Effects of Alterations in Aortic Input Impedance on the Force-Velocity-Length Relationship in the Intact Canine Heart

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SUMMARY We studied the effects of changes in aortic input impedance on the force-velocity-length relationship of the left ventricle in open-chest dogs, using a right heart bypass preparation. The control relationship between wall stress and ventricular diameter or mean velocity of shortening (MVCF) was determined first by using maneuvers (changes in venous return and phenylephrine infusion) that did not alter impedance moduli or phase angle above 0 Hz. Aortic impedance then was increased by occlusion of the descending aorta (+89% increase in the first harmonic $P < 0.02$, +49% increase in characteristic impedance, $P < 0.005$, and a constant -20° phase shift between 2 and 10 Hz; $P < 0.05$). When compared to a phenylephrine infusion at the same mean aortic pressure and cardiac output, aortic occlusion increased the level of peak stress (+43%, $P < 0.005$) and decreased the extent of shortening (from 28.6 ± 6.9 to 14.8 ± 3.1%, $P < 0.01$) and the MVCF (from 2.00 ± 0.30 to 1.15 ± 0.14 cm/s, $P < 0.02$). However, left ventricular end systolic diameter and MVCF fell in the 95% confidence interval of their respective control relations with end-systolic wall stress. Similar data were obtained when aortic occlusion was performed during a nitroprusside infusion or during an inotropic stimulation. Moreover, we found that when venous return was reduced by 25% during aortic occlusion, the characteristic impedance and the aortic input resistance increased further (respectively, +18%, $P < 0.01$, and +18%, $P < 0.005$) but the wall stress decreased and the MVCF increased slightly. It is concluded that changes in impedance affect shortening and wall stress but not the force-velocity-length framework and, furthermore, that the wall stress provided a better description of the afterload than the impedance alone. Circ Res 45: 126-135, 1979

AFTERLOAD, defined as those factors that affect the active shortening of cardiac muscle, is an important determinant of myocardial and cardiac performance (Imperial et al., 1961; Sonnenblick and Downing, 1963; Wilcken et al., 1964; Milnor, 1975; Ross et al., 1966). In the whole heart, most of the studies evaluating ventricular afterload relate ventricular pressure and geometry in order to estimate ventricular wall stress (Taylor et al., 1969; Burns et al., 1971; Ross, 1966; Weber and Janicki, 1977). Despite its usefulness in both experimental and clinical situations, it has been said that this approach may not provide adequate measurement of the afterload when the heart is integrated in a physiological pumping system. Therefore the arterial impedance as a measure of the ventricular afterload was proposed (Milnor, 1975; Brutsaert and Paulus, 1977). The main theoretical argument in favor of this view is that the physical properties of the arterial system into which the ventricle tries to move the blood are constant during ejection, and do not depend on cardiac function, which is not the case for wall stress (Milnor, 1975). Some experimental arguments to support this concept were also recently furnished by Paulus et al. (1976). These authors demonstrated that, when loading feedback was imposed on an isolated papillary muscle during systole, shortening velocity at any length and total load deviated from the previously defined time-independent force-velocity-length relation obtained under static conditions. Accordingly, "the application of the concept of contractility, or of any derived index, resulting from statically loaded isolated cardiac muscle experiments becomes quite unreliable for the interpretation of data derived under dynamically changing loads as encountered in a pumping ejecting ventricle" (Brutsaert and Paulus, 1977). However, these experimental results have not yet been verified in the intact circulation by simultaneous determination of the impedance spectrum, the wall stress, and wall-shortening characteristics.

The aim of this study was to investigate whether the aortic impedance provides a better means of analyzing loading conditions on the heart than systolic wall stress. The relations between extent and mean velocity of wall shortening and wall stress were determined under several conditions and compared to those found on impedance analysis. The results indicate that increases in characteristic impedance usually are associated with significant alterations in wall stress, extent of shortening, and velocity of shortening. However, these changes can be described completely within the force-velocity-length framework.

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Methods

Experimental data were obtained from six mongrel dogs (mean weight 27.5 kg; range 22–32 kg) anesthetized with sodium pentobarbital (25 mg/kg, intravenously). Ventilation was maintained by a Harvard respirator.

Instrumentation and Experimental Procedures

After median sternotomy and bilateral thoracotomy, the heart was suspended in a pericardial cradle. An electromagnetic flow probe (Biotronex Inc.) was placed around the ascending aorta distal to the origins of the coronary arteries. Probe diameter was selected carefully to obtain a satisfactory signal during diastole and to minimize the constriction of the vessel (average gradient measured by moving the catheter across the flow probe, less than 2 mm Hg). A high fidelity micromanometer (Millar 8F catheter model Pc482) was introduced through the right femoral artery, and its tip was advanced to a position between the aortic valve and the flow meter. A 3-mm i.d. stainless steel cannula was inserted into the left ventricle through a stab incision at the apex and connected to a Statham P23Db transducer. Zero pressure levels were referred to the mid right atrium, and the aortic pressure level was calibrated by adjusting it to match peak left ventricular systolic pressure (±1 mm Hg).

Experimental Protocol

One pair of ultrasonic crystals (5-MHz piezoelectric discs, each 5 mm in diameter) was positioned at the posterior and anterior endocardial surfaces near the minor equator and calibrated in vivo as previously described (Sasayama et al., 1977). The dogs then were placed on right heart bypass as described previously (Sonnenblick et al., 1965). In brief, the superior vena cava, inferior vena cava, and the right ventricle were cannulated, a Bardic cannula (26F) was introduced in the main pulmonary artery through the right ventricular outflow tract, and a snare was tied around the pulmonary artery and the cannula. The whole venous return was therefore permitted to drain into a reservoir primed with whole heparinized fresh blood (+30 mEq sodium bicarbonate per liter) from three donor dogs while venous return to the left ventricle was maintained by a peristaltic pump. Four interventions were examined in the following order, the preparation being allowed to stabilize and return to control hemodynamic status between each intervention.

1. Control data: In each of five dogs, 4 to 10 steady states at different mean aortic pressures ranging from 80 to 160 mm Hg were obtained by altering the venous return or by phenylephrine infusion (0.095–0.380 mg/min).

2. Aortic clamping (Fig. 1): All preparations were set at a venous return sufficient to keep the left ventricular filling pressure between 6 and 10 mm Hg at a mean aortic pressure between 80 and 110 mm Hg (Fig. 1A). Then, while this level of venous return was kept constant, the descending aorta was occluded completely by tying a snare below the left subclavian artery; after equilibration of pressures and flow, a steady state of 30–40 seconds was recorded (aortic occlusion at constant cardiac output, Fig. 1B); at the end of this recording, venous return was reduced to bring the left ventricular filling pressure to near the previous control level, and a new steady state was similarly recorded (aortic clamping at decreased cardiac output, Fig. 1C). After the clamping release, venous return was returned to the first control value and phenylephrine was infused in sufficient amount (0.095–0.380 mg/min) to obtain the same mean aortic pressure at the same mean cardiac output as during the first aortic occlusion. This steady state was recorded as "phenylephrine data at identical resistance as aortic clamping," Fig. 1D).

3. Nitroprusside infusion: In all six dogs a total aortic occlusion was repeated at the control cardiac output during nitroprusside infusion in doses sufficient to keep the mean aortic pressure at the control level during the clamping (190–760 µg/min) (aortic occlusion + nitroprusside, Fig. 2B). Steady states also were recorded during the same infusion of nitroprusside at the control level of venous return (nitroprusside at control cardiac output, Fig. 2C) and after an increase in venous return sufficient to

![Figure 1](http://circres.ahajournals.org/)

Figure 1: Hemodynamic data obtained from averaged beats (redrawn at a sampling time of 9 msec) in a typical dog. A: Control conditions; B: aortic clamping at the same cardiac output in A; C: aortic clamping with a decreased cardiac output; D: phenylephrine infusion at the same mean aortic pressure and mean flow as in B. The circles on wall stress curves indicate the timing of aortic valve opening and closure.
bring the left ventricular filling pressure to its control level (nitropressure at increased cardiac output, Fig. 2D).

4. Inotropic stimulation: In five dogs, aortic clamping and new control data also were obtained during inotropic stimulation (Ca\textsuperscript{2+} infusion, 20 mg CaCl\textsubscript{2}/min).

After completion of this protocol, the heart was arrested by an injection of 20 ml of saturated KCl solution. The left ventricular long axis (aortic valve to apex) was measured during diastolic arrest; the atria and right ventricular free wall were removed and the left ventricular mass was determined. Crystal positions also were checked at this time. The anterior crystal always was located on the free wall, anterior to the anterior papillary muscle and the posterior crystal was positioned on the posterior papillary muscle; therefore, the measured diameter was generally 3 to 5 mm less than the maximal left ventricular diameter at the level of the crystals.

Measurements and Computation

Analog data were digitized from FM tape recordings every 3 msec by an EAI 590 computer and 10-25 beats were averaged in which R-R intervals were within 2% during each steady state.

Aortic Impedance Determinations

The flowmeter (Biotronex model BL610) used in this study had a flat frequency response (~3 dB) from 0 to 100 Hz, a transit time of 6 msec, and a linear phase shift of 1.9°/Hz. The Millar micromanometer and its amplifying unit after prewarming had a stable electrical zero with a drift of ±0.2 mm Hg/hour, a constant and linear gain up to 200 mm Hg, and a frequency response flat to above 2000 Hz. Analysis of the averaged data was carried out on a Burroughs 5700 computer which converted pressure and flow signals to Fourier series following methods previously described (Bergel and Milnor, 1965; McDonald, 1974). The input resistance (Zo) was calculated by dividing mean flow into mean pressure. Since the right atrial pressure was kept at zero, Zo was also equal to the total peripheral resistance. Input impedance modulus at each frequency was computed by dividing flow modulus into pressure modulus, and the corresponding phase was computed by subtracting the phase angle of flow from that of pressure (Bergel and Milnor, 1965; McDonald, 1974). Appropriate corrections were introduced for the transit time and the phase shift of the flow meter, but no attempt was made to correct the phase lag between pressure and flow-sampling points. Since in our preparation the pressure tip was proximal to the flow probe, the calculated phases are probably slightly less negative than those previously published for pressure measured distal to flow (Noble et al., 1967; O'Rourke, 1967; O'Rourke and Taylor, 1967).

Calculated impedances were considered significant for harmonics in which the pressure modulus was greater than 0.3 mm Hg or the flow modulus greater than 1 ml/sec, values that represent the noise level of our measurement system. Characteristic impedance (Zi 2-12) was estimated by averaging impedance moduli between 2 and 12 Hz (Nichols et al., 1977). Steady potential energy was calculated from mean values of pressure and flow and pulsatile potential energy from the first 10 harmonics of pressure and flow; both were expressed as power and calculated by methods previously reported (Milnor et al., 1966).

Left Ventricular Wall Stress Computation

From the end diastolic diameter obtained in vivo and from the postmortem measurement of apex to base length, a theoretical end-diastolic volume was calculated from an ellipsoidal model. In each contraction analyzed, instantaneous volume during systole was calculated by subtracting from it the integrated flow rate. Assuming a constant left ventricular mass, instantaneous wall stress during systole was computed as shown below for a thick walled ellipsoid model:

\[ \text{stress} = \frac{P R_i \left[ 1 - \left(2 R_i^2/L^2 \right) \right]}{(R_o - R_i)} \]

where P = left ventricular pressure, L = base-to-apex length, Ri = internal radius, and Ro = external radius. Mean systolic wall stress was determined by averaging the data from the start to the end of the ejection; end-systolic wall stress was also measured at the end of ejection, i.e, the point at which the flow velocity signal first crossed the zero flow line.

The average velocity of circumferential shortening MVCF (in mm/sec) was estimated by dividing the change in internal diameter during systole by the ejection time and normalized by dividing MVCF by the end-diastolic diameter.

Statistical analysis of the impedance spectrum and power was performed by repeated measures of analysis of variance (Tukey's least significant difference for comparisons among means) (Winer, 1971). Paired hemodynamic data were compared by the paired t-test; the linear regression analysis and the 95% confidence intervals between end-systolic wall stress and end-systolic diameter or end-systolic wall stress and in VCF were calculated using linear least-square regression techniques.

Results

A typical set of observations is illustrated in Figures 1 and 2. The mean venous return was kept constant in all situations except in aortic clamping with decreased cardiac output (Fig. 1C) and nitropressure with increased cardiac output (Fig. 2D). Aortic occlusion, when compared with other data at a similar mean aortic pressure (1B and 1D, 2A and 2B), always produced a more peaked left ventricular systolic pressure and a wider pulse pressure. Left ventricular wall stress was also different during aortic clamping, the peak occurring later and exhibiting a more rounded configuration. Our experi-
mental protocol was designed to examine, first, the effects of a change in characteristic impedance on the shortening characteristics when the mean resistance and the venous return were kept constant and, second, the effects of a change in impedance when the end-diastolic volume was not allowed to vary significantly.

In the Results section, we will present the impedance change and the left ventricular response observed with those two experimental maneuvers and then will analyze the ventricular response in terms of the force-velocity-length relation.

Effect of Changes in Characteristic Impedance (by Aortic Clamping) at Constant Resistance and Venous Return

The mean changes in aortic impedance during aortic clamping, averaged harmonic by harmonic, are illustrated in Figure 3A and compared to the aortic impedance during phenylephrine infusion at the same mean aortic pressure and cardiac output. Aortic clamping significantly increased the modulus of the first two harmonics (respectively, +89%; \( P < 0.02 \) and +27%, \( P < 0.03 \)). The entire spectrum also was shifted upward as illustrated by the higher level of \( Z_i \) (233 ± 21 SEM vs. 156 ± 10 dyn·s·cm\(^{-5} \) \( P < 0.005 \)). There was no significant change in phase for the first harmonic, but a negative phase shift of about—20° was found consistently between 2 and 10 Hz. Under these circumstances (constant Zo, increased Zi at constant venous return) we observed significant increases in end-diastolic pressure and volume of the left ventricle (Table 1) as well as in peak, mean, or end-systolic wall stress. At the same time, MVCF and percent shortening were markedly reduced. The mean external power was unchanged (identical mean pressure and mean flow), but the pulsatile power increased significantly from 23.4 ± 4.1 to 37.0 ± 8.1 mW; \( P < 0.035 \).

Similar patterns of impedance changes and ventricular response were determined when these two maneuvers were repeated during inotropic stimulation by CaCl\(_2\) infusion (Fig. 3B and Table 1).

When nitroprusside was infused during aortic clamping to keep the mean aortic pressure at the control level (Fig. 4A), we also noted a significant increase in characteristic impedance (from 161 ± 12 to 223 ± 36 dyn·s·cm\(^{-5} \); \( P < 0.025 \)) and in the first (+100%, \( P < 0.01 \)) and third (+150%, \( P < 0.01 \)) harmonics. Phase angles were not different at the first three harmonics, but there was a negative shift at the fourth (−50°; \( P < 0.01 \)) and fifth (−35°, \( P < 0.01 \)) harmonics. In this setting, also, the left ventricular response was characterized by significant increases in end-diastolic pressure and wall stress, whereas the percent shortening and the MVCF decreased (Table 1) and the pulsatile power increased from 25.7 ± 3.7 to 33.2 ± 4.0 mW; \( P < 0.05 \).

In summary, when the venous return to the left heart was kept constant, the left ventricular response to an isolated increase in characteristic impedance was characterized by an increase in end-diastolic volume and wall stress and by a decrease in percent shortening and MVCF. This was true when the mean resistance, Zo, was either normal or high and during inotropic stimulation.

Effects of Changes in Impedance at Comparable End-Diastolic Volume

These effects of a change in characteristic impedance at constant venous return are in contrast to those observed when the venous return was reduced to bring the end-diastolic pressure near its control level.

A first example is provided when the venous return is decreased during an aortic clamping (Table 1). In this case we consistently observed increases in Zo (+18%; \( P < 0.01 \)) and Zi (+16%; \( P < 0.035 \)) without significant changes in phase. Despite this significant increase in both components of the aortic impedance, the left ventricular response was characterized this time by a significant decrease in peak wall stress (from 140.2 ± 11.4 to 99.0 ± 14.4 g·cm\(^{-2} \); \( P < 0.02 \)) while MVCF and percent shortening increased slightly.

This difference in left ventricular response to an increase in impedance was even more striking when we compared in five dogs the effects of aortic clamping and of a phenylephrine infusion at similar end-diastolic volume [25.8 ± 5.2, vs. 26.1 ± 5.0 ml, not significant (NS)]; the mean wall stresses were al-
TABLE 1  Hemodynamic Changes during Alterations in Characteristic Impedance

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>n</th>
<th>Heart rate (beats/min)</th>
<th>Mean aortic pressure (mm Hg)</th>
<th>Mean systolic LV wall stress (g · cm⁻²)</th>
<th>End systolic LV wall stress (g · cm⁻²)</th>
<th>Mean VCF normalized (circ · s⁻¹)</th>
<th>Percent shortening</th>
<th>Total peripheral resistance (dyn · s · cm⁻²)</th>
<th>Characteristic impedance (dyn · s · cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left ventricular pressure (mm Hg)</td>
<td>Left ventricular end-diastolic volume (ml)</td>
<td>Cardiac output (l/min)</td>
<td>Left ventricular dp/dt (mm Hg/sec)</td>
<td>Mean LV end-diastolic volume (ml)</td>
<td>Mean LV dp/dt (mm Hg/sec)</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>6</td>
<td>138±11</td>
<td>129±11</td>
<td>8.6±2.2</td>
<td>139±10</td>
<td>1236±159</td>
<td>1.43±0.15</td>
<td>26.7±4.3</td>
<td>83.2±11.5</td>
</tr>
<tr>
<td>Aortic clamping</td>
<td>6</td>
<td>138±11</td>
<td>133±11</td>
<td>120±12</td>
<td>1.51±0.1*</td>
<td>37.6±3.9*</td>
<td>&lt;0.003</td>
<td>131.2±16.4</td>
<td>109.9±16.8</td>
</tr>
<tr>
<td>Phenylephrine + Ca infusion</td>
<td>5</td>
<td>132±15</td>
<td>156±8</td>
<td>5.9±1.9</td>
<td>169±8</td>
<td>1801±388</td>
<td>1.63±0.14</td>
<td>21.5±5.7</td>
<td>77.0±13.1</td>
</tr>
<tr>
<td>Aortic clamping + Ca infusion</td>
<td>5</td>
<td>138±11</td>
<td>156±11</td>
<td>10.3±3.3*</td>
<td>190±14*</td>
<td>1734±400</td>
<td>1.63±0.14</td>
<td>28.6±6.5*</td>
<td>114.2±17.8</td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>132±10</td>
<td>107±3</td>
<td>6.7±1.2</td>
<td>119±2</td>
<td>1193±102</td>
<td>1.65±0.12</td>
<td>25.0±4.4</td>
<td>63.7±8.0</td>
</tr>
<tr>
<td>Aortic clamping, nitroprusside infusion</td>
<td>6</td>
<td>128±6</td>
<td>106±5</td>
<td>13.2±2.5*</td>
<td>129±4*</td>
<td>1225±147</td>
<td>1.69±0.13</td>
<td>33.5±5.0*</td>
<td>83.4±10.0</td>
</tr>
<tr>
<td>Aortic clamping, decreased venous return</td>
<td>5</td>
<td>134±4</td>
<td>131±7</td>
<td>18.0±2.6</td>
<td>156±7</td>
<td>1237±147</td>
<td>1.45±0.09</td>
<td>35.7±4.6</td>
<td>121.0±10.7</td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>132±10</td>
<td>107±3</td>
<td>6.7±1.2</td>
<td>119±2</td>
<td>1183±102</td>
<td>1.65±0.12</td>
<td>25.0±4.4</td>
<td>63.7±8.0</td>
</tr>
<tr>
<td>Nitroprusside infusion</td>
<td>6</td>
<td>131±7</td>
<td>112±7</td>
<td>7.6±6*</td>
<td>88±6*</td>
<td>1171±376</td>
<td>1.68±0.11</td>
<td>20.4±4.5*</td>
<td>37.6±6.8*</td>
</tr>
<tr>
<td>Nitroprusside infusion</td>
<td>6</td>
<td>127±7</td>
<td>84±6†</td>
<td>6.9±0.7</td>
<td>100±6†</td>
<td>1157±414</td>
<td>2.36±0.19†</td>
<td>25.2±4.5</td>
<td>50.0±5.9†</td>
</tr>
</tbody>
</table>

Averaged hemodynamic data during the different maneuvers used in the study. Nitroprusside infusion I = nitroprusside infusion at constant venous return; nitroprusside infusion II = nitroprusside infusion at increased venous return. n = number of dogs.

* Comparison between paired maneuvers; P values are given only when < 0.05
† Comparison between control and nitroprusside infusion II.
A second example of the difference in response to an increase in Zi 2-12 was provided when the venous return was altered during a nitroprusside infusion. When nitroprusside was infused while keeping venous return constant (Fig. 4B), there was a significant decrease in Zo (−30%, P < 0.05). Zi 2-12, considered as an independent parameter, increased significantly from 160 ± 10 to 210 ± 18 dyn·s·cm⁻²; P < 0.025. There was also a constant positive phase shift at the first harmonic (+34°, P < 0.01), but no other changes in impedance moduli were noted.

The left ventricular response in this case was characterized by a decrease in end-diastolic pressure and wall stress (Table 1), while MVCF and percent shortening (+52%, P < 0.01) markedly increased. At the same time, the total external power decreased (426 ± 56 to 302 ± 30 mW, P < 0.05) and the pulsatile power increased from 25.7 ± 3.7 to 40.8 ± 7.3 mW, P < 0.03. By contrast, when the venous return was increased during constant nitroprusside infusion, there was a small but insignificant further decrease in Zo (−16%, NS), whereas Zi 2-12 consistently decreased to the previous control level from 210 ± 18 to 166 ± 15 dyn·s·cm⁻²; P < 0.05. The phase angle remained almost unchanged (Fig. 4C).

Such a decrease in Zi 2-12 would have been expected to reduce significantly the wall stress and increase the MVCF and percent shortening had it occurred at constant venous return; but at increasing venous return we observed instead small increases in wall stress and slight decreases in MVCF and percent shortening, compared to the previous nitroprusside infusion (Table 1), and the total external power increased significantly to 490 ± 35 mW (P < 0.01).
Effects of Changes in Aortic Impedance on Force-Velocity-Length Relations

To determine the effects of alterations in characteristic impedance on the mechanics of left ventricular contraction, changes in resistance alone were first obtained by altering the venous return and during phentolamine infusion, with mean aortic pressure ranging from 80 to 160 mm Hg. Contractile state was assumed to be constant by the following criteria: less than 10% change in heart rate between the steady states and less than 20% increase in dp/dt for increases in left ventricular filling pressure up to 20 mm Hg (Mahler et al., 1975a). When the impedance spectra of the maneuvers were compared, Zo changed markedly from 4.0 to 9.5 × 10³ dyn·s·cm⁻² but no significant changes in impedance moduli, phase, or Zi 2-12 were observed. This was true, not only within each experiment, but also when all phentolamine data and control data were pooled [i.e., mean Zi 2-12 during all controls = 156 ± 6 SEM (n = 16) and Zi 2-12 = 161 ± 4 (n = 18) dyn·s·cm⁻² during all phentolamine infusion (NS)].

Steady states based on the same criteria also were recorded during inotropic stimulation. Once more, despite Zo changes ranging from 3.7 to 13.3 × 10³ dyn·s·cm⁻², no significant changes in impedance above 0 Hz were observed. The typical shapes of these spectra are illustrated in Figures 3 and 4. The steady states obtained in five dogs at a wide range of Zo, but without change in Zi 2-12 or contractile state, were used to construct individual control relations between end-systolic wall stress and end-systolic diameter, and end or mean systolic wall stress and ln MVCF. The data obtained during the other interventions (as illustrated in Fig. 1) were then compared to this control relationship and its 95% confidence intervals in each dog.

Linear Relation between End-Systolic Wall Stress and Diameter

Figure 5 illustrates that, despite different aortic impedances, all points during aortic occlusion and nitroprusside infusion fell within the 95% confidence interval of the control relation. This was the case for all dogs, with the exception of one point.

On the other hand, during inotropic stimulation (mean increase in dp/dt + 45%, P < 0.05), all new control points fell out of the control confidence interval (Fig. 5), whereas the data obtained during changes in impedance again fell within the new relation.

Relations between MVCF and Left Ventricular Wall Stress

Using the same control data as above, linear relations and their confidence interval were fitted between end-systolic wall stress and ln MVCF or mean systolic wall stress and ln MVCF. In both cases, all points calculated during aortic impedance changes fell on the control relation, and changes in contractile state could be distinguished easily.*

Discussion

This study was designed to determine whether the force-velocity-length framework of the intact heart is altered by changes in aortic input impedance and to compare impedance and wall stress as measures of the ventricular afterload. It will be useful first to analyze the changes in aortic impedance produced by the different maneuvers employed and then to consider the behavior of the left ventricle while facing these input impedances.

Impedance Findings

The general shape of the control impedance spectra obtained agree well with previously published data (Noble et al., 1967; O'Rourke, 1967; O'Rourke and Taylor, 1967; Westerhof et al., 1973; Cox et al., 1975). The moduli of impedance were small compared with peripheral resistance; the phase angles were negative at low frequencies (flow leading pressure), crossed zero between 3 and 6 Hz, and then became positive (pressure leading flow). This general pattern was not significantly altered when aor-

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tic pressure was modified by changes in cardiac output in the control conditions or by phenylephrine infusion; this finding suggests that, within the range of aortic pressures used during the control studies (80-160 mm Hg), the nonlinearity of the arterial bed was probably small (Noble et al., 1967) at frequencies above 0 Hz. The effects of an increase of cardiac contractility on these control spectra were also minimal, as expected from the data of Noble et al. (1967).

During aortic occlusion, all the vascular bed below the left subclavian artery was cut off. In addition to increasing the mean resistance, this maneuver theoretically also decreased the global aortic capacity and should introduce a new reflection site very close to the heart with a reflection coefficient close to 1 (O'Rourke and Taylor, 1967; Westerhof et al., 1973). This decrease in aortic compliance was reflected in the spectra obtained (Fig. 3, A and B) which showed a significant increase in the characteristic impedance $Z_i 2-12$; indeed, characteristic impedance essentially depends on the physical properties of the vessels near the measuring points (McDonald, 1974; O'Rourke, 1967; Nichols et al., 1977). Experimental data as well as theoretical considerations on models (O'Rourke, 1967; Westerhof et al., 1973; Pouleur et al., 1978) indicate that the impedance spectra obtained during aortic clamping represent a significant increase in the opposition to pulsatile flow, particularly at the first two harmonics which contain the greater part of the energy in the pulsatile pressure and flow waves (O'Rourke, 1967). Thus, to eject the same volume of blood into the vascular bed modified by aortic occlusion, the heart had to furnish more pulsatile energy than during a phenylephrine infusion at the same mean aortic pressure.

During nitroprusside infusion with cardiac output constant (Fig. 4B), an intense vasodilation occurred concomitantly with a decrease in aortic pressure. This decrease in peripheral resistance is expected to decrease the reflection coefficient at the arterioles (O'Rourke, 1967; McDonald, 1974). Accordingly, the impedance spectrum between 2 and 12 Hz was practically flat and the phase angle at low frequency was significantly reduced (Fig. 4B). Moreover, we also observed a significant increase in $Z_i 2-12$. This increase in $Z_i 2-12$ is not specific to nitroprusside, but depends on vasodilation per se, since it has been found by others during acetylcholine or isoproterenol infusion (O'Rourke, 1967; O'Rourke and Taylor, 1967). The exact significance of this increase in $Z_i 2-12$ associated with a decrease in blood pressure and its disappearance when cardiac output is increased is not clear. O'Rourke and Taylor (1967) suggest that with the decrease in blood pressure the previous equilibrium between wave velocity and aortic diameter was lost, which increased $Z_i 2-12$.

Whatever explanation is correct, our data indicate that the characteristic impedance may depend on the cardiac output, at least in some circumstances such as decrease in aortic compliance or nitroprusside infusion. Therefore, this fact always should be kept in mind before interpreting aortic impedance changes in patients (Nichols et al., 1977). Moreover, our data demonstrate that it is not correct to interpret the values of mean and pulsatile power as indices of the pumping function of the ventricle. Indeed, both the mean and pulsatile power depend intrinsically on the level of the venous return, the pumping ability of the ventricle, and the aortic input impedance. It is only when two of those parameters are kept constant that the directional change in power can be predicted.

**Significance of Input Impedance Changes on Left Ventricular Function**

By means of the different maneuvers used in this study, we were able to alter significantly the pulsatile impedances at fixed levels of $Z_o$, and to examine the effects of alterations in pulsatile impedance on ventricular performance. The effects of a decrease in compliance on left ventricular pump function have been described extensively in the intact (Imperial et al., 1961; Urschel et al., 1968) or isolated heart (Elzinga and Westerhof, 1973). When the characteristic impedance is increased, to assume the same cardiac output at the same mean pressure, the left ventricle has to generate more force. If it does not produce this extra amount of energy, cardiac output and mean pressure will fall (Imperial et al., 1961; Urschel et al., 1968; Elzinga and Westerhof, 1973). One goal of this study was to determine whether or not the force-velocity-length framework was altered when the left ventricle was producing this extra amount of force to match the increase in characteristic impedance.

Force was estimated by calculating wall stress for a thick-walled ellipsoid model, which has been shown to approximate measured ventricular wall stress (Burns et al., 1971). The shortening characteristics of the left ventricular wall during ejection were assessed by the mean velocity of circumferential shortening at the minor equator and by the relation between wall stress and ventricular diameter at end ejection. Under normal conditions, the relationship between wall shortening velocity and the wall stress can be used as an index of basal inotropic state. We determined the control relation between MVCF and wall stress (end-systolic or mean) at different levels of afterload (Karliner et al., 1971; Mahler et al., 1975b) when only the mean term of the impedance spectrum was changing. In the same way, we also examined the relation between ventricular diameter and wall stress at the end of ejection as a further measure of the level of inotropic state. Except at low muscle lengths, the length-tension relation of cat papillary muscles contracting isometrically tends to be similar to that obtained with variably afterloaded isotonic contractions (Sonnenblick, 1965). In the length-tension dia-
grams described for closed-chest sedated dogs (Taylor et al., 1969) subjected to variable afterloading, isolated heart preparations contracting isotonically (Burns et al., 1973) and, in pressure-diameter loops recorded during serial changes following phenylephrine injection (Mahler et al., 1975a), the points at the end of shortening were shown to fall on a straight line with high correlation coefficients. Pressure-volume data points near end ejection obtained in denervated hearts with arterial pressure fixed at different levels and constant cardiac output showed a linear correlation between volume and pressure (Suga et al., 1973), and other acute studies in isolated hearts have shown that the time-varying ratio of pressure to volume was independent of end-diastolic volume and arterial pressure but was affected by acute changes in inotropic state (Suga and Sagawa, 1974). Thus, although some discrepancies between isometric and isotonic length tension relationships may be encountered (Taylor et al., 1969) several studies in the whole heart have indicated that analysis of the length-tension relationship at the end of ejection generally approximates the isovolumic length-tension relation (Sonnenblick, 1965; Burns et al., 1973; Suga et al., 1973; Mahler et al., 1975a; Weber and Janicki, 1977).

When these two measures of the level of the contractile state obtained without significant change in impedance moduli or phase above 0 Hz were compared for the different maneuvers changing the aortic impedance spectrum, no change from the control state was obtained. Moreover, the results were qualitatively similar when an increase in contractile state was produced, and it was easily possible to distinguish these new data from the first control relation (Fig. 5). These results clearly demonstrate that, even when the aortic impedance is altered, the left ventricle does not deviate significantly from the force-velocity-length framework. This conclusion is different from those previously reported (Paulus et al., 1976) when a cat papillary muscle is incorporated in a theoretical thin-walled cylindrical ejecting ventricle. Since it has been shown that the wall stress calculated during systole depended on the geometrical model used (Burns et al., 1971), and since no significant deviation of the force-velocity-length relations are observed in the intact heart when an adequate geometrical model is used, these effects of impedance changes on papillary muscle could therefore represent an inadequate ventricular model rather than true changes in the mechanics of the muscle.

The second major question apparent in the present study was to determine whether the impedance spectrum would be more adequate than the wall stress calculation for predicting the shortening characteristics of the left ventricle. Our data indicate that an increase in characteristic impedance markedly increased the left ventricular wall stress, but we also furnished some evidence that the wall stress is more useful for this purpose than the impedance spectrum alone. If we compare a phenylephrine infusion and an aortic clamping at the same Zo (Table 1), the percent of shortening and the MVCF fell during the clamping (respectively, from 29 ± 5 to 15 ± 3%, P < 0.009; and from 2.00 ± 0.30 to 1.15 ± 0.14 circ. s.−1, P < 0.02) which could be predicted either from the change in impedance (Zi + 50%) or from the change in wall stress (mean wall stress 58%). However, when the venous return was reduced, the end-diastolic volume of the left ventricle decreased while both Zo and Zi further increased. When this new situation was compared with the previous phenylephrine infusion, the results are the following for five dogs; Zo during clamping +20%, P < 0.01; Zi +84%, P < 0.001; percent shortening −12%, NS; MVCF −15%, NS; mean wall stress, +5%, NS. Thus, there was not a significant change in shortening characteristics in spite of increases (+84%) in characteristic impedance and in resistance (+20%). These changes can be explained only if the afterload is better represented by the wall stress than by the impedance, which increased significantly. Such a result does not mean that the heart was not sensitive to this further increase in impedance; indeed, cardiac output was reduced in this case (−25%). In fact, this result means that the decrease in ventricular volume had sufficiently reduced the internal part of the afterload (ventricular geometry) and that, despite the increase in impedance (external afterload), wall stress and shortening were unchanged.

The importance of this matching between the "external" (i.e., aortic impedance) and "internal" (i.e., the geometry of the ventricle) factors of the afterload are illustrated in Figure 6. In this figure, it can be seen that at constant venous return, an identical increase in Zi does not produce the same increase in wall stress at all levels of Zo. At low Zo (which could represent the normal value, since the preparation is generally vasoconstricted), an increase in Zi has little effect; this means that the matching between the preload reserve used to keep the output constant and the resulting total afterload (increase in left ventricular volume and increase in Zi) is optimal. On the other hand, at higher Zo the same increase in Zi produced a marked effect on the wall stress, suggesting a less than optimal matching between preload and afterload.

In conclusion, our study demonstrates that, during aortic impedance changes, the corresponding changes in wall stress and shortening characteristics are completely described within the force-velocity-length framework. Consequently, the classical muscle mechanics and the concepts of preload reserve and afterload mismatch still apply in the physiological pumping conditions (Ross, 1976). We also found that not only the internal (geometry of the left ventricle) components of the afterload but also the aortic impedance itself could be modified by the venous return. Moreover, it should be kept in mind that in the intact circulation, the matching between
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FIGURE 6  This figure illustrates the changes in mean wall stress required to keep the cardiac output constant (1600 ml/min in six dogs) when the input resistance (Zo) is altered. When the characteristic impedance (Zi) is increased by 150% of the control, the increase in wall stress required to keep the cardiac output constant is much greater at high than at low Zo. This difference reflects the changes in the internal part of the afterload which occurs during the Frank-Starling mechanism. The importance of the internal part of the afterload is also illustrated by the points obtained during changes in venous return: it is possible to reduce markedly the wall stress required to keep the cardiac output constant by bringing the end-diastolic volume is brought back to control (increase in venous return) at a low level of Zo and Zi. Mean wall stress is expressed in g cm$^{-2}$.

"internal" and "external" part of the afterload will be a very complex function, depending also on the right ventricle and the pericardium. All these observations indicate that the heart function cannot be considered only as a linear source of impedance ejecting in a linear circuit (Elzinga and Westerhof, 1973).

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Comparison of the Hemodynamic Changes Produced by Electrical Stimulation of the Area Postrema and Nucleus Tractus Solitarii in the Dog

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SUMMARY Previous studies have implicated the area postrema (AP) as a site responsible for the centrally mediated neurogenic effects of angiotensin II. To clarify further its possible role in the central control of blood pressure, stainless steel electrodes were lowered stereotaxically into the AP of morphine-chloralose-anesthetized dogs after surgical exposure of the walls of the 4th ventricle just anterior to the obex. In all experiments, large pressor responses were obtained at a relatively low stimulus strength (range: 20-80 μA, 20-60 Hz); the increases in pressure (average: 30 ± 4 mm Hg) were rapid in onset and sustained for the 10- to 20-second duration of the stimulus. Hemodynamically, the pressor response during AP stimulation was due to increases in both cardiac output (+211 ± 37 ml/min) and peripheral resistance (+0.81 ± 0.33 U). An increase in heart rate contributed to the onset but not the plateau of the pressor response. Reconstruction of electrode tracts in all experiments corroborated that these pressor responses originated in the AP. The specificity of these cardiovascular responses was confirmed further by repeating the same kind of stimuli with electrodes placed in the nucleus tractus solitarii (NTS). In contrast to the effects obtained during AP stimulation, bradycardia (−41 ± 6 beats/min) and hypotension (−29 ± 5 mm Hg) were characteristic features. The fall in blood pressure during NTS stimulation was secondary to the pronounced bradycardia and decreased cardiac output. The data suggest that the AP is part of a previously unrecognized pathway which is distinct from the primary baroreflex pathway with relays in the adjacent NTS. Circ Res 45:136-143, 1979

THE MULTIPLICITY of actions of angiotensin II has led several investigators to explore the possibility that this hormone could have an effect within the central nervous system. This idea, first suggested by Bickerton and Buckley in 1961, lay dormant until recent years when Scroop and Lowe (1968) and Ferrario et al. (1970) showed that the infusion of angiotensin into the circulation of the dog's brain raised arterial blood pressure by a mechanism not involving direct vascular smooth muscle constriction. Since previous experiments (Ferrario et al., 1972; Gildenberg et al., 1973; Joy and Lowe, 1970) showed that the pressor effects of angiotensin in the medulla required the integrity of the area postrema (AP), a more detailed investigation of this structure was warranted. Important initial steps in this direction were: (1) to determine whether the facilitative action of angiotensin on vasomotor centers could be reproduced by means of electrical rather than chemical stimulation; and (2) to compare these hemodynamic effects with those obtained during the application of similar stimuli to the nucleus tractus solitarii (NTS), an area also involved in the central regulation of blood pressure (Doba and Reis, 1973; Nathan and Reis, 1977).

Methods

Animal Preparation

Electromagnetic flowmeters (Micron Instruments) were placed around the ascending aorta of 13 mongrel dogs (19-22 kg body weight) 1 week prior to the experiments, using a sterile technique (Ferrario et al., 1969). After anesthesia with morphine (2 mg/kg im) and chloralose (60 mg/kg, iv), catheters were placed in a femoral artery to monitor arterial pressure with a strain gauge pressure trans-
Effects of alterations in aortic input impedance on the force-velocity-length relationship in the intact canine heart.

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