Determinants of stroke volume and systolic and diastolic aortic pressure

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Stergiopulos, Nikos, Jean-Jacques Meister, and Nico Westerhof. Determinants of stroke volume and systolic and diastolic aortic pressure. Am. J. Physiol. 270 (Heart Circ. Physiol. 90): H2050-H2059, 1996.—We investigated how parameters describing the heart and the arterial system contribute to the systolic and diastolic pressures (Ps and Pd, respectively) and stroke volume (SV). We have described the heart by the varying-elastance model with six parameters and the systemic arterial tree by the three-element windkessel model, leading to a total of nine parameters. Application of dimensional analysis led to a total of six dimensionless parameters, respectively. With this limited number of parameters, it was then possible to obtain empirical analytical expressions for Ps/Ps, Pd/Pd, and SVN. The analytic predictions were tested against the model values and found to be as follows: Ps predicted = (1.0007 ± 0.0062) Ps, r = 0.987; Pd predicted = (1.016 ± 0.0085) Pd, r = 0.992; and SVN predicted = (0.9997 ± 0.0028) SVN, r = 0.996. We conclude that aortic Ps, Pd, and SV can be accurately described by a limited number of parameters and that, for any condition of the heart and the arterial system, Ps, Pd, and SV can be presented in analytical form.

varying-elastance model; three-element windkessel model; dimensional analysis; coupling of heart and arterial system.

THE PRESSURE AND FLOW in the ascending aorta arise from the interaction between the heart and the arterial system; i.e., both heart and arterial load determine aortic pressure and cardiac output. The determinants of aortic systolic and diastolic pressures (Ps and Pd, respectively) and stroke volume (SV) are not quantitatively known. A number of studies have been performed to obtain insight into the effects of changes in parameters such as peripheral resistance (R), total arterial compliance (C) on aortic pressure and flow (3, 8). However, a general and quantitative approach to obtain all determinants of Ps, Pd, and SV has, to the best of our knowledge, not been carried out. This is in part due to the fact that a model of both the heart and the arterial system could not be formulated in a quantitative way with a limited number of parameters. Such a quantitative description is achieved by use of the varying-elastance model for the heart and the three-element windkessel model for the arterial system, both of which contain a minimal number of essential parameters. The three-element windkessel model is a generally accepted and rather accurate description of the arterial system (9, 16). The varying-elastance model of the heart has also been shown to be an acceptable limited-parameter model (10, 14). Thus heart and arterial system can be described with a limited number of independent parameters, and heart and load can be coupled to yield aortic pressure and flow. From these, Ps, Pd, and SV are determined and used to quantify their sensitivity to cardiac and arterial parameters. We will use dimensional analysis to reduce the number of independent parameters by combining them into dimensionless groups (7). Subsequently, we will study the effects of these dimensionless groups of variables on pressures and SV. This analysis will allow us to decide which parameters are important determinants of Ps, Pd, and SV. This information will be used to derive empirical formulas for Ps, Pd, and SV.

METHODS

Mathematical model. The mathematical model for the heart and the arterial system (14) consists of the varying-elastance model for the heart (10) and the three-element windkessel model (16) representing the arterial load. An electrical analog of the entire heart-arterial system model is shown in Fig. 1A.

The varying-elastance model for the heart consists of a pressure source (venous pressure, P) emptying into the left ventricle with a time-varying elastance, E(t). Elastance relates ventricular pressure, P, to ventricular volume, V, through the formula

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

where \( V_d \) is the unloaded volume defined as the intercept of the end-systolic pressure-volume relationship with the volume axis (10).

Changes in elastance are due to the contraction of the myocardium. A typical heart cycle of the elastance of an isolated cat heart is depicted in Fig. 1D. The minimum value of the elastance, \( E_{min} \), together with \( P_s \), determine filling and thus end-diastolic volume \( V_d \). The maximum value of the elastance, the end-systolic pressure-volume relationship or \( E_{max} \), is considered a measure of the contractility of the heart. For a given cardiac state (heart rate and contractility constant), the elastance-time curve is assumed to remain unchanged and independent of alterations on the load (10).

We found that the shape of the elastance curve is best approximated by the following periodic “double-Hill” function

\[ E(t) = E_{max} \left[ a \left( \frac{t}{\alpha_s T} \right)^{\eta_s} \right] \left[ \frac{1}{1 + \left( \frac{t}{\alpha_d T} \right)^{\eta_d}} \right] + E_{min} \]  

where \( \alpha_s \) and \( \alpha_d \) are relaxation times for the systolic and diastolic curves, respectively, and \( \eta_s \) and \( \eta_d \) determine the height and width of these curves. The constants used to fit the experimental data were \( \alpha_s = 1000 \), \( \alpha_d = 1000 \), \( \eta_s = 1 \), and \( \eta_d = 1 \).
The first term in the brackets (Hill function) describes the ascending part of the E(t) curve and the second (inverted Hill function) the descending part. The curve is shown in Fig. 1A, where only a single heartbeat is presented. Dimensionless shape parameters, $\alpha_1$ and $\alpha_2$, define the relative appearance time of each curve within the heart period, $T_p$, and exponents, $n_1$ and $n_2$, determine the steepness of the ascending and descending parts, respectively.

The arterial system is represented with a linear three-element windkessel (16). Thus the whole arterial system is conceived as a point load with the characteristic impedance, $R_c$, which models the inertial and compliant effects of the ascending aorta, connected in series with a parallel combination of $R_p$, total arterial resistance, and $C$, total arterial compliance) are indicated. B: waveform of time-varying elastance with its minimum ($E_{\text{min}}$), maximum ($E_{\text{max}}$), and peak time ($T_p$) values pertaining to the cat heart.

The logical way of approaching this problem is to use the theory of dimensional analysis (7). By virtue of the Buckingham Ï theorem (7), we can rewrite Eqs. 3–5 in dimensionless form, in which the independent dimensionless parameters, often called Ï terms, are formed by groups of the original independent parameters. The major advantage of this approach is that the number of Î terms is equal to the number of original independent parameters (9) minus the number of basic dimensions (units) of the system (Ref. 3; namely, time, volume, and pressure). Thus the number of Î terms in our equations reduces to six. Therefore, without any loss of

**Table 1. Basic model parameters**

<table>
<thead>
<tr>
<th>Independent Cardiac and Arterial System Parameters</th>
<th>Human</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic impedance ($R_c$), mmHg s ml^{-1}</td>
<td>0.51</td>
<td>1.50</td>
</tr>
<tr>
<td>Peripheral resistance ($R_p$), mmHg s ml^{-1}</td>
<td>1.05</td>
<td>21.5</td>
</tr>
<tr>
<td>Total arterial compliance, C, ml/mmHg</td>
<td>1.60</td>
<td>0.57</td>
</tr>
<tr>
<td>Heart period ($T_p$), s</td>
<td>1.00</td>
<td>0.85</td>
</tr>
<tr>
<td>Maximum elastance ($E_{\text{max}}$), mmHg/ml</td>
<td>2.31</td>
<td>41.3</td>
</tr>
<tr>
<td>Minimum elastance ($E_{\text{min}}$), mmHg/ml</td>
<td>0.06</td>
<td>2.00</td>
</tr>
<tr>
<td>Unloaded volume ($V_d$), ml</td>
<td>20.0</td>
<td>0.75</td>
</tr>
<tr>
<td>Venous pressure ($P_v$), mmHg</td>
<td>7.50</td>
<td>7.50</td>
</tr>
<tr>
<td>Time to peak elastance ($T_{\text{peak}}$), s</td>
<td>0.43</td>
<td>0.25</td>
</tr>
<tr>
<td>Shape factor $\alpha_1$</td>
<td>0.303</td>
<td>0.25</td>
</tr>
<tr>
<td>Shape factor $\alpha_2$</td>
<td>0.506</td>
<td>0.63</td>
</tr>
<tr>
<td>Exponent $n_1$</td>
<td>1.32</td>
<td>2.00</td>
</tr>
<tr>
<td>Exponent $n_2$</td>
<td>21.9</td>
<td>15.0</td>
</tr>
</tbody>
</table>
DETERMINANTS OF STROKE VOLUME AND AORTIC PRESSURE

In general, Eqs. 3–5 are rewritten as

\[
\frac{P_s}{P_v} = \Phi_1 \left( \frac{R_C}{R_p} \cdot \frac{R_C}{T} \cdot \frac{C_{Em}}{E_{max}} \cdot \frac{E_{max}}{E_{min}} \cdot \frac{P_v}{T_p} \right) \quad (6)
\]

\[
\frac{P_d}{P_v} = \Phi_2 \left( \frac{R_C}{R_p} \cdot \frac{R_C}{T} \cdot \frac{C_{Em}}{E_{max}} \cdot \frac{E_{max}}{E_{min}} \cdot \frac{P_v}{T_p} \right) \quad (7)
\]

\[
\frac{SV}{V_d} = \Phi_3 \left( \frac{R_C}{R_p} \cdot \frac{R_C}{T} \cdot \frac{C_{Em}}{E_{max}} \cdot \frac{E_{max}}{E_{min}} \cdot \frac{P_v}{T_p} \right) \quad (8)
\]

The choice of II terms in the right-hand side of Eqs. 6–8 is not unique; however, it was made such that each term refers to easily identified ratios of the independent variables. The dimensionless parameter \( \Pi_1 = R_s/R_p \) is a pure arterial parameter. The parameters \( \Pi_2 = R_sC/T \) and \( \Pi_3 = 1/(C_{Em}E_{max}) \) pertain to both heart and arterial system and are considered "coupling parameters." The parameters \( \Pi_4 = E_{max}/E_{min} \) and \( \Pi_5 = T_p/T \) are cardiac parameters. The parameter \( \Pi_6 = P_v/(E_{min}V_d) \) gives the coupling of the heart with the venous system.

The dependence of \( P_s/P_v, P_d/P_v, \) and \( SV/V_d \) on the II terms will be derived. First, a sensitivity analysis will be performed to assess which of the II terms are important in the determination of \( P_s, P_d, \) and \( SV. \) By retaining only the II terms that are important, we can derive an analytic description of the functions, \( \Phi_1, \Phi_2, \) and \( \Phi_3. \)

RESULTS

Validation of model. The model was tested by use of available data from experiments on the isolated cat heart loaded with the three-element windkessel. The windkessel parameters were taken directly from the original paper. The cardiac parameters were also taken in this article. By plotting the relation between mean ventricular pressure and SV and fitting this with a paraabola, maximal SV and mean isovolumic pressure were determined. Maximal SV and \( P_s, \) together with an assumed dead volume of 0.75 ml, gave the value of \( E_{min}. \) Isovolumic pressure was used to estimate \( E_{max}. \) The parameters of the Hill functions were chosen such that the ventricular pressure wave shape resembled the measured one. The resulting \( E(t) \) curve is shown in Fig. 1B. All parameter values are presented in Table 1.

The cat model produces ventricular and aortic pressures and aortic flow as given in Fig. 2A. Pressure–volume loops for control, increased contractility (\( E_{max} \times 2 \)), and increased filling (\( P_v \) from 7.5 to 8.5 mmHg) are given in Fig. 2B. In Fig. 3, the changes in \( P_s, P_d, \) and \( SV \) for changes in \( R_p, C, \) and \( C \) in the model and the isolated cat heart are compared. We conclude that model predictions and experimental data compare very well in many aspects.

Human model. The model was then converted to the human cardiovascular system. The parameters are given in Table 1. The dependence of the variables \( P_s/P_v, P_d/P_v, \) and \( SV/V_d \) on the II terms are given in Figs. 4 and 5. We have calculated only a limited number of points \((0.5, 0.75, 1, 1.5, \) and 2 of control) of the dimensionless parameters. More data would have increased the computational effort considerably without large gain in information. It may be seen that \( P_s \) mainly depends on \( \Pi_1, \Pi_2, \Pi_3, \) and \( \Pi_4. \) \( P_d \) depends on \( \Pi_2, \Pi_3, \) and \( \Pi_4. \) SV depends on \( \Pi_2, \Pi_3, \) and \( \Pi_5. \) It may also be seen that the relation between \( P_s \) and \( P_d \) with \( \Pi_4 \) is linearly proportional. The same is true for SV in relation to \( \Pi_5. \)

Based on the results, Eqs. 6–8 are rewritten in the following simplified form

\[
\frac{P_s}{P_v} = \Phi_1 \left( \frac{R_C}{R_p} \cdot \frac{R_C}{T} \cdot \frac{C_{Em}}{E_{max}} \cdot \frac{E_{max}}{E_{min}} \cdot \frac{P_v}{T_p} \right) \quad (9)
\]

\[
\frac{P_d}{P_v} = \Phi_2 \left( \frac{R_pC}{T} \cdot \frac{1}{C_{Em}E_{max}} \cdot \frac{E_{max}}{E_{min}} \cdot \frac{P_v}{T_p} \right) \quad (10)
\]

\[
\frac{SV}{V_d} = \Phi_3 \left( \frac{R_pC}{T} \cdot \frac{1}{C_{Em}E_{max}} \cdot \frac{P_v}{E_{min}V_d} \right) \quad (11)
\]

Equations 9–11 were used to fit the data presented in Figs. 4 and 5, following a standard procedure described in the appendix. The analysis was limited to II values in the range of half to twice the control values, fitting the data over this range only with arbitrary formulas. The empirical formulas for \( P_s, P_d, \) and SV resulting from the
where the last term in the exponent of Eq. 14 is the product of $\Pi_2$ and $\Pi_3$. The values of the empirically determined coefficients $b_i$ ($i = 1,...,8$), $c_i$ ($i = 1,...,6$), and $d_i$ ($i = 1,...,4$) are given in Table 2.

The predictions of these analytical expressions for $P_s$, $P_d$, and $SV$ were tested against their actual values (given by model) in Fig. 6. $P_s$ predicted = $(1.0007 \pm 0.0062) P_s$, $r = 0.987$; $P_d$ predicted = $(1.016 \pm 0.0085) P_d$, $r = 0.992$; $SV$ predicted = $(0.9987 \pm 0.0028) SV$, $r = 0.996$. We conclude that the formulas are accurate over a wide range of pressures and $SV$s.

The empirical formulas for the $P_s$, $P_d$, and $SV$ (Eqs. 12–14) were derived for the human and do not necessarily apply to all mammals. We have checked this by applying the empirical formulas to the isolated cat experiments and significant differences were found. This is mainly due to the fact that the elastance function for the human is quite different from that of other mammals.
Fig. 4. Relations between dimensionless $P_s$ and $P_d$ and 6 II terms. Horizontal axis is normalized with respect to control. $P_v$, venous (filling) pressure; $V_u$, unloaded volume; $T$, heart period.

The analysis was performed with a model of the heart and arterial system. In principle, this approach can be applied to the intact animal but in such a preparation it is extremely difficult to induce variations in certain parameters while leaving other parameters unaffected. For instance, a change in $C$ in the intact animal will result in changes in pressure, leading to baroreflex control changes in heart rate and contractility (8). It will also lead to changes in cardiac filling. Moreover, the analysis requires a large number of data points, even if the sensitivity to the parameters that are of major importance is investigated. In general, experiments would require very long measurement times in a stable preparation. The present study...
Fig. 5. Relations between dimensionless SV and 6 II terms. Horizontal axis is normalized with respect to control.

A triangular-like wave shape in the \( E(t) \) curve was chosen for the human model. By changing the wave shape of \( E(t) \), we found similar sensitivity of the variables \( P_s \) and \( P_d \) to the independent parameters, although the quantitative relations varied.

By assuming a triangular wave shape of \( E(t) \), we have limited the shape factors of the \( E(t) \) to a single parameter, \( T_p \). If the Hill equations were taken into account, this would have implied four parameters, i.e.,

Table 2. Parameter values of Eqs. 12–14 estimated by least-squares fit

<table>
<thead>
<tr>
<th>Parameters</th>
<th>( b_1 )</th>
<th>( b_2 )</th>
<th>( b_3 )</th>
<th>( b_4 )</th>
<th>( b_5 )</th>
<th>( b_6 )</th>
<th>( b_7 )</th>
<th>( c_1 )</th>
<th>( c_2 )</th>
<th>( c_3 )</th>
<th>( c_4 )</th>
<th>( c_5 )</th>
<th>( c_6 )</th>
<th>( d_1 )</th>
<th>( d_2 )</th>
<th>( d_3 )</th>
<th>( d_4 )</th>
</tr>
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<tbody>
<tr>
<td>( b_1 )</td>
<td>0.337</td>
<td>1.87</td>
<td>0.651</td>
<td>0.93</td>
<td>0.595</td>
<td>0.60</td>
<td>0.369</td>
<td>0.595</td>
<td>1.09</td>
<td>0.346</td>
<td>0.271</td>
<td>0.866</td>
<td>0.111</td>
<td>1.04</td>
<td>0.0589</td>
<td>0.568</td>
<td>0.389</td>
</tr>
</tbody>
</table>
The way we derived the empirical formulas was as follows. We have started from a chosen dimensionless parameter and studied its relation to the variable of interest. Subsequently, we studied the contributions of the other parameters on this relation (see APPENDIX). By doing so, we have chosen a certain path to arrive at our results. If we had started the analysis from a different dimensionless parameter, the formulas would have had a different form. However, the same parameters would have appeared in the formulas. We have also fitted the relations with linear, exponential or power curves. The choices were made on the basis of the quality of the fit during the search for a minimal number of coefficients in the fitted curve, since the dependence of each coefficient on the other parameters needed to be quantified.

We have carried out the analysis for a limited range of the dimensionless parameters (from 0.5 to 2 of their control values). Again this was done to limit the amount of work. Most variations in the parameters cover the physiological working range. For instance, during exercise, heart rate increases considerably (i.e., factor of 3–4) so that $T$ decreases by the same amount, but $R_p$ decreases considerably as well. Thus the dimensionless parameter $R_p C/T$ does not undergo large changes. However, for changes in a single parameter, the formulas apply only for the range 0.5–2 of control.

Implications. Figures 7 and 8 show the variations of $P_s$, $P_d$, and SV for changes in $R_p$ and $C$ (arterial) and for changes in the end-systolic pressure-volume relation and heart rate (cardiac). The values derived from pressure and flow in time are given by the symbols. The fully drawn lines are from the derived equations. It may be seen that our empirical formulas, when applied within the allowed range, predict these variables well.

The sensitivity of $P_s$, $P_d$, and SV to the independent cardiac and arterial parameters is given in Table 3. It may be seen from Table 3 that characteristic impedance has a small effect on $P_s$ only.

Increased $R_p$ decreases SV and increases mean pressure (4). If the pressure wave shape remains the same, the increase in mean pressure would result in proportional increases in $P_s$ and $P_d$. However, with an increase in $R_p$, the arterial pressure in diastole will decrease more slowly due to increased $R_p C$ time, so that $P_d$ remains higher. This then results in a relatively larger increase in $P_d$ than $P_s$. In Table 3 of Elzinga and Westerhof (3), we indeed see that with an increase in $R_p$ (by a factor of ~2) $P_d$ increased by 50% compared with $P_s$. This is in good agreement with the theoretical predictions given in Table 3.

For a decrease in $C$, SV increases slightly and mean pressure increases somewhat. This is again in agreement with experimental findings in (3). When $C$ decreases, the decay of pressure in diastole will be faster so that $P_d$ will be lower. Elzinga and Westerhof (3) showed that a decrease in $C$ (by a factor of ~3) resulted in a decrease in $P_d$ that was about twice as much as the increase in $P_s$. Randall et al. (8) studied $P_s$ and $P_d$ in the intact dog by replacing the aorta with a stiff tube while keeping $R_p$ and heart rate unchanged. However, in increasing the number of parameters by three. Better fits, i.e., fits with more parameters, will improve the final result and make it possible to accurately account for changes in the $E(t)$ curve.

The pressure-volume relations in diastole and systole were approximated by straight lines. There is evidence that these relations are curved with convexity toward the volume axis in diastole and concavity in systole (2, 13). This second-order effect was not included to keep relations simple and the number of parameters small.
their preparation in contrast to the isolated heart studies by Elzinga and Westerhof (3), end-diastolic pressure increased. They found that $P_s$ increased slightly, whereas $P_d$ decreased. This may be explained from the fact that end-diastolic ventricular pressure (cardiac filling) increased somewhat and contractility was also possibly increased.

Comparison of the sensitivities to $R_p$ and $C$ shows that $P_s$ and $P_d$ are about four times less sensitive to changes in $C$ than to changes in $R_p$. For SV, the sensitivity to $C$ is even smaller compared with the sensitivity to $R_p$.

When heart rate decreases (and $T$ increases), we predict an increase in SV, and a decrease in $P_s$ and $P_d$. This is in agreement with the findings on the isolated feline heart (5). With an increase in $T$, the pressure in diastole decreases over a longer period in time so that $P_d$ is decreased more than $P_s$. Thus the sensitivity of $P_d$ to $T$ is greater than the sensitivity of $P_s$.

With an increase in the end-systolic pressure-volume relation, interpreted as an increase in contractility, both cardiac output (and thus SV) and mean pressure are predicted to increase, in agreement with (4). Because the duration of diastole and the speed of decay of $P_d$ are not affected, $P_s$ and $P_d$ changes will be about the same. Suga et al. (see Fig. 3 in (10)) showed that an increase in contractility resulted in roughly the same changes in SV and $P_s$, in good agreement with our prediction of similar sensitivity of these parameters (Table 3).

The $P_d$-volume relation is a very important parameter in the determination of both pressure and SV. The sensitivities to this parameter are similar for pressures and flow. A decrease in $E_{min}$ will result in a larger $V_{ed}$, resulting in changes similar to those due to increased $P_s$. The large sensitivity shows that, with poor relaxation of the cardiac muscle as in ischemia, the pumping function of the heart is strongly reduced.

$P_s$ has a large effect on pressures and flow. This is the Frank-Starling mechanism. The predictions (Table 3) are in agreement with animal data (4). In these animal experiments, similar changes in SV and pressure were found for changes in $P_s$.

We have presented a method to derive the effects of the major parameters that characterize the heart and arterial tree on $P_s$, $P_d$, and SV. Taking into account all major determinants, one can derive to empirical analytical formula for these three variables under all possible conditions. We have performed a limited analysis that takes into account the major effects and arrived at empirical formulas. The effects of changes in single parameters such as $C$ and $R_p$ or heart rate and contrac-
The methodology used in deriving an appropriate form of the function \( \Phi \) was as follows. We first determined the functional relationship between \( \frac{P_d}{P_v} \Pi_4 \) and \( \Pi_4 \) for a range of values of \( \Pi_2 \) from 0.5 to 2. The data were best fitted by a power law suggesting that Eq. A1 can be written as

\[
\frac{P_d}{P_v} = \Pi_4 \Phi(\Pi_2, \Pi_4) = \frac{P_4}{P_v} = \Phi(\Pi_2, \Pi_4)
\]

with \( \frac{P_4}{P_v} \) obtained by nonlinear and linear regression. Substituting \( \Pi_2 = R_p C/T \), \( \Pi_3 = 1/(CE_{max}) \), and \( \Pi_4 = E_{max}/E_{min} \) into Eq. A3 and normalizing with respect to the \( \Pi_4 \) values of control (see Table 1), we obtain Eq. 13 in the text. A similar approach was followed for deriving the other two empirical formulas.

### Appendix

Dimensional analysis (Figs. 5, A - F) showed that \( \frac{P_d}{P_v} \) is a function only of \( \Pi_0 \), \( \Pi_2 \), and \( \Pi_4 \). Furthermore, \( \frac{P_d}{P_v} \) is proportional to \( \Pi_4 \) which means that the relation simplifies to

\[
\frac{P_d}{P_v} = \Phi(\Pi_2, \Pi_4)
\]

with \( \frac{P_4}{P_v} \) obtained by nonlinear and linear regression. Substituting \( \Pi_2 = R_p C/T \), \( \Pi_3 = 1/(CE_{max}) \), and \( \Pi_4 = E_{max}/E_{min} \) into Eq. A3 and normalizing with respect to the \( \Pi_4 \) values of control (see Table 1), we obtain Eq. 13 in the text. A similar approach was followed for deriving the other two empirical formulas.

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