Influence of Temperature on the Mechanical Properties of Cardiac Muscle

By Gordon H. Templeton, Kern Wildenthal, James T. Willerson, and William C. Reardon

ABSTRACT

The influence of temperature on contractile performance, total myocardial stiffness, and the elastic and viscous components of stiffness was studied in intact hearts (dog) and isolated cardiac muscle (cat). In 12 dogs on whole-heart bypass, stiffness (ΔP/ΔV) was determined by inducing sinusoidal 0.5-ml volume changes in paced, isovolumically contracting left ventricles and measuring the resultant pressure changes (ΔP). In eight cat papillary muscles contracting isometrically at Lmax, stiffness (ΔT/ΔL) was similarly determined from the changes in tension and length during sinusoidal length changes of 0.25% Lmax. Total stiffness was linearly related to ventricular pressure or muscular tension during both contraction and rest. As the temperature rose from 33° to 40°C in vivo and from 22° to 40°C in vitro, the slopes of the stiffness-pressure and stiffness-tension relationships and the intercept of the latter declined; therefore, stiffness is inversely related to temperature. Since both preparations responded as linear second-order systems, stiffness could be separated into its elastic and viscous components. The moduli of both components varied in the same direction as total stiffness during temperature changes; however, the viscous component was more sensitive to the influence of temperature.

KEY WORDS viscous stiffness elastic stiffness compliance hypothermia cat papillary muscle isovolumic canine ventricle second-order mechanical system sinusoidal forcing function

Temperature variations alter the contractile strength of the left ventricle and the duration of systole (1-4), but the influence of hypo- and hyperthermia on total myocardial stiffness and the separate mechanical properties underlying total stiffness remains unclear. Diastolic stiffness determined from the pressure at any given end-diastolic volume appears to increase (1, 2) or remain unchanged (3, 4) during hypothermia. The stiffness of contracting muscle, which is usually determined from quick-release experiments and called series elastic stiffness, appears to increase as temperature falls (5).

In the present paper, the influence of temperature on myocardial stiffness was evaluated by a new technique. Unlike the methods used previously to measure myocardial stiffness, the new technique employed sinusoidal forcing functions to measure stiffness continuously during the entire cardiac cycle; diastolic and systolic stiffness did not have to be analyzed separately. Also, comparable sinusoidal forcing techniques were used in both the intact ventricle and the papillary muscle preparation; thus, the influence of temperature in both in vivo and in vitro experiments was compared. Finally, since recent evidence has shown that the heart responds to these sinusoidal forcing functions as a linear second-order mechanical system (6), the data obtained by this technique were used to separate the influences of temperature on total stiffness into its effects on the elastic and viscous moduli of cardiac muscle.

Theoretical Considerations

A second-order mechanical system displays elasticity, viscosity, and inertia. Elastic stiffness is considered to be a static or time-independent property. Consequently, an elastic component responds to a stretch with a change in tension that is dependent only on the magnitude of the stretch and not on the rapidity of the stretch. In contrast, viscous and inertial stiffness both reflect dynamic or time-dependent properties. The tension of a viscous component is dependent on the velocity of the stretch, and the tension of an inertial component is dependent on the acceleration. Acceleration is the second derivative of length; since it is the highest order derivative in the system, the system is called second order.
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Linearity within a second-order mechanical system implies that sinusoidal changes in the system will induce sinusoidal responses. In most analyses, this observation is considered sufficient to assume linearity. However, to satisfy the principle of linearity mathematically, a mechanical system must display additivity and homogeneity (7).

In response to the sinusoidal forcing functions used in this study, both the ventricle and the papillary muscle preparation behaved as linear second-order mechanical systems. The ventricle and papillary muscle systems were linear, since their pressure or tension responses to the sinusoidal forcing functions were nearly sinusoidal. Moreover, the induced sinusoidally varying pressure in the ventricle and the tension in the papillary muscle were displaced in time from the forcing functions, indicating that the viscosity and the inertia present in the preparations were affected by the forcing functions and that the systems were indeed second order.

If a mechanical system, such as the ventricle or the papillary muscle preparation, which behaves as a linear second-order system is stretched by some external means, it can be described mathematically by an equation of motion.

\[
\frac{1}{K} \frac{d^2 \sigma(t)}{dt^2} + \frac{1}{\eta} \frac{d \sigma(t)}{dt} + \frac{1}{m} \sigma(t) = \frac{1}{x} \frac{d^2 \gamma(t)}{dt^2}, \tag{1}
\]

where \( K \) is the elastic stiffness, \( \eta \) is the damping constant, and \( m \) is the equivalent mass (6). For the ventricular preparation, \( \gamma(t) \) is the applied sinusoidal volume \((\gamma_0 \cos \omega t, \text{ where } \omega \text{ is angular frequency})\), \( \sigma(t) \) is the sinusoidal pressure response, and \( x \) is a constant relating linear displacement to spherical volume changes. For the papillary muscle, \( \gamma(t) \) is length, \( \sigma(t) \) is tension, and \( x \) is unity. The three terms forming the sum of the left side of the equation represent the elasticity, viscosity, and inertia of the system, respectively. The term on the right side of the equation is the forcing function of the system. For the ventricle, the steady-state solution for Eq. 1 is

\[
\sigma(t) = \sigma_0 \cos(\omega t + \psi). \tag{2}
\]

The phase angle \( \psi \) indicates the time difference between the occurrence of the peak of a pressure cycle and the peak of a volume cycle. Substitution of Eq. 2 into Eq. 1 yields equations for viscous stiffness \( \eta \omega \) and elastic stiffness \( G \) in terms of the total stiffness \( \sigma_0 / \gamma_0 \) and the phase angle \( \psi \) at a particular time.

\[
\eta \omega = \frac{(x \omega \sigma_0)}{(\gamma_0 \sin \psi)}, \tag{3}
\]

\[
G = \frac{(x \omega \sigma_0)}{(\gamma_0 \omega^2 \cos \psi + \sigma_0 x)}, \tag{4}
\]

where \( \eta \) is the damping constant and \( \omega \) is the angular frequency.

Figure 1 is a sinor diagram representing the applied sinusoidal forcing function of either length or volume and its elastic, viscous, and inertial components represented by \( \gamma K, \gamma \eta, \) and \( \gamma M \), respectively. The reference sinor, \( \sigma \), is the system response to the forcing function and is shown leading it by an angle, \( \psi \).

Previous investigations of skeletal (8, 9) and insect (10) muscle have used second-order system analysis for measuring elastic and viscous stiffness. Separation of stiffness into its elastic and viscous components required the assumption that a linear second-order system was being analyzed; the separation of stiffness was accomplished by dividing the sinusoidal tension \( \sigma \) into two component sinusoids that were 90° out of phase; these two sinusoids were the elastic component plus the inertial component and the viscous component (Fig. 1). The study on insect muscle (10) did not separate the elastic and inertial components but assumed that the inertial contribution to stiffness was negligible. Since the mass of the muscle strips was small, this assumption is probably valid. Such an assumption is not valid for the intact heart, however. With the forcing function used in the present study a sizable contribution to stiffness by its inertial component does occur as indicated by the measurement of phase angles greater than...
90° in some hearts. In evaluating changes in stiffness, the properties of the inertial component can be considered to be constant as long as both the mass of the heart and the perturbation frequency of the forcing function remain constant; thus, any changes observed in total stiffness can be ascribed to changes in the viscous modulus, the elastic modulus, or both.

Methods

INTACT DOG VENTRICLES

The basic experimental preparation and the evaluation of the instrumentation have been described in detail previously (6, 11, 12). Briefly, mongrel dogs (16–21 kg) anesthetized with sodium pentobarbital were put on a complete heart-lung bypass after a midline thoracotomy. The extracorporeal circuit contained a water bath for temperature regulation. Ligation of the bundle of His produced complete heart block, and the ventricular rate was controlled by a Grass stimulator through pacing electrodes sutured to the right ventricle. The left ventricle was made isovolumic by occluding the mitral and aortic valve orifices with Teflon buttons and inserting a distensible, fluid-filled rubber balloon into the chamber through a stab incision in the apex. The balloon, which was of negligible stiffness, was attached to the end of a metal cannula. After insertion it was filled with 20–25 ml of saline to yield a diastolic pressure of 1–5 mm Hg. On the external end of the fluid-filled cannula was a piston that produced sinusoidal volume changes with a peak magnitude of 0.5 ml and a frequency of 22 Hz. The ventricular pressure was measured with a Konigsberg P21 pressure transducer positioned within the balloon; a nearly sinusoidal pressure response to the sinusoidal volume changes was observed. The transducer had a flat frequency response to 1.2 kHz. Mean aortic blood pressure was measured with a Statham P23Db transducer. The pressures, the electrical pulses from the Grass stimulator, and the piston displacement, which was measured by a differential transformer, were recorded on an analog tape recorder. Bilateral vagotomy and injection of propranolol (1 mg/kg) 10 minutes before the experiment began minimized neural and hormonal effects and reduced control developed pressure up to one-half.

Sixteen successive ventricular pressure wave forms were averaged by a Digital Equipment Corporation PDP-12 computer to yield one wave form. With Fourier analysis, that portion of the pressure wave form resulting from the piston perturbations (harmonics 8–15) was separated from that portion representing the unperturbed ventricular pressure wave form (harmonics 1–7). This approach yielded the same results as that in which an unperturbed wave form is subtracted from a comparable perturbed wave form (12). The peak changes of the sinusoidal pressure cycles (ΔP) were determined from the time-domain wave form containing the eighth to the fifteenth harmonics of the original averaged pressure wave form. Dividing each of the peak pressure changes by the 0.5-ml peak volume change (ΔV) yielded a measurement of ventricular stiffness (ΔP/ΔV) at 22 points throughout the cardiac cycle. For each experimental condition, each value of stiffness was compared to the simultaneously measured pressure (P) at that point in the cardiac cycle. The two values were always related linearly throughout the cycle (r > 0.87), so that

\[ \Delta P / \Delta V = \alpha P + \beta, \]

where \( \alpha \) and \( \beta \) are the slope and y-axis intercept of the relationship, respectively. Changes in \( \alpha \) and \( \beta \) were assumed to reflect net changes in the static (elastic) or the dynamic (viscoinertial) components of myocardial stiffness.

In addition, the exact times of the various peak pressure changes and of maximal and minimal piston displacements were determined. Because the sampling frequency was 100 Hz, the relative error in these measurements was 8° for the pressure cycle of 22 Hz. Consequently, the sampling theorem (13, 14) was used to reconstruct the pressure and displacement wave forms between the sampled data points. This procedure increased the accuracy of the phase angle measurement to 1°. From these time measurements, the time difference between the peak of each sinusoidal pressure cycle and the peak of the corresponding sinusoidal volume cycle was determined. These time differences were then expressed in terms of phase angles (ψ). As

\[ \psi = (\Delta t / T)(360°), \]

where \( \Delta t \) is the difference in time in seconds separating the pressure cycle peak and the volume cycle peak and \( T \) is the period of the pressure and volume cycles (0.0455 seconds for 22 Hz). Expression of the time differences in terms of degrees allowed stiffness to be separated into its elastic and viscous components, which are functions of the sine and cosine of ψ.

The system generating the sinusoidal volume changes was studied to determine the inherent time delay between the piston movement and the pressure response (6). For a forcing frequency of 22 Hz, no time difference between the peak of a volume perturbation and the peak of a pressure perturbation was seen for system pressures below 90 mm Hg. Above this pressure, a phase angle of 6° was measured. Consequently, this 6° error was subtracted from the phase angles measured in this study when ventricular pressures were above 90 mm Hg.

Control temperatures were kept constant at 37°C by a water bath that circulated around the extracorporeal circuit. Hyperthermia (33.6°C) was induced in eight dogs and hyperthermia (40°C) was induced in four dogs by changing the temperature of the water bath. Heart rate, aortic blood pressure, and piston frequency were held constant. Ventricular volume was unchanged except for the 0.5-ml peak volume changes induced by the sinusoidally varying piston. In other experiments, end-diastolic pressure in the isovolumic ventricle was determined at a slow heart rate (<40 beats/min) without volume perturbations to yield an.
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ISOLATED CAT PAPILLARY MUSCLES

Eight papillary muscles were excised from the right ventricles of cats previously anesthetized with sodium pentobarbital (60 mg/kg, ip). The muscles were mounted in a bath for mechanical studies by procedures that have been described previously (15). A Hewlett-Packard pen motor (model 7700) modified with stiff springs and driven by a sinusoidal generator was used to induce sinusoidal length changes with a peak amplitude of 0.25% of the length of the muscle at which developed tension was greatest (Lmax) and a frequency of 60 Hz. The sinusoidal response of the muscles was measured with a tension transducer. Unlike the ventricular preparation in which the frequency of the sinusoidal forcing function was limited to below 30 Hz because of cavitation or bubble formation, the papillary muscle could be sinusoidally stretched over a wide frequency range. Accordingly, a higher frequency of 60 Hz was used to stretch the papillary muscle; this procedure enabled more stiffness measurements to be determined during each contraction cycle. None of the muscles had a resonant frequency of 60 Hz; therefore, the same equations for viscous and elastic stiffness could be used for both the intact ventricle and the papillary muscle experiments.

An initial study on 14 papillary muscles determined an optimal amplitude and frequency for the sinusoidal forcing function for the papillary muscle study. The relationship between stiffness (ΔT/ΔL) and muscle tension was linear for all frequencies below 150 Hz and for amplitude below 2% Lmax. As the frequency of the forcing function was increased in 10-Hz increments from zero, the slope and the intercept of the stiffness-tension linear relationship continually increased to a maximal value at a frequency between 80 and 100 Hz. When the amplitude of the forcing function was increased from 0.25% to 1% and to 2% Lmax, the slope and the intercepts again increased.

The compliance of the system without the muscle was less than 0.5 μ with 20 g of force applied to the lever. The muscles contracted isometrically at Lmax, except for the small imposed sinusoidal stretch, at a frequency of 13.2 contractions/min. The temperature of the Krebs-Ringer’s bicarbonate solution (with 18 mM glucose and 2.5 mM calcium) perfusing the muscles was varied from 22°C to 30°C, 37°C, and 40°C. Muscle weights varied from 1.6 to 6.5 mg and muscle cross-sectional areas averaged 1.29 ± 0.15 (SE) mm².

The tension data were digitized and partially processed with a PDP-12 computer. Successive tension wave forms obtained during the isometric contractions displayed the sinusoidal response; they were overlaid to form an envelope of the tension perturbations (15). Measurements of the amplitude of the tension envelope (ΔT) were made at 2-msec intervals from the composite tension wave form, and the corresponding mean values of tension (T) were obtained by averaging the maximal and minimal values of the envelope. The resulting relationships between stiffness (ΔT/ΔL) and tension (T) had correlation coefficients above 0.9; consequently, the slope and the intercept of the linear regression fitting the stiffness-tension relationships were determined for each cat papillary muscle at each temperature studied (just as was done for the intact dog ventricle using ΔP/ΔV). The tension wave forms recorded at each temperature in the presence and the absence of the sinusoidal forcing function were also analyzed for resting tension, developed tension, initial rate of tension development (dT/dt), and rate of decline in tension (−dT/dt) during relaxation.

Further computer analysis on a Univac 1108 measured the time displacement between the tension and length cycles. Similar to the relationship between pressure and volume, the tension cycle led the displacement cycle in time by a small phase angle. The sampling frequency used was 1000 Hz; to be able to accurately measure the phase angles within 2° out of 360° for a forcing function frequency of 60 Hz, the sampling theorem (13, 14) was used to reconstruct the tension and length wave forms between the sampled data points. Measurements of stiffness (ΔT/ΔL) and the phase angles were used to determine the elastic and viscous components of stiffness and to show how these mechanical properties were influenced by temperature.

Results

INTACT DOG VENTRICLES

Hypothermia consistently caused increases in end-diastolic pressure, total pressure develop-

| TABLE 1 |

| Influence of Temperature on the Mechanics of the Intact Left Ventricle |

<table>
<thead>
<tr>
<th>Effect of hypothermia (N = 8)</th>
<th>Effect of hyperthermia (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37°C</td>
<td>33°C</td>
</tr>
<tr>
<td>End-diastolic pressure (mm Hg)</td>
<td>1.8 ± 0.57</td>
</tr>
<tr>
<td>Developed pressure (mm Hg)</td>
<td>88.6 ± 4.36</td>
</tr>
<tr>
<td>Time to peak pressure (% of cardiac cycle)</td>
<td>32 ± 1.3</td>
</tr>
<tr>
<td>Duration of systole (% of cardiac cycle)</td>
<td>58 ± 1.1</td>
</tr>
<tr>
<td>37°C</td>
<td>33°C</td>
</tr>
<tr>
<td>40°C</td>
<td>80.3 ± 2.39</td>
</tr>
<tr>
<td>Time to peak pressure (% of cardiac cycle)</td>
<td>28 ± 1.3</td>
</tr>
<tr>
<td>Duration of systole (% of cardiac cycle)</td>
<td>56 ± 2.0</td>
</tr>
</tbody>
</table>

All values are means ± SE.

*P < 0.001.

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ment, time to peak pressure, and total duration of systole (Table 1). Hyperthermia had the opposite effect (Table 1).

In all experiments, left ventricular stiffness ($\Delta P/\Delta V$) was a linear function of pressure ($P$) throughout the cardiac cycle. Changes in blood temperature did not influence the linearity of the stiffness-pressure relationship, but the slope ($\alpha$) of the equation describing this relationship was altered significantly. Hypothermia increased $\alpha$, and hyperthermia decreased it; this observation indicates that stiffness varies as an inverse function of temperature. Data from a single dog (Fig. 2) show the influence of hypothermia on the stiffness-pressure relationship. Points near the origin were obtained during diastole and those in the uppermost portion of the figure were obtained at the peak of systole. When the blood temperature was decreased from 37°C to 33°C, the slope of the stiffness-pressure relationship increased from 0.055 to 0.076 ml$^{-1}$. The y-axis intercept ($\beta$) was not altered significantly. Diastolic pressure was higher during hypothermia, in part because of incomplete relaxation at a heart rate of 120 beats/min. Such an increase in pressure would increase stiffness; however, stiffness was higher than that at a comparable pressure in the control state. This observation suggests that the inadequate relaxation time was not the sole factor and that an intrinsic change in stiffness had occurred in diastole as well as in systole.

Complete data for changes in the stiffness-pressure relationships due to hypothermia (33°C) in all eight dogs are given in Table 2, and changes due to fever (40°C) are shown in Table 3. Two sets of control data are shown for each condition; one set was collected before a change in temperature was induced and the second set was obtained after the return to control conditions. During hypothermia the slope of the stiffness-pressure relationship increased ($P < 0.005$), but the y-axis intercept was not changed significantly. When the blood temperature was raised to 40°C, the slope was significantly diminished ($P < 0.001$) and the intercept again remained unchanged. These observations could have been due to changes in either the static elastic component of myocardial stiffness or the dynamic (time-dependent) mechanical components (viscosity or inertia); measurement of $\Delta P/\Delta V$ alone does not distinguish between these two components. The dynamic components of stiffness are emphasized by experiments in which rapid changes in ventricular volume occur.
TEMPERATURE AND MYOCARDIAL STIFFNESS

TABLE 2
Influence of Hypothermia on the Stiffness of the Intact Left Ventricle

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control (37°C)</th>
<th>Hypothermia (33°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (α) (ml⁻¹)</td>
<td>Intercept (β) (mm Hg/ml)</td>
</tr>
<tr>
<td>1</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>2</td>
<td>0.024</td>
<td>0.025</td>
</tr>
<tr>
<td>3</td>
<td>0.055</td>
<td>0.058</td>
</tr>
<tr>
<td>4</td>
<td>0.068</td>
<td>0.072</td>
</tr>
<tr>
<td>5</td>
<td>0.022</td>
<td>0.031</td>
</tr>
<tr>
<td>6</td>
<td>0.062</td>
<td>0.052</td>
</tr>
<tr>
<td>7</td>
<td>0.030</td>
<td>0.033</td>
</tr>
<tr>
<td>8</td>
<td>0.042</td>
<td>0.042</td>
</tr>
</tbody>
</table>

For each condition, values relating ΔP/ΔV and P defined a linear regression line with a positive slope (α) and a y-axis intercept (β), so that ΔP/ΔV = αP + β. Two control values are shown for each dog: the first value was obtained before hypothermia was induced and the second control value was recorded after hypothermia when control conditions again prevailed. NS = not significant.

The data are presented as in Table 2.

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Results of a typical experiment showing the elastic and viscous stiffness are given in Figure 4. Both elastic and viscous stiffness increased proportionally with pressure during the cardiac cycle. Hypothermia increased viscous stiffness for any given pressure both during diastole and systole; elastic stiffness was not as sensitive to the temperature change.

Tables 4 and 5 show values for elastic and viscous stiffness in all dogs that could be tested.
TABLE 5
Influence of Hyperthermia on the Elastic and the Viscous Stiffness of the Intact Left Ventricle

<table>
<thead>
<tr>
<th>Dog</th>
<th>Elastic stiffness (x10^6 dyne/cm)</th>
<th>Viscous stiffness (x10^6 dyne/cm)</th>
<th>Left ventricular pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1</td>
<td>1.5</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>0.6</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>1.4</td>
<td>1.1</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>1.8</td>
<td>0.9</td>
<td>40</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>1.7 ± 0.16</td>
<td>1.1 ± 0.21</td>
<td>44 ± 2.5</td>
</tr>
<tr>
<td>Mean difference ± SE</td>
<td>0.0 ± 0.11</td>
<td>0.2 ± 0.16</td>
<td>45 ± 2.8</td>
</tr>
</tbody>
</table>

at comparable ventricular pressures. Viscous and elastic stiffness could not be compared during diastole due to the changes in ventricular pressure associated with the temperature changes. In five hypothermic dogs and four hyperthermic dogs, the elastic and the viscous stiffness at the same ventricular pressures during systole were determined. Table 4 shows the influence of lowering the temperature from 37°C to 33°C, and Table 5 allows comparison at 37°C and 40°C. Both elastic and viscous stiffness tended to rise as temperature decreased; the change in viscous stiffness was significant. Likewise, with hyperthermia, viscous and elastic stiffness decreased; viscous stiffness seemed to be more sensitive to the temperature change. Thus, the results suggest that ventricular viscous stiffness is more sensitive to temperature changes than is elastic stiffness.

ISOLATED CAT PAPILLARY MUSCLES

The influence of temperature changes on resting tension, developed tension, maximal rate of tension development, and relaxation of cat papillary muscle strips is shown in Table 6. In the unperturbed state, resting tension and developed tension declined progressively as temperature rose from 22°C to 40°C. Simultaneously, the maximal rate of tension change during both contraction and relaxation increased with temperature, but the duration of the twitch decreased.

Mean resting tension was similar in the perturbed and unperturbed states. However, there was a consistent decline in developed tension in the presence of the length changes induced by the sinusoidal forcing function. This difference between the effects on resting tension and developed tension, called the "uncoupling phenomenon" by Brady (16), gradually increased with temperature and in this study averaged 7.8% at 22°C and 14.8% at 40°C.

Just as a linear relationship between stiffness (∆P/∆V) and pressure was observed in the intact ventricle, the comparable technique used on papillary muscle also yielded a modulus (∆T/∆L) which was linearly related to tension (T) (r > 0.9). The slopes (α) and intercepts (β) for the stiffness-tension relationships are shown in Table 6. As temperature rose, both slopes and intercepts decreased in value; this result indicates a decline in stiffness for any given tension.

As observed in the whole ventricle, both elastic and viscous stiffness rose as tension increased during papillary muscle contraction at a constant temperature. At any given tension, both elastic and viscous stiffness varied inversely with temperature (Fig. 5). Again, as with the ventricular preparation, viscous stiffness appeared to be more sensitive to the changes in temperature (Fig. 5).

Discussion

Previous experiments (1-4) have established that hypothermia prolongs the time course of cardiac contraction and increases total tension development. These findings were also observed in our studies both in intact hearts and in isolated muscle strips.

Although it has not been observed invariably (3, 4), hypothermia has been shown to increase stiffness during diastole, as evidenced by an increase in left ventricular end-diastolic pressure for a given diastolic circumference (1) or by a
Influence of Temperature on Papillary Muscle Mechanics and Stiffness

<table>
<thead>
<tr>
<th></th>
<th>22°C (absolute values)</th>
<th>Change from 22° to 27°C</th>
<th>Change from 27° to 30°C</th>
<th>Change from 30° to 37°C</th>
<th>Change from 37° to 40°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting tension (g/mm²)</td>
<td>0.521 ± 0.1213</td>
<td>+0.019 ± 0.0236</td>
<td>−0.011 ± 0.0257</td>
<td>−0.009 ± 0.0156</td>
<td>−0.021 ± 0.0170</td>
</tr>
<tr>
<td>Developed tension (g/mm²)</td>
<td>3.492 ± 0.2533</td>
<td>−0.376 ± 0.1607</td>
<td>−0.088 ± 0.0828</td>
<td>−0.193 ± 0.1719</td>
<td>−0.375 ± 0.1542</td>
</tr>
<tr>
<td>Maximum + dT/dt (g/mm² sec⁻¹)</td>
<td>8.18 ± 1.253</td>
<td>+1.62 ± 1.068</td>
<td>+0.92 ± 0.3621</td>
<td>+7.37 ± 1.4821</td>
<td>−0.07 ± 1.453</td>
</tr>
<tr>
<td>Maximum − dT/dt (g/mm² sec⁻¹)</td>
<td>0.06 ± 0.851</td>
<td>+2.09 ± 0.4821</td>
<td>+3.11 ± 0.4931</td>
<td>+11.40 ± 2.0591</td>
<td>+1.67 ± 1.749</td>
</tr>
<tr>
<td>Slope (α) (1%/L_max)</td>
<td>8.18 ± 1.253</td>
<td>+1.62 ± 1.068</td>
<td>+0.92 ± 0.3621</td>
<td>+7.37 ± 1.4821</td>
<td>−0.07 ± 1.453</td>
</tr>
<tr>
<td>Intercept (β) (g/%L_max mm⁻²)</td>
<td>6.06 ± 0.851</td>
<td>+2.09 ± 0.4821</td>
<td>+3.11 ± 0.4931</td>
<td>+11.40 ± 2.0591</td>
<td>+1.67 ± 1.749</td>
</tr>
</tbody>
</table>

Mean control values ± SE are shown for resting tension, developed tension, maximum dT/dt, the slope of the stiffness-tension relationship (α), and its intercept (β) at 22°C for eight muscles. Temperature was raised incrementally to 27°, 30°, 37°, and 40°C. *P < 0.05 compared with the value at the immediately preceding temperature. †P < 0.025 compared with the value at the immediately preceding temperature. ‡P < 0.001 compared with the value at the immediately preceding temperature. §P < 0.02 compared with the value at the immediately preceding temperature.

shift in the diastolic pressure-volume curve (2). Increased end-diastolic stiffness with hypothermia is confirmed by this study (Fig. 3).

Another aspect of mechanical effects of hypothermia on the myocardium has been investigated in papillary muscle with the use of systolic quick-release techniques (5). These experiments have demonstrated an increase in quick-release stiffness with a decrease in temperature. Such a change is usually identified as a change in series elasticity. However, as pointed out previously (12, 17), this term may be a misnomer in the sense that time-dependent (viscous and inertial) properties as well as true elastic stiffness may contribute to the total stiffness that is observed (18, 19). Indeed, the quickness of the quick release would serve to emphasize changes in viscous stiffness over those in elastic stiffness (17). The same is true, of course, for the fairly rapid sinusoidal stretches and releases which were used in the present study.

The present technique provided a means for mathematically separating the relative contributions of the elastic and viscous components of ventricular stiffness (6) and for quantifying overall stiffness throughout the cardiac cycle (11, 12, 15, 20). The data revealed that the overall stiffness of the ventricular muscle varied inversely with temperature, both during diastole and systole, at any given pressure or tension. This inverse variation was achieved by changes in both the static and the dynamic components of the muscle, and viscous stiffness was affected even more than static elastic stiffness. Previous experiments have established that overall myocardial stiffness as assessed by these techniques is not altered following simple changes in the contractile state on the order of magnitude of those encountered in this study (15, 20). Thus, the changes in stiffness that occur as temperature fluctuates cannot be solely ascribed to a simple inotropic influence.

In the present analysis, the elastic and viscous components were considered to be arranged in series with each other to simplify the mathematical treatment of the data. Anatomical identification of these components has not been attempted; clearly, a given anatomical structure could have both elastic and viscous stiffness and different structures could display differing proportions of the two. Complete identification of the various components defined by the present model in terms of the classically described model of A. V. Hill (21) has not been attempted, but a few comparisons can be made. Hill assumed that the elastic elements in his model would display time-independent elastic properties (18). In that framework, during diastole the viscoelastic stiffness of our model is equivalent to the net stiffness of either the parallel elastic element (Maxwell model) or to a combination of the parallel and series elastic elements (Voigt model). During systole viscoelastic stiffness in our model corresponds to the net stiffness of the series elastic element plus the contractile element. If, as Brady has done (22), one assumes that the series elastic element displays only time-independent elastic properties
and that all viscous properties reside in the contractile element, then the elastic stiffness of our model during systole and that of Brady’s model are identical. Both Brady’s analysis and ours reveal that the elastic stiffness of cardiac muscle is proportionally related to tension; this observation implies that the relationship between length and tension is exponential and supports the concept of nonlinear elastic stiffness in cardiac muscle.

Elastic and viscous stiffness measured by the sinusoidal forcing technique provide a means of characterizing cardiac mechanics in terms other than those of the Hill model which, after all, is not without major inadequacies (23, 24). We hope that the new approach described in this manuscript has validity even if the various components of our model do not fall under labels of contractile element, series elastic element, and parallel elastic element. Indeed, neither myocardial tissue nor the sarcomere is structured in such a way that their anatomical components can be compartmentalized neatly and unequivocally as purely parallel elastic, etc. Perhaps an alternative way of describing mechanical events and identifying model components may provide fresh insights into structure-function correlations, just as the Hill concept has done for the past several decades.

The purpose of this study was to define relative changes in viscous and elastic stiffness. For this purpose, the use of a single standard perturbation frequency is completely sufficient. Almost any frequency would do, and we arbitrarily chose a convenient one for each preparation; the only stipulation in the choice of frequencies was that viscous stiffness had to be measurable at the selected frequency. The absolute values derived from this approach are obviously not applicable to all conditions, but the relative degree of change in viscous and elastic components (with each muscle serving as its own control) should provide useful and broadly applicable information.

Finally, the results obtained in intact dog hearts were qualitatively similar to those observed in isolated cat papillary muscles. One interesting difference was noted in the influence of the sinusoidal perturbations on the ability of the myocardium to develop tension or pressure. Papillary muscles were not able to develop as much tension during the perturbed state as they were during the unperturbed state (Table 6). This and related phenomena have been observed previously in cardiac muscle in vitro (15). Brady
(16) has reported that any contractile element shortening or stretching that is imposed externally during contraction causes an uncoupling of the active state and a decline in contractility. Analysis of the data shown in Table 6 suggests that the extent of uncoupling is temperature dependent. The average developed tension during the sinusoidal stretch is 7.8% less than the tension achieved without the stretch. The extent of uncoupling increases with temperature until a maximum of 14.8% difference is reached at 40°C. Similar uncoupling was not observed in vivo; the reason that such a phenomenon is restricted to the isolated system remains unclear. It is interesting to speculate that this difference may be related to a difference in the sinusoidal forcing functions used in vivo and in vitro. Whereas length changes are imposed on the papillary muscle, a combination of length and load changes might have been imposed by the volumetric forcing function. If this speculation is true, then the observed difference in the active state destruction is understandable, since Brutsaert et al. (25) have shown that load damping, i.e., instantaneous changes in load, does not alter the active state.

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