Physiological Loading of Isolated Mammalian Cardiac Muscle

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SUMMARY Cat papillary muscles were subjected to a complex loading function resulting from an analysis of the heart as a pump. The papillary muscle was assumed to be a hypothetical bundle of circumferential muscle fibers in the wall of a simplified cylindrical ventricle. The loading included inertial, resistive, and capacitive components of the cardiovascular system. Changes of ventricular dimensions were taken into account by application of a Laplace relationship. When this complex dynamic loading function was imposed on a shortening muscle by means of an electromagnetic feedback system, the developed force continuously changed with time. The time course of this changing force corresponded to the time course of calculated stress in the intact ejecting heart. Directly displayed force-velocity loops also were similar to loops obtained for the intact heart. Loads proportional to velocity of shortening (damping), acceleration of shortening (inertia), and to the square of shortening velocity (Bernoulli) were investigated separately. Cardiac muscle appeared rather insensitive to inertial loads, and the contribution of inertial loads in the early phase of a contraction under physiological pump loading was minimal. Moreover, during all these dynamic loadings, as long as loading was dynamically increasing or decreasing, velocity of shortening was respectively lower or higher at any muscle length and total load, when compared to velocity at the same length and load under static (constant preload and afterload only) loading.

Methods

In this study we used 37 papillary muscles from the right ventricle of the cat. The criteria for selection of suitable muscles have been published previously. The muscles were suspended vertically in a bath containing modified Krebs-Ringer solution containing (in mM): NaCl, 118; KCl, 4.7; MgSO4, 1.2; KH2PO4, 1.1; NaHCO3, 24; CaCl2, 2.5; and glucose, 4.5. This solution was gassed with 95% O2-5% CO2. The muscles were stimulated at 30/min with rectangular pulses, 5 msec in duration and about 10% above threshold. The stimulus was provided through two platinum electrodes arranged longitudinally with one on each side of the muscle. In order better to mimic physiological conditions temperature of the muscle was held at 36°C. We allowed an initial recovery period of 3–4 hours at 29°C and at a stimulation frequency of 12/min prior to the actual experiment. The lower, nontendinous end of the muscle was held by a light phosphor bronze clip soldered to the middle of the spring of a force transducer. The tendinous end of the muscle was tied with a short thread (7.0 braided, noncapillary, moisture- and serum-resistant, Deknatel, Surgical Tevdek, Code 103-T) extending upward to the electromagnetic lever system. The electromagnetic lever system, the force transducer, and the force generating control systems with the electronic circuits for additional damping force have been described previously.

The preload on the muscle was adjusted so that the initial muscle length corresponded to Lmax, that is, the length at which active tension development was maximal. All test contractions were recorded under "stable" conditions; i.e., separated by a series of at least six equally loaded standardized contractions. Throughout the experiment the loading of these intervening standardized contractions was the preload at Lmax.

For each contraction, the time courses of shortening, shortening velocity, acceleration, force, work, and power were recorded on a storage display unit (Tektronix 611) and photographed with a hard copy unit (Tektronix 4601). For a few experiments simultaneous phase-plane velocity-length
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Analyses were recorded and displayed in a three-dimensional way by subtracting the force signal simultaneously from the length and velocity signals by means of two operational amplifiers. Because of the complex influence caused by the dynamic loadings on relaxation, this phase was omitted from the present study.

Analysis of Physiological Pump Loading

The load of an ejecting ventricle includes inertial, resistive, and elastic components. The ventricular pressure during systole, P

\[ \text{P}_{\text{ventr}} = M' \times \frac{dQ}{dt} + R \times Q + \frac{1}{C} \int_{t_1}^{t_2} Q \, dt + P_{\text{Aorta}} \]  

(1)

where \( P_{\text{ventr}} \) is ventricular pressure, \( M' \) is the mass of the ejected blood, \( Q \) is the blood flow, \( R \) and \( C \) are resistive and capacitive constants of the vascular system, and \( t_i \) and \( t_f \) refer to onset and end of ejection.

In the present study the papillary muscle was assumed to be a circumferential bundle of muscle fibers in the wall of a cylindrical ventricular model. The long axis of this simplified ventricle was assumed as being constant and the thickness to diameter ratio of its wall, small. The ends of the cylinder remained flat and the area changed without affecting the cylindrical surface. During ejection only circumferential fiber shortening was considered. For this ventricle,

\[ V = \pi r^2 L \]

(2)

where \( V \), \( r \), and \( L \) are volume, radius, and length of the ventricle. Since the papillary muscle was assumed to be a bundle of fibers in a hypothetical circumferential ring of this cylindrical ventricle,

\[ 2\pi r = kl_m \]

(3)

or

\[ r = \frac{kl_m}{2\pi} \]

(4)

where \( l_m \) is the papillary muscle length and \( k \) is a constant, that is, the ratio of ventricular circumference to papillary muscle length.

From Equations 2 and 4:

\[ V = \frac{k}{4\pi} l_m \]

(5)

and since cylinder length \( L \) was assumed to be constant,

\[ Q = \frac{dV}{dt} = \frac{k}{2\pi} l_m \frac{dl_m}{dt} \]

(6)

From Equation 6:

\[ \frac{dQ}{dt} = \frac{k}{2\pi} (v^2 + l_m a) \]

(7)

where \( v \) is the velocity of shortening, and \( a \) is the acceleration of the papillary muscle (or hypothetical ventricular wall).

From Equations 1, 6, and 7:

\[ P_{\text{ventr}} = \frac{M'kL}{2\pi} (v^2 + l_m a) + R \frac{kL}{2\pi} (v l_m) + \frac{l}{C} \int_{t_1}^{t_2} Q \, dt + P_{\text{Aorta}} \]

(8)

Since \( l_m \) \( Q \) dt is the volume of blood being ejected during systole and hence leaving the ventricle:

\[ \int_{t_1}^{t_2} Q \, dt = - \frac{kL}{2\pi} l_m dl_m \]

or

\[ \int_{t_1}^{t_2} Q \, dt = + \frac{kL}{4\pi} (2l_m \Delta l - \Delta l') \]

where \( l_i \) and \( l_f \) are initial and final muscle lengths of the ejected muscles, and \( \Delta l \) is the length over which the muscle has shortened.

Accordingly, Equation 8 can be written as:

\[ P_{\text{ventr}} = \frac{M'kL}{2\pi} (v^2 + l_m a) + \frac{RkL}{2\pi} (v l_m) + \frac{kL}{4\pi} (2l_m \Delta l - \Delta l') + P_{\text{Aorta}} \]

(9)

When \( F \) is the force developed by a single bundle in one ring, then for \( n \) circular rings of end-to-end attached bundles of fibers in the ventricular wall:

\[ nF = rLP_{\text{ventr}} \]

(10)

From Equations 11 and 4:

\[ F = \frac{k}{2\pi} \frac{l_m L}{P_{\text{ventr}}} \]

(11)

From Equations 10 and 12 it follows that the force developed by a single bundle of fibers in a circumferential ring can be approximated as:

\[ F = \frac{M'kL}{2\pi} (v^2 + l_m a) + \frac{RkL}{2\pi} (v l_m) + \frac{kL}{4\pi} (2l_m \Delta l - \Delta l') + P_{\text{Aorta}} \]

(12)

The actual values used for the different constants were: \( R = 4.720 \text{ g-cm}^{-x} \text{sec}^{-1} \) (Westerhof et al.); \( P = 80 \text{ mm Hg} \) or \( 10.6 \times 10^4 \text{ dyne/cm}^2 \); \( C = 55 \times 10^{-9} \text{ g}^2 \text{cm}^4 \text{sec}^{-1} \) (Westerhof et al.); \( L = 3.6 \text{ cm} \) (Gabe); \( M' = 12 \text{ g-cm}^{-x} \); and \( N = 500 \) for cross-sectional area of 1 mm² (Gabe). \( M' \) was defined as \( \rho \lambda \) divided by \( d \), where \( \rho \) (1 g-cm⁻³) was the blood density, \( d \) the area of the ventricular outflow tract (0.78 cm² for a ventricular diameter of 2 cm), and \( \lambda \) the length of the ejected blood column. The estimated ratio of the amount of blood ejected to ventricular volume was 8/13, and for a ventricular volume of 11.3 cm³ the stroke volume was 7 cm³, and \( \lambda \) was 9 cm. Hence the calculated value of \( M' \) was 12 g-cm⁻⁴. This value was augmented by 25%, to 16 g-cm⁻⁴, to encompass a larger range and account for less well defined inertial effects.

The number, \( n \), of circumferential rings of end-to-end attached bundles of muscle fibers in the wall is defined as \( n = (N/k) \), where \( k = (2\pi/k_m) \) (Eq. 4) or the number of isolated bundles of fibers (or papillary muscles) in one circumferential ring. For a given papillary muscle the \( k \) value was not changed. The relative constancy of \( k \) was justified by the simultaneous increases of \( r \) and \( l_m \) when the hypothetical ventricular volume was altered. For papillary muscles with a cross-sectional area different from 1 mm², the number of fiber bundles in the ventricular wall.
was proportionally altered according to \( N = 500 \) divided by the cross-sectional area.

After omission of some terms, i.e.,

\[
\left[ \frac{M^2}{2\pi} v^2 \right]^{2} - \frac{k^2 L^2}{4\pi C} \left( \frac{k l_m}{2\pi} \right)
\]

which could be neglected as based on the data for \( v^2 \) and \( \Delta L^2 \) in an afterloaded (at about 50% of peak force) contraction of an isolated cat papillary muscle, Equation 13 was rewritten (see Appendix) as:

\[
F = \frac{k^2 L^2}{4\pi^2} \left[ \frac{M^2}{2\pi} v^2 + \frac{1}{C} \right] + \frac{k L}{2\pi} l_m P_{Aerio}.
\]

This complex dynamic loading of a simplified ejecting ventricle was imposed on 19 contracting papillary muscles by means of electrical analog computing techniques which controlled the current through the coil of the electromagnetic lever system to which the muscles were attached. The characteristics of the 19 muscles used in this part of the study are summarized in Table I. The results were uniform for all muscles. For the electronic circuit the formula was rewritten (see Appendix) as:

\[
F = K_1 l_m ^2 \left[ K_2 v + K_3 \Delta L \right] + K_4 l_m P_{Aerio}.
\]

where \( a, v, l_m, \) and \( \Delta L \) were acceleration, velocity of shortening, instantaneous total length, and change of length of the contracting papillary muscle, and \( K_1, K_2, K_3, K_4 \) were constants of the circuit. \( K_1, K_2, K_3, \) and \( K_4 \) were known constants which did not change with muscle size. \( K_1, K_2, \) and \( K_4 \) did change with muscle size and were computed for every muscle using the modified version of Equation 13 (Table 1). At the beginning of each experiment muscle length, \( l_m \), was measured at \( l_{max} \), where cross-sectional area was estimated, assuming that the preload at \( l_{max} \) was approximately 10 mN/mm² for most muscles.

**SEPARATE ANALYSIS OF DAMPING, INERTIA, AND BERNOULLI EFFECT**

To simulate loads due to damping, acceleration, and the Bernoulli effect the voltage applied at the input of the current source of the electromagnetic lever system must be proportional to \( v, a, \) and \( v^2 \). In order to analyze the effects of these three dynamic loadings separately and over a continuously varying range, a second analog electronic circuit (see Appendix) was designed to obtain \( C_v, C_a, \) and \( C_{v^2} \), where the constants \( C_v, C_a, \) and \( C_{v^2} \) could be set anywhere between zero and their maximal value. The Bernoulli effect, which had been omitted in Equation 13, was included in the new circuit as \( C_{v^2} \). Eighteen papillary muscles were used for this analysis. Data for these muscles are not included in Table 1.

**Results**

**INFLUENCE OF PHYSIOLOGICAL PUMP LOADING ON A CONTRACTING PAPILLARY MUSCLE**

Figure 1 (bottom) shows the time course of shortening (1), velocity of shortening (v), mechanical work (W), power (P), and force (f) of a papillary muscle subjected to the simulated loading of an ejecting ventricle. For comparison, an afterloaded isotonic contraction is illustrated above. During physiological loading force continuously changed with

**Table 1 Basic Characteristics of Muscles**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>( l_{max} ) (mm)</th>
<th>Preload at ( l_{max} ) (mN/mm²)</th>
<th>Cross-sectional area (mm²)</th>
<th>( K_1 ) (cm⁻¹)</th>
<th>( K_2 ) (cm)</th>
<th>Unloaded shortening velocity at zero load (mN/sec)</th>
<th>RT/TT</th>
<th>Time to peak tension (msec)</th>
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<td>8.7</td>
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<td>0.12</td>
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</table>

Basic characteristics of the 19 muscles used in the first part of the study. All measurements were made at \( l_{max} \), i.e., the length at which maximal active tension was developed. RT/TT = ratio of resting to total tension at \( l_{max} \). Maximal unloaded velocity of shortening at zero load was obtained by a critically damped zero load clamp. * Since active peak tension of these muscles was too low with respect to the cross-sectional area, somewhat lower values for \( K_1, K_2 \) were used than the ones calculated on basis of muscular dimensions (\( K_1, K_2 \) are calculated from the simplified version of Equation 13) and from Equation 14.
Figure 1 Effects of physiological pump loading on a shortening cat papillary muscle (Table 1, muscle 13). Above: control contraction with constant preload and afterload. Below: contraction with $K_1/A = (K_d + K_{1v} + K_2\Delta l) + K_1P_{ref}$. Relaxation is not shown. $I =$ amount of shortening (refers to $\Delta l$ in Equation 14); $V =$ velocity of shortening; $W =$ mechanical work; $P =$ power; $f =$ force.

Figure 2 illustrates the influence of this loading for a low (Fig. 2, top) and high (Fig. 2, bottom) value of $l_{max}$ in Equation 13 or, alternatively, for a low and high value of the potentiometer $P_1$ (see Fig. 9, Appendix). These alterations mimicked the loading on a bundle of fibers in the wall of a smaller vs. a larger ventricle, but not accompanied by changes in resting tension. The higher value for $l_{max}$ corresponded to the measured value of $l_{max}$ for this papillary muscle, whereas the lower one was nearly 35% less. For this latter condition (Fig. 2, top) force development was markedly diminished owing to a more favorable Laplace relationship during the isometric phase and to the lower loading during ejection (Eq. 13). In the former condition mimicking the larger ventricle (Fig. 2, bottom), times to peak force, power, and work were prolonged by 35, 30, and 15 msec, respectively. Because of the difference in loading, peak shortening and peak velocity were highest for the case in which the smaller ventricle was simulated, whereas peak work and peak power were highest for the larger ventricle.

In Figure 3, the contractions illustrated in Figure 2 are simultaneously displayed in a velocity-force coordinate system. The loop on the left corresponds to the smaller length, i.e., smaller ventricle, the loop on the right corresponds to the longer length, i.e., larger ventricle. The middle loop was recorded at an intermediate length, not shown in Figure 2. The arrows indicate the direction of the loop during ejection.
Figure 2. The influence of changes in dimensions of the hypothetical ventricle on papillary muscle contraction with ventricular pump loading (Table I, muscle 13). Upper panel is for a low value of $l_m$ and the lower panel is for a higher value of $l_m$. Symbols as for Figure 1.

Figure 4 illustrates the effects of two values of $K_1$ in Equation 14, mimicking variations in peripheral vascular impedance. For the upper contraction, $K_1$ was 0.56 cm$^2$. This value for $K_1$ corresponds to a measured $l_{max}$ length of 11 mm and an estimated cross-sectional area of 0.8 mm$^2$. In the lower panel, the value for $K_1$ was augmented to 1.10 cm$^2$, thus simulating an increased contribution of the vascular impedance. During the isometric phase force development was equal for both contractions. During ejection, with the higher $K_1$ value force was markedly enhanced with a concomitant diminution in extent and velocity of shortening but with work and power being nearly unchanged due to the augmented force.

In Figure 5, force and velocity of shortening of the same two contractions were displayed simultaneously in a velocity-force coordinate system. The left loop corresponds to the contraction with the lower $K_1$ value, hence with the lower simulated peripheral impedance. In Figure 6 the relative contribution of the different terms in Equation 14 are analyzed. The top curve represents the contraction of a papillary muscle (length = 11 mm, estimated cross-sectional area = 0.8 mm$^2$) with the entire feedback system working. The middle curve was registered after omission of the capacitive term, that is, $K_4 = 0$. The lower curve represents the loading resulting from the last term, that is, $K_1 = 0$. The curve obtained with a loading where $K_4 = 0$ and $K_1 = 0$, i.e., with inertial force and $K_1{l_{max}}$P term only, coincides with the lower curve. Despite the fact that $K_1$ had been increased by
Figure 3 Velocity-force relationships for contractions recorded at various ventricular dimensions. See Figure 2.

more than 25% with respect to the initial calculated value, it was clear that inertial forces made a negligible contribution to the loading.

SEPARATE ANALYSIS OF VARIOUS DYNAMIC LOADINGS ON A CONTRACTING PAPILLARY MUSCLE: DAMPING, INERTIA, AND BERNOULLI EFFECT

Figure 7 (left) shows the effects of three degrees of damping \( C_{1/2} \) on shortening, velocity of shortening, acceleration, and force of a preloaded contraction. The highest damping corresponds to the maximal value for the proportionality constant \( C_1 \). The middle curve corresponds to a damping which was intermediate between the inherent damping of the muscle and system (control curve) and the higher damping. As damping was augmented peak velocity of shortening and peak acceleration were proportionally decreased. At any time during the contraction the extent of shortening also was proportionally less. Due to the continuous increasing load at any damping, peak shortening and peak velocity of shortening were progressively delayed in time.

Figure 7 (middle), shows the effects of inertia \( C_{4/2} \) on a preloaded contraction of the same muscle. Two degrees of inertia were imposed. As outlined in Methods, the higher inertia corresponded to 8 g or about 50 times the moving mass of the muscle-lever system. When inertia was augmented, the initial courses of shortening, velocity, and acceleration were slowed. Though delayed, peak acceleration was only slightly decreased, despite the rather high inertial value. Most surprising was the higher peak velocity at the higher inertia after the initial retardation of velocity and before the point at which force became lower than the preload. Hence, it is clear that this higher peak velocity did not ensue from an increased momentum of the lever with a concomitant retardation of deceleration.

Figure 7 (right) shows the influence of a force proportional to \( \nu^3 \) \( C_{1/3} \) on a preloaded contraction. Two degrees of \( C_{1/3} \) loading were imposed on the muscle by using two values for the proportionality constant \( C_3 \). The higher value corresponded to the maximal proportionality constant \( C_3 \) of the electronic circuit. The intermediate load was obtained by choosing an arbitrary intermediate value for \( C_3 \) [approximately 0.12 mN/(mm/sec)^3]. The observations were qualitatively similar to the findings with increased damping. They were more pronounced owing to the relatively wider range of the proportionality constant \( C_3 \), and since, for any value of shortening velocity higher than 1 mm/sec, the additional force of \( \nu^3 \) load \( \Delta f = C_{1/3} \nu^3 \) would be higher than the damping force \( \Delta f = C_{1/2} \nu^2 \) when unit values were used for the proportionality constants.

Figure 8 displays the force-velocity-length relations of a "dynamic" loading in a three-dimensional manner. All oscilloscope tracings were directly displayed on the left and redrawn on the right for clarity. The control force-velocity-length surface was constructed with four contractions (curves A, B, C, and D) with "static" (i.e., constant preload and afterload only) loads of 8.0 mN/mm^2 (preload 1 mN), 14.7 mN/mm^2, 19.3 mN/mm^2, and 34.7 mN/mm^2. This surface defines the contractile performance of the muscle under the given conditions of 36°C and 30 stimuli per minute. Superimposed is shown a contraction (curve E) with a \( C_{1/3} \nu^3 \) load. The projections of this contraction on the velocity-length (curve G) and force-length (curve F) plane were directly displayed by removing either the force or the velocity signal at the input of the two-operational amplifiers which were used for these three-dimensional constructions. As long as loading was increasing, the dynamically loaded contraction at any given length and total force moved beneath the surface derived from the statically loaded contractions. This is clearly illustrated by considering point d, which is the intersection of the projection of the dynamically loaded contraction with the projection of the 14.7 mN/mm^2 static load reference curve on the force-length plane. In both contractions point d corresponded to the same muscle length, ob, and the same total load of 14.7 mN/mm^2. Under static loading a velocity of 0.78 m/sec (dc) was noted. Under dynamic loading at the same muscle length (ob) a velocity of 0.57 m/sec (ab) was registered on the projection in the velocity-length plane. This velocity value (ab) was nearly 27% lower than under static loading (dc).

On the other hand, the increased velocity of the dynamically unloaded part of the contraction is quantitatively illustrated at point h. This point is the intersection of the projection of the dynamically loaded contraction with the projection of the 14.7 mN/mm^2 static load reference curve on the force-length plane. In both contractions point h corresponded to the same muscle length (of) and the same total load of 14.7 mN/mm^2. At this static total load a velocity of 0.47 m/sec (gh) was noted, whereas under dynamic unloading at the same muscle length (of) a velocity of 0.52 m/sec (fc), that is, 10% higher, was registered on the projection in the velocity-length plane. At muscle length (oj) the projection of the static load curve at 19.3 mN/mm^2 on the force-length plane was tangent to the top of the projection of the dynamically loaded contraction. At this
length the same velocity ($ij = kl = 0.65 l_{max}/sec$) was observed. Hence, when total load was neither increasing nor decreasing, velocities measured under conditions of static and dynamic loading were equal at the same muscle length and total load. Qualitatively comparable results were obtained when the influence of either damping or inertial loadings or the more complex dynamic loading of Equation 13 were analyzed in terms of the force-velocity-length relation.

**Discussion**

By analogy to skeletal muscle, cardiac muscle was formerly analyzed in terms of basic muscle concepts, i.e., force (F) as determined by constant preload and afterload, shortening ($\Delta l$), length ($l_m$), and velocity of shortening ($v$). Only recently attention was called to aspects inherent to a combined muscle pump system. In the present study, force, length, and velocity and derivations, i.e., acceleration ($a$), work (W), and power (P) were analyzed for papillary muscles which were assumed to be hypothetical bundles of muscle fibers in the wall of a simplified ejecting ventricle. In addition to static preload and afterload, the load sensed by these muscle fibers encompassed inertial, resistive, and capacitive components:

$$F = K_{la} l_m^2 + K_{av} + K_{a\Delta l} + K_{a\Delta l} P_{Aor.}$$

(1) (2) (3) (4) (5)

Term 2, or the inertial term, resulted from the acceleration of the ejected mass of blood. The range of this term was...
increased by approximately 25% through alterations of the constant $K_i$ in order to encompass less well defined moving masses in the system, e.g., moving walls of ventricle and of the vascular system, the downward propulsion of the heart during ejection, etc. Term 3 included the resistive components of the vascular impedance. Internal friction and viscosity within the ventricular wall fibers and intramural compressive forces were omitted in this term. Term 4 accounted for the capacitive elastic distention of the vascular system during ejection, e.g., Windkessel phenomenon, etc. Multiplication of all three terms with term $l_m^1$ reflected the influence of changing ventricular dimensions during ejection, i.e., Laplace relationship. Term 5 was the pressure required to open the aortic valves ($P_{Aoa}$ - aortic diastolic pressure) and reflected the combined preload and afterload. It also included a Laplace relationship.

When this complex dynamic loading was imposed on a shortening papillary muscle by means of an electromagnetic feedback system, the developed force changed continuously with time. The time course of this changing force corresponded to the time course of calculated stress in the intact ejecting heart. This agreement with model-dependent stress curves derived from the intact heart is the more striking when it is realized that the present analysis of muscle pump integration has taken into account only the most relevant variable loadings.

Agreement with data obtained from the intact heart also was found when the present experiments were directly displayed as force-velocity loops. The opposite sense of rotation of the stress-velocity loops, in the studies of the intact heart, could perhaps be ascribed to the different methods used for velocity standardization.

As is obvious from Figure 6, the contribution of inertial loads to the total physiological pump loading was negligible. Moreover when, for Figure 7, constant $C_i$ was set at 8 g of mass, hardly any deviation of the performance of a pre-loaded contraction was noted. This minimal deviation totally disappeared when the same inertial load was imposed on an afterloaded contraction. In a few experiments, inertial load was further augmented to extremely high values of 45 g, that is, 270 times the inherent inertia of the muscle-lever system, by increasing constant $K_i$ with maximal $K_s$ and with $K_s$ and $K_i$ at zero. Except for a slightly more marked, though still negligible, delay of initial velocity, the results with respect to the augmented peak velocity were essentially similar. Moreover, this peak velocity value appeared to be maintained at a plateau for a short period. Hence, the assumption that initial pressure or force development in the intact heart or cardiac muscle would depend entirely on inertia and would induce a concomitant preload-independent acceleration is challenged by the present results. Cardiac muscle appears rather insensitive to inertia, and the impact of inertia on the early phase of a contraction under conditions of physiological pump loading is minimal. As initial force development is determined by dynamic loadings other than inertia, maximum acceleration, which depends on this initial force, ought to depend mainly on changes in the vascular impedance or the ventricular geometry.

Furthermore, all three "dynamic" loadings, i.e., damping, inertia, and Bernoulli effect, although distinct in nature, elicited similar changes of the various aspects of isolated cardiac muscle contraction when compared to those derived from "static" (constant preload and afterload) loading experiments. Velocity of shortening during dynamic loading, when considered as a function of time, was lower than in the statically loaded contractions as long as additional "dynamic" loading was positive. It reached higher values during part of the unloading phase of the dynamically loaded contraction. Since damping loads were proportional to shortening velocity and shortening velocity reached a peak value in the middle portion of the contraction, maximal damping load and the transition of a continuously changing loading to a continuously changing unloading occurred almost halfway during the contraction. During subsequent unloading following peak shortening velocity, higher velocities were recorded than in the control contractions. These observations were more marked with inertial loads ($C_{ia}$). As peak acceleration occurred early in the contraction, peak inertial load, too, occurred early in the contraction. Since peak velocity occurred in the declining part of this dynamic loading, the transition from loading to unloading occurred prior to peak shortening velocity, which
was consequently higher. With $C_v^2$ loads, findings similar to those as with damping were encountered.

The deviation between dynamic and static loading could most clearly be shown by the interpretation of three-dimensional plottings of the force-velocity-length relation of contractions under both conditions. These three-dimensional constructs illustrated the depressive effect of increasing dynamic loading on cardiac muscle performance compared to the contractile behavior under static loading. On the other hand, as soon as load was decreasing, contractile performance of the muscle was increased. Only when there were no load alterations did cardiac muscle performance coincide under static and dynamic loading. This result would not be surprising if one would accept the presence of a so-called series elastic element in cardiac muscle, since it is only when the series elastic element is not changing in length, and therefore only at this point, that one is measuring true contractile element velocity. This point, at which the dynamically loaded contraction crossed the three-dimensional surface, would be the only point at which the principles of cardiac muscle contractility, as defined in static loading experiments, could be applied in conditions of dynamically changing loading as encountered in the pumping heart.

Hence, as long as the loading conditions were changing, shortening velocity at any length and total load deviated from the previously defined time-independent force-velocity-length relation derived from isolated cardiac muscle under static loading conditions. Accordingly, the application of
this concept of cardiac muscle contractility or of any derived index resulting from statically loaded isolated cardiac muscle experiments might be rather unreliable for the interpretation of data derived under dynamically changing loads as encountered in a pumping ventricle. Hence, the validity of force-velocity measurements or of any derived index resulting from statically loaded isolated cardiac muscle experiments might be rather unreliable for the interpretation of data derived under dynamically changing loads as encountered in a pumping ventricle. Hence, the validity of force-velocity measurements or of any derived index in the heart might be doubtful, since there is no way to distinguish these deviations of shortening velocity due to changing loading from true alterations in contractility. It thus seems that muscle concepts as directly derived from skeletal muscle physiology should no longer forcibly be applied to the intact heart. The nature of the loading during muscle shortening in the ventricular wall is quite different from that in previous studies on isolated papillary muscle. The ventricle is not called on to lift a constant load but to eject a viscous fluid into a viscoelastic vascular system. Further investigations on muscle pump integration and on pump vascular load interaction might open new perspectives in the evaluation of ventricular function. Obviously, results as described in the present experiments can merely provide directional information at present rather than new definitions or new so-called indices.

**Appendix: Electronic Circuits**

**ANALYSIS OF PHYSIOLOGICAL PUMP LOADING**

Figure 9A illustrates the analog computation technique for the load simulation (Eq. 14),

\[ F = K_1lm[K_{aA} + K_{av} + K_{a} \Delta l] + K_{s}lmP. \]

Each term of the formula can be considered separately.

1. **\( l_m \)**: The length transducer provided the \( \Delta l \) signal. To obtain the instantaneous total muscle length, \( l_m \), the \( \Delta l \) signal was subtracted from a constant voltage, representing a resting length \( L_0 \). Prior to the experiment, this voltage was set by a potentiometer \( (P_s) \) using the measured \( l_{max} \) as reference length. The dial was calibrated from 5 to 11 mm, corresponding to the normal length range of papillary muscles. The length signal \( l_m \) was squared by a transconductance multiplier to obtain \( l_m^2 \).

2. **\( K_{a} (K_{aA} + K_{aV} + K_{a} \Delta l) \)**: The \( M \) signal was differentiated twice to obtain velocity and acceleration. Because the \( \Delta l \) and the acceleration signals were negative, the sign of the velocity signal was changed by an operational amplifier (\( R_7 = R_8 \)). Since the amplification of the operational adder...
equals the ratio of the feedback resistor (R₁) to the input
resistors (R₂, R₃, and R₄), the three signals were added with a
weighting network. By proper scaling, these ratios represented
the constants K₁, K₂, and K₃, where K₃ = R₂/ R₁; K₂ = R₃/ R₁;
K₁ = R₄/ R₁. The output voltage, providing K₃v + K₄Δl, was amplified by an additional
operational amplifier with potentiometer P₁ as feedback re-
sistor and hence the amplification (P₂ > R₁) or attenuation
(P₂ < R₁) of the circuit was K₆ = P₂/ R₁. The dial of this
10-turn potentiometer was set to the computed value of K₆
to the experiment. The output voltage of the ampli-
fier was K₅(P₅m). This signal was multi-
plied with lₘ to obtain K₆(lₘ² + K₅v + K₆Δl). A negative
current was added to the amplifier: its output was zero in the relaxing
phase of the muscle.

The output voltage of each circuit was scaled by appropriate
time constants and amplification or attenuation factors.
These voltages were checked during the contraction of a
representative papillary muscle.

SEPARATE ANALYSIS (FIG. 9B) OF DAMPING (C₃t),
INERTIA (C₄m), AND BERNOULLI EFFECT (C₅t)

C₃t: A voltage proportional to the velocity of shortening
was delivered by an active differentiator. The damping
constant C₃t was computed from the transducer constants of the
electromagnetic lever system. The resulting force of a hypothetical muscle contracting from a
given resting length with a given length change, velocity,
and acceleration. The actual values for R, C, M, P₉, R₈, L, and N, mentioned under Methods, were taken into ac-
count for computing the resulting forces. With these data,
the output voltage of each circuit was scaled by appropriate
time constants and amplification or attenuation factors.

These voltages were checked during the contraction of a
representative papillary muscle.

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CORONARY COMPRESSION DURING FIBRILLATION/Downey

Summary We performed experiments to test whether the subendocardial ischemia which reportedly accompanies elective ventricular fibrillation (VF) during cardiopulmonary bypass might be the result of mechanical compression of the coronary vessels. The left coronary artery of the open-chest, anesthetized dog was cannulated and perfused with arterial blood through an extracorporeal circuit. Coronary inflow rate was held constant with a pump and the coronary vessels were dilated maximally by infusing adenosine. Any change in perfusion pressure or the transmural distribution of flow in these hearts would have to be due to changes in compression. When the hearts were stopped in diastole by vagal stimulation, infusion of microspheres 15 μm in diameter revealed a subendocardial to subepicardial (inner to outer) flow ratio (I/O) of 1.2. When the same hearts were caused to fibrillate spontaneously (not electrically maintained) the I/O fell to 0.9. Little change in coronary perfusion pressure occurred between arrest and VF. When the contractile activity during VF was attenuated by intracoronary sodium pentobarbital (120 mg) the I/O rose toward that seen during arrest. However, augmentation of muscle activity by infusion of isoproterenol during VF failed to change the I/O. Finally the I/O fell in proportion to the degree of distention in the fibrillating ventricle. The results that we observed indicate that muscular contraction during VF preferentially inhibits subendocardial flow through vascular compression.

There is evidence that elective ventricular fibrillation performed during cardiopulmonary bypass often is associated with subendocardial ischemia. Myocardial necrosis and infarction commonly occur in these patients. Experiments on animals also have demonstrated that fibrillation redistributes coronary blood flow away from the subendocardium. This effect is most pronounced when fibrillation is maintained electrically, when isotropic drugs are present, or when perfusion pressure is reduced.

It has been assumed that this redistribution of flow is the result of an elevated subendocardial tissue pressure that compresses the vasculature and thus reduces blood flow during fibrillation. However, previous studies of the beating heart indicate that shortening of the myocardial fibers per se does not contribute to the genesis of a transmural pressure gradient; rather, pressure development in the ventricular lumen was the only determinant of this gradient. Even when the length of shortening is altered greatly by changing the isotropic state, if afterload remains constant there is little effect on the degree of vascular compression. It must be asked, therefore, whether the redistribution of flow during fibrillation is due to some bizarre pattern of vasomotion which is unique to fibrillation, or whether in fibrillation there is selective compression of subendocardial vessel in the absence of an elevated ventricular pressure. The present study is an attempt to answer this question by examining the distribution of coronary flow in hearts in which the coronary vessels were maximally dilated by infusion of adenosine and coronary flow was held constant with a pump. Any change in perfusion pressure or distribution of coronary blood flow in these hearts, then, would have to result from changes in intramyocardial compression. With this preparation the effects of vagal arrest and spontaneous fibrillation were compared. The effects of altering the inotropic state and of distention in the fibrillating ventricle also were examined.

Methods

Seventeen mongrel dogs of either sex and 16–21 kg in weight were anesthetized with sodium pentobarbital (30 mg/kg), supplemented thereafter with additional anesthesia as required. A thoracotomy was performed in the left fourth interspace and respiration was monitored with a positive pressure respirator and 100% oxygen. The left coronary artery was exposed at its origin and cannulated with a double-lumen cannula. The perfusion apparatus was used to withdraw blood from the aorta via the outer lumen of the cannula (Fig. 1). Flow in the circuit was measured using a Carolina Medical Electronics 501 flowmeter and an extracorporeal flow probe. Cuffs were glued to the perfusion line, and the tubing was placed in a Sigma motor.

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Physiological loading of isolated mammalian cardiac muscle.
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