Constraints on cardiac hypertrophy imposed by myocardial viscosity

STEWART DENSLOW
South Carolina Children’s Heart Center, Medical University of South Carolina,
Charleston, South Carolina 29425

Received 16 December 1999; accepted in final form 28 April 2000

Denslow, Stewart. Constraints on cardiac hypertrophy imposed by myocardial viscosity. J Appl Physiol 89: 1022–1032, 2000.—Laplace’s law constrains how thin the ventricular wall may be without experiencing excessive stress. The present study investigated constraints imposed by myocardial viscosity (resistance to internal rearrangement), on how thick the wall may be. The ventricle was modeled as a contracting, spherical shell. The analysis demonstrated that viscosity generates stress and energy dissipation with inverse fourth- and eighth-power dependence, respectively, on distance from the cavity center. This result derives from the combination of squared dependence of viscous forces on shearing velocity gradients and the greater shear rearrangement required for inner layers of a contracting sphere. These predictions are based solely on geometry and fundamentals of viscosity and are independent of material properties, cytoskeletal structure, and internal structural forces. Calculated values of energy and force required to overcome viscosity were clearly large enough to affect the extent of thickening of the left ventricle. It is concluded that load-independent viscous resistance to contraction is an important factor in cardiac mechanics, especially of the thickened ventricles of concentric hypertrophy.

ventricular mechanics; myocardial energetics; ventricular contraction

ONE RESPONSE OF THE LEFT VENTRICLE to prolonged arterial hypertension is the development of concentric hypertrophy (2, 13). This adaptation lowers the stress experienced by the ventricular wall and normalizes the elevated stress resulting from increased pressure. Laplace’s law of the heart relates wall stress to pressure in terms of the ratio of wall thickness to lumen radius. Lower ratios (relatively thin walls) result in greater internal stress. Because of this pattern of stress increases, there is a lower limit to the thickness of the myocardial wall at a particular operating pressure (2, 21).

Investigators have found that normal wall thickness-to-radius ratios are nearly constant over a group of mammalian species that are widely disparate in size but relatively close in blood pressure (5, 19). Ratios that are much lower than this normal value are indicative of pathological eccentric hypertrophy, which results in elevated wall stress at normal pressures. It is not clear, however, what is constraining the ratio in the opposite direction.

A small amount of nonobstructive hypertrophy would lower wall stress, and this is believed to be one benefit of exercise (9). It is, therefore, not obvious why concentric hypertrophy often regresses after developing in response to transient conditions such as pregnancy (22) or repaired valve stenosis (4). The stress reduction is apparently not enough of an advantage for the mild hypertrophy to be maintained. It is unclear what disadvantages may result from concentric hypertrophy that would counterbalance the advantage of stress reduction.

Recently suggested counteracting factors have included problems in perfusion observed in the endocardial layers of concentrically hypertrophied ventricles (15, 24), nonischemic decrease in myocardial function (12), and the increased oxygen demand due to greater deformation occurring at the endocardium (1). Whereas the significant cellular and biochemical issues underlying cardiac function have been extensively investigated, comparatively less attention has been directed toward analysis of the purely physics-based factors that may play a role (3, 11, 18, 21, 29). Because deformation or internal rearrangement of the myocardium, whether achieved by slippage between layers or by cellular distortion, occurs in a viscous medium, the effects of viscosity are a possible factor in determining chamber geometry and behavior. This study is an examination of the magnitude and patterns of predicted viscous effects in a thick-walled chamber such as the left ventricle. These effects are 1) stresses that resist contraction (viscous drag) and 2) extra energy consumed to overcome these stresses (viscous energy losses).

Glossary

\( \alpha \) Proportionality constant between lumen radius \( r \) and intermediate radius \( \rho \)

\( A_\gamma \) Chemical affinities

Address for reprint requests and other correspondence: S. Denslow, The Children’s Heart Center of South Carolina, Medical Univ. of South Carolina, 165 Ashley Ave., PO Box 250915, Charleston, SC 29425–0680 (E-mail: denslows@musc.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
METHODS

**Geometric model.** The model selected for analysis was a homogeneous, thick-walled spherical shell. This model was chosen to elucidate the patterns of viscous effects that are due only to bulk geometry and the fundamental laws of hydrodynamics. Whereas the actual left ventricle of the heart has a much greater complexity than that of the model, the ventricle must still, in the mean, behave within the boundaries established by the fundamental physics of this model. More specifically, whereas patterns of fibrous structure, layering, and particular cytoskeletal structure within the wall may change the absolute level of viscous effects, the overall pattern of stress and energy losses across the thickness of the wall will be determined by the constraints of geometry and hydrodynamics.

The behavior of a contracting spherical shell can be described in terms of circumferential and radial velocities. The circumferential component velocities in the present analysis should not be equated directly to the velocities of contraction of the sarcomeres. As has been shown (3), the varying helical arrangement of fibers in the myocardium allows for nearly homogeneous contraction along fiber directions. This pattern of contraction does not alter the geometric necessity of increasing net velocity gradients along the purely circumferential directions (partially or completely across fibers). If these gradients did not occur, the shell would not be able to contract due to the constraints of the geometry. As the fibers contract along their length, rearrangements and distortions also have to occur across the direction of the fibers. The mean net effect of these movements must be to produce the motion prescribed by a shell with a thick, constant-volume wall.

**Stresses within a thick-walled shell.** There will be components of stress (force per unit area) due to viscosity stemming from any gradient in velocities of contraction between adjacent elements in a mass (shearing). These stresses are expressed counter to the direction of motion of the mass element. The stress components are proportional to the first spatial derivatives of the velocities taken in directions normal to the velocities themselves (10)

\[
\varepsilon_{ij} = -P\delta_{ij} - \eta \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right)
\]  

Here \(P\) is hydrostatic pressure and \(\delta_{ij}\) is the Kroneker delta, which equals unity when \(i = j\); it is zero otherwise. Note that the double subscript, as used here, does not indicate summation but signifies the row and column of an overall stress tensor. Eq. 1 can be split into diagonal \((\delta_{ij} = 1)\) and off-diagonal \((\delta_{ij} = 0)\) terms

\[
\varepsilon_{ii} = -P - \eta \left( \frac{\partial v_i}{\partial x_i} + \frac{\partial v_i}{\partial x_i} \right) = -P - 2\eta \frac{\partial v_i}{\partial x_i},
\]

\[
\varepsilon_{ij} = -\eta \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right)
\]

Note that the sign convention used here requires that \(\eta\), the viscosity coefficient, be positive so that the viscous stress component will be counter to the direction of motion. Most importantly, note also that Eq. 2, right, as well as Eq. 2, left, second term, represents stress components that occur independently of external loads or internal restoring forces. They occur with all contractions, even those generating no transmural pressure.

Although there are undoubtedly variations in contraction velocities occurring at different sites over the surface of the ventricle (29), the present approach uses a simplified model in which the rates of contraction are homogeneous over the circumference of a ventricle modeled as a thick-walled sphere. This model allows a qualitative analysis of the endocardial-to-epicardial variation in viscous effects, which is the object of the investigation. In a nonhomogeneous contraction, specific areas would be contracting at higher and lower velocities to achieve the same overall rate of contraction. The present model may thus be viewed as an analysis of mean behavior.

For this model, there are two components of velocity that may have gradients across the wall thickness. The first is the radial velocity toward the contracting lumen. The second is that of different structures moving with respect to one another along circumferences. This second motion is modeled as a completely balanced net contraction, with no net circumferential displacement. Each unit of volume of myocardium stays in the same angular position while decreasing in circumferential dimension.

This model is completely general with respect to the fine structure of the thick shell itself, the myocardium. The overall geometry requires a particular fundamental pattern of net circumferential and radial velocities. Different patterns of fiber direction, spiral and helical layer rearrangements, or restoring forces undoubtedly exist within the myocardium. Although these factors may achieve more efficient contraction, the net displacement must still lie within the constraints of geometry.

**Viscous energy losses.** In any system, some portion of the total energy flux is lost as heat (dissipated) in entropy production. The equation for total net energy losses, \(\sigma[S]\), in a nonequilibrium system such as myocardium is (10, 14)

\[
\sigma[S] = \sum_j W_j \left( \frac{\partial}{\partial x} \right) \left( \frac{1}{T} \right) - \sum \omega_i A_i - \sum_j \sum_i \varepsilon_{ij} \frac{\partial v_i}{\partial x_j} \frac{1}{T}
\]

In this equation, \(W_j\) is heat flow, \(T\) is temperature, \(\varepsilon_{ij}\) is the components of the stress tensor, \(v_i\) is the components of velocity, \(A_i\) is the affinities of the chemical reactions, and \(\omega_i\) is the reaction rates. The first term represents entropy produced due to temperature gradients and heat flows. The second term is the contribution due to chemical affinity, a function of changes in chemical potential, and chemical flow. The third term represents the entropy increase due to velo-
RMYOCARDIAL VISCOSITY IN HYPERTROPHY

results

General framework of analysis. The first part of RESULTS addresses the patterns of motion that are dictated by the geometry of contraction of a thick shell with constant wall volume. The analysis in the section below shows that the constancy of wall volume, combined with shell geometry, requires that inner and outer regions must behave in fundamentally differing ways for contraction to take place. Compared with the outer regions, the inner regions of the wall are subject to much greater rearrangements in both the radial and circumferential directions during contraction. Accordingly, the spatial rates of change (gradients) in displacement and velocity are also much greater toward the inner surface of the shell.

The second part of RESULTS is an accounting of the stresses and viscous energy losses that are predicted as a result of the patterns of velocity in a contracting shell. The most important aspect of this accounting results from the dependence of energy loss on the square of the gradient of velocities in a fluid medium. In a contracting shell, the magnitude of energy loss is very sensitive to radius as a result of the shell velocity patterns combined with the dependence of the square of the gradient.

The final part of RESULTS is a calculation of levels of stress and energy loss based on a typical set of ventricular proportions.

Patterns of stress and dissipation across the wall. Viscous stresses in a deforming mass are determined by the gradients in motion of adjacent mass elements. To determine what these gradients are in the present study, one can define an intermediate radius \( r_i \), within the myocardium, that represents the position of a particular physical fiber throughout contraction of a thick-walled spherical shell (see Fig. 1). This fiber will be positioned at a changing radius within which is enclosed a constant proportion \( \beta \) of total wall volume, \( V_w \).

The radius of the lumen itself, \( r \), is related to \( r_i \), the intermediate radius, by a variable factor, \( \alpha \), that depends on \( r \) itself and the proportion \( \beta \).

As shown in the APPENDIX, equations can be derived for the spatial gradients in velocity at an instantaneous value of lumen radius \( r \)

\[
\begin{align*}
\frac{\partial v_r}{\partial x_i} &= -2 \frac{r^2}{\rho^3} : \text{relaxation} \\
\frac{\partial (-v_r)}{\partial x_i} &= 2 \frac{r^2}{\rho^3} : \text{contraction} \\
\frac{\partial v_c}{\partial x_i} &= -\frac{2r^2}{\rho^3}
\end{align*}
\]

Equation 4 shows that the rates of change of velocity, and consequently the absolute resultant velocities, are much greater at lower values of \( \rho \), i.e., near the endocardium. Substitution of these results into the expressions for viscous stress (Eq. 2) gives radial and circumferential stresses

\[
\zeta_r = -P - 4\eta \frac{r^2}{\rho^3} \quad \zeta_c = 2\eta \left( \frac{r^2}{\rho^3} \right)
\]

Equation 5, left, shows the radial viscous drag (stress-resisting contraction) acting in parallel with pressure during contraction. The direction of the circumferential component, expressed in Eq. 5, right, is arbitrary. Both equations show the rapid increase in viscous drag as \( \rho \), the relative distance from the center of the lumen, decreases.

The APPENDIX also shows the derivation of an expression for viscous energy losses in terms of radial and circumferential velocities \( (v_r \) and \( v_c \), respectively)

\[
-\sum_i \sum_j \frac{\zeta_{ij} \partial v_i}{T \partial x_j} = \frac{1}{T} \left[ P \frac{\partial v_r}{\partial x_i} + 2\eta \left( \frac{\partial v_r}{\partial x_i} \right)^2 + 2\eta \left( \frac{\partial v_c}{\partial x_i} \right)^2 \right]
\]

= viscous energy losses

This result indicates the nonlinear (quadratic) sensitivity of viscous loss to gradients in radial and circumferential velocity across the thickness of the wall. The expressions for velocity gradients (Eq. 4) within a thick-walled shell can be substituted to produce

\[
-\sum_i \sum_j \frac{\zeta_{ij} \partial v_i}{T \partial x_j} = \frac{1}{T} \left[ P \frac{2r^2}{\rho^3} + 2\eta \left( \frac{-2r^2}{\rho^3} \right)^2 + 2\eta \left( \frac{-2r^2}{\rho^3} \right)^2 \right]
\]

= viscous energy losses

This equation displays the consequences of combining the effects of 1) the quadratic dependence of viscous energy loss on velocity gradients and 2) the magnified strain (distortion) and rate of strain generation near the inner surface necessary for the contraction of a constant-volume shell. Together, these two factors result in an expression that includes terms up to an
inverse eighth power of the radial coordinate \( r \). It is worth stating again that the terms in Eqs. 5 and 7 that do not include pressure are independent of external load. They represent the stresses and energy losses that will occur even when contraction is against zero transmural pressure.

To see what Eqs. 5 and 7 predict for a “typically proportioned” ventricle, a sphere can be defined with a \( V_w \) of \( 4/3 \pi (1)^3 \) or 4.19 cubic units. Typical mammalian thickness-to-radius ratios are obtained by using wall thicknesses of 0.33 and 0.55 units at average minimum and maximum contraction, respectively. These points correspond roughly to end diastole and end systole, respectively. Based on the relationship between \( h \) and lumen radius for a thick-walled sphere

\[
r = \frac{h}{2} + \sqrt{\frac{h^2}{4} + \frac{V_w}{12 + \pi h}} \tag{8}
\]

the end-diastolic radius will be 0.84 units, with a corresponding volume of 2.44 cubic units. The end-systolic values are 0.49 and 0.48 units. This gives an ejection fraction of 0.80 and a shortening fraction of 0.42. Using these numbers in Eq. 5 gives the results shown in Table 1, which demonstrate the extent of variation in viscous stresses due to velocity gradients in the course of a typical ventricular contraction. As can be seen, the differences are dramatic.

When these typical ratios are used to determine energy losses (Eq. 7), the results are even more dramatic (Table 2). At an extent of contraction corresponding to a normal end systole, the energy used to overcome circumferential viscous resistance rearrangement is >400 times greater at the endocardium than at the epicardium.

Relative magnitudes of viscous stress and energy losses (dissipation) are shown graphically in Figs. 2 and 3, respectively. The units on the x-axis are in terms of the endocardial radius so that the thickness of the ventricular wall is represented as extending from unity to a larger value, depending on relative contraction of the chamber. The endocardial end-diastolic stress or dissipation value is defined as 1.0. The simplifying assumption has been made that the values at the epicardium remain constant. The lowest curve in Fig. 2A represents the relative values of pressure-independent radial stress (2nd term in Eq. 5) across the wall at end diastole, with the wall extending between 1 and 1.4. At end systole, the plot shows that the wall is thickened relative to the lumen and that the endocardial radial stress is 3.4 times higher than it was at end diastole. If the wall thickens to the relative proportion seen in hypertrophy, the relative stress rises to almost nine times that seen at normal end diastole.

The predictions for circumferential stress are more pronounced than for radial stress, as shown in Fig. 2B. Endocardial circumferential stress increases by ~5 and 18 times at end systole for normal and proportionately greater contractions, respectively.

Figure 3 shows the relative energy dissipation across the wall for normal and hypertrophic contractions. The increase in relative rate of loss at the endocardium is quite pronounced, as is the localiza-

### Table 1. Relative magnitudes of radial and circumferential stresses due to viscous drag

<table>
<thead>
<tr>
<th>State</th>
<th>( h )</th>
<th>( r )</th>
<th>( h/r )</th>
<th>( R )</th>
<th>Relative Radial Stress</th>
<th>Relative Circumferential Stress</th>
<th>Endo-to-Epi Stress Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Endo</td>
<td>Epi</td>
<td>Endo</td>
</tr>
<tr>
<td>Dilated end diastole</td>
<td>0.22</td>
<td>1.119</td>
<td>0.197</td>
<td>1.339</td>
<td>1.787</td>
<td>1.043</td>
<td>1.597</td>
</tr>
<tr>
<td>Normal end diastole</td>
<td>0.33</td>
<td>0.836</td>
<td>0.395</td>
<td>1.166</td>
<td>2.392</td>
<td>0.882</td>
<td>2.862</td>
</tr>
<tr>
<td>Normal midjection</td>
<td>0.44</td>
<td>0.641</td>
<td>0.686</td>
<td>1.081</td>
<td>3.120</td>
<td>0.651</td>
<td>4.868</td>
</tr>
<tr>
<td>Normal end systole</td>
<td>0.55</td>
<td>0.487</td>
<td>1.299</td>
<td>1.037</td>
<td>4.106</td>
<td>0.425</td>
<td>8.433</td>
</tr>
<tr>
<td>Hypertrophic end systole</td>
<td>0.66</td>
<td>0.355</td>
<td>1.859</td>
<td>1.015</td>
<td>5.633</td>
<td>0.241</td>
<td>15.870</td>
</tr>
</tbody>
</table>

\( h \), Wall thickness; \( r \), endocardial radius; \( h/r \), relative wall thickness; \( R \), epicardial radius; Endo, endocardial; Epi, epicardial. Magnitudes have been calculated based on Eq. A13 in the text and typical values of relative wall thickness. Wall thickness and lumen radius are expressed in arbitrary units.

### Table 2. Relative magnitudes of energy dissipation due to radial and circumferential components of viscous drag

<table>
<thead>
<tr>
<th>State</th>
<th>( h )</th>
<th>( r )</th>
<th>( h/r )</th>
<th>( R )</th>
<th>Relative Radial Dissipation</th>
<th>Relative Circumferential Dissipation</th>
<th>Endo-to-Epi Dissipation Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Endo</td>
<td>Epi</td>
<td>Endo</td>
</tr>
<tr>
<td>Dilated end diastole</td>
<td>0.22</td>
<td>1.119</td>
<td>0.197</td>
<td>1.339</td>
<td>3.194</td>
<td>1.088</td>
<td>2.551</td>
</tr>
<tr>
<td>Normal end diastole</td>
<td>0.33</td>
<td>0.836</td>
<td>0.395</td>
<td>1.166</td>
<td>5.723</td>
<td>0.777</td>
<td>8.189</td>
</tr>
<tr>
<td>Normal midjection</td>
<td>0.44</td>
<td>0.641</td>
<td>0.686</td>
<td>1.081</td>
<td>9.735</td>
<td>0.423</td>
<td>23.693</td>
</tr>
<tr>
<td>Normal end systole</td>
<td>0.55</td>
<td>0.487</td>
<td>1.299</td>
<td>1.037</td>
<td>16.866</td>
<td>0.181</td>
<td>71.112</td>
</tr>
<tr>
<td>Hypertrophic end systole</td>
<td>0.66</td>
<td>0.355</td>
<td>1.859</td>
<td>1.015</td>
<td>31.740</td>
<td>0.058</td>
<td>251.853</td>
</tr>
</tbody>
</table>

Magnitudes have been calculated based on Eq. A14 in the text and typical values of relative wall thickness. Wall thickness and lumen radius are expressed in arbitrary units.
tion of the greatest losses at the inner layers of the wall.

Are energy losses large enough to be significant? Whereas the stress and entropy equations have terms that behave qualitatively in ways that would explain observed limits to myocardial thickening, it is not established whether these quantities are of sufficient magnitude to be significant in cardiac function and pathology. To determine a possible answer to this question, the present study investigated possible sizes of energy losses rather than the more difficult estimation of local stress values.

It was estimated how much heat would be generated in myocardium based on published values of viscosity coefficients and calculated gradients in velocity of contraction. The resulting estimates were compared with published estimates of myocardial total losses to entropy (i.e., from all three terms of Eq. 1: heat flow, chemical reaction, and viscosity). These estimates were based on comparisons between heat generated in isometric contractions and the corresponding pressure-volume areas (27, 28).

Modeling of viscoelastic properties of the myocardium (6, 7, 25, 26) has been done in terms of series and
parallel elastic elements. Chiu et al. (6, 7) made estimates of parallel and series viscous coefficients by using the model in Fig. 4. An iterative procedure of viscosity estimates was used to fit empirical results, giving values of $39$ and $0.15 \text{ mN s}^{-1} \text{ L}_{\text{max}}^{-1}$ (where $L_{\text{max}}$ is maximum length), respectively, for a muscle $6 \text{ mm long and 0.92 mm}^2$ in cross section. Converting to centipoise gives $3,815$ and $14.7 \text{ cP}$, respectively. Because the series contribution is negligible, it will be dropped from the following estimations.

The heat output from any level of viscosity varies with the distance between sliding elements. At an effective distance of $10 \mu \text{m}$ between elements (~1/2 the thickness of a myocyte) and viscosity of $3,815 \text{ cP}$, the heat output would be $156.26 \text{ ergs cm}^{-3} \text{ s}^{-1} \text{ K}^{-1}$. These estimates are found by using $293 \text{K}$ and a velocity of $0.3 \text{ mm/s}$ for the series element in an $8\text{-mm muscle}$ (26).

Based on observations of carbon granule motion on the muscles and of the microscopic behavior of sarco-
Fig. 4. Lumped model used by Chiu et al. (6, 7) for modeling viscosity in myocardium. CE, contractile element; PE, parallel elastic element; SE, series elastic element; V, viscous elements.

meres, Chiu et al. (6, 7) concluded that only a portion of the elastance that they observed resulted in internal shear. If this fraction were low, say 1/10, the velocity differences would be reduced by 10. This would decrease the overall heat calculated by a factor of 10 (keeping 3,815 cP as the viscosity coefficient and 10 μm as the distance), leading to 1.56 ergs·cm⁻³·s⁻¹·K⁻¹ as the estimate.

The total heat measured by Mast and Elzinga (20) during isometric contraction was 112.29 ergs·cm⁻³·s⁻¹·K⁻¹. According to their regression analysis, this heat averaged ~5% above the energy represented by the pressure-volume areas, or 5.6 ergs·cm⁻³·s⁻¹·K⁻¹. This 5% is the excess energy expended that did not contribute to the pressure increase during the contraction. Based on the error inherent in the estimated slope of the regression line (95% confidence interval), the excess might have been as high as 20%, or 22.5 ergs·cm⁻³·s⁻¹·K⁻¹.

Accordingly, these calculations lead to an estimated range of viscous contributions to total entropy losses from 7% (1.56–22.5 ergs·cm⁻³·s⁻¹·K⁻¹) to 28% (1.56–5.6 ergs·cm⁻³·s⁻¹·K⁻¹). The viscous losses would amount to 1.4% (1.56–112.29 ergs·cm⁻³·s⁻¹·K⁻¹) of the total energy used (losses plus work). This percentage is the level that occurs in a linearly contracting piece of papillary muscle with no magnification of distortion due to thick-shell geometry. This linear result can be taken as approximating the percentage of losses near the epicardium (where contraction is closest to linear) at end systole. As shown in Table 2, the losses near the endocardium would be 400 times higher after normal systolic thickening, far exceeding the total of losses plus work at the epicardium. Relative thickening to the extent observed in hypertrophic ventricles would result in an increase of >4,000 times. This calculation of viscous losses does not include the losses due to gradients in radial velocity (1st and 2nd terms in Eq. 7; Table 2) for which no empirical results were available.

This result strongly suggests that the inner layers of muscle somehow avoid being subjected to either the full velocity gradients imposed by spherical shell geometry or the full observed viscosity coefficient. The existence of helical- and spiral-oriented layers, angular torsion, or nonhomogeneous contraction may allow gradients of velocity to be redirected largely across spaces between layers in which the effective viscosity was much lower than within muscle bundles. Displacements along the borders between layers could be such that the vectorial components of displacement in the circumferential direction were of a magnitude required for shell contraction. In this fashion, the net deformation required for contraction could still be achieved (by sliding between low-viscosity layers) while avoiding runaway viscous losses.

However, to reduce the overall energy loss by a factor of 4,000 would require that the average viscosity both between and within layers be at or lower than the viscosity of water (1 cP). Such a lowering seems clearly unreasonable to expect within the myocardium. Further hypertrophy would lead to further eighth-power increases in losses. This pattern appears to represent a sharp energetic barrier to the development of hypertrophy beyond the upper limit of what is observed physiologically.

**DISCUSSION**

The preceding analysis demonstrates that the interaction of myocardial geometry and viscosity is a qualitatively and quantitatively significant factor in constraining the maximum relative thickness of the left ventricular myocardium. This interaction is thus strongly implicated in the limitations observed in the extent and persistence of hypertrophy.

The constraint imposed by viscosity on ventricular geometry is the opposite of the minimum thickness constraint imposed by Laplace’s law. The overall picture is one of a balance between load increases at higher relative distensions (eccentric hypertrophy) due to the Laplace law and load increases at lower relative distensions (concentric hypertrophy) due to viscosity. This pattern of variation results in a minimum total load at some particular ratio of wall thickness to lumen radius. Such a minimum indicates a mechanism for the observed small variation in end-systolic relative wall thickness over large ranges of ventricular mass, both within and between mammalian species (5, 19). Systolic thickening beyond a certain point will result in a cost, in total stress and energy dissipation, that will exceed the benefit to be gained in cardiac output or mechanical advantage against pressure. Thus there would be no net advantage to be gained by maintenance of concentric hypertrophy after load is normalized, such as after pregnancy or after valve repair.
The nonisotropic structure of the actual myocardium could change the quantitative levels of stress and energy loss but not the overall epicardial-endocardial pattern set by physics and demonstrated in RESULTS. It is certainly reasonable to assume that some aspects of the microstructure of the myocardium have reduction of viscosity as their function. Due to the extreme steepness of the increase in viscous effects with thickening, it is clear that only relatively small, overall increments in thickening could be achieved without large increases in stress and energy loss.

The extent of similarity of mammalian relative wall thicknesses at systole may be further determined, not only by the existence of a minimum load as indicated in RESULTS, but also by the steepness of the increase in viscous stress and energy loss with further contraction. The eighth-power dependence contained in Eq. 7 presents a sharply defined barrier to further contraction, which will occur within a tight range of the relative extent of contraction. Due to the steepness of the function, the variations in velocity, cytoskeletal mechanics, and viscosity that undoubtedly occur between species would have minimal effects on the particular proportional extent of contraction that marks the limits of what is physiologically attainable. It would be interesting to investigate whether significant variations in overall geometry, such as the elongated geometry in the ferret heart, are accompanied by significant variations in the thickness-to-radius ratio.

The widely observed dysfunction of the endocardial layers during tachycardia in hypertrophy (12, 15, 24) is completely consistent with the predictions of the currently presented analysis. Indeed, the marked endocardial-epicardial difference in energy dissipation would suggest that dysfunction may occur without any other underlying pathologies, such as impeded blood flow (15, 24) or Ca\(^{2+}\)-ATPase (12) levels. Much more oxygen must be consumed at the endocardium than at the epicardium to overcome local viscous resistance to contraction. The selective ischemia (15, 24) and the greater oxygen demand (1) observed at the endocardium agree with this physics-based pattern of energy demand.

The predictions of the present study agree with the observations of Young et al. (29). Their results, obtained using magnetic resonance tagging, suggest that greater mechanical work is expended in wall shearing (as opposed to lumen reduction) in hypertrophic than in normal hearts. Additionally, these studies show that, as approximated by the present circumferentially homogenous model, radial strain is maximal and total strain along the fibers is minimal (i.e., little change in angular position is observed).

The increase in the endocardial shear with contraction (as shown graphically in Figs. 2 and 3) may indeed result in the attainment of a point of maximum load beyond which sarcomeres cannot proceed. As successively greater thicknesses of the endocardial myocardium reach this point of limiting viscous load from shear, more and more of the lumen pressure load must be born by the remaining outer layers of muscle. Indeed, this is the pattern observed by Aoyagi et al. (1) with increasing dobutamine administration. After a certain point, only the velocity of the contraction increases and not the extent of the contraction, a result the investigators attribute to the load imposed by increased distortion necessary at greater extents of contraction. As demonstrated here, such increased distortion would result in increased viscous resistance to contraction and increased energy lost to overcoming viscosity.

The results of LeGrice et al. (17) with a tachycardia model are also in agreement with the present results. Whereas their work does not address concentric hypertrophy, it does demonstrate the mismatch between oxygen supply and demand that occurs at the endocardium and not the epicardium. Considering the epicardium-to-endocardium gradient in predicted energy dissipation even at normal systole, as shown in Fig. 3, it is reasonable to expect that the extra stress of tachycardia would affect the endocardium much sooner than the epicardium. The greater overall velocities of contraction would increase the energy dissipation in all layers, but the endocardial layers would be more likely to exceed physiological limits because these layers are already functioning at a greater level of viscous loss.

The present results apparently contradict those of Izzi et al. (16), who were not able to find differences in efficiency between normal and hypertrophic hearts. If more energy were wasted overcoming viscosity in hypertrophic hearts, it would be expected that these hearts would display lower energetic efficiency. However, the study contained relatively large standard deviations in the results, such that an existing difference in efficiencies may not have been detected. Calculation of the statistical power (8) of the t-test that was used to compare regression slopes gives a result of 0.10 (1-tailed test, \(\alpha = 0.05\)). This means that there was only a 10% probability that a real difference of the size observed would indeed have produced a statistically significant result in a given experiment. In fact, a real difference as large as 40% between the efficiencies of the two groups of hearts would still have had a 20% probability of producing a statistically nonsignificant \(t\)-value in a given experiment. Additionally, the hearts were studied under isovolumic conditions; therefore, not all viscous properties would have been observable. Considering these factors, a real and substantial difference might have existed between the normal and hypertrophic hearts in this study in agreement with the present analysis.

**Limitations of the present study.** The geometry of the left ventricle is much more closely approximated by an ellipsoidal shell than a spherical shell. The choice was made to present the analysis in terms of a sphere due to the much simpler mathematics involved. The qualitative pattern of the results also applies to ellipsoids and even cylinders. If the analysis is carried out in terms of a cylinder, the inverse eighth- and sixth-power terms are replaced by inverse sixth- and fourth-power terms, respectively. An ellipsoidal ventricular geometry may be represented as something between these...
two models, implying that the dependence of viscous losses, while possibly not inverse eighth power, are at least on the order of inverse seventh power. Such a dependence would not change any of the implications of the present work.

There may be inaccuracies in the values used in this study for viscosity coefficients, separation of contracting elements, and contraction velocity. However, the values used are all in the range of what is physiologically reasonable and hence demonstrate that the effects of viscosity are clearly not orders of magnitude too small for significant impact. Due to the eighth-order (or perhaps seventh-order) increase in the magnitude of the circumferential (shear) dissipative losses with radius, even a much smaller set of values would still give physiologically significant results. In fact, as discussed in Results, the magnitudes predicted for typical ventricular proportions are almost certainly too large to exist in the myocardium. Such magnitudes would require all of the energy in the endocardial layers to be lost to viscous drag, even at normal end systole.

In summary, the mechanical and thermodynamic analysis presented in this study strongly suggests that the basic geometry and material properties of the left ventricle are a sufficient basis, by themselves, for constraints on the extent to which hypertrophy can progress and for the selective dysfunction often observed in the endocardium. Whereas biochemical, cellular, and physiological mechanisms are most certainly not excluded by this analysis, the implication is that such factors act in addition to, or on top of, the more fundamental geometric and hydrodynamic principles.

APPENDIX

To determine velocity gradients in a thick-walled, spherical shell, an intermediate radius \( r \) was defined to represent the position of a particular physical fiber throughout contraction.

This radius encloses a constant proportion \( \beta \) of total wall volume \( V_w \). The lumen radius \( r \) is related to \( \rho \) by a factor \( \alpha \), depending on \( r \) and \( \beta \). The outer radius of the sphere is \( R \) (Fig. 1).

\[
\rho = \alpha r \quad V_w = \frac{2}{3} \pi R^3 - \frac{4}{3} \pi r^3
\]

The rate of change of the intermediate radius and circumference are then found as shown here

\[
\rho^3 = \frac{\beta V_w}{\frac{4}{3} \pi} + r^3 \Rightarrow 3 \rho^2 \frac{d \rho}{d r} = 3 r^2 \Rightarrow \frac{d \rho}{d r} = \frac{r^2}{\rho^2} (A2)
\]

\[
2 \pi \frac{d \rho}{d r} = 2 \pi \frac{2 r^2}{\rho^2} \Rightarrow \frac{d C_o}{d r} = 2 \pi \frac{2 r^2}{\rho^2} (A3)
\]

In Eq. A3, the equality \( C_o = 2 \pi \rho \) has been used for substitution, where \( C_o \) is the circumference at intermediate radius \( \rho \).

The circumferential rate of change is the total for a full circumference, \( C_o \). To compare the rates at different radii, one needs to normalize by the length of the circumference

\[
\frac{d}{d r} (C_o) = \frac{2 \pi r^2}{\rho^2}. (A4)
\]

For a given lumen radius \( r \), the normalized change of \( C_o \) with changes in \( r \) is smaller as one approaches the outer surface (\( \rho \) increases).

Spatial gradients in velocity at instantaneous \( r \), \( \frac{\partial v_i}{\partial x_j} \) and \( \frac{\partial v_j}{\partial x_i} \), are found by differentiation of Eqs. A3 and A4 with respect to \( \rho \) and again dividing by \( C_o \) for the circumferential direction. To keep track of the sign for radial velocities, \( v_i \) is required to represent only positive quantities. Contraction is denoted with an explicit negative sign: \( -v_i \). The sign in the circumferential directions is arbitrary and is not denoted explicitly

\[
\frac{\partial v_i}{\partial x_j} = \frac{\partial}{\partial \rho} \frac{\partial}{\partial r} (C_o) = -2 \pi r \rho = \frac{-2 \pi r^2}{\rho^2} (A5)
\]

Components of viscous stress, \( \zeta_{ij} \), are found as the spatial derivatives of velocity in directions normal to the velocities themselves (10)

\[
\zeta_{ij} = -P \delta_{ij} - \eta \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) (A6)
\]

Here \( P \) is hydrostatic pressure and \( \delta_{ij} \) is the Kroneker delta. Eq. A2 can be split into diagonal (\( \delta_{ij} = 1 \)) and off-diagonal (\( \delta_{ij} = 0 \)) terms

\[
\zeta_{ii} = -P - \eta \left( \frac{\partial v_i}{\partial x_i} + \frac{\partial v_i}{\partial x_i} \right) = -P - 2 \eta \frac{\partial v_i}{\partial x_i} (A7)
\]

The sign convention used here requires that \( \eta \) be positive so that the viscous stress component will be counter to the direction of motion.

Substitution using Eq. A5 for velocity gradients at a given \( r \) and \( \rho \) gives

\[
\zeta_{rr} = -P - 4 \eta \frac{r^2}{\rho^2} \quad \zeta_{rr} = 2 \eta \left( \frac{r^2}{\rho^2} \right) (A8)
\]

Eq. A8, left, shows the viscous drag acting in parallel with pressure during contraction. The direction of the circumferential component, expressed in Eq. A8, right, is arbitrary.

The equation for entropy production, \( \sigma[S] \), in a nonequilibrium system is (10, 14)

\[
\sigma[S] = \sum_j \sum_{\gamma} W_j \frac{\partial}{\partial x_j} \left( \frac{1}{T} \right) - \sum \sum_a \frac{C_o}{T} \sum \sum \frac{\zeta_{ij} v_i}{T} \frac{\partial v_j}{\partial x_j} (A9)
\]

Using Eq. A7 to expand Eq. A9, right, third term, will give a quadratic expression in the velocity gradients (14, 23)
\[
\sum \sum \frac{\xi_{ij}}{T} \frac{\partial u_i}{\partial x_j} = \frac{1}{T} \left[ -P - 2\eta \frac{\partial v_1}{\partial x_1} \right] \left[ \frac{\partial v_1}{\partial x_1} \right] + \left[ -P - 2\eta \frac{\partial v_2}{\partial x_2} \right] \left[ \frac{\partial v_2}{\partial x_2} \right] + \left[ -P - 2\eta \frac{\partial v_3}{\partial x_3} \right] \left[ \frac{\partial v_3}{\partial x_3} \right] \\
+ \frac{1}{T} \left[ -\eta \left( \frac{\partial v_1}{\partial x_2} \right) + \left( \frac{\partial v_2}{\partial x_1} \right) - \eta \left( \frac{\partial v_2}{\partial x_1} \right) + \left( \frac{\partial v_1}{\partial x_2} \right) - \eta \left( \frac{\partial v_3}{\partial x_1} \right) + \left( \frac{\partial v_1}{\partial x_3} \right) - \eta \left( \frac{\partial v_3}{\partial x_2} \right) + \left( \frac{\partial v_2}{\partial x_3} \right) \right]
\]

Further expanding and collecting terms gives

\[
\sum \sum \frac{\xi_{ij}}{T} \frac{\partial u_i}{\partial x_j} = \frac{1}{T} \left[ -P \left( \frac{\partial v_1}{\partial x_1} \right) - P \left( \frac{\partial v_2}{\partial x_2} \right) - P \left( \frac{\partial v_3}{\partial x_3} \right) - 2\eta \left( \frac{\partial v_1}{\partial x_1} \right)^2 - 2\eta \left( \frac{\partial v_2}{\partial x_2} \right)^2 - 2\eta \left( \frac{\partial v_3}{\partial x_3} \right)^2 \right] \\
+ \frac{1}{T} \left[ -\eta \left( \frac{\partial v_2}{\partial x_2} \right)^2 - \eta \left( \frac{\partial v_1}{\partial x_3} \right)^2 - \eta \left( \frac{\partial v_1}{\partial x_2} \right)^2 - \eta \left( \frac{\partial v_2}{\partial x_3} \right)^2 - \eta \left( \frac{\partial v_3}{\partial x_1} \right)^2 - \eta \left( \frac{\partial v_3}{\partial x_2} \right)^2 \right]
\]

Because there are no spatial changes in velocity along the dimensions parallel to the surface ($x_2$ and $x_3$), the derivatives along those directions are zero, and these terms drop out

\[
\sum \sum \frac{\xi_{ij}}{T} \frac{\partial u_i}{\partial x_j} = \frac{1}{T} \left[ -P \left( \frac{\partial v_1}{\partial x_1} \right) - 2\eta \left( \frac{\partial v_1}{\partial x_1} \right)^2 \right] \\

= \text{viscous losses}
\]

Substitution using Eq. A5 gives

\[
\sum \sum \frac{\xi_{ij}}{T} \frac{\partial v_i}{\partial x_j} = \frac{1}{T} \left[ P \left( \frac{\partial v_1}{\partial p} \right) + 2\eta \left( \frac{\partial v_1}{\partial p} \right)^2 \right] \\

= \text{viscous losses}
\]

REFERENCES