Stiffness- and relaxation-based quantification of radial left ventricular oscillations: elucidation of regional diastolic function mechanisms

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Riordan MM, Kovács SJ. Stiffness- and relaxation-based quantitation of radial left ventricular oscillations: elucidation of regional diastolic function mechanisms. J Appl Physiol 102: 1862–1870, 2007. First published January 25, 2007; doi:10.1152/japplphysiol.01219.2006.—Traditionally, global and longitudinal (i.e., regional) left ventricular (LV) diastolic function (DF) assessment has utilized features of transmitral Doppler E and A waves or Doppler tissue imaging (DTI)-derived mitral annular E’ and A’ waves, respectively. Quantitation of regional DF has included M-mode echocardiography-based approaches and strain and strain rate imaging (in selected imaging planes), while analysis of mitral annular “oscillations” has recently provided a new window into longitudinal (long-axis) function. The remaining major spatial degree of kinematic freedom during diastole, radial (short-axis) motion, has not been fully characterized, nor has it been exploited for its potential to provide radial LV stiffness ($k_{rad}$) and relaxation/damping ($c_{rad}$) indexes. Prior characterization of regional (longitudinal) DF used only annular E’- and A’-wave peak velocities or, alternatively, myocardial strain and strain rate. By kinematically modeling short-axis tissue motion as damped radial oscillation, we present a novel method of estimating $k_{rad}$ and $c_{rad}$ during early filling. As required by the (near) constant-volume property of the heart and tissue/blood incompressibility, in subjects ($n = 10$) with normal DF, we show that oscillation duration-determined longitudinal ($k_{long}$ and $c_{long}$) and radial ($k_{rad}$ and $c_{rad}$) parameters are highly correlated ($R = 0.69$ and $0.92$, respectively). Selected examples of diabetic and LV hypertrophic subjects yield radial ($k_{long}$ and $c_{rad}$) parameters that differ substantially from controls. Results underscore the utility of the incompressibility-based causal relation between DTI-determined mitral annular long-axis (longitudinal mode) and short-axis (radial mode) oscillations in healthy subjects. Selected pathological examples provide mechanistic insight and illustrate the value and potential role of regional (longitudinal and radial) DF indexes in fully characterizing normal vs. impaired DF states.

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Characterization of left ventricular (LV) diastolic function (DF) has gained increasing importance in recent years because of the recognition that heart failure can stem from impaired filling (i.e., diastolic) function as well as impaired contractile (i.e., systolic) function. Indeed, so-called diastolic heart failure (DHF) (40) accounts for 40–50% of heart failure (31). Furthermore, survival rate of subjects with DHF is similar to that of subjects with systolic heart failure 1 and 5 yr after diagnosis (5, 28). These statistics underscore the importance of identifying the presence and severity of diastolic dysfunction (DD) as early as possible so that therapies can be instituted before LV chamber function is irreversibly impaired.

Diagnosis of diastolic dysfunction. There is considerable evidence that DHF and even DD stem from abnormalities in LV stiffness and relaxation (18, 41). However, diagnosis of DHF and DD is largely empirical and relies on numerous echocardiographic- and MRI-derived phenomenological indexes that do not quantify and, in many cases, are not related to stiffness- and relaxation-based chamber properties. Although many of these indexes have demonstrated utility on the basis of clinical correlation, they lack the mechanistic advantage of causality-based indexes derived from conceptual/physiological principles that have also been validated in vivo.

Current state of DF analysis. Noninvasive assessment of DF is conventionally achieved by two-dimensional pulsed Doppler echocardiography (1, 25). Geometric features of the transmitral flow pattern that have been previously correlated with the presence of DD, such as the ratio of peak E- to A-wave velocity (E/A), E-wave deceleration time (DT), acceleration time (AT), and E-wave velocity-time integral (VTI) are usually determined. However, because these global indexes neglect the information content of the entire curvilinear shape of the E wave, in addition to being load dependent, their utility in characterizing the intrinsic stiffness and relaxation properties of the LV is limited.

In part because of these limitations, Doppler tissue imaging (DTI) is commonly incorporated into echocardiographic examinations. With the sample volume positioned at the (septal or lateral) mitral annulus, continuous annular velocity can be recorded. During early rapid filling, the E’ wave is inscribed, and during atrial filling, the A’ wave is inscribed. Since the apical epicardium remains essentially spatially fixed during the cardiac cycle relative to sternal structures, annular velocity is a direct measurement of the rate of change of LV dimension in the long-axis (longitudinal) direction. Thus, if $E’ = dL/dt$, where $L(t)$ denotes the long-axis dimension of the ventricle and $t$ is time. Although DTI is useful in facilitating detection of abnormalities that may be undetectable via conventional shape-based analysis of the transmitral flow pattern, its use is similarly limited to that of conventional Doppler echocardiography. The only commonly determined DTI-based indexes are E’, A’, E/A’, and E/E’, all of which are computed from one or two points of the entire annular velocity contour. Therefore, information contained in the curvilinear E’-wave contour is neglected. Nevertheless,
DTI has become a routine component of the standard echocardiographic examination. E/E', in particular, has been correlated with LV end-diastolic pressure (LVEDP), and the observed correlation has been causally elucidated via kinematic modeling and the constant-volume attribute of the heart (20).

Although DTI can, in principle and in practice, be applied to short-axis (radial) myocardial motion and has been used to quantify radial myocardial velocity (11, 27), several technical considerations contribute to the noise and unreliability of DTI-generated radial velocity contours. As a result, short-axis DTI is not performed as part of a standard echocardiographic examination. However, short-axis M-mode and color M-mode echocardiography are commonly incorporated into standard echocardiographic examinations to determine LV dimension, mass, and fractional shortening. Although M-mode echocardiography displays myocardial positional, rather than velocity, contours (even though color M-mode echocardiography provides a rough estimate of myocardial velocity at all time points), it contains information on intrinsic, short-axis LV properties. The measurements routinely obtained from short-axis M-mode or color M-mode echocardiography are wall thickness and chamber dimensions; in addition, the only index of LV function routinely derived from short-axis M-mode echocardiography is a systolic function index, i.e., fractional (radial) shortening. Thus short-axis (radial) DF remains incompletely characterized, particularly in contrast to long-axis (longitudinal) DF characterization.

Cardiac anatomy and modeling. As in prior work (9, 20), for conceptual simplicity, the kinematics of radial myocardial motion can be appreciated if we consider the simultaneous radial and longitudinal expansion of an idealized, two-chambered left heart modeled as a right circular cylinder with a fixed height and fixed outer (epicardial) dimension but with variable inner (endocardial) dimension (Fig. 1). The cylinder is subdivided into an upper, atrial outer (epicardial) dimension but with variable inner (endocardial) modeled as a right circular cylinder with a fixed height and fixed can be appreciated if we consider the simultaneous radial and

\[
\frac{dV}{dt} = 2\pi r L_V \left(\frac{dr}{dt}\right) + \pi r^2 \left(\frac{dL_V}{dt}\right)
\]

where the first term includes the rate of endocardial displacement in the radial (short-axis) dimension and the second term includes the rate of longitudinal displacement of the mitral annulus, which is routinely measured by DTI as E'. Because the epicardial dimension is essentially constant throughout filling in normal subjects (9, 20), expansion of the LV in the longitudinal dimension with concomitant wall thinning is the dominant kinematic degree of freedom during filling in the normal heart. A recent cardiac MRI study (37) demonstrating that the ~5% decrease in pericardial sac volume during mechanical systole is recovered by an increase in the radial dimension of the epicardial-pericardial junction during early filling ("crescent effect") supports this view.

The myocardial (tissue) volume (MV) of the LV, given the cylindrical model, is

\[
MV = \pi R^2 L_V - \pi r^2 L_V
\]

By invoking myocardial incompressibility (conservation of MV), we obtain the following expression

\[
\frac{dMV}{dt} = \frac{d}{dt}(\pi R^2 L_V - \pi r^2 L_V) = 0
\]

Since the epicardial dimension R is treated as a constant, Eq. 4 simplifies to

\[
\frac{dr}{dt} = \frac{(R^2 - r^2)}{2r L_V} \frac{dL_V}{dt}
\]

This result, based on incompressibility and simplified geometry, provides mechanistic insight. The sign of the differential

Fig. 1. Atrioventricular geometry of the normal left heart idealized as a constant-volume cylinder with fixed height and cross-sectional area, allowing for longitudinal (long-axis) motion of the mitral annulus with simultaneous wall thinning as the primary mechanism of filling volume accommodation. A: ventricular systole. B: ventricular diastole at the end of early rapid filling. Note increased length of the left ventricle (LV), due to atrially directed annular motion, and thinner LV walls, as required by conservation of tissue mass/volume. Epicardial dimensions remain constant during diastole. \(L_V\), ventricular segment length; \(L_A\), atrial segment length.
quantities is the same; therefore, when the LV lengths during filling, the radial dimension must also increase. Equation 5 also shows that the two spatial rates of change of dimension (dr/dt and dLv/dt) are related by a coefficient that depends on the geometry (i.e., shape) of the chamber. Stated differently, within the assumptions of the derivation, longitudinal motion of the mitral annulus and chamber geometry determine endocardial radial motion. It follows from these assumptions that the myocardium is treated as a homogeneous, isotropic material with no “internal” structure (i.e., fiber orientation within the wall is not considered).

Recent work has shown that, in analogy to kinematic modeling of the E wave, the longitudinal motion of the mitral annulus during early filling can be modeled in accordance with damped simple harmonic oscillatory (SHO) motion (32). As LV pressure falls during isovolumic relaxation, the residual strain energy stored in the tissue during the previous systole overcomes decaying systolic forces until, at mitral valve opening, mechanical suction (dP/dV < 0, where P is pressure and V is volume) aspirates atrial blood into the chamber accompanied by simultaneous longitudinal motion (actually, ringing) of the mitral annulus and radial wall thinning. This model, the parameterized diastolic filling (PDF) formalism (19), applied to the motion of the annulus, utilizes the equation of motion for a damped SHO

$$m \left( \frac{d^2x_{\text{long}}}{dt^2} \right) + c_{\text{long}} \left( \frac{dx_{\text{long}}}{dt} \right) + k_{\text{long}} x_{\text{long}} = 0 \quad (6)$$

where $x_{\text{long}}$ is the displacement of the annulus in centimeters, $m$ denotes the inertial term, and $c_{\text{long}}$ and $k_{\text{long}}$ are lumped parameters that denote the relaxation/damping constant and spring constant of the system, respectively. All parameters can be normalized for mass, $m$, eliminating $m$ as an explicit variable (19). When fit to the velocity contour of the mitral annulus obtained via DTI, the expression for velocity obtained by solving Eq. 6 uniquely quantifies longitudinal stiffness ($k_{\text{long}}$), relaxation/damping ($c_{\text{long}}$), and stored elastic strain ($x_{\text{long}}$, initial longitudinal displacement) at the onset of early filling. It also naturally predicts the frequently observed oscillatory motion (i.e., “ringing”) of the mitral annulus back toward the LV apex after its initial atrially directed motion (E” wave) (16, 32, 38). In modeling terms, oscillations are the result of underdamped ($c_{\text{long}}^2 - 4mk_{\text{long}} < 0$) kinematics.

Although the PDF formalism as applied to the longitudinal motion of the mitral annulus permits, for the first time, quantitation of longitudinal myocardial stiffness and relaxation/damping, the kinematic paradigm of SHO motion can be similarly applied to radial (short-axis) myocardial motion during early filling because of the constant volume of the myocardium (6). Equation 5 demonstrates that the rate of LV cavity expansion in the radial dimension (i.e., radial velocity) is a function of the rate of LV elongation (i.e., mitral annulus velocity, E’). Therefore, it is reasonable to model radial kinematics using the paradigm of damped SHO as well. The resulting equation of motion in the radial dimension is

$$m \left( \frac{d^2x_{\text{rad}}}{dt^2} \right) + c_{\text{rad}} \left( \frac{dx_{\text{rad}}}{dt} \right) + k_{\text{rad}} x_{\text{rad}} = 0 \quad (7)$$

where the parameters are defined similarly to those in Eq. 6 (i.e., $x_{\text{rad}}$ is radial displacement and $k_{\text{rad}}$ and $c_{\text{rad}}$ denote radial stiffness and relaxation/damping, respectively). The SHO paradigm also permits testing of the model-predicted phenomenon of diastolic radial ringing of the LV chamber in the short-axis dimension, as has been observed in the longitudinal dimension, and assessment of its physiological significance.

**METHODS**

**Subject selection.** A sample of 10 subjects (the control group, 7 men and 3 women) was selected from an existing database (21) that includes simultaneous high-fidelity (Millar) ventricular pressure, Doppler echocardiographic recordings of transmural flow, DTI recordings of the velocity of the lateral mitral annulus, and color M-mode recordings of short-axis LV wall motion. The subjects were 29–61 (50 ± 13) yr old. Demographic information for the group is provided in Table 1. Inclusion criteria included a normal (i.e., ±50%) LV ejection fraction (EF), normal LVEDP (≤20 mmHg), 1 < E/A < 2, and normal DT (<220 ms) (29). Subjects were also required to be normotensive, in normal sinus rhythm, have normal valvular function, and have clearly discernible E’ and A’ waves on DTI and clearly discernible color bands on color M-mode echocardiography of the LV posterior wall on short-axis views. Subjects with comorbidities including, but not limited to, previous myocardial infarction, wall motion abnormalities on ventriculography, diabetes, nontrivial coronary artery disease (CAD) or active ischemia, cardiomyopathy, congestive heart failure, or renal insufficiency were excluded. Two additional subjects, one with diabetes and one with hypertrophic cardiomyopathy, were selected from the database for illustrative purposes to compare radial stiffness and relaxation/damping index magnitudes with those of the control group. The diabetic subject typifies DD, having elevated LVEDP (25 mmHg) and a normal EF; this subject also was being treated for hypertension and CAD. The subject with hypertrophic cardiomyopathy had an EF of 45% and elevated LVEDP (20 mmHg). Although this EF is below normal as defined in this study, 45% is often considered the cutoff value for normal vs. impaired LVEF (29). Because all subjects in the control group and, to a lesser extent, the two pathophysiologically examples exhibited longitudinal (anular) and radial oscillations, an additional subject without longitudinal or radial oscillations on any recorded beat was also selected from the database solely for illustrative comparison. This subject had a normal EF, slightly elevated LVEDP (18 mmHg), and significant triple-vessel CAD. Elective cardiac catheterization was performed in all subjects at the request of their referring physician on the basis of suspected CAD. All subjects gave informed consent in accordance with a protocol approved by the Washington University Medical Center Human Studies Committee (Institutional Review Board) before data acquisition.

**Data acquisition.** The simultaneous echocardiography-catheterization method has been described previously (3, 21). Briefly, immedi-

| Table 1. Demographic and clinical variables for control subjects |
| --- | --- | --- |
| Age, yr | Mean (SD) | Range |
| 50 (13) | 29–71 |
| BMI, kg/m² | 30.6 (5.0) | 19.2–36.5 |
| EF, % | 73 (11) | 52–88 |
| HR, beats/min | 63 (6) | 55–70 |
| LVEDP, mmHg | 16 (4) | 10–20 |
| E/A | 1.30 (0.26) | 1.01–1.83 |
| DT, ms | 166 (25) | 131–203 |

Values represent data from 7 men. BMI, body mass index; DT, deceleration time; E/A, ratio of peak E- to A-wave velocity; EF, ejection fraction by ventriculography; HR, heart rate; LVEDP, left ventricular end-diastolic pressure.
ate before cardiac catheterization, a full two-dimensional echo-Doppler examination was performed in the catheterization laboratory. Transmitral flow velocity acquisition was performed simultaneously with LV pressure recording, as previously described. None of the control subjects had substantial (>50%) narrowing of any coronary arteries or active ischemia. After advancement of the micrometeorometric 6-Fr pigtail catheter (model SPC-474A, Millar Instruments, Houston, TX) into the LV, transmitral Doppler images were obtained using a standard clinical imaging system (Acuson, Mountain View, CA) with a 4-MHz transducer. With the subject supine, apical four-chamber views were obtained with the sample volume gated at 1.5–2.5 mm and placed at the tips of the mitral valve leaflets. Color Doppler was used as a guide to orient the sonification direction orthogonal to the valve plane. The wall filter was set at 125 or 250 Hz with the baseline adjusted to take advantage of the full height of the cathode ray tube display, and the velocity scale was adjusted to exploit the dynamic range of the output without aliasing. Simultaneous limb lead II ECG was displayed on all images, which were captured simultaneously with LV pressure and recorded continuously via VHS or magneto-optical disk. DTI was performed with the sample volume gated at 5 mm and positioned at the lateral aspect of the mitral annulus. Color M-mode imaging was performed in the parasternal short-axis view just above the tips of the papillary muscles. All images were digitized offline via a dedicated custom video capture station.

Doppler analysis. For each subject, three to five cardiac cycles of transmitral flow, mitral anular motion via DTI, and short-axis wall motion via color M-mode echocardiography were selected, clipped, and imported into Paint Shop Pro 7 (Jasc Software, Minnetonka, MN) for analysis. Before analysis, transmitral flow and DTI frames were converted to eight-bit gray-scale images. Heart rates were similar (i.e., within 10%) for analyzed DTI and color M-mode beats for all subjects. Peak E- and A-wave velocities were measured manually, and E/A was computed and averaged for each subject. Peak E’- and E’-wave velocities, their durations, and the separation in time between the E’- and E’-wave peaks were measured manually from DTI and averaged. Finally, the temporal duration (i.e., the width) of the adjacent blue and red bands corresponding to outward (epicardially directed) and inward (cavity directed) motion of the lateral wall during early filling (the radial analogs of the longitudinal E’- and E’-wave) were measured from color M-mode images. The initial portion of the blue band corresponds to the latter part of isovolumic relaxation associated with torsion (4) and, thus, does not provide information on radial stiffness and relaxation during early filling. This isovolumic relaxation (torsion-related) portion of the blue band can be reliably identified as the time from the onset of the blue band to the onset of a green band, denoting an abrupt increase in wall thinning velocity, which coincides with mitral valve opening and the onset of transmitral flow (E wave). The isovolumic relaxation portion defined in this manner was subtracted from the width of the entire blue band recorded for each beat, and the resulting width was averaged across the number of beats analyzed. For simplicity and in keeping with the uniform cylindrical geometric assumptions, septal wall motion was not included in the analysis.

From the known relation of the spring constant to the period of oscillation, longitudinal stiffness can be derived from annular E’-wave duration (E’dur_long) as $k_{long} = \pi^2/E’^2\text{dur}_{long}^2$. While this expression neglects relaxation/damping, we have found that $k_{long}$ is generally quite small relative to $k_{rad}$, as reflected by the nearly sinusoidal shape of most E’ waves (as opposed to E’ waves with prolonged deceleration portions) (32). Therefore, this expression provides an excellent estimate of longitudinal stiffness. Similarly, radial stiffness can be derived from the duration of the portion of the M-mode color band (reflecting outward wall motion) corresponding to the E’ (E’dur_rad). The resulting expression for radial stiffness is $k_{rad} = 4\pi^2/E’^2\text{dur}_{rad}^2$.

Longitudinal relaxation/damping can be determined from DTI by fitting a damped exponential from the peak of the E’ wave to the peak of the E’ wave (when present), resulting in the following expression: $c_{long} = -2\cdot\ln(E’_{peak}/E’_{peak})(t_f - t_0)$ (32), where $t_f$ and $t_0$ denote the times at peak E’- and peak E’-wave velocity, respectively. A component of this expression for $c_{long}$ specifically $1/(t_f - t_0)$, was used to approximate longitudinal relaxation/damping on the basis of previous work examining the same characteristic in longitudinal function (32). We defined radial relaxation/damping $c_{rad}$ analogously to this component of longitudinal relaxation/damping (32). However, since the timing of the radial E’- and E’-wave peaks is unknown, we instead express their separation in time in terms of radial E’- and E’-wave duration as follows: $c_{rad} = 2/(E’\text{dur}_{rad} + E’\text{dur}_{rad})$. While this expression assumes that the radial E’ and E’ waves are perfectly sinusoidal, this assumption is reasonable given that the longitudinal E’ and E’ waves examined in this and a previous study (32) are very nearly sinusoidal and because longitudinal and radial motion are coupled by myocardial incompressibility, as shown in Eq. 5. Figure 2 illustrates the calculation of radial stiffness and relaxation/damping indexes from color M-mode echocardiography.

RESULTS

The values of longitudinal and radial stiffness and relaxation/damping, as well as their ratios, for the control group and the selected pathophysiological examples are displayed in Table 2. Radial stiffness was greater than longitudinal stiffness, except for one subject (a control), and radial relaxation/damping exceeded longitudinal relaxation/damping, except in the subject with hypertrophic cardiomyopathy. In accordance with Eq. 5, longitudinal and radial stiffness were linearly correlated in the control group ($R = 0.69$), and longitudinal and radial relaxation/damping were also strongly correlated ($R = 0.92$; Fig. 3). The stiffness and relaxation/damping data points for the diabetic subject fell reasonably close to the regression lines for the control group, while those for the subject with hypertrophic cardiomyopathy did not. Values for longitudinal and radial stiffness for the diabetic subject were similar to the...
average values for the control group, but the radial relaxation/damping value was substantially higher (longitudinal relaxation/damping was comparable to the control group average) for the diabetic subject. Except for one control subject who had a slightly smaller value, the diabetic subject also had the lowest ratio of longitudinal to radial relaxation/damping. In the subject with hypertrophic cardiomyopathy, longitudinal and radial stiffness and relaxation/damping values were substantially elevated compared with those of the control subjects. Also, this subject had by far the greatest ratio of longitudinal to radial relaxation/damping, which was substantially higher than the control group average. The ratio of longitudinal to radial stiffness was somewhat elevated as well.

**DISCUSSION**

As required by Newton’s laws and by incompressibility and volume conservation, this study tests the hypothesis of, and confirms the existence of, radial myocardial oscillations (i.e., short-axis ringing of the LV) during early filling. These oscillations are predicted on the basis of the longitudinal oscillations during the E wave often exhibited by the mitral annulus (16, 32, 38) and coupling of longitudinal and radial motion via tissue/blood incompressibility. Modeling radial myocardial motion in analogy to a validated model of longitudinal motion of the mitral annulus (32) can accurately characterize this observed oscillatory behavior. The interesting fact that an additional subject chosen from the database did not exhibit longitudinal or radial oscillations on any recorded beat further reinforces the coupling of radial and longitudinal motion and the strong linear correlation between longitudinal and radial stiffness and relaxation/damping indexes predicted by Eq. 5.

Figure 4 shows a typical color M-mode echocardiogram and DTI display (as well as transmitral flow) for this subject and a representative control subject with longitudinal and radial oscillations to facilitate visual comparison.

The rationale for approximating radial relaxation/damping as the inverse of the time separation of the radial E\textsuperscript{−} and E\textsuperscript{+} wave peaks is based on theory and due to the reality that the peak velocities of the radial E\textsuperscript{−} and E\textsuperscript{+} waves cannot be reliably determined without application of an algorithm to the color M-mode image. Since the approximation for longitudinal relaxation/damping as the inverse of the time separation of the longitudinal E\textsuperscript{−} and E\textsuperscript{+} wave peaks was different between a group of diabetic subjects and age-matched controls that could not be differentiated on the basis of conventional echocardiographic or hemodynamic indexes (32), and because the physiological mechanisms that govern longitudinal and radial relaxation/damping are likely to be the same mechanistically, we believe that temporal separation of the peaks is appropriate for characterization of longitudinal and radial relaxation/damping.

For nearly all subjects, radial stiffness exceeded longitudinal stiffness (i.e., longitudinal E\textsuperscript{−}wave duration exceeded radial E\textsuperscript{−}wave duration). Although it may appear that the constraints imposed by myocardial incompressibility require essentially equal durations of longitudinal and radial oscillations, our simplified approximation neglects the known geometrically complex torsional and circumferential deformations that occur during early filling, as well as the associated fiber architecture and known temporal nonsimultaneity of tissue activation and relaxation. Furthermore, the fact that other studies (13, 26) have shown greater stiffness along the myofiber direction than in the cross-fiber direction (i.e., orthogonal to the fiber direction) appears to contradict our findings. However, these studies were either performed on excised myocardium or employed finite element models under the assumption of homogeneous transmural material properties. In reality, the endocardial and epicardial layers have different mechanical properties and the fiber architecture is less idealized than commonly assumed in these models.

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<tr>
<th>Table 2. Longitudinal and radial stiffness and relaxation/damping indexes and their ratios in controls and selected pathophysiological subjects</th>
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<tr>
<td><strong>Control Group</strong></td>
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<td>(n = 10)</td>
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<tr>
<td>Diabetic</td>
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<td>(k_{\text{long}}), g/s(^2)</td>
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<td>(k_{\text{long}}/k_{\text{rad}})</td>
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Values are means (SD). HCM, hypertrophic cardiomyopathy; \(k_{\text{long}}\) and \(k_{\text{rad}}\), longitudinal and radial LV stiffness, respectively; \(c_{\text{long}}\) and \(c_{\text{rad}}\), longitudinal and radial LV relaxation/damping, respectively.

Fig. 3. A: longitudinal stiffness (\(k_{\text{long}}\)) from E\textsuperscript{−}-wave duration on Doppler tissue imaging (DTI) vs. radial stiffness (\(k_{\text{rad}}\)) from radial E\textsuperscript{−}-wave duration on color M-mode echocardiography. Linear regression is as follows: \(k_{\text{long}} = 0.38 k_{\text{rad}} + 148.41 (R = 0.69)\). B: longitudinal relaxation/damping (\(c_{\text{long}}\)) from E\textsuperscript{−} and E\textsuperscript{+} wave duration on DTI vs. radial relaxation/damping (\(c_{\text{rad}}\)) from radial E\textsuperscript{−} and E\textsuperscript{+} wave duration on color M-mode echocardiography. Linear regression is as follows: \(k_{\text{long}} = 0.87 k_{\text{rad}} - 0.71 (R = 0.92)\). Regressions are based on data from controls. ●, Controls; □, diabetic subject; ○, subject with hypertrophic cardiomyopathy.
epicardial layers, which are stiffer than the underlying myocardium (26), influence radial myocardial motion and are considered to be important determinants of cardiac mechanics (17). Even more importantly, the pericardium restricts ventricular expansion during filling, as evidenced by the data reported by Chew et al. (8) revealing that the pericardium experiences considerable multiaxial strain in situ, even under conditions of minimal preload. The combination of all these effects on radial wall motion becomes manifest via color M-mode echocardiography. Annular DTI, on the other hand, displays motion only within the sample volume positioned at the mitral annulus, in a direction essentially orthogonal to possible pericardial motion. Therefore, for geometric reasons, the influence of the normal pericardium, the motion of which, if any, is radial, on (longitudinal) motion of the mitral annulus should be relatively minor. The radially oriented collagen struts connecting transmural myofiber layers are potential contributors to radial stiffness, but their experimentally determined stiffness exceeds myofiber stiffness (mediated, in part, by titin) at sarcomere lengths near the upper end of the chamber’s normal working range (12). Although we speculate that these sarcomere lengths were probably not attained in the control subjects in this study, who were imaged in the resting state and had ventricles with relatively normal preload, elucidation of their role awaits further work.

While this study is not the first to quantify radial myocardial stiffness, to our knowledge, it is the first to do so in vivo (just as for radial myocardial relaxation). Halperin et al. (14) determined the transverse (radial) stiffness of excised canine septa from the stress-strain curve derived from an indentation protocol. More recently, using a damped SHO model, Shishido et al. (34) determined time-varying radial myocardial stiffness by applying high-frequency sinusoidal vibration to the LV surface. On the basis of this model, stiffness was determined to be the intercept of the linear relation between the vibrational contact force and the square of the angular vibration frequency. These investigators found that their measure of radial stiffness differentiated between ischemic and nonischemic regions of the LV in a canine model, demonstrating the potential clinical utility of radial stiffness in characterizing segmental LV dysfunction.

Previous studies by our group have provided preliminary evidence that features of radial wall motion (specifically, the lateral LV wall) can differentiate between normal and pathological ventricles. Cook et al. (9) found that, while the color M-mode echocardiography-determined peak rate of lateral wall thinning during early filling correlated highly with model prediction for normal ventricles, this correlation was not maintained for pathological ventricles (likely, in part, because of abnormal radial wall motion patterns). More recently, we showed that displacement of the LV epicardial/pericardial boundary during diastole deviates substantially from its normal range in ventricles associated with pathophysiological states (33).

The two pathophysiological examples included in this study exhibited interesting segmental stiffness and relaxation properties compared with the controls. The fact that radial relaxation/damping in the diabetic subject was exceeded by that of only one control subject suggests that diabetes may be associated with increased values for radial relaxation/damping. We previously showed that both global relaxation/damping, in the form of parameter \( c_{\text{rad}} \) (10), and longitudinal relaxation/damping, in the form of parameter \( c_{\text{long}} \) (32), are increased in the diabetic heart, so this observation is reassuring. Since longitudinal relaxation/damping was only slightly elevated to unchanged in this subject, it is possible that radial relaxation/damping (\( c_{\text{rad}} \))...
may be a more sensitive index than longitudinal relaxation/damping (c_long) for characterizing DD in the diabetic heart.

Substantially greater longitudinal and radial stiffness in the subject with hypertrophic cardiomyopathy (and elevated LV EDV and elevated LV ESP) than in the controls is expected because increased LV mass and elevated LV ESP are associated with increased ventricular stiffness. Similarly, the elevated longitudinal and radial relaxation/damping in this subject are expected since hypertrophic cardiomyopathy is associated with myofiber disarray (36, 23) and interstitial fibrosis (23, 24), both of which should increase frictional losses. Other mechanisms, such as abnormal calcium handling, are reported to play a role as well (35, 39). The elevated LV EDV in this subject can also be associated with impaired relaxation. Interestingly, the ratio of longitudinal to radial relaxation/damping was higher in the subject with hypertrophic cardiomyopathy (the only subject in which it was >1) than in any other subject, suggesting less relative impairment of radial function in hypertrophic cardiomyopathy, or alternatively, the intriguing possibility that, to preserve stroke volume, radial function may compensate for impaired longitudinal function. The assumption of constant epicardial dimension R in Eq. 5 was not violated in this subject, suggesting that these findings are the result of intrinsic physiology rather than model simplifications.

While the segmental stiffness and relaxation/damping data points for the diabetic subject are close to the regression lines computed for segmental stiffness and relaxation/damping in the control group, the data points for the subject with hypertrophic cardiomyopathy are not. The strong correlation coefficients obtained for longitudinal and radial stiffness and relaxation/damping in the control group suggest that incompressibility couples longitudinal and radial myocardial motion, at least in the lateral LV wall, in a predictable manner in normal hearts. However, it is possible, perhaps even likely, that the slopes of the regression relations depend on fiber orientation and chamber geometry, both of which are altered in the presence of pathophysiology, including hypertrophic cardiomyopathy (36). Therefore, the ratios of longitudinal to radial stiffness and relaxation/damping may be useful indexes for characterizing these effects on segmental DF and, perhaps, identifying impaired DF before it can be detected by conventional measures. Future studies are needed to evaluate the clinical utility of these indexes in larger and more well-defined pathophysiological subgroups.

The importance of characterizing both longitudinal and radial function to identify subclinical LV dysfunction is highlighted by a recent study in which longitudinal and radial myocardial peak velocities were combined into a composite velocity that was able to differentiate ischemic and nonischemic LV segments better than either longitudinal or radial velocity alone (7). This study also found that the ratio of peak longitudinal to peak radial velocity was decreased in ischemic segments, suggesting compensatory radial function. While these investigators used a single point of the entire tissue velocity profile of each spatial degree of freedom, namely, longitudinal and radial peak velocities, as indexes of segmental function, it is expected that our modeling-derived indexes of longitudinal and radial stiffness and relaxation/damping should have superior sensitivity because of their characterization of the underlying kinematics in physiological terms.

It is well established that the third heart sound (S3) manifests at or near the peak of the transmural E wave and, as far as timing is concerned, may be related to oscillatory longitudinal or radial motion during E-wave deceleration. Although the timing of S3 relative to radial oscillations is favorable, the longitudinal and radial oscillations generally have a frequency below those reported for S3 (>20 Hz via phonocardiography). For instance, radial E’-wave frequency of the control subjects in this study was ~7.8 ± 1.8 Hz. Since longitudinal oscillations generally occur at even lower frequencies, they are unlikely to be the direct source of S3. However, it is reasonable and indeed attractive to speculate that, on the basis of timing alone, S3 and radial/longitudinal oscillations may be manifestations at different frequencies and may be transduced by different mechanisms of the same ultimate energy source.

Limitations. Because of the nature of M-mode imaging, the short-axis color M-mode data analyzed in this study were acquired only along the direction of the echo beam. Therefore, the resulting images reflect the motion of only the points at which the echo beam intersects the lateral and septal LV walls and, as such, do not convey potential azimuthal (torsional) variation in motion in the short-axis dimension. Similarly, DTI acquired at the lateral aspect of the annulus does not account for varying extents and patterns of motion at other annular sites. However, these factors do not alter the results of this study, inasmuch as longitudinal and radial stiffness and relaxation/damping were determined from the lateral wall. Nevertheless, we emphasize that the segmental stiffness and relaxation/damping indexes determined in this study reflect the motion of the lateral LV myocardium and that their values are likely to vary in other LV regions.

It is possible that sample volume positioning during DTI and echo beam orientation during color M-mode acquisition may affect the longitudinal annular motion contour and the time course of radial wall motion, respectively. However, the presence of longitudinal and radial oscillations, as well as their durations, should not be affected. Also, although the ratios of longitudinal to radial stiffness and relaxation/damping were computed from nonsimultaneous DTI and color M-mode images, they were obtained during the same recording session. Moreover, the averaging of these indexes from three to five cardiac cycles and the similar heart rates in each subject during DTI and color M-mode echocardiography should minimize its effect. Furthermore, while only high-quality color M-mode images with discernible radial E’ and E” waves were analyzed in this study, we caution that accurate estimation of radial stiffness and relaxation/damping depends critically on E’- and E”-wave duration. Determination of radial E”-wave duration is facilitated by the presence of the green high-velocity band coinciding with the onset of annular motion and early filling. Although we observed this green high-velocity band in all subjects included in the study, it is possible that it may be absent or difficult to reliably detect in certain subjects. In these cases, the time from the onset of the blue band on color M-mode echocardiography to the onset of the mitral annular E” wave on DTI should be determined from DTI and color M-mode images aligned by a fiducial marker, such as the R wave of the ECG.

Although the focus of this study is regional (specifically, radial) DF, it should be possible, in a theoretical sense, to derive global chamber properties of stiffness and relaxation/
damping from longitudinal and radial stiffness and relaxation/damping and suitable geometric assumptions. While the relation between these regional and global indexes will be geometry dependent, we believe that longitudinal and radial stiffness and relaxation/damping/viscoelasticity should sum in parallel (30) to yield the global chamber properties. However, to investigate the global-to-segmental stiffness relation that naturally arises from this work, we compared our longitudinal and radial measures of stiffness (k_{long} and k_{rad}, respectively) with LV stiffness (K_{LV}) calculated from E-wave deceleration time (22). The correlation between k_{long} and k_{rad} and K_{LV} was modest (R = 0.62 and 0.46, respectively). Because K_{LV} has been shown by Little et al. (22) to be linearly related to catheterization-determined chamber stiffness \( \Delta P/\Delta V \), we did not compute \( \Delta P/\Delta V \) from catheterization data as an independent measure of chamber stiffness but, rather, relied on DT to determine K_{LV}.

In this study, all subjects exhibited longitudinal and radial oscillations, i.e., ringing, or E' waves in each dimension, allowing computation of longitudinal and radial relaxation/damping according to the equations for c_{long} and c_{rad} (see METHODS). However, it is documented that longitudinal oscillations of the mitral annulus are not present in all subjects (16, 32, 38), a finding that can be extended to radial myocardial oscillations (probably in the same subjects), as observed in the additional subject who lacked oscillations in either dimension. While longitudinal relaxation/damping can be estimated under the assumption of critical damping, it is unclear how radial relaxation/damping can be computed from color M-mode echocardiography in the absence of the radial E' wave because of the lack of delineation of the end of the radial E' wave.

In three subjects in the control group, LVEDP was near 20 mmHg, which is above the range for normal DF, generally defined as LVEDP <18 mmHg, but is only slightly abnormal. Furthermore, E/A for each of these subjects was substantially <2, and DT was neither too short (140 ms) nor too long (>185 ms). These subjects did not exhibit a clear trend toward increased or decreased longitudinal or radial stiffness and relaxation/damping or their ratios, and, notably, exclusion of these subjects would have yielded improved correlations between longitudinal and radial stiffness (R = 0.84) and relaxation/damping (R = 0.94). Finally, although the pathophysiological examples had abnormalities other than diabetes and hypertrophy, these subjects were included for illustrative purposes to allow a preliminary order-of-magnitude comparison between longitudinal and radial indexes of stiffness and relaxation/damping. Accordingly, we emphasize that the present study was not intended to be, nor should it be interpreted as, a clinical study because of the small sample size.

In conclusion, kinematic modeling of radial wall motion during the E wave using the laws of damped oscillatory motion predicts short-axis diastolic ring of the LV and facilitates determination of indexes of radial stiffness and relaxation/damping. These correlate strongly with previously derived analogous indexes of longitudinal stiffness and relaxation/damping in controls. These indexes permit noninvasive characterization of radial DF in terms of stiffness and relaxation/damping. The radial DF characterization approach complements the longitudinal DF approach and permits quantitative elucidation of the relation between global (E-wave-derived) and segmental (longitudinal, radial) DF indexes. Analysis of radial and longitudinal kinematics during early filling as components of global DF provides novel insight into the spatial mechanisms of diastolic dysfunction in terms of radial and longitudinal motion. Specifically, the role of radial vs. longitudinal DF can be determined, and which spatial mode compensates for impairment of the other to maintain global chamber function can be assessed. Future studies are needed to investigate the effects of specific pathologies on radial and longitudinal LV stiffness and relaxation/damping and their relation to global indexes to fully evaluate the clinical potential of these indexes in characterizing the presence and severity of DD.

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