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Automated Method for Calculation of a Load-Independent Index of Isovolumic Pressure Decay from Left Ventricular Pressure Data

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***Abstract*— Diastolic heart failure (DHF) is present in over 50% of hospitalized heart failure patients, and diastolic dysfunction is known to play a critical pathophysiologic role. Measurement of left-ventricular pressure (LVP) via catheterization is the gold standard for diastolic function (DF) evaluation, but current methods fail to fully capitalize on the complete information content of the pressure contour. We have previously demonstrated that a kinematic model of isovolumic pressure decay (IVPD), which accounts for restoring force (stiffness) and resistance (viscoelasticity/relaxation), provides mechanistic insight into IVPD physiology and provides an accurate fit to the recorded contour. Recently we derived a novel load-independent index of isovolumic pressure decay (LIIIVPD) involving IVPD kinematic model stiffness and resistance parameters. In this work we detail methods and provide guidelines by which LIIIVPD computation may be achieved in real-time from the pressure contour recorded during cardiac catheterization.**

I. Introduction

DIASTOLIC heart failure, characterized by signs and symptoms of heart failure in the face of normal ejection fraction, has become a clinical problem of epidemic proportions [1]. Despite numerous advances in echocardiography-based noninvasive assessment of DF, measurement of left-ventricular pressure (LVP) using fluid-filled or high-fidelity (Millar) catheters, remains the gold standard by which DF is assessed. Assessment includes analysis of the pressure contour from aortic valve closure to mitral valve closure (the IVPD contour), and the LVP contour from mitral valve opening to mitral valve closure at end-diastole. The isovolumic portion beyond peak negative *dP/dt* is traditionally characterized via the time-constant of isovolumic pressure decay (τ), a monoexponential pressure decay rate constant. Peak negative *dP/dt* itself ($\dot{P}_{MIN}$) is also employed. Both τ and $\dot{P}_{MIN}$ may be easily determined from the pressure phase plane (PPP), defined by the $P(t)$ vs. $\dot{P}$ (t) plot (Fig 1). Prolonged τ and blunted $\dot{P}_{MIN}$ are interpreted clinically as evidence of relaxation abnormalities and diastolic dysfunction [2]. However, beat-to-beat load variation, from respiration or physiological intervention, may significantly impact the IVPD contour, thereby altering τ and $\dot{P}_{MIN}$. Thus prolonged τ and blunted $\dot{P}_{MIN}$ may be due to load alteration alone, and may not be reflective of intrinsic chamber properties determining IVPD.

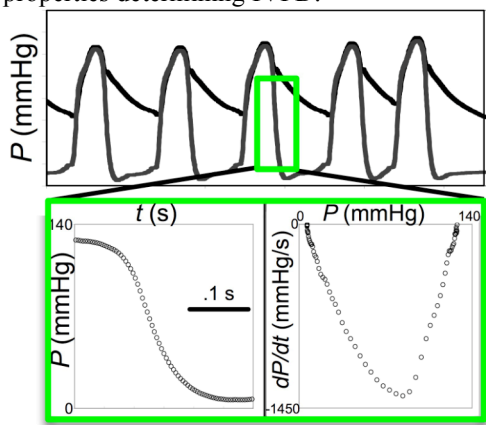

Fig. 1 *The physiology of IVPD may be visualized in the pressure vs time plane, where pressure decay is typically modeled monoexponentially, or in the pressure phase plane.*

The problem of predicting IVPD contour from first principles has been recently solved. [3] We employed a kinematic model that incorporates restoring force opposed by inertia and resistance as the determinant of IVPD. Model parameters are obtained by solution of the 'inverse problem' using IVPD as input and generating model parameters as output. We have also derived and validated a mathematical expression utilizing the kinematic model parameters that is load-independent [4]. The load-independent index of isovolumic pressure decay (LIIIVPD) is denoted by $M_{LIIIVPD}$. It is the slope of the linear regression relating peak restoring force driving pressure decay, vs. the peak opposing resistive force. Each point of the regression is extracted from an individual IVPD contour. Thus, by analyzing a set of load-varying IVPD contours, we determine a mathematically conserved parameter, and this parameter by definition, must be independent of load.

Initial results show that $M_{LIIIVPD}$ is indeed conserved in the face of load variation and is correlated with the ability of the chamber to quickly and effectively relax from the previous systolic contraction. Because of the obvious impact that $M_{LIIIVPD}$ may have clinically, it is important to develop methods by which $M_{LIIIVPD}$ may be automatically calculated in real-time during cardiac catheterization. While previous work has utilized semi-automated methods, in this work we present a fully automated approach for analysis of hemodynamic data that provides clinicians and investigators with the value of $M_{LIIIVPD}$ in real time.

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II. Model and Methods

A. Kinematic Model of Isovolumic Pressure Decay

In recent work, Chung et al unified existing models of IVPD with a general model that completely characterizes the wide range of physiologically observed IVPD trajectories in the PPP. Utilizing Laplace's law to transform displacements to pressures, Chung et al proposed the following differential equation to account for IVPD:

$$\ddot{P} + \tau_c \dot{P} + E_k (P - P_\infty) = 0 \qquad (1)$$

where τ_c is a relaxation parameter, E_k is a stiffness parameter, P_∞ is the pressure asymptote, and $\dot{P}$ and $\ddot{P}$ are the first and second time derivatives of pressure. This equation can be solved in the underdamped regime ($4E_k > \tau_c$) for pressure:

$$P(t) = e^{-t\cdot\frac{\tau_c}{2}}\left[\frac{2\dot{P}_o + P_o\tau_c}{2\omega}\sin(\omega t) + P_o\cos(\omega t)\right] + P_\infty \qquad (2)$$

where P_o is the initial pressure assuming zero pressure asymptote, $\dot{P}_o$ is the initial time derivative of pressure, and $\omega = \sqrt{E_k - \frac{(\tau_c)^2}{4}}$. The critically damped and overdamped solutions can be determined by evaluating equation (2) at $\omega = 0$ or $\omega = i\beta$ limits, respectively.

B. Derivation of Load Independent Index of IVPD

The LIIIVPD derivation has been discussed previously, and we review it briefly here. We begin by noting that (1), the governing differential equation of IVPD is obeyed independent of load. We consider this equation at the minimum of the phase-plane bowl, i.e. at minimum *dP/dt*. At this point Eq. 1 becomes:

$$\tau_c \dot{P}_{MIN} = -E_k\left(P(t_{\dot{P}_{MIN}}) - P_\infty\right) \qquad (3)$$

Eq. (3) demands that the plot of $\dot{P}$ vs. t yields an inverted damped sine wave, and at $t = 0$, $\dot{P} = \dot{P}_o$. Indeed, $\dot{P} = 0$ at the LVP maximum pressure, which is before the start of the isovolumic regime. However, *Eq.* (3) may be extrapolated to the time where $\dot{P} = 0$. This time point defines a maximum pressure assuming an isovolumic condition, and we therefore call this value P^*_{MAX}. The time at which P^*_{MAX} occurs, t_{P^*MAX}, can be found by differentiating *Eq.* (*3*) and solving for the time at which $\dot{P} = 0$. Evaluating *Eq.* (*3*) at t_{P^*MAX} yields P^*_{MAX}.

The short time between P^*_{MAX} and $\dot{P}_{MIN}$ allows the initial pressure contour decay to be approximated as linear, and therefore the pressure at $\dot{P}_{MIN}$ is approximated by P^*_{MAX}:

$$P(t_{\dot{P}_{MIN}}) = \alpha \cdot \left(P^*_{MAX}\right) + \beta \qquad (4)$$

where α and β are constants.

Combining Eq. 3 with Eq. 1 and rearranging we find:

$$E_k\left(P^*_{MAX} - P_\infty\right) = M_{LIIIVPD}\left(\tau_c \dot{P}_{MIN}\right) + B_{LIIIVPD} \qquad (5)$$

where $M_{LIIIVPD}$ and $B_{LIIIVPD}$ are constants and the magnitude of $\dot{P}_{MIN}$ is used. Thus, while traditional IVPD parameters may change with load, the slope $M_{LIIIVPD}$ is predicted to remain constant in the face of load variation, and thus is the predicted LIIIVPD.

C. Automated Method of $M_{LIIIVPD}$ Calculation

The algorithm for real-time $M_{LIIIVPD}$ calculation during catheterization is summarized in Figure 2, and described in more detail below. The entire process detailed in Figure 2 was implemented with custom Matlab scripts (Matlab 6.0; MathWorks, Natick, MA) and applied retrospectively to archived hemodynamic data.

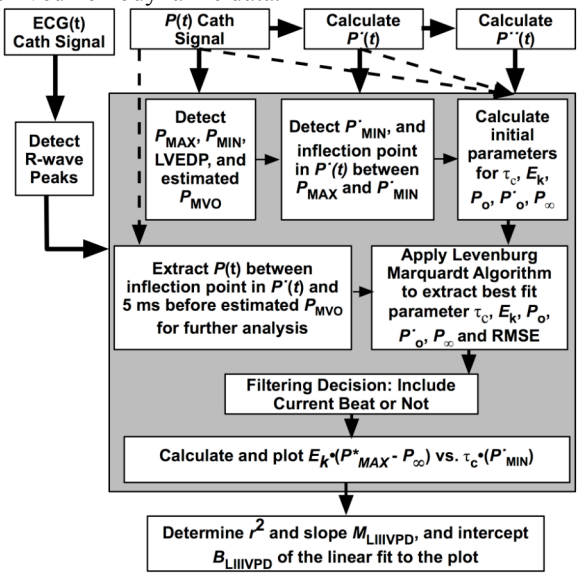

Fig. 2 The automated process by which $M_{LIIIVPD}$ is calculated is presented. The gray area contains steps that are repeated for each heart cycle, defined by successive *R*-wave peaks. See text for details.

Automated Hemodynamic Data Preprocessing

The typical hemodynamic signal recorded in the catheterization laboratory consists of simultaneous pressure and ECG signals. Because $M_{LIIIVPD}$ requires analysis of IVPD contours from individual beats, the first step in data analysis involves the determination of all ECG *R*-wave peaks. Our code achieves this task by searching for local maxima in the DC filtered ECG signal over successive windows defined by the dominant period (determined by the frequency of the peak in the Fourier power spectrum).

The sequence of *R*-wave peaks defines successive cardiac cycles. For each cycle, the IVPD contour is detected, kinematic parameters are extracted, and if proper filtering conditions are met, the LIIIVPD analysis is performed. The specific process for an individual beat is detailed in the gray box in Fig 2, and this process is repeated for the desired set of cardiac cycles.

Further analysis involves pressure derivatives, requiring that the first and second pressure derivatives with respect to time are calculated from the pressure signal. The kinematic model applies to IVPD, and therefore an appropriate IVPD contour must be extracted from each cardiac cycle. We begin by determining key $P(t)$ and $\dot{P}(t)$ landmarks. For any given beat, the maximum and minimum pressure, P_{MAX} and P_{MIN}, are determined as the local maximum and minimum

respectively in $P(t)$ between the defining consecutive R-wave peaks. The $\dot{P}_{MIN}$ value is similarly determined from $\dot{P}(t)$ values between defining consecutive R-wave peaks. The end-diastolic pressure LVEDP is taken to be the pressure at the R-wave peak at the end of the current beat, and the estimated mitral valve opening time t_{MVO} is defined as the time between P_{MAX} and P_{MIN} where the pressure is closest to LVEDP. Next the inflection point in $\dot{P}(t)$ is determined from the local minimum in $\ddot{P}(t)$ between the time of P_{MAX} and $\dot{P}_{MIN}$. Finally the IVPD contour is taken to be the pressure signal beginning at the determined inflection point in $\dot{P}(t)$ and ending 5 msec before t_{MVO}.

Automated Kinematic Model Parameter Extraction

Kinematic model parameters τ_c, E_k, P_o, and $\dot{P}_o$, are extracted for each individual beat by applying a Levenberg-Marquardt (LM) algorithm to the $\dot{P}(t)$ data defined by the extracted IVPD contour. The algorithm is described in detail elsewhere [5], but the salient features are described briefly below. The algorithm requires the $\dot{P}(t)$ data over the IVPD contour, as well as the initial guesses for the kinematic parameters.

Initial model parameters are determined by evaluating both *Eq*. (1) and the derivative of *Eq*. (1) at t_o, the time of inflection point in $\dot{P}$, and at $t_{P\cdot MIN}$, the time of $\dot{P}_{MIN}$.

At t_o, the derivative of *Eq*. (1) simplifies to:

$$\frac{\tau_c}{E_k} = -\frac{\left(\dot{P}_o\right)}{\ddot{P}\left(t_o\right)} \qquad (6)$$

Where $\dot{P}_o$ and $\ddot{P}(t_o)$ are the values of the first and second pressure derivatives at the start of the already determined IVPD contour.

Similarly, at $t_{P\cdot MIN}$, *Eq*. (1) simplifies to

$$\frac{\tau_c}{E_k}\dot{P}_{MIN} + P\left(t_{\dot{P}_{MIN}}\right) = P_\infty \qquad (7)$$

Applying Eq. (6) and (7) provides an expression for P_∞:

$$P_\infty = -\frac{\dot{P}_o}{\ddot{P}\left(t_o\right)}\dot{P}_{MIN} + P\left(t_{\dot{P}_{MIN}}\right) \qquad (8)$$

Applying *Eq*. (8) and *Eq*. (2) at t=0 yields:

$$P_o = P\left(t_o\right) + \frac{\dot{P}_o}{\ddot{P}\left(t_o\right)}\dot{P}_{MIN} - P\left(t_{\dot{P}_{MIN}}\right) \qquad (9)$$

Note that $P(t_o)$ is the pressure at the start of the automatically determined IVPD contour.

Eq. (1) evaluated at $t = t_o$ can be solved for E_k, in terms of P_o, $\dot{P}_o$, τ_c/E_k, and $\ddot{P}_o$. Applying *Eq*. (6) and *Eq*. (9), we may express E_k in terms of already measured parameters:

$$E_k = \frac{\left[\ddot{P}(t_o)\right]^2}{\left[\dot{P}_o\right]^2 - \ddot{P}(t_o)\left(P(t_o) + \frac{\dot{P}_o}{\ddot{P}(t_o)}\dot{P}_{MIN} - P\left(t_{\dot{P}_{MIN}}\right)\right)} \qquad (10)$$

Finally, from (6) and (10) we solve for τ_c:

$$\tau_c = -\frac{\ddot{P}\left(t_o\right)\dot{P}_o}{\left[\dot{P}_o\right]^2 - \ddot{P}(t_o)\left(P(t_o) + \frac{\dot{P}_o}{\ddot{P}\left(t_o\right)}\dot{P}_{MIN} - P\left(t_{\dot{P}_{MIN}}\right)\right)} \qquad (11)$$

Beginning with the initial parameter estimates determined from $\dot{P}_o$ and *Eq*. 9-11, the LM algorithm minimizes χ^2 by iterating through parameter space, where χ^2 is defined by $\sum(\Delta P)/\sigma$, with ΔP defined by the error between model predicted and measured $\dot{P}(t)$ along the IVPD contour, and σ defined as the error in measured $\dot{P}(t)$. Iteration ends when subsequent χ^2 values change by less than a predetermined threshold value. Upon completion, the root mean square error (RMSE) between model-predicted $\dot{P}(t)$ and measured $\dot{P}(t)$ is calculated using the LM-determined best fit kinematic parameters.

Automated Determination of $M_{LIIIVPD}$

If the RMSE is within an appropriate threshold, then P^*_{MAX} is determined as described above. Then the effective peak force driving pressure decay, $E_k\bullet(P^*_{MAX}-P_\infty)$, and the effective peak force resisting pressure decay, $\tau_c\bullet\dot{P}_{MIN}$, is calculated. Each analyzed cardiac cycle therefore provides individual $\{\tau_c\bullet\dot{P}_{MIN}, E_k\bullet(P^*_{MAX}-P_\infty)\}$ coordinates. The slope ($M_{LIIIVPD}$), intercept ($B_{LIIIVPD}$), and r^2 of the best fit line through the points defined by these coordinates is then updated with each analyzed IVPD contour and output in real time. The appropriate RMSE threshold for robust automated analysis is discussed in section *D* below.

D. Experimental Exploration of Tuning Parameters

In the current work we utilized data presented in a previous study. The data consists of twenty-five datasets from the Cardiovascular Biophysics Laboratory Database of simultaneous micromanometric catheter recorded left ventricular pressure (LVP) and echocardiographic data [4].

$M_{LIIIVPD}$, RMSE Cutoff, and Number of Cardiac Cycles

Because physiological data may contain cardiac cycles with unanticipated noise in the pressure signal, it is important for the automated methodology to detect inappropriately noisy IVPD contours so that they are not included in the $M_{LIIIVPD}$ analysis. In previous work we discarded beats with $\dot{P}(t)$ RMSE above the mean RMSE value. This however required a large number of beats, which may not be practical for real-time clinical application. Aggressive filtering, however, reduces the total number of beats analyzed, and may reduce the robustness of the linear fit determining $M_{LIIIVPD}$. To better characterize the appropriate RMSE cutoff, we perform an exploratory analysis in one of the 25 previously recorded datasets. We apply 7 different RMSE cutoff values. For each set of filtered beats, we calculate $M_{LIIIVPD}$ from n random beats, where n ranges from 2 to the total number of filtered beats.

III. RESULTS

The final $M_{LIIIVPD}$ values were strongly correlated with clinical parameters of interest, and the r^2 values were very close to unity, as described previously [4]. The initial estimates input to the LM algorithm proved to be close to the final parameters, and less than 100 iterations were required on average to converge to a best-fit solution.

Among the 340 beats analyzed in the subject of interest, $\dot{P}(t)$ RMSE varied between 10.6 mmHg/s and 66.3 mmHg/s, with the mean equal to 32.1 mmHg/s. RMSE cutoff values of 16.0, 21.4, 26.8, 32.1, 37.5, 42.9, and 48.3 were chosen.

For each chosen RMSE cutoff value, n beats, varying form 2 to the total number of remaining beats, were chosen randomly and analyzed according to the LIIIVPD methods described above. Fig 3 shows the M_{LIIIVPD} and r^2 values vs.

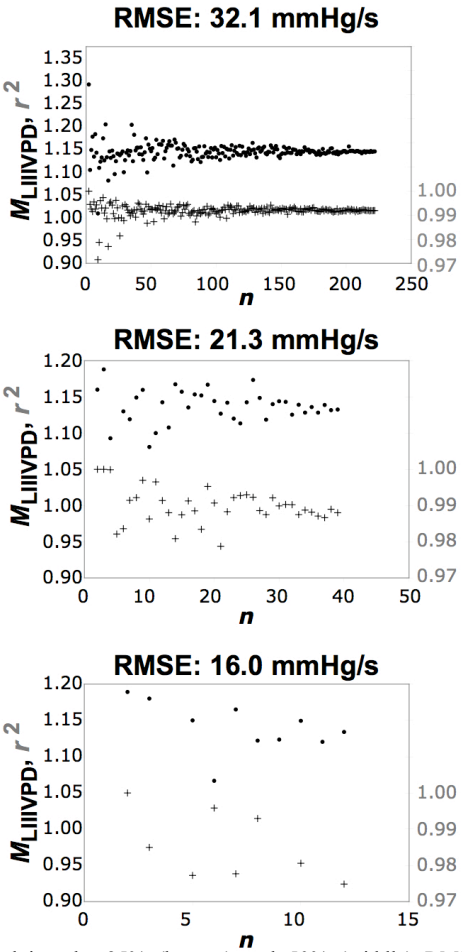

Fig3. Applying the 25% (bottom) and 50% (middle) RMSE cutoff between minimum RMSE and mean RMSE, as well as the mean RMSE cutoff (top) leaves 11, 38, and 222 beats respectively. For each case the M_{LIIIVPD} (dots) and r^2 of the line whose slope is M_{LIIIVPD} (crosses) defined by n random beats chosen from the remaining beats is shown.

number of beats analyzed n for the lowest 2 RMSE values, as well as the mean RMSE value. Remaining RMSE cutoff values provided similar M_{LIIIVPD} vs. n plots. Note that while the lower RMSE cutoff leaves far fewer total beats with which to generate M_{LIIIVPD}, it appears that fewer beats are needed to generate the appropriate M_{LIIIVPD} value when those beats are chosen from among the lower RMSE group.

IV. Discussion

Figure 3 clearly demonstrates an important trade-off that must be considered in the design of an automated process for determination of M_{LIIIVPD} in real time. The typical catheterization case has a limited number of cardiac cycles that can be measured, because arterial access time must be minimized, whereas the calculation of M_{LIIIVPD} requires numerous beats to be analyzed, especially if the data is noisy. When only data with RMSE below the mean RMSE is included, as shown in the top panel of Fig 3, M_{LIIIVPD} shows approximately 10% variation before the first 50 beats are analyzed. This variation decreases as more beats are analyzed, until a final value of 1.15 is reached. When a more stringent RMSE cutoff is applied (21.3 mmHg), the M_{LIIIVPD} variation remains until 30 beats are analyzed, but inclusion of all 40 beats results in a convergence on $M_{\mathrm{LIIIVPD}} = 1.13$. Finally, with the most stringent RMSE cutoff applied (16.0 mmHg), only 11 beats are available and there is significant variation in M_{LIIIVPD}, but the final value remains 1.13.

These results suggest that while low RMSE data is ideal, given typical data with a normal distribution of RMSE values, finding enough beats with low RMSE values may not be possible because the total number of recorded cardiac cycles may be limited. However, an interesting property emerges from the top panel of Fig 3, where the mean RMSE was chosen as the cutoff. It is evident that M_{LIIIVPD} shows a symmetry around the final M_{LIIIVPD} value. Indeed, a running average of M_{LIIIVPD} in the top panel stabilizes between 1.14 and 1.15 within 9 beats. For normally distributed data that would imply 18 measured cardiac cycles in total, which is reasonable in the catheterization laboratory. Further work regarding the symmetry of M_{LIIIVPD} vs. n and the appropriate averaging techniques to minimize the needed number of cardiac cycles to be analyzed is warranted.

V. Conclusion

M_{LIIIVPD} has been shown to correlate with conventional IVPD clinical parameters, and to be load-independent. To ensure clinical utility, we provide a methodologic algorithm by which M_{LIIIVPD} can be determined from pressure and ECG data alone in a real-time, automated fashion. Future work defining criteria for recording the number of beats necessary for robust M_{LIIIVPD} determination is planned.

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VI. References

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