Isovolumic pressure-to-early rapid filling decay rate relation: model-based derivation and validation via simultaneous catheterization echocardiography

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Chung, Charles S., David M. Ajo, and Sándor J. Kovács. Isovolumic pressure-to-early rapid filling decay rate relation: model-based derivation and validation via simultaneous catheterization echocardiography. J Appl Physiol 100: 528–534, 2006. First published October 13, 2005; doi:10.1152/japplphysiol.00617.2005.—Transmitral Doppler echocardiography is the preferred method of noninvasive diastolic function assessment. Correlations between catheterization-based measures of isovolumic relaxation (IVR) and transmitral, early rapid filling (Doppler E-wave)-derived parameters have been observed, but no model-based, causal explanation has been offered. IVR has also been characterized in terms of its duration as IVR time (IVRT) and by τ, the time-constant of IVR, by approximating the terminal left ventricular IVR pressure contour as \( P(t) = P_o + P_o e^{-\frac{t}{\tau}} \), where \( P(t) \) is the continuity of pressure, \( P_o \) and \( P_o \) are constants, \( t \) is time, and \( \tau \) is the time constant of IVR. To characterize the relation between IVR and early rapid filling more fully, simultaneous (micromanometric) left ventricular pressure and transmitral Doppler E-wave data from 25 subjects undergoing elective cardiac catheterization and having normal physiology were analyzed. The constant \( \tau \) was determined from the dp/dr vs. \( P \) (phase) plane and, simultaneous Doppler E-waves provided global indexes of chamber stiffness (c), chamber stiffness (k), and load (x). We hypothesize that temporal continuity of pressure decay at mitral valve opening and physiological constraints permit the algebraic derivation of linear relations relating 1/τ to both peak atrioventricular pressure gradient (k<sub>∞</sub>) and E-wave-derived viscosity/relaxation (c) but does not support a similar, causal (linear) relation between deceleration time and τ or IVRT. Both predicted linear relations were observed: \( k<sub>∞</sub>, \) to 1/τ (\( r = 0.71 \)) and viscosity/relaxation to 1/τ (\( r = 0.71 \)). Similarly, as anticipated, only a weak linear correlation between deceleration time and IVRT or τ was observed (\( r = 0.41 \)). The observed in vivo relationship provides insight into the isovolumic mechanism of relaxation and the changing-volume mechanism of early rapid filling via a link of the respective relaxation properties.

isovolumic relaxation; deceleration time; diastole; kinematic modeling

**METHODS**

Inclusion criteria. Twenty-five subjects were selected from an existing Cardiovascular Biophysics Laboratory database of simultaneous Doppler echocardiographic transmitral flow recordings and micromanometric catheter-derived intraventricular (e.g., LV) pressure obtained during diagnostic cardiac catheterization (23). All subjects were referred by their personal physician for diagnostic cardiac catheterization to evaluate the possibility of coronary artery disease. Before data acquisition and cardiac catheterization, all subjects provided signed, informed consent in accordance with Washington University Medical Center Human Studies Committee requirements. Criteria for selection from the database required that subjects have normal sinus rhythm, normal valvular function, clearly identifiable E- and A-waves, and no history of dilated or hypertrophic cardiomyopathy or significant coronary artery disease. Table 1 summarizes the demographic information for the group.

Simultaneous echocardiographic and hemodynamic data acquisition. Our methodology for simultaneous micromanometric LV pressure-transmitral flow acquisition has been previously described (2, 7, 23). Briefly, after appropriate sterile skin preparation and drape, local anesthesia (1% xylocaine) is administered and percutaneous right or left femoral arterial access is obtained using a valved sheath (6 Fr, Arrow International, Reading, PA). A 6-Fr micrometer-tipped pigtail pressure-volume (conductance) catheter (model SPC 562, Millar Instruments, Houston, TX) is directed into the mid-LV in a retrograde fashion across the aortic valve under fluoroscopic control. Before insertion, the manometer-tipped catheter is calibrated against hydrostatic “zero” pressure by submersion just below the surface of a 37°C normal saline bath. It is balanced using a transducer control unit (model TC-510, Millar Instruments). The ventricular pressures are fed to the catheterization laboratory amplifier (Quinton Diagnostics, Both-

Although catheterization, by quantitating LV hemodynamics, is the ideal, gold standard for characterizing function, Doppler echocardiography is the simplest and most common noninvasive method of characterizing diastolic function. Currently, there is no clear link between isovolumic relaxation (IVR) parameters and early rapid filling (E-wave) parameters derived from Doppler echocardiography. Particularly important is the need to link invasive, catheterization-based measurements such as τ obtained during IVR and noninvasive derived measures such as E-wave deceleration time (DT). We hypothesize that continuity of pressure \( P(t) \) and its rate of change \( (dp/dr) \) before and after mitral valve opening will permit derivation of quantitative (algebraic) relationships that explicitly connect IVR time (IVRT) to early rapid filling while elucidating the underlying physiology in terms of stiffness and relaxation.

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ell, WA), then output simultaneously into the auxiliary input port of the Doppler imaging system (Acuson, Mountain View CA) and into a digital converter connected to a customized personal computer. With the subject supine, apical four-chamber views are obtained by the sonographer with the sample volume gated at 1.5–2.5 mm and directed between the tips of the mitral valve leaflets orthogonal to the mitral value plane. To synchronize the hemodynamic and Doppler data, a fiducial marker in the form of a square wave signal is fed from the catheter transducer control unit to both the echocardiographic imager and the computer. Approximately 25–50 beats of continuous, simultaneous transmitral Doppler and LV pressure signals are recorded on VHS tape and the imager’s magneto-optical disk.

Determination of $\tau$. IVR is typically characterized noninvasively via the duration of IVR, i.e., the IVRT. Invasive characterization assumes the pressure decays exponentially and approximates the terminal LV IVR pressure contour as:

$$P(t) = P_e + P_o e^{-\lambda t}$$

where $P_e$ and $P_o$ are constants and $\lambda$ is the time constant of IVR. The reciprocal of $\lambda$, $1/\lambda$, is the rate of the exponential pressure decay during the terminal portion of IVR, i.e., just after peak negative $dP/dt$ until opening of the mitral valve; by convention, mitral valve opening during the terminal portion of IVR, i.e., just after peak negative $dP/dt$ is assumed to occur at (very nearly) the same pressure as LV end-diastolic pressure (2). Thus increased time for pressure to drop, suggestive of altered relaxation properties (prolonged $\tau$), is equivalently expressed as a decreased rate of pressure decay (smaller $1/\lambda$).

We have previously shown that phase-plane ($dP/dV$ vs. $P$) analysis of LV pressure facilitates calculation of $\tau$ (7, 14). The time derivative of pressure is linearly related to pressure according to:

$$\frac{dP}{dt} = -\frac{1}{\tau} P(t) + \frac{P_0}{\tau}$$

When written in the form $dP/dt = mP + b$, the slope $m$ is $-1/\tau$ and the $y$-intercept $b$ is $P_0/\tau$. This shows that $\tau$ is the negative reciprocal of the slope of the linear portion of the loop in the phase plane (Fig. 1A). Five LV pressure phase-plane loops were selected to determine an averaged value for $\tau$ for each subject.

Doppler analysis. Doppler data was aligned with simultaneous pressure data via a fiducial square wave and five E-waves, and simultaneous LV pressure data were used for determination of $\tau$. Standard echocardiographic indexes (IVRT, E-wave peak velocity, acceleration time, DT) were calculated manually for the five simultaneous Doppler images. According to convention, IVRT was measured from the termination of aortic outflow to the beginning of the E-wave. DT was calculated as the base of the triangle approximating the deceleration portion of the E-wave (8) (Fig. 1B).

In each subject, the selected Doppler E-waves were clipped in preparation for model-based image processing (MBIP) with Paint Shop Pro 7 (Jasc Software, Minnetonka, MN). E-wave contours were fit according to the previously validated method (2, 6, 7, 11, 18, 20, 21, 23) using a custom analysis program written in LabVIEW 6 (National Instruments, Austin, TX) (Fig. 1B). The parameterized diastolic filling formalism treats the kinematics of filling in analogy to the motion of a damped simple harmonic oscillator (10, 11, 18). For the kinematic “under-damped” ($\epsilon < 4\sqrt{mk}$) regime of simple harmonic oscillator motion accounting for early rapid filling, the solution for the contour of the E-wave is given by:

$$v(t) = \frac{k_o}{\epsilon^2} e^{-\epsilon t} \sin(\omega t)$$

where $x_0$ is the initial spring displacement in centimeters (i.e., initial load); $c$ and $k$ are the damping constant and spring constant, respectively; $m$ is set to 1, allowing the parameters to be computed per unit mass; $\alpha = c/2m$; and $\omega = \sqrt{4mk - c^2/2m}$. In contrast to characterizing of filling in terms of fluid streamlines (16, 19), the parameterized diastolic filling formalism represents a lumped-parameter, kinematic view of the physiology. Model parameters are obtained by solving this (kinematic) form of the “inverse problem” of diastole (18, 19, 20) by MBIP using clinical echocardiographic (E-wave) data as input (11, 18). In this formalism, chamber stiffness ($dP/dV$) is linearly related to the spring constant $k$ (21, 23), the peak atrioventricular

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**Table 1. Demographic information**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>58 ± 9</td>
<td>40–78</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83 ± 16</td>
<td>50–118</td>
</tr>
<tr>
<td>EF, %</td>
<td>69 ± 13</td>
<td>36–85</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>70 ± 10</td>
<td>56–91</td>
</tr>
</tbody>
</table>

EF, ejection fraction; HR, heart rate.
pressure gradient (mmHg/cm) can be expressed in terms of the peak elastic force $k_x$, (2), and the stored (potential) energy available for filling can be defined as $\frac{1}{2}k_x^2$ (18). The physical consequences of relaxation are accounted for by the parameter $c$. Delayed relaxation is known to be associated with impaired Ca$^{2+}$ reuptake and cross-bridge detachment (14) and continues for longer intervals than $3\tau$ (1, 31). Such impairment results in a kinetically resistive or viscoelastic effect that alters the E-wave contour and can be accounted for via the parameter $c$. By minimizing the nonlinear least squares error between the model-predicted E-wave contour and the actual E-wave contour, the MBIP algorithm calculates the parameters $c$, $k$, and $x_0$, and provides a measure of the goodness of fit for each parameter (11). The index $k_x$, was computed from these primary parameters.

Quantitative prediction and analysis. Although IVR and early rapid filling are consecutive and continuous, only weak correlation has been observed between indexes used to characterize the two phases (5). Early rapid ventricular filling (E-wave) is generated by the pressure difference between the LV and the left atrium, which passively opens the mitral valve. At a given inotropic state, the main factors that affect the time-dependent diastolic transvalvular (atrioventricular) pressure gradient are the load (mean end-diastolic volume or pressure), the rate of LV relaxation during IVR ($\tau$), left atrial pressure, LV compliance, and chamber stiffness (dV/dP) (1). A mathematical relationship has been proposed and validated that ascribes the duration of the deceleration portion of the E-wave (DT) as being solely due to chamber stiffness (24). Kinematic modeling of filling predicts that DT is determined by both chamber stiffness and chamber relaxation/viscosity (6, 11, 18, 20, 21, 23). Thus one may predict and test that a weaker correlation should exist between DT and IVR because DT is modulated by both relaxation and stiffness, whereas $\tau$ is modulated primarily by relaxation.

Due to continuity of pressure and its derivative at mitral valve opening, we predict relations linking IVR with $k_x$, via the Bernoulli equation and application of Eqs. 1 and 3. By applying the Bernoulli equation at mitral valve opening, we can invoke Eqs. 1 and 3 as surrogates for the pressure and acceleration of blood in the LV. The continuity of the time derivative of pressure and its gradient then yields:

$$k_xo = \frac{W}{\tau} + Bo_o$$

where $W$ is the slope and $Bo_o$ is an intercept of the observed regression relation. This relation relates the maximum pressure gradient to $\tau$. The derivation of Eq. 4 is provided in APPENDIX A.

There are known relations between the decay of the calcium concentration ([Ca$^{2+}$]) and $\tau$ (3, 25) and flow ($c$) (6). Our models of pressure (Eq. 1) and flow (Eq. 3) suggest that the energy in the ventricle can be written as $E = V(PT)$ during IVR and $E = \frac{1}{2}k_x(t)^2 + \frac{1}{2}mv(t)^2$ during flow. These relationships allow us to derive a relation between $c$ and $\tau$ via the average rate of decrease in energy:

$$c = \frac{1}{\tau} + B_p$$

where $Z$ is the slope and $B_p$ is the intercept of this relation. The derivation of Eq. 5 relating the decay rate of ventricular pressure ($\tau$) to the decay rate of early rapid filling ($c$) due to viscoelastic/relaxation effects is provided in APPENDIX B.

For each subject, the values of IVRT, DT, $\tau$, $c$, $k$, and $x_0$, were averaged for five beats. Using a linear least squares fit (Microsoft Excel, Seattle, WA), the correlation between IVR and early rapid filling was determined for each of the 25 subjects. IVRT and $\tau$ were compared with DT to assess their correlation. The product $k_xo$, and the parameter $c$ were compared with $1/\tau$ to validate the physiological hypothesis linking IVR and early filling. Dependence of relaxation on LV end-diastolic pressure was also assessed.

**RESULTS**

Table 2 summarizes the average parameter values for the study group; $\tau$ was well fit for all subjects ($r^2 > 0.96$ for all data).

No substantial correlation was observed between DT and $\tau$ ($r = 0.17; P = 0.39$), and weak, but statistically significant, correlation was observed between IVRT and DT ($r = 0.41; P < 0.005$) (Fig. 2). No significant relation was found between $\tau$ and LV end-diastolic pressure ($r = 0.30; P = 0.15$), confirming that relaxation was not significantly filling pressure dependent. We found that $k_{x0}$ correlated positively with $1/\tau$ ($r = 0.71; P < 0.0001$) (Fig. 3.) and that $c$ correlated positively with $1/\tau$ ($r = 0.71; P < 0.0001$) (Fig. 4).

**DISCUSSION**

Relation of IVRT to DT and $\tau$ to DT. It is commonly held that alterations in LV relaxation, indicated by IVRT or $\tau$, are determinants of E-wave size and/or shape (1, 5). In addition, physiological modeling (28) predicts that, when all other independent model parameters are held fixed, an increase in $\tau$ manifests as an increase in DT. In models that include IVRT and $\tau$ as input parameters and generate DT and other features as output, holding all other input parameters constant is easily achieved, allowing characterization of the IVRT-to-DT or $\tau$-to-DT relation (28).

However, the in vivo data from this study indicate that both IVRT and $\tau$ are at most weakly linearly coupled to DT (Fig. 2). IVRT measures the time between the closing of the aortic valve and the opening of the mitral valve and is determined by the rate of LV pressure decay from the dicrotic notch to mitral valve opening. The $\tau$ is the $e$-folding time for pressure to drop by a factor of $1/e$ in the left ventricle. The rate of this pressure decay is given by $-1/\tau$, a relaxation parameter, so its relation to DT can be modulated by other factors such as stiffness. As made mathematically explicit by the parameterized diastolic filling formalism, the DT of the E-wave is determined by viscoelastic chamber properties including stiffness (6, 11, 18, 20, 21, 23). Therefore, the observed weak correlation between IVRT and DT, and $\tau$ and DT likely includes factors, such as stiffness, that modulate DT, as opposed to relaxation, which primarily modulates $\tau$. The observed correlation indicates that characterizing the E-wave via MBIP provides additional information about the chamber not available by attributing DT solely to stiffness (24). Specifically, MBIP of E-waves pro-

Table 2. Parameter values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>IVRT, ms</td>
<td>71 ± 16</td>
<td>38–97</td>
</tr>
<tr>
<td>$\tau$, ms</td>
<td>53 ± 15</td>
<td>31–82</td>
</tr>
<tr>
<td>$r^2$ for $\tau$ regression</td>
<td>0.987 ± 0.001</td>
<td>0.962–0.997</td>
</tr>
<tr>
<td>DT, ms</td>
<td>194 ± 41</td>
<td>134–293</td>
</tr>
<tr>
<td>Model parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$c$, l/s</td>
<td>21.1 ± 7.5</td>
<td>9.3–37.5</td>
</tr>
<tr>
<td>$k$, l/s$^2$</td>
<td>200 ± 55</td>
<td>70–296</td>
</tr>
<tr>
<td>$x_0$, cm</td>
<td>10.9 ± 3.2</td>
<td>6.5–17.9</td>
</tr>
<tr>
<td>$k_{x0}$, cm/l/s$^2$</td>
<td>2078 ± 677</td>
<td>710–3679</td>
</tr>
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</table>

IVRT, isovolumetric relaxation time; $\tau$, isovolumetric relaxation time constant; DT, deceleration time; $c$, damping constant; $k$, spring constant; $x_0$, initial spring displacement; DF, diastolic function.
Relaxation and the peak atrioventricular pressure gradient: \( \tau \) and \( k_{x_0} \). Because the time-varying atrioventricular pressure gradient generates the E-wave, it follows that the peak force in the simple harmonic oscillator spring \( (k_{x_0}) \) is the kinematic analog that should correlate with the peak gradient during catheterization, a prediction that has been previously validated (2). By observing the continuity of \( dP/dr \) at mitral valve opening, we can derive a relationship between \( 1/\tau \) and \( k_{x_0} \) (see Appendix A). This relationship relates IVR and early rapid filling and indicates that relaxation affects the pressure gradient. Our observation that \( k_{x_0} \) and \( \tau \) are substantially and inversely correlated also agrees with prior model-based predictions (28) and is in concert with the assertion that stored energy for filling, \( 1/2k_{x_0}c_0^2 \), is related to \( \tau \), in analogy to how the energy of negative wave reflections is related to \( \tau \), as observed by Wang et al. (30). Furthermore, decreased or incomplete LV relaxation leads to an increase in minimum LV pressure, which can lead to elevation of the mean atrial pressure. Because the rate of pressure decay during late IVR is rapid, it closely approximates the actual rate of LV pressure decay immediately after mitral valve opening and the onset of early rapid filling. Consequently, in the setting of stable mean atrial pressures, a rapid rate of LV relaxation (large \( 1/\tau \)) generates a higher instantaneous atrioventricular gradient \( (k_{x_0}) \), whereas a slower rate of LV relaxation during IVR can result in a lower atrioventricular pressure gradient for early rapid filling. Our observations reinforce the view that the transmitral pressure gradient after mitral valve opening is proportional to the decay rate of LV pressure.

Relaxation and damping/viscosity: \( \tau \) and \( c \). A novel prediction of our study is that a relationship exists between relaxation during IVR, as measured via \( \tau \), and relaxation and chamber viscoelastic attributes during early rapid filling, as measured via \( c \). The common feature of both indexes \( (c \) and \( 1/\tau \)) is that they both serve as rate constants for relaxation processes that are known to be and predicted to be related to Ca\(^{2+}\) reuptake and cross-bridge detachment (3, 6). The damping constant \( c \) determines the exponential decay rate of the sinusoidal transmitral velocity (Eq. 3), whereas \( 1/\tau \) is the rate of exponential pressure decay during the terminal portion of IVR (Eq. 2).

The rate of energy loss is likely related to the remaining \([Ca^{2+}]\) and resistive force constraining the elastic recoil in diastole; thus we predict mathematically that \( c \) and \( 1/\tau \) should be linearly related (Appendix B). This assertion is supported by intracellular myocyte measurements that show that both \([Ca^{2+}]\) decay and the relaxation of the force can be well fit by a monoexponential function (22) and evidence that the rate of \([Ca^{2+}]\) decline is related to the decline in \( \tau \) (3). If the process of calcium sequestration during IVR is prolonged, it delays relaxation, lengthens IVR and \( \tau \), and prolongs the E-wave (15).

For relaxation to follow contraction, cross bridges must detach and calcium must be sequestered. This permits elastic recoil to become manifest and facilitates a damped-oscillator-based kinematic paradigm by which the physiology of filling can be modeled. Accordingly, to characterize diastolic suction kinematically and explain and predict E-wave contours, a simple harmonic oscillator utilizing a bidirectional spring has been proposed and validated (10, 11, 18–21, 23). Furthermore, the molecular and cellular source of such recoil, such as extracellular matrix elements (collagen, elastin) (27) or (intra-

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**Fig. 2.** Plot of IVRT vs. DT. Best-fit linear regression yields IVRT = 0.13·DT + 43m, \( r = 0.41, P < 0.005 \). Note that, although it is significant \((P < 0.01)\), it is not a strong correlation. See text for details.

**Fig. 3.** Plot of model-derived force (analog of atrioventricular pressure gradient), \( k_{x_0} \), vs. \( 1/\tau \). A linear relation is predictable via the continuity of pressure decay. Best-fit linear regression yields \( k_{x_0} = 85·(1/\tau) + 355, r = 0.71, P < 0.0001 \). See text for details.

**Fig. 4.** Plot of model-derived chamber viscosity/relaxation constant \( c \) vs. \( 1/\tau \). A physiologically based linear relation is predictable. Best-fit linear regression yields \( c = 0.94·(1/\tau) + 2.0, r = 0.71, P < 0.0001 \). See text for details.
Because the parameterized diastolic filling parameters are computed per unit mass, both \( c \) and \( 1/\tau \) have units of 1/s and, because the peak transmural pressure gradient must overcome relaxation/viscosity effects, a higher pressure gradient \( (k_{x0}) \) is expected in the presence of increased viscoelastic resistance \( (c) \). Thus the expected \( k_{x0} \)-to-\( c \) relation and the observed \( k_{x0} \)-to-1/\( \tau \) relation predict a correlation between \( c \) and 1/\( \tau \), which, to lowest order, is linear. This physiological link between IVR (measured invasively) and early filling (measured via Doppler echocardiography) provides insight into how invasive measures are related to noninvasive ones.

Limitations. We are cognizant that detailed modeling of flow, relaxation, pressure decay, and pressure gradients is necessarily nonlinear (16, 20, 32). Therefore, our hypotheses and our derivations presented in the appendixes should be properly viewed as the dominant, linear leading term, which allows for smaller nonlinear contributions. Specifically, the maximum pressure gradient and the deceleration of the E-wave may be affected by left atrial compliance and mitral valve area (29). There are reports that question the relation between the decay of calcium and the relaxation of muscle (13), but there is mounting evidence that calcium cycling is a primary factor in delayed relaxation (3, 15). Furthermore, the parameterized diastolic filling parameters are lumped global parameters. Thus, for example, \( c \) can be considered a lumped resistive, viscoelastic parameter that includes both tissue-derived and flow-derived damping effects. Although tissue-based resistance (by impaired \( \text{Ca}^{2+} \) reuptake) is likely the primary determinant of \( \tau \) (3), additional contributions to \( c \), such as the mitral valvular resistance to flow (29), or blood viscosity may contribute in addition to the calcium flux. Factors, including changes in mitral valve area, may affect our correlations slightly; however, all subjects had normal mitral valves. Heart rate is known to affect the duration of diastole significantly by modulation of the duration of diastasis (4, 17). Because heart rate affects IVRT and the duration of the E-wave only slightly (4, 33), our derivation of linear relations should be minimally heart rate dependent.

Both micromanometric pressure data and Doppler images are subject to noise. Noise in pressure data can be minimized via filtering of the signal, whereas physiological noise, such as that due to respiratory variation, in E-wave contours was minimized by averaging over five beats. IVRT was measured from transmural flow images obtained via pulsed wave rather than continuous wave Doppler in the mid-LV. Although this may introduce a slight systematic shift in the absolute values of IVRT measured, the same method was used in all subjects, and therefore it is unlikely to affect the results of correlative analysis. Ideally, both pressure recording and transmural flow velocity recording should be obtained at the same spatial location in the LV. This is not possible in general, but mid-LV catheter placement, verified under fluoroscopy, provided a reasonable and acceptable compromise.

In conclusion, using simultaneous Doppler echocardiography and micromanometric catheter-based LV pressure measurements, the relationship between IVR and early rapid filling was characterized. The peak atrioventricular pressure gradient, expressed as \( k_{x0} \), is causally and linearly related to the rate of pressure decay during IVR, 1/\( \tau \). A novel finding was that the decay rate of IVR, 1/\( \tau \), was directly correlated with the chamber’s viscous damping/relaxation rate, \( c \), relations that are modulated by [\( \text{Ca}^{2+} \)]. Furthermore, the decay of pressure during IVR, characterized via \( \tau \), affects the peak atrioventricular pressure gradient and is related to the decay of the E-wave contour. We observed a weak correlation between traditional IVR (IVRT, \( \tau \)) and early filling (DT) measures. Because IVR is modulated by the difference between relaxation rate and stored elastic strain serving as the restoring force (at a constant volume), whereas DT is modulated by changing volume, relaxation, and stiffness, the observed weak correlation could be anticipated. These observed in vivo relationships provide novel insight into the physiological isovolumic mechanism of relaxation and the changing-volume mechanism of early rapid filling via a link of the respective time-decay properties.

APPENDIX A

The \( k_{x0} \) vs. 1/\( \tau \) Relation

The relationship between rate of pressure decay during IVR, 1/\( \tau \), and the peak atrioventricular pressure gradient in early filling, \( k_{x0} \), is derivable via the pressure-flow relation at mitral valve opening. Before valve opening, the pressure follows the relations given by Eqs. 1 and 2. Immediately after mitral valve opening, the pressure-flow relation is usually written as (32):

\[
L \frac{dQ}{dt} + RQ^2 - DP = 0 \tag{A1}
\]

where \( L \) is inertia, \( R \) is resistance, \( Q \) is volumetric flow, and \( DP \) is the atrioventricular pressure gradient. In the presence of a normal valve, the resistance term in Eq. A1 is well approximated with linear flow (RQ instead of RQ\(^2 \)) (32). By a change of variables from flow (ml/s) to (constant effective mitral valve) area \( A \) (cm\(^2 \)) times flow velocity (Adv/dt), it is equivalent to the equation of motion of a harmonic oscillator in the parameterized diastolic filling formalism (32), yielding:

\[
m \frac{d^2x}{dt^2} + c \frac{dx}{dt} + kx = 0 \tag{A2}
\]

The initial conditions at the instant of mitral valve opening are no flow before valve opening, i.e., dx/dt = v(0) = 0, and stored elastic strain powers recoil, \( x = x_0 \), at \( t = 0 \). The solution for the oscillator displacement \( x(t) \) is given by:

\[
x(t) = \frac{x_0}{\omega} e^{\omega t} [\sin(\omega t) + \omega \cos(\omega t)] \tag{A3}
\]

The contour of the E-wave is the oscillator velocity \( \nu(t) \) and is given in Eq. 2. It is established from the pressure (dP/dt vs. P) phase plane (Fig. 1) that dP/dt is continuous at mitral valve opening. We obtain the two expressions at the end of IVR and beginning of early rapid filling. From the assumed form of ventricular pressure \( P(t) = P_\infty + P_0 e^{-t/\tau} \) (Eq. 1), we obtain:

\[
\frac{dP_\text{LV}}{dt} = -\frac{P_\infty}{\tau} e^{-\omega t/\tau} \tag{A4}
\]

where LV denotes the ventricle (left). From Eqs. A2 and A3 at \( t = 0 \) when dx/dt = 0, we obtain:

\[
m \frac{d^2x}{dt^2} = -kx_0 \tag{A5}
\]

The non-steady Bernoulli Equation relates pressure and flow between two points as:
ISOVOLUMIC-TO-E-WAVE DECAY RATE RELATION

\[ P_A + \frac{1}{2} \rho \cdot v_L^2 = P_{LV} + \frac{1}{2} \rho \cdot v_{LV}^2 + \rho \int_L^A \frac{dv}{dy} \frac{dy}{dt} \quad (A6) \]

where the subscript A denotes the atrium, \( v \) is transmitial flow velocity, and \( dy \) is the path of the streamline for assumed plug-flow from the atrium to the ventricle. At the instant of mitral valve opening, as the atrioventricular pressure gradient develops, the velocity of the blood is essentially zero in both the atrium and ventricle, eliminating the standard \( v^2 \) terms.

Our continuity condition from the phase-plane requires that \( dP/dt \) be constant, so we differentiate this function. The \( dP/dt \) term is negligible with respect to \( dP_L/dt \) at the time of mitral valve opening, and therefore we obtain the relation:

\[ 0 = \frac{dP_L}{dt} + \rho \int_A^{\infty} \frac{dV}{dv} \frac{dy}{dt} + \rho \int_A^{\infty} \frac{dV}{dv} \frac{dy}{dt} \quad (A7) \]

At the instant of mitral valve opening, the acceleration of the blood is constant (Eq. A5), which sets the \( dV/dt \) term to zero or, at most, a constant of integration (B). Since \( v(t) \) does not rely on the position because initial transmitial flow is plug-flow, the integral of \( dV/dt \) is a constant (N).

By substituting Eqs. A3 and A4, we obtain the linear relationship:

\[- \frac{P_v}{\tau} e^{-\tau v/\tau} = \frac{2N}{m} k_{x_0} + B \quad (A8) \]

Since \( t_{\text{iso}} \) is on the order of milliseconds and \( \tau \) is on the order of many tens of milliseconds, \( e^{-\tau v/\tau} \) is merely a small nonlinear correction. Thus Eq. A8 can be approximated as a linear relation between \( k_{x_0} \) and \( 1/\tau \) as:

\[ k_{x_0} = W \frac{1}{\tau} + B_p \quad (A9) \]

where \( W \) and \( B_p \) are constants. Physiologically, in the presence of stable mean atrial pressures, a more rapid rate of isovolumic pressure decay (1/\( \tau \)) causes a larger atrioventricular pressure gradient. Thus, based on the above approximations, at mitral valve opening, we obtain a linear relationship between IVR decay rate (1/\( \tau \)) and the subsequent maximum pressure gradient (\( k_{x_0} \)) with an offset (\( B_p \)) by requiring continuity of \( dP/dt \) at the instant of mitral valve opening.

APPENDIX B

The \( c \) vs. 1/\( \tau \) Relation

Because delayed relaxation opposes elastic recoil, we hypothesize that this phenomenon can be observed in IVR and early filling, e.g., that a physiological relation between the rate of relaxation during IVR, 1/\( \tau \), and the rate of decay of early rapid filling (E-wave), \( c \), exists. First, we assume that stored elastic strain, i.e., a spring (titin, extracellular matrix, etc.) is the source of stored elastic energy that overcomes viscoelastic effects (is lost) and drives flow in diastole. Second, we assume that [Ca\(^{2+}\)] plays a dominant role in relaxation. Relaxation is known to be related to decay of cytosolic [Ca\(^{2+}\)] (15), reuptake of calcium into the sarcoplasmic reticulum, and the resulting resistive force opposing relaxation. It has been shown to be well approximated by a monoeponential decay (similar to Eq. 1) (12, 22). It has also been shown that the time constants (\( \tau \)) for the relaxation of the [Ca\(^{2+}\)] and pressure during IVR are related (3). Furthermore, it has been shown that the [Ca\(^{2+}\)] has been related to both cell shortening or lengthening (e.g., diastole) (3), (22). Last, it has been shown that altered calcium uptake can cause changes in IVR, as manifested by changes in \( \tau \) (25) and E-wave-derived relaxation (6).

Thus, before transmitial flow begins, the ventricle has a certain amount of stored elastic strain energy in titin, extracellular membrane, and similar elastic elements. It is this stored strain energy that overcomes the actin-myosin cross bridges (whose uncoupling is modulated by calcium) and is the source of ultimate mechanical recoil, which will drive suction. Therefore, considering the change in energy via pressure or flow allows us to characterize the system. If we assume the energy during IVR is expressed as \( E_{\text{IVR}} = V^2/P(t) \), where \( V \) is a constant and \( P(t) \) is given by Eq. 1, the average rate of change of energy must be of the form:

\[ \frac{dE_{\text{IVR}}}{dt} = \frac{\overline{V}}{\tau} \frac{dP}{dt} = -\frac{V}{\tau} Pe^{-\tau v} = -\frac{\overline{v}}{\tau} \quad (A10) \]

where \( \overline{P} \) is an average pressure. Thus 1/\( \tau \) must be related to the rate or energy decrease, which is modulated by [Ca\(^{2+}\)] (3, 25). It is known that [Ca\(^{2+}\)] continues to diminish during early filling in a monoeponential fashion (13, 22), and unquiescented calcium (residual actin-myosin interaction or delayed cross-bridge detachment) is a major source of the resistive force (15, 22) that opposes pressure decay. Using a kinematic perspective (Eqs. 3 and A4), we calculate the energy during early rapid filling as:

\[ E_{\text{ERF}} = 1/2 k \cdot x(t)^2 + 1/2m \cdot v(t)^2 \quad (A11) \]

Assuming normalized mass (\( m = 1 \)) and the relations given in Eqs. 3 and A3, we differentiate Eq. A11 and obtain:

\[ \frac{dE_{\text{ERF}}}{dt} = -c \cdot \overline{v} \quad (A12) \]

where \( \overline{v}(t) \) is the average velocity over the E-wave. Therefore, the kinematically determined rate of energy decay of the E-wave is linearly related to the viscoelastic parameter \( c \), which reflects energy loss. Because a decreased rate of [Ca\(^{2+}\)] is known to cause delayed relaxation of muscle (15), we assume that rates of energy loss during IVR and early rapid filling are related as:

\[ \frac{dE_{\text{ERF}}}{dt} \approx A \frac{dE_{\text{IVR}}}{dt} + B \quad (A13) \]

where \( A \) and \( B \) are constants to be determined from the data. Thus, using Eqs. A10, A12, and A13 yields:

\[ c = Z \frac{1}{\tau} + B \quad (A14) \]

where \( Z \) is a slope and \( B \) is a constant. Thus relating the respective rates of energy loss before and after opening of the mitral valve permits determination of a linear relation between \( c \) and 1/\( \tau \).

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