EFFECT OF AGE ON PASSIVE ELASTIC STIFFNESS OF RAT HEART MUSCLE

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ABSTRACT A thick-wall spherical model for the rat left ventricle was used to deduce passive wall stiffness from diastolic pressure-volume data. This was done for rats in three age classes: young (1 mo), adult (7 mo) and old (17 mo). The model was based on finite deformation elasticity theory consistent with the magnitude of observed deformation. A least-squares procedure was used to determine elastic constants in postulated nonlinear stress-stretch relations for the myocardium. It was found that at a given level of stress, wall stiffness for ventricles in the young age class was consistently greater than wall stiffness in the other two classes. In addition, the difference in wall stiffness between rats in the adult and old age classes was found to be approximately 10%.

INTRODUCTION

As pointed out by Diamond et al. (1971), there are two primary determinants of the diastolic pressure-volume (P-V) relationship of the left ventricle: (*1*) geometric factors including shape, size, and wall thickness, and (*2*) material factors such as intrinsic muscle compliance. (Implicit in the latter category is the degree of nonhomogeneity and anisotropy of the ventricular wall.) A change in any one of these factors as a result of the presence of some abnormality such as hypertrophy or acute myocardial infarction may have a substantial effect on the P-V relationship, i.e., the diastolic ventricular compliance. Conversely, a ventricle exhibiting elevated diastolic filling pressures resulting from a reduction in ventricular compliance may indicate, for example, an increase in wall thickness with normal end diastolic volume (concentric hypertrophy), a decrease in diastolic muscle compliance, or some combination of the two.

At least two methods have been suggested for detecting changes in intrinsic muscle compliance from changes in ventricular compliance (Diamond et al., 1971; Mirsky and Parmley, 1973). The procedure explored in this study is similar to the approach considered in the second of the above investigations. However, in this study the more exact methods of finite deformation elasticity theory (see e.g., Mirsky, 1973) were applied to the problem.

The model considered in this study is a homogeneous, isotropic, thick-wall sphere. This simplified representation of ventricular anatomy did not appear to preclude the ability of the model to duplicate observed P-V relationships, provided the nonlinear elastic character of the myocardium was taken into account. The age-dependent, diastolic, left ventricular wall stiffness implied by the theoretical model and observed P-V behavior is discussed below.

METHODS

In order to study diastolic compliance and to determine the absolute volumes of the left ventricle in the rat where small changes of pressure and volume have to be accurately recorded, an automatic servocontrolled system was developed which gives reproducible results (Korecky et al., 1974).

Procedure: The heart of a closed chest anesthetized rat is arrested by injecting KCl into the jugular vein and is subsequently perfused with low Ca Krebs-Ringer solution at approximately 10°C. After thoracotomy the heart is cannulated through the aortic valve by a vinyl catheter to which the root of the aorta is secured. The right ventricle is slit open, the heart with the cannula is removed from the thorax and mounted into a P-V setup filled with saline.

The continuous P-V changes are obtained from this closed system by amplifying the output signals of pressure and volume tranducers and displaying them on an X-Y recorder. The direction of the constant flow is reversed by pressure sensors preset to the required maximum positive and negative pressures, as well as by a back-up volume sensor. A calibrator checks the pressure sensor and with a bath level indicator provides a reference point for zero transmural pressure.

Pressure-volume data were acquired for a total of 28 rats in three age classes: 1 mo (9), 7 mo (9), 17 mo (10). A graph of mean volume at each of 13 pressures for each class is shown in Fig. 1. As indicated in this figure, there is relatively little difference between the P-V behavior of rats in the 7 mo and 17 mo age classes.

THEORETICAL CONSIDERATIONS

Myocardial Stiffness

Under conditions of infinitesimal deformation and strain, the stress-strain relations for an isotropic, homogeneous, incompressible material are of the following form:

$$\sigma_\rho = \tfrac{2}{3}E\epsilon_\rho + Q(\rho),$$
$$\sigma_\phi = \tfrac{2}{3}E\epsilon_\phi + Q(\rho), \tag{1}$$

where, E denotes Young's Modulus, ϵ_ρ and ϵ_ϕ are the radial and circumferential components of Lagrangian strain, σ_ρ and σ_ϕ are the radial and circumferential stresses (i.e., forces per unit cross-sectional area), and $Q(\rho)$ denotes the "hydrostatic" term introduced to account for incompressibility. It follows from Eq. 1 and the incompressibility condition in linear elasticity theory ($\epsilon_\rho + 2\epsilon_\phi = 0$) that,

$$\sigma_\phi - \sigma_\rho = 2E\,\epsilon_\phi.$$

Differentiating this equation with respect to ϵ_ϕ and rearranging the result,

$$E = \tfrac{1}{2}[\mathrm{d}(\sigma_\phi - \sigma_\rho)/\mathrm{d}\epsilon_\phi]. \tag{2}$$

Since Young's Modulus is normally used to characterize the stiffness of elastic ma-

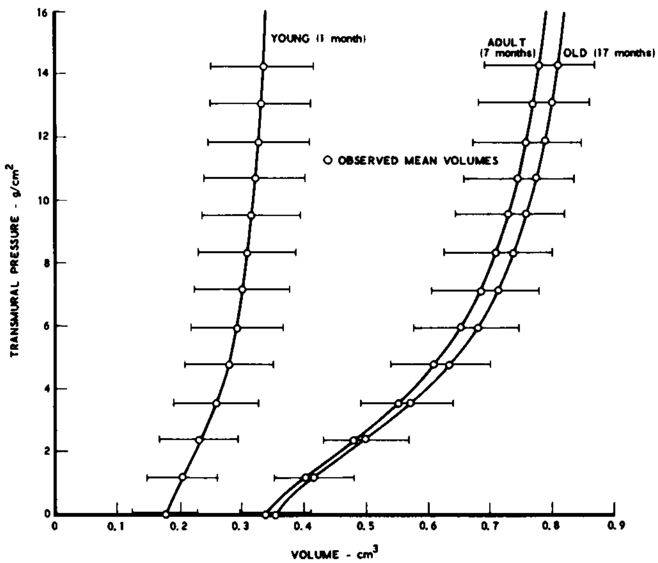

FIGURE 1 Comparison of the observed pressure-volume behavior of the diastolic rat left ventricle with the behavior of a theoretical model whose parameters have been adjusted by the method of least squares to fit the observed data. For each pressure, mean volumes are shown plus or minus one standard deviation (±SD). For rats in the adult and old age classes the union of the intervals defined by ±SD for each class are shown.

terials, the expression on the right-hand side of Eq. 2 is used in this study to characterize the stiffness of the myocardium. In terms of stretch (λ = ratio of deformed length relative to undeformed length of a line element) Eq. 2 becomes,

$$E = (1/2\lambda_\phi)[d(\sigma_\phi - \sigma_\rho)/d\lambda_\phi], \tag{3}$$

since, $\lambda_\phi = (1 + 2\epsilon_\phi)^{1/2}$.

For nonlinear elastic materials such as the myocardium, the expression on the right-hand side of Eq. 3 depends on the level of stress or stretch. This will be demonstrated more graphically later in the discussion.

Determination of $\sigma_\phi - \sigma_\rho$

It is shown in Appendix I that the theoretical *P-V* relationship for a thick-wall sphere in elastic equilibrium is given by the following expression:

$$\Delta P = -2 \int_{\left(\frac{V + V_w}{V_0 + V_w}\right)^{1/3}}^{(V/V_0)^{1/3}} \frac{(\sigma_\phi - \sigma_\rho)d\lambda_\phi}{\lambda_\phi(1 - \lambda_\phi^3)}, \tag{4}$$

where ΔP is transmural pressure, V is deformed cavity volume, V_w is wall volume, V_0 is cavity volume at zero transmural pressure, and λ_ϕ is the variable of integration which may be interpreted as circumferential stretch. This equation can be used to determine $\sigma_\phi - \sigma_\rho$ as a function of λ_ϕ given ΔP as a function of V. It is possible to do this directly without postulating an explicit dependence of the stresses on the stretches. This approach would result in a table of values of the quantity $\sigma_\phi - \sigma_\rho$ corresponding to discrete values of λ_ϕ. However, in this study it was decided to investigate specific stress-stretch relations and use a curve-fitting technique to determine the unknown parameters in these relations.

It should be pointed out that if a function, $G(\lambda_\phi)$, can be found such that the following equation is satisfied for all subsets of data points $(\Delta P_i, V_i)$ along the P-V curve,

$$\Delta P_i = \int_{\left(\frac{V_i + V_w}{V_0 + V_w}\right)^{1/3}}^{(V_i/V_0)^{1/3}} G(\lambda_\phi) d\lambda_\phi. \tag{5}$$

$G(\lambda_\phi)$ is unique for the range in λ_ϕ defined by,

$$[(V_{\min} + V_w)/(V_o + V_w)]^{1/3} < \lambda_\phi < (V_{\max}/V_0)^{1/3},$$

where $V_{\min}$ and $V_{\max}$ are the bounds on volume for which P-V data were recorded. Because of this uniqueness property, the explicit dependence of $G(\lambda_\phi)$ on λ_ϕ (i.e., quadratic, exponential, etc. . . .) is unimportant with respect to computing numerical values of stiffness for given values of circumferential stretch.

In this study mean cavity volumes at 13 values of transmural pressure were used to determine ventricular wall stiffness. It was found that while a two-parameter form for $G(\lambda_\phi)$ did not appear to be adequate, a four-parameter form was sufficient to force Eq. 5 through each of these data points (Fig. 1). This function was constructed in the following way.

Myocardial Stress-Stretch Relations

Generalizing a suggestion by Blatz et al. (1969), the stress-stretch relationships for the myocardium were assumed to be of the following form:

$$\sigma_\rho = A\lambda_\rho^\alpha + B\lambda_\rho^\beta + Q(\rho),$$
$$\sigma_\phi = A\lambda_\phi^\alpha + B\lambda_\phi^\beta + Q(\rho). \tag{6}$$

Substituting Eq. 6 into Eq. 4 it follows that,

$$\Delta P = -2 \int_{\left(\frac{V + V_w}{V_0 + V_w}\right)^{1/3}}^{(V/V_0)^{1/3}} \frac{[A(\lambda_\phi^\alpha - \lambda_\phi^{-2\alpha}) + B(\lambda_\phi^\beta - \lambda_\phi^{-2\beta})] d\lambda_\phi}{\lambda_\phi(1 - \lambda_\phi^3)}, \tag{7}$$

where use has been made of the incompressibility condition,

$$\lambda_\rho \lambda_\phi^2 = 1.$$

(As indicated in Appendix I, the integral in Eq. 7 can be evaluated analytically only when α and β are integers.) Rewriting Eq. 7 with more compact notation,

$$\Delta P = F(V; A, \alpha, B, \beta, V_o, V_w). \tag{8}$$

That is, transmural pressure is some well-defined function of cavity volume and the constant parameters A, α, B, β, V_0, and V_w.

In this study, the following data were determined experimentally for each age class: $\overline{V}_0$, $\overline{V}_w$, and $(\Delta P_i, \overline{V}_i) i = 1, 13$, where, $\overline{V}$ denotes mean volume. The method of least squares was used to determine the parameters A, α, B, and β given this data (Appendix II).

RESULTS AND DISCUSSION

The values which were obtained for the four parameters which appear in the stress-stretch relations (Eq. 6) using the least squares procedure are shown in Table I. The table contains not only the converged values, but also the initial estimates which were obtained using a procedure described in Appendix II.

The theoretical P-V curves which were obtained by substituting the converged values of the parameters into Eq. 7 are shown superimposed on the mean P-V data for all three age classes in Fig. 1. As indicated in this figure, the theoretical curves are in excellent agreement with the measured data. This agreement was expected from a

TABLE I
ELASTIC CONSTANTS FOR RAT MYOCARDIUM

	Initial Estimates			
	A	α	B	β
Young	1.33	18.0	0.0002	65.0
Adult	1.00	16.0	0.00001	60.0
Old	1.24	14.0	0.0002	48.5
	Converged Values			
	A	α	B	β
Young	1.24	18.9	0.000235	62.9
Adult	1.14	14.9	0.0000114	59.1
Old	1.38	13.1	0.000195	49.4

purely mathematical standpoint since four parameters are probably more than adequate to fit these data. This, however, is unimportant with respect to the primary objective of this study which is to compute ventricular wall stiffness rather than determine stress-stretch relations for the myocardium which will fit the P-V data with a minimal number of parameters.

In terms of Eq. 6, wall stiffness as defined by Eq. 3 has the following form:

$$(1/2\lambda_\phi)[d(\sigma_\phi - \sigma_\rho)/d\lambda_\phi] = \tfrac{1}{2}[A\alpha(\lambda_\phi^{\alpha-2} + 2\lambda_\phi^{-2\alpha-2}) + B\beta(\lambda_\phi^{\beta-2} + 2\lambda_\phi^{-2\beta-2})], \quad (9)$$

where,

$$\lambda_\phi = \left[1 + \frac{(V - V_0)}{\frac{4}{3}\pi\rho_0^3}\right]^{1/3}$$

and ρ_0 = undeformed radial coordinate.

There are several options available for representing Eq. 9, graphically. One could simply plot the right-hand side of this equation as a function of λ_ϕ. Alternately, one could choose some value of ρ_0 [e.g., $\rho_0 = a_0$ in which case $V_0 = 4\pi a_0^3/3$ and $\lambda_\phi = (V/V_0)^{1/3}$] and plot stiffness as a function of normalized cavity volume, V/V_0. (Because of the inherent assumption of homogeneity in the model, the choice of ρ_0 is unimportant.) However, since it is customary in cardiac mechanics to relate stiffness to stress, it was decided to plot the right-hand side of Eq. 9 as a function of $\sigma_\phi - \sigma_\rho$, where from Eq. 6,

$$\sigma_\phi - \sigma_\rho = A(\lambda_\phi^\alpha - \lambda_\phi^{-2\alpha}) + B(\lambda_\phi^\beta - \lambda_\phi^{-2\beta}). \quad (10)$$

(It would be misleading to plot Eq. 9 as a function of circumferential stress alone since this would imply a dependence of wall stiffness on position, characteristic of a nonhomogeneous material. This apparent inconsistency in the model can be explained by the fact that stress in incompressible structures is not wholly determined by elastic deformation as indicated by Eq. 6. However, the quantity $\sigma_\phi - \sigma_\rho$ is completely determined by the elastic stretch, λ_ϕ, as indicated by Eq. 10.)

Using the converged values for the parameters A, α, B, and β listed in Table I for rats of each age class, wall stiffness is shown plotted as a function of $\sigma_\phi - \sigma_\rho$ in Fig. 2. Several observations can be made with respect to the results shown in this figure. First, wall stiffness as defined in this study appears to be essentially a linear function of $\sigma_\phi - \sigma_\rho$ for sufficiently large values of this quantity, i.e., values which correspond to transmural pressures greater than or equal to approximately 6 g/cm^2 for rats of each age class. Second, at a given value of $\sigma_\phi - \sigma_\rho$, wall stiffness in the "young" rat left ventricle is consistently greater than wall stiffness in the adult and old ventricles. Third, the difference in wall stiffness implied by mean P-V behavior of rats in the adult and old age classes is small (approximately 10%).

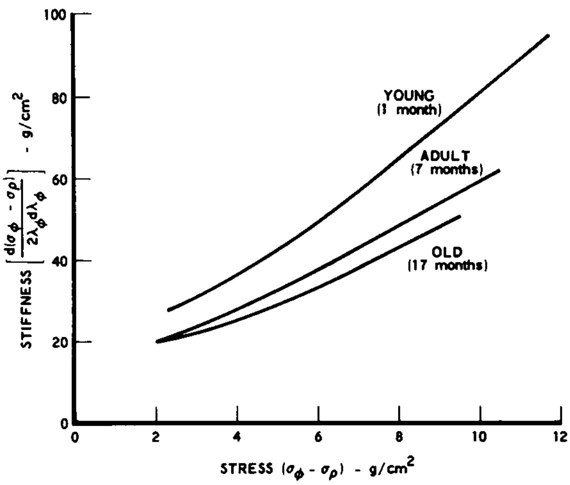

FIGURE 2 Diastolic, left ventricular wall stiffness (implied by the theoretical model and observed pressure-volume behavior) for three age classes.

APPENDIX I

Derivation of Pressure-Volume Relationship for an Incompressible, Thick-Wall Hollow Sphere

The equation of equilibrium for spherically symmetric deformation is given by:

$$(\mathrm{d}\sigma_\rho/\mathrm{d}\rho) + (2/\rho)(\sigma_\rho - \sigma_\phi) = 0 \tag{11}$$

where, σ_ρ equals radial stress, and σ_ϕ equals circumferential stress. The variable, ρ, denotes the radial coordinate in the deformed sphere.

The boundary conditions of interest are as follows:

$$\begin{aligned} \sigma_\rho(a) &= -P_i \\ \sigma_\rho(b) &= -P_o \end{aligned} \tag{12}$$

where a is the interior radius of the deformed sphere, b is the exterior radius of the deformed sphere, P_i is the hydrostatic pressure on the interior wall of the sphere, and P_o is the hydrostatic pressure on the exterior wall of the sphere.

Eq. 11 implies,

$$\sigma_\rho(\rho) = -2\int_a^\rho (\sigma_\rho - \sigma_\phi)(\mathrm{d}\zeta/\zeta) + \sigma_\rho(a). \tag{13}$$

Applying the boundary conditions to Eq. 13 yields the following result:

$$\Delta P = -2\int_a^b (\sigma_\rho - \sigma_\phi)(\mathrm{d}\zeta/\zeta), \tag{14}$$

where, ΔP is the transmural pressure; that is,

$$\Delta P = P_i - P_o.$$

The incompressibility condition (in finite deformation elasticity theory) is equivalent to the following relation between the radial stretch, λ_ρ, and the circumferential stretch, λ_ϕ

$$\lambda_\rho \lambda_\phi^2 = 1. \tag{15}$$

These stretches, in turn, are related to the deformed and undeformed radial coordinates (ρ and ρ_0, respectively) in the following way:

$$\lambda_\rho = \mathrm{d}\rho/\mathrm{d}\rho_0,$$
$$\lambda_\phi = \rho/\rho_0. \tag{16}$$

Eqs. 15 and 16 imply the following relationship between ρ and ρ_0:

$$\rho^3 = \rho_0^3 + K, \tag{17}$$

where, K is a constant of integration. That is,

$$\lambda_\phi = \rho/(\rho^3 - K)^{1/3}. \tag{18}$$

Eq. 18 may be used to change the variable of integration in Eq. 14; i.e.,

$$\mathrm{d}\rho/\rho = \mathrm{d}\lambda_\phi/\lambda_\phi(1 - \lambda_\phi^3).$$

With regard to the transformed limits of integration,

$$\lambda_\phi(a) = a/a_0 = (V/V_0)^{1/3}$$
$$\lambda_\phi(b) = b/b_0 = \left[\frac{a^3 + (b^3 - a^3)}{a_0^3 + (b_0^3 - a_0^3)}\right]^{1/3} = \left(\frac{V + V_w}{V_0 + V_w}\right)^{1/3},$$

where V is the deformed cavity volume, V_w is the volume of the wall (independent of deformation because of incompressibility) and a_0, b_0, and V_0 are the undeformed analogues of a, b, and V.

Therefore, Eq. 14 may be transformed into the form:

$$\Delta P = -2 \int_{(V/V_0)^{1/3}}^{\left(\frac{V + V_w}{V_0 + V_w}\right)^{1/3}} \frac{(\sigma_\rho - \sigma_\phi)\mathrm{d}\lambda_\phi}{\lambda_\phi(1 - \lambda_\phi^3)}. \tag{19}$$

Eq. 19 is the exact mathematical representation of the pressure-volume relationship of an incompressible, thick-wall elastic sphere. In order to evaluate ΔP in terms of V, two parameters are required: (*1*) V_w, the wall volume, and (*2*) V_0, the cavity volume at zero transmural pressure. In addition, a mathematical description of the elastic behavior of the wall must be available. That is, the stress-stretch (or strain) relationships must be given. If the wall material is anisotropic and/or nonhomogeneous, these relationships should ideally reflect this fact. For the purposes of this study, however, the assumption is made that the wall material is homogeneous, isotropic and nonlinearly elastic (Eq. 6).

Combining Eq. 15 and Eq. 6 and substituting the result into Eq. 19 yields the following result:

$$\Delta P = -2 \int_{(V/V_0)^{1/3}}^{\left(\frac{V+V_w}{V_0+V_w}\right)^{1/3}} \frac{[A(\lambda_\phi^{-2\alpha} - \lambda_\phi^{\alpha}) + B(\lambda_\phi^{-2\beta} - \lambda_\phi^{\beta})]\mathrm{d}\lambda_\phi}{\lambda_\phi(1 - \lambda_\phi^3)}. \tag{20}$$

The integral in Eq. 20 can be evaluated analytically only when α and β are integers. In this case, the result of performing this integration is as follows:

$$\Delta P = \frac{2A}{3}\sum_{n=1}^{\alpha}\left[(V/V_0)^{n-(2\alpha/3)-1} - \left(\frac{V+V_w}{V_0+V_w}\right)^{n-(2\alpha/3)-1}\right]\Big/[n - (2\alpha/3) - 1]$$

$$+ \frac{2B}{3}\sum_{n=1}^{\beta}\left[(V/V_0)^{n-(2\beta/3)-1} - \left(\frac{V+V_w}{V_0+V_w}\right)^{n-(2\beta/3)-1}\right]\Big/[n - 2\beta/3 - 1]. \tag{21}$$

(Eq. 21 must be modified slightly when α and/or β are divisible by 3.)

APPENDIX II

Computation of the Parameters: A, α, B, β

These parameters were determined using the method of least squares (Draper and Smith, 1966); that is, the following quantity was minimized with respect to the four parameters to be determined:

$$H(A,\alpha,B,\beta) = \sum_{i=1}^{N}[\Delta P_i - F(\overline{V}_i; A,\alpha,B,\beta,\overline{V}_0,\overline{V}_w)]^2. \tag{22}$$

Four nonlinear equations were obtained by differentiating H with respect A, α, B, and β and equating the resulting derivatives to zero. These equations were solved numerically on a digital computer using a modified Newton-Raphson iterative procedure (Henrici, 1964).

The above approach is limited by the fact that even though the iterative procedure converges to a solution of these nonlinear equations there is no guarantee that the global minimum of H has been determined or that the solution obtained is unique. However, the method which was used to obtain initial estimates of the four parameters for the iterative procedure did appear to produce the desired results. This method was based on the assumption that at relatively low transmural pressures,

$$\Delta P \simeq F(V; A,\alpha,0,0,V_0,V_w). \tag{23}$$

By varying A and α and superimposing the P-V curves predicted by Eq. 23 onto the observed P-V curve, it was evident that the theoretical curve coincided with the observed curve at low pressures for only one set of values of A and α. These values were then substituted into Eq. 8 and the procedure was repeated for B and β.

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