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The Pressure Recovery Ratio: The Invasive Index of LV Relaxation During Filling. Model-based Prediction With *in-Vivo* Validation

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Abstract—**Using a simple harmonic oscillator model (PDF formalism), every early filling E-wave can be uniquely described by a set of parameters, (x_o, c, and k). Parameter c in the PDF formalism is a damping or relaxation parameter that measures the energy loss during the filling process.**

Based on Bernoulli's equation and kinematic modeling, we derived a causal correlation between the relaxation parameter c in the PDF formalism and a feature of the pressure contour during filling – the pressure recovery ratio defined by the left ventricular pressure difference between diastasis and minimum pressure, normalized to the pressure difference between a fiducial pressure and minimum pressure [$PRR=(P_{Diastasis}-P_{Min})/(P_{Fiducial}-P_{Min})$].

We analyzed multiple heart beats from one human subject to validate the correlation. Further validation among more patients is warranted. *PRR* is the invasive causal analogue of the noninvasive E-wave relaxation parameter c. *PRR* has the potential to be calculated using automated methodology in the catheterization lab in real time.

I. INTRODUCTION

Echocardiography is the preferred method by which diastolic function is noninvasively assessed.

The echocardiographically measured transmitral flow E- and A- wave velocity profiles have been extensively used to characterize diastolic function. In the clinical setting, E- and A- wave profiles are often approximated as triangles.

More insights can be gained by analyzing the E- and A- waves using a kinematic approach, called the Parametrized Diastolic Filling (PDF) formalism. In this formalism, developed by Kovács et al. in 1987, a simple harmonic oscillator paradigm was used to model the motion of the ventricle and the blood across the mitral valve during diastolic filling. The governing equation of motion is:

$$m\frac{d^2x}{dt^2}+c\frac{dx}{dt}+kx=0 \qquad (1)$$

The formalism solves the 'inverse problem' by providing (mathematically) unique parameters c, k, and x_o that determine each Doppler E-wave contour [1]. The initial displacement of the oscillator x_o (cm) is linearly related to the E-wave VTI (i.e. a measure of volumetric preload), chamber stiffness ($\Delta P/\Delta V$) is linearly related to the model's spring constant k (g/s^2) while the oscillator's damping constant or chamber viscoelasticity/relaxation index c (g/s) characterizes the resistance (relaxation/viscosity) and energy loss associated with filling. E-waves with long concave up deceleration portions have high c values, while E-waves that closely resemble symmetric sine waves have low c values. The contour of the clinical E-wave is predicted by the solution for the velocity of a damped oscillator, given by:

$$v(t)=-\frac{x_o k}{\omega}\exp(-\alpha t)\sin(\omega t) \qquad (2)$$

For underdamped motion, where $\alpha=c/2m$, $\omega=\sqrt{4mk-c^2}/2m$

$$v(t)=\frac{kx_o}{\beta}e^{-\alpha t}\sinh(\beta t) \qquad (3)$$

for overdamped motion ($c^2>4k$), and

$$v(t)=kx_o te^{-\alpha t} \qquad (4)$$

for critically damped motion ($c^2=4k$). In the equations above, ω is defined as $(4k-c^2)^{1/2}/2$, β as $(c^2-4k)^{1/2}/2$, and α as $c/2$.

PDF parameter values for x_o, c, and k are determined using the Levenberg-Marquardt algorithm fit to the E-wave maximum velocity envelope via a custom LabVIEW (National Instruments, Austin, TX) interface [2]. By setting m=1, we calculate the parameters per unit mass.

The process of obtaining the PDF parameters (model-based image processing (MBIP)) is briefly illustrated in Figure 1.

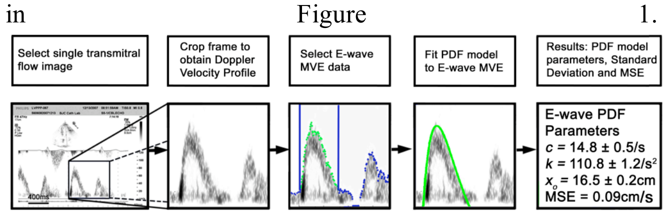

Fig. 1 Illustration of the Model Based Image Processing (MBIP) process. After the E-wave is cropped, the maximum velocity envelope is identified and is fit numerically by the solution to the PDF equation, yielding the three, best-fit PDF parameters (x_o, c, k) and a measure of goodness-of-fit.

Fluid mechanics dictates that the pressure gradient across the mitral valve (the atrioventricular pressure gradient) is responsible for transmitral blood flow according to Bernoulli's equation.

In this work, we sought to show that normalizing the pressure rise between minimum pressure and diastatic pressure to the pressure difference between the minimum pressure and a fiducial filling pressure provides a causal

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analogue of the PDF relaxation parameter *c*. Several fiducial pressures can be chosen to calculate *PRR*, in this study, mitral valve opening pressure is chosen as the fiducial pressure.

II. Model and Methods

A. Relationship between PRR and PDF parameter c

The relation between *PRR* and the PDF parameter *c* can be derived from Bernoulli's equation for non-steady flow:

$$LAP = LVP + \frac{1}{2}\rho v^2 + \rho \int_{LA}^{LV} \frac{\partial v(s,t)}{\partial s} ds \tag{5}$$

where we assume that blood flow velocity in the atrium is small compared with the blood flow velocity in the ventricle, and fluid viscous energy losses are negligible. In Equation 5, ρ is the density of blood, *v* is the transmitral velocity and is a function of both location along the streamline and time, LAP is the left atrial pressure, and LVP is the left ventricular pressure. The integral is the acceleration term, and can be can be approximated as *M(dv/dt)*, [Yellin *et al*. [3, 4]] where *M (constant)* is the mitral inertiance. Equation 5 becomes:

$$LAP = LVP + \frac{1}{2}\rho v^2 + M\frac{dv}{dt} \tag{6}$$

The pressure gradient *ΔP* is:

$$\Delta P = LAP - LVP = \frac{1}{2}\rho v^2 + M\frac{dv}{dt} \tag{7}$$

It is established that both LVP and LAP decrease and then recover during early filling [5], eventually both converging to the same diastatic pressure. Thus, while in final form we define *PRR* in terms of the LVP, one could easily justify defining a similar pressure recovery ratio in terms of LAP, or in terms of the pressure gradient ΔP. Indeed, the pressure gradient reaches maximum shortly after mitral valve opening, and reverses sign, thereby reaching a negative peak near the end of early filling. Thus, for ease of derivation, we define the peak pressure-gradient ratio (*PPGR*) as

$$PPGR = \left|\frac{\Delta P_{PeakPositiveGradient}}{\Delta P_{PeakNegativeGradient}}\right| \tag{8}$$

and we make the assumption that the peak pressure gradient ratio can serve as a reasonable surrogate for the *PRR* defined using LVP measurements because LAP is not routinely measured clinically. This assumption is reasonable because of the (time-lagged) relative similarity of the LAP contour relative to the LVP contour [5]. Although this simplification facilitates a clear derivation, it would not be useful clinically because LAP is not routinely measured during catheterization. Thus, for clinical purposes the *PRR* derived solely from LVP is ideal.

Before we can evaluate (8), we further simplify the Bernoulli expression. According to the PDF formalism, transmitral blood flow velocity is accurately predicted by simple harmonic oscillatory motion. The velocity of the E-wave (per unit mass) in the underdamped regime is given in Equation 2:

$$v(t) = -\frac{x_o k}{\omega}\exp(-ct/2)\sin(\omega t) \tag{9}$$

in the underdamped regime ($4k>c^2$). The derivative of velocity is acceleration:

$$\dot{v}(t) = -\frac{x_o k}{\omega}\left(\omega\exp(-ct/2)\cos(\omega t) - \frac{c}{2}\exp(-ct/2)\sin(\omega t)\right) \tag{10}$$

Thus Equations (6) and (9) can be used to expand (7).

Previous work [6] has shown that PDF displacement $x(t)=0$, implying LAP=LVP, occurs at a time DT from the onset of the E-wave. Furthermore, DT and AT are given by:

$$DT = \frac{\pi}{\omega} - \frac{\pi}{\omega} a\tan\left(\frac{\omega}{\alpha}\right) \tag{11}$$

$$AT = \frac{\pi}{\omega} a\tan\left(\frac{\omega}{\alpha}\right)$$

where AT is acceleration time. At time *t* =DT Eq. 5 becomes,

$$LAP - LVP = 0 = \frac{1}{2}\rho v^2\big|_{DT} + M\frac{dv}{dt}\big|_{DT} \tag{12}$$

Thus, we can solve for the mitral inertiance factor and ensure internal consistency of equations.

$$M = -\frac{(1/2)\rho v^2\big|_{DT}}{\dot{v}\big|_{DT}} = \frac{1}{2}\rho x_o\left(\frac{\sqrt{k}}{c}\right)e^{(-cDT/2)} \tag{13}$$

Hence the pressure gradient at any given time *t* is:

$$\Delta P(t) = LAP(t) - LVP(t) = \frac{1}{2}\rho v(t)^2 + M\frac{dv(t)}{dt}$$
$$= \frac{1}{2}\rho[v(t)^2 + x_0\frac{\sqrt{k}}{c}e^{(-cDT/2)}\dot{v}(t)] \tag{14}$$

Now we can use (13) for our expression (8) for the peak pressure gradient ratio:

$$PPGR = \left|\frac{\Delta P_{PeakPositiveGradient}}{\Delta P_{PeakNegativeGradient}}\right| \tag{8}$$

To simplify, we note that the peak positive pressure gradient occurs near a time *t*=DT+AT/2, and the peak negative pressure gradient occurs near *t*=DT/2 (where *t*=0 at mitral valve opening (MVO)), since the pressure gradient is similar to a damped sinusoid, as shown in Figure 2A. Numerical simulation (in Matlab) with 180 randomly picked physiologic *c* and *k* values was performed to confirm this simplification. The result showed that the peak pressure gradient recovery ratio measured at these two estimated time points is a very good approximation to the value of the peak pressure gradient recovery ratio at the actual peaks of the gradients, shown in Figure 2B. With this approximation, the peak pressure gradient recovery ratio becomes:

$$PPGR = \left|\frac{\Delta P_{DT+AT/2}}{\Delta P_{DT/2}}\right|$$
$$= \exp\left(-\frac{c(AT+DT)}{2}\right)\frac{\frac{1}{1+c/2\sqrt{k}} - \frac{\sqrt{2k}}{c}e^{\frac{cAT}{4}}\frac{(1+c/\sqrt{k})}{\sqrt{1+c/2\sqrt{k}}}}{\frac{1}{1-c/2\sqrt{k}} + \frac{\sqrt{2k}}{c}e^{-\frac{cDT}{4}}\frac{(1-c/\sqrt{k})}{\sqrt{1-c/2\sqrt{k}}}} \tag{15}$$

This expression can be simplified by substituting $y = \frac{c}{2\sqrt{k}}$ as:

$$PPGR = \exp\left(-\frac{c(AT+DT)}{2}\right)\frac{\frac{1}{1+y} - \frac{1}{y\sqrt{2}}e^{\frac{cAT}{4}}\frac{(1+2y)}{\sqrt{1+y}}}{\frac{1}{1-y} + \frac{1}{y\sqrt{2}}e^{-\frac{cDT}{4}}\frac{(1-2y)}{\sqrt{1-y}}} \tag{16}$$

For the clinical data analyzed, underdamped E-waves had y values between 0.3 and 1.0. Thus *PPGR* becomes a function of y, and a Matlab numerical simulation was performed whereby the relationship of *PPGR* to y was visually assessed. Figure 2C shows the strong linear relationship between *PPGR* and y. Thus, the *PPGR*, which is our numerical surrogate for the *PRR*, is predicted to be linearly related to $y = c / 2\sqrt{k}$. To assess the relationship between *PPGR* and c alone, we picked 180 random combinations of c and k and calculated the expression in (16). Figure 2D shows the strong linear relationship between *PPGR* and c for these random (k, c) combinations. Since in our study, the range of c values is much wider than the range of k values, and because the *PPGR* is a reasonable surrogate for the *PRR*, we expect a strong negative linear relationship between *PRR* and relaxation/viscoelastic parameter c similar to the one derived and observed in figure 2D.

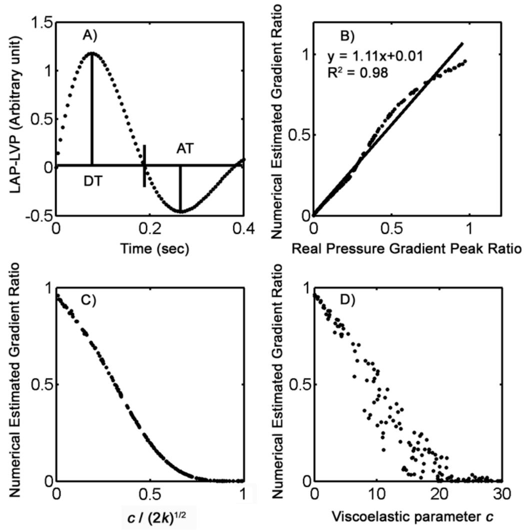

Figure 2. Results of numerical experiments demonstrating the linear relationship between theoretically calculated pressure gradient recovery ratio (*PPGR*, a surrogate of *PRR*) and *c,* derived from Bernoulli's equation. A) Numerical example of atrioventricular pressure gradient that generates the E-wave. B) Correlation between the simulated pressure gradient peak ratio and the numerically estimated pressure gradient peak ratio. C) Relationship between the numerically estimated peak pressure gradient ratio and y=c/2√k. D) Relationship between the numerically estimated peak pressure gradient ratio and the E-wave derived relaxation/viscoelastic parameter *c*.

B. *Definition of Pressure Recovery Ratio*

Because atrial pressures are rarely available in the clinical setting, the PPGR must be converted to a purely ventricular pressure based index in order to be clinically useful. The purely ventricular analogue of the peak gradient driving flow is the pressure difference between mitral valve opening and minimum pressure, while the analogue of the peak negative gradient opposing flow is the difference between ventricular minimum and diastasis pressure. The resulting expression defines the Pressure Recovery Ratio (*PRR*):

$$PRR = \frac{P_{Diastatic} - P_{Min}}{P_{MVO} - P_{Min}} \tag{17}$$

For subjects in normal sinus rhythm (NSR) we choose the left ventricular end-diastolic pressure (LVEDP) to be a surrogate for P_{MVO}. This choice is supported by studies showing that LVEDP is a reasonable approximation to P_{MVO} in subjects with NSR and no significant pathophysiology. Thus in the current study we calculated *PRR* for NSR subjects by the following equation:

$$PRR = \frac{P_{Diastatic} - P_{Min}}{LVEDP - P_{Min}} \tag{18}$$

C. *Experimental Validation of PRR*

<u>*Subjects*</u>

One subject with normal diastolic function and one subject with delayed relaxation filling pattern were selected from the Cardiovascular Biophysics Laboratory Database of simultaneous micromanometric catheter recorded left ventricular pressure (LVP) and echocardiographic data [6] to test the predicted correlation between *PRR* and *c*. This patient had normal valvular function, no active ischemia, no significant merging between echocardiographic E- and A-waves, no previous myocardial infarction, no peripheral vascular disease, and normal ejection fraction. Simultaneous invasive pressure and echocardiographic transmitral E- and A- waves were recorded and analyzed offline.

<u>*Hemodynamic Analysis*</u>

Hemodynamic values and parameters (P_{Min}, $P_{Diastasis}$, LVEDP) were determined from the LVP data for each beat. Diastatic pressure and LVEDP values were measured at the peaks of the *P*- and *R*- waves of the simultaneous ECG, respectively.

The *PRR* was calculated according to Equation 2 for all heart beats.

<u>*Doppler E-wave Analysis*</u>

A total of 10 heart beats from the normal subject and 17 beats from the delayed relaxation patient were analyzed. The PDF parameters mathematically determine the E-wave contour according to equation 2.

<u>*Comparison of Invasive and Noninvasive Relaxation Parameters*</u>

The linear correlations between c and *PRR* for the two patients were calculated using MS-Excel (Microsoft, Redmond, WA).

III. Results

Representative E- and A- wave patterns from the two patients are shown in Figure 3A, the PDF relaxation parameter c highly correlates with *PRR* $c = -16.9 * PRR + 26.5$ R^2=0.88 in subject t with normal diastolic function, $c = -32.2 * PRR + 30.0$, R^2=0.71 in subject whose E-wave fulfills the criteria for 'delayed relaxation', as shown in Figure 3B.

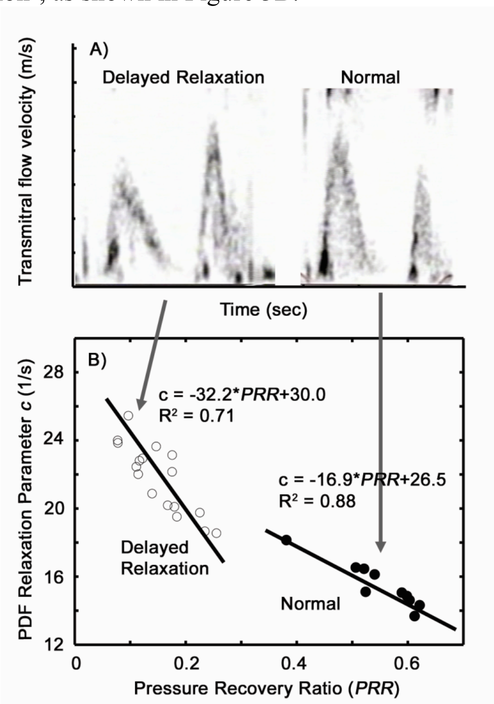

Fig. 3 A) Representative beats from a subject with normal diastolic function and a subject with delayed relaxation pattern on the E-wave. B) Correlations between PDF relaxation parameter *c* and pressure recovery ratio (PRR) in the normal and delayed relaxation patient.

IV. Discussion

The laws of fluid mechanics require that the shapes of the E-wave contour and the LV pressure contour are causally related. We derived and validated the *PRR*, an invasive hemodynamic index defined after mitral valve opening that is causally related to the noninvasive E-wave relaxation parameter *c*.

A. Description of c, and the Physical Meaning of PRR

Fluid mechanics dictates that the *PRR* is related to energy loss and the relative efficiency of filling. We have shown in previous work that the E-wave transmitral velocity contour may be modeled causally as the result of lumped tissue recoil and resistive forces [1]. The energy loss in the system is reflected by the magnitude of the damping parameter, *c*. A ventricle with no energy loss during filling would have a symmetric E-wave with $c = 0$. In contrast a ventricle with significant energy losses during filling would have an E-wave with lower peak amplitude and a prolonged deceleration portion, and an elevated value of *c*. Therefore, $c=0$ theoretically corresponds to a *PRR* value of 1.

B. Automated calculation of PRR

Currently, several catheterization systems with the accompanying software packages offer the real-time pressure and ECG display, recording, and measurement capability. In clinical practice, LVEDP, minimum, and maximum pressures can be automatically measured with minimum user input during the catheterization procedure. Using these systems, ECG P- and R- waves can be automatically identified and $P_{Diastasis}$ can be measured at ECG P-wave at sufficiently low heart rates where E- and A-wave separation is maintained. Hence, knowledge of LVEDP and minimum pressure, the *PRR* can be automatically calculated in real-time. The easy computation feature of *PRR* can aid clinicians in assessing filling efficiency and chamber relaxation, and can aid physiologists in the phenotypic characterization of experimental animal models in terms of chamber relaxation attributes.

V. Conclusion

Currently, no hemodynamic measure of the E-wave relaxation properties has been established. We demonstrate that the dimensionless pressure recovery ratio (*PRR*), defined by the ratio of pressure difference between minimum and diastatic LVP to the difference between MVO and minimum LVP, conveys early-rapid filling related chamber relaxation properties. Thus *PRR* serves as the hemodynamic analogue of the E-wave derived PDF formalism based relaxation parameter *c*.

Furthermore, the establishment and validation of the causal connection between *PRR* and the E-wave deceleration provides mechanistic insight into the chamber property-to-transmitral flow relation.

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