Dynamics of flow, resistance, and intramural vascular volume in canine coronary circulation

JOS A. E. SPAAN,1 ANNEMIEK J. M. CORNELISSEN,2 CHARLES CHAN,2 JENNY DANKELMAN,3 AND FRANK C. P. YIN4

1Department of Medical Physics, Cardiovascular Research Institute Amsterdam, Academic Medical Center, University of Amsterdam, 1100 DE Amsterdam, The Netherlands; 2Cardiology Division, Johns Hopkins University, School of Medicine, Baltimore, MD 21287; 3Man-Machine Systems and Control Group, Faculty of Design, Engineering and Production, Delft University of Technology, 2628 CD Delft, The Netherlands; and 4Department of Biomedical Engineering, Washington University in St. Louis, St. Louis, Missouri 63130

Spaan, J osA. E., Annemiek J. M. Cornelissen, Charles Chan, Jenny Dankelman, and Frank C. P. Yin. Dynamics of flow, resistance, and intramural vascular volume in canine coronary circulation. Am. J. Physiol. Heart Circ. Physiol. 278: H383–H403, 2000.—Varying coronary volume will vary vascular resistance and thereby have an effect on coronary hemodynamics. Six ventricular septa were isolated from anesthetized dogs, dispersed in a biaxial stretch apparatus at diastolic stress, and perfused artificially with an oxygenated perfluorochemical emulsion at maximal vasodilation. Flow and thickness were measured continuously by an electromagnetic flow probe and sonomicrometer. Pressure was varied sinusoidally around 30, 50, and 70 mmHg with an amplitude of 7.5 mmHg; frequencies ranged between 0.015 and 7 Hz. Bode plots of admittance (flow/pressure) and capacitance (scaled thickness/pressure) were constructed. A two-compartment model was used in which the resistances vary with volume. Realistic values of microvascular compliance (−0.3 ml·mmHg−1·100 g−1) were found. Values 10 times higher were then found when resistances were forced to be constant. We concluded that volume dependence of resistances have to be taken into account when dynamic or static pressure-flow relations are studied and conceal the effect of a large intramyocardial compliance on arterial hemodynamics.

intramyocardial compliance; model; transfer function; admittance; pressure-dependent resistance

CHARACTERIZATION of the dynamic interrelationship among coronary arterial pressure, flow, and volume is essential to our understanding of coronary physiology not only in relation to coronary resistance and capacitance but also to myocardial oxygen consumption and control of coronary flow (3, 11, 12). Resistance and capacitance are the two physical parameters relating pressure and flow and are clearly dependent on variations of intravascular volume (16). However, because it is difficult to accurately measure intravascular volume, the results of many studies are implicitly or explicitly interpreted as if resistance and/or capacitance were constant, at least in certain working conditions (7).

When coronary pressure is changed, diameters of vessels of all size vary with pressure, indicating that their resistances vary as well (21). The assumption of constant resistance during variations in arterial pressure may be responsible for some of the controversy in this field (4, 13, 22, 23, 27, 28).

Although some of the determinants of intravascular volume such as perfusion pressure (25), contraction (15, 18, 31), and vasomotor tone (3, 12) are recognized in a general sense, little information is available about the dynamics of the volume changes. The available data consist primarily of either direct or indirect estimates of the time constant of volume change after a perturbation. For example, based on the time course of arterial pressure change after coronary occlusion, a time constant of ~1.8 s was estimated (29). Similar values were obtained from comparison of the differences of the time integrals of the coronary arterial inflow and venous outflow (9, 20, 31). A recent study using digital subtraction angiography of an intravascular contrast agent in isolated dog interventricular septa (19) directly measured intravascular volume change after a step change in pressure and found a time constant of ~3–4 s. The only detailed studies on the dynamics of the coronary vasculature examined input impedance (7, 30) over the frequency range of 2–10 Hz. On the basis of the time constant estimates, however, this frequency range is likely to be too high to provide useful information on volume responses because the volume changes of the microcirculation occur over a much longer time frame.

The hypothesis of this study is that dynamic coronary flow responses to changes in perfusion pressure are affected by the continuous change of resistance as dictated by its volume dependence. Hence, an average resistance value at a certain mean perfusion pressure would not suffice; one has to take into account the resistance variations as induced by the pressure variations around that mean as well.

METHODS

Specimen Preparation

We used the canine isolated, perfused interventricular septal preparation previously described (26). Briefly, mongrel...
dogs of either sex weighing 18–22 kg were anesthetized with intravenous pentobarbital sodium (35 mg/kg). The animals were intubated and ventilated, and the heart was exposed via a midline sternotomy. Heparin sodium (5,000 U) was infused to minimize thrombi formation. Each dog was systemically cooled to 28°C, at which time the heart was arrested by rapid injection into the ascending aorta of cold (4°C) cardioplegic solution with the composition (in mM) 120 Na, 16.0 K, 16 Mg, 1.2 Ca, 160.4 Cl, 10 HCO3−, and 1.0 adenosine. The heart, which usually fibrillated and then became asystolic within 1–2 min, was removed, and the septal artery was quickly cannulated and connected to a reservoir so that the specimen was continually perfused with cold cardioplegic solution for the duration of the preparatory time. The perfusion pressure was kept <30 mmHg throughout the preparatory steps to minimize tissue edema.

The left anterior descending, left circumflex, and right coronary arteries were individually cannulated and filled (by injection via a syringe) with dental rubber to which a few drops of catalyst had been added. Once the dental rubber filled the smallest visible arteries on the surface of the heart wall, the left and right ventricular free walls were removed by cutting within the perfusion boundary of these emboiled arteries. We have verified that this methodology results in an isolated, perfused septal bed with no shunts or leaks (26). Four edges of the septum, roughly defining a rectangle, were connected by a series of threads in a trampoline-like fashion to the carriages of a biaxial stretching apparatus so that the specimen could be stretched in the base-to-apex and circumferential directions [see Fig. 1 in Resar et al. (26)]. The forces in each direction were measured by force transducers (model sf-10; Interface) mounted on the carriages. Septal thickness was measured with a pair of sonomicrometer crystals (Triton Technology, La Jolla, CA) glued onto the left and right ventricular surfaces of the septum. The crystals were placed in an area adjacent to the area demarcated by the markers. Two platinum pacing wires connected to a stimulator (model S88; Grass Instruments, Quincy, MA) were sewn onto the outer edges of the specimen. After the septum was mounted onto the stretching apparatus, the cannula was connected to a pressurized reservoir with stiff tubing. The air pressure in the reservoir was controlled by an electrically controlled pneumatic needle valve connected to a signal generator. Flow at the entrance to the septum was measured by means of a 1-mm-inner diameter cannulating flow probe (model 774-100-2.0; Skalar Medical, Delft, The Netherlands) connected to a flowmeter (model 1401, Skalar Medical). The inlet pressure in a plastic T piece connecting the cannula and tubing was measured with a micromanometer (model PC-450; Millar Instruments, Houston, TX).

The cold cardioplegic perfusate was then changed to a perfluorocchemical emulsion (FC-43; Green Cross, Osaka, Japan) with the following composition of the aqueous solution (in mM): 137 Na, 5.2 K, 2.6 Ca, 2.1 Mg, 1.54 H2PO4−, 119 Cl−, 25.8 HCO3−, and 11.5 glucose, along with 2 mg/100 ml adenosine and 5.8 g/100 ml albumin. Adenosine was sufficient to fully dilate the vascular bed. The emulsion was perfused at room temperature. The perfusate was gently bubbled with 95% O2–5% CO2 to maintain pH between 7.4 and 7.5 and to keep oxygen tension >600 mmHg. After a few minutes the specimen could be electrically stimulated to beat, at which time the pressure was increased sufficiently to produce diastolic flows of ~25 ml/min. The specimen was paced at a rate of 0.4 Hz for ~30–45 min to allow recovery and stabilization from the cardioplegia. Sufficient lidocaine was added to the perfusate so that no spontaneous contractions ensued if the specimen was not electrically stimulated. All measurements were done in noncontracting conditions and at diastolic stretch of the septum.

Protocols and Data Analysis

Tissue thickness as an index of vascular volume. In six septa we used our previously reported digital subtraction angiographic method (19) to directly measure intravascular volume while also measuring tissue thickness during some interventions to verify that thickness could serve as an index of volume. Briefly, the specimen was suspended under an X-ray tube and video camera system. An approximately 1-cm2 region without any visible venous effluent was identified and demarcated by four lead markers. These lead markers also served to correct for scatter and veiling glare when the images were analyzed. Tissue thickness immediately adjacent to this region was measured by sonomicrometer crystals glued to the right and left ventricular surfaces. A calibration wedge consisting of a chamber with linearly increasing depth was placed in-line with the perfusion system and positioned under the X-ray tube next to the specimen. Mask images were first taken at a nominal input pressure of 60 mmHg, with the specimen slightly stretched to biaxial forces of 300 g (to prevent it from sagging). An emulsion of ethiodol (10 ml) containing 475 mg/ml iodine that had been previously sonicated for 2 min at 100 W (model W-385; Heat System-Ultronics, Farmington, NY) in the presence of 10 ml of physiologically balanced solution with 5 g/100 ml Pluronic F-68 was then added to the perfusate after an equal volume of the original perfusate was removed. We previously verified that the spheres of emulsion prepared in this manner (~3 µm in diameter) were too large to leak out of the vasculature (19). Once the iodine-containing perfusate equilibrated in both the wedge and specimen, we imposed an inflow occlusion and/or a constant amplitude sinusoidal input pressure. For the latter, the input pressure was varied sinusoidally with a peak-to-peak amplitude of ~40 mmHg around a mean pressure of 60 mmHg at frequencies of ~0.002, 0.04, and 0.4 Hz. For both interventions, simultaneous X-ray images and thickness measurements were recorded. The data from the X-ray images were converted into an equivalent thickness of iodine according to previously reported methods by using the wedge as a calibration device (19). Dividing this iodine thickness by the thickness of the specimen yields the vascular volume as a percentage.

Coronary dynamics. In another six specimens, comprising the main set of studies, the dynamic responses of flow and thickness (i.e., vascular volume) to pressure perturbations were examined. With the specimen completely unloaded, we imposed constant amplitude (15 mmHg peak to peak) sinusoidal pressure oscillations at frequencies ranging from ~0.015 to 10 Hz. The perturbations were performed at mean pressures (Pm) of 30, 50, and 70 mmHg. After each change in frequency and mean pressure, the system was allowed to equilibrate for a few minutes. The order of the mean pressures was chosen arbitrarily. In the lower frequency range (0.015–0.5 Hz) the data were digitized at a sampling rate of 10 Hz. The higher frequency (0.75–10 Hz) data were digitized at a sampling rate of 100 Hz. The amplitude of the pressure...
oscillations was chosen to provide sufficient resolution for the thickness signal and yet still be in the linear response range of flow and thickness variations as forced by the pressure variations. Linearity of responses was verified in several specimens by imposing pressure amplitudes varying from ~4 to 24 mmHg peak to peak at frequencies of 0.2 and 2 Hz at each mean pressure.

A segment of digitized pressure, flow, and thickness data, consisting of an integer number of waves, was analyzed with custom software. First, any baseline drift was removed by applying a linear interpolation algorithm to the entire data set. The data at each discrete frequency were then centered about the mean, after which at least two complete periods from a steady-state condition at each frequency and pressure were extracted. These extracted files were further analyzed to obtain the amplitude and phase angle of the pressure, flow, and thickness by spectral analysis using the MATLAB fast Fourier algorithm. Amplitude and phase of each variable resulted in complex expressions of those variables as $P(n)$, $Q(n)$, and $Th(n)$, respectively, where $P$ is pressure, $Q$ is flow, and $Th$ is thickness, and $n$ is the frequency in Hz.

To correct for the pressure drop from the reservoir to the tip of the cannula, we first measured the system impedance with the cannula open to air. Measured $P(n)$ [$P_{\text{measured}}(n)$] was then corrected for the pressure drop using $Q(n)$ and the perfusion system impedance to obtain the real perfusion pressure [$P_{\text{perf}}(n)$]. Unless mentioned otherwise, perfusion pressures reported are pressures corrected for the cannula influence.

A few times between changes in perfusion pressures, the perfusion line was occluded for 50 s. The peripheral pressure at the end of the occlusion was taken as the value for $P_{\text{ZF}}$ used in some calculations as described below.

After the experiment, the perfusion area was delineated by Evans blue, cut out of the septum, and weighed. Flow was then normalized to 100 g of tissue weight.

Descriptive parameters for Bode plots. The dynamic responses are reported in terms of transfer functions in a standard Bode plot format. The pressure-flow (i.e., admittance) transfer function consists of plots of the ratio of flow to pressure modulus versus frequency and the difference between the flow and pressure phase angles versus frequency. Similarly, the pressure-volume (i.e., capacitance) transfer function consists of the ratio of volume to pressure modulus versus frequency and the difference between the volume and pressure phase angles versus frequency. Volume was calculated from thickness by applying a correction factor derived

![Figure 1](http://ajpheart.physiology.org.org/ Downloaded from)

**Fig. 1.** Typical Bode plots of admittance and relative ratio of thickness to pressure for canine septum and definitions of parameters for descriptions of these curves. Admittance at frequency $n$ (left) is defined as $Q(n)/P(n)$, where $Q$ is arterial flow and $P$ is pressure. Modulus of admittance (top left) is rather constant up to a corner frequency ($n_{\text{Ac}}$). For higher frequencies, the relation between modulus and $n$ is approximated by a straight line, the slope of which is also used to parameterize the admittance plot. Phase ($\phi$) of admittance (bottom left) starts out at 0 but increases to a maximum value ($\phi_{\text{max}}$) at a frequency $n_{\text{max}}$. $Th(n)/P(n)$ (right), where $Th$ represents thickness divided by its mean, is equal to capacitance multiplied by a constant. Above a certain corner frequency ($n_{\text{Cc}}$), with modulus $Th(n)/P(n)_{\text{Cc}}$, the log-log plot of modulus of $Th(n)/P(n)$ (top right) decreases linearly with frequency. A linear curve for lower frequency also was fitted through the data. Modulus at $n = 0.05$ ($Th(n)/P(n)_{n=0.05}$) was determined as an additional descriptive parameter. The phase-frequency plot of the $Th(n)/P(n)$ curve (bottom right) was not parameterized.
from the fitting procedure explained below. To facilitate interspecimen comparisons, a few key descriptive parameters were defined as shown in Fig. 1. For the admittance transfer function we averaged the moduli in the low-frequency (<0.2 Hz) range and performed a linear regression of moduli versus frequency in the high-frequency (1–9 Hz) range. The frequency at which these two lines intersected was denoted as the corner frequency ($\nu_{c1}$). The lines fitted to the data in the high-frequency range for the three pressures intersected at a common frequency, which we defined as the “crossover” frequency ($\nu_{c2}$; not shown in Fig. 1). The phase angle responses were described by the maximum phase, the frequency at which the maximum occurred ($\nu_{max}$), and the frequency at which the phase angle crossed zero after reaching its maximum ($\nu_0$).

Similarly, the modulus of the capacitance transfer function was parameterized by fitting the data with linear regressions in the low-frequency (0.015–0.2 Hz) and high-frequency (0.5–9 Hz) ranges. The intercept of the low-frequency regression at a frequency of 0.05 Hz, the slope of the low-frequency data, the slope of the high-frequency data, and the corner frequency ($\nu_{c3}$) of the intersections of these two lines are reported. The phase of the pressure-volume response could not be simply parameterized, and these results will be reported implicitly by the parameters reported below.

Fitting of Bode plots by second-order transfer functions. The Bode plots were fitted using the following second-order transfer functions (see Fig. 2)

$$Q(\omega) = \frac{G_{q1} + j\omega}{1 + j\omega(\alpha_1 + \alpha_2^{1/2})}$$

$$P(\omega) = \frac{G_{q2} + j\omega}{1 + j\omega(\alpha_3 + \alpha_4^{1/2})}$$

where $G_{q1}$ and $G_{q2}$ are parameters to be determined, $G_{TV}$ is the conversion factor for expressing volume in terms of thickness, $\omega$ is frequency in radians per second, and $j$ is an imaginary unit. The two equations were simultaneously fitted to the experimental data by minimizing the following cost function

$$Cost = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (\epsilon_i^2 + \epsilon_i^2)^2} + \sqrt{\frac{1}{n} \sum_{i=1}^{n} (\epsilon_i^2 + \epsilon_i^2)^2}$$

The factors $\epsilon_1$-$\epsilon_6$ are relative differences between the theoretical and experimental values of modulus and phase of the admittance and capacitance at the different frequencies as detailed in the APPENDIX; $n$ is no. of frequencies, and $i$ is index. Note that $\omega$ is expressed in radians/s and that $\omega = 2\pi f$, where $f$ is the frequency in Hz. The value of “cost” was minimized by varying the parameters of the admittance and capacitance functions. The contributions to the cost function for frequencies <1 Hz were 1.5 times the contributions for higher frequencies.

We used the technique of simulated annealing (1) to find the parameters that optimally fit the data. Using this technique, we first defined the range over which each parameter was allowed to vary. Randomly selecting a value for each parameter within its range defined an initial vector of parameters. The cost function for this vector was calculated. A parameter was then randomly selected and its value changed randomly but within 5% of its original range, resulting in a new vector and a new value for the cost function. This new parameter vector was accepted as a new start at a certain probability value (P). Another parameter was then randomly selected and varied within 5% of its current value, and so on, until the procedure had been repeated 500 times. From this group of accepted vectors the one with the minimum cost value was selected as a new starting value for another repetition of 500 calculations, each with a decrement in P value. When the cost no longer decreased, the procedure was stopped. The associated parameter vector is called a candidate vector. The whole procedure was repeated 10 times to generate 10 candidate vectors. From this set of 10, the vector

![Fig. 2. Two-compartment model of septal circulation. The division between the 2 compartments is somewhere within the middle resistance ($R_m$). Each compartment consists of a resistance-capacitance-resistance network. Note that $R_m$ is thought to be divided between the 2 compartments. $Q_1$, $Q_m$, and $Q_2$ are flows through $R_1$, $R_m$, and $R_2$, which are resistances within the model. $C_1$ reflects the capacitance of the proximal compartment and is thought to be determined predominantly by the larger arteries and larger resistance vessels. Capacitance $C_2$ reflects the compliance of the microcirculation predominantly. $P_m$ and $P_0$ are inlet and outlet pressures; $P_{c1}$ and $P_{c2}$ reflect pressures over $C_1$ and $C_2$, and $Q_{c1}$ and $Q_{c2}$ are flows over $C_1$ and $C_2$. $R_1$, $R_m$, and $R_2$ are assumed to vary with the load (volume) of the capacitances but are forced to be constant for the results presented in Figs. 9 and 10.](image-url)
with the lowest cost function value was deemed to be the best parameter fit to the data. If the cost function had a unique solution, these 10 parameter vectors would be about equal; otherwise, a scatter in parameter values would be found.

Two-Compartment Model of Coronary Circulation

We chose a two-compartment model consisting of a network of resistors and capacitors as depicted in Fig. 2. The capacitances are intended to reflect those of the proximal and distal portions of the bed, i.e., the arteries and arterioles and the capillaries and venules, respectively.

To account for the volume dependencies of the resistances and capacitances during the sinusoidal changes of pressure around a mean, the resistances and capacitances were assumed to vary linearly around their nominal working values. That is, around nominal working values of resistance ($R_0$) and capacitance ($C_0$), the resistances and capacitances were allowed to vary linearly according to the formulas $R(V) = R_0 + K_R \cdot \Delta V$ and $C(V) = C_0 + K_C \cdot \Delta V$, where $\Delta V$ is the variation in volume around the working value of volume ($V_0$). The equations describe the tangent lines at the $(R(V)$ and $C(V)$ curves at the coordinates ($R_0, V_0$) and ($C_0, V_0$), respectively. The $K$ values are the slopes of these lines and quantify the “sensitivity constants,” $K_R$ and $K_C$. Note that these approximations are only allowed for limited variations in resistances and capacitances.

Because the model consists of two compartments, there are two sensitivities for capacitance ($K_{C1}$ and $K_{C2}$) and two capacitance working points ($C_{1.0}$ and $C_{2.0}$). Similarly, there are four sensitivity values for resistance ($K_R$, $K_{R1}$, $K_{R2}$, and $K_{R3}$) and three resistance working points ($R_{1.0}$, $R_{m.0}$, and $R_{2.0}$). Hence, the middle resistance ($R_m$) depends on the volume in both the first and second compartment. Note that when the sensitivity constants are zero, the model reduces to the more classic model with constant resistances and capacitances.

The Simulink program within MATLAB was used initially to evaluate the nonlinear model and to assess the role of the different parameters. These simulations resulted in several conclusions. 1) We found that the sensitivities of the capacitances to volume had minimal effects on the simulated transfer functions at a fixed mean perfusion pressure. Specifically, moduli and phases of the transfer functions changed only by tenths of a percentage over a wide range of values of $K_C$. With larger values of $K_C$, exceeding the range that seems realistic, the model became unstable. Consequently, $K_{C1}$ and $K_{C2}$ were assumed to be zero. 2) For a wide range of values of $K_R$ and realistic values of resistances and volumes, flow and volume variations changed linearly with pressure variations for amplitudes $\leq 15$ mmHg, not withstanding the dependence of resistance on volume. Hence, in terms of signal analysis the responses remained linear, not withstanding our expectation for nonlinear responses based on the variations in resistance values induced by the pressure variations. 3) Inductance calculated on the basis of geometrical properties of arteries and the specific mass of blood affected the transfer functions only for frequencies $> 7$ Hz.

As outlined in the Appendix, the model results in more parameters than can be obtained with the use of the admittance and capacitance equations provided above. Therefore, additional relations are needed to obtain an estimation of the parameters of the model from the parameters of the fitting equation. For this purpose, we used the additional constraint $P_{\text{mean}}/Q_{\text{mean}} = R_1 + R_m + R_2$. The assumption that the resistance of each of the compartments depends on volume according to the law of Poiseuille yields an additional equation. By further assuming that only the radii of the vessels vary with volume, we may write $R = A/V^2$, and therefore $\frac{\partial R}{\partial V} = -2AV^{-3} = -2R/V$, where $\partial R/\partial V$ is the first derivative of the resistance-volume relationship and $A$ is assumed to be constant and, according to Poiseuille, is equal to $8n_1^2\pi$, where $n_1$ is viscosity and $l$ is length. Hence, for each $K_R$ an equation is found. Note that absolute volume now appears in the equations for the model. Therefore, the model enables one to estimate absolute volumes, whereas this cannot be done when resistances are assumed constant during the pressure variations (all $K$ values = 0). Nevertheless, although four additional equations are defined, two more unknowns (the volumes in each compartment) are added. The proportion of the intermediate resistance attributable to each compartment becomes an important parameter. Hence, a factor $X$ had to be introduced to define which fraction of $R_m$ was sensitive to the variation in the proximal capacitance. Consequently, $(1 - X)$ is the fraction of $R_m$ that is dependent on the volume in the distal capacitance. Hence, for $X = 0$, $R_m$ is only sensitive to the distal capacitance, and for $X = 1$, $R_m$ is only sensitive to the proximal capacitance.

The resulting set of equations is still overparameterized because we have a total of 10 equations and 12 unknowns. Therefore, as discussed later, rather than finding values for each parameter, we obtain relationships between some parameters. Some additional constraints will then lead to a unique set of parameters coupled to each set of Bode plots. Because volume will be predicted from the parameter set, an independent test of the validation of the model is obtained.

Statistical Analysis

Statistical analysis of the correlation between X-ray contrast agent thickness and tissue thickness was performed using standard linear regression analysis. Analyses of each parameter describing both the admittance and capacitance transfer functions were performed using one-way repeated-measures ANOVA. Pairwise comparisons for effects at the three mean pressures were made using the Student-Newman-Keuls test. Statistical significance was defined to be the $P = 0.05$ level.

RESULTS

Tissue Thickness as an Index of Vascular Volume

Figure 3, top, shows a representative recording of the input pressure along with simultaneous iodine and tissue thicknesses during an inflow occlusion. Note that the two thicknesses initially fall with the same time course. At about 120 s into the occlusion the iodine thickness plateaus, whereas the tissue thickness continues to fall. Because the iodine is contained in the emulsion, which is too large to leave the vasculature, the continued decrease in tissue thickness in the absence of inflow and any further change in vascular volume likely represents continued emptying of the interstitial volume. Figure 3, bottom, shows the iodine and tissue thickness responses of the same specimen to approximately sinusoidal pressure inputs with 40-
mmHg peak-to-peak amplitudes at a mean pressure of 50 mmHg at 0.01 and 0.04 Hz. Note the similar responses for both thicknesses and that the amplitudes of both are lower at the higher frequency.

Figure 4 demonstrates the regression lines between the iodine and tissue thickness variations for the interventions shown in Fig. 3. For the inflow occlusion, only the data before the point at which the tissue and iodine responses begin to deviate are included. The results of the regression analysis for all of the specimens subjected to at least one of these interventions are summarized in Table 1. There was a uniformly high degree of correlation between the iodine and the tissue thickness variations. Note that the specimen that was subjected to both the sinusoidal and occlusion interventions had slopes of nearly equal value.

Coronary Dynamics

Bode plots. Typical results of the linearity tests for pressure, flow, and thickness changes at three mean pressures (Pp) are shown in Fig. 5. For pressure amplitudes ≤10 mmHg (20 mmHg peak to peak), the amplitudes of flow and thickness were proportional to pressure amplitude. Hence, the amplitude of 7.5 mmHg chosen for this study was well within the linear response range.

Figure 6 shows representative results in one specimen of the input pressure and the flow and thickness responses for three different frequencies at a mean pressure of 50 mmHg. Note that the magnitude of the thickness response decreases, whereas the magnitude of the flow response increases, with increasing frequency.
The characteristic features of the responses are more completely illustrated by the admittance and capacitance transfer functions at all three pressure levels as shown in Fig. 7. The pressure dependence of the responses is evident. Specifically, the low-frequency admittance modulus increases with increasing pressure, but the slopes of the moduli in the high-frequency range decrease with increasing pressure. This results in a crossover frequency at 1 Hz and an increase of the corner frequency with pressure. The maximum value of the phase angle and corner frequency with pressure. The maximum value of the phase angle changes sign at a frequency close to 10 Hz, which is caused by inertial effects playing a role only for frequencies > 7 Hz. Similarly to the admittance transfer function, there is some pressure dependence of the capacitance transfer function, particularly in the low-frequency range. The intercept of the regression for the low-frequency moduli decreases and the slope becomes less negative as the pressure increases. However, neither the corner frequency nor the slopes of the moduli in the high-frequency range are pressure dependent. There is, however, no clear pressure dependence of the phase angle responses.

Responses similar to those shown in Fig. 7 were observed in all six specimens. Tables 2-5 summarize the various descriptive parameters obtained from the admittance and capacitance transfer functions as defined in Fig. 1, at conditions defined in Table 6.

Typical fits of the experimental data by the admittance and capacitance equations over the frequency range of 0.01-5 Hz are also demonstrated in Fig. 7. The sets of 10 candidate parameters for each specimen generated by the procedure of annealing are reported in Fig. 8. The means with standard deviations are provided. Note that there is considerable interspecimen variation but that, with some exceptions, the parameters are defined rather uniquely by the estimation procedure. For the results derived below, the parameters obtained with the curve of best fit were used.

Parameter estimation assuming that resistances do not vary with volume. Figure 9 provides estimates of the parameters of the model using the fitting parameters of Fig. 8 and assuming that the sensitivities of the resistances for volume are zero. Note that in all septa R1 increased and Rm decreased with increasing perfusion pressure.

In each specimen the sum of the resistances decreased as pressure increased. However, the sum of resistances was smaller than \((P_p - P_{ct})/Q\), which again was smaller than \(P_p/Q\). For the average data, the results from these resistance calculations are provided in Fig. 10 as a function of perfusion pressure.

Parameter estimation assuming that resistances vary with volume. Figure 11 demonstrates the relationships between \(R_m\) and most of the other parameters for different values of \(X\) at a pressure of 50 mmHg for the same specimen whose data are shown in Fig. 7. As shown in the appendix, \(R_1\) is independent of \(R_m\) and \(X\) and is therefore not plotted. Note that for a certain range in \(R_m\) unrealistic values for parameters are found. For example, at low values of \(R_m\), the volume of the first compartment (\(V_1\)) becomes negative and \(K_1\) and \(K_{m1}\) are positive. These values are not realistic, and hence this range of \(R_m\) can be rejected. Likewise, very large values of \(R_m\) result in positive values of \(K_{m2}\) and negative values for volume of the second compartment (\(V_2\)), which again is unrealistic. Finally, for the lower and upper value of \(R_m\), either both \(C_2\) and \(C_3\) or \(C_3\) alone becomes infinitely large. With a lack of additional constraints, the minimum of the \(R_m\)/\(C_3\) relationship was used to determine the actual value of \(R_m\). That, along with arbitrarily choosing \(X = 0.75\), allowed all parameters to be estimated uniquely. This value of \(X\) implies that \(R_m\) is assumed to be more influenced by the proximal compartment than by the distal compart-

---

**Table 1. Regression results between iodine thickness and septal thickness variations**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Experiment</th>
<th>Slope</th>
<th>Intercept</th>
<th>(R^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sine wave</td>
<td>A</td>
<td>1.129</td>
<td>0.021</td>
<td>0.987</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.041</td>
<td>0.009</td>
<td>0.906</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.863</td>
<td>0.015</td>
<td>0.976*</td>
</tr>
<tr>
<td>Average</td>
<td>C</td>
<td>1.011</td>
<td>0.015</td>
<td>0.956</td>
</tr>
<tr>
<td>Inflow occlusion</td>
<td>C</td>
<td>0.878</td>
<td>0.075</td>
<td>0.986*</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.633</td>
<td>0.015</td>
<td>0.998</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>0.738</td>
<td>0.004</td>
<td>0.981</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0.661</td>
<td>0.031</td>
<td>0.976</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>0.728</td>
<td>0.031</td>
<td>0.985</td>
</tr>
</tbody>
</table>

Data are from interventions presented in Fig. 4. *Same specimen was used in both protocols.
Fig. 5. Check of linearity of flow and thickness responses to pressure variations. Pressure amplitude at 2 frequencies were varied from 2 to 12 mmHg for 3 different perfusion pressures ($P_p = 30, 50,$ and $70 \text{ mmHg}$). Note difference in scaling of thickness axis between the 2 frequencies. For determination of Bode plots, a pressure amplitude of 7.5 mmHg was taken, well within linear range of responses.

Fig. 6. Typical response of flow ($Q$) and thickness to pressure variations around a mean of 50 mmHg with an amplitude of 7.5 mmHg at $\nu = 0.01, 1,$ and $2 \text{ Hz}$. Note that there was a mean pressure drop over the cannula of 5 mmHg. With increasing frequency the thickness amplitude decreased but flow amplitude increased. Note that at 0.01 Hz there is no phase difference between flow and pressure, but thickness lags pressure by a few degrees. At 1 Hz, flow leads pressure by $16^\circ$ and the lag of thickness toward pressure has increased to $65^\circ$. These phase differences are even higher at 2 Hz.
ment. These criteria are in sync with realistic constraints on the values for V1 and V2.

Figure 12 depicts the estimated parameters as a function of perfusion pressure. In all experiments, R1 increased and Rm decreased with increasing perfusion pressure. R2 at Pf = 70 mmHg was always lower than at Pf = 30 mmHg. The capacitance of the first compartment at Pf = 70 mmHg was higher than that at 30 mmHg except for experiment 4. The capacitance of the second compartment was larger than that of the first compartment. As shown in Fig. 12B, in most specimens the dependency of total resistance on volume decreased with increasing perfusion pressure. Total volume, the sum of the volumes of the two compartments, increased with perfusion pressure, with one experiment yielding an unrealistic value because it exceeds tissue volume. Note that the absolute values of K for this experiment at this pressure are very low. A small absolute error in K therefore results in a very large change in estimated volume.

**DISCUSSION**

The data clearly demonstrate that the admittance and capacitance transfer functions are dependent on the level of mean pressure. A two-compartment model of the coronary bed was employed to help interpret the results. Resistances and capacitances were estimated in two conditions. With the first condition, resistances were assumed not to vary with volume; with the second condition, resistances varied with volume. In most experiments, the admittance and capacitance transfer functions were dependent on the level of mean pressure.

**Table 2. Results of parameterization of Bode plots for admittance modulus**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Pf 30</th>
<th>50</th>
<th>70</th>
<th>Pf 30</th>
<th>50</th>
<th>70</th>
<th>Pf 30</th>
<th>50</th>
<th>70</th>
<th>vAc, Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.032</td>
<td>0.036</td>
<td>0.039</td>
<td>0.58</td>
<td>0.48</td>
<td>0.24</td>
<td>0.60</td>
<td>0.38</td>
<td>0.17</td>
<td>0.45</td>
</tr>
<tr>
<td>2</td>
<td>0.064</td>
<td>0.076</td>
<td>0.092</td>
<td>0.55</td>
<td>0.29</td>
<td>0.29</td>
<td>0.60</td>
<td>0.38</td>
<td>0.17</td>
<td>0.45</td>
</tr>
<tr>
<td>3</td>
<td>0.054</td>
<td>0.057</td>
<td>0.057</td>
<td>0.76</td>
<td>0.61</td>
<td>0.41</td>
<td>0.73</td>
<td>0.40</td>
<td>0.25</td>
<td>0.52</td>
</tr>
<tr>
<td>4</td>
<td>0.033</td>
<td>0.035</td>
<td>0.039</td>
<td>0.22</td>
<td>0.13</td>
<td>0.08</td>
<td>0.41</td>
<td>0.52</td>
<td>0.58</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>0.025</td>
<td>0.042</td>
<td>0.042</td>
<td>0.57</td>
<td>0.38</td>
<td>0.23</td>
<td>0.19</td>
<td>0.16</td>
<td>0.12</td>
<td>0.10</td>
</tr>
<tr>
<td>6</td>
<td>0.047</td>
<td>0.047</td>
<td>0.047</td>
<td>0.57</td>
<td>0.38</td>
<td>0.23</td>
<td>0.19</td>
<td>0.16</td>
<td>0.12</td>
<td>0.10</td>
</tr>
<tr>
<td>Average</td>
<td>0.044</td>
<td>0.049</td>
<td>0.052</td>
<td>0.57</td>
<td>0.38</td>
<td>0.23</td>
<td>0.19</td>
<td>0.16</td>
<td>0.12</td>
<td>0.10</td>
</tr>
<tr>
<td>SD</td>
<td>0.013</td>
<td>0.016</td>
<td>0.023</td>
<td>0.19</td>
<td>0.16</td>
<td>0.12</td>
<td>0.10</td>
<td>0.07</td>
<td>0.09</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Parameters were determined during perturbations at 3 mean pressures (Pf) of 30, 50, and 70 mmHg. vAc, corner frequency of admittance; vX, crossover frequency of admittance.
condition, the sensitivities of resistances were allowed to vary and were then estimated as well. The values of the first resistance and capacitance were rather similar for both conditions. However, when resistances were volume dependent, the middle resistance and outflow resistance were much higher (2 times) and the distal compliance much lower (10 times) than in the condition in which resistances were assumed constant at a mean perfusion pressure. The vascular volume of the septa calculated from the estimated parameters for which resistances were assumed to be volume dependent appeared to be pressure dependent and in a realistic range, indicating that the model assumptions are not unrealistic.

Critique of Experimental Method

Interstitial volume changes were not accounted for with the interpretation of the data. However, if interstitial volume changed during our interventions, it did so with the interpretation of the data. However, if interstitial volume changed during a set of measurements at a given pressure, it did not affect the correspondence between thickness and intravascular volume changes.

If a crystal were to be positioned over a large vessel, some or all of the thickness variations would manifest as pulsations of the vessel walls rather than as volume changes in the small vessels. We took care to avoid these large vessels when placing the crystals. The hallmark of such a problem is a variation of thickness in phase with perfusion pressure.

The relations between iodine thickness variation and tissue thickness variation do not have a slope of unity. The major reason is that the regions of interest for tissue thickness and iodine thickness measurements were not at identical physical locations on the specimen. Nevertheless, the high correlations strongly support our contention that intravascular volume changes are linearly indexed by the overall tissue thickness changes. Although the thickness changes may not be a one-to-one measure of volume changes, an exact relationship is not needed for estimates of capacitance and volume from our data analysis. These values are obtained from the frequency dependence of both the flow and thickness responses to sinusoidal perfusion pressure variations. Absolute volume is the result of integration over time of the calibrated flow signal by the function of the capacitance.

VanHuis et al. (30) concluded that wave reflections should be taken into account when admittance for frequencies >7 Hz is interpreted. Moreover, as described in methods, inertial effects were discernible at >7 Hz. Hence, 7 Hz was chosen as the upper limit for the frequency range subjected to quantitative analysis.

Critique of Model and Parameter Estimation

The admittance curves alone would be able to deliver all the fitting parameters because all \( \alpha \) values are present in this fitting equation. However, the uncertainty of the distal parameters (\( R_m \), \( R_2 \), and \( C_2 \)) would increase because the more distal they are, the less influence these factors have on the admittance curves. On the other hand, the capacitance curves do not provide the same information as the admittance curves because the capacitance equation is missing the quadratic term in the nominator. However, the capacitance curves strongly relate to the distal parameters. Hence, fitting the two relations in one procedure optimizes the determination of all parameters involved. However, in doing so, a less satisfactory fit of the admittance at some frequencies may be the result of the attempt to fit the capacitance data. The phase angle of the admittance phase becomes negative. *Because there were no values below zero, the intercept cannot be determined.

The admittance curves alone would be able to deliver all the fitting parameters because all \( \alpha \) values are present in this fitting equation. However, the uncertainty of the distal parameters (\( R_m \), \( R_2 \), and \( C_2 \)) would increase because the more distal they are, the less influence these factors have on the admittance curves. On the other hand, the capacitance curves do not provide the same information as the admittance curves because the capacitance equation is missing the quadratic term in the nominator. However, the capacitance curves strongly relate to the distal parameters. Hence, fitting the two relations in one procedure optimizes the determination of all parameters involved. However, in doing so, a less satisfactory fit of the admittance at some frequencies may be the result of the attempt to fit the capacitance data. The phase angle of the admittance phase becomes negative. *Because there were no values below zero, the intercept cannot be determined.

The admittance curves alone would be able to deliver all the fitting parameters because all \( \alpha \) values are present in this fitting equation. However, the uncertainty of the distal parameters (\( R_m \), \( R_2 \), and \( C_2 \)) would increase because the more distal they are, the less influence these factors have on the admittance curves. On the other hand, the capacitance curves do not provide the same information as the admittance curves because the capacitance equation is missing the quadratic term in the nominator. However, the capacitance curves strongly relate to the distal parameters. Hence, fitting the two relations in one procedure optimizes the determination of all parameters involved. However, in doing so, a less satisfactory fit of the admittance at some frequencies may be the result of the attempt to fit the capacitance data. The phase angle of the admittance phase becomes negative. *Because there were no values below zero, the intercept cannot be determined.

The admittance curves alone would be able to deliver all the fitting parameters because all \( \alpha \) values are present in this fitting equation. However, the uncertainty of the distal parameters (\( R_m \), \( R_2 \), and \( C_2 \)) would increase because the more distal they are, the less influence these factors have on the admittance curves. On the other hand, the capacitance curves do not provide the same information as the admittance curves because the capacitance equation is missing the quadratic term in the nominator. However, the capacitance curves strongly relate to the distal parameters. Hence, fitting the two relations in one procedure optimizes the determination of all parameters involved. However, in doing so, a less satisfactory fit of the admittance at some frequencies may be the result of the attempt to fit the capacitance data. The phase angle of the admittance phase becomes negative. *Because there were no values below zero, the intercept cannot be determined.

The admittance curves alone would be able to deliver all the fitting parameters because all \( \alpha \) values are present in this fitting equation. However, the uncertainty of the distal parameters (\( R_m \), \( R_2 \), and \( C_2 \)) would increase because the more distal they are, the less influence these factors have on the admittance curves. On the other hand, the capacitance curves do not provide the same information as the admittance curves because the capacitance equation is missing the quadratic term in the nominator. However, the capacitance curves strongly relate to the distal parameters. Hence, fitting the two relations in one procedure optimizes the determination of all parameters involved. However, in doing so, a less satisfactory fit of the admittance at some frequencies may be the result of the attempt to fit the capacitance data. The phase angle of the admittance phase becomes negative. *Because there were no values below zero, the intercept cannot be determined.
tance function was the one with the largest contribution to the cost function.

The present model of the coronary circulation is not the first to assume volume dependence of resistance. Earlier models (2, 6, 8, 24) predicted well several aspects of hemodynamic behavior of the coronary circulation. However, because of the specific form of the nonlinear pressure-volume and volume-resistance relationships assumed, those models were not well suited for parameter estimations. This was the reason for our use of the approach of piecewise linearization for the resistance-volume and capacitance-volume relations around a working point. The analysis with Simulink then demonstrated that Bode plots generated by the model were hardly influenced by the sensitivity constant of capacitance to volume. Therefore, for fitting the experimental results in the model, only the dependence of resistance on volume was accounted for.

Note that we substituted the sensitivity of resistance to volume with dR/dV in the working point according to Poiseuille’s law. This is only allowed when it is assumed that the vessel lengths are not affected by the pressure variations. In fact, it is this substitution that allows for the determination of absolute volume in this study. It should be noted that if the sensitivities of resistances are taken as zero, it is impossible to estimate absolute volume as a function of perfusion pressure. Only volume variations around a working point can then be determined.

A limitation of the present model is that only two compartments are considered. The distal compartment reflects the capillary and venous bed, whereas a differentiation between the two probably would be better. However, more compartments imply more parameters, and without additional measurements this is not very useful. Moreover, the shapes of the transfer functions do not suggest that a higher-order model is applicable. It should be appreciated that in a compartmental model distributed functions are lumped into single compartments.

It may very well be that the two lumped compartments each reflect a portion of the coronary circulation that is different at different pressures. The estimates of the first resistance and, in most cases, the first capacitance increase as pressure increases. Increasing perfusion pressure may change not only the caliber of vessels but also the distribution of resistance and capacitance. An increase in perfusion pressure decreases the resistance and capacitance per vessel in the proximal bed, but the pressure effect is transmitted farther into the bed. Thus, more distal vessels, with greater resistance than the proximal ones, are incorporated in series into the proximal bed. This more than compensates for the decrease in resistance caused by distention of the proximal vessels, so the net effect is an increase in overall resistance of the proximal bed.

This explanation for the increasing value of $R_1$ with increasing mean perfusion pressure seems to be in conflict with the assumption of constant vessel length in the application of Poiseuille’s law to define the sensitivity of resistance on volume. However, we assume that for the variations around the working points the effect of diameter changes will be much stronger than the variations in vessel lengths to be considered. However, this aspect certainly deserves further study in the future.

As explained in METHODS the model has two parameters too many compared with the experimental information we have. In relation to Fig. 11, we discussed the rationale for the choice of additional constraints, such
as the requirement that volumes have to be positive, allowing the unique determination of all parameters in the model. Obviously, one can think of additional constraints resulting from different experiments. For example, one can find reasonable estimates for the volume of the proximal large and small arteries. This volume does not exceed 3.5 ml/100 g for the full proximal coronary circulation including the large epicardial arteries (27) at a perfusion pressure of 100 mmHg. As is clear from Fig. 11, the criteria we chose fulfill this particular constraint as well.

As discussed below, the total intravascular volume and its dependence on perfusion pressure do agree with values published independently. We have tried to perform the parameter analysis by entering the total volume at a certain perfusion pressure as a known value. However, this did not provide stable solutions of our equations, probably because the value taken for volume was too far off that of the actual volume in the specific experiment. Hence, in the absence of actual measurements of additional parameters or signals in the same septum from which Bode plots are constructed, one cannot do better than formulating additional constraints.

Although the problem of overparameterization is not solved completely, the ranges of model parameters are narrowed such that any uncertainty of estimation of a parameter from a single data set due to the uncertainty in constraints arrives in the 10–20% range. The consistent application of criteria makes it likely that trends found in the parameter estimation reflect physiological ones. However, with the interpretation of absolute values presented in this study, the limitations left by overparameterization should be taken into account.
Comparison with Literature

There are only a few studies of the dynamic response of the coronary vasculature with which to compare our results. Canty et al. (7) measured the input impedance (from 1 to 10 Hz) of the circumflex arterial bed in intact hearts during prolonged diastole. Over this frequency range our findings of increasing flow amplitude with increasing frequency and a larger change at lower mean pressure, as well as a peak in phase difference around 4 Hz, are all concordant with their results. Canty et al. concluded that the input impedance could be described well by a first-order model representing only one compartment with a characteristic time constant on the order of a few tenths of a second. That model contained resistances independent of volume. Their conclusion does not contradict our present results. The authors concluded that a rather high back pressure had to be assumed for the model. With constant resistances, our model fit finds a very large distal compliance, which causes a virtual constant back pressure for the first compartment in the frequency range studied by Canty et al. It should be noted that these authors believed that the course of the admittance Bode plot was determined by viscoelastic effects of small arteries (7). However, such effects have not been found in capacitance measurements on isolated small arteries (14) and were therefore not accounted for in our model.

Coronary arterial input impedance was also reported by VanHuis et al. (30), albeit at only one perfusion pressure. Using an impulse response technique, which is better suited for examining high than low frequen-
cies, they studied a frequency range \(\leq 20\) Hz and found results similar to ours and those of Canty et al. (7). Because the impedance was not different between diastole and systole, they concluded that, at these frequencies, little information about the deeper portions of the vasculature could be obtained.

There are no data on the frequency dependence of vascular volume with which to compare our results. However, the nearly monotonic decrease in capacitance transfer function with increasing frequency beginning at \(\sim 0.1\) Hz suggests a time constant for volume changes of several seconds. This corresponds with previously reported time constants found, for example, in studies in which intramural blood volume changes were measured indirectly by integrating the difference between arterial and venous flows (9, 27, 31). These data are also consistent with the slow decay of volume after steps in perfusion pressure demonstrated previously with the use of the same intravascular Roentgen contrast method used in the present study.

The value estimated for the distal capacitance is in concordance with other estimates. For example, Bosman et al. (5) demonstrated that capillary diameter in rabbit tenissimus muscle may change by 5% between control and arterial occlusion and by 14% between control and maximal reactive hyperemia. This implies a total change in volume of 38%. The capacitance value to be calculated from this diameter change depends on the assumed capillary pressure change with this intervention. With the assumption of a 20-mmHg variation in capillary pressure between occlusion and peak reactive hyperemia and an average volume fraction of 10 ml/100 g, microcirculatory capacitance may be 3.8/20 = 0.19 ml \cdot mmHg\(^{-1}\) \cdot 100 g tissue\(^{-1}\). Moreover, Morgenstern et al. (25) demonstrated that total coronary volume changed with arterial pressure by 0.075 ml \cdot mmHg\(^{-1}\) \cdot 100 g\(^{-1}\). Because the majority of volume change is within the microcirculation, this change in volume is brought about by a much smaller variation in microvascular pressure. With a distal resistance in the order of 20% of total resistance, the pressure variations would be only 20% of the arterial pressure variations, and hence microvascular compliance would be \(-0.375\) ml \cdot mmHg\(^{-1}\) \cdot 100 g\(^{-1}\). One may therefore conclude that the value for the microvascular capacitance found in the present study is not unrealistic, at least when the volume dependence of resistance is taken into account. Disregarding this volume dependence results in estimates of distal compliance that are 10 times higher and therefore unrealistic.

The estimates of total intravascular volume range between 4 and 14 vol% depending on perfusion pressure and not including the one data point predicting a vascular volume exceeding tissue volume. These values agree well with other data in the literature. In freshly excised heart, intramural blood volume is \(-4\) ml \cdot mmHg\(^{-1}\) \cdot 100 g\(^{-1}\) (10) but can increase up to 14 ml \cdot mmHg\(^{-1}\) \cdot 100 g\(^{-1}\) at 100 mmHg, depending on perfusion pressure and the degree of autoregulation (27).

### Interpretation of Data

In the experiments we could change the amplitude of pressure variations \(-15\) mmHg around a mean \(P_o\) of 50 mmHg without finding the introduction of a higher harmonic with an amplitude higher than that expected on the basis of the higher harmonics in the pressure signal. Also, in the Simulink model and with the use of parameters corresponding with the parameters found from the fits with the model, pressure amplitudes could be increased up to 15 mmHg and yet higher harmonics in flow and volume would remain lower than 5% compared with the base frequency. Because of the volume dependence of resistance in the model and in the circulation, one would expect a nonlinear relation between pressure on one hand and predicted flow and volume on the other hand. However, we have to conclude that a linear relation between the different variables at play does not necessarily imply that resistances therefore have to be assumed constant in the working range of these variables. Vice versa, having resistances and capacitances that are volume dependent does not imply that relationships between variables have to be nonlinear. In other words, although our model consists of physical elements that each give rise to nonlinear input-output relations, the combination of these elements into one system results in a linear dependence of output signals (flow and volume) on variations over a wide range of input signals (pressure).
Because there is sufficient evidence that vessels with a significant resistance in the coronary bed do vary in diameter, and therefore in their resistance value, it seems justified to require that an analysis of coronary hemodynamics incorporates this effect.

To gain insight into the dependence of the transfer functions on the volume sensitivities of resistance, we set some sensitivities equal to zero while keeping all other model parameters at the same value. A typical result of such an analysis is shown in Fig. 13, in which the solid lines represent a fit with the admittance and capacitance equations. The corresponding model parameters are also provided in Fig. 13. Consequently, if only $K_2$ is made equal to zero, i.e., only the outflow resistance is not volume dependent, then the predicted admittances are hardly altered. In contrast, the amplitude of the capacitance transfer function increases by a factor of two. Hence, the volume sensitivity of the distal resistance is of particular importance in estimating the distal compliance. In addition, if the other $K$ values also are made equal to zero, the admittance transfer functions become quite different as well. Not only is the modulus of admittance much lower but also the frequency at which the admittance modulus starts to increase shifts to lower frequencies. Moreover, the modulus-frequency relationship exhibits a shoulder. The additional effect of taking $K_1$, $K_{m1}$, and $K_{m2}$ as zero has little additional effect on the capacitance transfer functions compared with the case when only $K_2$ is zero.

---

**Fig. 11.** For a typical Bode plot at a pressure of 50 mmHg, the estimated dependence of parameters on $R_m$ are provided for several values of $X$, the weighing factor of how the sensitivities of $R_m$ on load in $C_1$ and $C_2$ are divided. For $X = 0$, $R_m$ is only influenced by distal volume; for $X = 1$, $R_m$ is only influenced by proximal volume. Because $R_1$ was independent of $R_m$, these curves are not provided. $C_1$ and $C_2$, capacitances of 1st and 2nd compartment (in ml·mmHg·g·100 g tissue$^{-1}$); $V_1$ and $V_2$, volumes (in ml/100 g tissue) in capacitances $C_1$ and $C_2$; $K_1$ and $K_{m1}$ (in mmHg·ml$^{-2}$·s$^{-1}$·100 g$^{-2}$), dependence of $R_1$ and $R_m$ on volume in $C_1$; $K_{m2}$ and $K_2$, dependence of $R_m$ and $R_2$ on volume in $C_2$. Because negative volumes are physically not realistic, there is only a limited range of $R_m$ that is realistic. To make a unique choice of $R_m$ objective, the value was estimated at minimal value for $C_2$. Arbitrarily, $X = 0.75$ was chosen. Symbols indicate minima of $C_2$ for different values of $X$. Note that $V_1$ would be infinitely high or low for $X = 0$ and $V_2$ for $X = 1$. 

$R_1 = 5.7$

$R_2 = 14.3 - R_m$

---

Because there is sufficient evidence that vessels with a significant resistance in the coronary bed do vary in diameter, and therefore in their resistance value, it seems justified to require that an analysis of coronary hemodynamics incorporates this effect.
Obviously, if the dotted lines in the admittance panels of Fig. 13 were experimental and were to be interpreted by either a single-compartment [e.g., model of Canty et al. (7) discussed earlier] or a two-compartment model with constant resistances, one would conclude that a large compliance is present. Because these curves are not found experimentally, several authors have concluded that such a large compliance either does not exist or has no effect on the admittance curve by some mechanism uncoupling the proximal and distal compartments (22). Figure 13, however, demonstrates that resistances that are changing in value with volume during the pressure variations applied can conceal the effect of a large compliance on the admittance curves.

This interpretation also explains how one can find small time constants in arterial flow response and simultaneously measured large time constants in venous flow responses induced by arterial pressure steps (16, 20, 22, 27). The volume dependence of resistance gives the input admittance the characteristics of a rapidly reacting system, whereas the venous flow responses remain slow because of the large intramyocardial compliance.

The volume dependence of resistance does have a physiological importance. Because outflow resistance increases with decreasing perfusion pressure, the microvascular pressure will be maintained rather constant. If we calculate the mean pressure in the distal capacitance averaged over all septa, excluding the one result-
In conclusion, the present study characterizes the dynamic response of vascular volume and coronary arterial flow to changes in perfusion pressure in the nonbeating septum. It is demonstrated that a two-compartment model in which the resistances are vascular volume dependent can describe these responses. If not taken into account, this volume dependency results in overestimation of the compliance of the distal compartment. Also, the volume dependence of resistance conceals the effects of the intramyocardial capacitance on dynamic arterial flow responses to arterial pressure variations. The slope of the coronary diastolic pressure-flow relation is determined not only by resistance but also by the dependence of resistance on vascular volume.
Fig. 13. Demonstration of effects of K constants on Bode plots predicted by model. Data were obtained at 50 mmHg but are different from the earlier typical examples. Continuous curves are curves of best fit; model parameters corresponding to this fit are shown. Dashed curves are results when the sensitivity of outflow resistance ($K_2$) is set to zero. As shown, this parameter has a strong effect on the predicted capacitance curve. When the sensitivities of the other 3 resistances also are set to zero, the predicted admittance curves are affected (dotted curves). A shoulder in the phase plot appears at low frequency and the modulus decreases. Moreover, the modulus starts to increase at lower frequency. As explained in text, curves demonstrate that the dependence of resistance on volume conceals the effect of large microvascular compliance.

APPENDIX

Basic Equations

\[
\begin{align*}
\frac{P_{in} - P_{C1}}{R(V_1)} &= Q_1 \\
\frac{P_{C1} - P_{C2}}{R_m(V_1, V_2)} &= Q_m \\
\frac{P_{C2} - P_o}{R_2(V_2)} &= Q_2 \\
dV_1 &= C_1(V_1) \frac{dP_{C1}}{dt} \\
dV_2 &= C_2(V_2) \frac{dP_{C2}}{dt} \\
Q_1 - Q_m &= \frac{dV_1}{dt} \\
Q_m - Q_2 &= \frac{dV_2}{dt}
\end{align*}
\]

Constant Parameters

\[
\begin{align*}
R_1 &= 10.2, \quad R_m = 8.5, \quad R_2 = 4.3 \\
C_1 &= 0.013, \quad C_2 = 0.24 \\
K_1 &= -5.4, \quad K_m = -3.4, \quad K_2 = -1.7, \quad K_2 = -3.3 \\
K_1 &= -5.4, \quad K_m = -3.4, \quad K_2 = -1.7, \quad K_2 = 0 \\
K_1 &= 0, \quad K_m = 0, \quad K_2 = 0, \quad K_2 = 0
\end{align*}
\]

By substituting Eqs. A8 and A9 in the basic equations and subtracting the static equations, after Laplace transformation the following functions can be derived:

\[
\begin{align*}
\frac{\delta Q(\omega)}{\delta P(\omega)} &= G_1 \frac{1 + \alpha_1(j\omega) + \alpha_2(j\omega)^2}{1 + \alpha_3(j\omega) + \alpha_4(j\omega)^2} \\
\frac{\delta V(\omega)}{\delta P(\omega)} &= G_{\delta} \frac{1 + (\alpha_2/\alpha_1)(j\omega)}{1 + \alpha_3(j\omega) + \alpha_4(j\omega)^2}
\end{align*}
\]
with
\[
\alpha_1 = R_{\min}C_{\text{lin}} + R_{2\text{lin}}C_{\text{lin}} + R_{2\text{lin}}C_{\text{lin}}
\]
\[
\alpha_2 = R_{\min}R_{2\text{lin}}C_{\text{lin}}C_{\text{lin}}
\]
\[
\alpha_3 = \frac{R_{1\text{lin}}R_{2\text{lin}}C_{\text{lin}} + R_{1\text{lin}}R_{\min}C_{\text{lin}}}{R_{1\text{lin}} + R_{\min} + R_{2\text{lin}}}
\]
\[
\alpha_4 = \frac{R_{1\text{lin}}R_{\min}R_{2\text{lin}}C_{\text{lin}}C_{\text{lin}}}{R_{1\text{lin}} + R_{\min} + R_{2\text{lin}}}
\]
\[
G_q = \frac{1}{R_{1\text{lin}} + R_{\min} + R_{2\text{lin}}}
\]
The parameter expressed in the coefficients of the transfer functions gives
\[
R_{1\text{lin}} = \frac{G_q}{\alpha_2}
\]
\[
R_{\text{lin}} = \frac{-\alpha_2^2 + \alpha_2 + 2\alpha_1\alpha_2\alpha_4}{G_q\alpha_2(\alpha_2\alpha_4 - \alpha_1^2 - \alpha_1^2)}
\]
\[
R_{2\text{lin}} = \frac{G_q(\alpha_2\alpha_4 - \alpha_1\alpha_3 - \alpha_2\alpha_4)}{-\alpha_2^2 + \alpha_2 - \alpha_1^2}
\]
\[
C_{1\text{lin}} = \frac{G_q\alpha_2^2}{\alpha_2(\alpha_2\alpha_4 - \alpha_1\alpha_3 - \alpha_2\alpha_4)}
\]
\[
C_{2\text{lin}} = \frac{G_q(-\alpha_2\alpha_3 - \alpha_2\alpha_3 - \alpha_1\alpha_3 - \alpha_2\alpha_4 + \alpha_3\alpha_4)}{\alpha_2^2 + \alpha_2 + \alpha_2 + \alpha_2}(\alpha_1\alpha_4 - \alpha_3\alpha_3)
\]

**Volume-Dependent Parameters**

Linearization (variations (δX) around a working point (X₀)]
\[
P_{\text{in}} = P_{\text{in},0} + \delta P_{\text{in}} \quad P_{\text{C}1} = P_{\text{C}1,0} + \delta P_{\text{C}1} \quad P_{\text{C}2} = P_{\text{C}2,0} + \delta P_{\text{C}2} \quad P_0 = 0
\]
\[
Q_1 = Q_0 + \delta Q_1 \quad Q_m = Q_0 + \delta Q_m \quad Q_2 = Q_0 + \delta Q_2
\]
\[
V_1 = V_{1,0} + \delta V_1 \quad V_2 = V_{2,0} + \delta V_2 \quad V_1 = V + V_2
\]

Because of the volume dependency, R_m cannot be seen as one resistance. One part, R_m1, is influenced by V_1 and the other, R_m2, by V_2
\[
R_m = X R_m \quad R_{m1} = (1 - X) R_m
\]
\[
R_1(V_1) = R_{1,0} + \frac{\delta R_1}{\delta V_1} \bigg|_{V_{1,0}} \delta V_1 = R_1 + K_1 \delta V_1
\]
\[
R_m(V_1,V_2) = R_{m,0} + \frac{\delta R_m}{\delta V_1} \bigg|_{V_{1,0}} \delta V_1 + \frac{\delta R_m}{\delta V_2} \bigg|_{V_{2,0}} \delta V_2
\]
\[
= R_m + K_{m1} \delta V_1 + K_{m2} \delta V_2
\]
\[
R_2(V_2) = R_{2,0} + \frac{\delta R_2}{\delta V_2} \bigg|_{V_{2,0}} \delta V_2 = R_2 + K_1 \delta V_2
\]
\[
C_1(V_1) = C_1 \quad C_2(V_2) = C_2
\]

By substituting these variations in the basic equations (A1–A7), neglecting the second- and higher-order terms, and subtracting the static equations, after Laplace transformation the following transfer functions can be derived
\[
\frac{\delta Q(\omega)}{\delta P(\omega)} = G_q \frac{1}{1 + \alpha_1(j\omega) + \alpha_2(j\omega)^2}
\]
\[
\frac{\delta V(\omega)}{\delta P(\omega)} = G_q \frac{1}{1 + \alpha_2(j\omega) + \alpha_3(j\omega)^2}
\]
\[
\alpha_1 = \frac{R_{m1}C_1 + R_2C_1 + R_2C_2 + Q_0(-R_2C_1C_2K_{m1} - R_{m1}C_2K_{m2} + R_{m1}C_2C_2K_{m2})}{1 - Q_0(C_1K_{m1} + C_2K_{m2}) + Q_0^2(C_1C_2K_{m1}K_{m2})}
\]
\[
\alpha_2 = \frac{R_{m2}C_2}{1 - Q_0(C_1K_{m1} + C_2K_{m2}) + Q_0^2(C_1C_2K_{m1}K_{m2})}
\]
\[
\alpha_3 = \frac{R_1R_{m1}C_1 + R_1R_{m1}C_1 + R_1R_2C_2 + R_{m1}R_2C_2 + Q_0X}{R_1 + R_{m1} + R_2 + Q_0Y + Q_0Z}
\]
\[
\frac{\delta Q(\omega)}{\delta P(\omega)} = G_q \frac{1}{R_1 + R_{m1} + R_2 + Q_0Y + Q_0Z}
\]
\[
\alpha_4 = \frac{1}{R_1 + R_{m1} + R_2 + Q_0Y + Q_0Z}
\]

where
\[
X = -R_1R_2C_2C_2K_{m1} + R_{m1}R_2C_1K_{m1}
\]
\[
- R_1R_{m1}C_2K_{m1} + R_1R_2C_1K_{m2}
\]
\[
Y = -R_mC_2K_{m2} + R_2C_2K_{m2} - R_1C_2K_{m1}
\]
\[
- R_2C_1K_{m1} + R_2C_1K_{m1} + R_{m1}C_2K_{m2}
\]
\[
Z = R_1C_2C_2K_{m1}K_{m2} - R_{m1}C_1C_2K_{m1} + R_{m1}C_2C_1K_{m1} + R_{m2}C_1C_1K_{m2}
\]

Additional equations are
\[
R_{\text{tot}} = R_1 + R_{m1} + R_2
\]
\[
R_{\text{tot}} = P_{\text{in},0} - \frac{X}{Q_0}
\]

According to Poiseuille and assuming only radial variations
\[
R_1 = \frac{A_1}{V_1^2} \quad R_3 = \frac{A_3}{V_3^2} \quad R_{m1} = \frac{A_{m1}}{V_{m1}^2} \quad R_{m2} = \frac{A_{m2}}{V_{m2}^2} \quad R_2 = \frac{A_2}{V_2^2}
\]
\[
K_1 = \frac{dR_1}{dV_1} = -\frac{2A_1}{V_1^3} \quad K_{m1} = \frac{dR_{m1}}{dV_{m1}} = -\frac{2A_{m1}}{V_{m1}^3}
\]
\[
K_{m2} = -\frac{dR_{m2}}{dV_2} = -\frac{2A_{m2}}{V_2^3} \quad K_2 = \frac{dR_2}{dV_2} = -\frac{2A_2}{V_2^3}
\]

Therefore
\[
K_1 = -\frac{2R_1}{V_1} \quad K_{m1} = -\frac{2R_{m1}}{V_{m1}} \quad K_{m2} = -\frac{2R_{m2}}{V_2} \quad K_2 = -\frac{2R_2}{V_2}
\]
The parameters of the model with volume-dependent \( R \) values can be expressed in the parameters of the model with fixed \( R \) values, which gives less complex equations

\[
R_1 = R_{1\text{lin}} \\
R_m = R_{\text{mlin}} (1 - C_1 \frac{Q_1 K_1}{C_2} - C_1 \frac{Q_0 K_0}{C_2}) \\
R_2 = R_{2\text{lin}} \frac{C_2}{C_2} - C_2 \frac{Q_0 K_0}{C_2} \\
C_1 = \frac{R_{\text{mlin}} C_2}{1 - C_1 \frac{Q_1 K_1}{C_2}} \\
C_2 = \frac{R_m - R_{\text{mlin}} C_2}{R_m - R_{\text{mlin}} C_2 \frac{Q_0 K_0}{C_2}} \\
R_{\text{tot}} = R_1 + R_m + R_2 \\
K_1 = \frac{-2R_1}{V_1} \\
K_m = \frac{-2R_m}{V_1} \\
K_{m1} = \frac{-2(1 - X)R_m}{V_2} \\
K_{m2} = \frac{-2R_2}{V_2} \\

\text{The Fitting Equations}

\[
V(\omega) / P(\omega) = G_{\text{th}}(\omega) / P(\omega) = \frac{\sum_{i=1}^{n} V_i(\omega)}{\sum_{i=1}^{n} P_i(\omega)} \\
G_{\text{th}}(\omega) = \frac{\sum_{i=1}^{n} V_i(\omega)}{P_i(\omega)} \\
\log \left[ \frac{Q_i(\omega)}{P_i(\omega)} \right]_{\text{theor}} - \log \left[ \frac{Q_i(\omega)}{P_i(\omega)} \right]_{\text{exp}} \\
e_i = \log \left[ \frac{\max \left[ V_i(\omega) / P_i(\omega) \right]}{\min \left[ V_i(\omega) / P_i(\omega) \right]} \right] - \log \left[ \frac{\max \left[ V_i(\omega) / P_i(\omega) \right]}{\min \left[ V_i(\omega) / P_i(\omega) \right]} \right] \\
\text{Cost} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} e_i^2} + 0.5 \sqrt{\frac{1}{m} \sum_{i=1}^{m} e_i^2} \\
v_1 \cdots v_m < 1 \text{ Hz}
\]

\[
v_1 \cdots v_n < 7 \text{ Hz}
\]

This work was supported in part by Dutch Heart Foundation Grant 43.016 (to J. A. E. Spaan and F. C. P. Yin), Dutch Heart Foundation Study Grant D94.011 (to A. J. M. Cornelissen), and National Heart, Lung, and Blood Institute Grant HL-44399 (to F. C. P. Yin).

Address for reprint requests and other correspondence: J. A. E. Spaan, Dept. of Medical Physics, Cardiovascular Research Institute Amsterdam, Academic Medical Center, Univ. of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands (E-mail: j.a.spaan@amc.uva.nl).

Received 22 September 1998; accepted in final form 23 July 1999.

REFERENCES


