CALL FOR PAPERS | Mechanisms of Diastolic Dysfunction in Cardiovascular Disease

What global diastolic function is, what it is not, and how to measure it

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1Department of Physiology and Center for Muscle Biology, University of Kentucky, Lexington, Kentucky, and Department of Physiology, Wayne State University, Detroit, Michigan; and 2Cardiovascular Biophysics Laboratory, Cardiovascular Division, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri

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Chung CS, Shmuylovich L, Kovács SJ. What global diastolic function is, what it is not, and how to measure it. Am J Physiol Heart Circ Physiol 309: H1392–H1406, 2015. First published August 28, 2015; doi:10.1152/ajpheart.00436.2015.—Despite Leonardo da Vinci’s observation (circa 1511) that “the atria or filling chambers contract together while the pumping chambers or ventricles are relaxing and vice versa,” the dynamics of four-chamber heart function, and of diastolic function (DF) in particular, are not generally appreciated. We view DF from a global perspective, while characterizing it in terms of causality and clinical relevance. Our models derive from the insight that global DF is ultimately a result of forces generated by elastic recoil, modulated by cross-bridge relaxation, and load. The interaction between recoil and relaxation results in physical wall motion that generates pressure gradients that drive fluid flow, while epicardial wall motion is constrained by the pericardial sac. Traditional DF indexes (τ, E/E’, etc.) are not derived from causal mechanisms and are interpreted as approximating either stiffness or relaxation, but not both, thereby limiting the accuracy of DF quantification. Our derived kinematic models of isovolumic relaxation and suction-initiated filling are extensively validated, quantify the balance between stiffness and relaxation, and provide novel mechanistic physiological insight. For example, causality-based modeling provides load-independent indexes of DF and reveals that both stiffness and relaxation modify traditional DF indexes. The method has revealed that the in vivo left ventricular equilibrium volume occurs at diastasis, predicted novel relationships between filling and wall motion, and quantified causal relationships between ventricular and atrial function. In summary, by using governing physiological principles as a guide, we define what global DF is, what it is not, and how to measure it.

diastolic function; echocardiography; hemodynamics; mathematical modeling; suction pump

LEFT VENTRICULAR (LV) DIASTOLIC dysfunction is typically reported and indexed as either an increase in myocardial stiffness or a slowing of relaxation (i.e., cross-bridge dissociation). In actuality, diastolic function (DF) is the result of the continuous interaction between the restoring force of elastic recoil and the opposing force generated by cross bridges that have yet to uncouple from the previous systole. The restoring forces seek to lengthen the muscle, while the cross-bridge forces previously acted to shorten the muscle. The simultaneous action of these two opposing forces during both isovolumic relaxation (IVR) and filling result in wall motion, constrained by pericardial sac volume, and simultaneous generation of pressure gradients. This review discusses the governing physical laws and the constraints of DF, as well as which indexes of DF are consistent with diastolic physiology. Deriving and evaluating indexes of DF using this conceptual framework both clarifies and advances our understanding of DF and diastolic dysfunction in health and disease.

Physiology of Diastole

Cardiovascular physiology is taught using the Wiggers diagram, which segments the cardiac cycle into systole and diastole (Fig. 1) (49, 124). Systole begins at the closing of the mitral valve, proceeds through isovolumic contraction, aortic valve opening, and ejection, and ends with aortic valve closure. Diastole begins at aortic valve closure and proceeds through IVR, mitral valve opening (MVO), early-rapid filling, diastasis, late-atrial filling, and finally mitral valve closure. This strict definition belies two important factors. First, the phases of the cardiac cycle are actually defined by the function of the LV. For this reason, we will refer to LV diastole throughout this

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review, even though left atrial (LA) diastolic attributes have been used as an index of DF (98). Second, the myocardium, while functioning as a muscle-powered oscillator, seamlessly transitions through these phases; kinematic measures of the myocardium, such as strain, strain rate, and torsion, for example, do not show discrete transitions when the valves open or close (26, 28, 84, 108, 116).

Heart failure, the failure of the heart to circulate sufficient blood to meet peripheral oxygen (metabolic) need, was historically associated with reduced LV ejection fraction and impaired cardiac output. However, an increasing number of patients diagnosed with heart failure (usually manifesting with pulmonary edema) have ejection fractions within the normal range (>45%). These patients are diagnosed with diastolic dysfunction (91) and are said to have heart failure with preserved ejection fraction (HFpEF) (27, 68, 92, 97). Given the HFpEF epidemic (90) and the prevalence of diastolic dysfunction in the setting of important comorbidities, such as obesity, hypertension, and diabetes (25, 93, 109, 117), accurate quantification of DF is receiving new attention. Parameters that correlate with relaxation or with myocardial stiffness are now commonly, but independently, reported in studies of HFpEF (91, 98). However, relaxation and stiffness are not independent of each other, nor are they free of physical constraints.

Relaxation and stiffness as global chamber properties ultimately originate from myocardial molecular biology and cellular physiology. Relaxation is the decay of systolic force that was generated by cross bridges (4, 14). There are three prominent factors in this decline in force: calcium reuptake, deactivation of cross-bridge binding sites, and detachment of cross bridges themselves. If calcium reuptake is slowed, for example in ischemia or hypoxia, then the rate of relaxation is reduced (13, 15). Altered deactivation of cross-bridge binding sites, for example due to phosphorylation or mutation of troponin complexes, is also associated with slow relaxation (73, 81, 118). In addition, cross-bridge detachment itself may modify the rate of relaxation (4, 42), with slowed cross-bridge detachment, for example by mutation, leading to prolonged generation of force.

Stiffness is a global measure of the elastic properties of the chamber, quantified by the slope (dP/dV) of the applicable (diastatic or end-diastatic) pressure-volume relation (111). The two most well-known and significant contributors to elastic forces are titin and the extracellular matrix (35), which includes the visceral pericardium (47). Titin is the largest protein expressed in the body and operates (in the physiological domain of sarcomere lengths) as a linear, bidirectional spring (33, 39, 40). Titin assists in keeping myofilaments in register and symmetric (34), and it is also required to quickly restore the cell to its rest length after contraction (39). Titin’s stiffness can be modified by alternative splicing and posttranslational modifications (61, 62). For example, β-adrenergic stimulation causes PKA to phosphorylate titin in its N2B unique sequence, which reduces the stiffness of titin (60, 125). PKA phosphorylation is reduced in patients with HFpEF and is associated with stiffening of their myocardium (5, 134). Activation of the cGMP-PKG pathway and CaMKII can similarly reduce the stiffness of titin (38, 59), while activating the PKC pathway increases its stiffness (41, 43). The extracellular matrix is the other dominant molecular component. The extracellular matrix is composed primarily of collagen and elastin (121). Both the relative content of collagen vs. myocardium and cross-linking of collagen can modify myocardial stiffness (12, 82).

As a physical index, diastolic stiffness characterizes an elastic driving force, while relaxation characterizes an inhibitory or viscous force. Elastic (restoring) forces are present whenever the myocardium moves out of its equilibrium position. For example, when an unloaded myocyte contracts and shortens, elastic intracellular forces are generated that restore the myocyte back to its rest length as the myocyte relaxes (39). Elastic forces are also revealed by myocardial kinematics. For example, a stiffer myocardium (assuming normal relaxation) will recoil or relengthen faster as it returns to its equilibrium length, and increasing myocardial stiffness will lead to increased force generation for a given stretch. This relationship between stiffness, stretch, and force is often thought to be revealed in the passive-pressure-volume relationship (16, 79). In contrast, relaxation is the result of decay of contractile forces that oppose recoil. Attached cross bridges behave as a resistive force, which elastic recoil forces generally counteract. Other filling-related resistive forces include tissue viscosity, resulting from muscle layers sliding past each other, as well as increased resistance due to a diseased and flow-limiting mitral valve.

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**Fig. 1. The phases of the cardiac cycle.** The ECG is shown above left ventricular (LV) pressure (black line) and aortic pressure (gray line). Systole includes isovolumic contraction and ejection. Mitral valve closure initiates systole, when QRS complex of the ECG is inscribed. Isovolumic contraction ends as LV pressure (LVP) rises above aortic pressure and the aortic valve opens to initiate ejection. Systole and ejection continue until the aortic valve closes. Diastole begins when the aortic valve closes, which initiates isovolumic relaxation (IVR) and rapid LVP decline. As LVP drops below left atrial (LA) pressure (LAP), the pressure gradient (LVP < LAP) initiates early rapid filling (suction). After the E-wave terminates but before A-wave begins, LAP = LVP, and diastasis is present while LV volume remains constant. The P-wave of the ECG initiates LA depolarization and onset of atrial filling. Diastole concludes when the next QRS complex is inscribed and the mitral valve closes.
**Is Relaxation Independent of Stiffness?**

While the cross-bridge generated force interacts with and opposes the elastic recoiling force, relaxation and stiffness are usually not indexed or discussed together. For example, IVR is generally referred to as a cross-bridge relaxation process (4, 14, 42). In general, if some cross-bridge modifying property (calcium reuptake, binding site deactivation, or cross-bridge detachment) is slowed or disrupted, relaxation is slowed, and indexes of IVR are prolonged. However, as can be plainly observed by isovolumic shape change of the chamber during left ventriculography (126), the LV is dynamic during the isovolumic phase. Recent studies demonstrate both strain and torsion during this phase (83, 108). Isovolumic shape change, which must involve motion, requires more than mere cross-bridge uncoupling. It also requires interaction between simultaneous elastic recoil, which relengthens the muscle, as cross bridges, which hold the muscle contracted, continue to relax (uncoupling) as diastole proceeds. Models accounting for this dynamic interplay are beginning to emerge (20, 111).

Early rapid filling is often viewed as a process dominated by chamber recoil or stiffness. A commonly reported index of DF is the E-wave deceleration time (DT) (17, 36, 91, 95, 98), which was proposed to be mathematically related to chamber stiffness (65, 86). However, one sign of diastolic dysfunction is a prolongation of the E-wave, referred to as the “delayed relaxation” pattern (1, 80, 88, 98). Furthermore, it is well known that cross-bridge uncoupling and relaxation do not abruptly terminate at MVO, and that they continue throughout much of the early rapid filling period (122). Thus early rapid filling is not solely determined by myocardial stiffness: it is modulated by both chamber stiffness and relaxation.

Another important example is end-diastolic pressure. Elevated end-diastolic pressure is associated with impaired DF and heart failure (91). The pressure itself is determined by the chamber’s end-diastolic pressure-volume relationship (EDPVR), a ventricle with impaired DF may have an EDPVR that defines a higher end-diastolic pressure at a given volume than a healthy ventricle. However, the EDPVR has been associated with not only passive myocardial stiffness of titin and the extracellular matrix (16, 35, 79, 107), but, especially at physiological pressures and conditions associated with abnormal energy utilization, with cross-bridge forces (21, 54, 119). Thus end-diastolic pressure is an index deeply connected to the chamber’s EDPVR, which, at a given volume, is modulated by both chamber stiffness and relaxation (rate and extent of cross-bridge uncoupling).

In general, DF, in the setting of a given overall intravascular volume, is the result of a continuous dynamic interaction between physiological properties of relaxation and elastic stiffness. These chamber properties manifest as physical wall motion that generates pressure gradients to drive fluid flow while the wall motion itself is physically constrained by the anatomy of the chamber and the pericardial sac. Therefore, DF is defined by the continuous interplay between cross-bridge uncoupling (relaxation) and elastic recoil, which is constrained by physical properties. The primary intent of this review is to highlight that the dominant mechanism responsible for global DF involves the continuous interplay between elastic recoil forces and cross-bridge forces, relative to the load encountered, and most importantly, the parameters that characterize these forces can be quantified rigorously from in vivo hemodynamic and echo data. To properly quantify global DF, we have derived parameters and indexes stemming from these chamber-property-determined forces and physical constraints. These indexes, their advantages relative to current DF indexes, and the importance of the dynamic interplay between forces of relaxation and elastic recoil are explored below.

**IVR**

The IVR phase of the cardiac cycle marks a period of rapid pressure decline within the LV. As noted above, this pressure decline is typically thought to be modulated by relaxation-related mechanisms, like calcium reuptake, binding site deactivation, and cross-bridge detachment. However, elastic recoil must also play a role.

Traditionally, IVR can be characterized noninvasively in terms of its duration or the IVR time (IVRT), or invasively by determination of time constant $\tau$ or peak negative change in pressure over time $(dP/dt)$. IVRT is the least specific in characterizing relaxation because it involves both aortic systolic and atrial pressures, neither of which is explicitly measured at the time of IVR determination by echocardiography. It is also limited in accuracy by the sampling and frame rates available on imagers to record this data. On the other hand, $\tau$ and peak negative $(dP/dt)$ are directly dependent on the time course of isovolumic pressure decline, which is most precisely recorded using high-fidelity micromanometric catheters (126). But what do these IVR parameters really mean, and how should they be interpreted?

**Indexing with relaxation alone.** We first consider $\tau$, which is a widely accepted index of relaxation and defined to be the time constant of isovolumic pressure decay (48). This index was based on the assumption of exponential decay that is empirically fit to the observed pressure decline vs. time curve starting (just below) minimum $dP/dt$ and ending just above MVO (123). Subsequent work showed that using the pressure phase plane (PPP; a plot of $(dP/dt)$ vs. pressure) improves the ability to assess the goodness of fit over the isovolumic period; the PPP also confirmed that a nonzero pressure asymptote was required (96). Therefore, pressure decay as a function of time during IVR was fit using:

$$P(t) = P_0 e^{-t/\tau} + P_x$$

or the differential form that defines the shape in the PPP:

$$\frac{dP}{dt} + \frac{1}{\tau} [P(t) - P_x] = 0$$

where $P_0$ and $P_x$ are constants, and $\tau$ is the time constant of IVR. Notably, the form of Eq. 1B plots a straight line with a slope $-1/\tau$ in the IVR portion of the PPP loop (Fig. 2A).

But the PPP also provides an opportunity to observe and examine the range of variation in normal physiology. For example, for some hearts, the IVR segment of the phase plane is not linear but is curved. To fit these curved segments, a logistic decline of pressure as a function of time was proposed (69), having the form:

$$P(t) = \frac{P_A}{1 + e^{-\tau_L t}} + P_B$$

or the differential form:
where \( P_A \) and \( P_B \) are constants and \( \tau_L \) is the logistic time constant. This model empirically fits curved contours (69, 74) for the IVR segments of the PPP loop (Fig. 2B).

Both the monoexponential and logistic forms of isovolumic pressure decay are equations that were empirically selected to fit pressure data while providing one relaxation parameter. In both cases, the extracted time constant (\( \tau_L \) or \( \tau \)) is generally associated with cross-bridge uncoupling/relaxation and is not thought to be related to elastic stiffness.

**Model of IVR with relaxation and stiffness parameters.** We have proposed a model of isovolumic pressure decline that includes both cross-bridge relaxation forces and elastic stiffness-generated restoring forces (20). We proposed the following relationship:

\[
\frac{d^2 P}{dt^2} + \frac{1}{\mu} \frac{dP}{dt} + E_k(P - P_0) = 0
\]  

(3)

Fig. 2. Quantifying diastolic function (DF) in the pressure phase plane (PPP) during IVR. The relaxation portion of PPPs are shown. A–C, insets, top right: PPP loop of an entire cardiac cycle. A: IVR inscribed contours are often linear. Monoexponential time dependence of pressure generates a straight line (solid) in the PPP and can be empirically fit to the IVR segment. Note inability of linear fit to account for peak negative change in pressure over time (\( dP/dt \)). B: some IVR contours are curvilinear, for which a logistic provides a good fit (shaded line). C: however, IVR segments in a heart can display both linear and curved shapes. D–F: the kinematic model that includes elastic stiffness and relaxation properties can fit (solid line) all three selected PPP loops’ IVR segments. G and H: variation of stiffness and relaxation parameters in the model influences both IVR segment curvature and values of peak negative \( dP/dt \). For example, increasing stiffness leads to an increased peak negative \( dP/dt \) (G), while increasing the relaxation parameter (solid to shaded line) tends to linearize the IVR segment and shifts peak negative \( dP/dt \) to a higher pressure value (H). See text for details. [Figure adapted from Chung and Kovács (20) with permission.]
where \( \mu \) is a parameter that characterizes cross-bridge relaxation, and \( E_\alpha \) is a stiffness parameter that characterizes elastic stiffness. Thus the model proposed in Eq. 3 accommodates inertia (\( d^2P/dt^2 \)), a surrogate of forces due to relaxation (\( 1/\mu \times dP/dt \)), and a surrogate of forces due to stiffness (\( E_\alpha (P - P_0) \)).

The solution for \( P(t) \) takes the form of damped oscillatory pressure decline, and this model accurately fits both linear and curvilinear shapes (Fig. 2, D–F). Mathematically, the two empirical fits (Eqs. 1B and 2B) and our physiological model (Eq. 3) of isovolumic pressure decline have clear similarities. Importantly, our model encompasses the empirical models’ features (linear vs. curved IVR PPP segments) as parametric limits of a single stiffness-relaxation model.

Significance of including elastic recoil during IVR. The primary benefit of a physiological model of IVR that includes both relaxation and elastic recoil terms is in accounting for the known physiology, in addition to accurately fitting the IVR pressure data. Specifically, the model proposed in Eq. 3 explains why PPP contours can change shape. A linear IVR PPP segment is one where the relaxation parameter (1/\( \mu \)) is large compared with the elastic term (\( E_\alpha \)). As the elastic term increases, the IVR PPP segment becomes more curvilinear.

It is the balance between relaxation and elastic recoil that ultimately determines the global pressure decay and the resultant measurement of DF. For example, another common index of pressure decline is peak negative dP/dt. The empirical fit models, particularly the monoexponential fit, provide no guidance or prediction with respect to peak negative dP/dt; mathematically speaking, peak negative dP/dt is undefined from the monoexponential fit equations. In contrast, our model (Eq. 3) is able not only to fit isovolumic pressure decline at pressures after peak negative dP/dt, as the other models, but can also fit pressure data before peak negative dP/dt. It, therefore, accounts for a larger segment of IVR than either of the empirical fits (Eqs. 1 and 2). Increasing stiffness will increase the magnitude of peak negative dP/dt, while slowing relaxation will reduce it (Fig. 2, G and H) (20). In addition, Eq. 3 reveals that peak negative dP/dt is insulated at the instant when \( d^2P/dt^2 = 0 \), requiring that the recoil and restoring forces balance at that instant (Fig. 2). This is just one example of the power and value of a more complete accounting of the physiology by inclusion of stiffness and relaxation terms.

Diastolic (dys)function during IVR. Normal DF during IVR inscribes a rapid pressure decline that is modulated by both cross-bridge relaxation and elastic recoil. Traditional rate constants (\( \tau_\alpha \)) oversimplify the physiology by ascribing a single parameter that is generally interpreted as accounting for only cross-bridge uncoupling (13, 69). Yet the time course of pressure decline must be determined by both cross-bridge and elastic recoil. If elastic recoil did not play a role during relaxation, one might assume that \( \tau \) would be unchanged if a heart were constrained to remain static and not allowed to move or untwist during diastole. This mechanical limit should only affect elastic recoil and not cross-bridge relaxation. However, Iwasaki et al. (45) recently showed the opposite: if elastic recoil is inhibited by limiting the apical rotation of the LV, pressure decline is slowed. This observation underscores the important interplay between cross-bridge function and elastic recoil, and it adds to our understanding of diastolic dysfunction, since hearts with dysfunction often have reduced elastic recoil. Thus optimal treatment of diastolic dysfunction, at a specific intravascular volume state, must aim for normalization of both cross-bridge uncoupling/relaxation and elastic recoil.

**Early Rapid Filling**

The cross-bridge uncoupling/relaxation and elastic recoil forces that manifest as shape change and pressure decay during IVR continue after MVO. The result is generation of an atriocentric pressure gradient that initially accelerates, and then decelerates, transmitral flow through early rapid filling. This transmitted blood flow can be visualized by Doppler echocardiography as the Doppler E-wave (78). During IVR, the helically woven myocardial layers slide past each other and generate an untwisting shape change: they cannot significantly lengthen. MVO allows for a significant lengthening of the myocardial fibers, and it introduces an inertial load for the global restoring and resistive forces to act on as the ventricle begins to aspirate atrial blood.

Physically, this has two effects. First, after MVO, LV pressure continues to decline below LA pressure so that the pressure gradient initiates filling (22, 23). Second, the ventricular volume increases dramatically. The drop in pressure with simultaneous rise in volume generates a negative slope in the pressure-volume plane (dP/dV < 0). Although controversy remains regarding the exact terminology and mechanism (11, 112, 127), L. N. Katz concluded that dP/dV < 0 proves “that the ventricle not only can but does exert a sucking action...” (50). This definition of mechanical suction (dP/dV < 0) is consistent with fluid dynamics, requires only that the LV pressure be lower than the source (atrial) pressure for filling, and is therefore independent of and unrelated to the atmospheric pressure. Furthermore, because LV pressure continues to decrease in all hearts at, and for a while after MVO, this definition ensures that mechanical suction is always operative during initiation of early rapid filling.

**Indexing filling with stiffness alone.** One well-known index of DF is the E-wave DT. In 1995, DT was proposed as an index of compliance (inverse of stiffness, \( DT = 1/\sqrt{K_LV} \)), where \( K_LV \) is LV chamber stiffness (65). This model is based on the reasonable physical assumption that the chamber property responsible for decelerating transmitral flow after the peak of the E-wave (Epeak) is chamber stiffness. This model includes stiffness, but no relaxation effects, and predicts that the deceleration portion of E-waves, starting at Epeak, should be well fit by the familiar, concave downwards, cosine function.

Although initial in vivo canine studies demonstrated the predicted correlation between DT and invasively derived stiffness (65, 86), there are several limitations to a stiffness-only approach. First, E-waves with long deceleration tails that markedly differ from the stiffness-only predicted cosine function are often encountered in clinical practice. Indeed, grade 1 diastolic dysfunction, termed a “delayed relaxation” pattern, consists of a prolonged DT, which exhibits an inflection point followed by convex (“cup-up”) rather than concave (“cup-down”) cosine shape (80, 98). It seems inconsistent for the deceleration portion of early filling, on the one hand, to be characterized by elastic stiffness only and, on the other hand, to be clinically referred to as manifesting relaxation-related dysfunction. An additional limitation is that a stiffness-only model would predict that two ventricles with indistinguishable cham-
ber stiffness should have indistinguishable DT. However, using simultaneous echocardiography and micromanometric pressure-volume catheter measurement, two E-waves from two different subjects having the same DT had different chamber stiffness (Fig. 3A) (64, 113). This indicates that a stiffness-only model for DT does not completely account for the determinants of diastolic physiology and cannot accurately account for the full range of clinically observed E-waves.

Model of filling with stiffness and relaxation parameters. Inspired by the suction-driven physiology of the filling ventricle and the need to explain the shape of E-wave contours, we proposed a model of diastole in 1985 that included both stiffness and relaxation components as determinants of early rapid filling (55). The parametrized diastolic filling (PDF) formalism approximates filling using a kinematic model having an equation of motion that includes inertial, resistive, and elastic forces. It has the form:

$$\frac{d^2x}{dt^2} + c \frac{dx}{dt} + kx = 0$$

(4)

where $x$ is displacement, $c$ is an index that characterizes relaxation, and $k$ is a term that characterizes stiffness. This is a well-known equation for the motion of an oscillating mass driven by a damped, linear spring. According to this model, the Doppler E-wave waveform is an inertial oscillation, analogous to the velocity of a damped spring with initial stretch that recoils from rest. The PDF parameters ($c$, $k$, and $x_o$) of the model can be uniquely extracted from mathematical analysis of any observed E-wave (Fig. 3). It is important to note that, unlike the PDF model, other more mathematically sophisticated nonlinear and multiparameter models of diastolic physiology do not allow for unique parameter extraction from clinically observed E-waves (85).

Just as with the stiffness and relaxation model of IVR above, the stiffness and relaxation model of the E-wave predicts different regimes of filling dynamics, depending on the relative values of model parameters. The “underdamped” regime, where the effects of stiffness exceed the effects of relaxation ($c^2 < 4k$), generates E-wave velocity waveforms that are fairly symmetric and appear nearly sinusoidal. The extreme limit where the stiffness term greatly exceeds the resistive term mathematically recapitulates the stiffness-only model of early rapid filling discussed above. On the other hand, the “overdamped” regime, where the effects of relaxation dominate the effects of stiffness ($c^2 > 4k$), generates asymmetric E-wave velocity waveforms with long deceleration tails, such as the delayed relaxation pattern associated with grade 1 diastolic dysfunction. Thus, just as described above regarding modeling IVR, while a stiffness-only model predicts only one kind of E-wave contour, a model of early rapid filling that accounts for stiffness and relaxation is able to account for the full range of clinically observed E-wave contours.

Physiology in a model with stiffness and relaxation. In addition to being consistent with the full range of clinically encountered E-waves, the PDF model parameters themselves, as well as indexes derived from the parameters, have useful physiological analogs. For example, the effect of cross-bridge uncoupling/relaxation and tissue viscosity on motion is accounted for by the model’s “damping constant” $c$.

Fig. 3. E-wave based DF quantification. A: two E-waves with same deceleration time (DT) but having different chamber stiffness [change in pressure ($\Delta P$)/change in volume ($\Delta V$)]. B: analyzing these E-waves via the parametrized diastolic filling (PDF) formalism quantifies DF differences between them, including the higher chamber stiffness $k$ in subject 1. C: the operational method for PDF-based E-wave analysis: select and digitize desired-wave image, select E-wave maximum velocity envelope, iteratively fit model-predicted contour to actual, selected contour by minimizing mean squared error, obtain PDF parameters, and measure of goodness of fit. The PDF parameters quantify chamber relaxation $c$, stiffness $k$, and load $x_o$. The parameters can be used to compute additional indexes of DF. For example, the initial peak pressure gradient, defined by the initial upslope (blue line) of the PDF-predicted (red) E-wave fit, can be calculated from the product ($kx_o$); the potential energy of filling ($1/2kx_o^2$) (see also Table 1) can also be computed. The method for quantifying IVR is similar, except that $dP/dt$ vs. $t$ is used as input in lieu of the maximum velocity envelope. See text for details. [Figure adapted from Shmuylovich and Kovács (113) with permission.]
The effect of intracellular and extracellular elastic molecules, such as titin, collagen, and elastin, is accounted for by the “spring constant” $k$. Finally, the volume load is accounted for by the initial displacement $x_0$ (55). Similarly, $kx_0$ is the analog of the initial atrioventricular pressure gradient that drives suction (3), and $1/2kx_0^2$ defines the potential energy residing within elastic elements that is available before valve opening and that drives filling (129).

These parameters have been used to facilitate diagnosis and provide mechanistic understanding of various clinical features and physiological scenarios (Table 1). One of the key insights provided by this conceptual framework is that early diastolic dysfunction can be associated with an increase in the parameter $c$, well before one might diagnose impaired relaxation based on DT alone (57, 100). The physiological consequence of this is that more of the potential energy that is available at the beginning of filling ($1/2kx_0^2$) is lost while overcoming an increase in resistive forces (77, 129). This formalism has also been used to show improvements in DF based on diet. Caloric restriction and low-sodium DASH (Dietary Approaches to Stop Hypertension) diets lead to a quantifiable decrease in myocardial stiffness and relaxation parameters, which indicates an overall improvement in DF.

**DF during early rapid filling.** Normal DF after MVO and E-wave onset is a continuation of cross-bridge uncoupling/relaxation and elastic recoil, which now includes a cardiohemic inertial load and physical interaction with the atrium through ascent of the plane of the mitral valve annulus.

There are potentially important molecular insights to be gained by measuring early rapid filling with the balance of stiffness and relaxation proposed in the PDF model (Eq. 4). Because filling is governed by the resultant effect of elastic recoil overcoming relaxation forces, we can make better predictions regarding how molecular changes might impact the

### Table 1. Clinical features and new insights for diastolic function characterization using stiffness and relaxation containing models that utilize physical properties of suction and pericardial constraint

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Benefits of Model Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological measure</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial stiffness</td>
<td>Predicts LV stiffness better than deceleration time alone (64, 113) and correlates highly with $dP/dV$ (58, 89)</td>
</tr>
<tr>
<td>Relaxation</td>
<td>Explains asymmetric pressure gradients during filling (113, 132) and relates physiologic indexes of resistance to flow (21).</td>
</tr>
<tr>
<td>Filling efficiency</td>
<td>The resistive forces of relaxation expend energy, which causes reduced filling efficiency (77, 114, 129)</td>
</tr>
<tr>
<td>Ventricular equilibrium</td>
<td>Diastasis defines the equilibrium volume of the left ventricle (130, 131)</td>
</tr>
<tr>
<td>Does E/E' predict LVEDP</td>
<td>Model can predict a linear E/E' vs. LVEDP relationship (63)</td>
</tr>
<tr>
<td>Pressure gradient</td>
<td>$kx_0$ is a better predictor of early filling pressure gradients than $4V^2$ (3)</td>
</tr>
<tr>
<td>Exercise tolerance</td>
<td>Model parameters predict exercise tolerance in patients with heart failure with reduced ejection fraction (71)</td>
</tr>
<tr>
<td>Heart sounds</td>
<td>Explains the presence or absence of the 3rd and 4th heart sound due to variable chamber stiffness (67, 70) and heart sounds below the threshold for hearing</td>
</tr>
<tr>
<td>Duration of diastole</td>
<td>Model-based properties predict duration of diastole and diastasis ($r^2 &gt; 0.98$) (18). Provides improved triggering precision for imaging</td>
</tr>
<tr>
<td>A-wave velocity</td>
<td>Model and physiological constraints provides a physically consistent measure of A-wave peak velocity when E- and A-waves are merged (HR &gt; 85 beats/min) (19)</td>
</tr>
<tr>
<td>Atrial filling</td>
<td>Left ventricular diastolic suction and constant volume attribute explain atrial filling via the pulmonary veins (9)</td>
</tr>
<tr>
<td>Intraventricular pressure gradient</td>
<td>Velocity of propagation ($V_p$) is a phase velocity, not a real velocity (110), and spatiotemporal features of stiffness and relaxation during IVR make $\tau$ recording location dependent in the LV (32)</td>
</tr>
<tr>
<td>Mitral annulus motion</td>
<td>Model explains mitral valve annulus velocity contour (101, 103)</td>
</tr>
<tr>
<td>Wall thinning</td>
<td>Constant volume attribute explains the relationship between wall-thinning and mitral valve annulus excursion (102, 104)</td>
</tr>
<tr>
<td>Mitral valve and pulmonary vein area</td>
<td>Constant volume allows for derivation of effective mitral and pulmonary valve area (7, 10). Impacts modeling of volumes/flow using MRI</td>
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<tr>
<td>Myocardial imaging</td>
<td>Myocardial integrated ultrasonic backscatter is associated with the initial pressure gradient ($kx_0$) and the balance between the elastic and relaxation properties ($c^2 - 4k$) (66)</td>
</tr>
</tbody>
</table>

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LV, left ventricle; LVEF, LV ejection fraction; CHF, congestive heart failure; PDF, parametrized diastolic filling; $c$, index that characterizes relaxation; $k$, term that characterizes stiffness; HFpEF, heart failure with preserved ejection fraction; DASH, Dietary Approaches to Stop Hypertension; $E'$, maximum velocity of the mitral valve annulus during early filling; $dP/dV$, change in pressure over change in volume; LVEDP, LV end-diastolic pressure; $x_0$, initial displacement of load; HR, heart rate; IVR, isovolumic relaxation; $\tau$, time constant of isovolumic relaxation.

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physiology. For example, it was shown that removing a viscous (resistive) force between titin and actin results in a reduced value for the resistive force parameter for early filling \( c \) (21). Furthermore, the inclusion of relaxation properties in a model of early filling suggests that cross-bridge-related factors also influence filling. Cross bridges are active at physiological temperatures (21, 54). Additionally, disease states such as obesity are related to reduced ATP availability, which might modify both calcium reuptake and cross-bridge detachment (49). However, cellular physiological studies directly linking the reduced ATP availability and early filling are lacking. Thus evaluating early filling as a balance between elastic recoil and relaxation might serve as a stimulus for studies involving the molecular mechanisms underlying relaxation.

**Physical Constraints**

Given the plethora of echo-derived indexes to quantify DF, be it \( E \), \( E' \), speckle tracking, or torsion, one may be left wondering how these different measures are related. After all, they are measuring the same global event or its regional aspects, one that is driven at multiple levels by the physics of damped recoil. Fortunately, the four-chambered heart’s (near perfect) constant-volume attribute provides tremendous insight into this question (8) and reveals the dominant causal connection between the multiple measures of DF, usually considered as unrelated.

\( E/E' \) is an important index that can be evaluated in this context. \( E/E' \) is the ratio between the maximum velocity of early rapid filling, measured via transmitral Doppler echocardiography, and the maximum velocity of the mitral valve annulus during early filling, measured via tissue Doppler echocardiography. This ratio is considered relatively “load-independent” and is often used as a noninvasive estimate or surrogate for increased end-diastolic pressure (29, 46). The correlation between \( E/E' \) and end-diastolic pressure was empirically observed, but, using the constant-volume attribute of the (left) heart, it is possible to derive an algebraic relationship between \( E \) and \( E' \) (63). To create a model that explains the relationship between \( E/E' \) and end-diastolic pressure, Lisauskas et al. (63) employed the constant-volume attribute by approximating the left heart as a cylinder of fixed external dimensions. The cylinder’s lower portion approximates the end-systolic LV as a thick-walled cylinder and upper portion approximates the thin-walled left atrium. The cylinder has constant volume, ensured by constant external dimension, and, therefore, ventricular filling is accompanied by vertical mitral annular displacement and LV wall thinning. A mathematical accounting of this volume conservation can be used to derive relationships between \( E \), \( E' \), and chamber dimensions. Extending these predictions through application of Hooke’s law yields a linear prediction between \( E/E' \) and LV end-diastolic pressure (LVEDP) that was validated using simultaneous echocardiography and micromanometric hemodynamic recording in 34 subjects \( (r = 0.92) \). This provides an example of the value of modeling and applying physiological constraints: instead of assuming an empirical or phenomenological relationship, the relationship between \( E/E' \) and LVEDP can be derived from first principles.

**Load Independence**

While \( E/E' \) can correlate with LVEDP, it fails to do so in some cases (94, 114), which limits its reliability as a load-independent index of DF. To address this limitation, we have derived and validated a load-independent index of DF by exploiting the balance between the cross-bridge uncoupling/relaxation and elastic stiffness forces (114). A set of E-waves acquired at different loads will have different shapes and, therefore, will have different values for the PDF parameters \( c \), \( k \), and \( \kappa_0 \) (Fig. 4). However, through mathematical analysis, it is possible to extract an index that remains constant, despite the variation in E-wave shape and the associated PDF parameters. The solution involves applying the PDF model to a set of

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**Fig. 4. Load-independent index of filling.** A: physiological load variation alters the E-wave by altering the balance between stiffness \( k \) and relaxation \( c \). The load-varying relationship between the peak elastic driving force of recoil \( (k\kappa_0) \) and peak resistive force \( (cE_{peak}) \) provides a load-independent index of filling \( (M) \), as the slope of the linear regression. \( B \): in a normal heart, elastic force of recoil \( k\kappa_0 \) \((y-axis)\) increases faster than the resistive force \( cE_{peak} \) \((x-axis)\). Whereas, when DF is abnormal, the filling recoil force cannot increase faster than the resistive force \( k\kappa_0 \) \((x-axis)\). The ordinate intercept \( B \) also defines the minimum elastic recoil force for filling. Abnormal DF is associated with a greater force requirement. \( B \), constant. See text for details. [Figure adapted from Shmuylovich and Kovács (114) with permission.]
load-varying E-waves to extract the initial peak driving force ($k x_o$) and the peak resistive force ($c E_{peak}$) for each measured E-wave. Plotting these values for each E-wave in a $k x_o$ vs. $c E_{peak}$ plot yields different individual points for each load-varying E-wave (Fig. 4). These points generate a single line, with a constant, and therefore load-independent, slope and intercept.

This finding can be explained mathematically. At the time of peak velocity the inertial term of Eq. 4 is zero and the therefore the resistive force would exactly balance the elastic driving force. Because the peak is achieved quickly, the elastic force at the peak can be linearly approximated in terms of the initial peak force, predicting that the plot of $k x_o$ vs. $c E_{peak}$ should yield a linear result:

$$k x_o = M(c E_{peak}) + B$$  \hspace{1cm} (5)

where $B$ is a constant, and $M$ is the load-independent index. We validated the predicted linearity of Eq. 5 in healthy subjects undergoing tilt table testing for load variation, as well as patients undergoing cardiac catheterization, where load variation was due to both significant respiratory variation and response to premature ventricular contraction (6, 114). In normal subjects, the peak driving force increases relatively more than the peak resistive force ($M > 1$) as preload increases. This suggests that, in normal hearts, the elastic restoring forces outperform the relaxation forces. However, in diastolic dysfunction subjects, this relationship is modified with $M < 1.0$, indicating that elastic forces are unable to compensate and overcome opposing relaxation forces in the face of changing load (Fig. 4).

The intercept, $B$, is the extrapolated point at which filling-related resistive forces vanish. It can be interpreted as the elastic restoring force that creates the pressure gradient to initiate filling in the context of residual IVR-related resistive forces alone, before filling-related resistive forces declare themselves. Patients with diastolic dysfunction show an increased intercept, indicating that chamber stiffness has increased to compensate for the abnormal relaxation. This is consistent with mechanisms present in clinical grading of DF, where myocardial stiffness is known to be increased as dysfunction progresses (98). Our model-derived, load-independent index of filling relationship shows that, to fulfill the chamber’s role in diastole as a volumetric suction pump (and thereby maintain cardiac output), stiffness must increase to compensate for impaired relaxation.

**Diastasis**

Another prediction of our conceptual framework is that the chamber pressure and volume at the end of the E-wave are physiologically important (130). At low heart rates (<85 beats/min in humans) E- and A-waves are separated by the diastatic interval (18). Before diastasis, the early-filling atrioventricular pressure gradient first accelerates and then decelerates blood. At diastasis, the atrioventricular pressure gradient is zero (22, 23), and there is no acceleration or deceleration of the chamber wall or blood. The time course of this pressure gradient, and the resultant final pressure, is quantified by the kinematic model of early filling (Eq. 4). As previously noted, the initial gradient is defined by $k x_o$ (3). The point at which LV pressure crosses LA pressure is defined by the balance between the relaxation and stiffness parameters (113, 132). A primary consequence of this work is that, if relaxation is slow or incomplete, the LV pressure does not rise (recover) much from

![Fig. 5. Model defined pressure gradient trends and pressures through early rapid filling and diastasis. A: LV filling is initiated by the time-varying atrioventricular pressure gradient ($\Delta P(t)$), based on the difference between the LVP and LAP. The kinematic model [$k x(t)$] can approximate the $\Delta P(t)$, with the peak driving force of the model ($k x_o$) being equivalent to the peak gradient ($\Delta P_{peak+}$). With delayed relaxation, relative to stiffness, the time point when LVP exceeds atrial pressure (pressure crossover) is delayed (and is equal to the deceleration time). The peak of the reverse pressure gradient ($\Delta P_{peak-}$) is, therefore, reduced, reducing pressure recovery relative to mitral valve opening pressure ($P_{MVO}$). B: the pressure recovery [diastatic pressure ($P_{Diastasis}$) relative to minimum pressure] in an LV with rapid, normal relaxation (left) is large, meaning $P_{Diastasis}$ is closer to the $P_{MVO}$ and end-diastolic pressure (LVEDP). However, when relaxation is delayed, LVP is unable to recover significantly, E-wave volume is decreased, and atrial filling is enhanced as a compensatory mechanism to preserve stroke volume. $P_{EDP}$, end-diastolic pressure; PPGR, peak pressure gradient ratio. See text for details. [Figure adapted from Zhang et al. (132) with permission.]](http://ajpheart.physiology.org/doi/10.1152/ajpheart.00436.2015)
its minimum pressure (Fig. 5), necessitating a larger compensatory Doppler A-wave to deliver the required filling volume.

Furthermore, during diastasis, tissue forces may be nonzero (87) but are in equilibrium, and, therefore, the ventricle is temporarily static. This force balance implies that the chamber volume at diastasis defines the equilibrium volume of the relaxed chamber. More importantly, the beat-to-beat variation of diastatic pressure and volume points can be fit linearly to provide the diastatic pressure-volume relation (DPVR), whose slope (dP/dV) provides passive chamber stiffness (131).

The DPVR has distinct advantages to the more familiar EDPVR. Consider that stiffness measured from the EDPVR must represent the combined effect of ventricular and atrial stiffness, because the atrial tissue is no longer passive but is at its end-systolic state (37, 55). Therefore, when heart rate is sufficiently low, the DPVR must be a more reliable metric of passive LV properties and less influenced by atrial properties than the EDPVR. Data supporting this intuitive argument show that, indeed, EDPVR is distinct from and typically defines a higher stiffness than the DPVR (131). Furthermore, the EDPVR is identical to the DPVR in the setting of atrial fibrillation, which indicates that the DPVR is an index determined by ventricular stiffness alone (75). Thus proper comparison of LV chamber stiffness between subjects with and without atrial fibrillation should utilize the (essentially) atrium-independent DPVR.

L-wave generation. In certain clinical circumstances, an apparent filling wave is observed during the diastatic interval. This wave is termed the “L-wave,” and, while it has been interpreted as pathological in patients with delayed relaxation and increased stiffness, it can also be observed in bradycardic patients with normal DF. It may appear that the presence of the L-wave during diastasis contradicts the chamber being at equilibrium; after all, how can there be transmural flow if there is a balance of forces? The key to resolving this apparent inconsistency is to carefully consider the physiology that determines the L-wave. Specifically, mitral valve leaflets can be open or closed during the L-wave (Fig. 6). When the leaflets transiently open during the L-wave, there is transmural flow, and the LV is not in equilibrium. This type of L-wave is thought to be associated with transmission of delayed right ventricular-generated flow (51) and may reflect diastolic dysfunction.

However, L-waves can appear even if the mitral leaflets remain closed (coapted) during diastasis. In this case, the LV is in equilibrium, and there is no net transmitral flow and zero net force. Instead, the L-wave is due to a toroidal vortex, or eddy, residing in the LV (52, 53). The inflow of blood creates the vortex, much like a smoke ring. Thus an L-wave that appears when the mitral leaflets remain closed during diastasis is the result of fluid mechanics. Because it is due to suction-initiated filling, we predicted that the right ventricle should also have L-waves if the Doppler sample volume is suitably located. This hypothesis was recently confirmed (30). This type of L-wave, where there is no leaflet separation, is, therefore, not an index of diastolic dysfunction, but is instead a predictable fluid mechanics consequence of early filling. It is present in every beat for both the left and right ventricles, but is only observed echocardiographically when the sonographer-defined sample volume happens to coincide with location of the early filling wave vortex ring’s reentrant portion.

**Left Atrium**

LA function is characterized according to LA reservoir, conduit, and pump attributes (9). LA size (or LA volume index) is an established index of DF (9, 106). Hence, atrial reservoir and conduit volumes, delivered via the pulmonary veins, are considered in the grading of DF (98). The physical laws and constraints noted above provide important insight into its function. Pulmonary vein flow occurs in three phases: inflow generated by ventricular systole (S-wave) generates “atrial reservoir volume”; inflow during ventricular diastole (D-wave) generated by ventricular suction generates “atrial conduit volume”; and, finally, regurgitation back to the pulmonary veins manifests during atrial systole (AR-wave). Impaired relaxation is associated with a reduced blood flow into the left atrium during diastole (decreased atrial conduit volume), while more significant diastolic dysfunction involves impaired systolic filling of the atrium (decreased reservoir volume) and increased regurgitation during atrial contraction (98).
The constant-volume attribute provides insight into atrial filling during ventricular systole (9). When the LV contracts, the closed mitral valve, its annulus, and the aortic root descend toward the apex, while the four pulmonary veins remain spatially fixed in the mediastinum. The descent of the annular plane and aortic root (which form the inferior and anterior boundary of the atrium) aspirates blood from the lung and generates the pulmonary vein S-wave (atrial reservoir volume).

Even though the left atrium is passive during this phase, ventricular systole causes the atrium to draw blood from the pulmonary circulation. Clinically, several grades of diastolic dysfunction involve impairment of LV longitudinal volume accommodation, manifesting as decreased pulmonary vein S-wave volume and associated decrease in mitral annular downward displacement (98) and \( E' \). Thus the clinical finding of reduced pulmonary vein flow is explained by the limited downward excursion of the mitral annulus and aortic root. In other words, the constant-volume property of the heart connects reduced S-wave pulmonary vein flow with decreased annular \( E' \) velocity.

Understanding the pulmonary vein D-wave (atrial conduit volume) brings together not just the volume constraints, but also a changing interaction between the cross-bridge relaxation and elastic stiffness properties of the LV. The pulmonary vein D-wave is simultaneous with the transmitral E-wave and is also initiated by ventricular suction (Fig. 7). Clinically, the D-wave is reduced during impaired relaxation, which also reduces diastolic suction (77, 129). As ventricular stiffness increases in more severe grades of diastolic dysfunction, the D-wave magnitude increases even though impaired longitudinal volume accommodation worsens (decreased \( E' \), decreased S-wave volume). This is because the ventricle compensates by relying on transverse volume accommodation associated with chamber remodeling, increased stiffness, and increased ventricular suction (3). This point is key. It is thought that relaxation is continuously impaired through all grades of diastolic dysfunction while myocardial stiffness progressively increases. Thus the initial reduction in D-wave magnitude is a result of increasing cross-bridge relaxation effects, which is then compensated for by progressively increasing stiffness.

Understanding these mechanisms also provides insight into the importance of LV DF as it relates to systole. First, consider the role of the LV as a “volume-pump” during diastole. Volume conservation for the left heart requires that volume leaving the left heart = volume entering the left heart for each cardiac cycle. Accordingly, LV (systolic) stroke volume = S-wave volume + D-wave volume. This shows that LV stroke volume (leaving the left heart) is always greater than simultaneous S-wave volume (entering the left heart). The difference between these two volumes is made up by the D-wave, which accounts for the \( \sim 5\% \) deviation from the constant-volume attribute of the four-chambered heart (9) and manifests as the “crescent effect” on cardiac MRI (120). If mitral annular displacement solely
GLOBAL DIASTOLIC FUNCTION

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accounted for LV filling, there would be no need for the D-wave. Thus mitral annular displacement cannot be the sole determinant of filling, as recently claimed (2).

Constant-volume physiology also clarifies that, although atrial size (best measured at diastasis) is an atrial anatomic feature, “left atrial reservoir volume” and “left atrial conduit volume” are dynamic quantities and are both directly generated by the LV, while the atrium remains passive. Only atrial pump function, which generates the transmirtal Doppler A-wave and pulmonary vein AR-wave, is a reflection of actual, active atrial function.

How To Measure DF

DF is the result of the continuous interaction between elastic recoil forces seeking to return the end-systolic ventricle to its diastatic (equilibrium) volume, and opposing cross-bond uncoupling/relaxation forces, together constrained by volume-conserving physical laws that couple the ventricle to the atrium. Measurement of DF during early filling is achieved by solving the “inverse problem of diastole” that uniquely determines chamber properties from E-waves via the PDF formalism (56, 76). The conceptual framework reframes pressure decline during IVR as the result of elastic recoil forces being “unmasked” by relaxation. The same process and interaction between elastic and resistive forces in early rapid filling generates diastolic suction and achieves mass transfer (inertial load) from atrium to ventricle. The physical, constant-volume constraint imposed by contents of the pericardial sac provides important insight into the relationship of ventricular function to atrial “function.” Understanding these principles guides our approach for how to measure DF.

What Global DF Is and Is Not

Relying on basic principles, we have presented IVR and E-wave generation as a physical problem amenable to mathematical modeling (20, 55), rather than a set of events to be characterized observationally (80, 88, 98). The key insight for these mathematical models is that DF represents an interaction between elastic stiffness and myocardial relaxation. Conventional global indexes still in use, such as τ, E/A, and DT, are the result, rather than the cause, of this interplay and cannot effectively quantify relaxation or stiffness independently. In contrast, the framework presented in this review allows the effects of, and interplay between, stiffness and relaxation to be appreciated, and, therefore, our approach provides a useful and physiologically legitimate way to quantify global DF. Application of this framework results in increased sensitivity and specificity in the clinical arena (57, 72, 77, 99, 100) and new precision and prediction of molecular and physiological phenomena (21, 31, 32, 66, 128).

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


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