Assessment of diastolic function: suggested methods and future considerations

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RECENT STUDIES in diseased hearts have demonstrated that diastolic dysfunction may precede abnormalities in systolic ventricular performance. Therefore, it is important to critically review methods currently being used in the assessment of diastolic function.

Many review articles and symposia that express differing points of view have been published recently. Several of the controversies stem from a misunderstanding of basic principles of physics and mathematics, the use of inappropriate analyses, and the desire to develop simple indexes of diastolic function. The emphasis here will therefore be on the development of relationships between pertinent physiologic parameters, the applications of various mathematical models, and suggestions of topics requiring further study. In particular, attention will be focused on methods for the assessment of chamber stiffness, myocardial stiffness, and the time constant of relaxation since these are important factors involved during shifts in the pressure-volume relationship after drug intervention or pacing-induced angina.

Methods and illustrative examples

Assessment of chamber stiffness. Chamber stiffness is generally defined as a change in pressure relative to a change in volume (i.e., dP/dV) of a hollow elastic structure such as the left or right ventricle. Its reciprocal (dV/dP) is termed chamber compliance.

Exponentiality of the diastolic pressure-volume relationships has been demonstrated in animal studies and therefore the relationship P = Ae^{kV} (where P is pressure and A and k are curve-fitting parameters) has often been invoked. Since the resulting chamber stiffness-pressure relationship is linear (dP/dV = kAe^{kV} = kP), the slope k is being used as an index of chamber stiffness. However, there are several reasons for abandoning the use of this index. (1) Pressure-volume data are better fitted with a three-constant exponential \( P = A_1e^{\alpha V} + B_1 \) or a power law function \( P = A_2V^m + B_2 \). (2) The constant k is dimensional and therefore unsuitable for patient-to-patient comparisons, especially when ventricular sizes are markedly different. (3) The expression \( P = Ae^{kV} \) does not allow for the possibility of a curve that passes through the origin \( P = 0 \).

The question that must now be addressed is whether dP/dV is an ideal parameter for comparing chamber stiffness between two different ventricles. Figure 1 illustrates two hypothetical parallel pressure-volume curves, portions of which could arise from either a normal \( V_1 \) or a dilated \( V_2 \) ventricle. At each common pressure level the slope of dP/dV is the same, implying equal chamber stiffnesses. However, if we account for ventricular size and define chamber stiffness or "volume elasticity" by \( dP/(dV/V) = VdP/dV \), we observe that at common pressure levels, volume elasticities are unequal. Thus a more suitable method is to develop VdP/dV vs pressure relationships and compare them at common pressure levels. Note that the slope of this relationship is dimensionless.

Assessment of myocardial stiffness. In contrast to chamber stiffness, which assesses the ability of a ventricle to distend under pressure, myocardial stiffness (d\( \sigma \)/d\( s \)) represents the resistance of the myocardium to stretching when it is subjected to a stress. Here d\( \sigma \) denotes an increment of stress \( \sigma \) (force/unit area) resulting in an increment of strain, \( \varepsilon \) (change in length/unit length).

The method described in Appendix 1 is a modification of an earlier one and is presented here because it has implications for the assessment of myocardial stiffness during the latter portion of systole.

Assuming an ellipsoidal geometry for the left ventricle, the incremental modulus (\( E_\varepsilon \)) is given approximately by

\[
E_\varepsilon = \frac{3}{2} (2 + \gamma) \frac{V}{(d\sigma_c/dV)/(2 + b^2\sigma_c^2)_{v_c}}
\]

where the various quantities are as defined in Appen-
The relationship between chamber and myocardial stiffness. It is well known that diastolic pressure-volume relationships depend on several factors, including myocardial stiffness, external pressures, size, and wall volume, but what is not well understood is the interrelationship between these factors.

In Appendix 3 it is shown that such a relationship is given by

\[ \frac{dP}{dV} \sim (4/9) \frac{E_s}{V} (1 + \frac{V}{V_w}) \]

where \( E_s \) is myocardial stiffness and \( V/V_w \) is the ratio cavity volume/wall volume. If transmural pressures are known, pressure is replaced by transmural pressure and myocardial stiffness is computed on the basis of the latter. Note that volume elasticity is directly related to myocardial stiffness and inversely related to the cavity volume/wall volume ratio, a parameter that is often used as an index in studies of left ventricular hypertrophy.

This expression enables one to interpret what often appears to be conflicting results obtained clinically or in the animal laboratory, namely that chamber stiffness may be normal in the presence of elevated myocardial stiffness or vice versa.

The determination of shift and shape changes in the pressure-volume relationship after various interventions. Dramatic shifts in the diastolic pressure-volume relationship after certain interventions have been observed both clinically and in animal studies. In particular there is substantial evidence to support the hypothesis that external pressures are the dominant factor during specific drug interventions. Assuming that these shifts are parallel, it is possible to quantify them as follows:

The pressure-volume relationship is obtained in the form

\[ P = (a_1V^4 + a_2V^3 + a_3V^2 + a_4V + a_5) + bS \]

where \( S \) is 0 under control conditions and \( S \) is 1 during the intervention. A t statistic is then used to test the significance of the shift. This method has been used to demonstrate that amyl nitrite produces no change whereas nitroglycerin results in a significant shift downward. A similar approach has been used to demonstrate the association between the right ventricular pressure and hypertrophy of the septum in right ventricular overload.

In pacing-induced angina, the shifts in the pressure-volume curves are not entirely parallel in general, and the above method must be modified. One approach is to assume exponential or power curve fits in the preintervention and postintervention states in the form \( P_{pre} = A_1 + B_1V^{\alpha_1} \) and \( P_{post} = A_2 + B_2V^{\alpha_2} \). Statistical analyses could then be conducted with the parameters B and \( \alpha \) to test for possible shape changes.

Illustrative examples for the quantitation of chamber stiffness and myocardial stiffness. In the clinical setting it is not always possible to obtain sufficient pressure-volume data points to conduct the analyses described earlier because of nonoverlapping ranges of pressure and stress. These problems may be circumvented in a number of cases by the use of appropriate drugs that do not result in significant parallel shifts in the pressure-volume relationships.

Figure 2, A, illustrates the pressure-volume relation-

\[ \text{FIGURE 1. Hypothetical parallel diastolic pressure (P)-volume (V) relationship. At common pressure levels (P_c), the slopes (dP/dV) representing chamber stiffness are equal, but the volume elasticities are unequal (i.e., } V_1dP/dV \neq V_2dP/dV). \]
ship based on four controls and on data taken from a hypertrophied left ventricle. In the control state there are no common pressure ranges; however, nifedipine infusion enables a comparison of chamber stiffness–pressure relationships to be made (figure 2, B and C).

The results displayed in figure 3 have important clinical implications since they demonstrate that, at least in normal ventricles, shape plays a secondary role in an assessment of myocardial stiffness (figure 3, A), confirming the theoretical studies of Janz et al., and that myocardial stiffness may be within normal limits in some hypertrophied hearts (figure 3, B).

A critical review of the quantitiation of a time constant of ventricular relaxation. In recent years there has been a concerted effort to develop indexesh of relaxation and particular attention has been focused on the time constant of relaxation \( \tau \). Since the mechanisms of relaxation remain obscure and nonstandard definitions for \( \tau \) have often been used, much controversy has resulted from these efforts.

For the purposes of the present discussion, the time constant of ventricular relaxation is defined as that time required for the cavity pressure at \(- (dp/dt)_{\text{min}}\) to be reduced by 1/e or 1/2 (e being the base of the natural logarithm).

If the prime interest is to quantitate a time constant, it is not necessary to conduct any curve-fitting analyses of the isovolumetric relaxation pressure-time data. On the other hand, if we wish to gain more insight into the processes of relaxation, the choice of a mathematic model must be made on the basis of known physiologic behavior and on what yields the “best fit” in the statistical sense.

*In some disease states \( A_0 \) (the time of aortic closure sound) may be preferable to \(- (dp/dt)_{\text{min}}\). The factor 1/e has often been used because of the exponentiality of the pressure-time data in general. Actually, the choice of a time constant is quite arbitrary and the factor 1/2 may be preferable to 1/e in many cases.
TABLE 1

Time constants of relaxation (before and after pacing) based on several models

<table>
<thead>
<tr>
<th></th>
<th>( \tau_{1e} ) by equation 1</th>
<th>Equation 2</th>
<th>T</th>
<th>Equation 3</th>
<th>Direct method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \tau_{1e} )</td>
<td>( \tau_{12} )</td>
<td>( T )</td>
<td>( \tau_{1e} )</td>
<td>( \tau_{12} )</td>
</tr>
<tr>
<td>Mean ± SEM (n = 10)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Before</td>
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<td>0.0337</td>
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<tr>
<td></td>
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<td>±0.0013</td>
<td>±0.0012</td>
<td>±0.0046</td>
<td>±0.0014</td>
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<tr>
<td>After</td>
<td>0.0551</td>
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<td>0.0574</td>
<td>0.0559</td>
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<td></td>
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<td>±0.0023</td>
<td>±0.0018</td>
<td>±0.0048</td>
<td>±0.0038</td>
</tr>
<tr>
<td>p value (paired t test)</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>NS</td>
<td>&gt;0.05^a</td>
</tr>
</tbody>
</table>

\( \tau_{1e}, \tau_{12} \) are the times (sec) required for the cavity pressure to decay respectively to \( 1/e \) and \( 1/2 \) of its value at \( -(dp/dt)_{max} \). \( T = \tau_{1e} = \) the time required for the pressure \( (p - A) \) to decay to \( 1/e \) of its value at \( -(dp/dt)_{max} \), where \( p = A + B e^{-\omega t} \). Equations 1, 2, and 3 are based on the curve fits \( p = A e^{-\alpha t}; p = A + B e^{-\omega t}; p = a_0 t^4 + a_1 t^3 + a_2 t^2 + a_3 t + a_4 \), where the various constants are determined from regression analyses. Note that equation 2 yields the relationship \( dp/dt = -\alpha (p - A) \), which has been used as an alternative method for computing a time constant \( T \), where the parameters \( A \) and \( \alpha \) have been replaced by \( A = p_0 \) and \( \alpha = 1/T \).

As an illustration of these points, consider the data taken from patients in whom angina was induced by atrial pacing. Based on these data, the time constants \( \tau_{1e} \) and \( \tau_{1/2} \) have been computed for the following mathematic models: (1) \( p = A e^{-\alpha t} \), (2) \( p = A + B e^{-\omega t} \), and (3) \( p = a_0 t^4 + a_1 t^3 + a_2 t^2 + a_3 t + a_4 \), where \( \omega \) is the wave frequency. These equations have been thoroughly tested by direct invasive methods should be abandoned.

For the assessment of myocardial stiffness, simpler spherical models (with adjusted stress ranges) may be used, although further studies might be necessary to justify their use in patients with heart disease.

Quantitation of a time constant of relaxation should be based on the definition for \( \tau_{1/2} \). The rationale for this choice is that times corresponding to \( \tau_{1e} \) often occur outside the period of isovolumetric relaxation, but more importantly drug or pacing interventions generally alter the exponentiality of the pressure-time data. Furthermore, it is recommended that the parameter \( T \) not be used since its definition is based on a nonphysiologic reference pressure \( (p - p_0) \).

Several important points need to be emphasized in relation to these analyses, namely: (1) Polynomial curve fits often demonstrate oscillatory behavior near the end points, resulting in spurious values for \( \tau \) even though the fits are usually the "best" in the statistical sense. (2) The time constant \( \tau_{1e} \) after pacing was often associated with a time after mitral valve opening (taken to be 5 mm Hg above end-diastolic pressure). (3) Except for one case, no such problems were associated with \( \tau_{1/2} \).

Conclusions and directions for future research

Because of the efficacy question and errors associated with the measurement of pleural/pericardial pressures, there will be limitations to the assessment of diastolic and systolic function in the clinical setting. Results of animal studies must therefore be relied on for guidance in quantifying these errors.

Reliable assessments of diastolic function are not only essential but assume added importance if indeed diastolic dysfunction precedes abnormal systolic pump function as has been observed in patients with congestive heart failure. Therefore, the practice of developing indexes based on noninvasive techniques before these indexes have been thoroughly tested by direct invasive methods should be abandoned.

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Future studies need to focus on a number of areas as outlined. (1) Although mathematic models are difficult to validate, recent clinical studies provide some encouragement for attempts to qualitatively validate models for the assessment of myocardial stiffness. Preliminary studies in which echocardiography was used also show promise. (2) The relationships between shape changes in the pressure-volume curves and pertinent physiologic parameters involved during various interventions need to be examined in more detail. (3) The factors that alter the time constant require further study and appropriate normalization for heart rate is
necessary. The indirect effect that end-diastolic pressure may have on $\tau$ must also be explored. Several approaches may be used to eliminate the possible effect of end-diastolic pressure. One method is to consider the concept of a developed pressure ($p_d$) decay ($p_d = p - EDP$) and compute $\tau$ directly from the raw data. Another approach is to translate the pressure-time trace so that end-diastolic pressure in the postintervention state coincides with end-diastolic pressure in the control state.* (4) More emphasis must be placed on the development of new mathematical models in order to better understand the physiology of the relaxation processes. In particular, the problem of asynchronous relaxation needs further study. (5) Although not discussed here, the period of rapid filling needs to be analyzed more appropriately. Indexes such as $(dV/\text{dt}_{\text{max}})$ and $(\text{dh}/\text{dt}_{\text{max}})$ that are currently being used have limited clinical utility. These indexes must be normalized to account for ventricular size, corrected for heart rate, and related to an appropriate wall stress (e.g., $(dV/\text{dt}/V_{\text{max}})$/heart rate vs stress at aortic valve closing or mitral valve opening, bearing in mind the limitations involved in the quantification of these parameters).

Since the mechanics of the heart in diastole are inseparable from those in systole, only after the additional studies described here are completed will we be better able to understand diastolic function and its relationship to systolic function.

This article could not have been written without the aid of several colleagues who provided me with pertinent data and as yet unpublished manuscripts. I am therefore particularly grateful to Drs. P. A. Ludbrook, P. Bourdillon, H. P. Krayenbuehl, O. M. Hess, and G. Martin. Because of space limitations, it was not possible to cite numerous other excellent papers on this subject and I am indebted to these investigators also.

**Appendix 1**

**Expressions for the incremental modulus based on ellipsoidal and spherical geometries for the left ventricle.**

Ellipsoid: Assuming an ellipsoidal geometry for the left ventricle, the endocardial circumferential stress ($\sigma_c$) at the equator is approximated by:

$$\sigma_c = P \left[ (B/h) \left( 1 - B^2/2A^2 + h^2/4A^2 \right) - (B^2/A^2) \left( 5/4 - 7B^2/12A^2 - B^4/64A^4 \right) \right] / (1 - hB/2A^2)$$

where $A$ and $B$ are the midwall semimajor and semiminor axes, respectively, $h$ is the wall thickness, and $P$ is the left ventricular cavity pressure.

At the endocardium, the difference ($\sigma_c$) in the circumferential ($\sigma_c$) and radial ($\sigma_r$) stress components is $\sigma_c = \sigma_{Bh} - \sigma_r = \sigma_{Bh} + P$, and the incremental modulus ($E_c$) is defined as $E_c = (3/2) \left( \text{d}E_c/\text{d}(b/b) \right) \left( (2 + b^2/a)^2 \right)$, where $a = A - h/2, b = B - h/2$ are the endocardial semimachines and $b/b$ is the endocardial strain.

From the expression for cavity volume $V = 4\pi ab^2/3$, we obtain $dV/V = (da/a) + (2db/b)$. If we express the log $a$ vs log $b$ relationship (from minimum to end-diastolic pressure) in the form $a = a_0 \log b + (\gamma + g)$, we obtain $da = ydb/b$. Hence, $dV/V = (2 + g) (db/b)$ and the incremental modulus is $E_c = (3/2) (2 + g) V (\text{d}E_c/\text{d}(b/b)) (2 + b^2/a^2)$. 

Sphere: Assuming a thick-walled sphere for the shape of the left ventricle, the endocardial stress components and stress difference are $\sigma_c = P(1 + 3V/V_e)/2; \sigma_r = -P$ and $\sigma_c = \sigma_{Bh} - \sigma_r = 3P(1 + V/V_e)/2$, where $V_e$ is the wall volume. The incremental modulus $E_c$ at the endocardium is thus expressed as $(1/2) (\text{d}E_c/\text{d}(b/b)) = (3/2) V dE_c/dV$, where the incremental strain $dE_c = dV/V$.

**Relationship between the expressions for $\sigma_c$ and $\sigma_r$.** A linear relationship may be obtained by a regression analysis in the form $\sigma_c = C \sigma_r + D$ on the basis of the expressions given above and can be used to convert the stress ranges. It is suggested that these relationships be developed separately for normal and diseased hearts.

**Appendix 2**

**Assessment of regional myocardial stiffness.** Two simple methods are presented here and are based on combined pressure and echocardiographic measurements. Assuming that at the site at which measurements are made the left ventricle may be represented by a cylindrical anulus, the expression for the stress difference and incremental modulus are $\sigma_c = P(D + 2h^2/D + h)$ and $E_c = (3/4) \text{d}E_c/\text{d}(b/b)$ where $D$ is the internal diameter and $dE_c = dV/D$ is the incremental endocardial strain.

An alternative method is to introduce the concept of a radial elastic modulus $E_r$ defined as $E_r = -dP/(dh/h)$, where $h$ is the instantaneous wall thickness. This expression may be plotted against the diastolic transmural pressure and comparisons of stiffness can be made at common levels of pressure.*

**Appendix 3**

**Relationship between chamber and myocardial stiffness.** From Appendix 1, $\sigma_c = (3P/2) (1 + V/V_e); \text{ hence, Myerski}$ stiffness $E_c = (3/2) V dE_c/dV = (3/2) (1 + V/V_e) dP/\text{d}V = 3P(1 + V/V_e)$ or $E_c = (9/4) V (1 + V/V_e) dP/\text{d}V + (9/4) P (V/V_e)$. Generally the latter term is small compared with the former, and hence $E_c = (9/4) V (1 + V/V_e) dP/\text{d}V$ or $dP/\text{d}V = (4/9) E_c V (1 + V/V_e)$.

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