Online-only Appendix: Indices of LV relaxation, filling, diastolic
distensibility and diastolic LV stiffness – Mathematical and Methodological
Aspects.

**Time constant of LV relaxation (τ)**

When reporting a time constant of LV relaxation, the method used to calculate the
time constant (monoexponential\textsuperscript{165} or logistic\textsuperscript{166}) as well as the LV loading conditions
need to be considered. At heavy afterload and elevated preload\textsuperscript{100}, slow LV relaxation
raises LV filling pressures, even LV end-diastolic pressure\textsuperscript{167}. Such a reversible
slowing of LV relaxation at high LV loading conditions is especially relevant to
pulmonary edema in hypertensive crises\textsuperscript{102,168}. When high LV loading conditions are
present, loading manipulations are desirable to correctly assess LV relaxation
kinetics\textsuperscript{169}.

**Diastolic LV stiffness**

As the slope of the diastolic LV pressure volume relation varies, LV stiffness
values need to be compared at common levels of LV filling pressures\textsuperscript{170}. In many
experimental set-ups (e.g. before and during pacing-induced angina), a common level
of LV filling pressures cannot be defined as the LV filling pressures diverged too far
from one another as a result of the intervention. To overcome this problem, diastolic
LV stiffness is no longer assessed by the slope of the diastolic LV pressure-volume
relation at a common level of LV filling pressures but by the constant $b$ of an
exponential curve fit to the diastolic LV pressure (LVP)-volume (LVV) points:

$$ LVP = a \cdot e^{LVV \cdot b} + c $$

where $b$=constant of chamber stiffness and $a,c$= asymptote and intercept of the
relation. Such a curve fit can be applied to a single diastolic LV pressure-volume
relation or to a diastolic LV pressure-volume relation constructed from multiple LV pressure-volume loops during balloon caval occlusion. The latter offers the advantage of a more accurate curve fit as the diastolic LV pressure-volume points are more widely apart and most probably devoid of interference caused by diastolic continuation of LV pressure decay, early diastolic viscous forces related to LV filling and late diastolic atrial contraction. As previously mentioned, at heavy LV load, diastolic continuation of LV pressure decay can extend all the way to end-diastole\textsuperscript{100}. The mathematical validity of an exponential curve fit to the diastolic LV pressure-volume relation has been challenged\textsuperscript{171}. Nevertheless, this approach to measure LV stiffness is frequently used and can easily be achieved through logarithmic transformation of the exponential diastolic LV pressure-volume relation into a linear equation\textsuperscript{172-174}:

$$\ln(LVP-c) = \ln a + bLVV$$

where $b=$ constant of chamber stiffness and $a,c=$ asymptote and intercept of the relation. Mean value and upper range of the constant of chamber stiffness ($b$) in control subjects are 0.21 and 0.27\textsuperscript{175}.

\textit{Muscle Stiffness}

As the slope of the diastolic stress-strain relation varies, muscle stiffness under varying experimental conditions can only be compared at a common diastolic stress level. Since a common diastolic stress level is frequently absent, an exponential curve fit to the LV diastolic stress-strain data has been proposed to derive the constant of muscle stiffness ($b'$). After logarithmic transformation, the exponential relation between diastolic LV stress and strain is transformed into a linear equation\textsuperscript{172-174}:

$$\ln(\sigma-c') = \ln a' + b'\varepsilon$$
where \( b' \) = constant of muscle stiffness and \( a', c' \) = asymptote and intercept of the relation. The mean value of the constant of muscle stiffness \( (b') \), observed in a control group, equals \( 9.9 \pm 3.3 \)\textsuperscript{176}. A \( b' \) value > 16 provides diagnostic evidence for diastolic LV dysfunction.

Diastolic stress within the myocardium can be split into three orthogonal components, which are usually indicated as circumferential, longitudinal and radial stress. To overcome the geometrical assumptions involved in calculating circumferential or longitudinal wall stress, calculation of a radial myocardial stiffness modulus \( (E) \) was introduced by Mirsky et al. to assess myocardial material properties\textsuperscript{177,178}. The radial stiffness modulus was defined as follows:

\[
E = \frac{\Delta \sigma_R}{\Delta \varepsilon_R}
\]

and derived in the following way:

\[
E = \frac{\Delta \sigma_R}{\Delta \varepsilon_R} = \frac{\Delta P}{(\Delta h/h)} = -\frac{\Delta P}{\Delta \ln h}
\]

This derivation assumes the increment in radial stress \( (\Delta \sigma_R) \) to be equal but opposite in sign to the increment in LV diastolic pressure \( (\Delta P) \) at the endocardium, and the increment in radial strain \( (\Delta \varepsilon_R) \) to be equal to the increment in wall thickness \( (\Delta h) \) relative to the instantaneous wall thickness. Because \( \Delta h/h = \Delta \ln h \), \( E \) equals the slope of an instantaneous \( P \) vs. \( \ln h \) plot\textsuperscript{61,62,177-180}. The \( P \) vs. \( \ln h \) plot is obtained from corresponding echocardiographic wall thickness and LV diastolic pressure recordings. Agreement between \( E \) and diastolic LV stiffness measurements derived from an exponential curve fit to multiple end-diastolic LV pressure-volume points during caval occlusion has previously been reported in patients with dilated cardiomyopathy\textsuperscript{181}. The normal value of \( E \) equals \( 2.2 \pm 0.7 \) kN/m\(^2\)\textsuperscript{62}.

The slope of the myocardial stress-strain relation varies and a myocardial stiffness modulus therefore needs to be compared at equal levels of myocardial stress.
As previously explained, this obstacle can be overcome by fitting an exponential curve to the diastolic LV pressure-volume or the diastolic myocardial stress-strain relations and calculating the constant of chamber stiffness (b) or of muscle stiffness (b’). Another method proposed to overcome this problem is to define a corresponding level of LV pressure or myocardial stress in all experimental conditions by subtracting extrapolated LV relaxation pressure from measured LV pressure during the diastolic LV filling phase\textsuperscript{182} and by subsequently constructing diastolic LV pressure-volume or stress-strain relations using the residual diastolic LV pressure resulting from this subtraction procedure. The extrapolated LV relaxation pressure after mitral valve opening is derived from the exponential curve to isovolumic LV pressure decay used to calculate the time constant (\(\tau\)) of LV pressure decay. Although residual LV relaxation pressure decay during LV filling deviates from an exponential course because of myocardial re-lengthening\textsuperscript{183}, this approach to obtain corresponding levels of LV filling pressures or myocardial wall stresses has previously been applied in experimental or clinical ischemic heart disease\textsuperscript{177-179} and recently in diastolic heart failure\textsuperscript{19}.

*Use of Blood flow Doppler*

Numerous studies using mitral valve blood flow Doppler showed a variable outcome in terms of predictive value for HFNEF. In the multicenter setting, assessment of LV diastolic function by means of E/A ratio or IVRT had a good reproducibility on repetitive examinations\textsuperscript{112} with respective \(\rho\) values of 0.89 and 0.81. Despite this acceptable reproducibility, mitral valve blood flow Doppler criteria proposed by the original report of the European Study Group were fulfilled in only 43% of patients hospitalized for HFNEF\textsuperscript{113}. In this patient cohort, wall thickness was
increased in 75% of cases. These results come close to the 48% abnormal E/A ratio observed in a study that required evidence of increased wall thickness for the diagnosis of HFNEF and in a study of newly diagnosed heart failure. Poor concordance between blood flow Doppler measures of diastolic LV dysfunction and HFNEF has also been observed for other sets of diagnostic criteria of diastolic LV dysfunction. This poor concordance is not surprising since E/A ratio was no significant predictor (p=0.07) of serum NT-proBNP in patients with suspected heart failure and normal LV EF in contrast to left atrial volume index (p<0.001) and LV septal wall thickness (p<0.004). In hypertensive patients with exertional dyspnea and normal LV ejection fraction, both IVRT (p<0.05) and E/A ratio (p<0.02) were also only weakly correlated with serum BNP levels.

Use of Tissue Doppler (TD)

S and E’ measure contractile performance of long axis left ventricular fibers, who have a large contribution to LV EF because of their unique wrap around the LV cavity and are also important for LV torsion or twisting. S and E’ decline with age consistent with an age related increase in LV sfericity. They can be obtained with low inter-observer variability and have important prognostic value. In animal experiments close correlations have been observed between E’ and invasive indices of LV relaxation such as \( \tau \) (p<0.001) and LVdP/dt min (p<0.001). Furthermore, compared to E, E’ is relatively preload-insensitive, as evident from patients with relaxation abnormalities during saline loading or after nitroglycerin. E’ also correlates closely with an invasively measured time constant of LV relaxation(\( \tau \)), even in patients with atrial fibrillation, and with invasively measured LV end-diastolic pressure both at rest and during exercise. The relative
preload insensitivity of E’ is explained by a delay of E’ relative to E during the LV filling phase so that E’ occurs at a time when LV pressure exceeds left atrial pressure whereas E coincides with the termination of the early diastolic left atrial to LV pressure gradient\textsuperscript{198}. The high sensitivity of E’ was nicely illustrated in asymptomatic carriers of genes responsible for development of hypertrophic cardiomyopathy, who had depressed values of E’ in the absence of LV hypertrophy\textsuperscript{199,200}.

*Strain and Strain Rate Imaging*

TD-derived strain and strain rate measure regional intrinsic cardiac deformation. These regional function measurements are more uniform throughout normal LV myocardium\textsuperscript{139} and become especially important in ischemic heart disease\textsuperscript{201}. As measures of regional myocardial deformation, they are also more sensitive to contractile dysfunction than measures of LV cavity dimension. In ischemic myocardium, strain rate imaging was able to quantify postsystolic shortening and to distinguish postsystolic shortening of overloaded and viable myocardium from passive recoil of noncontracting and necrotic myocardium\textsuperscript{201,202}. Problems of tissue Doppler derived strain and strain rate imaging mainly involve angle dependency, signal noise and signal drifting. Using a speckle tracking echocardiographic technique, angle independent strain measurements can be obtained. Measurements of long-axis strain by speckle tracking echocardiography correlated closely with measures obtained by sonomicrometry in anesthetized dogs and by magnetic resonance imaging in human subjects\textsuperscript{203}. Speckle tracking echocardiography also allows for appreciation of accentuated regional myocardial rotation, “torsion” and “twist” during positive inotropic stimulation with dobutamine or during ischemia\textsuperscript{204}. Assessment of postsystolic strain and early diastolic “untwist” by echocardiography provides important insights into mechanisms of diastolic function. There is however, need for further
studies on how to incorporate these measures into clinical routine. Use of regional deformation indices such as strain and strain rate obviously implies that all myocardial segments are investigated to rule out myocardial disease. In contrast, left ventricular basal longitudinal myocardial shortening or lengthening velocities interrogate global left ventricular performance\textsuperscript{184} and are therefore more easily applicable to detect myocardial disease. Strain and strain rate imaging also offers great potential for the assessment of left atrial function.

\textit{Left atrial conduit, reservoir and pump functions.}

During early LV filling, the left atrium is presumed to be functioning as a passive conduit from the pulmonary veins to the left ventricle. As blood enters the left atrium from the left ventricle, it is immediately replaced by blood entering the left atrium from the pulmonary veins so that left atrial pressure and volume remain constant during early LV filling. Based on this assumption, mitral valve deceleration time was validated as an estimate of LV chamber stiffness in conscious dogs\textsuperscript{205}, in patients undergoing open-heart surgery\textsuperscript{206} and in conscious patients with a wide range of LV sizes and function under varying loading conditions\textsuperscript{207}. Although subsequent measurements in instrumented patients immediately after cardiopulmonary bypass documented a significant decrease in left atrial volume during early LV filling, this decrease did not affect left atrial stiffness and therefore did not invalidate the relation between mitral valve deceleration time and LV chamber stiffness\textsuperscript{208}.

Apart from this conduit function, the left atrium also fulfills a reservoir and a pump function. The relative importance of these three functions varies in accordance to the LV filling profile: left atrial reservoir and pump functions predominate in patients with a slow relaxation LV filling pattern whereas left atrial conduit function
predominates in patients with a restrictive LV filling pattern\textsuperscript{209}. These observations are consistent with a left atrial Starling mechanism being operative in early-stage LV filling impairment and becoming inefficient in end-stage LV filling impairment.

\textit{Cardiac Magnetic Resonance (CMR)}

CMR provides morphologic, functional and flow information as well as tissue characterization by utilization of a series of dedicated acquisition schemes or sequences. Since the development of steady-state free-precession (SSFP) sequences the distinction between morphologic and functional acquisitions has slightly faded, as this technique provides a bright blood image of the moving heart with a very high spatial (1.2 \times 1.2 \text{ mm in-plane and 5mm slice thickness}) and reasonable temporal resolution (20ms). If needed, additional T1 and T2 weighted images can be acquired for morphology and tissue characterization; images can also be acquired after administration of a contrast agent (Gadolinium DTPA) either in 3D to look at general cardiac and vascular features or for perfusion (first pass), late enhancement and distinctive tissue features.

By contouring the epi- and endocardial borders of the different cavities, left and right heart volumes (end-diastolic volume, end-systolic volume, stroke volume, ejection fraction) and LV mass are provided. Since images from the entire cardiac cycle are available, emptying and filling rates can be calculated as well\textsuperscript{210-212}. Qualitative (visual) assessment of regional function (wall displacement and thickening) is possible but also quantitative wall thickening (from the contours using the chord technique) is easily available with the existing software tools. Atrial volume and global function can similarly be obtained. Such functional imaging can be repeated
during dobutamine administration to look for viability (response to low dose
dobutamine) or ischemia (decrease in function at high dose). The three dimensional
nature of the data permits reconstruction of the heart and quantification of the global
and regional shape of the cavities (sphericity, radii of curvature)\textsuperscript{213}.

By placing the interrogating plane at the level of the AV valves, the outlet
valves or the venous connections (caval veins\textsuperscript{214}, sushepatic veins, pulmonary veins),
and using a specific flow sensitive sequence, flow at these sites during the cardiac
cycle is obtained much as with pulsed wave Doppler in echocardiography\textsuperscript{215}. A
difference is that CMR provides velocities (m/s) as well as volume flow (ml/s)\textsuperscript{216,217}
and is less angle dependent\textsuperscript{218}. Flow in the cavities can be quantified as well\textsuperscript{219},
giving insight in the presence and distribution of flow divergence and vortices.
Adjusting the maximal velocity encoding, the low velocities in the myocardial wall
can be obtained as with myocardial velocity imaging\textsuperscript{220-222}. Although mostly
velocities through the image plane are interrogated, CMR intrinsically can obtain all 3
components of the true velocity vector\textsuperscript{223} but this requires several subsequent
acquisitions and a significant amount of post-processing.

After administration of gadolinium-chelated contrast media (Gd) in a peripheral
vein, the passage of the contrast through the right heart, the left heart and the
myocardium can be followed and semi-quantitated, providing information about
regional myocardial perfusion and, if repeated during administration of adenosine,
perfusion reserve. Specific imaging with nulling of the signal of the normal
myocardium some 10 to 20 minutes after Gd administration, allows the visualization
of areas of late contrast captation or late enhancement, which corresponds to either
infarcted tissue or zones of inflammation/fibrosis.
Using a specific pre-pulse, the myocardium can be marked with a line or grid pattern at end diastole, which deforms with the myocardium on which it is inscribed\textsuperscript{224,225}; this myocardial tagging can be applied to any image plane and when performed on a series of short and long axis images, the full spectrum of myocardial deformation can be quantified as myocardial strains. Using a local myocardial coordinate system, the normal strains (thickening, circumferential and longitudinal shortening) as well as the shear strains (circumferential-radial, radial-longitudinal and circumferential-longitudinal, i.e. torsion) can be obtained throughout the entire ventricle\textsuperscript{226}.

Finally, using diffusion tensor imaging, fiber orientations within the myocardial mass can be visualized and quantified. Although obtaining this diffusion tensor is much easier in the ex-vivo\textsuperscript{227} than the moving in-vivo situation\textsuperscript{228,229}, such information about regional fiber orientation can be combined with tagging to calculate fiber mechanics.
References


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