Balance between myoegenic, flow-dependent, and metabolic flow control in coronary arterial tree: a model study

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1Faculty of Design, Engineering, and Production, Department of Medical Technology and Mechanics, Man Machine Systems and Control Group, Delft University of Technology, 2628 CD Delft; and 2Department of Medical Physics, Cardiovascular Research Institute Amsterdam, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands

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Cornelissen, Annemiek J. M., Jenny Dankelman, Ed VanBavel, and Jos A. E. Spaan. Balance between myogenic, flow-dependent, and metabolic flow control in the coronary arterial tree: a model study. Am J Physiol Heart Circ Physiol 282: H2224–H2237, 2002—Myogenic response, flow-dependent dilation, and direct metabolic control are important mechanisms controlling coronary flow. A model was developed to study how these control mechanisms interact at different locations in the arteriolar tree and to evaluate their contribution to autoregulatory and metabolic flow control. The model consists of 10 resistance compartments in series, each representing parallel vessel units, with their diameters determined by tone depending on either flow and pressure [flow-dependent tone reduction factor (TRFflow) × Tone myo] or directly on metabolic factors (Tone meta). The pressure-Tone myo and flow-TRFflow relations depend on the vessel size obtained from interpolation of data on isolated vessels. Flow-dependent dilation diminishes autoregulatory properties compared with pressure-flow lines obtained from vessels solely influenced by Tone myo. By applying Tone meta to the four distal compartments, the autoregulatory properties are restored and tone is equally distributed over the compartments. Also, metabolic control and blockage of nitric oxide are simulated. We conclude that a balance is required between the flow-dependent properties upstream and the constrictive metabolic properties downstream. Myogenic response contributes significantly to flow regulation.

myogenic response; flow-dependent dilation; metabolic control; autoregulation; mathematical model

CORONARY FLOW CONTROL is the result of modulation of tone in resistance arteries. On the basis of measurements and theoretical predictions of pressure profiles, the resistance vasculature spans vessels with diameter up to 400 μm (3, 20, 43). Because of this substantial distribution of resistance, a coordinated action of control mechanisms at different locations in the arteriolar tree is required to adapt flow to metabolism. The control mechanisms proposed are 1) metabolic factors, which are believed to have an effect only on the small arterioles (2, 18, 19); 2) myogenic control, constricting the arteries and arterioles with rising pressure and vice versa (5, 6, 14, 15, 21–23, 30, 37); and 3) flow-induced dilation, dilating the vessels in response to an increase in shear stress, modulated by nitric oxide (NO) (18, 22, 24, 25, 40). These mechanisms have been shown to play a role in regulating tone both in isolated coronary arteries and arterioles and in vivo. Theories integrating these mechanisms are proposed in the literature (7, 8, 17, 28, 31); however, a quantitative analysis that bridges the knowledge from isolated vessel studies and whole organ studies is lacking. We developed a mathematical model to study the possible interactions of these control mechanisms during flow control.

In an earlier study, we (5) demonstrated that pressure-induced myogenic tone alone, taking into account the diameter dependence of myogenic strength, could predict well the course of coronary autoregulation curves. However, this model raises two concerns: 1) flow-dependent dilation will diminish autoregulation; and 2) tone (myogenic) in the smallest vessels is almost absent because of the low level of pressure. The current study has the hypothesis that flow-dependent dilation in upstream vessels is compensated by vasoconstriction of the metabolically controlled smaller vessels, resulting in 1) restoration of autoregulation properties to the levels found for the model with pressure-induced myogenic tone alone and 2) increase in tone in the smaller vessels, leading to the possibility of dilation by increasing metabolism and to a more equal distribution of tone over the resistance vessels.

METHODS

A theoretical model of flow control in the arterial tree was made based on a series arrangement of vessel units, each unit having either myogenic and flow-induced dilatory properties or metabolic properties. The parameters for these units are obtained from experimental data of Liao and Kuo (27) and Kuo et al. (25) on the myogenic response and flow-dependent dilation.

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Compartmental Model of Arterial Tree

The model of the arterial tree was described previously (5). The first nine compartments describe the behavior of the coronary arterial tree covering diameters ranging from 10 to 500 μm. The resistance of the capillaries and the venules are assumed to be constant and are lumped in the tenth compartment.

We assume that each compartment \( i \) (\( i = 1 \ldots 9 \)), represents \( N_i \) identical vessels in parallel. According to Poiseuille, the resistance of the first nine compartments \( (R_i) \) can then be described with

\[
R_i = \frac{128\eta_i L_i}{N_i \pi d_i^4}
\]  

(1)

where \( i \) is the index referring to the resistance compartment number; \( \eta_i \) is the viscosity of the perfusate and is taken to be dependent on the diameter of the vessel as determined in the rat mesentery vasculature by Pries et al. (35), assuming a systemic hematocrit of 45%  

\[
\eta_i = \left( 1 + [1.6 \times 10^{-3} (6e^{-0.085d_i} + 3.2 - 2.44e^{-0.06d_i^{1.6}}) - 1] \right) \times \left( \frac{d_i}{d_i - 1.1} \right)^2 \left( \frac{d_i}{d_i - 1.1} \right)^2
\]  

(2)

\( L_i \) is the length of the vessel; \( N_i \) is the number of parallel vessels in the compartment; and \( d_i \) is the diameter of the vessel that is dependent on the hemodynamic parameters of flow and pressure in the vessel. Hence, the resistances of the first nine compartments vary depending on the hemodynamic parameters of flow and pressure in the vessel. The resistance of the first nine compartments is assumed when inlet pressure equals 90 mmHg and outflow pressure of the ninth compartment equals 30 mmHg (5). These assumptions yield values for average pressure \( (P_i) \) in each vessel unit, which allowed us to calculate \( d_i \) and \( Q_i \) for the fully dilated tree at 90 mmHg, resulting in values for \( N_i \), shown in Table 1.

The resistance of the vessel compartments \( (R_i) \) at a perfusion pressure of 90 mmHg at full dilation can be calculated from the assumed pressure drop \( (\Delta P = 60/9 \text{ mmHg}) \) and the flow distribution over the tree: \( R_i = \Delta P / (Q_i N_i) \). With Eq. 1, the values for the length of the vessel units \( (L_i) \) follow, which are also shown in Table 1. The constant resistance in the tenth compartment equals \( 15.4 \times 10^6 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{s} \) for \( 30/(Q_i N_i) \).

Control Mechanisms of Isolated Vessels

Experimental data defining control mechanisms. Liao and Kuo (27) and Kuo et al. (25) performed experiments in four different sizes of isolated porcine subepicardial microvessels with anatomic diameters of 65, 100, 165, and 255 μm. The vessels constricted to stepwise increase in luminal pressure (20, 40, 60, 80, 100, and 120 cmH₂O), and the strongest myogenic response was found in arterioles of 100 μm. The vessels also demonstrated flow-dependent dilation. The strongest response to shear occurred in arterioles of 165 μm. Furthermore, because NO mediates the flow-dependent response, they investigated the dose-response curve for nitroprusside in these vessels. For the four different sizes of microvessels, identical dose-dependent dilation for this NO donor was found.

Description of vessel unit in model. A set of equations was derived that describes the data of Liao and Kuo (27) and Kuo et al. (25) and allows for interpolation and extrapolation of responses within and outside the range of tone and diameters studied by these authors. We developed these equations on the basis of a biophysical model of vessel wall behavior as described earlier by VanBavel and Mulvany (42).

The biophysical model for the isolated vessel is based on a mechanical equilibrium involving passive and active tensions in the arteriolar wall, luminal pressure, and vessel diameter (36, 42). The relations on which this equilibrium is based are shown in Fig. 1. The passive tension \( (T_{pas}) \) is the tension developed when the vessel wall is stretched while the smooth muscle is completely inactive. When the smooth muscle is active, an active component of tension \( (T_{act}) \) comes into play. For a particular diameter, when the vessel wall is in an equilibrium state the wall tension \( (T_{wall}) \), defined as the sum of these tensions \( (T_{wall} = T_{act} + T_{pas}) \), is assumed to fulfill the law of Laplace: \( T_{wall} = T_{plac} = \frac{P L}{d} \). In this equation \( T_{plac} \) is the Laplace tension, which is the tangential force component acting on the wall per unit length; \( P \) is the average transmural pressure of the vessel; and \( d \) is the inner diameter of the vessel. The tensions are normalized to the Laplace tension of a passive vessel at 100 mmHg, in which the diameter by definition equals the anatomic diameter \( (d_{anat}) \). Therefore, normalized wall tension equals \( T_{wall} = \frac{T_{wall}}{d_{anat}} \), where \( d^* \) is the normalized diameter: \( d^* = d / d_{anat} \). This results in the relation \( T_{act} + T_{pas} = (P/100)d^* \), which for a fixed pressure yields a straight line as indicated in Fig. 1. Tone is defined as the ratio between the active tension \( (T_{act}) \) and the maximal active tension \( (T_{max}) \) at a given diameter and by definition ranges between zero and unity.

The simulation model for each vessel segment, characterized by \( d_{anat} \), is shown in Fig. 2 (36). The inputs of the model

\[
\begin{array}{ccc}
\text{i} & d_{anat}, \mu m & L_i, \mu m & N_i \\
1 & 400 & 56,816 & 1 \\
2 & 268 & 27,845 & 2.4 \\
3 & 181 & 14,092 & 5.6 \\
4 & 123 & 7,343 & 12.9 \\
5 & 84 & 3,912 & 29.4 \\
6 & 58 & 2,084 & 66.2 \\
7 & 40 & 1,053 & 147.2 \\
8 & 28 & 481 & 324.2 \\
9 & 20 & 203 & 709.0 \\
\end{array}
\]

\( i \), Compartment index; \( d_{anat} \), anatomic diameter; \( L \), length; \( N \), no. of parallel vessels.

Table 1. Assigned anatomic diameters, lengths of vessel units, and number of parallel units

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The output of the model is the normalized diameter ($d^*$, active and maximal active tension.

\[ \text{Tone} = \frac{T^{*\text{act}}}{T^{*\text{max}}} \]

Fig. 1. Diameter-tension relations for vessel wall behavior of a vessel unit with anatomic diameter of 255 μm. Shown are the normalized relations between 1) diameter ($d^*$) and passive tension ($T^{*\text{pass}}$), 2) $d^*$ and sum of the passive and maximal tension ($T^{*\text{pass}} + T^{*\text{max}}$), and 3) $d^*$ and tension relation as dictated by the law of Laplace ($T^{*\text{laplace}}$) at mean pressure of 60 mmHg. Tone is defined as the ratio between active and maximal active tension.

are either pressure ($P_i$) and flow ($Q_i$) or pressure and an intrinsic vascular tone modulated by metabolism (Tone\text{\_meta}); the output of the model is the normalized diameter ($d^*$).

When flow and pressure are the inputs, both flow and pressure determine tone and the pressure-induced myogenic tone ($\text{Tone}_{\text{\_myo}}$) is attenuated by a flow-dependent tone reduction factor (TRF\text{\_flow}); tone $= \text{Tone}_{\text{\_myo}} \times \text{TRF}_{\text{\_flow}}$. When the inputs are pressure and metabolism-dependent tone, tone is determined by Tone\text{\_meta} alone, whereas $P_i$ is involved in only the mechanical equilibrium. Values for $Q_i$, $P_i$, and Tone\text{\_meta} follow from the behavior of the model tree as described in Algorithm for Network Simulations.

For a given initial diameter, $T^{*\text{max}}$, $T^{*\text{pass}}$, and $T^{*\text{laplace}}$ are determined. Tone multiplied by $T^{*\text{max}}$ gives $T^{*\text{act}}$, and adding $T^{*\text{pass}}$ gives $T^{*\text{wall}}$. Comparing $T^{*\text{wall}}$ with $T^{*\text{laplace}}$ gives an error ($\epsilon$) indicating the imbalance in tensions in the vessel wall. When $T^{*\text{laplace}}$ is larger than $T^{*\text{wall}}$, the diameter is increased; when $T^{*\text{laplace}}$ is smaller, the diameter is decreased. With this new diameter, a new error is calculated. This iteration is continued until the relative error is smaller than $0.001$.

Relations within vessel units. We first present equations describing $T^{*\text{pass}}$, $T^{*\text{max}}$, and Tone\text{\_myo} and estimate their parameters in the absence of flow-dependent influences (TRF\text{\_flow} = 1). The relations for the flow-dependent tone reduction factor, which is considered to be an attenuation factor of pressure-induced myogenic tone (Tone $= \text{Tone}_{\text{\_myo}} \times \text{TRF}_{\text{\_flow}}$), are then presented, and its parameters are estimated. The parameter estimation procedure is described in detail in the appendix. Below we describe the basics for this approach and the results.

Active Tone Equations. The passive behavior of the blood vessels is approximately the same for all vessels in the arterial tree (5). The passive diameter-pressure relation was described in our previous study (5) and is converted to a

**Fig. 2.** Diagram of the model for a vessel unit, characterized by the anatomic diameter ($d_{\text{\_anat}}$). The inputs of the model are either pressure ($P$) and flow ($Q$) or $P$ and metabolism-dependent tone (Tone\text{\_meta}). For a given initial diameter at a certain $P$, maximal active tension ($T^{*\text{\_max}}$), passive tension ($T^{*\text{\_pass}}$), and wall tension ($T^{*\text{\_laplace}}$) are determined. Tone multiplied by $T^{*\text{\_max}}$ gives $T^{*\text{\_act}}$; adding $T^{*\text{\_pass}}$ gives $T^{*\text{\_wall}}$. Comparing $T^{*\text{\_wall}}$ with $T^{*\text{\_laplace}}$ results in an error ($\epsilon$) representing the imbalance in tensions in the vessel wall. When $T^{*\text{\_laplace}}$ is larger than $T^{*\text{\_wall}}$, the diameter is increased; when $T^{*\text{\_laplace}}$ is smaller the diameter is decreased. With this new diameter, a new error is calculated. This iteration is continued until the error is $< 0.001$. Tone is either determined by Tone\text{\_meta} or by the product of TRF\text{\_flow} and Tone\text{\_myo}, as is indicated by the switch. Tone\text{\_myo} follows from the P-Tone\text{\_myo} relation, which depends on $d_{\text{\_anat}}$, TRF\text{\_flow} is calculated in 3 steps. First, shear stress ($\tau$) is calculated; $\tau = 32 \cdot Q_i \cdot \eta / (\pi \cdot (d_{\text{\_anat}})^2)$. Second, the effective concentration of nitric oxide (NO) in the vessel ([NO]) follows from the shear stress-NO relation, which depends on the attenuation factor (A) and $d_{\text{\_anat}}$. Third, TRF\text{\_flow} follows from the [NO]-TRF\text{\_flow} relation. Tone\text{\_meta} is only applied in the distal compartments in the network, and its value is determined by assuming a certain flow and having Tone\text{\_myo} and TRF\text{\_flow} in the other proximal compartments intact.
normalized diameter-passive tension relation

\[ T_{\text{pas}} = 0.227d_i^6 - 0.705 \frac{1}{1.07} d_i^6 \]  

(3)

This normalized diameter-passive tension relation is shown in Figs. 1 and 3A.

The experimental data sets of Kuo et al. (25) and Liao and Kuo (27) lack the relations for the maximal active state, and other data are not available for the diameter-tension relation of coronary resistance vessels at full contraction. Therefore, we took a realistic curve similar to the curve that VanBavel and Mulvany (42) fitted to the data of Mulvany and Warshaw (32), who recorded these data on isolated rat mesentery vessels with diameters between 100 and 200 \( \mu \)m in an isometric wire myograph.

\[ T_{\text{max},i} = T_{\text{max},\text{top},i} + e^{-b_i d_i^m - e^{-b_i d_i^m}} \]  

(4)

where \( T_{\text{max},i} \) is the maximal possible active tension at a given normalized diameter, \( d_i^m \) is the optimal normalized diameter for active tension development, \( T_{\text{max},\text{top},i} \) is the tension at \( d_i^m \), and \( b \) determines the width of the curve. For given \( d_i^m, b \), and \( T_{\text{max},\text{top},i} \) Eqs. 3 and 4 result in the sum of \( T_{\text{max}} \) and \( T_{\text{pas}} \) as defined in Fig. 1.

It is assumed that the pressure-Tone\(_{\text{myo}}\) relation has a sigmoid shape, described with a Hill curve

\[ \text{Tone}_{\text{myo},i} = y_{0,i} + \frac{p_{\text{Hill},i}}{P_{50,i}^n + p_{\text{Hill},i}} \]  

HS\(_i\) is the Hill slope; \( y_{0,i} \) is the offset; and \( P_{50} \) is the pressure where Tone\(_{\text{myo}} = 0.5\).

**PARAMETER ESTIMATION OF PRESSURE-MYOGENIC TONE RELATION AND NORMALIZED DIAMETER-MAXIMAL TENSION RELATION.** The experimental data of Liao and Kuo (27) available for estimation of the six unknown parameters in Eqs. 4 and 5 are provided in Fig. 3A. Note that the experimental data are recalculated from pressure-diameter relations to normalized diameter-tension relations. The procedure of fitting Eqs. 4 and 5 to these data is described in the APPENDIX. The results of this fitting procedure are depicted in Fig. 3 as well. The parameters obtained from these fits were interpolated and extrapolated with respect to the anatomic diameter and further used in the model study.

In Fig. 3A, the calculated normalized diameter-tension relations for three more vessel segments that are part of the network model are provided as well. The curve for \( d_{\text{anat},i} = 123 \mu \)m is given because this generated the extremely strong myogenic response. The curves for \( d_{\text{anat},i} = 20 \) and \( 400 \mu \)m are given because they form the boundary diameters in the model and they form the extremely weak myogenic response. The fact that these curves are quite similar is forced by the similarity between the pressure-diameter relation of the smallest and largest vessels in the experimental data set.

The consequence of the model fits is that the pressure-myogenic tone relations are also diameter dependent, as is shown for the four model curves in Fig. 3B corresponding with the data of Liao and Kuo (27).

**EQUATIONS AND PARAMETER ESTIMATION FOR FLOW-DEPENDENT DILATION.** The dose-response curve for nitroprusside for the four vessels determined by Kuo et al. (25) is transformed to a NO concentration ([NO]-)TRF\(_{\text{flow}}\) relation. When vasodilation, expressed as the percentage of maximal diameter, equals 100%, TRF\(_{\text{flow}}\) equals zero. When vasodilation equals 0%, TRF\(_{\text{flow}}\) equals unity. In Fig. 4A, the recalculated experimental data for the four different-sized vessels are shown by the filled symbols. There is no marked difference between the response to nitroprusside for the four vessels; therefore, the data are pooled and fitted by a single Hill curve

\[ \text{TRF}_{\text{flow}} = 1 - \frac{[\text{NO}]_{\text{HSTRF}_{\text{flow}}}^{100} + [\text{NO}]_{\text{HSTRF}_{\text{flow}}}^{50}}{[\text{NO}]_{\text{HSTRF}_{\text{flow}}}^{100} + [\text{NO}]_{\text{HSTRF}_{\text{flow}}}^{50}} \]  

(6)

where HSTRF\(_{\text{flow}}\) is the slope of the Hill curve and \([\text{NO}]_{50}\) is the [NO] at which 50% of dilation is reached. The values of these parameters are shown in Table 2.

The recalculated shear-stress-TRF\(_{\text{flow}}\) data of Liao and Kuo (27) are shown in Fig. 4B. The four diameter groups show clearly different tone responses to shear stress and
Algorithm for Network Simulations

The iterative procedure used for the network simulations can be found in Cornelissen et al. (5) and is described briefly below. For a certain initial resistance distribution \( R_i = R_{\text{start},i} \), the flow \( Q \) and the pressure distribution [average pressure \( P_i \), inflow pressure \( P_{\text{in},i} \), and outflow pressure \( P_{\text{out},i} \)] of the vessel units are calculated. With the model for the vessel unit (Fig. 2), \( d_i \) is determined. Applying Poiseuille’s law (Eq. 2), a new resistance distribution \( R_i \) follows. With the pressure drop over the compartments, new \( Q \) for each compartment can be calculated. With the new resistance distribution, the flow rate is recalculated. The iterative procedure is stopped when convergence is reached.

\[
\begin{align*}
\frac{\partial Q}{\partial t} &= \frac{Q_{\text{in}} - Q_{\text{out}}}{A_i} \\
\frac{\partial P}{\partial t} &= -\frac{Q}{R_i} \\
R_i &= \sum_{j} R_{ij} \\
\end{align*}
\]

**Table 2. Parameters for vessel unit**

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<thead>
<tr>
<th>Equation Parameter</th>
<th>Value</th>
<th>Figure</th>
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<tr>
<td>( a )</td>
<td>0.063</td>
<td>12, middle right panel</td>
</tr>
<tr>
<td>( b )</td>
<td>0.038</td>
<td>12, middle right panel</td>
</tr>
<tr>
<td>( x_0 )</td>
<td>86 ( \mu )m</td>
<td>12, middle right panel</td>
</tr>
<tr>
<td>( S_{50} )</td>
<td>–0.065 ( \mu )m/mmHg</td>
<td>12, middle center panel</td>
</tr>
<tr>
<td>( O_{50} )</td>
<td>109 mmHg</td>
<td>12, middle center panel</td>
</tr>
<tr>
<td>( b_{50} )</td>
<td>19 mmHg</td>
<td>12, middle center panel</td>
</tr>
<tr>
<td>( x_0 )</td>
<td>104 ( \mu )m</td>
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\( T_{\text{max},i} \), normalized maximal active tension (\( T_{\text{act}} \)); \( d_{\text{anat}} \), optimal normalized diameter for \( T_{\text{act}} \) development; \( T_{\text{max},i} \), tension at \( d_{\text{anat}} \); \( x_0 \), diameter at which top occurs; \( \text{Tone}_{\text{myo}} \), pressure-induced myogenic tone; \( y_0 \), offset; \( P \), mean pressure; \( H_s \), Hill slope; \( P_{\text{in},i} \), pressure at \( \text{Tone}_{\text{myo}} = 0.5 \); \( S \), slope; \( O \), offset; \( \text{TRF}_{\text{flow}} \), flow-dependent tone-reduction factor; \( [\text{NO}] \), nitric oxide concentration; \( \tau \), shear stress; \( S_{50} \), \( O_{50} \) at which 50% of maximal \([\text{NO}]\) is reached; \( [\text{NO}]_{50} \), \([\text{NO}]\) at which 50% dilation is reached.

\( [\text{NO}]_{\text{max},i} \) is the maximal NO concentration at infinite shear stress, \( H_{\text{SSNO},i} \), is the slope of the Hill curve, and \( S_{50,i} \) is the shear stress where 50% of \([\text{NO}]_{\text{max},i} \) is reached. In this way, we obtained for each diameter group a set of parameters that can be used for prediction of shear stress-[NO] relations for vessel units with different anatomic diameters (for details see APPENDIX).

\[
[\text{NO}] = [\text{NO}]_{\text{max},i} \frac{H_{\text{SSNO},i} + H_{\text{NO},i}}{T_{50,i} + T_{50,i}}.
\]
The attenuation factor \( A \) that modifies the shear stress-[NO] relation is set to 0.046. In Fig. 5B, the effect of the attenuation factor on normalized flow at perfusion pressure of 90 mmHg is demonstrated. When \( A = 1 \), the flow equals 74% of the flow at maximal dilation; when \( A < 0.2 \), the flow decreases rapidly until \( A \) approaches zero and the normalized flow converges to the flow in the case of pressure-induced myogenic tone alone. To make sure that the flow-dependent mechanism is effective, the attenuation factor was set for further analyses to 0.046.

The distributions of normalized diameter and tone at a perfusion pressure of 90 mmHg are depicted in Fig. 6. With pressure-induced myogenic activity alone, tone distribution, the flow (Q) and the pressure distribution \((P_i, P_{in,i}, \text{ and } P_{out,i})\) are calculated. When the relative error between \( Q_i \) and \( Q \) is \( <10^{-10} \), the iterative process stops.

The data of Kuo et al. (25) show that the effect of shear stress on TRF\(_{flow} \) is saturated above 4 dyn/cm\(^2\). The estimates for shear stresses in vivo are in general \( >4 \) dyn/cm\(^2\), whereas flow-dependent dilation is believed to be still involved in control of blood flow. We considered the possibility that shear stress sensitivity is different in vivo from that in vitro and accordingly studied the effect of shifts in \( \tau_{50,i} \) of Eq. 7. Therefore, we introduce an attenuation factor \( A \) by which \( \tau_{50} \) is divided.

When metabolism-dependent tone was added to a number of the most distal compartments the procedure was as follows. The model solutions were obtained for pressure-induced myogenic tone alone, and the resulting flow was used as set point flow for the network. Flow-dependent dilation was made active, resulting in an increase in flow above the set point flow. Tone in the metabolic units was then increased to bring back flow to its set point level. The level of tone in the distal vessel units needed for this flow decrease is referred as metabolism-dependent tone (Tone\(_{meta} \)).

**RESULTS**

Simulations were performed for perfusion pressures ranging from 5 to 140 mmHg and outflow pressure of 0 mmHg. The simulated pressure-flow relations are shown in Fig. 5A. The simulated pressure-flow relation for maximal dilation is slightly curved as a result of the pressure dependence of resistances. When tone in the vessel units is determined by pressure-induced myogenic tone alone, autoregulation is revealed: flow rises less than proportionally with pressure. Flow-dependent dilation reduces the autoregulation characteristics of the pressure-flow line. The attenuation factor \( A \) that modifies the shear stress-[NO] relation is set to 0.046.

Insert, accompanying figures.
drops gradually from the larger resistance vessels to the smaller vessels. Note that normalized diameters of the largest and smallest vessels are close to one. Flow-dependent dilation changes the tone and diameter distribution over the compartments, but the resulting changes in pressure distribution introduce marginal changes in pressure-induced myogenic tone distribution (Fig. 6C). Flow-dependent dilation gives a plateau in the diameter-tone relation and gives an increase in diameter, most emphatically apparent in the larger resistance vessels (Fig. 6A).

Figure 7 demonstrates the effect of balancing flow-dependent dilation with metabolic constriction on the distribution of diameter and tone. This effect is presented for a perfusion pressure of 90 mmHg and an attenuation factor of 0.046. Restricting metabolic compartment of flow to the most distal compartment requires a high tone (Tone\text{meta} = 0.99). Distributing the required resistance increase equally over more than one compartment reduces the amount of tone per vessel unit (Fig. 7). Having four compartments under the influence of metabolism-dependent tone results in a more or less equal tone distribution over the compartments (Fig. 7A).

In Fig. 8, the distributions of tone at perfusion pressures of 60, 90, and 120 mmHg are depicted. To bring flow back to the autoregulation curve obtained with pressure-induced myogenic tone alone, a lower level of metabolism-dependent tone is required at lower perfusion pressure. Most of the changes in tone of the larger vessels are due to pressure-induced myogenic tone variations. The changes in TRF\textsubscript{flow} oppose the desired effect; however, the changes are small, which is to be expected because flow is kept in a narrow range.

Full dilation of the smaller vessels is simulated by reducing the tone of the metabolic vessels to zero. Such local dilation has been observed to result from adeno-

Fig. 7. Distributions of tone for increasing number of compartments under influence of metabolism-dependent tone (Tone\text{meta}) at perfusion pressure of 90 mmHg. A–D: tone, Tone\text{myo}, TRF\text{flow}, and Tone\text{meta}, respectively, as a function of the diameters of the vessel units. Distributions without influence of Tone\text{meta} are also shown (circles). Inset, accompanying flows at P = 90 mmHg and the pressure-flow lines for the fully dilated case and with all compartments having pressure-induced myogenic tone alone. Tone\text{meta} is set such that the total distal resistance under metabolic influence was increased to a value such that flow equals the value in the case of pressure-induced myogenic tone alone. Symbols refer to different numbers of distal compartments under metabolic influence. When Tone\text{meta} is restricted to only the most distal compartment, Tone\text{meta} equals almost unity, and thus wall tension equals almost our defined maximal wall tension. Distributing the required resistance increase over more than 1 distal compartment reduces the amount of tone per vessel unit.

Fig. 8. Autoregulation and distribution of tone with 4 distal compartments under metabolism-dependent tone. Results are for a perfusion pressure (P\text{p}) of 60 (inverted triangles), 90 (triangles), and 120 (diamonds) mmHg. A–D, tone, Tone\text{myo}, TRF\text{flow}, and Tone\text{meta}, respectively. Inset, flows for the pressures simulated as well as the pressure-flow line for full dilation and with all compartments having pressure-induced myogenic tone alone.
sine infusion and metabolic dilation induced by NO synthesis inhibition of larger resistance vessels (18). The effect of metabolic dilation for these two conditions is demonstrated in Fig. 9. Distal dilation without inhibition of NO synthesis increases flow from 37% to 80% of maximal dilated values. A substantial part of the decrease in total resistance is due to the dilation of the proximal vessel units (14%). Tone in these vessels decreases (Fig. 9A), and it is clear that both the pressure-induced myogenic mechanism (Fig. 9B) and the flow-dependent mechanism (Fig. 9C) enhance the effect of distal dilation on reduction of overall coronary resistance.

Inhibition of NO synthesis in our model is simulated by setting the TRF<sub>flow</sub> of the proximal vessels to 1. Flow increases only from 37% to 47% of maximal dilated values. The behavior of the vessels in the proximal compartments depends on location in the circuit. As indicated in Fig. 9A, the vessels in the third compartment decrease diameter with increasing tone, whereas in the fifth compartment both diameter and tone decrease. The pressure-induced myogenic tone (Fig. 9B) in compartments 1–5 is always reduced by dilation of compartments 6–9. Thus constriction of the larger vessels by inhibition of NO synthesis is attenuated by the myogenic mechanism, indicating that the upstream constriction is not only compensated by the metabolic mechanism but the myogenic mechanism also contributes to this compensating effect.

**DISCUSSION**

Pressure-induced myogenic tone alone results in autoregulatory properties of the coronary model, independent of factors related to metabolic control, i.e., the flow is rather independent of arterial pressure. When the flow rate through this myogenically controlled tree matches flow demand, a stable perfusion system is obtained. However, flow-dependent dilation induces a flow rate higher than needed. Therefore, an increase in tone in the smaller downstream vessels should compensate for this. When vessels with diameters ranging from ~10 to ~40 μm are assumed to have a higher intrinsic tone than found in isolated vessels, this tone can then be modulated by metabolism and tone is more or less equally distributed over the arterial tree. Moreover, the level of tone in all compartments is such that a sufficient range of tone in these compartments is available to adjust flow to the large variations in tissue oxygen demand. To distinguish the responses in the smallest resistance vessels from those in the larger ones we introduced the notion of “metabolism-dependent tone” to indicate that this tone is modulated predominantly by metabolism.

**Previous Model Studies**

Liao and Kuo (27) used a network model similar to ours to investigate the interaction of shear stress, pressure, and adenosine, an endogenous vasodilator. They used a four-compartment model with vessel units based on the same data as used in our study.

However, an essential difference is that their model is diameter based and ours is wall tension based, which seems to better fit a biophysical description of vessel wall mechanics. The effect of shear stress-dependent dilation on the adenosine-flow dose–response relation was investigated, a problem different from the one addressed here.

Granger (11) used a three-compartment model. However, each compartment was characterized by a single control mechanism, which is different from the present model, in which the strength of myogenic tone and flow-dependent dilation vary gradually in a realistic way over the different compartments. Ursino et al. (41) developed a theoretical network model based on wall tension with five branched elements to analyze the functional role of dynamic vasomotion in blood flow control, but they did not study interactions between control mechanisms.
Evaluation of Model Structure and Parameter Choice

The model consists of a series of resistances, neglecting the stochastic nature of branching within the coronary tree. Obviously, the responses of individual vessel units depend on the assumption of the resistance and velocity distributions over the vessel units. The resistance distribution under dilated conditions was based on the epicardial pressure diameter measurements of Chilian et al. (1) and was justified in our earlier study on myogenic tone (5). The velocity distribution over the different units was based on the average data of Stepp et al. (40). Both experiments demonstrated a considerable intervessel variability. We have not addressed this variability because it would require a stochastic branching model that would have obscured the interactions between control mechanisms. This interaction was the main purpose of this study. The limitation of the model structure is an important reason for some quantitative differences between predictions and experimental data, although the characteristics of the model and the experimental responses tally well.

In the vascular wall of veins and venules smooth muscle cells are observed, as well as diameter changes in response to sympathetic activity and certain agonists. However, the contribution to resistance of this part of the circulation under physiological conditions is small compared with the contribution to resistance of the vessels studied here (resistance vessels ranging from 20 to 500 \( \mu \text{m} \)). Therefore, the assumption of a constant resistance contribution of capillaries and veins during flow control under physiological conditions seems quite realistic.

Important to the model is the law of Laplace. We used the law of Laplace for thin-walled vessels, whereas a more general formula is \( T = 0.5(P_1d - P_2(d + 2t)) \) (34), where \( P_1 \) and \( P_2 \) are the pressure inside and outside the vessel, respectively, \( d \) is the inner diameter, and \( t \) is the wall thickness. The deviation between the thin and thick wall equations increases with the wall thickness-to-diameter ratio but is diminished when the transmural pressure \( (P_1 - P_2) \) increases. This deviation is not the same for all vessel diameters, and for a single vessel it varies with tone. All these effects are neglected in the model. The application of the thin wall formula simplifies the mathematics of the model because it results in a linear tension-diameter relation for a given pressure. The simplification seems justified in the context of other uncertainties, especially with respect to the diameter- \( T_{\text{max}} \), pressure- \( T_{\text{myo}} \), and shear- \( \text{TRF}_{\text{flow}} \) relations in the model.

The relations chosen to determine \( T_{\text{max}} \) and \( T_{\text{myo}} \) are not uniquely defined by the data of Liao and Kuo (25). For example, applying a different diameter- \( T_{\text{max}} \) relation, where \( T_{\text{max},\text{opt}} \) is twice the original value and \( d_m \) is 90% of the original value, results in less steep pressure- \( T_{\text{myo}} \) relations. However, the resulting autoregulation curve for myogenic tone alone is hardly different from the original one and, furthermore, the number of compartments under influence of metabolic control required to have an approximately equal distribution of tone is still four. The only difference is that the value of tone is smaller under these circumstances than when the original diameter- \( T_{\text{max}} \) and pressure- \( T_{\text{myo}} \) relations are used.

Flow-dependent dilation is mediated by shear stress-induced production of NO. We have modeled this in three steps to reconcile the observations that the shear stress- \( \text{TRF}_{\text{flow}} \) relation is dependent on anatomic diameter but the [NO]- \( \text{TRF}_{\text{flow}} \) relation is not. Both relations were measured by Kuo et al. (25). Our model fits their relations by having components providing the diameter-dependent relation between shear stress and [NO] and the relation between [NO] and \( \text{TRF}_{\text{flow}} \). The data of Kuo et al. (25) suggest that for high shear stresses, [NO] saturates such that vasodilatation is submaximal. The level of [NO] would therefore depend on vessel size. The reason for submaximal vasodilatation is unknown.

The attenuation factor \( (A) \) in the model modifies the relation between shear stress and [NO] and by definition equals unity for the experiments of Kuo et al. (25). This factor deviates from unity to compensate for scavengers and other factors that may affect the shear stress- \( \text{TRF}_{\text{flow}} \) relations. This factor only affects the effective working range of the [NO]-shear stress relation and not the level of [NO] at infinitely high shear stress. As shown in Fig. 5B, a large \( A \) results in a large flow, and thus, in our concept, a large countering metabolic resistance is needed. However, because the shear stresses in the vessel units of the network are all \( >7 \text{ dyn/cm}^2 \), the flow-dependent mechanism would hardly be effective: possible changes in shear stress do not result in changes in [NO] and thus do not result in changes in \( \text{TRF}_{\text{flow}} \). When \( A \) is too low, the countering metabolic resistance is low and metabolic control in the sense of metabolic dilatation is limited. With, for instance, \( A = 0.01 \), it is sufficient to set only the last compartment under the influence of metabolic control. \( T_{\text{myo}} \) would then be only 0.47.

There may be several reasons why the in vitro vessels behave differently in response to shear stress compared with the in vivo vessels. An important reason is obviously the fact that in vitro the red blood cells are missing that are metabolizing NO at a high rate. To study this would require a dedicated model in itself, to compensate for all the factors involved in controlling it, including the endothelial glycocalyx (4). Moreover, we left out other mechanisms that influence local vascular tone and concentrated on the interaction of two mechanisms well defined in vitro studies. Hence, it is assumed that the attenuation factor, scaling the data from isolated single vessels to the whole heart, takes all these unknown factors into account.

Application of Model to Interpretation of Distributed Response in Coronary Circulation

Distributed vascular diameter response during metabolic regulation. Several elegant experiments (18, 40) have attempted to study the distributed response of
flow-dependent dilation and metabolic influence over the vessels of different diameters in the coronary tree. However, the pressure-induced myogenic tone is always present as an additional factor of tone generation, and it is not always clear how this is affected by the interventions.

In experiments of Jones et al. (18) on subepicardial microcirculation in the beating dog heart it was demonstrated that NO blockade by N^\text{G}-nitro-L-arginine methyl ester resulted in vasoconstriction of resistance vessels >100 \, \mu m, but in dilation of vessels smaller than this threshold diameter (in another study of Jones et al. (16) NO synthesis inhibitor was administered intravenously, and these data are not considered here). This dilation was explained as a metabolic dilation and/or myogenic mechanism for compensation of the upstream constriction. Because adenosine could not further dilate the vessels smaller than 100 \, \mu m it was assumed that a metabolic stimulus for dilation was already maximal. Further evidence for a 100-\mu m threshold for feedback of metabolic vasodilatation was obtained from the pacing experiments reported in the same study. Adenosine administration alone also dilated only the vessels with diameter <100 \, \mu m.

In our study we also found a threshold for metabolic dominance in the smaller resistance vessels. It is difficult to give an exact threshold. We did not go beyond 40-\mu m vessels under metabolic influence. As is clear from Fig. 7, we would be able to further equalize tone over the compartments by including more compartments under metabolic influence. However, we are then confronted with the problem introduced by considering only nine discrete compartments, and defining a threshold for metabolic control becomes arbitrary. On the other hand, most likely, the segments now assumed to be affected by metabolism alone will also have a shear stress-related dilatory factor. Without knowing the mediator responsible for metabolic vaso-motor control, the combination of these mechanisms is difficult to model, which is why we used a strict threshold. Besides these limitations, the model behavior clearly agrees with metabolic compensation by distal resistance vessels for proximal flow-dependent dilatation, and it demonstrates that pressure-induced myogenic tone in the proximal vessels remains important for coronary flow control.

In our model the effect of full dilation of the smaller vessels was simulated by reducing the tone of the metabolic vessels to zero. In Fig. 10A, the percent change in diameter of the vessel units is compared with the diameter change after administration of adenosine as observed by Jones et al. (18). The model predictions deviate from the experimental obtained data in two ways. First, for the larger vessels, Jones et al. observed small constriction of the vessels, which we could not predict. Second, Fig. 10A also shows that the threshold for metabolic dominance should shift to somewhat larger vessels. In our model the threshold can be shifted either by changing the number of compartments assumed to be under metabolic control or by assuming a different anatomic diameter distribution.

Inhibition of NO synthesis in our model is simulated by setting the TRF_{flow} of the proximal vessels to 1, and to comply with the observed metabolic dilation while NO is blocked Tone_{meta} of the four distal compartments are set to zero (Fig. 9). In Fig. 10B the percent diameter change after inhibition of NO as observed by Jones et al. (18) is compared with the prediction of the model. Again, the distribution and the amount of diameter change are predicted well by the model. In the model these diameter changes correspond to a flow increase from 37% to 47% of maximal dilated values, which is in fair agreement with Jones et al. (18), who did not find a significant change in flow. The agreement between model predictions and the data of Jones et al. (18) clearly underlines the relevance of isolated-vessel experiments (9, 21–25, 30, 33, 37) to understanding of the integrated vascular bed.

Distributed shear stress and velocity response during metabolic regulation. In a study of Stepp et al. (40) microvascular diameters and microsphere velocities were measured. Measurements in arterioles (30–160 \, \mu m) and small arteries (160–450 \, \mu m) were obtained under basal conditions and after administration of adenosine. Wall shear stress was calculated using the formula \( \tau_{\text{wall}} = 8 \nu \eta \eta d \), where \( \tau_{\text{wall}} \) is the wall shear stress, \( \eta \) is blood viscosity, \( d \) is vascular diameter, and \( v \) is the mean velocity in the vessel cross-sectional area.

![Fig. 10. Changes in diameter induced by adenosine (A) and inhibition of NO synthesis (B). Open symbols reflect experimental data obtained from the epicardial microcirculation of an open-chest dog and are redrawn from Jones et al. (18). Filled symbols are the model results. Metabolic dilation caused by adenosine is simulated by reducing metabolism-dependent tone of the 4 distal compartments to zero (A; in Fig. 9, circles vs. squares). Inhibition of NO by N^G-nitro-L-arginine methyl ester is simulated by setting TRF_{flow} of the proximal compartments to 1 and reducing metabolism-dependent tone of the 4 distal compartments to 0 (B; Fig. 9, circles vs. inverted triangles). Model predictions of the percent diameter change after administration of adenosine and after administration of the NO synthesis inhibitor are in fair agreement with the experimentally observed values.](https://www.ajpheart.org)
which was assumed to equal the microsphere velocity. The data of these experiments are presented in Fig. 11, A and B.

From the simulations reported above (Figs. 9 and 10) shear stress and velocity changes as induced by distal dilation are calculated, and the results are depicted in Fig. 11, A and B. Velocities in the distal compartments hardly changed. The adenosine-induced increase in flow in the model is therefore the result of increasing cross-sectional area at constant velocity in the distal vessels.

The differences between the model and the experiments are accentuated by comparing the changes in velocity and shear stress induced by adenosine as shown in Fig. 11C. In arterioles Stepp et al. (40) reported a parallel increase in velocity and shear stress, whereas in small arteries the increase in velocity was much larger compared with the increase in calculated shear stress (Fig. 11C). The model simulation (Fig. 11C) could not demonstrate this much smaller variation in shear stress than in velocity for the small arteries. However, the cause for the discrepancy between model and experiment is not necessarily in the model alone, because the study of Stepp et al. (40) seems also to be in controversy with other experimental studies.

In the study of Stepp et al. (40), as a result of adenosine, velocity increased by a factor of 2.1 and shear stress by a factor of 1.3 in the resistance vessels with diameter >160 μm. These two numbers are only consistent if the diameter of these vessels increased by 60% (2.1/1.3) after infusion of adenosine. These diameter changes on adenosine infusion are in contrast with observations of Jones et al. (18; Fig. 10A) and other experimental data (2, 19), which demonstrate an absence of diameter variation in the small arteries. It should be noted that the calculated diameter changes of Stepp et al. (40) are not the result of paired measurements, whereas in the other studies this was the case.

Predictions of flow and flow reserve by model. The model predicts a flow reserve a little over a factor of 2, whereas in humans and dogs this can easily be a factor of 4, although in goats it is less; a factor of ~3. The only conclusion can be that tone in our reference network is too low to provide sufficient vasoconstriction to allow the flow reserve to be a factor of 4. It should be noted, however, that we found an agreement between experi-

![Fig. 11. Distribution of velocity (A) and shear stress (B). Open symbols represent measured and calculated data of Stepp et al. (40). Filled symbols are model simulations. Administration of adenosine was simulated by full dilation of the 4 distal compartments (Fig. 9, circles vs. squares). C: percent changes in shear stress (diamonds) and percent changes in velocity (circles). Open symbols are the average changes as provided by Stepp et al. (40). Filled symbols are the simulated changes. Our model could not predict the much smaller increase in shear stress than in velocity in small arteries as reported by Stepp et al. (40).](http://ajpheart.physiology.org/)

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imental and predicted diameter changes, which suggests that the distribution in tone is quite realistic. Therefore, both tone in the proximal vessels as well as tone in the distal metabolic vessels are somewhat too low. Tone in the proximal vessels was based on in vitro studies, and the conclusion must then be that in these studies the level of intrinsic tone was too low as well. Such differences between in vivo and in vitro observations may well be possible by changing vascular smooth muscle preconstrictor factors between dissection and mounting in the pressure myograph. For example, endothelin concentrations (26) might have been altered. The required increase in tone does not need to be very large. The law of Poiseuille dictates an inverse fourth-power relation between resistance and diameter. Hence, a 10% reduction in diameter of all segments would result in an increase of 40% resistance and diameter. Hence, a 10% reduction in diameter, and the relation was assumed to be log normal

\[ T_{\text{max}top,i} = d_{\text{max}top,i} e^{-0.5 \ln \left( \frac{d_{\text{anat},i}}{d_{\text{anat},\text{anat},i}} \right)} \]  

(A1)

The estimated parameters for Eqs. 4 and A1 are shown in Table 2, and the relation between \( d_{\text{anat},i} \) and \( T_{\text{max}top,i} \) is shown in Fig. 12, top.

The fits to the experimental pressure-diameter data of the four vessel groups were not satisfactory. The pressure-diameter data of Liao and Kuo (27) was transformed to pressure-tone data with Eqs. 3, 4, and A1. For the four vessel groups, different relations were found and Eq. 5 was fitted to the pressure-tone data of each vessel group (Fig. 3B). As shown in Fig. 12, middle, the parameters found for Eq. 5 were related to \( d_{\text{anat},i} \). The following equations were fitted to the \( d_{\text{anat},i} \)–HS\(_{\text{myo},i} \), \( d_{\text{anat},i} \)–\( y_{\text{myo},i} \), and \( d_{\text{anat},i} \)–\( P_{50,i} \) relations

\[ \text{HS}_{\text{myo},i} = O_{\text{HS}_{\text{myo}}} + d_{\text{anat},i} S_{\text{HS}_{\text{myo}}} + a_{\text{HS}_{\text{myo}}} e^{-0.5 \ln \left( \frac{d_{\text{anat},i}}{d_{\text{anat},\text{anat},i}} \right)^2} \]  

(A2)

\[ \text{P}_{50,i} = O_{\text{P}_{50}} + d_{\text{anat},i} S_{\text{P}_{50}} + a_{\text{P}_{50}} e^{-0.5 \ln \left( \frac{d_{\text{anat},i}}{d_{\text{anat},\text{anat},i}} \right)^2} \]  

(A3)

\[ y_{\text{myo},i} = a_{y} e^{0.5 \ln \left( \frac{1000 - d_{\text{anat},i}}{d_{\text{anat},\text{anat},i}} \right)^2} \]  

(A4)

The obtained parameters are shown in Table 2, and the fits are depicted in the middle panels of Fig. 12. Equations A2–A4 allowed us to estimate the parameters for Equation 5 for all other \( d_{\text{anat},i} \) as applied in the network model, as shown in Fig. 12.

Parameter Estimation for Shear Stress-[NO] Relation

The shear stress-[NO] relation as obtained for the four vessel groups of Liao and Kuo (27) are clearly different (Fig. 4C). The parameters of Eq. 7, found by fitting this equation to the transformed data of Liao and Kuo (27), are related to their anatomic diameter and are shown in the bottom panels in Fig. 12. The following equations were fitted to the \( d_{\text{anat},i} \)–HS\(_{\text{NO}_{i}} \), \( d_{\text{anat},i} \)–\( \tau_{50,i} \), and \( d_{\text{anat},i} \)–\( \text{NO}_{\max} \) relations

\[ \text{HS}_{\text{NO}_{i}} = \text{HS}_{\text{NO}_{\max}} \frac{d_{\text{anat},i} S_{\text{HS}_{\text{NO}_{i}}}}{d_{50} \text{HS}_{\text{NO}_{i}} + d_{\text{anat},i} S_{\text{HS}_{\text{NO}_{i}}}} \]  

(A5)

\[ \tau_{50,i} = O_{50} + S_{50} d_{\text{anat},i} \]  

(A6)

\[ 10 \log ([\text{NO}]_{\max,i}) = O_{\text{NO}_{\max}} + a_{\text{NO}_{\max}} e^{-0.5 \ln \left( \frac{d_{\text{anat},i} - x_{\text{NO}_{\max}}} {d_{\text{anat},\text{anat},i}} \right)^2} \]  

(A7)

where \( O \) is offset and \( S \) is slope. The obtained parameters are shown in Table 2, and the fits are depicted in the bottom panels of Fig. 12. Equations A5–A7 allowed us to estimate the parameters for Equation 7 for all other \( d_{\text{anat},i} \) as applied in the network model, as shown in Fig. 12.

APPENDIX

The control behavior of isolated vessels as described by Liao and Kuo (27) and Kuo et al. (25) is implemented in the model of the vessel unit depicted in Fig. 2. The switch in Fig. 2 points from \( \text{Ton}e_{\text{myo}} \times \text{TRF}_{\text{flow}} \) to Tone, i.e., tone of the vessel unit is determined by myogenic and flow-dependent properties. Here we give empirical relations of the model and estimate their variables based on the data experimentally obtained by Liao and Kuo (27) and Kuo et al (25). This allows for interpolation and extrapolation of these data, giving the necessary relations for each vessel segment used in the model. We first estimated parameters of our model equations without flow-dependent tone (TRF\(_{\text{flow}} = 1\)).

Parameter Estimation of Pressure-Myogenic Tone Relation and Diameter-Maximal Tension Relation

The fitting procedure was done in two steps. First, rough fits through the experimental data of the four vessel groups of Liao and Kuo (Ref. 27; \( d_{\text{anat},i} = 255, 165, 100, \) and 65 \( \mu \text{m} \) resulted in estimates of parameters in Eqs. 4 and 5. At this stage, only \( T_{\text{max}top,i} \), a variable in Eq. 4, is dependent on the anatomic diameter, and the relation was assumed to be log normal

\[ T_{\text{max}top,i} = d_{\text{max}top,i} e^{-0.5 \ln \left( \frac{d_{\text{anat},i}}{d_{\text{anat},\text{anat},i}} \right)^2} \]  

(A1)
Fig. 12. Relations used for the interpolation and extrapolation of the experimental data of Liao and Kuo (27) and Kuo et al. (25). Top, middle, and bottom, relations between parameters of Eqs. 4, 5, and 7, respectively, and the anatomic diameter ($d_{anat,i}$). Closed symbols are the calculated parameters for the vessel groups of the experimental data of Liao and Kuo. Lines are the interpolations used, and open symbols are the parameters used in the model.
REFERENCES


