Diastolic chamber properties of the left ventricle assessed by global fitting of pressure-volume data: improving the gold standard of diastolic function

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Bermejo J, Yotti R, Pérez del Villar C, del Álamo JC, Rodríguez-Pérez D, Martínez-Legazpi P, Benito Y, Antoranz JC, Desco MM, González-Mansilla A, Barrio A, Elizaga J, Fernández-Avilés F. Diastolic chamber properties of the left ventricle assessed by global fitting of pressure-volume data: improving the gold standard of diastolic function. J Appl Physiol 115: 556–568, 2013. First published June 6, 2013; doi:10.1152/japplphysiol.00363.2013.—In cardiovascular research, relaxation and stiffness are calculated from pressure-volume (PV) curves by separately fitting the data during the isovolumic and end-diastolic phases (end-diastolic PV relationship), respectively. This method is limited because it assumes uncoupled active and passive properties during these phases, it penalizes statistical power, and it cannot account for elastic restoring forces. We aimed to improve this analysis by implementing a method based on global optimization of all PV diastolic data. In 1,000 Monte Carlo experiments, the optimization algorithm recovered entered parameters of diastolic properties below and above the equilibrium volume (intraclass correlation coefficients = 0.99). Inotropic modulation experiments in 26 pigs modified passive pressure generated by restoring forces due to changes in the operative and/or equilibrium volumes. Volume overload and coronary microembolization caused incomplete relaxation at end diastole (active pressure > 0.5 mmHg), rendering the end-diastolic PV relationship method ill-posed. In 28 patients undergoing PV cardiac catheterization, the new algorithm reduced the confidence intervals of stiffness parameters by one-fifth. The Jacobian matrix allowed visualizing the contribution of each property to instantaneous diastolic pressure on a per-patient basis. The algorithm allowed estimating stiffness from single-beat PV data (derivative of left ventricular pressure with respect to volume at end-diastolic volume intraclass correlation coefficient = 0.65, error = 0.07 ± 0.24 mmHg/ml). Thus, in clinical and preclinical research, global optimization algorithms provide the most complete, accurate, and reproducible assessment of global left ventricular diastolic chamber properties from PV data. Using global optimization, we were able to fully uncouple relaxation and passive PV curves for the first time in the intact heart.

diastolic function; hemodynamics; relaxation; diastolic stiffness; mechanical properties; left ventricle; pressure; diastole

DIASTOLIC DYSFUNCTION is present to some degree in virtually all structural myocardial diseases, and, independent of its primary cause, this condition per se has become a major source of cardiovascular morbidity and mortality (23). Although the physiology of diastole has been a key field of preclinical research for decades, all treatments aimed to improve clinical outcome on the basis of modifying diastolic properties have been unsuccessful (8). Diastolic dysfunction is a generic term designating diverse abnormalities of left ventricular (LV) mechanical chamber properties, which all share a final stage of elevated left atrial pressure, pulmonary congestion, and heart failure. To improve therapeutic strategies, it is recognized that developing independent, unbiased, and robust indexes of each intrinsic diastolic property is mandatory (16).

At the full-organ integration level, the analysis of LV pressure-volume (PV) data obtained during acute load manipulation is the current gold standard method for assessing diastolic chamber properties in vivo as well as ex vivo in isolated beating-heart preparations (1, 10). This method is used in cardiovascular research to characterize new animal models of disease, to analyze the effect of therapies, and to validate noninvasive surrogate indexes of diastolic function.

Active and volume mediated passive mechanical properties are the major determinants of diastolic function, and a number of constitutive equations have been established (3, 15, 39). Relaxation designates the active phenomenon related to myofilament unbridling. Passive mechanical properties regulate chamber deformation below (elastic restoring) or above ventricular equilibrium volume (V0). Because active and passive properties act simultaneously during diastole, uncoupling their physical effects is particularly challenging. Current methods attempt to isolate diastolic properties by focusing on specific temporal windows of diastole (18). The rate of relaxation has been characterized using several mathematical models, most frequently using exponential (35), or logistic (15), functions, or even a kinematic-inspired differential equation (3). These approaches share in common that they fit the pressure-time data during the nonfilling period of diastole, under the assumption that passive volume dependent forces are negligible or constant during this period. Stiffness is estimated by fitting the curvilinear end-diastolic PV relationship (EDPVR) from a number of beats during preload manipulation, with each beat contributing with a single point, and assuming that relaxation has been completed by end diastole (ED) (1). These assumptions do not always hold in vivo (34). Also, confining parameter fitting to the isovolumic phase and to the instants of ED heavily penalizes statistical power, because all data recorded during filling are dismissed. Additionally, determining the fitting window landmarks introduces an important
Current computation methods used to assess chamber properties from PV signals use linear or nonlinear numerical algorithms developed more than 20 years ago (3, 15, 35). Since then, curve-fitting methods have evolved substantially, and algorithms for multidimensional optimization have been widely implemented (7). Stochastic optimization methods are particularly useful in biology, as they are able to fit nonlinear equations in a multivariate environment under prespecified constraints representative of physically sound parameter values (2).

We hypothesized that global optimization is a suitable numerical method for uncoupling active and passive diastolic mechanical chamber properties of the LV from conventional PV data, which improves current methods used to characterize diastolic function in the experimental and clinical environments.

The general objective of the present study was to improve the analysis of diastolic PV data by developing and validating a novel numerical algorithm based on global optimization. We aimed to fully implement well-established constitutive equations, obtaining indexes of diastolic function by multivariate fitting of all points in multiple-beat data sets. Specific objectives were as follows: 1) to test the accuracy, reliability, and uncertainty of the global optimization method when analyzing data from in silico, animal, and clinical sources; 2) to test its performance when assessing single beats; and 3) to analyze the relative contribution of each mechanical property to instantaneous diastolic pressure on an individual per-patient basis. We also analyzed the algorithm’s performance under acute hemodynamic interventions. We finally tested the optimization algorithm when fitting alternative, more complex mathematical models of relaxation (3, 15).

Mathematical modeling and optimization algorithm. We attempted to implement a numerical algorithm capable of fitting constitutive equations that, until now, were only obtainable using volume clamp interventions (see APPENDIX) (39). Thus we did not intend to establish a new conceptual scheme of formulation of diastolic properties. Instead, we aimed to combine previously validated models to obtain a global fitting of the diastolic data. For this purpose, we adapted numerical methods frequently used for the analysis of other multidimensional processes in biology, such as allosteric protein regulation (7).

Diastolic pressure is defined as the resultant of adding active (Pa) and passive (Pp) forces acting throughout the full diastolic period (Fig. 1). Although passive forces are modulated by energy-consuming phosphorylation processes (and therefore are not fully passive sensu

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**Glossary**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CME</td>
<td>Left main coronary artery microembolization</td>
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<td>DCM</td>
<td>Dilated cardiomyopathy</td>
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<tr>
<td>dP/dV</td>
<td>Derivative of left ventricular pressure with respect to volume</td>
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<td>ED</td>
<td>End diastole</td>
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<tr>
<td>EDV</td>
<td>End-diastolic volume</td>
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<tr>
<td>ESV</td>
<td>End-systolic volume</td>
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<tr>
<td>EDPVVR</td>
<td>End-diastolic pressure-volume relationship</td>
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<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
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<tr>
<td>PV</td>
<td>Pressure-volume</td>
</tr>
<tr>
<td>Pa</td>
<td>Active diastolic pressure</td>
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<tr>
<td>Pp</td>
<td>Passive diastolic pressure</td>
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<tr>
<td>S+</td>
<td>Constant of diastolic passive stiffness</td>
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<td>S-</td>
<td>Constant of diastolic elastic recoil</td>
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<tr>
<td>τ</td>
<td>Time constant of relaxation</td>
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<tr>
<td>V0</td>
<td>Equilibrium volume</td>
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<tr>
<td>Vd</td>
<td>Left ventricular minimum dead volume</td>
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<tr>
<td>Vm</td>
<td>Left ventricular maximal achievable volume</td>
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**METHODS**

The algorithm was first tested using Monte Carlo simulation to assess its capacity to recover a prespecified parameter space as in reverse engineering (14). Next, we performed animal experiments to test the algorithm’s performance under acute hemodynamic interventions. We finally studied a human population to demonstrate its accuracy in the clinical setting. We introduced individual sensitivity analyses, plotting the relative contribution of each mechanical property to instantaneous diastolic pressure on an individual per-patient basis. We also analyzed the performance of the new method for the purpose of single-beat analysis. Finally, we tested the optimization algorithm when fitting alternative, more complex mathematical models of relaxation (3, 15).

Diastolic pressure is defined as the resultant of adding active (Pa) and passive (Pp) forces acting throughout the full diastolic period (Fig. 1). Although passive forces are modulated by energy-consuming phosphorylation processes (and therefore are not completely passive sensu...
To describe the fitted passive PV curve we used the following:

As the LV relaxes during the isovolumic phase, pressure falls toward the volume-dependent value of passive pressure. The time constant of relaxation (τ) characterizes the rate of relaxation and is generally calculated from a monoexponential equation. In our global model, the passive time-varying volume-dependent pressure is taken as the asymptote of relaxation used in the conventional method for measuring τ (coefficient A in APPENDIX Eq. A7). Additionally, because signals are analyzed for the full diastolic period at a time, fitting τ is not only confined to the isovolumic phase. Instead, the Pa waveform is obtained from aortic valve closing to mitral valve opening. Alternative to the experimental formulation of relaxation, a logistic model has been proposed that has shown Pp to be less load dependent (15).

And recently, a more complete physical model has been implemented that best fits the pressure phase plane and integrates both the exponential and logistic relationships (3). Designated “kinematic” model of diastole, the latter includes an additional parameter to define diastolic properties. We tested the performance of the optimization algorithm to fit these alternative formulations, which include additional degrees of freedom (see APPENDIX for details).

Passive pressure is defined using a piecewise continuous and differentiable function that has different constitutive parameters for volume values below and beyond V0. Consequently, LV instantaneous pressure is expressed as a function of volume and time, as well as of six parameters that define diastolic properties: τ, V0, the passive stiffness constants below (S−) and above V0 (S+), and well as LV minimum dead (Vd) and maximal achievable volumes (Vm).

Until today, these mathematical foundations could only be fully solved using volume clamp experiments to uncouple Pp from Pd. We hypothesized that a proper optimization algorithm is capable of separating both effects if solutions are confined to physiologically sound values of the parameters. First, one degree of freedom was reduced by the smoothness assumption for the piecewise expression of Pp below and beyond V0 (22). Second, we defined a cost function as the squared distance from observed to predicted pressure, based on the remaining five parameters. Third, we implemented a global optimization algorithm to search for the best set of solutions that minimizes this cost function (7). Notice that, because of the high input dimensionality, conventional nonlinear fitting algorithms are highly sensitive to initialization, frequently reaching convergence on spurious solutions. Instead, global optimization methods are designed to provide solutions to problems that may contain multiple local minima. Thus we selected a multiple-initialization trust-reflective algorithm, allowing constrained boundaries of parameters, within user-defined values (4, 5). We seeded the algorithm with 50 random initializations in parallel. When more than one local minimum was reached, the solution with lowest cost function was automatically selected. Importantly, if time is referenced to end systole and constitutive indexes remain unchanged by definition, the algorithm can process multiple or single beats, interchangeably. Normalized Jacobian and resolution matrices were calculated and plotted to assess dependencies and index sensitivity.

We defined “conventional methods” as the exponential fitting of τ confined to the isovolumic period for characterizing relaxation (as defined in the APPENDIX Eq. A7) and the curvilinear fitting of the EDPVR for assessing stiffness. We described the active relaxation curve using τ, as well as the estimated residual active pressure at ED. To describe the fitted passive PV curve we used the following: 1) the coefficients from Eqs. A2 and A3; 2) the estimated Pm at aortic valve closure and filling onset (optimization method only); and) j) its slope dP/dVp = Vc/Vm − V at V = Vm and V = end-diastolic volume (EDV) (EDPVR and global optimization methods).

Monte Carlo simulation. Because there is no true gold standard of diastolic function in vivo, we used synthetic data to compare the performance of the global fitting algorithm against the conventional isovolumic and EDPVR methods (see APPENDIX for details). From measured volume signals, we generated 1000 synthetic pressure tracings by entering random values of τ, S−, V0, Vm, and Vd and forcing physiological bounds. We added random noise and compared the capability of conventional and global optimization algorithms to recover the input space of randomly entered values.

Animal study. Twenty-six adult minipigs (60 ± 10 kg) underwent high-fidelity instrumentation experiments. Animals were preanesthetized with ketamine and xylazine and mechanically ventilated. Complete anesthesia and relaxation were maintained by propofol infusion (0.2 mg·kg⁻¹ min⁻¹), as well as repetitive intravenous boluses of pentobarbital (15 mg·kg⁻¹ 0.15 min⁻¹) and pancuronium (0.2 mg·kg⁻¹ 15 min⁻¹). Through the right carotid artery, we placed a 7F pigtail conductance PV catheter (CD-Leycom) into the LV and connected it to a dual-field conductance processor (Sigma 5DF, CD-Leycom). An occlusion balloon was placed in the inferior vena cava (IVC) for preload manipulation. Twenty-two animals were studied in a studied a closed-chest design, at baseline, and during dobutamine (1–10 µg·kg⁻¹ min⁻¹) and esmolol (25–200 µg·kg⁻¹ min⁻¹) infusions. Fourteen animals underwent median sternotomy without opening the pericardium. These animals were studied at baseline, during dobutamine (1–10 µg·kg⁻¹ min⁻¹) and esmolol (25–200 µg·kg⁻¹ min⁻¹) infusions, after acute volume overload (1,000–1,500-ml saline isotonic solution in 5–10 min), and after left main coronary artery microembolization (CME) of polystyrene microspheres (mean diameter 45 µm, Polysciences, Warrington, PA). PV data were acquired during transient IVC occlusion, three times for each state. Simultaneous B-mode echocardiographic images and V signals were recorded for calibration (40). All data were collected during ventilator disconnection and digitized at 1,000 Hz. Animals were euthanized at the end of the experiments. Experimental protocols were approved by the local Institutional Animal Care Committee.

Clinical study. Twenty-eight patients (58 ± 11 yr old, 13 women) were in sinus rhythm undergoing left heart catheterization were included. Indications for catheterization were ruling out coronary artery disease in 7 patients with dilated cardiomyopathy (DCM), 12 patients with chest pain and normal ejection fraction, and 9 cirrhotic patients under evaluation for liver transplantation. A conductance PV 7F pig-tail catheter was placed in the LV, connected to a dual-field conductance processor (CD Leycom CPU-512), and calibrated by the hypertonic saline method (36). For acute preload reduction, an occlusion balloon (Nu-Vasive 40 mm) was introduced by the right femoral vein and placed in the junction of IVC and right atrium. PV loops were acquired during transient IVC occlusion at end-expiration apnea (36). Simultaneous Doppler-echocardiographic examinations were performed during the catheterization study. We used a broadband 1.75–4 MHz transducer on a Vivid 7 ultrasound system (General Electric Healthcare). We measured pulsed-wave Doppler flow parameters (transmitral E-wave deceleration time, E/A ratio, and isovolumic relaxation time), and averaged septal and lateral tissue-Doppler mitral annulus velocities (20, 41). The study protocol was approved by the local Institutional Review Committee, and all subjects provided written informed consent.

Statistical analysis. Animal experiments were analyzed using paired t-tests and linear mixed-effects models (S-Plus version 8.0, Tibco), where appropriate. The effects of interventions on hemodynamic indexes were calculated as the fixed-effect estimates and their 95% confidence intervals. Fixed effects were adjusted for an open/closed chest design. Differences among phases were tested using simulation contrasts against baseline measurements. For the clinical study, three to five beats were averaged for each patient, and variables are described as means ± SD. Determinants of error of the conventional methods was assessed by multivariate linear regression and backwards stepwise variable selection based on Akaike’s information criterion. Asymptotic confidence intervals are inaccurate in nonlinear fitting problems. Instead, we used the Monte Carlo method (1,500 random replicates of a clinical example) (7) to calculate the confi-
passive PV curve were also accurately estimated, and the performance of the global fitting algorithm outweighed that of the conventional methods.

**Animal study.** The algorithm converged in all except 8 of 274 data sets (97%), with a root mean square error (RMSE) between measured and fitted pressure of 1.62 ± 1.13 mmHg (Table 2). The full decoupled active and passive pressure curves were obtained in all experimental conditions. Pooled data from all experiments showed good agreement between the optimization algorithm and the conventional EDPVR method for assessing V₀ (R² = 0.74, error = ± 8 ± 8 mmHg), but limited agreement to assess LV stiffness both in terms of dP/dV at V₀,

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**Table 2. Animal study: effects of acute hemodynamic interventions on diastolic properties**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Esmolol</th>
<th>Dobutamine</th>
<th>Volume</th>
<th>CME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals, n</td>
<td>102</td>
<td>75</td>
<td>60</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Runs, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodynamic data</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>91 (83–99)</td>
<td>79 (71–87)*</td>
<td>111 (103–118)*</td>
<td>90 (81–100)</td>
<td>74 (63–85)*</td>
</tr>
<tr>
<td>Duration of diastole, ms</td>
<td>357 (304–410)</td>
<td>435 (381–488)*</td>
<td>308 (255–362)*</td>
<td>296 (235–357)*</td>
<td>470 (400–539)*</td>
</tr>
<tr>
<td>ESV, ml</td>
<td>23 (20–26)</td>
<td>24 (21–27)</td>
<td>18 (15–21)*</td>
<td>26 (22–30)</td>
<td>41 (37–45)*</td>
</tr>
<tr>
<td>EDV, ml</td>
<td>48 (43–53)</td>
<td>49 (44–53)</td>
<td>44 (39–49)*</td>
<td>57 (51–63)*</td>
<td>60 (53–66)*</td>
</tr>
<tr>
<td>EDP, mmHg</td>
<td>9 (7–10)</td>
<td>9 (8–11)</td>
<td>9 (7–10)</td>
<td>14 (12–16)*</td>
<td>14 (12–17)*</td>
</tr>
<tr>
<td>Peak systolic pressure, mmHg</td>
<td>94 (85–103)</td>
<td>85 (76–94)*</td>
<td>105 (96–113)*</td>
<td>95 (84–105)</td>
<td>47 (35–59)*</td>
</tr>
<tr>
<td>ESP, mmHg</td>
<td>66 (53–70)</td>
<td>55 (47–62)*</td>
<td>63 (56–71)</td>
<td>63 (54–71)</td>
<td>25 (15–36)*</td>
</tr>
<tr>
<td>dP/dV at V₀, mmHg/ml</td>
<td>1.19 (1.1–1.2)</td>
<td>1.21 (1.0–1.2)</td>
<td>1.25 (1.1–1.3)</td>
<td>1.27 (1.1–1.4)</td>
<td>1.3 (1.1–1.5)</td>
</tr>
<tr>
<td>dP/dV at EDV, mmHg/ml</td>
<td>0.21 (0.2–0.3)</td>
<td>0.20 (0.1–0.2)</td>
<td>0.28 (0.23–0.32)</td>
<td>0.26 (0.20–0.32)</td>
<td>0.44 (0.36–0.52)*</td>
</tr>
</tbody>
</table>

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Values show the estimated fixed effects (with 95% confidence interval in parentheses) from mixed models controlling for repeated measures within animal and open/closed chest design. CME, coronary microembolization; ESV, end-systolic volume; EDP, end-diastolic pressure; ESP, end-systolic pressure; dP/dV, derivative of LV pressure with respect to volume; EDV, end-diastolic volume; Pp, passive diastolic pressure. *P < 0.05 vs. baseline.
(Rc = 0.41, error = 0.40 ± 0.19 mmHg/ml), and dP/dV at EDV (Rc = 0.43, error = 0.43 ± 0.36 mmHg/ml).

As expected, the most extreme changes in LV passive properties (dP/dV and V0) were obtained by CME (Table 2 and Fig. 2A). Inotropic interventions did not modify passive properties below V0 (no changes in S or Vd). However, inotropic modulation changed the operative V range and/or the V0, resulting in significant changes in Pa at aortic valve closure and at mitral valve opening. Importantly, small changes in LV volume during the isovolumic phase increased passive pressure from −0.8 ± 3.6 mmHg at aortic valve closure to −0.1 ± 3.3 mmHg (P < 0.0001) at mitral valve opening (pooled data sets). In 32 of the data sets (12% of total number), Pa at ED was > 0.5 mmHg, reflecting incomplete relaxation during volume infusion and CME.

Clinical study. The algorithm converged in all data sets with a RMSE of 2.6 ± 2.9 mmHg. A wide range of relaxation rates, elastic restoring forces, and stiffness was observed (Table 3; Figs. 2B and 3). The agreement with the isovolumic method to assess τ was good. The EDPVR method returned higher autocorrelation and much wider confidence intervals of stiffness parameters than the global optimization method (Fig. 2, C–E). The agreement of the optimization algorithm with the EDPVR method for dP/dV was only moderate, particularly at EDV (Table 3). The V0 was below end-systolic volume (ESV) in 16 patients and between ESV and EDV in 12. In consequence, the role of passive forces during early diastole was found to be highly variable (Pp at mitral valve opening ranging from −5.3 to +13.7 mmHg). Pp at mitral valve opening was the only determinant of the error of the conventional method to estimate τ (P < 0.001).

Absolute error of the EDPVR to estimate dP/dV at V0 and at EDV was higher in patients with ejection fraction < 0.45 (P < 0.001 and P = 0.02, respectively).

Doppler-derived transmitral E-wave deceleration time, E/A ratio, isovolumic relaxation time, or tissue-Doppler mitral annulus velocity did not correlate with reference indexes of diastolic properties obtained using the optimization algorithm (τ, V0, S, S, dP/dV at V0 and at EDV, all P > 0.05).

Fig. 2. Full characterization of passive diastolic pressure-volume (PV) relationship. A: three phases obtained during hemodynamic interventions in a representative animal experiment. B: curves obtained from a control subject (red) and a dilated cardiomyopathy (DCM) patient (blue). Dotted lines represent the full PV relationship, whereas solid lines represent the curve operated by the ventricle during the cardiac cycle. C–E: uncertainty of stiffness parameters measured from the DCM patient in B. Charts show the scatter plot (C) and distribution functions (D and E) results of Monte Carlo estimation of stiffness parameters obtained by the end-diastolic PV relationship (EDPVR) (blue) and global methods (red) for that particular data set. Notice the narrowing in confidence intervals and reduction in cross-correlation between parameters obtained using the global optimization method. dP/dV, derivative of LV pressure with respect to volume; Edv, end-diastolic volume.
The sensitivity analysis demonstrated the relative contribution of each property to the instantaneous LV pressure (Fig. 4). Resolution matrices showed relatively low autocorrelation among diastolic parameters (Fig. 4). Incomplete relaxation was observed in two patients with DCM (Pₐ values of 0.6 and 1.4 mmHg at ED, respectively; Fig. 4B).

**Reliability analysis.** High $R_{ic}$ values for intra- and interobserver reproducibility (15 randomly selected data sets, blinded analysis 3 mo apart) were obtained for $\tau$ (0.96 and 0.99, respectively), $V_0$ (0.99 and 0.92), dp/dV at $V_0$ (0.96 and 0.83), and dp/dV at EDV (0.81 and 0.87) using the global optimization method. Inter- and intraobserver reproducibility $R_{ic}$ values of the EDPVR method for assessing LV stiffness were remarkably lower for $V_0$ (0.89 and 0.75), dp/dV at $V_0$ (0.70 and 0.67), and dp/dV at EDV (0.73 and 0.25, respectively).

**Single-beat analysis.** Excellent agreement between entered values and single-beat coefficients were obtained for $\tau$ and dp/dV in the Monte Carlo simulation study. Also, the accuracy of the single-beat method was acceptable in the animal and clinical studies for dp/dV and $V_0$ (Table 4).

**DISCUSSION**

The present study validates a new method that yields the most complete, accurate, and reproducible assessment of main diastolic chamber properties available to date for the intact heart.

### Table 3. Clinical study

<table>
<thead>
<tr>
<th></th>
<th>Optimization Method</th>
<th>Conventional Method</th>
<th>Agreement</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>$\tau$, ms</td>
<td>50 ± 10</td>
<td>36–77</td>
<td>50 ± 9</td>
</tr>
<tr>
<td>$V_0$, ml</td>
<td>55 ± 47</td>
<td>8–166</td>
<td>53 ± 33</td>
</tr>
<tr>
<td>$S_\infty$, mmHg</td>
<td>9 ± 11</td>
<td>0–39</td>
<td>18 ± 14</td>
</tr>
<tr>
<td>$V_d$, ml</td>
<td>15 ± 17</td>
<td>1–60</td>
<td>149 ± 74</td>
</tr>
<tr>
<td>$V_m$, ml</td>
<td>160 ± 77</td>
<td>61–354</td>
<td>18 ± 14</td>
</tr>
<tr>
<td>dp/dV at $V_0$, mmHg/ml</td>
<td>0.22 ± 0.12</td>
<td>0.07–0.51</td>
<td>0.20 ± 0.11</td>
</tr>
<tr>
<td>dp/dV at EDV, mmHg/ml</td>
<td>0.46 ± 0.30</td>
<td>0.13–0.46</td>
<td>0.73 ± 0.65</td>
</tr>
</tbody>
</table>

Fig. 3. Full characterization of LV main diastolic properties by PV analysis in a control subject. A: PV data sets of 9 beats obtained during inferior vena cava (IVC) occlusion. B: beat-by-beat representation of each measured diastolic PV curve (black), fitted pressure (red), as well as active (yellow) and passive (green) contributions to total pressure. End-diastolic PV points for all beats are also shown (black dots).
Global fitting methods have demonstrated increased robustness in a number of biological processes (7, 17), but had never been used to analyze LV chamber properties. With this method, we have been able to assess for the first time the full active and passive mechanical properties in the intact heart (1, 18, 24) using conventional PV data. A number of factors account for this improved characterization: 1) increased statistical power resulting from combining within-beat and between-beat analysis, thereby including all measured data points during diastole; 2) simultaneous fitting multiple beats; 3) reduced sensitivity to exact identification of ED; and 4) accurate identification of the full passive PV relationship below and beyond the V0. The performance of the method to fit a number of mathematical models demonstrates that the well-established foundations of diastolic function can now be incorporated to the data analysis, improving the reliability of translational and clinical research without any modification in the experimental setups.

The present study shows important limitations of the EDPVR method to characterize LV stiffness. A number of sources of error were identified. Among them were single-point fitting, variable degrees of residual relaxation at ED, the development of negative ED pressure (EDP) during severe occlusions, and the wide confidence intervals of fitted parameters in vivo (Fig. 2, C–E). We believe these findings question the single-point EDPVR fitting method as the true gold standard of passive stiffness in cardiovascular research.

According to our findings, current methods for measuring relaxation can also be improved. Because of the impossibility of decoupling passive pressure, it is recognized that the isovolumic τ amalgamates, in variable degrees, the effects of relaxation and restoring forces in ways that are not fully understood (11, 38). Conventional algorithms for measuring τ in the intact heart are based on fitting the LV pressure-time data during the time interval between aortic valve closure [or at minimal derivative of left ventricular pressure with respect to time (dP/dt)] and 5 mmHg above EDP. The kinematic model represents a comprehensive approach to the physical properties of relaxation, is capable of fitting pressure data even before minimal dP/dt, and has established a causal connection between the parametric limits of isovolumic relaxation as a physical process (3). However, whatever formulation is pre-
Animal study the estimation of APPENDIX Eq. A7 as asymptote of conventional single-beat nonfilling methods (during early diastole (39). Importantly, we showed that the in the intact heart, dissecting it from the effect of elastic recoil changes in volume during the early relaxation phase translate into a significant time-varying pressure (average 80% in our animal data set). Whenever instantaneous volume data are included (3, 6, 15, 38), all of these methods share in common the assumption of a constant volume (and therefore asymptotic pressure) throughout the isovolumic period (10). A number of factors acting immediately after aortic valve closure, including aortic valve regurgitation or valve bulging, frequently cause small changes in chamber volume. Because the slope of the negative passive PV curve is steep at that point, even small changes in volume during the early relaxation phase translate into a significant time-varying pressure (average 80% in our animal data set). Whenever instantaneous volume data are available, our global fitting can measure pure active relaxation in the intact heart, dissecting it from the effect of elastic recoil during early diastole (39). Importantly, we showed that the asymptote of conventional single-beat nonfilling methods (A in APPENDIX Eq. A7) does not capture the variable passive pressure during relaxation. This inaccuracy induces a significant error in the estimation of τ and may be partially responsible for the previously reported load dependence of relaxation constants (Fig. 6) (28). The finding of a significant effect of inotropic state on restoring forces (e.g., Pp at aortic valve closure and mitral valve opening in Table 2) suggests that thelusotropic effects in vivo of drugs that concomitantly affect inotropy may need to be revisited. In fact, we found that esmolol had no effect on true relaxation. Instead, by shifting the passive PV relationship to the left (i.e., lowering V0), this drug blunted negative suction pressure.

For the first time in humans, we have been able to quantify the effects of restoring forces facilitating depressurization and early filling in the intact heart. Our observations confirm the findings of volume clamp experiments demonstrating the abolition of restoring forces in the failing ventricle (33). By means of the Jacobian matrix, the new solving method additionally provided a sensitivity analysis of the contribution of each parameter to diastolic pressure in every particular data set, as illustrated in Fig. 4. It is now possible to identify to what extent impaired relaxation, stiffness, or operating stiffness (changes in the operating EDV and ESV volume values, which shift position in the PV curve) is responsible for abnormal filling pressures in a particular patient (12, 16, 33). The automatic identification of those cases in which incomplete relaxation may mimic increased stiffness (34) constitutes an illuminating example of the advantages of uncoupling active diastolic forces from passive ones.

Based on fitting all of the PV diastolic data, the global optimization method does not require identifying the end of the isovolumic period and is much less sensitive to an exact identification of ED. These features render the method particularly promising in the right ventricle, a location where precisely defining these temporal events is challenging (26).

To avoid the need for IVC occlusion, three studies have proposed using within-beat filling data to measure stiffness (9, 25, 43). These methods rely on first subtracting isovolumic relaxation pressure to measured pressure and then nonlinearly fitting the resultant PV curve. However, all single-beat methods estimate relaxation pressure assuming a zero asymptote (9, 25, 43). As shown in our study, conditions of extreme loading, inotropic interventions, CME, and DCM can remarkably shift the ESV away from V0, introducing a significant contribution of the passive component to total early diastolic pressure.

| Table 4. Agreement between single-beat and multiple-beat analysis using the global optimization method |
|---|---|---|
| Monte Carlo study* |
| τ, ms | 0.97 | 0.20 | 3.8 |
| V0, ml | 0.98 | 0.17 | 2.6 |
| dP/dV at V0, mmHg/ml | 0.99 × 10^{-4} | 0.02 |
| dP/dV at EDV, mmHg/ml | 0.99 × 10^{-3} | 0.04 |

Animal study

| τ, ms | 0.77 | 14 | 20 |
| V0, ml | 0.59 | 10 | 11 |
| dP/dV at V0, mmHg/ml | 0.14 | 0.36 | 0.52 |
| dP/dV at EDV, mmHg/ml | 0.41 | 0.02 | 0.44 |

Clinical study

| τ, ms | 0.69 | 3 | 8 |
| V0, ml | 0.94 | 8 | 15 |
| dP/dV at V0, mmHg/ml | 0.39 | 0.08 | 0.16 |
| dP/dV at EDV, mmHg/ml | 0.65 | 0.07 | 0.24 |

*Compared with entered reference values.

**Fig. 5. Alternative mathematical model fittings for pressure data during isovolumic relaxation shown in the pressure phase plane. The results of adjusting pressure-time data using the optimization algorithm implementing different relaxation functions are shown in a representative animal data set of 14 beats obtained during IVC occlusion. Active relaxation is described using the exponential (Eq. A1, green), the logistic (Eq. A9, blue), and the kinematic models (Eq. A10, red), overlaid on measured pressure (black, from peak LV pressure to end diastole). In the pressure-phase plane, these models are depicted as linear, one parameter curvilinear, and two parameter curvilinear, respectively. Beats 1, 7, and 14 are shown. Notice that, by design, the optimization algorithm estimates a single set of relaxation parameters [τ, τ-logistic, and μ (resistive parameter equivalent to τ) and Ee (lumped elastic parameter accounting for the elastic restoring force)] for the exponential, logistic, and kinematic models, respectively, from the 14 beats in the data set. Thus individual beat fitting results are necessarily worse than if each beat were fitted independently. dP/dt, minimal derivative of LV pressure with respect to time.
Figure 6 clearly confirms volume clamp observations that passive forces during early filling cannot be denied, yielding previous single-beat methods (9, 25, 43) ill posed. Moreover, our method has an additional advantage over these previous single-beat approximations. Because the algorithm processes data from multiple beats in an integral fashion, the spontaneous variations in load caused by breathing (19) can be incorporated in future developments. For these reasons, we believe that global optimization is the most accurate method available to date to characterize diastolic properties in vivo without the need of occluding the vena cava. In the future, when combined with image based methods for measuring LV volume values, this type of algorithms will improve the assessing of LV diastolic properties in clinical practice.

Doppler echocardiography is the noninvasive method most frequently used to assess diastolic function in bedside clinical examinations, but the present study showed a poor correlation of currently recommended methods (20) with intrinsic global chamber properties. E-wave deceleration time is known to physically depend on average diastolic operating stiffness, measured as the average intrabeat PV linear relationship, from minimum pressure to ED (13). The lack of correlation of the deceleration time with passive PV curve parameters observed in our study is probably related to its sensitivity to relaxation (32). Operating stiffness during diastasis can also be accurately determined by fitting the transmitral flow spectrogram to a kinematic mathematical model (19). Despite the fact that LV relaxation is still frequently not completed during this phase (Fig. 4B), the relationship of Doppler-derived diastatic operating stiffness with passive PV curve parameters deserves further investigation. Advances in imaging techniques are rapidly improving the clinical assessment of myocardial deformation.

Fig. 6. Impact of passive pressure during the isovolumic phase on the estimation of relaxation. A: Bland-Altman plot of pooled data of all beats from all animal experiments showing the bias (solid line) ± SD (dashed line) showing the individual variation of passive pressure from AVC to MVO. The lack of full agreement demonstrates volume-mediated changes in passive pressure in this phase. B: scatterplot between asymptotic pressure obtained by single-beat analysis using Eq. A7 (horizontal axis) and average isovolumic passive pressure obtained by the global optimization method (vertical axis). The lack of correlation demonstrates the limitations of the conventional method for measuring relaxation to accurately uncouple passive pressure during the isovolumic phase. C: impact of the uncertainty of estimating passive pressure during the isovolumic phase for the characterization of relaxation using the conventional exponential method (Eq. A7 analytic derivative solved for a \(\tau\) value of 50 ms and \(P_0\) of 80 mmHg). Notice that 1-mmHg error in the estimation of \(P_p\) induces an error up to 4.5 ms in measured \(\tau\). As shown in B, these errors are frequently much higher. We believe that this mechanism may partially account for the preload dependence of relaxation previously reported using the conventional single-beat isovolumic method.
Further studies on how deformation-based measurements, such as myocardial strain, untwisting, and detorsion, reciprocally interact with intrinsic global chamber properties are warranted; the possibility of now measuring global chamber elastic recoil is particularly promising in this context.

Limitations and future directions. Analysing the effects of inotropic interventions in patients would have added interesting translational evidence from the clinical setting. However, we did not perform repeated-measures experiments in patients due to the highly invasive nature of the simultaneous left and right catheterization procedure of measuring PV loops during balloon caval occlusion.

Although our method fitted the PV-time relationship acceptably well during rapid filling, there are additional factors influencing this relationship that were not taken into account (30). Flow inertia, vorticity, ventricular interdependence, pericardial properties, myocardial viscoelasticity, and non volume dependent untwisting deformation may have a complementary effect on the PV relationship (39). Also, extreme concentric remodeling moves the pressure-decay curve away from the exponential model (10). Additionally, it has been suggested that atrial inotropic attributes may confound the EDPVR (42), and the interpretation of the $V_0$ is a matter of debate (31, 37). By design, our method assumes fixed indexes of relaxation for all beats during preload manipulation. Because it accounts for volume-dependent passive pressure during relaxation, we introduce, for the first time, a method that is not sensitive to the assumption of a free asymptote (Fig. 6). However, relaxation per se may be dependent both on volume and on cycle length (28, 29). It is also well recognized that passive properties (as characterized by our method) are influenced by chamber stiffness, and also by myocardial stiffness and chamber size remodeling (1). Due to these factors, there is still room for improvement in the mathematical modeling of diastole (Fig. 3). However, the choice of extra parameters should be guided by physiological insight and verified by experimental and clinical data. The sensitivity and resolution analyses proposed in this study provide an efficient systematic methodology to benchmark these prospective models. For example, incorporating an additional coefficient that accounts for load-influencing $\tau$ can be readily tested. Also, further mathematical modeling can be incorporated to characterize the passive stress-strain relationship and account for true myocardial diastolic stiffness (1). Finally, the implementation of data weights to particularly meaningful events of diastole (e.g., minimum dP/dt) may further improve the robustness of fitted parameters, particularly when using the largest parameter space such as required for Eq. A10.

Conclusions. The results of accuracy, precision, applicability, sensitivity, and reliability demonstrate that optimization algorithms are the best methods for assessing LV global diastolic chamber properties in clinical and preclinical research. A more accurate, robust, reliable, and complete characterization of diastolic function may have important applications in clinical cardiovascular research. With the type of methods proposed, the independent role of a prolonged relaxation, increased passive stiffness, and operating volume can be isolated as the cause of diastolic chamber function in a given patient. This can be relevant in conditions of extreme load, such as valvular regurgitation or congenital heart disease, in which true chamber abnormalities are particularly complex to address. In patients with hypertrophic or hypertensive cardio-myopathy, prolonged relaxation frequently coexists with increased stiffness, and the mechanism responsible for high filling pressures can now be isolated. Interestingly, the role of elastic recoil forces in these conditions has never been addressed. Finally, due to the issues discussed above, the global optimization tool seems a promising tool for understanding the particular forces governing the diastolic function of the right ventricle. The combination of imaging modalities and data processing algorithms that do not require a catheter-driven manipulation of preload will facilitate a better understanding of diastolic dysfunction in these clinical disorders. Therefore, we believe that global optimization of PV data is the best available method to characterize diastolic function. Researchers aiming to understand the effects of drugs on diastolic function, to characterize new animal models of disease, or to test noninvasive surrogate techniques for assessing diastolic function in the clinical setting should benefit from this new method.

APPENDIX

Theoretical model. To date, active and passive mechanical properties can only be completely decoupled by driving nonfilling beats using volume clamp experiments (22, 27, 38, 39). In these experiments, relaxation is typically described using an exponential equation as

$$P_{a(V)} = [P_0 - P_{p(V)}] \cdot e^{-\tau t}$$

where $P_a$ designates active relaxation pressure, $P_0$ measures LV pressure at the onset of diastole, $P_p$ designates passive pressure, $\tau$ is diastolic time measured from end systole to mitral valve closing, and $\tau$ is the time constant of LV relaxation. Passive mechanical diastolic properties are governed by a piecewise PV logarithmic relationship. The elastic restoring pressure generated when volume $V < V_0$ is modeled by

$$P_{p(V < V_0)} = S_+ \cdot \log \frac{V(V < V_0) - V_d}{V_0 - V_d}$$

where $V_0$ is defined as LV V when $P_0 = 0$, $S_+$ designates the stiffness constant for $V < V_0$, and $V_d$ is the LV dead V asymptotic. Above $V_0$, the PV relationship is

$$P_{p(V > V_0)} = -S_- \cdot \log \frac{V_m - V(V > V_0)}{V_m - V_0}$$

where $S_-$ designates the stiffness constant for $V > V_0$, and $V_m$ is the maximal achievable volume asymptote.

For a relatively homogenous solid body undergoing elastic deformation, the slope of $P_p$ is continuous. Therefore, at $V_0$, it must hold that $dP_p < dV/V = dP_p > dV/V$ (22), and $S_-$ can be expressed as a volume normalization of $S_+$:

$$S_- = \frac{S_+(V_0 - V_d)}{V_m - V_0}$$

thereby reducing the number of parameters by one.

Active and passive mechanical properties act simultaneously during the full diastolic period, from aortic valve closure to mitral valve opening, such that full estimated pressure $\hat{P}$ is a function of time and volume (Fig. 1):

$$\hat{P}(V,t) = P_{a(V,t)} + P_{p(V)}$$

If Eqs. A1-A4 are substituted into Eq. A5, the characterization of diastolic properties ($\tau$, $V_0$, $S_+$, $V_m$, and $V_0$) can be formulated as the minimization of a cost function defined by the following expression of the difference between the theoretical pressure and the measured pressure, i.e.
where \( P \) stands for measured pressure, and \( \|d\|_2 \) is the Euclidean norm of the vector \( d \). In this vector, the difference between the pressures estimated, \( \hat{P}_{V,d} \), and measured, \( P \), at all of the recorded time points. If all diastolic parameters are assumed to be load independent and time is normalized at end systole, Eq. A5 is valid for all beats in a data set. Thus Eq. A6 can be fitted interchangeably for a single beat and for a full hemodynamic run of IVC occlusion. \( S - \) and \( V_d \) are undetermined, if \( V \) does not fall below \( V_0 \) in any of the beats. Notice that identifying \( V \prec V_0 \) in a data set is not equivalent to measuring negative diastolic pressures, because \( P \) contributes with positive pressure (Eq. A5).

**Algorithm solving.** For solving Eq. A6, we adapted Matlab built-in global optimization algorithms (release 7.13, Optimization and Global Optimization toolboxes, Natick, MA). All pressure and volume signals underwent low-pass filtering at 50 Hz. End systole (aortic valve closure) was defined as the instant of peak negative pressure derivative. End diastole (ED) was defined as the peak of the R-wave slope, confirmed visually by beat at the bottom-right corner of the PV diagram. Tolerance values for \( P \) and input space \((V,t)\) were set to \( 10^{-10} \) mmHg, \( 10^{-10} \) ml, and \( 10^{-10} \) s, respectively, with a maximum of 300 iterations and \( 10^4 \), function evaluations. Due to the nonlinear nature of the fit, it is probable that the cost function has more than one minimum. This probability is enhanced by the relatively large (five) number of degrees of freedom in Eq. A6. To ensure that the optimization method finds the global minimum and neglects spurious local minima, we selected a trust-reflective algorithm because prespecified lower and upper constraints can be entered for each parameter (4, 5). Additionally, 50 random initialization sets of constrained parameters were seeded to the global optimization algorithms (release 7.13, Optimization and Global

**Random parameters for equation parameters.** Thus a total of 1,000 PV data sets were obtained. The simulated \( P_o \) was calculated from measured ESVs by assuming a linear end-systolic PV relationship, and entering random values for peak elastance (range: 0.7 to 5 mmHg/ml) and volume intercept (80–300% of ESV). We generated random values for \( r, s, V_0, V_m \), and \( V_d \) uniformly distributed in the same parameter intervals used for the constrains described for solving. Parameters and volume values were then entered in Eqs. A1–A4 to obtain a simulated pressure measurement. Because not all parameter combinations are physiologically plausible, we regenerated random values of the parameters until the following constraints were met: 1) \( P_o \prec 200 \) mmHg for the first beat and \( >50 \) mmHg for the last one; 2) \( ED \prec 30 \) mmHg; 3) minimal pressure achieved during the first half of the diastolic period; and 4) pressure span during diastole from \( P_o \) to minimum pressure \( >30 \) mmHg. The final entered values of diastolic parameters were stored as reference. Before entering the fitting algorithm, Gaussian white noise was added to the simulated pressure signals, matching the signal-to-noise ratio found in animal and clinical experiments (45 and 42 dB, respectively). Each PV simulated waveform was visually verified before processing. An example is shown in Fig. 7.

**Alternative models of relaxation.** Additionally, to the exponential function showed in Eq. A1, other models have been proposed to describe the pressure-time relationship during isovolumic relaxation. We also attempted to test the performance of the global fitting algorithm to incorporate these alternative mathematical relationships. The physical assumptions underlying the different models of isovolumic relaxation are best illustrated plotting the time derivative of pressure against instantaneous pressure (as a pressure-phase plot) (3).

The logistic function defines:

\[
P_{d(t)} = \frac{A}{1 + e^{-\tau_t}} \quad (A8)
\]

Where \( A \) is an amplitude constant, and \( \tau_t \) is the time constant of relaxation measured using this method (15). \( A \) can be expressed in terms of \( P_o \), and Eq. A8 becomes:

\[
P_{d(V,t)} = \frac{2[P_o + P_{p(V)}]}{1 + e^{\tau_t}} \quad (A9)
\]

For the conventional method used for comparison, relaxation pressure was fitted to

\[
P_{d(t)} = P_o \cdot e^{-\tau_{t}} + A \quad (A7)
\]

during the isovolumic period only (up to 5 mmHg above EDP). The constant \( A \) represents a positive or negative asymptotic pressure value that is equivalent to the term \( P_{d(V)} \) in Eq. A5, if the volume is constant. The same applies to \( \tau \) (Fig. 1). Conventional values of this parameter were fitted to Eq. A7 beat by beat (41) and then averaged for the full data set. Conventional assessment of the ED-PVR was done by fitting Eq. A3 to ED multiple-beat PV data (12, 39). Single-beat analysis was performed on all Monte Carlo, animal, and clinical data, with reprocessing of the data only for the first beat in the data set.

**Monte Carlo simulation.** We used Monte Carlo simulation (14) to test the performance of the novel fitting algorithm in finding a prespecified set of diastolic parameters (6). First, 20 experimental volume signals recorded during IVC occlusion (10 animals and 10 patients; 7–15 beats each) were randomly selected. Next, 50 synthetic “pressure” series were generated applying model equations (Eqs. A1–A5) to each of these experimentally measured volume signals, using physiologically sound random parameters for equation parameters. Thus a total of 1,000 PV data sets were obtained. The simulated \( P_o \) was calculated from measured ESVs by assuming a linear end-systolic PV relationship, and entering random values for peak elastance (range: 0.7 to 5 mmHg/ml) and volume intercept (80–300% of ESV). We generated random values for \( r, s, V_0, V_m \), and \( V_d \) uniformly distributed in the same parameter intervals used for the constrains described for solving. Parameters and volume values were then entered in Eqs. A1–A4 to obtain a simulated pressure measurement. Because not all parameter combinations are physiologically plausible, we regenerated random values of the parameters until the following constraints were met: 1) \( P_o \prec 200 \) mmHg for the first beat and \( >50 \) mmHg for the last one; 2) \( ED \prec 30 \) mmHg; 3) minimal pressure achieved during the first half of the diastolic period; and 4) pressure span during diastole from \( P_o \) to minimum pressure \( >30 \) mmHg. The final entered values of diastolic parameters were stored as reference. Before entering the fitting algorithm, Gaussian white noise was added to the simulated pressure signals, matching the signal-to-noise ratio found in animal and clinical experiments (45 and 42 dB, respectively). Each PV simulated waveform was visually verified before processing. An example is shown in Fig. 7.

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Alternatively, a more generic relationship of the pressure-time relationship has been proposed that does incorporate passive pressure in its definition (3). This approach avoids the noise amplification caused by numerically differentiating the measured pressure signal. As in Eqs. A1 and A9, in Eq. A11 the asymptote of Pa is replaced by Pp(V), allowing the merge of active and passive constitutive equations throughout the full diastolic period. A more complex integration of passive restoring forces in Eq. A11 is beyond the scope of this study. Local minima algorithms were forced to iterate until noncomplex values of the coefficients were returned.

In Eqs. A10 and A11, LV relaxation properties are characterized by two parameters, \( \mu \) and \( E_k \), representing a more generic formulation of the relaxation pressure decay than the exponential and logistic models. Furthermore, it has been shown that the kinematic model is capable of fitting the pressure data before minimal dP/dt. Replicating previously published methodology (3), we began analyzing from the instant when the second time derivative of pressure fell below 50% of the peak value (a few ms earlier than dP/dt(min)).

Notice that using the global optimization method, instead of single-beat fitting of pressure data measured before mitral valve opening, we fit Eq. A11 for the full hemodynamic run obtained during IVC occlusion. The returned single values of \( \mu \) and \( E_k \), therefore, account for the best fit to all of the diastolic period of a number of beats. Individual beat fitting must be necessarily worse than if beats were fitted individually. Differences between the exponential, logistic, and kinematic methods for fitting early diastolic filling data are best illustrated in the pressure phase plane (Fig. 5), as previously proposed (3).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES

Innovative Methodology


