuracy of the model fit, particularly in disease conditions in which it so often is used. We used a controlled large mammalian model of heart failure and showed how the pressure decay deviates from a monoexponential decrease function as heart failure worsens but that β-adrenergic stimulation restores relaxation toward this wave shape. These deviations result in inaccuracies of relaxation analysis based on monoexponential waveforms when comparing healthy with failing hearts or studying the impact of agents that stimulate β-adrenergic (and related) pathways, leading to a systematic overestimation of changes in baseline relaxation rate and the load sensitivity of such rates. An alternative mathematical model based on a logistic equation better describes actual pressure decay, yielding more stable estimates of relaxation with minimal load sensitivity under control and failing conditions. These data have important practical implications for the assessment of relaxation in the failing heart and indicate the importance of confirming that the mathematical model used is appropriate to the conditions being studied.
Analysis of Isovolumic Relaxation in Failing Hearts by Monoexponential Time Constants Overestimates Lusitropic Change and Load Dependence: Mechanisms and Advantages of Alternative Logistic Fit

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