Physical determinants of left ventricular isovolumic pressure decline: model prediction with in vivo validation

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The rapid decline in pressure during isovolumic relaxation (IVR) is traditionally fit algebraically via two empiric indexes: τ, the time constant of IVR, or τL, a logistic time constant. Although these indexes are used for in vivo diastolic function characterization of the same physiological process, their characterization of IVR in the pressure phase plane is strikingly different, and no smooth and continuous transformation between them exists. To avoid the parametric discontinuity between τ and τL and more fully characterize isovolumic relaxation in mechanistic terms, we modeled ventricular IVR kinematically, employing a traditional, lumped relaxation (resistive) and a novel elastic parameter. The model predicts IVR pressure as a function of time as the solution of d^2P/dt^2 + (1/μ) dP/dt + E_p = 0, where μ (ms) is a relaxation rate (resistance) similar to τ or τL and E_p (1/s^2) is an elastic (stiffness) parameter (per unit mass). Validation involved analysis of 310 beats (10 consecutive beats for 31 subjects). This model fit the IVR data as well as or better than τ or τL in all cases (average root mean squared error for dP/dt vs. t: 29 mmHg/s for model and 35 and 65 mmHg/s for τ and τL, respectively). The solution naturally encompasses τ and τL as parametric limits, and good correlation between τ and 1/μE_p (τ = 1.15/μE_p - 11.85; r^2 = 0.96) indicates that isovolumic pressure decline is determined jointly by elastic (E_p) and resistive (1/μ) parameters. We conclude that pressure decline during IVR is incompletely characterized by resistance (i.e., τ and τL) alone but is determined jointly by elastic (E_p) and resistive (1/μ) mechanisms.

relaxation; stiffness; hemodynamics; diastole; mechanics; pressure phase plane; isovolumic relaxation

IN VIVO ANALYSIS of isovolumic relaxation (IVR) in mammalian hearts has traditionally relied on τ, the time constant of IVR, to characterize pressure decline. Typically, the rate of pressure decline as a function of time is assumed to be proportional to pressure itself and is therefore a solution to

$$\frac{\tau}{dP}{dP}{dt} + (P - P_\infty) = 0 \quad (IA)$$

or

$$P(t) = (P_0 - P_\infty)e^{-\frac{t}{\tau}} + P_\infty \quad (IB)$$

where P_0 is a constant and P_\infty is the pressure asymptote (19). A geometrically convenient way to determine τ is to plot Eq. IA in the time derivative of pressure (dP/dt) vs. time-varying pressure [P(t)] (pressure phase plane, PPP), where it inscribes a straight line (19, 33) with a slope of -1/τ, and fit it to the IVR portion of the loop inscribed by P(t) for the cardiac cycle (Fig. 1A). However, a straight line fit to the IVR portion of the loop may not always be physiological, since curvilinear IVR segments exist (Fig. 1B).

An alternative empiric constant has been proposed to fit these frequently occurring “curved” IVR segments of PPP trajectories (19). Like τ, the logistic time constant τL provides an empirical fit, where pressure as a function of time obeys a relationship in which the rate of pressure decline is proportional to the square of the pressure and is given by

$$\frac{P^2}{P_\infty} + \frac{\tauL}{dP}{dP}{dt} + P - P_B = 0 \quad (2A)$$

or

$$P(t) = \frac{P_\infty}{1 + e^{-\frac{t}{\tauL}}} + P_B \quad (2B)$$

where P_\infty is a constant and P_B is the pressure asymptote (19). Unlike the monoexponential expression (Eq. 1), which can only generate a straight line (linear) relation in the PPP, the logistic relation is quadratic in P, and in the PPP, it can only generate, and therefore best fit, curvilinear PPP IVR contours (Fig. 1B). Therefore, two parameters are required (τ and τL) to fit the range of isovolumic pressure decline shapes encountered physiologically.

Both of these measures of IVR have been used in characterization of diastolic heart failure (11, 12, 31, 35). On the molecular level, both τ and τL have been shown to correlate with “relaxation” as defined by deactivation events such as cross-bridge cycling, calcium handing, or lusitropism (5, 20). However, although both τ and τL have been found to be related to deactivation events, neither can fully characterize the full range of IVR PPP trajectories encountered. Furthermore, although transition between curvilinear and linear IVR PPP segments in the same heart is physiologically permitted, some segments cannot be well fit by either τ or τL (Fig. 1C). Although particular IVR segments in the PPP may be curved, suggesting that τL should be best suited for its characterization, the example in Fig. 1C shows that neither τ nor τL can adequately characterize these physiologically allowable IVR segments. Indeed, because these types of PPP IVR segments exist, and because neither a mathematical nor physiological link between τ and τL has been proposed, we have proposed a

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kinematic model-based solution of the isovolumic pressure decay problem.

We hypothesized that the same physical and physiological principles govern IVR for all hearts; what differs from heart to heart are the parameters of the model. Specifically, mathematical modeling of elastic recoil forces, opposed by resistance (physiologically, relaxation) and inertial forces, jointly determine pressure decline during IVR. Furthermore, because this model should be able to predict (i.e., fit) all IVR PPP trajectories, straight or curvilinear, we also hypothesized that the two distinct and previously (mathematically) unrelated empirical curve-fitting parameters (τ and τ1) are in fact subject to the same physical principles (inertial, elastic, and resistive forces) such that their variation is a reflection of altered balance between inertial, elastic, and resistive mechanisms.

METHODS

Modeling pressure decay kinematically. Deactivation necessarily plays a role in any attempt to characterize IVR, and τ and τ1 have been shown to be good correlates of relaxation or deactivation (5, 20, 22, 28). The effects of the residual cross bridges or delayed calcium sequestration manifest as a resistive modulator against elastic recoil (22); thus we lump the standard deactivation parameters along with any additional viscous consequences into a resistive parameter. End-systolic stored elastic forces that drive filling (13, 14) have been attributed to extracellular matrix, intracellular titin (8, 24), microtubules (21), and the heart’s visceral pericardium (10). Such an elastic restoring force at end systole must overcome the residual forces of contraction (22). Therefore, inclusion of a restoring force, characterized by a spring constant-like, elastic parameter, is required.

If deactivation were solely responsible for the pressure drop during IVR, cross bridges would uncouple, but no sarcomere or myocyte lengthening would accompany the reduction in wall tension. The presence of wall motion, in the form of myocardial torsion during IVR (25) and chamber shape change, indicates that tissue motion accompanies relaxation/deactivation. Newton’s law requires that restoring forces that generate (tissue) motion be subject to the laws of inertia, and therefore an inertial term is required in modeling IVR.

Empirical models commonly relate myocardial properties with pressure decline and other physiological factors (1, 2). LaPlace’s law is used to relate wall strain (displacement) to wall stress and chamber pressure for a particular choice of chamber geometry. Thus LaPlace’s law permits a change of variable from displacement (x) to chamber pressure (P) in Newton’s law (per unit mass), expressing the balance among inertial, resistive, and restoring force terms (d2x/dt2 + Rdx/dt + kx = 0), where R and k are suitable resistive and elastic parameters. This is the familiar equation of damped harmonic motion (7). With these forces in mind, the equation of motion that kinematically models IVR is

\[
\frac{d^2P}{dt^2} + \frac{1}{\mu} \frac{dP}{dt} + E_k(P - P_e) = 0
\]

where d2P/dt2 is the inertial term required by Newton’s Law; \( \mu \) is a resistive parameter maintaining the deactivation effects typically characterized via \( \tau \) or \( \tau_1 \), producing a resistive “force,” \((1/\mu)dp/dt\); and \( E_k \) is a lumped elastic parameter characterizing the component responsible for the elastic restoring force, \( E_kP \). The fit to the IVR segment of any PPP contour, ranging from linear (overdamped) to curvilinear (underdamped) shapes is achieved by suitable variation of \( \mu \) and \( E_k \) in the solution to Eq. 3 (see APPENDIX) and determining the goodness of fit using standard methods (23).

Patient data. We analyzed data from 31 subjects in the existing Cardiovascular Biophysics Laboratory Database of high-fidelity micromanometric left ventricular (LV) pressure recordings (18). Criteria for including data in this study were normal sinus rhythm, absence of valvular abnormalities (including regurgitation or stenosis), and absence of wall motion abnormalities. Washington University Medical Center Human Studies Committee (Institutional Review Board) approved informed consent was obtained before catheterization. Subject demographics are summarized in Table 1. Data sets were acquired during elective cardiac catheterization at the request of a referring cardiologist for the evaluation of suspected coronary artery disease. Data acquisition methods have been described previously (3, 4, 18, 27, 34). Briefly, high-fidelity simultaneous LV pressure-volume and aortic root pressure measurements were obtained using a 6-F multiple transducer-tipped pigtail pressure-volume-conductance catheter (SPC-562 or SSD-1034; Millar Instruments, Houston, TX) amplified and calibrated via standard transducer control units (TC-510; Millar Instruments). Pressure signals were input simultaneously to clinical monitoring systems (Quinton Diagnostics, Bothell, WA or GE Healthcare, Milwaukee, WI) and a custom personal computer via a research interface (Sigma-5DF; CD Leycom, Zoetermeer, The Netherlands) at a sampling rate of 200 Hz. Conductance signals were also stored on the research interface but were not used in this study. No subjects had active ischemia during catheterization, and ejection fraction was computed from the suitably calibrated ventriculogram.

Hemodynamic data sets were converted for analysis via a custom Matlab script (Matlab 6.0; MathWorks, Natick, MA) and analyzed off-line via custom analysis software (LabVIEW 6; National Instru-

Fig. 1. Pressure phase plane (PPP) trajectories focusing on the isovolumic relaxation (IVR) period. The full PPP loop for 1 cardiac cycle, which is inscribed clockwise, is also shown (insets). A: normal relaxation generates a linear IVR segment after (moving clockwise) peak negative time derivative of pressure (dP/dtmax), allowing fit via monoexponential decay (solid line, \( \tau = 42 \) ms). B: example of a curvilinear IVR PPP segment conventionally fit after dP/dtmax using a logistic time constant (dotted line, \( \tau_1 = 34 \) ms). C: example of an intermediate PPP IVR trajectory that is not well fit by either monoexponential (solid line, \( \tau = 33 \) ms) or logistic formulation (dotted line, \( \tau_1 = 20 \) ms), indicating the need for an improved model of IVR to describe this process. See text for details.
LV ISOVOLUMIC PRESSURE DECLINE

Table 1. Summary of patient demographics

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EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure, measured in the pressure phase plane (PPP); HR, heart rate; DT, E-wave deceleration time, measured via echocardiography; C, curvilinear PPP; V, Valsalva analyzed; P, premature ventricular contraction analyzed.

ments, Austin, TX). For each subject, 10 continuous cardiac cycles of Millar catheter-recorded pressure data were considered to minimize respiratory or similar physiological variations. Data sets were smoothed digitally by using a five-point average to suppress small noise in the derivative (19), attenuating 50% of signal at 40 Hz and 90% above 60 Hz, followed by calculation of continuous dP/dt vs. time t from the smoothed data. For each beat, LV end-diastolic pressure (LVEDP) and peak negative dP/dt (dP/dt_min) were extracted from the PPP (3, 6, 34) or equivalent time-domain contours.

The estimation of model parameters (μ and Eκ) was achieved using a Levenberg-Marquardt fitting algorithm from the dP/dt data (23). The start point was defined by a drop in d2P(t)/dt2 of one-half after the inflection point in dP(t)/dt, which defined Pp. Data were fit until 5 ms before mitral valve opening pressure (defined by LVEDP) (3, 19). The algorithm provided parameters for μ, Eκ, and Pp, whereas Pp was calculated by minimizing the root mean squared error (RMSE) in the P(t) vs. t contour. For comparison with traditional methods of analysis, τ (Eq. 1) was estimated as conventionally done using data from 5 ms after dP/dt_min until 5 ms before mitral valve opening pressure as determined by LVEDP via a linear regression to the IVR portion of the PPP loop instead of a Levenberg-Marquardt algorithm with no difference in results. The logistic time constant (τL) was estimated via Eq. 2, using a Levenberg-Marquardt fitting algorithm on the same data as for τ (23), as described by Matsubara et al. (19). All parameterization was done using LabVIEW.

Model validation. Quality of fit was assessed by calculating RMSE for model-based, monoexponential, and logistic fits for all 310 beats from 5 ms after dP/dt_min until 5 ms before mitral valve opening for consistent comparison for both the P(t) vs. t and dP(t)/dt vs. t contours (19). We also calculated correlation coefficients (r values) for both the P(t) vs. t and dP(t)/dt vs. t contours for all fits versus actual data and tested the significance of the difference of these r values after their Z transformation [Z = ½[ln(1 + r) - ln(1 - r)] as described by Matsubara et al. (19).

Additional analysis was performed to test the kinematic model’s ability to predict/fit data obtained under physiological load variation. LV pressure data during the Valsalva maneuver in three subjects was analyzed (Table 1). Data during the strain and release phases were analyzed for parameters as described above. In four subjects, pressure data for a nonejecting premature ventricular contraction (PVC) (Table 1), producing load variation and eliminating ventricular-arterial interactions, was analyzed. Both the PVC beat and the normal beat immediately preceding it were analyzed, while simultaneous aortic root pressure verified LV pressures did not cause ejection.

Model predictions. When the differential equation governing the monoexponential (τ) relationship (Eq. 1) as its solution is compared with Eq. 3, it provides mechanistic insight into the relation between τ and μ and Eκ. Note that Eqs. 1 and 3 differ by the inertial term (d2P/dt2). When the recoil (E κ) and relaxation [(1/μ) dP/dt] terms numerically dominate the inertial term (d2P/dt2 = 0) (27), Eq. 3 reduces to Eq. 1, requiring that τ = 1/μEκ and being valid in the “overdamped regime” (1/μ2 < 4Eκ > 0). In descriptive terms, τ is the e-folding time, i.e., the time required for IVR pressure to drop by a factor of 1/e (0.367879). Thus we tested the prediction that, for linear IVR segments in the PPP, τ will be significantly correlated with 1/μEκ. The P2 term in the logistic equation is mathematically similar to the inertial term. Although no quantitative relationship can be made between τk and 1/μEκ, the logistic relationship was also compared statistically based on the presence of the P2 term (Eq. 2).

Neither the monoexponential nor the logistic parameter-predicted pressure declines are able to characterize data before dP/dt_min. In other words, in the PPP, these empirical choices for isovolumic pressure decay are unable to fit the U-shaped bowl of the PPP at dP/dt_min. We tested the prediction that the values predicted by either of the two empirical characterizations or our model of pressure decline would be different from the actual dP/dt_min for all beats. Predictions for dP/dt_min were made using the best fit-determined values for τ, τL, μ, and Eκ and were compared with actual dP/dt_min values. Comparisons were done via linear regression with zero intercept.

RESULTS

Model validation. The obtained parameter values for monoexponential, logistic, and kinematic model parameters are provided in Supplemental Tables (supplemental data for this article is available online at the American Journal of Physiology-Heart and Circulatory Physiology website). Large standard deviations relative to mean values in the parameters such as (μ) are indicative of beat-to-beat variation. Variation in model fit is comparable, whereas large deviation in τ and τL-predicted dP/dt_min values further indicates their inability to accurately fit the measured dP/dt_min.

Statistically, the model-predicted contour provided the best and most consistent fit to the IVR portion of the PPP contour (Table 2). Examining RMSE for linear versus curvilinear PPP subjects clearly indicated that neither τ nor τL was able to accurately fit the data. Only the model fit was able to consistently indicate low error in both P vs. t and dP/dt vs. t planes consistently for all subjects, indicating it may be a more physiologically accurate model of IVR. Model fit provided the best fit (r = 0.996) to the data (P < 0.001 by paired t-test of Z transform values) compared with the monoexponential (r = 0.989) and logistic (r = 0.980) fits (310 beats), and all were statistically different.
Table 2. Averaged root mean squared error

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<td>MonoeXponential (( \tau ))</td>
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<tr>
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<td>0.57±0.25</td>
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<td>RMSE P vs. ( t ), mmHg</td>
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<td>0.41±0.18</td>
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<td>RMSE dP/dt vs. ( t ), mmHg/s</td>
<td>65±50*</td>
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<td>Model (( \mu ) and ( E_k ))</td>
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<td>RMSE P vs. ( t ), mmHg</td>
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<td>RMSE dP/dt vs. ( t ), mmHg/s</td>
<td>29±12</td>
<td>30±12</td>
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Data are means ± SD of root mean squared error (RMSE) vs. actual data in the P vs. \( t \) or dP/dt vs. \( t \) plane. RMSE was consistent only in model fits, indicating poor fit of empirical models is likely high due to the large number of linear PPP beats.

Although the statistics favor our model over empirical (\( \tau, \tau_L \)) characterizations, the PPP is the ideal arena for visual characterization and determination of the goodness of fit for any IVR pressure decay model, because the PPP coordinate system easily differentiates between various empirical fits that are more difficult to differentiate from the P(\( t \)) contour alone. Figure 2 illustrates the benefit of the model for characterization of all three approaches by comparison with Fig. 1. For all cases, the model proposed (Eq. 3) adequately fits the pressure decay, whereas the monoeXponential (\( \tau \)) and logistic (\( \tau_L \)) models have limitations based on various amounts of linearity or curvilinearity of the individual IVR portions of the PPP contour.

In analyzing data in three subjects performing a Valsalva maneuver, significant changes in pressure were observed (Fig. 3A). During the Valsalva (Fig. 3), \( \mu \) had no dependence on LVEDP (average \( r = 0.19 \)), whereas \( \tau \) (average \( r = 0.61 \)) and \( \tau_L \) (average \( r = 0.67 \)) were significantly related to LVEDP; \( \tau \) and 1/\( \mu E_k \) remained tightly correlated. The four cases of nonejecting premature ventricular contraction show that the isovolumic relaxation portion of the inscribed PPP contour differs markedly from the relaxation portion of the preceding ejecting beat contour (34) (Fig. 4). In comparing the sequence of beats plotted, it is self-evident that one would have to choose between \( \tau \) (preceding and following beat; Fig. 4B) and \( \tau_L \) (premature contraction; Fig. 4C) to fit the relaxation portion of the respective contours.

Comparison of model predictions. Average measured and predicted dP/dt\(_{\text{min}}\) values are provided in detail in the Supplemental Tables. The model-predicted versus measured dP/dt\(_{\text{min}}\) values were not distinguishable [model dP/dt\(_{\text{min}}\), \( r = 0.99 \)]. Because the monoeXponential fit is linear and the actual PPP is always curvilinear near dP/dt\(_{\text{min}}\), the monoeXponential fit systematically overestimates the magnitude of dP/dt\(_{\text{min}}\) by nearly 10% [predicted dP/dt\(_{\text{min}}\) = 1.09(actual dP/dt\(_{\text{min}}\)), \( r = 0.98 \)]. Furthermore, the logistic fit was shown to underestimate the actual magnitude of dP/dt\(_{\text{min}}\) [predicted dP/dt\(_{\text{min}}\) = 0.88(actual dP/dt\(_{\text{min}}\)), \( r = 0.94 \)], as would be predicted due to its curvilinearity. Utilizing floating intercepts does not significantly alter regression relations (model: slope = 1.01, \( r = 0.99 \); monoeXponential: slope = 1.14, \( r = 0.99 \); logistic: slope = 0.86, \( r = 0.96 \)).

Figure 5A shows the linear regression between \( \tau \) and 1/\( \mu E_k \) for all 31 subjects and a separate regression for 23 subjects having linear IVR portions of the loop for which \( \tau \) provided an excellent fit (\( \tau = 1.15/\mu E_k - 11.85, r = 0.98 \)). As expected, data from subjects with curvilinear PPP trajectories drastically altered the relationship (\( \tau = 0.70/\mu E_k - 19.10, r = 0.40 \)). Figure 5B shows the linear regression relation between \( \tau_L \) and 1/\( \mu E_k \) for the 23 subjects with linear IVR segments in the PPP. Because of the dominating factors (Eq. 2 with \( \mu^2 \) for logistic vs. Eq. 3 with \( d^2P/dt^2 \) for model), the regression relation continues to deviate from a linear relationship.

DISCUSSION

Although \( \tau \), traditionally referred to as the time constant of IVR, has been applied as an index of diastolic function and also has been correlated with deactivation events (5, 22), there are limitations to its application. The logistic time constant was proposed as a solution to the problem of pressure decay shapes that are not well fit by a monoeXponential (19). The P(\( t \)) vs. \( t \) contours can generally be well approximated by either \( \tau \) or \( \tau_L \) but have limitations, since neither can adequately model the full range of PPP contours encountered. Also, although \( \mu \) and \( E_k \) differ for each of the isovolumic pressure decay portions of the three contours, our proposed single kinematic model (Eq. 3) is the only method that can continuously accommodate all of the observed data in the setting of this load perturbation and provides a unifying physics- and physiology-based mechanistic model for characterizing isovolumic pressure decay in ejecting...
Peak negative dP/dt is a required component of the kinematic model incorporating inertia, elasticity, and resistance (Eq. 3), and the model provides insight into why dP/dt_{min} always occurs as part of IVR and the factors that determine pressure decline both before and after dP/dt_{min}. The model (Eq. 3) is motivated by the existence of elastic elements that generate a restoring force during IVR (8). To the extent that these assumptions are justified, the force balance between the elastic and resistive forces predicts that dP/dt_{min} must exist. After the inertial effects of ejection and subsequent aortic valve closure, pressure decline accelerates until dP/dt_{min} is reached, when the restoring force (E_{k}P) is exactly balanced by resistive forces [(1/μ)(dP/dt)] and, as expected, the inertial term is small (d^2P/dt^2 ≈ 0). Beyond dP/dt_{min}, restoring forces persist and pressure continues to decline, while resistive effects continue to slow the rate of pressure decline.

The mechanistic insights afforded by this model are apparent in both its derivation and interpretation. Inertia, from tissue motion and torsion (25); inclusion of resistance, from the deactivation events traditionally thought to be characterized by τ and τ_L (5, 20, 22, 28); and elasticity, generated recoil force from the stiff, springlike intra- and extracellular elements such as titin, extracellular matrix, and visceral pericardium (8, 10, 13, 21, 24); these three terms constitute three physiologically and physically required force-generating mechanisms that contribute to pressure decline during IVR. Characterization of the elastic and resistive mechanisms of IVR are significant, given that resistance (or traditionally relaxation, via τ) has been offered as a major cause of “diastolic heart failure,” concluding that abnormal “relaxation” is significant based on τ being viewed as a “pure” measure of relaxation (35). However, prior findings indicate that chamber stiffness is also altered (12, 31) in diastolic heart failure. By testing a hypothesis motivated by physical mechanisms (17), we believe a more robust characterization of IVR mechanisms can be provided.

This approach elucidates the physiological mechanisms underlying the traditional empirical (τ, τ_L) indexes of IVR. Previous work also has shown high correlation between τ and alternate kinematic elastic parameters along with windkessel parameters, which have compliant properties (4). We note the good linear relationship (r^2 = 0.96) that exists between τ and 1/μE_k (Fig. 5A) in subjects with linear IVR PPP portions, indicating how τ is related to elasticity (E_k). Furthermore, the model solution indicates that the resistance term (or deactivation, driven by calcium cycling, cross-bridge deactivation, or other) is the dominant mechanism during IVR, manifesting as linear IVR segments in the PPP. The logistic approach via τ_L is the kinematic opposite, where elastic restoring forces exceed resistive forces (generating curved PPP segment). As Fig. 5A indicates, elastic restoring force dominates resistance and inertia, resulting in curvilinearity in the IVR segment of the PPP.

The logistic time constant also has some correlation with our viscoelastic parameter 1/μE_k (Fig. 5B), indicating that it is related to both resistance and elasticity. These comparisons and results (Figs. 2, 4, 5, and 6) indicate that the two historically independent and mathematically unrelated empirical parameters (τ or τ_L) comprise the elastic (E_k) dominance and resistive (relaxation, 1/μ) dominance parametric limits of our model. Increasing restoring force relative to resistive force alters the PPP contour to become more curvilinear, increasing dP/dt_{min} and shifting the pressure at which it occurs, whereas increasing

or nonejecting beats. Furthermore, no clear relationship exists between the original monoexponential characterization and the logistic constant, even though both are supposed to characterize the same physiological IVR event. This may be especially apparent for IVR PPP segments that fall “in between” the monoexponential and logistic fits (Fig. 1C) or where curvature alters (PVC; Fig. 4).

Because LV pressure follows an oscillatory course between systole and diastole, its second derivative (i.e., curvature, d^2P/dt^2) necessarily changes sign from negative to positive. This requires that d^2P/dt^2 go through zero and that dP/dt_{min} exist. However, the τ- and τ_L-based fits accommodate data only after dP/dt_{min} (19, 32) and therefore characterize only a limited part of the IVR period or give physical meaning for the minimum value (dP/dt_{min}), manifesting as the bottom of the U-shaped “bowl” in the PPP.
resistive force \( \mu \) (relative to restoring force) creates a more linear PPP segment and causes an opposite shift in \( dP/dt_{\min} \) (Fig. 6). What appeared to be two disparate, unrelated characterizations of isovolumic pressure decline are now fully encompassed and mechanistically (i.e., kinematically) explained by a single causality-based, kinematic modeling paradigm.

**Model considerations and limitations.** Our approach may be subjected to the criticism that two model parameters, \( \mu \) and \( E_k \), can always provide a better curve fit to data than a single parameter such as \( \tau \) or \( \tau_L \). Although two free parameters is in general always better than one free parameter when performing conventional curve fitting to data points (such as comparing linear vs. quadratic vs. cubic spline fitting methods), the necessity for two parameters was dictated by modeling the physics and physiology in elastic and resistive terms, in addition to the fact that two parameters, \( \tau \) and \( \tau_L \), are already used to characterize IVR. Because a linear equation of motion has a unique invertible solution (15), it provides a set of best-fit model parameters by which specific, testable predictions (\( dP/dV \), where \( V \) is volume) and elastance \( P/(V-V_0) \) change significantly and nonlinearly during the entire cardiac cycle (26) our concern is with the IVR segment only, where we assume the simplest linear pressure-displacement relationship. This is justified, because a key elastic component (titin) of the tissue is known to have a time-independent, linear force-length relationship (8) and function, as originally presented from requirements for diastolic suction (14), that is, as a linear, bidirectional spring. Alternatively, one may view this as a solution of the “inverse problem” (i.e., model parameter determination from pressure data) rather than simple curve fitting, because the model is based on a set of physical, physiological, and kinematic hypotheses that apply to all hearts (17).

**Equation 3** is a linear second-order differential equation, but in modeling the physiology it is always possible to consider alternative (and more complicated) formulations of elastic or resistive forces. The resistive force term could be modeled nonlinearly [for example, as \( P(dP/dt) \text{ or } (1/\mu_k)(dP/dt)^2 \) (16)], but such a choice provides a poor match with previous findings regarding \( \tau \) or \( \tau_L \) (5, 19, 32). Although ventricular operating stiffness \( \text{dP/dV} \), where \( V \) is volume) and elastance \( P/(V-V_0) \) change significantly and nonlinearly during the entire cardiac cycle (26) our concern is with the IVR segment only, where we assume the simplest linear pressure-displacement relationship. This is justified, because a key elastic component (titin) of the tissue is known to have a time-independent, linear force-length relationship (8) and function, as originally predicted from requirements for diastolic suction (14), that is, as a linear, bidirectional spring. Alternatively, one may view this formulation as a linear approximation to nonlinear phenomena confined to a limited physiological domain, i.e., IVR. This is analogous to using maximum elastance \( E_{\text{max}} \) to characterize (i.e., linearize) the end-systolic pressure-volume relationship.
of (tensorial) stresses, and inclusion of sarcomeric and cross-
bridge dynamics. These have been developed (9) but were not
intended for human in vivo data as input to compute model
parameters as output. A more complete analysis utilizing
pharmacological intervention in animal models would clearly
improve our detailed understanding of the mechanisms and
physiological meaning of our model’s parameters. However,
because of the excellent agreement between model-predicted
and experimentally measured pressure decay and peak negative
dP/dt, including in the setting of load variation and PVCs, our
lumped approach of including elastic restoring force opposed
by inertia and resistance as a paradigm for modeling IVR (22)
is reasonable.

Physiologically, our model only considers inertia, resistance
(e.g., deactivation or relaxation events), and elastic compo-
ments (e.g., stiffness) of the ventricle. Additional physiological
mechanisms have not been considered, such as the contribu-
tion of aortic blood momentum (29), which may produce PPP
trajectories that have a concave downward feature.

We provided robust examples but not quantitative rela-
tionships for load dependence via Valsalva and nonejecting PVC,
since they were the only available load-varying phenomena in
our data set. Although the relative load independence during
Valsalva is reassuring, a more complete, systematic evaluation
of load dependence is required before the load dependence or
load independence of the parameters can be determined. Spec-
sic interventions (inotropes, vasodilators, and IVC occlu-
sion, among others) are required to further characterize the
role of elastic and resistive forces, the load (in)dependence of
the proposed indexes, and their use in characterization of
the different load states (34).

Conclusions. Left ventricular isovolumic pressure decline is
incompletely characterized by the traditional relaxation
indexes  and . We have elucidated the physiology of isovolu-
metric pressure relaxation/decay (IVR) by considering the forces
(recoil, resistance, inertia) that determine it. The model ex-
plains the circumstance that determines peak negative dP/dt
and unifies the previously disjointed curve fits provided by  and
under a single, easily understood physical/physiological
prediction-based parametric limit mechanism. We found that
recoil forces opposed by relaxation-related resistive and iner-
tial effects determine isovolumic pressure decline.

**APPENDIX**

**Solutions to Eq. 3**

**Equation 3** is a linear differential equation characterizing
damped oscillatory motion. It has unique solutions depending
on the relative magnitudes of the relaxation ( ) and elastic ( ) parameters. The
three cases are 1) , 2) , and 3) .

A complete, detailed physical description of IVR requires
models containing detailed three-dimensional fiber orientation,
electrical activation, electromechanical coupling, development

Accordingly, we treat  and as constants when the chamber
is isovolumic (4), a choice that is further supported by a
validated model of early, rapid filling (14).

However, we recognize that it may be advantageous to
modify Eq. 3 by altering the resistance term. Specifically, if
one wished to explicitly include residual cross-bridge interac-
tions in  (22) (i.e., rate of cross-bridge uncoupling), a time-
varying coefficient for the dP/dt term could be considered.
Alternatively, relaxation could be modeled as force decay,
leaving  as a pure viscosity constant and including relaxation
as a separate time-varying term, acting as a “forcing function”
on the right side of the equation. Although the exact algebraic
form for such a forcing function is unknown [linear or ex-
ponential decline would be expected for cross bridges (3, 5)],
there also might be a problem with parameter uniqueness in
solving the inverse problem. However, such a formulation
might allow for better characterization of certain isometric
states (34).

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Fig. 6. Comparison of the effect of altering recoil force via elastic force (E) or resistive force via relaxation (µ) in the kinematic model-predicted IVR portion of the PPP contour. A: increasing stiffness from E = 1.042 l/s² (solid line) to 1.500 l/s² (shaded line) shifts the trajectory downward (increase in dP/dtmax) and to the left, generating smaller values for τ. B: increasing the rate of relaxation by lowering µ from 16 ms (solid line) to 10 ms (shaded line) shifts the trajectory upward and to the right, causing dP/dtmin to decrease in magnitude and occur at a higher P; the IVR trajectory becomes more linear, and τ increases. Varying model parameters allows fitting of all PPP shapes. See text for details.
\[
P(t) = \frac{1}{\beta} \left( P_a + \frac{P_a}{2\mu} \right) \sinh(\beta) + P_a \cosh(\beta) + P_\infty (A3)
\]

where

\[
\omega = \sqrt{4E_k - 1/\mu^2}/2 (A4)
\]

and

\[
\beta = \sqrt{1/\mu^2 - 4E_k}/2 (A5)
\]

where \(P_a\) and \(P_\infty\) are the pressure and dP/dt at \(t = 0\) and \(P_a\) is a constant.

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