Significance of microvascular remodelling for the vascular flow reserve in hypertension

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Vascular flow reserve (VFR) is the relative increase in tissue perfusion from the resting state to a state with maximum vasodilatation. Longstanding hypertension reduces the VFR, which in turn reduces the maximum working capacity of the tissue. In principle, both inward arteriolar remodelling and rarefaction of the microvascular network may contribute to this reduction. These processes are known to occur simultaneously in the microcirculation of the hypertensive individual and both cause a reduction in the luminal trans-sectional area available for perfusion. Which of them is the main factor responsible for the reduction in VFR is, however, not known. Here we present simulations performed on large microvascular networks to assess the VFR in various situations. Particular attention is paid to the VFR in networks in which the vessels have structurally adapted to a sustained increase in pressure by inward eutrophic remodelling (IER), i.e. by redistributing the same amount of wall material around a smaller lumen. Collectively, the results indicate that the IER may not per se be the main factor responsible for the hypertensive reduction in VFR. Rather, it may be explained by the presence of arteriolar and capillary rarefaction.

Keywords: vascular flow reserve; rarefaction; remodelling; model; hypertension; autoregulation

1. INTRODUCTION

Vascular flow reserve (VFR) of a tissue is the maximum degree to which local flow can increase relative to flow in the resting state [1]. Under physiological conditions in vivo, this ratio reflects the ability of the local circulation to respond to an increase in tissue demand following, e.g., physical exercise. To that end studies in both humans and animals have shown a reduction in VFR in longstanding hypertension in tissues such as the heart (here termed coronary flow reserve, CFR) [2,3], the tissues of the forearm [4–6] and the skin [7].

Essential hypertension is characterized by an elevated peripheral resistance residing at the level of the microcirculation [8]. The increased physical hindrance to blood flow appears to be structural in nature as there is little evidence of a general increase in vascular tone in established hypertension [9]. The resistance increase may therefore in principle be caused by either thinning of the microvascular net (rarefaction) or structural remodelling of the resistance vasculature. Rarefaction may encompass both capillaries [10] and small arterioles [11] and it increases with severity of the hypertensive state [12]. The mechanisms causing rarefaction are largely unknown. Experimentally, rarefaction is found in animal models of induced hypertension [13]. Under these circumstances, rarefaction seems to depend on the blood-pressure elevation per se. This may however not necessarily be the case in human essential hypertension. In genetically hypertension-prone individuals (one or two hypertensive parents), rarefaction is present already, before the onset of a clinical elevation in blood pressure [14]. Hence, rarefaction may be a cause of hypertension rather than a consequence. Also it may have a different origin than disappearance of the existing vessels, for instance a diminished formation of new capillaries [15].

A reduction in capillary density can also be relative, i.e. owing to hypertrophy of the surrounding tissue without an appropriate simultaneous growth of the microvasculature. This may be the case for instance in left ventricular hypertrophy [2], which typically follows sustained hypertension.

The structural changes found in small muscular arteries and arterioles in human essential hypertension as well as in experimental hypertension in animals, results from a process known as inward eutrophic remodelling (IER). This process is characterized by a redistribution of the wall material around a smaller vessel lumen, but without a change in the total amount of wall material ([16,17] see also [18]). In
essential hypertension, IER appears to be associated with little or no change in the composition of the vascular wall or in the biophysical properties of the vascular smooth muscle cell (SMC) [9]. Intuitively, it seems that IER should give rise to a reduced vascular reserve. On the other hand, in hypertensive individuals blood is circulated through the microcirculation under a larger pressure difference and hence under a larger driving force. This is the case both during rest and during maximum local vasodilatation. As regards the VFR, the larger intravascular pressure head and the larger decline in pressure along the microvascular tree could therefore in principle offset the effect of IER. Hence, the role of vascular remodelling in the hypertensive reduction of the VFR remains unclear.

Consequently, we address the question: Does IER contribute to a reduced VFR in hypertension? This question is difficult to answer experimentally as in vivo a reduced VFR may represent the combined effect of remodelling and rarefaction. In a computational model, however, possible consequences of IER can be investigated separately allowing for assessment of its relative role. Hence we present simulations of remodelling in a simple, bifurcating network with properties common to many vascular beds in the body.

2. THE MODEL

2.1. Model of the vascular wall

A detailed description of the wall model is given in Jacobsen et al. [19]. In brief, idealized circumferential wall stress, \( \sigma \), can be expressed as [20]:

\[
\sigma = \sigma_c + \sigma_s, \tag{2.1}
\]

where ‘c’ and ‘a’ refer to elastic and active muscular components that are arranged in parallel. The elastic part is modelled to consist of two components:

\[
\sigma_c = C_1(e^{pe} - 1) + C_2(e^{pe} - 1), \tag{2.2}
\]

where \( e = (L_i/L_0) - 1 \) is the strain and \( L_0 \) denotes tissue length at zero transmural pressure (constants in table 1). The active component was modelled as a Gaussian function [19,20]:

\[
\sigma_s = \psi \exp[1 - ((e - m)/s)^2], \tag{2.3}
\]

reflecting that the contribution from the active contractile machinery will decline if the wall is distended beyond a certain point (see fig. 1a of reference [19]). In equation (2.3), the dimensionless parameter \( \psi \) expresses the degree of SMC activation, normalized to its relative role. Hence we present simulations of remodelling in a simple, bifurcating network with properties common to many vascular beds in the body.

During active short-term regulation of vessel radius, the trans-sectional area of the wall is conserved. The amount of wall material inside or outside a layer in the wall of radius \( r \) in the active pressurized state is therefore equal to that of the same layer in the relaxed, unpressurized vessel, in which case radius of the layer is denoted as \( \rho \). With ‘i’ and ‘o’ referring to the inner and outer radii of the vessel, respectively, the transmural pressure, \( P \), is given by Laplace’s law:

\[
P = \int_{r_i}^{r_o} \frac{S}{r^2} dr = \int \frac{\sigma_r}{r} dr + \psi \int \frac{\sigma_r}{r} \phi^2 dr, \tag{2.4}
\]

where \( S = \sigma(1 + e) \) is the Cauchy stress, \( r_p = r_i/\rho_i \) is the normalized internal radius, \( \eta = \rho_o/\rho_i \) is the relative thickness of the relaxed wall, \( z = \rho/\rho_i \) is an integration variable and where the strain has been expressed as:

\[
e = (1/z) \sqrt{r_p^2 - 1 + z^2 - 1}.
\]

2.2. Activation of the vascular wall and wall remodelling

In the present model, distinction is made between habitual activation (\( \phi_{\text{habitual}} \)), steady-state activation (\( \phi_{ss} \)) and actual activation (\( \phi \)). The arteriolar and venous vessels typically possess a certain level of tone in vivo. The SMC activation giving rise to that basal tone is denoted here as the habitual activation [19]. Supposedly, the habitual activation represents the point where the system operates optimally regarding its ability to regulate local flow acutely. Hence, in case of a sustained external or internal influence that shifts \( \phi \) away from \( \phi_{\text{habitual}} \), the system will seek to restore the basal level of tone, i.e. to let \( \phi \rightarrow \phi_{\text{habitual}} \) by structural adaptation (see below). For simplicity we assume that, unless otherwise stated, \( \phi_{\text{habitual}} \) is uniform throughout the network.

The steady-state activation, \( \phi_{ss} \), of a vessel in a specific state, i.e. at a given radius and level of transmural pressure and flow, is in principle determined by the summed contributions (positive or negative) from each of the different vasomotor mechanisms operating

<p>| Table 1. Standard parameter values of the model. |</p>
<table>
<thead>
<tr>
<th>symbol</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_1 )</td>
<td>13 500 Pa</td>
</tr>
<tr>
<td>( \alpha_1 )</td>
<td>1.9</td>
</tr>
<tr>
<td>( C_2 )</td>
<td>40.0 Pa</td>
</tr>
<tr>
<td>( b )</td>
<td>0.1828E6 Pa</td>
</tr>
<tr>
<td>( m )</td>
<td>0.5</td>
</tr>
<tr>
<td>( s )</td>
<td>0.7</td>
</tr>
<tr>
<td>( \tau_{\text{activation}} )</td>
<td>75 s</td>
</tr>
<tr>
<td>( \tau_{\text{remodelling}} )</td>
<td>750 s</td>
</tr>
<tr>
<td>( k_s )</td>
<td>256E6 Pa</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>0.624</td>
</tr>
<tr>
<td>( \kappa )</td>
<td>0.1E6 Pa</td>
</tr>
<tr>
<td>( \mu )</td>
<td>0.004 Pa s (^{-1} )</td>
</tr>
<tr>
<td>capillary length</td>
<td>50E-6 m</td>
</tr>
<tr>
<td>capillary radius</td>
<td>5E-6 m</td>
</tr>
<tr>
<td>( l_1 )</td>
<td>100E-6 m</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>0.5</td>
</tr>
<tr>
<td>( e )</td>
<td>3</td>
</tr>
<tr>
<td>( \delta_{\text{arteriolar}} )</td>
<td>6E-6 m</td>
</tr>
<tr>
<td>( \delta_{\text{venous}} )</td>
<td>15E-6 m</td>
</tr>
<tr>
<td>( \delta_{\text{mural}} )</td>
<td>7500 s</td>
</tr>
<tr>
<td>( \delta )</td>
<td>1E-4</td>
</tr>
<tr>
<td>integration time-step</td>
<td>1E-2 s</td>
</tr>
<tr>
<td>radial wall discretization</td>
<td>10</td>
</tr>
</tbody>
</table>
in that specific state, i.e. at the local levels of flow and pressure, etc.:

\[ \psi_{ss} = \sum x \psi_{ss,x} \]  

(2.5)

where \( x \) represents the different vasomotor mechanisms. In the present case, we only consider the reaction of the vascular wall to circumferential stress, i.e. the myogenic response, and hence \( \psi_{ss} = \psi_{myogenic} \).

Since time is required to change the contractile state of the SMC, the actual activation, \( \psi \), does not reach \( \psi_{ss} \) instantaneously, but rather approaches it at a certain rate. The process was modelled as a simple first-order process [19]:

\[ \frac{d\psi}{dt} = \frac{1}{\tau_{activation}} (\psi_{ss} - \psi). \]  

(2.6)

**Restoration of \( \psi_{habitual} \) through eutrophic remodelling:**

It is assumed that vessels exhibit remodelling responses in order to remain at \( \psi_{habitual} \) in the long run [19]. The remodelling response induced by changes in activation is eutrophic in nature; the same amount of wall material is restructured around a lumen of a different size [21]. Experimental studies suggest that a sustained increase in SMC activation is associated with IER [22–24], whereas outward eutrophic remodelling follows a sustained decrease in activation [25]. As earlier [19], this was formulated as a simple first-order process with the change in structural internal radius, \( \rho \), being:

\[ \frac{d\rho}{dt} = \frac{1}{\tau_{remodeling}} (\psi_{habitual} - \psi)\rho. \]  

(2.7)

Hence, if \( \psi > \psi_{habitual} \) structural radius will decrease and vice versa until \( \psi = \psi_{habitual} \). This process does not in itself elicit any change in the local trans-sectional area of the wall.

### 2.3. Average circumferential wall stress and the trophic response

In the present model, distinction is made between the habitual wall stress (\( \bar{S}_{habitual} \)) and the actual wall stress (\( \bar{S} \)), with the bar symbolizing the average of the circumferential stress component through the wall. In analogy with \( \psi_{habitual} \), it is assumed that \( \bar{S}_{habitual} \) represents a homeostatic point where vascular function as regards acute flow regulation is optimal. As an approximation for \( \bar{S}_{habitual} \), we use an estimate of the average circumferential wall stress as a function of vessel size given by Pries et al. [26]:

\[ \bar{S}_{habitual}(r) = \bar{S}_{experimental}(r) = kr_i^p, \]  

(2.8)

where it is assumed that the experimentally measured radius represents the active, pressurized, internal radius, i.e. the width of the blood cell column (constant values in table 1).

The actual average circumferential stress, \( \bar{S} \), in the wall is given by:

\[ \bar{S} = \frac{Pr_i}{r_o - r_i}. \]  

(2.9)

By rearranging the existing amount of wall material around another luminal radius, it is possible to bring \( \bar{S} \) back to \( \bar{S}_{habitual} \) following a permanent change, e.g. in pressure. Since \( \psi_{ss} \) is a function of \( \bar{S} \) (see description of the myogenic response below), equations (2.6) and (2.7) enables the realization of this structural rearrangement.

### 2.4. Changes in smooth muscle cell activation

For simplicity, only the vascular reaction to intravascular pressure is considered in the present model. The myogenic response is the intrinsic reaction of the SMC wall to the (circumferential) stress caused by the intravascular pressure head [27]. An increase in \( \bar{S} \) will cause an increase in SMC activation and a more pronounced constriction. The myogenic responsiveness depends on the specific vascular bed and arteriolar networks tend to have a myogenic response gradient such that a given vessel can operate in the physiological pressure range of that vessel [28]. Larger upstream arteriolar vessels operate over a broader range of pressures but seem to be less myogenically responsive than smaller arterioles [28, see §4]. A simple formulation of myogenic SMC activation in a given vessel therefore requires both normalization to the habitual stress level in that vessel and inclusion of a term, here \( f(\bar{S}) \), which acts to modify myogenic responsiveness depending on the position within the network:

\[ \psi_{ss} = \psi_{habitual} \left( \frac{\bar{S}}{\bar{S}_{habitual}} \right)^{f(\bar{S}_{habitual})}. \]  

(2.10)

\( f(\bar{S}_{habitual}) \) will determine the slope of the pressure–radius curve over the range of pressures where the myogenic response is operating. Specifically, \( f \) was given the form:

\[ f(\bar{S}_{habitual}) = 2 - \left( \frac{\bar{S}_{habitual}}{\kappa} \right) \]  

(2.11)

(constants in table 1). \( \psi_{ss} \) is constrained to the interval \( 0 \leq \psi_{ss} \leq 1 \). Should \( \psi_{ss} \) during a simulation attain a value \( <0 \) or \( >1 \) it is truncated to 0 or 1, respectively.

### 2.5. Network haemodynamics

A node is a junction of three vessels, i.e. a bifurcation point in the vascular tree. Assuming no significant flux of fluid across the vascular wall, the sum of the flows, \( Q \), entering and leaving any node equals zero (Kirchhoff’s law) so that [29]:

\[ \sum_j Q_j^o = \sum_j C_j^o \Delta P_j^o = 0, \]  

(2.12)

where \( Q_j^o \) is the flow, \( C_j^o \) is the vascular conductance and \( \Delta P_j^o \) is the pressure drop in \( j \)th vessel entering the \( n \)th node. As an approximation, flow is considered to be laminar throughout the network. As a further approximation, non-Newtonian properties of the blood are ignored and consequently the flow is assumed to obey Poiseuille’s law. With \( \mu \) and \( l \) being blood viscosity (table 1) and vessel length, respectively, vascular
The conductance of a given vessel can be calculated as:

\[ C = \frac{\pi r^4}{8l}. \]

### 2.6. Networks and initial conditions

Networks on which flow simulations were performed had in all cases a regularly bifurcating structure with an equal number of generations on each side of the central capillary bed (figure 1a, with generation number indicated above). To perform a simulation, two values were assigned to each vessel: vessel length \( l \) and structural internal radius \( r_i \). The values assigned were not specific for any particular vasculature but rather reflects the general structure of a bifurcating microvascular bed.

#### 2.6.1. Vessel length

With \( n \) being the generation number in question (cf. figure 1a), vessel length was assigned according to:

\[ l = k \lambda e^{\lambda n}, \]

where \( k \) and \( \lambda \) are constants (table 1). As a consequence, vessel length decreased in a uniform exponential fashion downstream along the network (figure 1b). A similar decrease, symmetric around the capillary bed, was imposed on the venous side. The smallest vessels, the capillaries, were assigned a length of 50 \( \mu \)m [30] as indicated in the middle of figure 1b (black circle). Once assigned, the vessel length remained constant.

The structural internal radius of the individual vessel was assigned in accordance with the Murray's Law for branching radii in the circulatory system. It states that the radius of the stem vessel relates to the radii of the branches as:

\[ r_i^{\text{stem}} = r_i^{\text{b}1} + r_i^{\text{b}2}, \]

where the exponent \( c \) is in the order of 3. With \( a \) denoting either the radius of the pre-capillary arterioles (\( a_{\text{arteriolar}} \), generation \( n = 1 \)) or the radius of the post capillary venoules (\( a_{\text{venoular}} \), generation \( n = -1 \)) and assuming symmetrical branching as regards vessel radius, the radius of any vessel of generation \( n \) is given by (figure 1c):

\[ r_i = a(2^{n-1})^{1/c}. \]

Note that the structural radius of a vessel may subsequently change owing to eutrophic remodelling.

Capillaries (shown in (a) as centrally placed, thin vessels) were assigned a radius of 5 \( \mu \)m (indicated in the middle of figure 1c), which remained fixed throughout each simulation. Hence, owing to the lack of an SMC coat, capillaries were assumed not to take part in tone-driven remodelling.

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Finally, the relative thickness of the wall, $\eta$, was assigned so as for every vessel in the network to have a level of stress corresponding to $S_{\text{habitual}}$ (cf. equation (2.8)). Specifically, every vessel was initially assigned an arbitrary value of $\eta$. The structural internal radius of every vessel in the pressurized network was then fixed at the value assigned using equation (2.16) (for this approximation, see appendix A). Hereafter, each vessel in the network exhibited a trophic response (hyper or hypotrophy) through a change in $\eta$:

$$\frac{d\eta}{dt} = \begin{cases} \frac{1}{1+\operatorname{trophic}} \left( \frac{S-S_{\text{habitual}}}{S_{\text{habitual}}-\bar{S}} \right), & \text{if } S_{\text{habitual}} \geq \bar{S} \\ \frac{1}{1-\operatorname{trophic}} \left( \frac{S-S_{\text{habitual}}}{S_{\text{habitual}}-\bar{S}} \right), & \text{if } \bar{S} > S_{\text{habitual}} \end{cases} \tag{2.17}$$

leading to a change in the trans-sectional area, $A$, of the vascular wall. Hence, if $\bar{S} > S_{\text{habitual}}$, the wall will increase slowly in relative thickness and vice versa. With $\bar{S} = S_{\text{habitual}}$ for all vessels in the network, no further trophic responses took place in a given simulation. The splitting of equation (2.17) in two branches allows $\bar{S}$ to relax continuously towards $S_{\text{habitual}}$ without numerical instability by restricting the last term in each branch to the interval $[0:1]$.

2.7. Perturbation

To mimic the functional and topological heterogeneity found in networks in vivo, a perturbation on the structural parameters was introduced by perturbing randomly ($\pm 10\%$) the value for the structural radius and vessel length of each generation after the initial assignment of values (cf. equations (2.14) and (2.16), also see appendix A).

2.8. Computational methods and programme flow

With defined arterial inlet pressure, $P_{\text{in}}$, and venous outlet pressure, $P_{\text{out}}$, node pressures were calculated throughout the network by solving a linear system based on equations (2.12) and (2.13). Subsequently, the average transmural pressure, $P$ (i.e. the average pressure of the two nodes connected by a given vessel), and pressure decline, $\Delta P$, was calculated in all vessels in the network.

In the case of the eutrophic remodelling process, node pressures were recalculated alternately with the new radii and new values for the relative wall thickness. The latter changes along with changes in $\rho_i$ when wall transsectional area is preserved. During each round of iteration, the active internal radius of each vessel was found by solving (iteratively) the expression:

$$\bar{P} - P = 0,$$

where $\bar{P}$ is the inwardly directed pressure generated by the vascular wall (cf. equation (2.4)) and $P$ is the average transmural pressure as defined above.

2.8.1. Convergence criteria

Convergence was evaluated by comparing values of selected variables between consecutive iteration rounds. With $\delta$ being the relative change in the value of a given variable $\chi$ between iteration round $n$ and $n+1$, the criterion was:

$$\delta = \left| \frac{X_{n+1} - X_n}{X_n} \right| < 10^{-4}. \tag{2.18}$$

A simulation was considered to have settled when this criterion was fulfilled simultaneously for each vessel and node in the network. The variables evaluated were: $\tau_i$, $\rho_i$, $\eta$, $\bar{S}$ and $P_{\text{node}}$.

In addition, it was a criterion in simulations involving eutrophic remodelling that at termination all vessels should be at their habitual levels of activation and stress, i.e. that for all vessels:

$$\delta_{\text{habitual}} = \left| \frac{\phi - 1}{\phi_{\text{habitual}}} \right| < 10^{-3} \quad \text{and} \quad \delta_{\text{habitual}} = \left| \frac{\bar{S} - S_{\text{habitual}}}{S_{\text{habitual}}} - 1 \right| < 10^{-3}. \tag{2.19}$$

3. RESULTS

3.1. Basic model properties

Figure 2a shows the basic myogenic properties for vessels with different size and, hence, different levels of $S_{\text{habitual}}$ (cf. equation (2.8)). In each case, vessel size is given as $r_F$ (active radius normalized to the structural radius); hence, all curves start at 1.0 and the passive curve (dashed) is the same in all cases. All three active vessels have a relative wall thickness, $\eta$, of 1.1. As seen from the figure, a lower $S_{\text{habitual}}$ is associated with a steeper negative slope and autoregulation over a more narrow range. Figure 2b shows how the myogenic response changes with $\eta$. An increase in $\eta$ (which is a consequence of IER), enables the vessel to autoregulate to a higher pressure level. In both figures, the sharp break point at the right end of each active curve is caused by the vessel reaching maximum activation ($\phi = 1$). A further increase in pressure forces the vessel to dilate despite being maximally activated.

Figure 3 shows the short- and long-term development of an arteriole inside the network (generation 4), following an abrupt 2 kPa rise in network inlet pressure (with the network outlet pressure maintained constant). The left part of the figure (fast time-scale) shows the early development, i.e. the consequences of the acute myogenic response, whereas the right part (slow time-scale) illustrates the consequences of the slow IER response. In both cases, time is given relative to the time constant of the given process (table 1). Figure 3a shows the transmural pressure in the vessel. As the vessel is located inside the network, the initial pressure is lower and the pressure step smaller than that of the inlet vessel. As upstream vessels develop a myogenic response, the effect of the pressure increase is partially offset. In the long run (right), the effect of the pressure increase is further attenuated by IER of upstream vessels. Figure 3b shows the development of the structural (dashed line) and active (solid line) radius. Initially, the vessel reacts by developing an acute myogenic response, with the structural radius remaining unaffected. In the long run, IER causes a
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adaption IER to a chronic increase in the network inlet pressure of 3 kPa. At this point, all vessels have here returned to their habitual levels of stress and activation. Note the more pronounced remodelling in the larger arterioles. Figure 4b shows the average pressure in each generation, with the grey upper curve representing the hypertensive network (pressure distribution as a function of vessel size is shown in figure 14 in appendix A [31]). The excess pressure is, owing to IER, effectively dissipated in the arteriolar bed. Independent of the magnitude of the pressure elevation, the process hereby tends to shield capillaries and venous side vessels from the increased pressure.

Figure 5a shows how flow is acutely regulated in a network of vessels, which has adapted structurally to an arterial inlet pressure of 5 kPa. After adaptation, only the myogenic response to changes in network perfusion pressure was considered (i.e. no remodelling). Venous outlet pressure was maintained constant at 2 kPa. For a given perfusion pressure, the dashed curve shows the total flow in the relaxed network, whereas the full curve is for the myogenically active network. Note the ability of the active network to keep the flow relatively constant over a range of pressures. The relative distance between the curves increases as the perfusion pressure is raised owing to increasing myogenic constriction in the active network. Hence, as shown in figure 5b, the VFR, defined as the ratio between the flow in the passive (dashed line) and the active (solid line) state, is larger if measured at a higher perfusion pressure.

Figure 6 shows the consequences of IER for the VFR. As before, the network initially adapted at 5 kPa inlet pressure. Perfusion pressure was hereafter shifted (up or down) and at each pressure level, the network re-adapted structurally through eutrophic remodelling until φ and S had reached $\phi_{\text{habitual}}$ and $S_{\text{habitual}}$, respectively, in all vessels simultaneously. For pressures below 5 kPa, the vessels will display outward remodelling, whereas remodelling will be inward for pressures above 5 kPa. Hereafter, the network flow was calculated (figure 6a) in both the passive (dashed line) and the active (full line) state and their ratio, i.e. the VFR, was found (figure 6b). Hence, the full line of figure 6a represents a ‘structural autoregulation’ enabling the network to maintain a constant flow over a wide range of pressures with a maintained level of stress and activation within each vessel in the network. Note also when compared with figure 5, the structural autoregulation response enables the VFR to remain fairly constant under a quadrupling of the perfusion pressure.

The habitual level of network tone strongly influences the VFR. This is illustrated in figure 7 which shows the VFR for networks all adapted to 5 kPa inlet pressure but under varying levels of intrinsic tone ($\phi_{\text{habitual}}$). As expected, networks having a high level of intrinsic tone have a much larger relaxation potential and hence a larger VFR.

4. DISCUSSION

The presence of pervasive changes in vascular structure in longstanding hypertension has been known for more...
than a century (historical aspects reviewed in [32]). In mesenteric arterioles, Short [33] noted early that these changes include a narrowing of the lumen and a thickening of the arterial wall but without any change in the wall trans-sectional area. Similar changes have since been found repeatedly [21,34] and the concept that structural vascular changes in essential hypertension tend to be eutrophic in nature now seem to be well established [9].

Figure 3. Acute and chronic responses to a sustained pressure increase (see text for details). Left side of the figure shows the acute response. Following a step increase in pressure, the vessel contracts to a lower radius, which is associated with an increase in $S$ and $\phi$. The structural remodelling response (right) reduces the structural radius (b, dashed) and brings $S$ and $\phi$ back to their habitual levels (indicated by dashed lines).

Figure 4. (a) Distribution of changes in radii in an arteriolar network following an increase in perfusion pressure. Generations are represented as equally high columns with the arterial inlet vessel to the far left. The normotensive network is represented in black. Grey columns represent the network after structural adaptation to a pressure increase of 3 kPa. (b) Network pressure distribution corresponding to the two situations in (a) with the hypertensive network shown in grey. Note how the inward remodelling process increases pressure dissipation in the network.
The smaller lumen and thicker wall following IER allows for maintenance of normotensive stress levels under an elevated transmural pressure (cf. equation (2.9)). The consequences of IER for the VFR are, however, not intuitively clear. On the one hand, the increased network resistance following IER may potentially impede perfusion during peak tissue activity. IER is, on the other hand, counterbalanced by the increased arterio-venous pressure difference and the increase in local transmural pressure acting to distend the vessel in the relaxed state. Both of the latter effects will, in principle, act to increase flow in the relaxed state and hence increase VFR.

As presented in §3, we found in the present simulations that vascular networks that had adapted to various levels of hypertension through IER consistently did not show any reduction in VFR. The simulations therefore suggest that the mechanism causing a reduced VFR should be sought elsewhere.

We found in the present simulations that structural adaptation through eutrophic remodelling (both inward and outward) is associated with a constant network flow over a broad range of pressures (cf. figure 6a, solid line). This effect is independent of the habitual level of tone in the network and is found also if the tone level is non-uniform through the network (see figures 9 and 10 in appendix A). Along the same line, we previously performed flow simulations in networks consisting of passive elastic vessels only, i.e. without tone, and found also here that eutrophic remodelling was associated with an invariant flow [29]. A maintained flow in the present model is not a consequence of myogenic autoregulation but is rather caused by the change in vascular structure. As the remodelling process ceases, all vessels in the network have returned to the same degree of activation as they had before the increase in perfusion pressure. This is not the case under sustained myogenic contraction (cf. figure 3d).

The results of the present study show that eutrophic remodelling leads to an unaltered network flow despite an increased pressure. This is in accordance with the observation of IER as the dominant mode of

![Figure 5](http://rsfs.royalsocietypublishing.org/)

Figure 5. (a) Myogenic network response: passive (dashed line) and myogenically active (solid line) flow in a network adapted to an inlet pressure of 5 kPa. Note the pronounced autoregulatory response. (b) The VFR (calculated on the basis of (a)) depends strongly on the pressure at which it is measured in a myogenically active network.

![Figure 6](http://rsfs.royalsocietypublishing.org/)

Figure 6. (a) Flow in a fully relaxed network (dashed curve) and in a network with tone (solid curve) adapted under various perfusion pressures. Flow is calculated at the pressure at which adaptation took place. Note the strong structural autoregulatory response caused by eutrophic remodelling. (b) VFR calculated on the basis of (a) remains fairly constant over a broad range of pressures.

![Figure 7](http://rsfs.royalsocietypublishing.org/)

Figure 7. Dependency of VFR on the level of habitual activation at which the network has adapted structurally. VFR increases with increasing habitual activation in the network owing to the increasing potential for relaxation.
remodelling in essential hypertension. The metabolic need of the tissues in hypertensive individuals is unlikely to differ from that of normotensives, and this is reflected in the observation that cardiac output in established hypertension is the same as in normotension [8]. Eutrophic remodelling therefore seems to represent a mechanism of structural autoregulation that sets the frame for long-term maintenance of the necessary flow, independent of the prevailing arterial pressure level. More surprising perhaps is that eutrophic remodelling and invariant network flow appears to coincide with the maintenance of homeostasis in the vascular wall as regards circumferential wall stress, SMC activation and SMC length (expressed as \( r_p \), not shown). By ensuring a maintained homeostasis in the vascular wall, eutrophic remodelling hence provides an optimal basis for activation-based, acute flow autoregulation, again independent of the prevailing pressure level.

The present results indicate that IER affects the VFR only to a limited degree. We find that, if anything, VFR tends to increase slightly (cf. figure 6b) with increasing IER. We tested this conclusion under a variety of circumstances (cf. appendix A) and uniformly came to that conclusion. As the structural autoregulation response enables the network to keep the flow practically constant in the active state, the slight increase in VFR is caused by an increase in flow in the vasodilated state (figure 6a). As regards the experimental circumstances, when measuring the VFR it is worth noting, as previously pointed out [1], the strong dependence on the perfusion pressure (figure 5b), and also that the situation in the heart is special owing to compression of the myocardium during the systole [1]. The physiologically most relevant picture of the organ VFR is found when measured at, or in vicinity of, the normal systemic blood pressure. As also intuitively clear, the vascular reserve will depend strongly on the intrinsic level of tone in a given tissue (figure 7). Blood vessels in, e.g., the clear parts of the mesentery have little tone in vivo; consequently the VFR of such areas is expected to be very low. Other vascular beds such as those in striated muscle tissue or brain hold a substantial level of intrinsic tone [35,36] and hence are expected to have a much higher VFR.

The question remains which factors other than IER could underlie the hypertensive reduction in VFR. To that end, hypertensive microvascular rarefaction is a candidate. Under resting conditions, only a certain fraction of the capillaries carries flow. As tissue need is increased, this fraction increases, a phenomenon known as capillary recruitment [37]. Therefore, a moderate increase in tissue need may not unveil a reduced vascular reserve as long as there is a sufficient pool of unperfused capillaries to recruit from. Only as the metabolic need becomes so high that all capillaries are recruited may a reduced number of capillaries become a limiting factor for a further increase in flow.

The concept of VFR is in principle applicable to any tissue in both normo- and hypertension. It is worth noting that in hypertension, the situation is again special for the heart. In order to generate an increased systemic blood pressure, the heart of the hypertensive typically shows some degree of left ventricular hypertrophy [3,38]. In this situation, myocyte hypertrophy may reduce microvascular density by causing an increase in the inter-vascular distance. Such ‘relative’ rarefaction may, as normal rarefaction, only become evident when the vascular bed is stressed by an increased tissue demand. In contrast to normal rarefaction, however, the VFR would be expected to normalize in parallel with regression of the ventricular hypertrophy under antihypertensive treatment, as this would result in an increase in micro-vessel density. Indeed, there are indications that this may happen in some cases [39,40].

### 4.1. Critique of the model

The present model is a simplified representation, regarding both structure and function, of a bifurcating microcirculatory network. The network does not represent the microvasculature of any specific tissue; rather, it is aimed at representing features common to many vascular beds in the body. Possible implications of model assumptions and simplifications are discussed in the following.

In essential hypertension, constituting 90–95% of all cases of human arterial hypertension [17], a large number of studies from a variety of tissues have collectively shown that the dominant mode of remodelling is eutrophic. Clearly, this is an average consideration which may encompass that some vessels may have undergone some degree of hyper- or hypotrophy. Measuring structural parameters on the same vessel before and after the onset of hypertension is not possible; comparison is therefore typically made between resistance vessels from normotensive and hypertensive individuals. On average, such measurements show IER as the dominating mode of remodelling. In specific secondary forms of hypertension caused by, e.g. primary aldosteronism or kidney artery stenosis, the dominant mode of remodelling may be hypertrophic rather than eutrophic [41] in which case the present model does not apply.

In simulations of hyper- or hypotension, venous outlet pressure was kept at the normotensive level, as in hypertensive networks in vivo, the vast majority of the increase in perfusion pressure is dissipated in arterial side vessels [8,42]. As shown in figure 4, IER is indeed a central player per se in the increased arteriolar pressure dissipation in hypertension, and hence in keeping the capillary and venular pressures at near-normotensive levels.

The present simulations of hypertension were performed assuming no changes in the biophysical properties of the wall material when compared with the normotensive state. The only change in properties of the individual vessel following IER is a small shift in the myogenic properties (cf. equation (2.11)) that stems from the change in structural radius and hence in \( S_{\text{habitual}} \). It is indeed a central issue if structural changes in hypertension are associated with changes in the biophysical properties of the arteriolar SMC and/or of the passive elastic components of the wall. Taken together, the evidence for changes in the
properties of the arteriolar SMC or arteriolar connective tissue in longstanding hypertension does not appear to be very strong at present [9,34,43] although changes have been detected in some cases [44]. As a consequence, we have not introduced any such changes along with the eutrophic remodelling process.

For simplicity, we also assumed that the biophysical properties of the wall material are uniform throughout the network. This is an approximation since the proportion of the vessel taken up by the media falls with the vessel size at least in the arterial microcirculation [45]. This approximation is however compensated for by the introduction of variable functional properties, i.e. variable myogenic responsiveness and variable $S_{\text{habital}}$ through the network.

In the present simulations, we have assumed that the habitual level of tone is similar in the normotensive state and in established hypertension. It has indeed been a matter of debate whether there is an increase in tone (i.e. in SMC activation) in the vascular wall in hypertension. It appears that, at least in the initial phases of hypertension, there may be an increased sympathetic outflow [46], which can give rise to an increased SMC activation. As hypertension becomes established, however, the increase in sympathetic outflow seems to cease [17] and there is little evidence for a general increase in vascular tone in established hypertension [9]. As a consequence, we have assumed in the present simulations that the hypertensive remodelling response is associated with the re-establishment of a normotensive level of tone.

For simplicity, it was assumed that the habitual level of tone was uniform throughout the network. This may not be the case in vivo where there is a tendency for the smaller arteriolar vessels to have a stronger myogenic reactivity [28], which may translate into a somewhat higher level of basal tone. We therefore performed test simulations in networks having a gradient in the habitual tone level, with an increase from the larger towards the smaller vessels on both sides of the capillary bed or on the arterial side alone (cf. figure 9 in appendix A). As this did not influence the conclusions, we retained the simplest approach and kept habitual tone level uniform.

In the present model, equations (2.10) and (2.11) describe a myogenic response gradient along the vascular tree similar to that of rat cremaster microcirculation [28], where myogenic reactivity increases downstream along the arteriolar tree (except in the smallest arterioles). In other tissues though, this gradient may have different characteristics [47]. Simulations were therefore performed in networks with other functional forms of the myogenic response gradient. As seen from figure 13 of appendix A, this did not change the behaviour of the network as regards structural autoregulation and VFR.

For simplicity, $\phi_{\text{os}}$ was assumed to be governed by the myogenic response alone (cf. equation (2.5)). In reality, $\phi_{\text{os}}$ (and $S_{\text{habital}}$) will represent the sum of constricting and dilating vasomotor mechanisms. These mechanisms originate from both within the tissue, e.g. the myogenic response, flow-induced dilatation, metabolic regulation and conducted responses, and from outside, e.g. nervous control and circulating hormones. The contribution from each mechanism shows substantial heterogeneity both among different vascular beds and longitudinally along the vascular tree of a given bed [48,49]. It is the collective action of these mechanisms that give rise to the active flow-autoregulation curve of a given tissue. Cornelissen et al. [47,50] showed in models of the coronary microcirculation that although the myogenic response alone can reproduce coronary autoregulation curves, inclusion of additional acute vasomotor mechanisms [51] known to act in that vascular bed (i.e. balanced flow-dependent dilatation and metabolic regulation) allows for a more realistic, uniform distribution of tone through the network. The corresponding curve shown in figure 5 includes only the action of the myogenic response; it can hence be considered only as an approximation and should not be taken as representative for the autoregulation curve of any specific tissue. Flow-induced dilatation plays a prominent role in many vascular beds [49,52] providing a tonic dilating influence on the vascular wall. In that case, the underlying contribution from the myogenic mechanism to $\phi_{\text{os}}$ may be larger than the apparent $\phi_{\text{os}}$ to compensate for flow-dependent deactivation. Despite these simplifications, figure 5 shows, in agreement with the conclusions of Cornelissen et al. [47,50], that the myogenic component may contribute substantially to acute flow autoregulation. More importantly, the integration with structural autoregulation, being a consequence of eutrophic remodelling (figure 6), allows for an invariant flow in the habitual state of the network. Eutrophic remodelling hence provides a basis for curves similar to that of figure 5 independently of the prevailing level of perfusion pressure.

In the present model, we have introduced a relation between vessel size and the homeostatic level of circumferential stress [26]. It is a general observation that the wall-to-lumen ratio decreases as the vessels become larger [53]. According to equation (2.9), this will tend to increase the local circumferential wall stress, an effect which, on the arterial side, is further enhanced by the higher transmural pressure in larger vessels. To the best of our knowledge, the physiological mechanisms leading to this relation is not known, but the resulting network structure become unrealistic if not taken into account. The specific relation applied in the simulations was derived from measurements on a variety of different networks including mesenteric, cardiac and cerebral vessels [26]. The relation may be different for vessels from other vascular beds. As shown in appendix A (figure 12) however, the conclusions of the model do not depend critically on the exact position or slope of this curve.

As a simplification, the present model does not take into account the effect of extravascular forces although these are known to affect the flow (e.g. in the coronary microcirculation [54,55]). The microvasculature is adherent to the tissue into which it is embedded. Stretch or compression of the tissue may therefore change the dimensions and properties of the individual vessel [56]. Moreover, contraction of skeletal or heart muscle tissue changes the interstitial pressure. In turn, this may change the transmural pressure gradient and hence the level of myogenic tone. Along the same line,
reduction or complete stoppage of flow during contraction may profoundly affect the input to the SMC wall from shear stress-dependent mechanisms. Hence, the effects of extravascular forces are complex [54,55,57,58] and a thorough analysis of this aspect is beyond the scope of the present model. However, it is probably safe to assume that in most tissues, the interstitial pressure is much lower than the intravascular pressure the vast majority of the time.

5. PERSPECTIVES AND CONCLUSION

The present model study indicates that IER may not *per se* reduce VFR. In some situations this may however be the case. One such situation could be at the onset of antihypertensive treatment, for instance with vaso-relaxing compounds. Although in the long run such treatment tends to normalize vascular structure as regards remodelling [59,60], the initial phases of the treatment will be characterized by perfusion of a hypertensively adapted microcirculation at a normalized perfusion pressure. In this situation, IER is likely to contribute to a reduced VFR.

At present it is not clear how the simulated result can be assessed experimentally. Whereas such verification is definitely needed, the complex structure of microvascular networks poses a substantial problem. Although possibly difficult, one could consider networks such as those from the *pia mater* that can be dissected out [61] and investigated *in vitro*. In this case, it would be possible to compare hyper- and normotentive networks.

In conclusion, simulations performed on networks with varying structure and remodelled under varying levels of arterial perfusion pressures, indicated that IER does not *per se* reduce VFR. We suggest that the explanation for the reduced VFR in hypertension may be found elsewhere, for instance in hypertensive microvascular rarefaction.

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APPENDIX A

The appendix summarizes the sensitivity of the simulated results to changes in selected parameters. As a ‘standard situation’, the simulation shown in figure 6 was chosen. The shape of the curves for the structural autoregulatory response and the VFR over a range of perfusion pressures were compared with similar curves produced under a specified parameter change.

As shown in figure 8, the VFR does not depend on the number of generations included in networks with uniform activation. The larger the network becomes, the more flow it can carry. This is the case both in the active and in the passive state and hence the VFR, being a ratio, remains constant.

The level of habitual activation was for simplicity set to a uniform value throughout the network. *In vivo*, however, the level of tone tend to increase downstream along the arteriolar tree. The consequence for the VFR of such a non-uniform distribution of \( c_{\text{habitual}} \) is shown in figure 9. Habitual activation was (arbitrarily) set to 0.7 in the pre-capillary vessels and declined by 0.1 for each upstream generation. The network showed a pronounced structural autoregulatory response and a uniform VFR over a broad pressure range, similar to that of figure 6.

Figure 10 shows the structural autoregulatory response and the VFR for networks adapted under habitual levels of tone corresponding to \( c_{\text{habitual}} = 0.85 \), \( c_{\text{habitual}} = 0.5 \) and \( c_{\text{habitual}} = 0.05 \). As shown, they all exhibit a similar structural autoregulatory response. For very high levels of intrinsic activation, there is a substantial rise in VFR with pressure.

In figure 11, the degree of perturbation of the structural parameters \( l \) and initial \( p_i \) was varied. As it is
apparent from the figure, this does not change the general appearance of the structural autoregulation curve or of the curve for the VFR.

Figure 12(b,c) shows the consequences for the VFR and structural autoregulation in using the different functional forms of (a) (same curve legend as in (a)).

Figure 13 shows the consequences of applying different functional forms for the relation between circumferential wall stress and activation through the network. Consequences for VFR and structural autoregulation. Grey lines: flat myogenic response in each vessel in the network. Dashed black lines: higher stress sensitivity in larger vessels.

response around the physiological pressure level in each vessel which was simulated using the relation $\psi_{\text{m}} = \psi_{\text{habitual}} \times (\overline{S}/\overline{S}_{\text{habitual}})$. The dashed black lines

\begin{align*}
\sigma_{\text{habitual}}(r) &= k_r \rho_{\text{habitual}}^{1.5} + 8E4 \\
\sigma_{\text{habitual}}(r) &= k_r \rho_{\text{habitual}}^{1.4} + 2E4 \\
\sigma_{\text{habitual}}(r) &= k_r \rho_{\text{habitual}}^{1.624}
\end{align*}
represent a relative increase in the sensitivity to circumferential wall stress in larger vessels which was simulated using:

\[ \psi_s = \psi_{\text{habitual}} \left( \frac{S}{S_{\text{habitual}}} \right) f \left( \frac{S_{\text{habitual}}}{\kappa} \right) \]

where \( f \left( \frac{S_{\text{habitual}}}{\kappa} \right) = 1 + \left( \frac{S_{\text{habitual}}}{\kappa} \right) \).

As seen from the panels, these changes did not affect the ability of the network to autoregulate through structural adaptation.

Finally, figure 14 shows the arterial pressure as a function of vessel diameter (for comparability with the experimental data, pressure and vessel size are given in mmHg and diameter, respectively). Initially, the network adapted structurally to an arterial inlet pressure of 37.5 mmHg (5 kPa). Hereafter, the network was exposed to lower or higher pressures as indicated in the figure. The network was then allowed to adapt structurally through eutrophic remodelling.

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Flow reserve in hypertension

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