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Solution of the 'Inverse Problem of Diastole' via Kinematic Modeling Allows Determination of Ventricular Properties and Provides Mechanistic Insights Into Diastolic Heart Failure

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Abstract- **Because 50% of heart failure hospital admissions have diastolic heart failure (DHF) quantifying diastolic function (DF) has reached new prominence. Conventionally DF indices have been computed from shape-based features (height, duration, area) of Doppler waveforms such as the E-wave, (transmitral flow velocity), or E'-wave (mitral annular velocity) without regard to causal mechanisms. Solution of the 'inverse problem' has been achieved via the parametrized diastolic filling (PDF) formalism, a linear, kinematic model which treats the elastic, recoil-driven suction-pump attribute of the left ventricle as a damped simple harmonic oscillator (SHO). PDF uses the E-wave as input and generates stiffness (k), relaxation/ damping (c) and load (x_o) as output. Scientific successes include the prediction that filling must be driven by a linear, bi-directional spring, later validated as a property of the giant cardiac protein titin, which generates a recoiling force at the cellular level in early diastole. Selected recent kinematic modeling achievements include: explanation why E-wave deceleration time must be determined jointly by stiffness (k) and relaxation (c), rather than by stiffness alone; LV equilibrium volume is the volume at diastasis; solution of the load-independent index of diastolic function (LIIDF) problem; solution of the isovolumic pressure decay (IVPD) problem. Clinical application reveals that contrary to dogma, chamber relaxation/viscoelasticity (PDF parameter c) rather than chamber stiffness (PDF parameter k) most often differentiates between controls vs. diastolic dysfunction subjects, thereby providing mechanistic insights into DHF.**

I. Introduction

There is an 'epidemic' of heart failure at the present time [1,2] and about 50% of patients admitted with heart failure (HF) have a normal ejection fraction (HFNEF) or diastolic heart failure (DHF) [3]. There is no difference in prognosis between DHF vs. HF with low ejection fraction patients [3]. The clinical data indicates that DHF patients are a heterogeneous group, are most often elderly, female and have hypertension. Because their filling function is abnormal the ability to quantify chamber stiffness and relaxation as determinants of diastolic dysfunction (DD) has gained prominence.

Echocardiography is the preferred noninvasive imaging modality for DF assessment. DF indexes are obtained from shape-based features (height, width, area) of the transmitral flow velocity contour (E-wave) obtained via Doppler echocardiography. These empiric indexes have been correlated with clinical features rather than being derived from causal mechanisms that determine how the heart works when it fills. Because the LV decreases its pressure while it increases its volume at the onset of filling (dP/dV<0) it is a mechanical suction pump. To explain the range of observed E-wave contours, quantify DF and provide insight into the mechanisms, LV filling has been modeled via the parametrized diastolic filling (PDF) formalism kinematically [4] as a damped simple harmonic oscillator, which incorporates the fundamental physiologic principle of mechanical suction initiated filling. The potential energy that powers the recoil is stored elastic strain, the release of which is modulated by spatiotemporal chamber wall relaxation. Because the energy source for diastolic recoil (wall-motion) resides in tissue, blood is passive and behaves in accordance with the laws of fluid mechanics and the atrioventricular pressure gradients generated by wall-motion. Since both blood and tissue are incompressible, their motions are necessarily closely coupled, particularly since the four-chambered heart is, to within about 95%, a constant-volume pump [5].

II. Methods

A. The PDF Formalism for DF Assessment

The equation of motion for a SHO is

$$m\ddot{x} + c\dot{x} + kx = 0 \qquad (1)$$

where setting m=1 expresses the damping constant c and spring constant k per unit mass, with: initial SHO spring displacement $x(0)=x_o$, and, $v(0)=0$, i.e. no transmitral flow prior to valve opening. The velocity of the oscillator is the analog of the Doppler E-wave. For underdamped kinematics ($c^2-4mk<0$) the E-wave is:

$$E(t) = -\frac{kx_o}{m\omega} e^{\frac{-ct}{2}} (\sin(\omega t)) \qquad (2)$$

and

$$\omega = \sqrt{(4mk - c^2)} / 2m \qquad (3)$$

Because Eq (1) is linear we can solve the 'inverse problem' by using the E-wave contour as input and determine the unique PDF model parameters x_o, c and k as output using the Levenberg-Marquardt algorithm to minimize error as shown below.

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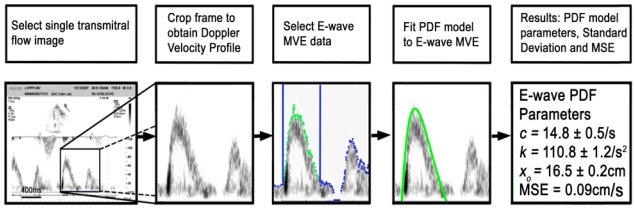

Fig. 1 *Model Based Image Processing (MBIP) requires cropping E-wave from echo machine image, maximum velocity envelope identification and its numerical fit by the solution to equation (1), yielding the three, best-fit PDF parameters (x_o, c, k) and a measure of goodness-of-fit.*

This paradigm [4] predicts that to explain the observed range of E-wave contour shapes the kinematics of filling requires a bi-directional, linear spring. This prediction has been independently validated at the cellular level, by the observation that the giant intracellular protein titin, acts as a bi-rectional spring by providing a restoring force (i.e. a push) in early diastole [6].

B. E-wave deceleration time determinants

Average left ventricular (LV) chamber stiffness $\Delta P/\Delta V$ has been predicted from E-wave deceleration time (DT) as: $\Delta P/\Delta V = N(\{\pi\}/DT)^2$ (where N is constant), implying that if DTs of two chambers are indistinguishable, their stiffness is indistinguishable also. It is known that LVs with indistinguishable DTs can have markedly different $\Delta P/\Delta V$ values determined by simultaneous echocardiography-catheterization. To elucidate this mechanism we used the PDF formalism with stiffness (k) and relaxation/ viscoelasticity (c) parameters [7]. Because the predicted linear relation between k and $\Delta P/\Delta V$ has been validated, we reexpress the $\Delta P/\Delta V = N(\{\pi\}/DT)^2$ relation as follows: $DT_k \approx \pi/(2\sqrt{k})$ Using the kinematic model, we derive the general DT-chamber stiffness/viscoelasticity relation as: $DT_{k,c} = \pi/(2\sqrt{k}) + c/(2k)$ (where c and k are determined directly from the E-wave as shown in Fig.1). This reduces to DT_k when $c << k$. Validation utilized 400 E-waves via five-beat averaged k and c values obtained from 80 subjects undergoing simultaneous echocardiography-catheterization.

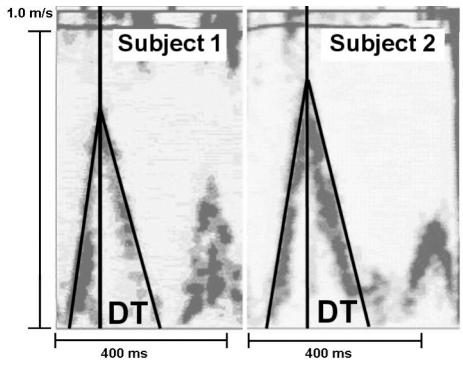

Fig. 2. *E-waves of 2 subjects with indistinguishable deceleration times (DTs) but significantly different values for E-wave-derived stiffness (k) and catheterization-derived averaged chamber stiffness $\Delta P/\Delta V$. See ref 7 for details.*

Clinical E-wave DTs were compared with model-predicted DT_k and $DT_{k,c}$. Clinical DT was better predicted by stiffness and relaxation/viscoelasticity (r^2 = 0.84, DT vs. $DT_{k,c}$) jointly rather than by stiffness alone (r^2 = 0.60, DT vs. DT_k). Thus LVs can have indistinguishable DTs but significantly different average $\Delta P/\Delta V$ if chamber relaxation/ viscoelasticity differs. Therefore, E-wave DT is a function of both chamber stiffness (k) and chamber relaxation/ viscoelasticity (c).

C. Diastasis Defines LV Equilibrium Volume and the DPVR

Equilibrium volume has been defined as the volume of the LV when the transmural pressure gradient = 0. Others have defined equilibrium volume as the LV volume at which the diastolic P-V relation crosses the P=0 axis. General agreement exists that ventricular suction at mitral valve opening requires that end systolic volume be less than the 'equilibrium volume'. These definitions have been further complicated by the definition used by some that ventricular suction exists only when LV pressure becomes sub atmospheric. The above exemplifies why prior conceptual and (closed chest vs. open chest) experimental results regarding diastolic suction and the equilibrium volume of the LV have lead to experimental and conceptual inconsistencies. To resolve the inconsistencies generated by different ('absolute' vs. 'relative') definitions and different (closed-chest vs. open chest) preparations, we define $dP/dV<0$ as the necessary and sufficient condition for definition of diastolic suction. This definition (ventricular recoil) follows not only from physiologic constraints but from kinematic considerations like the release of stored elastic strain in the chamber wall so it expands faster than it can fill. This definition guarantees that suction manifests only when ESV<Veq and naturally leads to the kinematics based definition that after the recoil process has terminated, the chamber settles down to the LV volume at diastasis, which must be the functional, in-vivo equilibrium volume.[8]

The end-diastolic pressure-volume relationship (EDPVR) is used to determine the passive left ventricular (LV) stiffness, although the diastatic P-V relationship (DPVR) has also been measured. Based on the physiological difference between diastasis (the LV and atrium are relaxed and static) and end-diastole (LV volume increased by atrial systole and the atrium is contracted), we hypothesized that, although both DPVR and EDPVR include LV chamber stiffness information, they are two different, distinguishable P-V relations. Cardiac catheterization determined LV pressures and volumes in 31 subjects were analyzed. Physiological, beat-to-beat variation of the diastatic and end-diastolic P-V points were fit by linear and exponential functions to generate the DPVR and EDPVR. The extrapolated exponential DPVR underestimated LVEDP in 82% of the heart beats ($P < 0.001$). The extrapolated EDPVR overestimated pressure at diastasis in 84% of the heart beats ($P < 0.001$). If each

subject's diastatic and end-diastolic P-V data were combined to form a continuous data set to be fit by one exponential relation, the goodness of fit was always worse than if the diastatic and end-diastolic data were grouped separately and fit by two distinct exponential relations. Diastatic chamber stiffness was less than EDPVR stiffness (defined by the slope of P-V relation) for all 31 subjects (0.16 ± 0.11 vs. 0.24 ± 0.15 mmHg/ml, P < 0.001). We conclude that the D-PVR and EDPVR are distinguishable. Because it is not coupled to a contracted atrium, the DPVR conveys passive LV stiffness better than the EDPVR. [9].

D. Load Independent index of Diastolic Function

Maximum elastance E_{max} is an experimentally validated, load-independent index of systolic function obtained from the time-varying elastance paradigm that experimentally decoupled (extrinsic) load from (intrinsic) contractility. Although Doppler echocardiography is the preferred method for diastolic function (DF) assessment, all echo-derived DF indexes are load dependent, {see Fig. 3} and no invasive or noninvasive load-independent index of filling (LIIF) exists. We recently derived and experimentally validated a LIIDF. We used a kinematic filling paradigm (the PDF formalism) to predict and derive the dimensionless index of kinematic diastolic efficiency *M*, defined by the slope of the peak driving force [maximum driving force (kx_o) ∝ peak atrioventricular (AV) gradient] to maximum viscoelastic resistive force [peak resistive force ∝ (cE_{peak})] relation [10]. {See Fig. 4} To validate load independence, we analyzed E-waves recorded while load was varied via tilt table (head up, horizontal, and head down) in 16 healthy volunteers. For the group, linear regression of E-wave derived kx_o vs. cE_{peak} yielded $kx_o = M(cE_{peak})+B$, r^2=0.98; where M=1.27±0.09 and B =5.69±1.70. Effects of diastolic dysfunction (DD) on *M* were assessed by analysis of preexisting simultaneous cath-echo data in six DD vs. five control subjects. Average *M* for the DD group (M=0.98+0.07) was significantly lower than controls (M=1.17+ 0.05, P< 0.001). We conclude that *M* is a LIIDF because it uncouples intrinsic DF (i.e., the pressure-flow relation) from extrinsic load (∝ left ventricular end-diastolic pressure). Larger *M* values imply better DF in that increasing AV pressure gradient results in relatively smaller increases in peak resistive losses (cE_{peak}). Conversely, lower *M* implies that increasing AV gradient leads to larger increases in resistive losses. Further prospective validation characterizing *M* in well-defined pathological states is in progress.

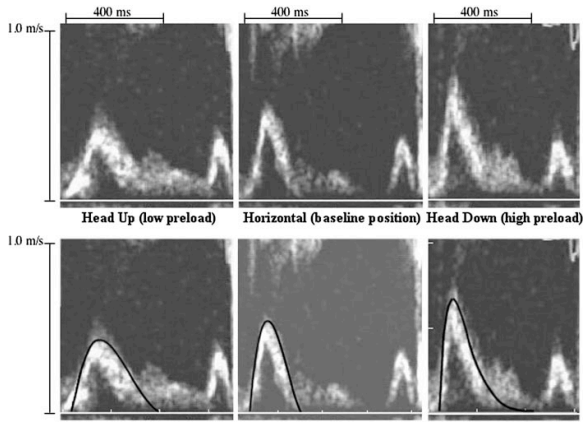

Fig. 3 *Pulsed wave transmitral flow-velocity images from a selected volunteer subject at 3 different preload (tilt table positions) states. Single diastolic interval at each tilt table position is shown. Parameterized diastolic filling (PDF) model-predicted fit to each E-wave is shown in bottom panels. See ref 10 for details.*

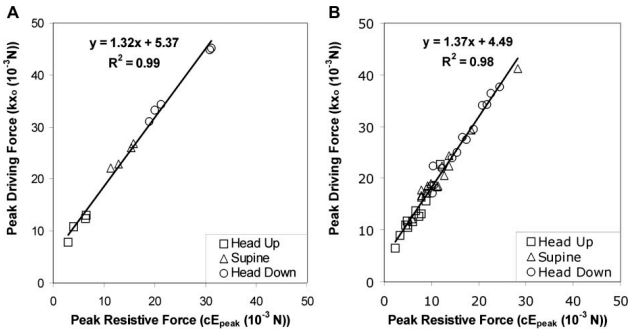

Fig. 4 *A: maximum driving force [kx_o, peak atrioventricular (AV) gradient] vs. peak resistive force (cE_{peak}) for 1 subject at 3 different preload states. Note slope of best linear fit is independent of tilt table position. B: kx_o vs. cE_{peak} for all (n =16) subjects at different preload states. Reported values represent 5-beat average for kx_o and cE_{peak} for each subject at each preload state. See ref 10 for details.*

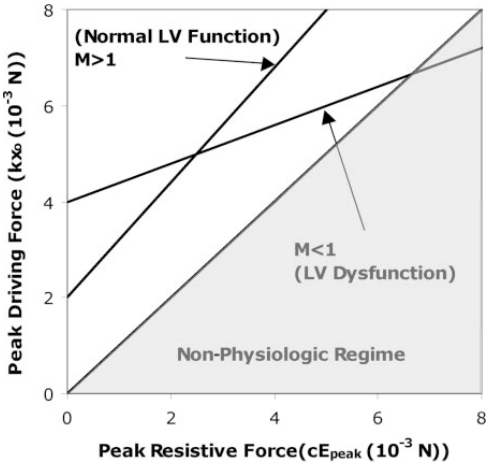

Fig. 5 *Equation governing filling constrains the physiology to the upper half of the plot because the peak resistive force can never exceed the maximum driving force. A chamber with M<1 operates on a regression line that may eventually reach the prohibited regime for sufficiently elevated peak driving force (AV gradient) values. In contrast, a chamber having M> 1 is not similarly constrained. See ref 10 for details.*

E. Kinematic Modeling of Isovolumic Pressure Decay

The rapid decline in pressure during isovolumic relaxation (IVR) is traditionally fit algebraically via two empiric indexes: τ, the time constant of IVR, or τ_L, 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 dP/dt vs. P, pressure phase plane is strikingly different. Furthermore, no smooth and continuous mathematical transformation between them exists. To avoid the parametric discontinuity between τ and τ_L 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.[11] The model predicts IVR pressure as a function of time as the solution of

$$d^2P/dt^2 + (1/\mu)dP/dt + E_kP = 0, \qquad (4)$$

where μ(ms) is a relaxation rate (resistance) similar to τ or τ_L and E_k ($1/s^2$) 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 τ_L 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 τ_L, respectively). The solution naturally encompasses τ and τ_L as parametric limits, and good correlation between τ and $1/\mu Ek$ ($\tau = 1.15/\mu E_k - 11.85$; $r^2 = 0.96$) indicates that isovolumic pressure decline is determined jointly by elastic (E_k) and resistive ($1/\mu$) parameters. Therefore pressure decline during IVR is incompletely characterized by resistance (i.e., τ and τ_L) alone but is determined jointly by elastic (E_k) and resistive ($1/\mu$) mechanisms.

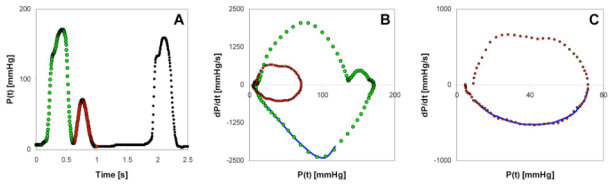

Fig. 5 *A: LV P(t) vs. time for normal (Δ) and nonejecting, premature ventricular contraction (PVC; O) from subject 2. B: PPP plot of P(t) from A including normal beat (Δ) and PVC (O). C: PPP plot of only the PVC (O). The preceding and following normal cardiac cycles are shown for reference. In B, note the kinematic model-generated linear fit (solid line) to the IVR portion of a normal beat (μ = 6 ms, E_k = 3,930 $1/s^2$). In C, note that the entire PVC pressure decay segment is isovolumic and curvilinear. The kinematic model provides excellent fit, shown as a solid line (μ = 146 ms, E_k = 270 $1/s^2$). The curvilinear (logistic) model can also provide a close fit to PVC, but not to normal beats having linear IVR segments. See ref 11 for details.*

III. Conclusion

The aforementioned insights achieved by kinematic modeling of the filling process and rigorous model validation using in-vivo human data, has advanced our understanding of the physiologic parameters that govern diastolic function. Prior clinical studies [12,13] using the PDF formalism to characterize filling in diabetics vs. controls, hypertensives vs. controls, elderly subjects with HF, subjects on caloric restriction vs. controls, as well as characterization of kinematic filling efficiency clearly lead to a paradigm shifting hypothesis that chamber relaxation/ viscoelasticity (PDF parameter *c*) rather than chamber stiffness (PDF parameter *k*) or load (PDF parameter x_o) is the dominant determinant of diastolic dysfunction.

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