Spontaneous oscillations in a model for active control of microvessel diameters

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A new theory is presented for the origin of spontaneous oscillations in blood vessel diameters that are observed experimentally in the microcirculation. These oscillations, known as vasomotion, involve time-varying contractions of the vascular smooth muscle in the walls of arterioles. It is shown that such oscillations can arise as a result of interactions between the mechanics of the vessel wall and the dynamics of the active contraction of smooth muscle cells in response to circumferential tension in the wall. A theoretical model is developed in which the diameter and the degree of activation in a vessel are dynamic variables. The model includes effects of wall shear stress and oxygen-dependent metabolic signals on smooth muscle activation and is applied to a single vessel and to simplified network structures. The model equations predict limit cycle oscillations for certain ranges of parameters such as wall shear stress, arterial pressure and oxygen consumption rate. Predicted characteristics of the oscillations, including their sensitivity to arterial pressure, are consistent with experimental observations.

Keywords: vasomotion; blood flow regulation; vascular tone; smooth muscle mechanics.

1. Introduction

1.1 *The phenomenon of vasomotion*

Spontaneous rhythmic oscillations in vessel diameter are known as vasomotion and occur primarily in small arteries and arterioles (Bertuglia *et al.*, 1996; Colantuoni *et al.*, 1984, 1990; Jackson *et al.*, 1991; Meyer *et al.*, 1988; Meyer & Intaglietta, 1987; Schmidt *et al.*, 1993; Slaaf *et al.*, 1987; Wiedeman, 1955). Generally, the frequencies of the oscillations are in the range $3\text{--}30\text{ min}^{-1}$ and the peak–peak amplitudes are large, 50–100% or more of the mean diameter (Tuma *et al.*, 2008). Peak–peak amplitude is defined here as the difference between the maximal and the minimal diameter value of an oscillating vessel. Vasomotion has been observed both *in vivo* and *in vitro*, but its occurrence and intensity are unpredictable. Wiedeman (1955) noted spontaneous contractility in the arterioles of a bat wing. The oscillations varied in frequency and duration and appeared independent of other vessels. Colantuoni *et al.* (1984) studied vasomotion in several different vessel types in a hamster skin fold window preparation. They showed that the oscillations were independent of the nervous system and that the fundamental

frequency and amplitude of the oscillations were related to vessel size. Meyer & Intaglietta (1987) showed that oscillations of parent transverse arterioles were synchronized with oscillations in terminal arterioles, suggesting that diameter oscillations in arterioles located in close proximity to one another are coordinated. In further studies, reducing perfusion pressure to 30–50 mmHg (4–6.7 kPa) was found to eliminate vasomotion in transverse and terminal arterioles (Meyer *et al.*, 1988). Vasomotion reappeared in these vessels when pressure was increased and stabilized at 75 mmHg (10 kPa). Similarly, Slaaf *et al.* (1987) found that gradual reduction in arterial pressure resulted in abrupt disappearance of vasomotion.

Several physiological effects of arteriolar vasomotion have been hypothesized (Secomb *et al.*, 1989). It causes fluctuations in the amount of blood flow that reaches capillaries and may reduce the occurrence of regional hypoxia in resting muscle (Clark *et al.*, 2008; Segal, 2008). Vasomotion may lead to improved blood flow and oxygenation to tissues that are adjacent to muscle (Nilsson & Aalkjaer, 2003). In small arteries and arterioles, vasomotion yields enhanced filtration through the vessel wall and lymphatic drainage (Parthimos *et al.*, 1999; Stergiopoulos *et al.*, 1998). Vasomotion ceases in pathological states such as hemorrhagic shock (Colantuoni *et al.*, 1985) but can help to improve perfusion once flow is restored in the system (Palumbo, 1998). Ursino *et al.* (1998) predicted that vasomotion may influence the regulatory capability of the microcirculation. These observations suggest that the effects of vasomotion on vessel diameter and tissue perfusion should be considered when analysing blood flow in the microcirculation and its regulation.

The coordinated contraction of smooth muscle cells in the vessel wall is achieved through electrical communication and changes in membrane potential, likely involving Ca^{2+} or K^{+} fluxes through voltage-gated channels (Nilsson & Aalkjaer, 2003). In addition, oscillations in adenosine triphosphate (ATP) may lead to oscillations in Na^{+} pump activity in membrane potential (Nilsson & Aalkjaer, 2003). Some studies have established a role for the sarcoplasmic reticulum, in which waves of released Ca^{2+} cause a rhythmic depolarization and result in synchronized contraction of vessel wall smooth muscle cells (Nilsson & Aalkjaer, 2003). Nitric oxide may also play a role in enhancing vasomotion (Gustafsson & Nilsson, 1993a).

1.2 Previous models

Theoretical models have been used to predict the conditions under which vasomotion may occur and to investigate potential mechanisms. Parthimos *et al.* (1999) studied vasomotion at the cellular level by defining the ion transport systems that regulate vascular tone. In particular, the non-linear interaction of intracellular and membrane oscillators that depend on the cyclic release and influx of Ca^{2+} was modelled, and irregular rhythmic behaviour was predicted. In a model developed by Achakri *et al.* (1994), arterial oscillations were assumed to result from the mechanisms governing vascular smooth muscle (VSM) behaviour. The model equations define changes in the arterial circumferential stretch ratio and the concentration of Ca^{2+} ions within smooth muscle cells. Ca^{2+} concentration is assumed to depend on the arterial pressure and shear stress acting on the endothelium. According to the model, inflow, resistance and artery length must fall within a range of critical values for oscillations to develop. Ursino *et al.* (1998) developed a model in which the level of smooth muscle contraction depends on the wall tension, the rate of change of wall tension and on the blood flow rate. According to this model, the appearance and characteristics of vasomotion are sensitive to the assumed mechanisms and parameters in the system. Vasomotion was seen to result in significant differences in perfusion and flow regulation. Gonzalez-Fernandez & Ermentrout (1994) included ionic transport, cell-membrane potential, muscle contraction of VSM cells and mechanics of the vessel wall in a model for vasomotion. The model

predicts that the interaction of Ca^{2+} and K^{+} mediated by voltage-gated channels in addition to changes in transmural pressure can lead to oscillatory behaviour.

1.3 Current investigation

The present study is based on a previous theoretical model for the regulation of blood flow in the circulation (Arciero *et al.*, 2008; Carlson *et al.*, 2008) in which the degree of activation (tone) of smooth muscle is assumed to depend on responses to several factors. An increase in intravascular pressure, and thus wall tension, results in arteriolar constriction (myogenic response). Increased luminal wall shear stress causes arteriolar dilation (shear-dependent response). Information about changes in metabolic status sensed at downstream locations is transferred upstream along vessel walls and initiates changes in arteriolar diameter (conducted response). The response of smooth muscle tone to changes in these factors is assumed to be governed by a first-order differential equation with a relatively long response time to represent the dynamics of force generation within smooth muscle. Changes in vessel diameter are also governed by a first-order differential equation, with a relatively short-time constant reflecting the viscoelastic properties of the vessel wall. For certain ranges of parameters, the model equations do not have stable steady-state solutions but instead give rise to oscillations in vessel tone and diameter. This finding suggests a novel mechanism for vasomotion. The conditions of pressure and shear stress for which the model leads to vasomotion are examined for a single isolated vessel and for simple networks.

2. Methods

2.1 Model formulation

The theoretical model is based on a description of the length–tension characteristics of vessel walls containing VSM (Arciero *et al.*, 2008; Carlson *et al.*, 2008; Carlson & Secomb, 2005). Tension, T_{total} , generated in the wall is represented as the sum of a passive component, T_{pass} , and an active component, expressed as the product of the maximal active tension generated by the VSM cells, $T_{\text{act}}^{\text{max}}$, and the degree of VSM activation or tone, A :

$$T_{\text{total}} = T_{\text{pass}} + AT_{\text{act}}^{\text{max}}, \quad (2.1)$$

where T_{pass} and $T_{\text{act}}^{\text{max}}$ are functions of diameter D :

$$T_{\text{pass}} = C_{\text{pass}} \exp \left[C'_{\text{pass}} \left(\frac{D}{D_0} - 1 \right) \right], \quad (2.2)$$

$$T_{\text{act}}^{\text{max}} = C_{\text{act}} \exp \left[- \left(\frac{D/D_0 - C'_{\text{act}}}{C''_{\text{act}}} \right)^2 \right]. \quad (2.3)$$

As defined in Carlson & Secomb (2005) and Carlson *et al.* (2008), the passive tension is assumed to be an exponential function of diameter since tension increases rapidly with increasing circumferential stretch. D_0 is the passive diameter of the vessel at an intraluminal pressure of 100 mmHg (13.33 kPa), C_{pass} is the passive tension at D_0 and C'_{pass} determines the steepness of the curve and was fit to experimental data. The total maximal active tension is described using a Gaussian function of diameter, representing the property of smooth muscle that active tension is highest at a specific muscle length and declines at

larger and smaller lengths. C_{act} , C'_{act} and C''_{act} represent the peak magnitude, peak location and curve width of the Gaussian.

Activation varies between 0 and 1. Under steady-state conditions, it is assumed to take a value, A_{total} , that has a sigmoidal dependence on a stimulus, S_{tone} , representing the combined effect of various response mechanisms:

$$A_{\text{total}} = \frac{1}{1 + \exp(-S_{\text{tone}})}, \quad (2.4)$$

where

$$S_{\text{tone}} = C_{\text{myo}}T - C_{\text{shear}}\tau - C_{\text{meta}}S_{\text{CR}} + C''_{\text{tone}}. \quad (2.5)$$

The first term gives the myogenic response, where $T = PD/2$ is the tension in the wall resulting from intravascular pressure P according to the law of Laplace in the thin-wall approximation. The rationale for representing myogenic activation as a function of tension rather than stress was discussed by Carlson & Secomb (2005). The second term gives the shear-dependent response, where τ is the wall shear stress resulting from blood flow. The third term represents a metabolic response, where S_{CR} is a signal dependent on downstream metabolic conditions that is propagated upstream by conducted responses along vessel walls, as described in Arciero *et al.* (2008). Finally, C''_{tone} is a constant. In most of the simulations presented here, a fixed metabolic signal is assumed, and so (2.5) is replaced by the simpler form

$$S_{\text{tone}} = C_{\text{myo}}T - C_{\text{shear}}\tau + C'_{\text{tone}}, \quad (2.6)$$

where C'_{tone} is a constant. The parameter values in (2.6) were fit to pressure and flow data as described in Arciero *et al.* (2008), Carlson *et al.* (2008), and the numerical values are restated in Table 1.

Under non-steady conditions, the activation A is assumed to approach A_{total} according to a first-order equation with a time constant τ_a , which reflects the dynamics of force generation within the VSM:

$$\frac{dA}{dt} = \frac{1}{\tau_a}(A_{\text{total}} - A). \quad (2.7)$$

Similarly, the diameter is assumed to vary with time according to the difference between the tension T resulting from intravascular pressure and the generated tension T_{total} :

$$\frac{dD}{dt} = \frac{1}{\tau_d} \frac{D_c}{T_c}(T - T_{\text{total}}), \quad (2.8)$$

where D_c and T_c are reference values of diameter and tension. The time scale τ_d is determined by the viscoelastic properties of the vessel wall and is much less than τ_a (Falcone *et al.*, 1991). The time constants are difficult to estimate accurately from experimental data. Here, the values $\tau_d = 1$ s and $\tau_a = 60$ s are used and effects of changing the time constants are examined.

Substituting the expressions for T , T_{pass} , $T_{\text{act}}^{\text{max}}$ and S_{tone} into the above equations gives the following system:

$$\frac{dD}{dt} = \frac{1}{\tau_d} \frac{D_c}{T_c}(F_1(D) - AF_2(D)), \quad (2.9)$$

$$\frac{dA}{dt} = \frac{1}{\tau_a}(G(D) - A), \quad (2.10)$$

TABLE 1 *Parameters for vasomotion model (values taken directly from Carlson et al., 2008)*

Parameter	Description	Large arteriole	Small arteriole	Unit
C_{myo}	VSM activation tension sensitivity	0.0101 (1.01×10^5)	0.0359 (3.59×10^5)	cm/dyn (m/N)
C_{shear}	VSM activation shear stress sensitivity	0.0258 (0.258)	0.0258 (0.258)	cm ² /dyn (m ² /N)
C_{meta}	VSM activation conducted response sensitivity	30	30	1/($\mu\text{M} \cdot \text{cm}$)
C'_{tone}	VSM constant	-2.22	-0.53	
C''_{tone}	VSM constant	10.11	10.66	
C_{pass}	Passive tension strength	1042.99 (1.04299)	259.90 (0.2599)	dyn/cm (N/m)
C'_{pass}	Passive tension sensitivity	8.293	11.467	
C_{act}	Maximally active VSM peak tension	1596.3 (0.15963)	274.193 (0.274193)	dyn/cm (N/m)
C'_{act}	Maximally active VSM length dependence	0.6804	0.750	
C''_{act}	Maximally active VSM tension range	0.2905	0.384	
D_0	Passive reference vessel diameter	156.49	38.99	μm

Numerical values in parentheses are the equivalent parameter value in SI units.

where

$$F_1 = \frac{PD}{2} - C_{\text{pass}} \exp \left[C'_{\text{pass}} \left(\frac{D}{D_0} - 1 \right) \right], \quad (2.11)$$

$$F_2 = C_{\text{act}} \exp \left[- \left(\frac{D/D_0 - C'_{\text{act}}}{C''_{\text{act}}} \right)^2 \right], \quad (2.12)$$

$$G = \frac{1}{1 + \exp(-C_{\text{myo}}PD/2 + C_{\text{shear}}\tau - C'_{\text{tone}})}. \quad (2.13)$$

2.2 Vessel configurations

Three vessel configurations are examined. In Network I (Fig. 1A), a single vessel with fixed wall shear stress and pressure is assumed. Network II (Fig. 1B) includes an active vessel segment connected in series with fixed upstream and downstream resistance vessels (R_u) and (R_d), such that wall shear stress depends on vessel diameter and flow rate. The diameter of the active segment changes according to the myogenic and shear-dependent responses as arterial pressure is varied. For Networks I and II, S_{tone} is given by (2.6). For a given input arterial pressure and arbitrary initial conditions for diameter and activation, the system in (2.7) and (2.8) is integrated with respect to time until the diameter of the vasoactive segment approaches either equilibrium or periodic oscillations.

Network III is a seven-compartment model (Arciero *et al.*, 2008) representing a complete vascular pathway (Fig. 1C), including two vasoactive segments (large and small arterioles). The other five

FIG. 1. (A) Network I. Single vessel with fixed pressure, P_0 . (B) Network II. Simple network model in which a vasoactive segment is connected in series to an upstream and downstream fixed resistance, R_u and R_d , respectively. Input arterial pressure (P_a) is varied, and downstream pressure is fixed: $P_v = 13$ mmHg (1.733 kPa). (C) Network III. Seven-compartment model in which the large and small arteriole compartments are vasoactive and connected in series to the remaining fixed resistance compartments, $R_u = R_A$ and $R_d = R_C + R_{SV} + R_{LV} + R_V$.

compartments are considered fixed resistances. The upstream resistance $R_u = R_A$ represents the arteries. The downstream resistance $R_d = R_C + R_{SV} + R_{LV} + R_V$ represents the capillaries, small venules, large venules and veins. This model includes a metabolic contribution to S_{tone} , as indicated in (2.5). It is assumed that a decrease in oxygen levels in the large and small venules triggers an increase in a metabolic signal S_{CR} , which is conducted upstream along vessel walls and induces arteriolar vasodilation (Arciero *et al.*, 2008). In the present study, this signal is assumed to be stimulated by intravascular ATP that is released from red blood cells at a rate that increases with decreasing oxygen saturation. Other mechanisms independent of red blood cells likely also contribute to the metabolic regulation of blood flow (Ngo *et al.*, 2010). The findings of the present study are not sensitively dependent on the assumed mechanism of metabolic flow regulation. For simplicity, the dynamics of the metabolic response are neglected in the present model, and the metabolic signal is assumed to vary instantaneously in response to changes in blood flow and oxygen delivery. This is equivalent to assuming that the metabolic response is rapid relative to the time scale τ_a for changes in vascular tone. For a given input arterial pressure and oxygen demand, with S_{tone} given by (2.5), the system in (2.7) and (2.8) is integrated as already described for Networks I and II.

3. Results

3.1 Network I

Figures 2 and 3 show the behaviour predicted by the model for a single vessel segment with a fixed pressure and two different fixed values of wall shear stress. In each figure, panel A shows the variation of vessel diameter with time. When $\tau = 30$ dyn/cm² (3 Pa; see Fig. 2), the solution approaches a stable equilibrium after an initial transient. The steady-state diameter and activation are $D^* = 90.2$ μm and $A^* = 0.36$. When $\tau = 60$ dyn/cm² (6 Pa; Fig. 3), the solution approaches a periodic solution with large amplitude oscillations and a period of about 60 s. In panel B, the tension-diameter phase plane is shown. The equilibrium point of the system is defined by the intersection of the line $T = PD/2$, which indicates the tension according to the law of Laplace, with the curve labelled $T = T_{\text{total}}$, which

FIG. 2. Behaviour of the system (2.9) and (2.10) for Network I, with $\tau = 30 \text{ dyn/cm}^2$ (3 Pa) and $P = 90 \text{ mmHg}$ (12 kPa). (A) Variation of diameter with time, showing approach to a stable equilibrium. (B) Tension-diameter plane. Multiple thin curves: tension generated in wall for fixed values of activation, from 0 to 1. Curve $T = T_{\text{total}}$: tension generated in wall by smooth muscle cells. Straight line: equilibrium tension for given pressure. Equilibrium point lies at the intersection of this line and the curve $T = T_{\text{total}}$. Thick curve: trajectory of solution approaching equilibrium point. (C) Activation-diameter phase plane, including nullclines. Arrows: directions of trajectories on nullclines. Thick curve: trajectory of solution approaching equilibrium point. (D) Activation-diameter phase plane, enlarged to show relationship between trajectory and nullclines.

indicates the tension generated by the active response of the vessel wall to pressure and wall shear stress. Higher wall shear stress ($\tau = 60 \text{ dyn/cm}^2$ or 6 Pa) causes partial relaxation of the wall. The generated tension is reduced, so that the intersection point is shifted to the right to $D^* = 102.1 \mu\text{m}$ and $A^* = 0.35$. This results in a loss of stability of the equilibrium point. In panel C, the activation-diameter phase plane is shown. The region near the steady-state solution is enlarged in panel D to show the slight deviation between the nullcline (dashed line) and trajectory (solid line). As discussed below, the loss of stability of the equilibrium point is associated with a change in the slope of the D-nullcline at the point where it crosses the A-nullcline. The change from stable to unstable equilibria indicates the

FIG. 3. Behaviour of the system (2.9) and (2.10) for Network I, with $\tau = 60 \text{ dyn/cm}^2$ (6 Pa) and $P = 90 \text{ mmHg}$ (12 kPa). (A) Variation of diameter with time, showing limit-cycle oscillations. (B) Tension-diameter plane, as in Fig. 2. Thick curve: trajectory of solution, showing limit-cycle oscillations. (C) Activation-diameter phase plane. Thick curve: trajectory of solution entering limit cycle. (D) Activation-diameter phase plane, enlarged to show relationship between trajectory and nullclines.

existence of a bifurcation point for some shear stress $\tau = \bar{\tau}$ between 30 and 60 dyn/cm^2 (3 and 6 Pa) when $P = 90 \text{ mmHg}$ (12 kPa). Stability is re-established for larger shear stress values (e.g. $\tau = 150 \text{ dyn/cm}^2$ (15 Pa); results not shown). The limit cycle oscillation shown in Fig. 3 may correspond to the experimentally observed phenomenon of vasomotion.

3.1.1 Conditions for stability. To analyse the stability of the system, (2.9) and (2.10) are linearized about the steady state (D^*, A^*) , giving

$$\frac{d}{dt} \begin{pmatrix} D - D^* \\ A - A^* \end{pmatrix} = \begin{bmatrix} \frac{D_c}{\tau_d T_c} (F'_1 - A^* F'_2) & \frac{-D_c}{\tau_d T_c} F_2 \\ \frac{1}{\tau_a} G' & \frac{-1}{\tau_a} \end{bmatrix} \begin{pmatrix} D - D^* \\ A - A^* \end{pmatrix}, \quad (3.1)$$

where the prime denotes the derivative with respect to diameter, and the derivatives are evaluated at (D^*, A^*) . For typical parameter values, the determinant of the Jacobian matrix in (3.1) is positive. The system is stable when the trace is negative, i.e. when

$$F'_1 - A^* F'_2 < \frac{\tau_d T_c}{\tau_s D_c}. \quad (3.2)$$

This result can be interpreted geometrically in terms of the slope of the D -nullcline at the equilibrium point in the phase plane. On the D -nullcline, $A = F_1/F_2$, and therefore, the condition for stability can be written as

$$\frac{dA}{dD} = \frac{1}{F_2} (F'_1 - A^* F'_2) < \frac{\tau_d T_c}{\tau_a D_c} \frac{1}{F_2}. \quad (3.3)$$

If $\tau_d/\tau_a \ll 1$, as is typically the case, then the region of instability coincides approximately with the region where the D -nullcline has positive slope at the equilibrium point. This behaviour is shown in Fig. 4. For low values of shear stress, the nullclines intersect at a point where the D -nullcline has negative slope. As shear stress is increased, the intersection point enters and then leaves a region where the D -nullcline has positive slope and so the equilibrium is unstable. Figure 4 also includes the A -nullclines corresponding to the values of shear stress ($\bar{\tau}_1 = 57.13 \text{ dyn/cm}^2$ (5.713 Pa) and $\bar{\tau}_2 = 126.3 \text{ dyn/cm}^2$ (12.63 Pa)) at which stability changes. This result (3.3) also shows how the occurrence of instability depends on the time constants of the system. As the ratio τ_d/τ_a is increased, the range of shear stresses leading to instability increases. Figure 5 shows the values of shear stress at which oscillations arise as a function of τ_d/τ_a for $P = 90 \text{ mmHg}$ (12 kPa).

3.1.2 Behaviour near bifurcation points. Insight into the behaviour of the system (2.9) and (2.10) and the appearance of limit cycles can be gained by transforming the system into normal form and

FIG. 4. Geometric interpretation of the stability of Network I, as shear stress τ is varied, for $P = 90 \text{ mmHg}$ (12 kPa). The D -nullcline is independent of τ , whereas the A -nullcline shifts rightward with increasing τ . The thick portion of the D -nullcline indicates the region where the equilibrium is unstable.

FIG. 5. Dependence of oscillations on ratio of time constants for Network I. Range of shear stress values for which oscillations occur for a given ratio of the diameter to activation time constants, where $\tau_D < \tau_A$.

examining the occurrence of a Hopf bifurcation (Guckenheimer & Holmes, 1983). As τ traverses a bifurcation point $\bar{\tau}$, the eigenvalues λ of the Jacobian become purely imaginary and the stability of the equilibrium switches. The change of coordinates $x = D - D^*$, $y = A - A^*$ is applied, and the resulting system is separated into linear and non-linear parts:

$$\begin{pmatrix} \dot{x} \\ \dot{y} \end{pmatrix} = \bar{M} \begin{pmatrix} x \\ y \end{pmatrix} + \begin{pmatrix} f(x, y, \bar{\tau}) \\ g(x, y, \bar{\tau}) \end{pmatrix}, \quad (3.4)$$

where $\bar{M}$ is the Jacobian of the system at $\tau = \bar{\tau}$. A matrix Q can be found such that

$$Q^{-1} \bar{M} Q = \begin{bmatrix} 0 & -\omega \\ \omega & 0 \end{bmatrix}, \quad (3.5)$$

where ω is the imaginary part of the eigenvalue. By defining $\begin{pmatrix} x \\ y \end{pmatrix} = Q \begin{pmatrix} u \\ v \end{pmatrix}$, (3.4) is transformed into

$$\begin{pmatrix} \dot{u} \\ \dot{v} \end{pmatrix} = \begin{bmatrix} 0 & -\omega \\ \omega & 0 \end{bmatrix} \begin{pmatrix} u \\ v \end{pmatrix} + \begin{pmatrix} p(u, v, \bar{\tau}) \\ q(u, v, \bar{\tau}) \end{pmatrix}, \quad (3.6)$$

where p and q and their derivatives with respect to u and v vanish when $\tau = \bar{\tau}$. The normal form of the system is then given in polar coordinates by

$$\dot{r} = d\mu r + ar^3, \quad (3.7)$$

$$\dot{\theta} = \omega + c\mu + br^2, \quad (3.8)$$

where $\mu = \tau - \bar{\tau}$, a, b, c and d are constants, and higher-order terms in r are neglected (Wiggins, 2003). The values of a and d are given by Guckenheimer & Holmes (1983):

$$a = \frac{1}{16}[p_{uuu} + p_{uvv} + q_{uuu} + q_{vvv}] + \frac{1}{16\omega}[p_{uv}(p_{uu} + p_{vv}) - q_{uv}(q_{uu} + q_{vv}) - p_{uu}q_{uu} + p_{vv}q_{vv}] \quad (3.9)$$

$$d = \frac{d}{d\mu}(\text{Re}\lambda(\mu))|_{\mu=0} . \quad (3.10)$$

If $\mu d/a < 1$, the system (3.7) and (3.8) has a solution in the form of a periodic orbit with amplitude $r = \sqrt{-\mu d/a}$ and phase $\theta = [\omega + (c - bd/a)\mu]t + \theta_0$. If, in addition, $a < 0$, the orbit is stable, giving a limit cycle. According to the Poincaré–Andronov–Hopf bifurcation theorem, this local analysis also holds when (3.7) and (3.8) contain higher-order terms in r , if μ is sufficiently small (Wiggins, 2003). This analysis was used here to predict the amplitude of limit-cycle solutions near the bifurcation points. The system was also integrated numerically to explore its behaviour.

Figure 6A shows the variation with τ of the amplitude of the diameter oscillations for $P = 90$ mmHg (12 kPa), obtained by numerical integration. The amplitude is defined as the difference between the maximum and the minimum of the oscillation in the last full period of the computed solution. Oscillations first appear at the lower bifurcation point $\bar{\tau}_1 = 57.13$ dyn/cm² (5.713 Pa) and continue until the upper bifurcation point at $\bar{\tau}_2 = 126.3$ dyn/cm² (12.63 Pa). The regions around these points are enlarged in Fig. 6(B and C). Good agreement between the numerical results and the Hopf bifurcation theory is seen for small ranges of τ near the critical values. However, the abrupt jumps in amplitude demonstrated numerically are not shown by the local analysis. The variation with τ of the unstable equilibrium diameter and the maxima and minima of the diameter oscillations is shown in Fig. 6D and serves to illustrate that for most shear stress values, oscillations are either absent or present with large amplitude.

Figure 7A shows the regions in the pressure-shear stress plane where oscillations develop, and Fig. 7B indicates the amplitude of these oscillations. Under the assumed conditions, no oscillations are predicted to occur if $P < 55$ mmHg (7.33 kPa). This is consistent with experimental findings (Slaaf *et al.*, 1987) in which oscillatory behaviour disappeared when pressure was decreased.

For the conditions considered here, $d > 0$ in all cases, but the value of a in (3.7) changes sign at $P = 96$ mmHg (12.8 kPa), with the appearance of a subcritical bifurcation for pressures above this value. Figure 8 gives an example of this behaviour for $P = 100$ mmHg (13.33 kPa). In a very narrow range of shear stresses between 74.57 and 74.63 dyn/cm² (7.457 and 7.463 Pa), a stable equilibrium coexists with a large amplitude limit cycle. The oscillation with amplitude predicted from Hopf analysis is unstable in this range.

3.2 Networks II and III

The effects of upstream and downstream resistances on a single active vessel are illustrated by Network II. In a reference state, the active segment has diameter 100 μm , shear stress 100 dyn/cm² (10 Pa), midpoint pressure 100 mmHg (13.33 kPa) and length 0.6 cm. The upstream and downstream resistances are $R_u = R_d = 2.4 \times 10^8$ mmHg $\cdot$ s/cm³ (3.2×10^7 kPa $\cdot$ s/cm³). The pressures at the upstream and downstream ends of the network are $P_a = 187$ mmHg (24.9 kPa) and $P_b = 13$ mmHg (1.73 kPa), so that the midpoint pressure remains constant. In this case, oscillations in diameter, flow and shear stress

FIG. 6. Amplitude of oscillation and diameters for Network I when $P = 90$ mmHg (12 kPa). (A) Dependence of amplitude on shear stress. (B) Enlarged scale near lower Hopf bifurcation, $\bar{\tau}_1 = 57.13$ dyn/cm² (5.713 Pa). (C) Enlarged scale near upper Hopf bifurcation, $\bar{\tau}_2 = 126.3$ dyn/cm² (12.63 Pa). (D) Dependence of equilibrium diameter (solid curve) and minimum and maximum diameters (dashed curves) on shear stress.

are predicted (Fig. 9). The diameter oscillation has period 51.7 s and amplitude 80.1 μm . This example shows that vasomotion can occur by this mechanism in a network as well as in an isolated segment. In an isolated vessel under corresponding conditions but with fixed shear stress, the period of oscillation is 59.8 s and the amplitude is 79.8 μm .

In a seven-compartment model (Network III) developed by Arciero *et al.* (2008), oscillations in vessel diameter and activation occur in both vasoactive segments for some values of pressure and oxygen demand (M_0). Figure 10 gives an example for $M_0 = 50$ cm³O₂/100 cm³/min at $P = 80$ mmHg (10.7 kPa) in the large arteriole. Experimentally, vasomotion is not typically observed under normal physiological conditions but is shown to be prevalent under conditions of reduced perfusion and metabolic stress (Schmidt, 1996). Consistent with these observations, the model does not predict vasomotion under most normal conditions but predicts the occurrence of oscillations for limited ranges of parameter values, such as high values of oxygen demand.

FIG. 7. Ranges of parameter values leading to oscillations for Network I. (A) Shear stress–pressure plane. (B) Amplitude–shear stress–pressure space, showing amplitude of oscillations.

FIG. 8. Subcritical bifurcation at $P = 100$ mmHg (13.33 kPa) for Network I. Values of amplitude given for different shear stress values near the Hopf bifurcation point. Dots: numerical values of amplitude. Line: approximate amplitude obtained from Hopf bifurcation analysis.

4. Discussion

Some previous models of vasomotion have assumed that oscillations are intrinsic to the intracellular dynamics of smooth muscle activation (Achakri *et al.*, 1994; Gonzalez-Fernandez & Ermentrout, 1994; Parthimos *et al.*, 1999, 2007; Peng *et al.*, 2001; Gustafsson & Nilsson, 1993b). In the present model, the dynamics of activation are governed by a simple first-order differential equation that has no intrinsic

FIG. 9. Predicted oscillations in Network II. (A) Diameter. (B) Flow. (C) Shear stress. A 200 s sample of the portion of the time series during which the oscillation has become regular is shown.

FIG. 10. Oscillations in the large arteriole in Network III, with $P = 80$ mmHg (10.7 kPa) and $M_0 = 50$ cm³ O₂/100 cm³/min. (A) Diameter oscillations. (B) Activation oscillations.

oscillatory behaviour. The oscillations arise through the interaction between the smooth muscle dynamics and the non-linear mechanics of the vessel wall. This is consistent with the findings of Ursino *et al.* (1998). In their model, the length dependence of passive and active tension was similar to that assumed here, (2.2) and (2.3). They similarly predicted the generation of vasomotion through the interaction of wall mechanics with the dynamics of tone generation by smooth muscle. In their model, either a strong rate-dependent myogenic response or a strong flow-dependent mechanism was needed to generate vasomotion. Neither of these effects is invoked here. The oscillatory behaviour results from a myogenic response dependent purely on wall tension, combined with strongly non-linear wall mechanics. The present study therefore represents a new theory for the origin of vasomotion.

The theoretical model implemented here provides insight into the origin of the oscillatory behaviour. For the case of a single vessel (Network I), this can be seen by considering the trajectories of the system in the activation-diameter phase plane (Figs. 2C and 3C). The time constant τ_d for diameter changes is relatively short, and rapid changes of diameter occur at nearly constant activation. Because the time constant τ_a for activation changes is relatively long, activation must change more slowly and the trajectory generally lies close to the D -nullcline during such changes. This nullcline is approximately cubic in form. With changing parameter values, the slope at the equilibrium point changes, and the equilibrium may become unstable. In that case, a limit cycle emerges in which the fast and slow behaviours alternate (Fig. 3).

A striking feature of the results is the abrupt appearance and disappearance of vasomotion with changing parameter values. This is illustrated in Fig. 7B, where it is seen that small changes in wall shear stress or pressure can cause a transition from a state of no vasomotion to a large amplitude oscillation. The abrupt appearance and disappearance of vasomotion with changing pressure has been noted experimentally (Slaaf *et al.*, 1987). The behaviour of the system near the transition to instability was analysed using Hopf bifurcation theory. The bifurcations were supercritical or subcritical, depending on the assumed pressure. The predicted amplitude of limit-cycle oscillations agreed with numerical predictions in narrow ranges of shear stress near the bifurcation points. Outside these ranges, the amplitude predicted by numerical solution jumped to much higher values.

The amplitude of the predicted oscillations varies widely according to the assumed parameter values, but in many cases, it is quite large, as illustrated in Fig. 7B. This is in agreement with the wide range of amplitudes seen experimentally. In experimental observations, the waveform frequently deviates strongly from a sinusoidal form. This is consistent with the model in which the oscillations arise as limit cycles in a highly non-linear system. In the examples presented here, the frequency is in the range $1\text{--}2\text{ min}^{-1}$, which is lower than the range seen experimentally. This suggests that the assumed time constant $\tau_a = 60\text{ s}$ is larger than actual typical values. As can be seen from (2.7) and (2.8), reductions of the assumed values of τ_a and τ_d by a given factor would lead to oscillations having frequencies increased by the same factor but being otherwise identical.

Predictions are given in Fig. 7A of the ranges of pressure and wall shear stress at which vasomotion could be expected for a particular case. However, the occurrence of vasomotion depends on other parameters, including the levels of metabolic stimuli and vasoactive substances and the properties of the vessel. Therefore, the present results do not allow direct quantitative predictions of the occurrence and amplitude of vasomotion *in vivo*.

With the addition of upstream and downstream resistances, the model represents in a simplified way the conditions experienced by a vessel within a network of vessels. For a single segment with fixed upstream and downstream resistances (Network II), vasomotion is predicted by the model for some values of input arterial pressure (Fig. 9). In this case, the flow, pressure and shear stress vary as the diameter changes, with minimum shear stress occurring when the diameter is at its maximum. In a seven-compartment model with two active segments (Network III), vasomotion is not predicted under most of the conditions examined, although it is found to occur for high levels of pressure or oxygen demand (Fig. 10). Under reference conditions, the pressure in the large arteriole is 82.5 mmHg (11 kPa) and the shear stress is 55 dyn/cm^2 (5.5 Pa), and no vasomotion is predicted. If these values are imposed at fixed levels in an isolated vessel, oscillations are predicted (see Fig. 7A). These results suggest that network effects may stabilize the system and inhibit vasomotion under some conditions.

The present model demonstrates a novel potential mechanism for vasomotion, involving the interaction between the dynamics of tone generation in smooth muscle and the non-linear viscoelastic properties of the vessel wall and occurring in the absence of intrinsic oscillatory behaviour in smooth muscle. It should be emphasized that the existence of this potential mechanism for vasomotion does not exclude the involvement of other mechanisms of oscillation, resulting for instance from spontaneous instability of intracellular calcium levels. Experimentally, it would not be easy to distinguish between these mechanisms because vasomotion by either type of mechanism would be characterized by oscillations in both diameter and cytosolic calcium in smooth muscle. One distinguishing feature of the present mechanism is that its amplitude is predicted to vary rapidly over narrow ranges of intravascular pressure, a property that could be experimentally tested. Further model studies in which the present theory for vascular wall mechanics is combined with more detailed theories of smooth muscle cell activation might also permit improved understanding of the origins of vasomotion under physiological conditions.

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