End-Systolic Pressure-Volume Relation Estimated from Physiologically Loaded Cat Papillary Muscle Contractions

WALTER J. PAULUS, VICTOR A. CLAES, AND DIRK L. BRUTSAERT

SUMMARY  Physiological loads were imposed on contracting isolated cat papillary muscles. The interaction of a hypothetical cylindrical ventricle with a three-element vascular impedance model dictated these physiological loads. The length-tension relation of the physiologically loaded muscle and the pressure-volume relation of the hypothetical ventricle were simultaneously analyzed while the resistive and capacitive components of the vascular impedance were varied widely. Both the end-systolic muscle length-tension relation and the end-systolic ventricular pressure-volume relation were constructed using stepwise increments in either peripheral vascular capacitance or peripheral vascular resistance. The slope of the relation line connecting the end-systolic pressure-volume points under stepwise increases in resistive load was smaller (p < 0.0005) than the slope of this line under stepwise increases in capacitive load. Therefore, the end-systolic pressure-volume relation behaves differently with respect to capacitive and resistive loads. The different loading pattern within the same beat under these varying loading conditions and the coincidence of end-systole with end-ejection in these naturally ejecting contractions are responsible for the shifts in slope of the end-systolic pressure-volume relation. Neither the slope nor the volume intercept of the end-systolic pressure-volume relation was changed when initial muscle length was decreased from 1.0 to 0.95 Lmax. When the Ca2+ concentration in the bathing solution was increased from 2.5 to 7.5 mM, the slope of the end-systolic pressure-volume relation increased (P < 0.0005), and the volume intercept of the curve decreased (P < 0.025). These results are similar to data reported for conscious animals and to data obtained from catheterization of the human left ventricle.


THE end-systolic pressure-volume relations of the intact ventricle and the end-systolic length-tension relations of isolated cardiac muscle have been the subject of considerable interest. However, conflicting experimental data have been obtained from isolated papillary muscles (Taylor, 1970), in situ papillary muscle preparations (Suga et al., 1977), isolated left ventricles (Suga and Sagawa, 1974; Weber et al., 1976) and during catheterization both in dog or in humans (Mahler et al., 1975; Grossman et al., 1977). End-systolic deactivation was shown to be important in isolated muscle preparations (Taylor, 1970; Suga et al., 1977; Brutsaert and Houmans, 1977), whereas in the isolated left ventricle, end-systolic isovolumetric and isobaric contractions nearly coincide (Weber et al., 1976; Suga and Sagawa, 1974). The volume intercept (Vd) of the end-systolic pressure-volume diagram is constant and time invariant in the isolated left ventricle, whereas it changes in clinical observations (Grossman et al., 1977). Positive inotropic interventions induce parallel shifts in the end-systolic pressure-volume relation during catheterization of conscious dogs (Mahler et al., 1975; Sagawa et al., 1977). In the isolated left ventricle, a positive inotropic intervention changes the slope of the end-systolic pressure-volume relation, while the Vd remains constant (Suga et al., 1973).

In previous work (Paulus et al., 1979), an analog computer system loaded isolated papillary muscles as if they were contracting in the wall of an ejecting ventricle. This computer feedback system used a cylindrical ventricular geometry and a three-element electrical analog of the hydraulic input imped-
Preparation and Apparatus

Ten papillary muscles of the right ventricle of the cat were used for this study (for muscle characteristics, see Table 1). After dissection, the muscles were mounted vertically in a bath containing a modified Krebs-Ringer’s solution containing (mm): NaCl, 118; KCl, 4.7; MgSO4, 1.2; KH2PO4, 1.1; NaHCO3, 24; CaCl2, 2.5; and glucose, 4.5. The solution was gassed with a mixture of 95% O2 and 5% CO2. Experiments were performed at a stimulation frequency of 36 stimuli per minute (5 msec in duration) and a temperature of 36°C after an initial stabilization period of 3–4 hours at a temperature of 29°C and a stimulation frequency of 12 stimuli per minute. The tendonous end of the muscle was connected to the electromagnetic lever system with a temperature of 36°C, 36/min.

Methods

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dous end was held by a bronze clip soldered to the middle of a force transducer (Brutsaert and Claes, 1974). Contractions were recorded on a storage display unit (Tektronix 611) and photographed with a hard copy unit (Tektronix 4601). Relaxation phase was omitted in the figures.

Impedance Loading Feedback Function

The papillary muscle was considered to be part of a circumferential bundle of muscle fibers in the wall of a hypothetical cylindrical ventricle. Instantaneous muscle length (l) and velocity of shortening (v) were converted to ventricular volume (V) and aortic flow (Q) by the use of analog computing techniques. A current source produced a current proportional to this flow (Q) signal. The current passed through a network of two resistors (Rc, the characteristic resistance and Rp, the peripheral resistance) and a capacitor (C) in parallel with Rp. This network served as an analog model of the vascular impedance. Hypothetical aortic pressure was derived from the voltage signal over the network. This signal was converted to wall tension or load on the muscle by the use of the Laplace relationship of the ventricle. Details of the mathematical analysis of the impedance-loading feedback function and of the electronic circuits have been described previously (Paulus et al., 1979). Stepwise increases of the peripheral vascular resistance (Rp) and capacitance (C) could be performed over the following range:

Rp: 4,000 → 6,000 → 8,000 → 10,000 → 12,000 g cm⁻¹ sec⁻¹
C: 55.10⁻⁶ → 100.10⁻⁶ → 160.10⁻⁶ → 260.10⁻⁶ → 360.10⁻⁶ g⁻¹ cm¹ sec².

The Rc was maintained at a fixed value of 220 g cm⁻¹ sec⁻¹. A valve-like effect was obtained by a diode (D) at the junction between the ventricular model and the arterial impedance model. Both the vascular impedance load and the valve-like effect turned the physiologically loaded contractions into “naturally ejecting” beats. Therefore, the end of ejection coincided with the end of systole, defined as the upper left corner of the pressure-volume loop trajectory (Suga et al., 1979).

Table 1 Muscle Characteristics

<table>
<thead>
<tr>
<th>Muscle</th>
<th>lmax (mm)</th>
<th>Cross-sectional area (mm²)</th>
<th>Preload at lmax (mN/mm²)</th>
<th>Unloaded maximal velocity of shortening (lmax/sec) at 36°C, 36/min</th>
<th>RT/TT at 36°C, 36/min</th>
<th>K (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0.9</td>
<td>7</td>
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<td>0.13</td>
<td>1.7</td>
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<tr>
<td>2</td>
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<td>3</td>
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<tr>
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</tr>
<tr>
<td>5</td>
<td>7</td>
<td>0.9</td>
<td>6</td>
<td>3.3</td>
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<tr>
<td>6</td>
<td>8</td>
<td>0.6</td>
<td>8</td>
<td>3.1</td>
<td>0.11</td>
<td>3.7</td>
</tr>
<tr>
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<td>0.6</td>
<td>7</td>
<td>1.9</td>
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<tr>
<td>8</td>
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<td>0.9</td>
<td>8</td>
<td>1.9</td>
<td>0.15</td>
<td>5.6</td>
</tr>
</tbody>
</table>

RT/TT = Ratio of resting to total tension at peak tension development of an isometric twitch contraction; K = Constant of the impedance-loading feedback (Paulus et al., 1979).
Experimental Protocol

After an initial stabilization period of 3-4 hours at a temperature of 29°C and a stimulation frequency of 12 stimuli per minute, an isotonic contraction at the preload of \( l_{\text{max}} \), an isometric contraction at \( l_{\text{max}} \), and a zero load clamp at \( l_{\text{max}} \) were recorded. These contractions served to evaluate muscle performance. After increasing bathing temperature and stimulation frequency to 36°C and 36 stimuli per minute, the same three contractions were recorded. The time course of a physiologically loaded contraction either at

\[
R_c = 220 \text{ g cm}^{-4} \text{ sec}^{-1}, \quad R_p = 12,000 \text{ g cm}^{-4} \text{ sec}^{-1}, \quad C = 260 \times 10^{-6} \text{ g}^{-1} \text{ cm}^4 \text{ sec}^2 \quad (n = 5, \text{ muscles 1 to 5}), \quad \text{or at} \quad R_c = 220 \text{ g cm}^{-4} \text{ sec}^{-1}, \quad R_p = 10,000 \text{ g cm}^{-4} \text{ sec}^{-1}, \quad C = 260 \times 10^{-6} \text{ g}^{-1} \text{ cm}^4 \text{ sec}^2 \quad (n = 5, \text{ muscles 5 to 10})
\]

was recorded and served as calibration and reference for the subsequent pressure-volume loops. Three types of runs were performed: (1) recording the pressure-volume and length-tension loops under stepwise increases in resistive and capacitive loading, (2) reduction of initial muscle length to 95% \( l_{\text{max}} \) and subsequent recording of the pressure-volume and length-tension loops under stepwise increases in resistive loading, and (3) recording the pressure-volume and length-tension loops under stepwise increases in resistive loading, both under control conditions and after a positive inotropic intervention (\( \text{Ca}^{2+} \) increased from 2.5 to 7.5 mM).

Results

End-Systolic Length-Tension Relation of the Papillary Muscle and the End-Systolic Pressure-Volume Relation of the Hypothetical Ventricle under Resistive and Capacitive Loading

Figure 1A shows the length-tension and pressure-volume loops of five contractions for stepwise increments in peripheral resistance \( R_p \) of the loading feedback system. The capacitance \( C \) was maintained at a constant value \((C = 260 \times 10^{-6} \text{ g}^{-1} \text{ cm}^4 \text{ sec}^2)\). Figure 1B shows the length-tension and pressure-volume loops for stepwise increases in arterial capacitance \( C \) of the load circuit. Within the range of capacitance variations \((100 \times 10^{-6} \rightarrow 360 \times 10^{-6} \text{ g}^{-1} \text{ cm}^4 \text{ sec}^2)\), only small differences in stroke volume were observed. The low initial loads under low capacitance constant \( C \) made the muscle shorten further than expected when a load the same in magnitude as the end-systolic load existed (Brutsaert et al., 1971). At a high capacitance constant \( C \), the high initial loads delayed muscle shortening so that at the time of end-systole the muscle had not shortened as far as expected with the end-systolic load throughout.

Figure 2A shows the pooled end-systolic pressure-volume points both under resistive and capacitive loading for five muscles \((n = 5, \text{ muscles 5 to 10})\). For each muscle, \( R_p \) in the loading feedback was increased stepwise \((8,000, 10,000, \text{ and } 12,000 \text{ g cm}^{-4} \text{ sec}^{-1})\), while \( C \) was kept constant at \( 260 \times 10^{-6} \text{ g}^{-1} \text{ cm}^4 \text{ sec}^2 \). Thereafter, \( C \) was increased stepwise \((100 \times 10^{-6}, 160 \times 10^{-6}, 260 \times 10^{-6}, \text{ and } 360 \times 10^{-6} \text{ g}^{-1} \text{ cm}^4 \text{ sec}^2)\), while \( R_p \) was kept constant at \( 10,000 \text{ g cm}^{-4} \text{ sec}^{-1} \). The contraction recorded at \( R_p = 10,000 \text{ g cm}^{-4} \text{ sec}^{-1} \) and \( C = 260 \times 10^{-6} \text{ g}^{-1} \text{ cm}^4 \text{ sec}^2 \) served as a common reference in both runs, and for each muscle, the end-systolic pressure-volume data in both runs were normalized by dividing them by the end-
Figure 2 The pooled end-systolic pressure-volume points for five muscles (muscles 5 to 10) both under stepwise increases in resistive load (●) and under stepwise increases in capacitive load (○) are shown in panel A. For each muscle, the values are expressed as percentage of the end-systolic pressure-volume data recorded under this reference loading. This normalization enabled us to pool the data from all runs and muscles for statistical analysis. In two muscles (muscles 6 and 7), a contraction at Rp = 6,000 g cm⁻¹ sec⁻¹ and C = 260.10⁻⁶ g⁻¹ cm⁻⁴ sec² was recorded. These data were included in the statistical analysis. In the other muscles at Rp = 6,000 g cm⁻¹ sec⁻¹ and C = 260.10⁻⁶ g⁻¹ cm⁻⁴ sec², the load was insufficiently high to maintain the muscle at a constant length during diastole (Paulus et al., 1979). Using linear regression analysis of the end-systolic pressure-volume points under stepwise increases in resistive load we obtained a rectilinear curve (%P = 4.53% V - 3.53; r = 0.96). Under stepwise increases in capacitive load, another rectilinear curve was obtained (%P = 8.01% V - 7.01; r = 0.94). The slopes of the two curves were statistically different (P < 0.0005). In two other runs during five experiments (muscles 1 to 5), the same curves were constructed using the contraction at Rp = 12,000 g cm⁻¹ sec⁻¹ and C = 260.10⁻⁶ g⁻¹ cm⁻⁴ sec² (as intersection and reference of normalization). Again, a statistically significant difference (P < 0.0005) was obtained between the slopes of the rectilinear curves fit to the end-systolic pressure-volume data.

The Influence of Initial Muscle Length on the End-Systolic Length-Tension and Pressure-Volume Relation of Physiologically Loaded Papillary Muscles

Figure 3A shows directly recorded pressure-volume curves of physiologically loaded contractions under stepwise increases in resistive load (Rp = 8,000, 10,000, and 12,000 g cm⁻¹ sec⁻¹; C = 260.10⁻⁶ g⁻¹ cm⁻⁴ sec²; muscle 7). At each resistive load, two contractions starting from two different end-diastolic volumes or initial muscle lengths (l_max and 0.95 l_max) are shown. A linear regression line was fitted to the end-systolic pressure-volume points of the three contractions starting from the same initial muscle length. The slopes of both lines were equal, but the volume intercepts were slightly different. A somewhat smaller volume intercept was observed when a linear regression line was fitted to the end-systolic pressure-volume points of contractions starting at a smaller end-diastolic ventricular volume or initial muscle length.

The end-systolic pressure-volume points obtained in five muscles under stepwise increases in resistive load for contractions starting from different initial muscle lengths are shown in Figure 2B. For each muscle (n = 5), linear regression lines were fitted to the end-systolic pressure-volume points of contractions starting at l_max and 95% l_max under stepwise increases in resistive load. For all curves, the correlation coefficient was significant at P < 0.05. For each experiment, the slope and volume intercept of the linear curve fit to the end-systolic pressure-volume points of contractions starting at
Positive Inotropic Stimulation and the End-Systolic Length-Tension and Pressure-Volume Relation of Physiologically Loaded Papillary Muscle

Figure 3B shows a direct oscilloscope display of pressure-volume loops under stepwise increases in resistive load (\(R_p = 6,000, 8,000, 10,000, 12,000 \text{ g cm}^{-4} \text{ sec}^{-1}\); \(C = 260.10^{-6} \text{ g}^{-1} \text{ cm}^4 \text{ sec}^2\); muscle 3) at two different calcium concentrations in the bathing solution (2.5 and 7.5 mM/liter). At each calcium concentration, a linear regression line was fitted to the end-systolic pressure-volume points. Both the slope and volume intercept of the two regression lines were different. An increase in muscle inotropism increased the slope of the end-systolic pressure-volume relation and decreased the volume intercept.

In Figure 2C, the end-systolic pressure-volume relation lines obtained in five muscle experiments (\(n = 5\)) were plotted for the two calcium concentrations. For all curves, correlation coefficient was significant at \(P < 0.05\). For each experiment, the slope and pressure intercept of the linear curve fit to the end-systolic pressure-volume points of contractions at the lower calcium concentration was paired to the slope and volume intercept of the linear curve fit to the end-systolic pressure-volume points at high calcium. A statistical analysis of the differences between the paired slope data and the paired volume intercept data from five muscles showed a significant difference both in slope (\(P < 0.0005\)) and volume intercept (\(P < 0.025\)).

Discussion

In a previous work (Paulus et al., 1976), a loading feedback system was developed that enabled physiological loads of a hypothetical ejecting ventricle to be imposed on a contracting cat papillary muscle. This loading feedback system was subsequently modified so that resistive and capacitive influences of the vascular impedance and changes of the cylindrical geometry of the hypothetical ventricle could be imposed (Paulus et al., 1979). With this physiological loading system, both the contraction properties of the isolated papillary muscle and the ejection characteristics of the ventricle can be analyzed simultaneously. In the present study, the force-length relation of physiologically loaded contractions of the papillary muscle was investigated simultaneously with the pressure-volume relation of the ejecting hypothetical ventricle. For stepwise increases in peripheral resistance, a series of length-tension and pressure-volume loops was obtained. In the present study, the end-systolic length-tension and pressure-volume relations were investigated not only for various peripheral resistances but also for various capacitances. Hence, for the first time, the interaction of vascular impedance and ventricular pressure-volume relations was extensively studied. The end-systolic pressure-volume relation

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**Figure 3** The directly recorded pressure-volume loops of physiologically loaded contractions starting from two different initial muscle lengths (\(l_{max}\) and 95% \(l_{max}\)) are displayed in panel A. The upper three loops were recorded when making stepwise increases in peripheral resistance (8,000, 10,000, 12,000 g cm\(^{-4}\) sec\(^{-1}\)) of contractions starting from \(l_{max}\). The lower three loops were recorded when one increased the peripheral resistance of contractions starting from 95% \(l_{max}\) (muscle 7). Panel B shows directly recorded pressure-volume loops of contractions under stepwise increases in resistive load (6,000, 8,000, 10,000, 12,000 g cm\(^{-4}\) sec\(^{-1}\); \(C = 260.10^{-6} \text{ g}^{-1} \text{ cm}^4 \text{ sec}^2\); muscle 3) at two different calcium concentrations in the bathing solution. The lower four curves were recorded at a Ca\(^{2+}\) concentration of 2.5 mM/liter. The upper four curves were recorded at a Ca\(^{2+}\) concentration of 7.5 mM/liter (muscle 3).

\(l_{max}\) was paired to the slope and volume intercept of the linear curve fit to the end-systolic pressure-volume points of contractions starting at 95% \(l_{max}\). A statistical analysis of the differences between the paired slope data and the paired volume intercept data for five muscles showed no significant difference.
line constructed from contractions under stepwise increases in resistance with fixed capacitance depicted a slope and volume intercept that was different from the slope and volume intercept of the end-systolic pressure-volume relation line under stepwise increases in capacitance with fixed resistance. This difference was due to a different loading history of both types of contraction. At a low peripheral capacitance (e.g., $C = 100.10^{-6}$ g$^{-1}$ cm$^4$ sec$^{-2}$; Fig. 1B), a small early systolic load preceded a larger end-systolic load. At a high peripheral resistance (e.g., $R_p = 12,000$ g cm$^{-4}$ sec$^{-1}$ in Fig. 1A), muscle load changed less during contraction. Accordingly, for the same end-systolic load, a contraction recorded at a low peripheral capacitance will have shortened further than a contraction recorded at a high peripheral resistance due to the different time course of muscle force development in both contraction types. At a high peripheral capacitance (e.g., $C = 360.10^{-6}$ g$^{-1}$ cm$^4$ sec$^{-2}$; Fig. 1B), the load was more evenly distributed throughout the ejection phase. At a low peripheral resistance (e.g., $R_p = 6,000$ g cm$^{-4}$ sec$^{-1}$; Fig. 1A), initial muscle load was smaller than at a high peripheral capacitance. Again, the different timing of muscle force development explains the smaller end-systolic lengths at the same end-systolic load of a contraction recorded at a low peripheral capacitance with respect to a contraction recorded at a high peripheral capacitance. A relative decrease in end-systolic length of a contraction at a high capacitance and a relative increase in end-systolic length of a contraction at a low capacitance explain the shift in slope of the end-systolic pressure-volume relation under stepwise increases in capacitive load with respect to the end-systolic pressure-volume relation under stepwise increases in resistive load.

Variations in peripheral resistance or capacitance induce distinct alterations in the ventricular loading pattern within a single beat. From the present observations, these load variations induced by the vascular impedance seem to affect the uniqueness of the end-systolic pressure-volume relation. Recently, the end-systolic pressure-volume relationship of the left ventricle has been proposed to be independent of the time course of ventricular loading (Suga et al., 1979). This conclusion was based on the analysis of left ventricular contractions under continuous ventricular volume control with both end-systolic and end-diastolic volume clamped. In these experiments, end-systolic pressure was little affected by wide variations in onset of ejection and ejection velocity. The ventricular end-systolic pressure-volume relation was, however, no longer unique when ventricular stroke volume was varied. In a similar set of experiments, the end-systolic pressure at a given end-systolic volume was independent both on stroke volume and ejection velocity (Suga and Yamakoshi, 1977). In these experiments, however, the pattern of ejection flow and, therefore, also the pattern of ventricular loading was different as peak velocity occurred much later in systole. This variation in the timing of the loading pattern is thought to have a critical influence on ventricular performance evaluation in terms of its end-systolic pressure-volume relation (Suga et al., 1979). In the present study, variations in the resistive and capacitive components of the vascular impedance distinctly influence the time course of ventricular loading throughout entire systole. This could explain the influences of the resistive and capacitive elements of the vascular impedance on the end-systolic pressure-volume relation in the present experiments.

Moreover, previous load clamp experiments on isolated papillary muscles documented the influence of loading shifts within one contraction on the end-systolic muscle length (Brutsaert et al., 1971). When muscle load was clamped for a short period to a higher load within one contraction, peak shortening was less than when the muscle contracted with the same initial load throughout the entire course of contraction. This deviation from the length- and time-independence of the force-velocity-length relation of cardiac muscle contraction is limited to the terminal portion of contraction. Therefore, the sensitivity of end-systolic muscle length to loading shifts within one contraction only becomes apparent when the moment of end-systole coincides with the moment of peak shortening. In the present experiments, the end of systole coincides with peak shortening, as we are dealing with "naturally ejecting beats" under vascular impedance-loading feedback.

The comparison of the end-systolic pressure-volume relation of physiologically loaded contractions starting from different initial muscle lengths did not reveal any statistically significant change, either in slope or volume intercept of the end-systolic pressure-volume relation. Most previous experiments on papillary muscles (Brutsaert and Housmans, 1977; Taylor et al., 1970; Suga et al., 1977) have shown that both isotonic and auxotonic contractions fall short of the end-systolic length-tension relation of isometric muscle contraction, thereby illustrating shortening deactivation of muscle contraction. Because of the ejection properties of the loading feedback system in the present experiments, no isovolumetric beats at a given end-systolic volume could be obtained. The effect of shortening deactivation was investigated therefore by changing initial muscle length from $l_{max}$ to 95% $l_{max}$. Within this range of initial muscle length, the effect of shortening deactivation on the end-systolic pressure-volume relation appeared to be minimal. Positive inotropic stimulation provoked large decreases in volume intercept and small increases in slope of the end-systolic pressure-volume relation. In previous experiments on excised hearts, the slope of the end-systolic pressure-volume relation increased with no significant change in the volume intercept (Suga et al., 1973). The same investigators, however,
recently reported controversial results in conscious
dogs (Sagawa et al., 1977). In some of these dogs,
nearly parallel shifts in the end-systolic pressure-
volume relation were obtained on positive inotropic
stimulation. Similar results had been reported pre-
viously by other investigators (Mahler et al., 1975)
for conscious animals. Cardiac catheterization stud-
ies on the human left ventricle showed steeper end-
systolic pressure-volume relations and smaller vol-
ume intercepts for normal ventricles than for poorly
contractile ventricles (Grossman et al., 1977). Fur-
ther investigations are needed on the time course
of ventricular loading at various vascular imped-
ances and on the influence of neural and humoral
factors to explain the difference in shift of the end-
systolic pressure-volume relation on positive ino-
tropic stimulation in all these different experimen-
tal conditions.

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