A Computer Study of the Relation Between Chamber Mechanical Properties and Mean Pressure–Mean Flow of the Left Ventricle

Jorge A. Negroni, Elena C. Lascano, and Ricardo H. Pichel

Computer simulation of left ventricular contraction was used to analyze the mean left ventricular pressure–mean flow relation with changes of parameter values: end-diastolic volume, contractile state, internal resistance, characteristic resistance, capacitance, end-diastolic stiffness, and heart rate with changes of experimental conditions: filling kinetics (constant atrial pressure as opposed to constant end-diastolic volume) and coronary perfusion pressure (constant or varying with atrial pressure, i.e., self-perfused). The chamber mechanical properties used in the simulation were defined in terms of a modified purely elastic behavior model with a flow-dependent resistive component. Computed results showed that at constant end-diastolic volume and constant ventricular perfusion pressure the mean pressure–mean flow relation was linear, except for changes in internal resistance where a cubic fit of points was more appropriate. In these conditions, parameter variations in the accepted linear relation produced changes in the slope and mean pressure axis intercept. Imposition of changes in experimental conditions gave rise to nonlinear mean pressure–mean flow relations. The results indicate that with elastic-resistive chamber mechanical properties as a starting point, the experimental conditions would be responsible for the different shapes of the mean pressure–mean flow relation obtained in isolated heart experiments. However, a more complete description of chamber properties (such as the addition of a deactivation component) could also give rise to nonlinear pump function graphs. (Circulation Research 1988;62:1121–1133)
All simulated $P$-$Q$ diagrams arising from our model were compared with the corresponding diagrams predicted from the Elzinga and Westerhof linear relation to evaluate the differences between these two predictive models.

**Materials and Methods**

**Mathematical Foundations of Digital Simulation of Left Ventricle**

The system that was simulated can be represented by the electric circuit shown in Figure 1. We used the same circuit and normal values as previously reported. These are characteristic resistance ($R_c$) = 0.2 mm Hg x sec/ml, capacitance ($C$) = 0.4 ml/mm Hg, and resistance ($R$) = 3 mm Hg x sec/ml for a 20-kg dog. Because we could not find in the literature a value for the filling resistance ($R_f$), we adapted the equation of Yellin et al for ventricular filling kinetics to our model, and using the data of Meisner et al, we obtained a value of $R_f = 0.04$ mm Hg x sec/ml (see Appendix 1). The diodes $D_1$ and $D_2$ characterize the mitral and aortic valves, respectively, with a diode forward resistance equal to zero and a very high diode inverse resistance, generally greater than 1,000 mm Hg x sec/ml. An infinite resistance was not chosen because reflux, though not significant, generally occurs during the relaxation phase and mitral valve closure. To describe the whole system as an electric analog, we defined the electric characteristics of the LV in terms of a pressure-flow relation. This was accomplished by adopting the chamber mechanical properties described by Shroff et al in which the instantaneous ventricular pressure $P(t)$ is a function of four independent variables: time ($t$) from the onset of contraction, chamber volume [$V(t)$], aortic flow [$Q_a(t)$] as the negative change of chamber volume [$-dV/dt(t)$], and myocardial contractile state (CS). Namely, this function can be expressed as

$$P(t, CS, V(t), dV/dt(t)) = P_e(t, CS, V(t)) + R(t) dV/dt(t)$$

where $P_e(t, CS, V(t))$ is ventricular pressure due to purely elastic behavior, and $R(t)$ is the instantaneous resistance that produces a drop in pressure when the ventricle is ejecting. For simplicity we will substitute $P(t, CS, V(t), dV/dt(t)) = P(t)$, and $P_e(t, CS, V(t))$ by $P_e(t)$.

To model ventricular properties in both isolated heart and isolated muscle, $R(t)$ was found to be related to $P_e(t)$ in the following way: $R(t) = K[P_e(t)]$, where $K$ is the resistance coefficient. The chosen value of $K = 0.0015$ sec/ml was that reported in isolated heart experiments. Therefore, we assumed that there were no major differences between the descriptions of Shroff et al and Suga et al of chamber mechanical properties and adopted the general formulation of Equation 2 to characterize ventricular performance for the whole cardiac cycle.

Early findings of Suga and Sagawa were adopted by Shroff et al. in their description of ventricular pressure due to purely elastic behavior [$P_e(t)$]. Namely,

$$P_e(t) = E(t) (V(t) - V_0)$$

where $E(t)$ depends only on time, and $V_0$ is the volume at which the ventricle is unable to generate supra-atmospheric pressure. $V_0$ has also been defined as the volume axis intercept of the end-systolic pressure-volume relation. Using Equation 4, Suga considered that $P_e(t)$ coursed on the surface of the pressure-volume-time relation generated when volume was taken as an independent variable.

Suga and Sagawa established that $E(t)$ could be normalized through maximum elastance ($E_{\text{max}}$) and time to $E_{\text{max}}$ ($T_{\text{max}}$) as follows:

$$E(t) = E_{\text{max}} \times F(t/T_{\text{max}})$$

where $F(t/T_{\text{max}})$ is the normalized time function that has a positive value at $t = 0$. This description implies that variations in $E_{\text{max}}$ result in changes in end-diastolic elastance [$E(0)$], $E(t)$ when $t = 0$. From Tables 4 and 5
of Shroff et al,11 we concluded that end-diastolic elastance (a3 for these authors) does not change when CS is enhanced, even though this intervention affects Emax and Tmax. Therefore, to avoid altering E(0) when inotropic situations are simulated, we propose the following formulation:

\[
E(t) = E(0) + [E_{max} - E(0)] \times F(t/T_{max}) \tag{5}
\]

Because information reported in the literature for F(t/T_{max}) or E(t) in isovolumic conditions was scarce for the whole cardiac cycle, the criterion of Shroff et al11 was used; that is, any functional form resembling the time course of isovolumic pressure would be representative of F(t/T_{max}). Then, this time function was built to conform with the following conditions: at t = 0 is equal to zero, has a maximum at t = Tmax, and returns asymptotically to zero, having a slight asymmetry with respect to Tmax (Figure 2A). These conditions were met by a fourth-order polynomial function as follows:

\[
F(t/T_{max}) = 0.463 \left(\frac{t}{T_{max}}\right) \left[\left(\frac{t}{T_{max}}\right) - 2.2\right]^2
\]

\[
\left[\left(\frac{t}{T_{max}}\right) + 0.5\right]
\]

for \(t \leq 2.2 \text{T}_{\text{max}}\). For \(t > 2.2 \text{T}_{\text{max}}\), \(F(t/T_{max})\) is defined as equal to zero. Less complex forms such as a sine wave19,23 or a third-order polynomial function11 did not satisfy the criterion adopted here for a whole beat. Figure 2A also shows previously published data (Figure 7 of Suga and Sagawa24) normalized with Equation 5. These data that were tested against our proposed \(F(t/T_{max})\) gave rise to a standard error of estimate of 0.0052 that represents about 1% of the mean value (0.5) of the estimated function (Equation 6) averaged over one cardiac cycle.

Substitution of \(E(t)\) in Equation 4 by its definition in Equation 5 yields

\[
Pe(t) = E(0) \left[\frac{V(t) - V_o}{V(t) - V_o} - E(0)\right] \times F(t/T_{max}) \tag{6}
\]

Then, we can write the generalized form of \(Pe(t)\) as

\[
Pe(t) = Pe(0) + \left[Pe(T_{max}) - Pe(0)\right] \times F(t/T_{max}) \tag{7}
\]

where \(Pe(0)\) is the volume-dependent ventricular pressure due to purely elastic behavior, which is equal to the end-diastolic pressure-volume relation, and \(Pe(T_{max})\) is the volume-dependent ventricular pressure due to purely elastic behavior, which is equal to the end-systolic pressure-volume relation.

According to Equation 4, both \(Pe(0)\) and \(Pe(T_{max})\) in Equation 7 are assumed to be linear functions. However, other studies24,25 indicated that the end-diastolic pressure-volume relation above a ventricular pressure of 5 mm Hg could be fitted to an exponential curve. Later, Sunagawa et al20 observed that the shape of the pressure-volume-time relation was more complex, yielding subatmospheric values of pressure for small volumes. From their results, it can be interpreted that the \(Pe(t)\) function with respect to volume at specified times after the onset of systole is a family of sigmoidal curves that gradually become more linear, reaching a maximum value at end-systole. Thus, the mathematical formulation of \(Pe(0)\) and \(Pe(T_{max})\) based on the results obtained by these authors was expressed by us as the summation of a cubic and a hyperbolic function:

\[
Pe(0) = D \left[b_3 \times V^3(t) + b_2 \times V^2(t) + b_1 \times V(t) + b_0\right] + H/V(t) \tag{8}
\]

and

\[
Pe(T_{max}) = E_{max} \left[d_3 \times V^3(t) + d_2 \times V^2(t) + d_1 \times V(t) + d_0 + M/V(t)\right] \tag{9}
\]

where \(D\) is a scale factor to change the end-diastolic pressure-volume relation and represents end-diastolic stiffness. In the normal state, \(D = 1\). Values above 1 indicate increased diastolic stiffness of the ventricle. The other symbols are coefficients for the polynomial function whose values for \(D = 1\) and \(E_{max} = 4\) were calculated from five pairs of pressure-volume data (Table 1) obtained as the best compromise from experimental results in canine hearts.30,35-37 Figure 2B shows that the shape of the pressure-volume-time relation obtained
TABLE

<table>
<thead>
<tr>
<th>Pe(0)</th>
<th>Pe(Tmax)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b₀</td>
<td>b₁</td>
</tr>
<tr>
<td>-13.7</td>
<td>1.87</td>
</tr>
<tr>
<td>d₀</td>
<td>d₁</td>
</tr>
<tr>
<td>-2.42</td>
<td>0.81</td>
</tr>
</tbody>
</table>

The coefficients were calculated with pairs of pressure-volume values for D = 1 and Eₘₐₓ = 4 mm Hg/ml (see text and Equations 8 and 9).

with the adopted model described in Equation 7 confirms the results of Sunagawa et al.20,27 As a result of the mathematical approach presented in this work, time and volume-dependent elastance Eₐ(t) is defined as the partial derivative of Pe(t) with respect to V(t):

\[ Eₐ(t) = \frac{∂[Pe(t)]}{∂V} \] (10)

Consequently, the generalized function for Eₐ(t) is obtained from Equation 7 and solved with Equations 8 and 9.

To describe the effects of heart rate (HR) on Eₘₐₓ and Tₘₐₓ, we used values of experimental results previously published (Table 7 of Shroff et al11). The linear fit of their data for changes in HR (range 100-150 beats/min) and normal CS yielded

\[ Tₘₐₓ = 0.35T + 0.013 \quad (r = 0.88) \]
\[ Eₘₐₓ = -5.76T + 6.88 \quad (r = 0.83) \]

where \( T = 60/HR \) is cardiac cycle period. We adopted 120 beats/min as normal HR because it is generally used in in vitro experiments.\(^{11,27} \) Then, for normal conditions, Eₘₐₓ = 4 mm Hg/ml, and Tₘₐₓ = 0.188 seconds. An enhanced CS due to dobutamine infusion, 3-9 /µg/min (with mean values from Shroff et al\(^{11} \)) changed the Eₘₐₓ and Tₘₐₓ values in the following way: Eₘₐₓ = 1.71 Eₘₐₓ (normal) and Tₘₐₓ = 0.81 Tₘₐₓ (normal).

To study the effects of self-perfusion, the influence of coronary arterial pressure (CAP) on Eₘₐₓ was taken into account. According to Sunagawa et al,\(^{20} \) the critical CAP below, which Eₘₐₓ decreases, was found to be 67 mm Hg (mean value). In our simulation of LV contraction, CAP was considered equal to mean arterial pressure \( \bar{P}_{a} \). Reported experimental data (Figure 4 of Sunagawa et al\(^{20} \)) were fitted to the following sigmoidal function\(^{29} \) (Figure 3A) because it yielded the best fit (\( r = 0.87 \)):

\[ Eₘₐₓ \text{ (self-perfusion)} = Eₘₐₓ \text{ (constant perfusion)} / \left[ 1 + 8.704 \times \exp(-0.0855 \bar{P}_{a}) \right] \] (11)

Figure 3B shows that with self-perfusion of the ventricle, the computer-simulated end-systolic pressure-volume relation adopted a nonlinear shape as experimentally observed in isolated canine heart.\(^{20} \)

![Figure 3](http://circres.ahajournals.org/)

**Computer Program**

The computer program was written in BASIC and run on a Hewlett-Packard 150 PC computer. The computer algorithm was developed to simulate ventricular contractions and to study the response to afterload maneuvers (changing R). The beats follow automatically one after another. Stabilized beats are processed according to the following criterion: a steady-state beat is that in which arterial and ventricular pressures do not differ more than 1% between the beginning and the end of the cardiac cycle and in which the difference between mean aortic and mean mitral flows is not greater than 1%. It takes 4-6 beats for the model to become stable after R changes. The filling kinetics is chosen between two alternatives, one at constant atrial pressure (AP) throughout the beat and the other with increasing AP after t = 2.2 Tₘₐₓ to ensure a constant end-diastolic volume (\( V_{ed} \)). Coronary perfusion is also chosen between two alternatives, one of constant perfusion pressure and the other of self-perfusion that changes \( Eₘₐₓ \) as seen in Equation 11.

The program starts with the choice of experimental conditions (coronary perfusion and filling kinetics); the input of parameter values (CS, HR, R, C, and D), which are kept constant throughout the whole maneuver; and the input of the initial values of \( P_{a}(t) \) and \( V_{ed} \).
The dV/dt(t) is obtained as in Equation 3. Ventricular volume is obtained as

\[ V(t) = V_0 + \int_0^t dV/dt(t) \times dt \]

Pressure is calculated by sequentially solving Equations 8, 9, 7, and 2. According to the Windkessel model, arterial pressure is obtained as follows:

\[ P(t) = C \times \frac{dP_o/\text{dt(t)}}{[P_o(t)/R]} + [P_o(t)/R] \]

The solution to this equation is

\[ P_o(t) = e^{-\alpha R_c} [P_o(0) + \frac{1}{C} \int_0^t e^{\alpha R_c} \times Q_o(t)dt] \]

\[ E(t) = \frac{P(t) - V(t) - V_0}{R} \]

All the integrals are obtained by means of the trapezoidal rule applied to each time step.

4) Comparison of new P(t) and P_o(t) values with the corresponding previous values. If the difference is greater than 0.2%, the values are averaged, and the process is reiterated for this particular time, t, until the values are accepted. Then, the corresponding values of P(t), P_o(t), V(t), and flows are stored, and time is incremented by 0.002 seconds. The program then begins a new computation cycle. This process reiterates until the end of a cardiac cycle.

The next beat starts with values of P(t), P_o(t), and V(t) corresponding to the last values of the preceding beat. Units used are millimeters of mercury, milliliters, and seconds. The value of R is changed according to the following relation:

\[ R = R_0/2^{n-1/2} \]

where \( R_0 \) is the highest resistance (48 mm Hg x sec/ml), and \( n \) is the beat number of the maneuver.

In the present work, a sequence of 15 beats could be obtained. When the resistance was so small that \( P_o(t) \) fell below diastolic pressure, the beat was discarded and further iteration suspended because arterial pressure then became so low that blood could flow directly from the atrium to the aorta, which contributed to Q without need for the pump. Finally, the P-Q relation curves and pressure-volume loop diagrams were constructed with all the accepted beats.

**Protocol of Runs**

The runs were planned to simulate the experimental conditions reported in different works. Accordingly, to establish how different factors affected the P-Q relation, we examined in stabilized beats the influence of all the parameter changes at constant \( V_{ed} \), the effect of changes in preload at constant \( AP \), and the influence of self-perfusion of the ventricle in a series of afterload maneuvers. To study the influence of parameter changes on the P-Q relation at constant \( V_{ed} \), values of \( R_c, C, CS, HR, V_{ed}, K, \) and \( D \) were increased and/or decreased from their normal values as shown in Table 2A. Only one parameter was changed in each run of the program, while normal values were kept for the others. To study the P-Q relation at constant AP as opposed to constant \( V_{ed} \), we performed three runs at AP values (runs 15, 16, and 17, Table 2B) calculated with Equation 8 [\( Pe(0) \) with \( D=1 \)] for volumes equal to those used in the constant \( V_{ed} \) experiments. The effect of self-perfusion on the P-Q relation was analyzed in runs 18 and 19 at constant AP and \( V_{ed} \), respectively.

**Statistical Analysis of Results**

Since the computer simulation does not give random variables, differences between runs cannot be tested with current statistical methods. In this case, errors are introduced by integral approximation, which were errors admitted in the iterative process and machine imprecision, and are propagated to final results by the great number of individual calculations performed by the computer program. Furthermore, since \( Q \) is not an independent variable, experimental \( \overline{P} \) values of different runs are not necessarily obtained at a given \( Q \). Consequently, differences between runs were analyzed on the following basis: experimental \( \overline{P} \)-Q points were joined to each other by a straight line. For each \( \overline{P} \)-Q diagram (including Elzinga and Westerhof relations), an associated maximum error in \( \overline{P} \) was calculated (\( \Delta P \)) (see Appendix 2), which was used to define maximum parallel error bands as \( \overline{P} \pm \Delta P \). Two \( \overline{P} \)-Q diagrams were considered to be significantly different if at least one point of nonsuperimposition between their respective \( \overline{P} \pm \Delta P \) error bands was found.

To separate linear from nonlinear \( \overline{P} \)-Q diagrams, each set of experimental points was approximated by least-squares fitting to linear and cubic polynomial
functions. The criterion to decide acceptance of a fit was the lowest-order polynomial function whose standard error of the estimate was not greater than the maximum error in $P$. Values of mean flow axis intercept used in the interpretation of linearly accepted $P$-$Q$ relations were obtained by regression of the corresponding fit. The other intercept values $[P(V_{ed})]$ were calculated by the computer program as the mean isovolumic pressure at the initial $V_{ed}$.

**Results**

In a first step, we tested the validity of the model to reproduce $P$-$Q$ relations. To this end, we obtained time courses of $P(t)$, $Pe(t)$, $Q(t)$, $E_{x}(t)$, $E_{s}(t)$, and pressure-volume relations (Figures 4A–D), which show fairly good agreement with experimental results of different authors.8,12,17,18

The $P$-$Q$ relations obtained for all the runs are shown in Figures 5 and 6. Each diagram in these figures represents the effect of variation in one parameter. For each $P$-$Q$ diagram, we calculated the linear $P$-$Q$ relation proposed by Elzinga and Westerhof9 as

$$P = P(V_{ed}) - E \times T \times Q$$

(12)

where $E \times T = P(V_{ed})/Q_{max} = \int_0^T E(t)dt$. The intercept value $P(V_{ed})$ is equal to maximal mean pressure when $Q = 0$, and $Q_{max}$ is the maximal mean flow defined for unloaded conditions as

$$Q_{max} = (V_{ed} - V_0)/T$$

(13)

$V_0$ is the volume at which $Pe(T_{max}) = 0$, its value being equal to 5.44 ml for all the simulated experimental conditions. Using the error criterion explained above, we found that all the assayed parameter changes yielded significant differences with respect to normal values, and in all the runs, the Elzinga and Westerhof linear relation differed significantly from the corresponding $P$-$Q$ diagrams.

**Effect of Parameter Changes on the $P$-$Q$ Relation**

Table 3 shows the coefficients of the accepted polynomial fit. It can be seen that for parameter changes at a constant $V_{ed}$ and normal constant perfusion, the lin-
ear fit \((r>0.999)\) was accepted except for \(K\) in which a cubic fit was necessary. Moreover, for all these runs (1–14), the data points were displaced upward with respect to the Elzinga and Westerhof linear relation (Figures 5A–F).

**Effect of \(R_c\).** The effect of changes in \(R_c\) (Table 2A, runs 2 and 3; Figure 5A) showed that for small flows the \(P-Q\) relation curves were very similar. For large flows, increased \(R_c\) shifted the \(P-Q\) curves upward, and decreased \(R_c\) produced the opposite effect, as observed by Maughan et al.\(^14\)

**Effect of \(CS\).** Enhanced \(CS\) (Tables 2A, run 6; Figure 5A) shifted the \(P-Q\) curve upward and increased its slope as seen by Elzinga and Westerhof\(^3\) and Maughan et al.\(^14\). With an enhanced \(CS\), the mean pressure axis intercept was 37% greater than that under normal conditions, whereas the mean flow axis intercept was decreased by only 2.7%.

### Table 3. Coefficients of Linear and Cubic Fits of Computer-Simulated \(P-Q\) Relations With Standard Error of the Estimate and Maximal Error in \(P\)

<table>
<thead>
<tr>
<th>Run</th>
<th>Coefficient of accepted fit</th>
<th>Maximal error in (P) (mm Hg)</th>
<th>Standard error of the estimate (mm Hg)</th>
<th>Linear fit</th>
<th>Cubic fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>(a_0 = 62.125) (a_1 = -0.850)</td>
<td>0.2</td>
<td>0.1</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>2*</td>
<td>(a_0 = 62.276) (a_1 = -0.887)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>3*</td>
<td>(a_0 = 61.840) (a_1 = -0.792)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>4*</td>
<td>(a_0 = 61.972) (a_1 = -0.859)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>5*</td>
<td>(a_0 = 62.186) (a_1 = -0.838)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>6*</td>
<td>(a_0 = 85.299) (a_1 = -1.203)</td>
<td>0.3</td>
<td>0.2</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>7*</td>
<td>(a_0 = 52.926) (a_1 = -0.872)</td>
<td>0.2</td>
<td>0.1</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>8*</td>
<td>(a_0 = 68.265) (a_1 = -0.814)</td>
<td>0.2</td>
<td>0.1</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>9*</td>
<td>(a_0 = 47.205) (a_1 = -0.833)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>10*</td>
<td>(a_0 = 78.665) (a_1 = -0.889)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>11*</td>
<td>(a_0 = 60.105) (a_1 = -0.826)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>12*</td>
<td>(a_0 = 64.098) (a_1 = -0.869)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>13†</td>
<td>(a_0 = 61.859) (a_1 = -0.659) (a_2 = -5.99 \times 10^{-3}) (a_3 = 6.68 \times 10^{-5})</td>
<td>0.2</td>
<td>0.3</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>14†</td>
<td>(a_0 = 61.82) (a_1 = -0.982) (a_2 = 1.88 \times 10^{-4}) (a_3 = 4.92 \times 10^{-5})</td>
<td>0.2</td>
<td>0.5</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>15†</td>
<td>(a_0 = 61.508) (a_1 = -0.0849) (a_2 = -0.045) (a_3 = 9 \times 10^{-4})</td>
<td>0.6</td>
<td>0.8</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>16†</td>
<td>(a_0 = 47.066) (a_1 = -2.279) (a_2 = 0.032) (a_3 = 1.3 \times 10^{-3})</td>
<td>0.5</td>
<td>1.6</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>17†</td>
<td>(a_0 = 79.051) (a_1 = -0.984)</td>
<td>0.8</td>
<td>0.2</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>(a_0 = 6.25) (a_1 = 9.4) (a_2 = 9.65)</td>
<td>0.6</td>
<td>9.4</td>
<td>9.65</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>0.2</td>
<td>11.6</td>
<td>11.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Accepted linear fit \((\hat{P} = a_0 + a_1Q)\), and † accepted cubic fit \((\hat{P} = a_0 + a_1Q + a_2Q^2 + a_3Q^3)\). No symbol indicates that neither linear nor cubic fits were accepted.

\(P-Q\), mean pressure and mean flow.
Effect of C. Changes in C (Table 2A, runs 4 and 5; Figure 5B) produced small, though significant, variations in the slope of the P-Q relation. For small Q, the P points decreased with decreasing C, and at high Q, the opposite result was observed, yielding a crossing over of the relation as experimentally reported.14

Effect of HR. Increased HR yielded an almost parallel upward shift of the P-Q relation, whereas decreased HR produced the opposite effect, as observed by Elzinga and Westerhof13 (Table 2A, runs 7 and 8; Figure 5C).

Effect of Vrd. Changes in Vrd (Table 2A, runs 9 and 10; Figure 5D) produced an effect similar to that of HR. This effect was similar to previous experimental findings.3,16

Effect of D. Changes in D (Table 2A, runs 11 and 12; Figure 5E) produced the same, though less evident, effect as CS. The Qmax-extrapolated values of linear fits differed by less than 0.9%, whereas the P intercept values differed by 3.2%.

Effect of K. Decreased K produced an upward shift, and increased K produced a downward shift of the P-Q relation with the same P intercept value (Table 2A, runs 13 and 14; Figure 5F).

Effects of Experimental Conditions on the P-Q Relation

Runs performed with changes in experimental conditions showed that at constant AP the P-Q relation was not linear (Tables 2B and 3, runs 15 and 16; Figure 6A) as opposed to constant Vrd (Figures 5A–E). In Figure 6A, it can be seen that only at an AP high enough to ensure adequate filling (13.5 mm Hg, run 17), could the P-Q pairs of points be linearly fitted (Table 3, run 17) and come to lie above the Elzinga and Westerhof linear relation. As AP became lower, the P-Q diagram adopted a sigmoidal shape, and a cubic fit was found to be more appropriate (Table 3, runs 15 and 16).

Self-perfusion at constant Vrd (Table 2B, run 19; Figure 6B) showed that the P-Q relation could be fitted to neither a linear nor a cubic function (Table 3, run 19). In the case of small flows, corresponding to high P values (Equation 11), the P-Q pairs of points lay above the Elzinga and Westerhof linear relation, with values similar to those obtained in normal perfusion. However, as Q increased, P decreased, and the pairs of P-Q points crossed the Elzinga and Westerhof linear relation to lie below it, thus abandoning the normal perfusion curve. Self-perfusion at constant AP (Table 2B, run 18; Figure 6B) simulates the experimental situation under which Elzinga and Westerhof2-3 studied the P-Q relation. In this condition, the P-Q diagram again could not be fitted to either linear or cubic functions, and its shape was similar to that obtained at constant Vrd and self-perfusion, except that all the P-Q pairs of points lay below the Elzinga and Westerhof proposed linear relation.
Discussion

Because an entire beat was used in the simulation model, some assumptions regarding the filling phase had to be made. To model filling kinetics, the value of Rf was obtained according to the methods of Yellin et al and Meisner et al. Because the value of K for the filling phase has not been reported in the literature, we have arbitrarily assumed it to be equal to that during ejection (i.e., K = 0.0015 sec/ml). Higher or lower values of K could, respectively, decrease or increase intraventricular pressure during filling. However, in runs at constant Vd, the values of Rf and K are not important since filling is forced through variations in AP to ensure the attainment of the fixed Vd. Moreover, independent of filling kinetics, the contribution of intraventricular filling pressure to P over the whole cardiac cycle is small, reducing the importance of the value of K during this phase in the prediction of the P-Q relations.

The general description of ventricular mechanics was made with the formulation (Equation 1) of Shroff et al of which the resistive component Rf(t)dV/dt(t) will be equal to P(t), V(t) only when outflow dV/dt(t) is equal to zero or less than Pe(t), VS, and V(t), that is, below the pressure-volume-time surface for negative values of dV/dt. This effect can be seen in Figure 4A where P(t) coincides with Pe(t), CS, and V(t) during isometric systole at V(t) = Vd and isometric diastole at V(t) = Vg (end-systolic volume) and courses below Pe(t), CS, V(t) during ejection, making it finish after Tmax = 0.188 seconds. Simulation of E(t) and pressure-volume loops (Figures 4B and 4D) with these chamber mechanical properties yielded results similar to those previously reported [Figure 3 of Sagawa et al for E(t), and Figure 2A of Sunagawa et al for pressure-volume loops], thus confirming the validity of our model. This good agreement between computer-simulated and experimental results was obtained even though no assumptions about ventricular geometry were made and even though the approximated and fitted functions used were extended for the whole cardiac cycle.

However, recent experimental studies have accounted for the need of adding a deactivation or decoupling effect to the chamber mechanical model. Suga et al found P(t) to depend not only on an elastic-resistive model but also on peak ejective outflow (peak dV/dt) and volume ejected by the specified time: Vd = V(t), and they attributed these findings to the manifestation of deactivation due to shortening of the cardiac muscle. Campbell et al observed a deviation in LV pump behavior, particularly during late systole, characterized by a biphasic waveform of P(t) = P(t) - P(t), where P(t) is isovolumic pressure. To explain these results, they suggested the need to specify a global property of the heart to represent late systolic pumping effects. In a validation of LV pump models, Campbell et al have also shown the inadequacy of different elastance-resistance models to predict observed responses in dog and rat hearts and have indicated that the deficiency would probably be due to not accounting for a deactivation effect. Moreover, in addition to elastic, resistive, and deactivation components, Hunter et al in studies of flow pulse response in dog hearts have demonstrated the existence of a volume-influence factor to express the dependence of elastance to the time in systole in which the change in volume is applied. Nevertheless, up to the present, deactivation and volume-influence components have not been incorporated into the models of chamber mechanical properties. Therefore, the present study was performed with an elastic-resistive model in which parameter dependence of coefficients has been numerically established.

Analysis of results showed that changes in parameter values (Vd, CS, HR, C, and R) yielded results similar to those experimentally obtained. However, it was observed that at constant Vd and constant perfusion of the ventricle, all pairs of points lay above the Elzinga and Westerhof linear relation (Equation 12), as theoretically supported in a previous report, except for P at Q = 0 in which they coincided. This indicates that for all the tested runs the slope of the simulated P-Q relation would be less than that of the corresponding Elzinga and Westerhof relation. Our results also showed that in the conditions of constant Vd and perfusion, the P-Q relations were linear except...
for very low (0 value) and very high (100% of control) values of \( K \), where a cubic fit was more appropriate. We feel that the nonlinearity observed here is the consequence of the elastic-resistive model used to describe chamber mechanical properties. In Equation 3, definition of \( Q(t) = dV/dt \) and substitution by mean values yields

\[
\mathcal{P} = \mathcal{P}_e - K \mathcal{P} e Q \tag{14}
\]

where \( \mathcal{P} e Q \) represents mean elastic power developed by the ventricle during a beat. Because during the effective phase, elastic pressure is greater than ejecting pressure, \( \mathcal{P} e Q \) would result greater than mean external power. However, if we can assume that \( \mathcal{P} e Q \) has approximately the same parabolic shape as mean external power as a function of \( Q \), we could predict the effect of \( K \) on the \( P-Q \) diagrams. Because \( K \) is a scale factor (Equation 14), its effect in the subtraction of \( K \mathcal{P} e Q \) from \( \mathcal{P} e \) would be progressively greater as \( K \) increases, particularly where the parabola reaches its maximum value at \( Q = \bar{Q} \text{max}/2 \). This would yield nonlinear (slightly downward convexity) \( P-Q \) diagrams for high \( K \) as seen in Figure SF. When \( K = 0 \), non-linear \( P-Q \) relations (slightly upward convexity) would be due to the shape of \( \mathcal{P} e = f(Q) \). Between these two extreme nonlinear relations, linearity in our model would be obtained for normal values of \( K \).

In contrast to results at constant \( V_{ed} \) and perfusion pressure, changes in experimental conditions (constant \( AP \) and self-perfusion) have shown different degrees of departure from the linear \( P-Q \) relation. When runs are performed at constant \( AP \), filling depends on \( AP \) if \( RF, K, \) and \( HR \) are assumed to be constant. In this case, a high afterload ensures an approximately constant \( V_{ed} \). As afterload decreases, increases in \( Q \) produce a progressive decrease in \( V_{ed} \) due to inadequate filling. This effect of constant \( AP \) on \( V_{ed} \) is reflected in the nonlinear shape of the \( P-Q \) relation shown in Figure 6A, which could be interpreted as the course of the \( P-Q \) relation through a family of parallel linear-fitted curves at different values of constant \( V_{ed} \). It must be noticed that with high \( AP \), which ensures a good filling and consequently a fairly constant \( V_{ed} \), the \( P-Q \) relation tends to be linear, whereas at a low \( AP \), the \( P-Q \) relation becomes nonlinear. Similar experimental results showed linear \( P-Q \) relations at \( AP = 9 \) and nonlinear ones at \( AP = 4 \) mm Hg (Figure 9 of Elzinga and Westerhof). Furthermore, nonlinearity is also observed with self-perfusion of the ventricle (Figure 6B) because of a progressive decrease in \( E_{max} \) as \( \mathcal{P} e \) diminishes (Equation 11). Thus, simulation of \( P-Q \) relations would indicate that the effects of constant \( AP \) and self-perfusion could explain the nonlinearity of some \( P-Q \) diagrams obtained in these experimental conditions.

However, not all curved \( P-Q \) relations can be explained by changes in experimental conditions. Recent studies performed on a beat-to-beat basis to avoid variations in LV filling, coronary perfusion pressure, and inotropic state have also shown nonlinear pump function graphs. Therefore, in spite of similar responses to parameter changes in experimental and computer-simulated \( P-Q \) relations, we must admit the shortcomings of an elastic-resistive model to predict pump-function graphs, and we must consider that with better defined chamber mechanical properties probably different shapes of \( P-Q \) diagrams would be obtained.

In an attempt to improve the characterization of ventricular mechanics, we analyzed the feasibility of incorporating a volume influence factor and a deactivation component into our elastic-resistive model. The volume influence factor \( B(T) \) as defined by Hunter et al describes the influence of volume on elastic pressure depending on the time \( T \) in systole in which a step in volume is applied. According to their results, ventricular pressure would be more sensitive to changes in volume early in systole compared with changes late in systole, counteracting the effect of deactivation that is more pronounced at the end of systole. However, because the effect of \( B(T) \) on elastic pressure was studied with the same step in volume \( (\Delta V) \) imposed at different times of systole, we have been unable to represent it in our model of elastic pressure \( [P_e(t)] \), which is both a \( V(t) \) and time-dependent function. Consequently, further studies on the effect of the volume-influenced factor with continuously changing volume, as is the case of an ejective beat, would be necessary in order to incorporate it in ventricular chamber models. To describe the deactivation component, we followed the study of Nwasokwa et al in situ dog papillary muscle. As also established in other species, they showed in afterloaded-isotonic contractions that the greater the amount of shortening, the earlier the onset of relaxation, except for very high afterloads that depart from this rule. Their findings, attributed to a deactivation effect, depended on the total amount of shortening, and were independent of the moment in systole in which they occurred. Therefore, in this respect, they differed from earlier ones in papillary muscle of other species or flow-pulse response in dog heart in which the effect of deactivation was found to be significant only in late systole. Nevertheless, the results of Nwasokwa et al were chosen to simulate deactivation because we considered that afterloaded-isotonic contractions reproduce fairly well the mechanical events of the cardiac cycle, making it easier to interpret a deactivation effect than quick length change or flow-pulse response experiments. Based on our observations, we assumed deactivation as the earlier termination of the time course of the normalized time function \( F(T/T_{max}) \) in proportion to the fraction of total ejected volume. The equation that best reproduced the results of Nwasokwa et al was the following:

\[
DF = 1.6 + 0.6 \exp[-2(V_{ed} - V_s)/(V_{ed} - V_b)] \tag{15}
\]

where \( DF \) is the deactivation factor that substitutes the 2.2 value in Equation 6 (Figure 7A). Figure 7 also
shows that the relaxation phase has a quick decay followed by a slower fall of pressure, similar to that observed in cat papillary muscle (Figure 3 of Parmley and Sonnenblick).

Using this new formulation of chamber mechanical properties, we obtained the two humps on the Pd curve found by Campbell et al. in opposition to one hump without DF (Figure 7B). When we performed a run at constant Vm and constant perfusion pressure, we found that even though the pump-function graph was not linear it did not reproduce experimentally observed shapes. Consequently, factors other than the ones studied up to the present could be responsible for the curved shape of experimental P-Q diagrams. Kil and Schiereck found that sudden changes in preload produced variations in Ema due to factors that altered the inotropic state of the heart. The effect of sudden changes in afterload, as performed by Van den Horn et al., is presently unknown. However, if the response was similar to that found for preload, the nonlinearity of P-Q relations could be accounted for by the changes in Ema as observed with self-perfusion.

In conclusion, using elastic-resistive chamber mechanical properties, we were able to simulate the experimental behavior of P-Q relations due to parameter changes reported in the literature. Under experimental conditions of constant Vm and perfusion pressure, all points of the calculated P-Q diagrams lay above the Elzinga and Westerhof relation. Moreover, contrary to some experimental evidence, we obtained linear P-Q relations (except for changes in K). Introduction of a deactivation component into the chamber mechanical properties yielded nonlinear diagrams, but it was unable to reproduce the sigmoidal or parabolic shapes of experimental pump-function graphs. Only with changes in experimental conditions, that is, constant atrial pressure or self-perfusion of the heart, were we able to obtain nonlinear P-Q relations as those reported in some in vitro heart experiments.

**Appendix 1**

**Calculation of Rf**

According to Yellin et al., filling kinetics can be described by the following equation:

\[
\Delta P = [A Q_m(t) + B Q_m(t)] + E D [V(t) - V_0] \tag{A-1}
\]

where A and B represent the inertial and resistive components, respectively. Since during filling

\[
\Delta P = A P - P(t)
\]

using Equation 4, we have

\[
\Delta P = A P - E_0 (V(t) - V_0) \tag{A-2}
\]

where E_0 = diastolic elastance.

In our model (only elastic-resistive), A = 0; then substitution of Equation A-2 into Equation A-1 yields

\[
B Q_m(t) + E_0 V(t) = A P + E_0 V_0
\]

Differentiation of this equation gives

\[
[B d Q_m(t)] + E_0 Q_m(t) = 0
\]
the solution of which is

\[ Q_m(t) = 140 e^{0.813S} \]

where \( E_\sigma/B = 4.8135 \).

Fitting experimental data for filling flow (Figure 5 of Meisner et al18) to Equation A-3, we approximately obtain

\[ Q_m(t) = 140 e^{0.813S} \]

In the simulation model, we consider end-diastolic pressure (\( P_{ed} \)) = 7 mm Hg, \( V_{ed} = 36 \) ml, and \( V_o = 5 \) ml. Consequently, the filling resistance value results as

\[ R_f = B = 0.0469 \]

Appendix 2

Maximal Errors in \( \overline{P} \)

Since in the simulation program, the calculation of variables involves many steps, the study of error propagation in the \( \overline{P}-Q \) relation becomes very complicated. Therefore, to obtain an approximate idea of maximal error magnitude in the computer-simulated \( \overline{P}-Q \) relations, we studied errors in the calculated Elzinga and Westerhof linear relation (Equation 12) because we saw that parameter changes affected both relations in a similar way. To calculate maximal errors, we chose the parameter whose variation yielded maximal changes in \( \overline{P} \) for a given \( Q \). This condition was met by \( V_{ed} \); therefore, we evaluated errors by using Equation 12 for constant \( V_{ed} \). For simplicity, we adopted Suga and Sagawa’s pressure-volume-relation (Equation 4), so by taking mean values at constant \( V_{ed} \), we have

\[ \overline{P}_{ed}(V_{ed}) = \overline{E}(V_{ed} - V_o) \]  

(B-1)

Since in isovolumic conditions \( \overline{P}_{ed}(V_{ed}) = \overline{P}(V_{ed}) \), we can write Equation 12 as

\[ \overline{P} = \overline{E}(V_{ed} - V_o) - ETQ \]

Differentiation of this equation with respect to \( V_{ed} \) (for a fixed \( Q \)) gives

\[ \frac{\Delta \overline{P}}{\Delta V_{ed}} \approx \frac{d\overline{P}}{dV_{ed}} = \overline{E} \]

\[ \Delta \overline{P} = \overline{E} \times \Delta V_{ed} \]  

(B-2)

This general equation shows that the maximal estimated error in \( \overline{P} (\Delta \overline{P}) \) for a constant \( Q \) is equal to \( \overline{E} \) multiplied by the estimated error in \( V_{ed} \).

At constant \( V_{ed} \), \( \Delta V_{ed} \) was 0.1 ml (maximal shift from the series of run’s results). Then, Equation B-2 becomes:

\[ \Delta \overline{P} = 0.1 \overline{E} \]  

(B-3)

At constant \( AP \), \( \Delta V_{ed} \) is calculated from Equation 13 in the following way:

\[ \Delta V_{ed} \]

and

\[ \frac{\Delta V_{ed}}{\Delta Q_{\text{max}}} \approx \frac{dV_{ed}}{dQ_{\text{max}}} = T \]

Then,

\[ \Delta V_{ed} = T \times \Delta Q_{\text{max}} \]

and substituting into Equation B-2, we can write

\[ \Delta \overline{P} = \overline{E} T \times \Delta Q_{\text{max}} \]  

(B-4)

Using Equation 12, Equation B-4 becomes

\[ \Delta \overline{P} = \frac{\Delta Q_{\text{max}}}{Q_{\text{max}}} \overline{P}(V_{ed}) \]  

(B-5)

From stabilization conditions, maximum difference between mean aortic and mean mitral flows is 1%. Then, by taking this difference as relative error in \( Q_{\text{max}} \) and substituting into Equation B-5, we have

\[ \Delta \overline{P} = 0.01 \overline{P}(V_{ed}) \]  

(B-6)

Table 3 shows the maximal estimated errors in \( \overline{P} \) for all runs, calculated from the corresponding \( \overline{E} \) (Equation B-3) or \( \overline{P}(V_{ed}) \) (Equation B-6).

Acknowledgment

We wish to thank Dr. Kiichi Sagawa for his valuable comments in the preparation of this manuscript.

References


**Key Words**: left ventricle • chamber mechanical properties • mean pressure • computer simulation • mean flow relations
A computer study of the relation between chamber mechanical properties and mean pressure-mean flow of the left ventricle.
J A Negroni, E C Lascano and R H Pichel

doi: 10.1161/01.RES.62.6.1121

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/62/6/1121

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/