Modelling carotid artery adaptations to dynamic alterations in pressure and flow over the cardiac cycle

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Motivated by recent clinical and laboratory findings of important effects of pulsatile pressure and flow on arterial adaptations, we employ and extend an established constrained mixture framework of growth (change in mass) and remodelling (change in structure) to include such dynamical effects. New descriptors of cell and tissue behavior (constitutive relations) are postulated and refined based on new experimental data from a transverse aortic arch banding model in the mouse that increases pulsatile pressure and flow in one carotid artery. In particular, it is shown that there was a need to refine constitutive relations for the active stress generated by smooth muscle, to include both stress- and stress rate-mediated control of the turnover of cells and matrix and to account for a cyclic stress-mediated loss of elastic fibre integrity and decrease in collagen stiffness in order to capture the reported evolution, over 8 weeks, of luminal radius, wall thickness, axial force and *in vivo* axial stretch of the hypertensive mouse carotid artery. We submit, therefore, that complex aspects of adaptation by elastic arteries can be predicted by constrained mixture models wherein individual constituents are produced or removed at individual rates and to individual extents depending on changes in both stress and stress rate from normal values.

Keywords: growth, remodelling, stress, stress rate, mechanobiology, mechanics, aortic banding.

1. Introduction

Hypertension is signalled by a systolic pressure exceeding 140 mmHg, a diastolic pressure exceeding 90 mmHg or both. Even in the absence of disease, systolic pressure increases later in life and elevated values correlate strongly with cardiovascular morbidity and mortality (Chobanian *et al.*, 2003). Diastolic pressure, on the other hand, often decreases after 50 years of age, thus leading to a higher pulse pressure ($P_{\text{sys}} - P_{\text{dias}}$) and associated increased dynamical stimulation of the arterial wall. Mounting evidence suggests that increased pulse pressure is a strong initiator or indicator of diverse cardiovascular diseases (Boutouyrie *et al.*, 1999; Safar & Boudier, 2005; O'Rourke & Hashimoto, 2007). Indeed,

Koffi *et al.* (1999) suggested that ‘mechano-sensitive elements within the vascular wall may be selectively sensitive to the dynamic aspects of physical forces and be able to convert frequency and amplitude information into cellular responses that lead to vascular remodeling’. Arteries adapt to changes in acute and chronic stimuli through short- (vasomotor) and long- (growth and remodelling) term responses. Smooth muscle provides both vasomotor and synthetic control, with extracellular matrix proteins synthesized either perinatally (i.e. elastin, which has a normal half-life on the order of 40+ years in humans; Arribas *et al.*, 2006; Wagenseil & Mecham, 2007) or continuously (i.e. fibrillar collagens, which have a normal half-life on the order of 70 days; Nissen *et al.*, 1978; Langille, 1993) serving as the primary load-bearing constituents involved in long-term biomechanical adaptations (Humphrey, 2002). This composite make-up of the normal arterial wall allows high distensibility at low pressures, due primarily to the elastin, and low distensibility at high pressures, due primarily to the collagen. Overall pulsatility within distal vessels is modulated by elastin-rich central arteries (e.g. aorta and carotids) that experience significant variations in diameter as well as in wall shear and circumferential stress and stress rates over the cardiac cycle. The extent of these cyclic variations depends on many factors, including cardiac contractility, up- and downstream compliances, and pressure waves reflected from distal arterial beds (Berne & Levy, 2001), each of which can change with aging, diverse disease conditions, or as a result of surgical intervention.

Many different mathematical frameworks have been proposed for modelling arterial growth and remodelling (G&R),¹ yet prior models have been based primarily on changes in mean values of pressure and flow or the associated stresses (e.g. Taber, 1998; Rachev, 2000; Gleason *et al.*, 2004; Hariton *et al.*, 2007; Kuhl *et al.*, 2007; Tsamis & Stergiopoulos, 2007; Alford *et al.*, 2008; Valentín *et al.*, 2009). Consistent with studies suggesting that dynamic contributions of pressure (e.g. Boutouyrie *et al.*, 1999; Koffi *et al.*, 1999) and flow (e.g. Guyton & Hartley, 1985) are fundamental to arterial adaptations and maladaptations, one goal of this paper is to extend a recent constrained mixture model of G&R in a muscular artery (Valentín *et al.*, 2009) to include effects of both stress- and stress rate-mediated cell and matrix turnover in an elastic artery. Specifically, we seek to describe data from a recent study in our laboratory on hypertensive mouse common carotid arteries, which reveal that marked changes in geometry, structure, mechanical properties and function correlate better with changes in pulse pressure and pulsatile flow than with changes in mean values (Eberth *et al.*, 2009a). We submit that modelling such changes will be fundamental to understanding many problems having clinical importance, including hypertension, tissue engineering of arterial grafts and design of medical devices such as ventricular assist devices that alter the pulsatility of the flow or intravascular stents that alter the cyclic strains experienced locally by the arterial wall.

2. Methods

2.1 A multiple timescales approach

The characteristic G&R timescale (days to weeks or months) is orders of magnitude longer than the cardiac cycle timescale (seconds to a fraction of a second depending on species). This difference justifies, if not demands, the assumption of a multiple timescales formulation of the overall G&R problem. Hence, we denote by s the G&R time and by t the cardiac cycle time at each fixed s and assume that negligible G&R occurs during a cardiac cycle. In other words, we assume a loose coupling between these two disparate timescales (cf. Figueroa *et al.*, 2009) and will account for integrated effects of the

¹By growth, we mean changes in mass or mass fractions of individual constituents due to altered cell and matrix turnover and, by remodelling, we mean changes in the microstructural organization of these constituents.

dynamics over the cardiac cycle timescale t on the evolution of geometry, structure and properties over the G&R timescale s by introducing below an average measure of the stress rate (or pulsatility), which in turn is dictated by the history of G&R. We will thus use the notation that a function $g = \hat{g}(s; t)$ can vary over the cardiac cycle time t at any fixed G&R time s . Functions denoted by $g = \hat{g}(s)$ or $g = \hat{g}(\tau)$, with $\tau \in [0, s]$, vary only over the G&R timescale.

We suggested previously that a 2D description of arterial wall mechanics allows one to capture salient aspects of G&R that are important clinically (e.g. changes in caliber and structural stiffness) and is particularly appropriate for small arteries having but a few smooth muscle layers within the media, such as the mouse common carotid artery. Consistent with a membrane theory (Humphrey, 2002), as well as prior work on the G&R of both intracranial aneurysms (Baek *et al.*, 2006) and thin-walled cerebral arteries (Valentín *et al.*, 2009), constitutive relations for Cauchy membrane stresses (i.e. stress resultants) in a pressurized and finitely extended cylindrical vessel, over the cardiac cycle timescale t , can be written at each G&R time s as

$$T_{\vartheta}(s; t) = \frac{1}{\lambda_z(s; t)} \frac{\partial w}{\partial \lambda_{\vartheta}} \Big|_{s; t} + h(s; t) \sigma_{\vartheta}^{\text{act}}(s; t), \quad (2.1)$$

$$T_z(s; t) = \frac{1}{\lambda_{\vartheta}(s; t)} \frac{\partial w}{\partial \lambda_z} \Big|_{s; t} + h(s; t) \sigma_z^{\text{act}}(s; t), \quad (2.2)$$

where w is the overall strain energy function for the arterial wall, λ_{ϑ} and λ_z are the principal stretches experienced by the artery, h is the current (i.e. deformed) thickness of the wall and $\sigma_{\vartheta}^{\text{act}}$ and σ_z^{act} are the principal Cauchy stresses due to active contributions to load bearing by the smooth muscle. We also suggested previously that a simple rule-of-mixtures relation for the stress response (or strain energy function) enables one to account for different mass fractions, natural (stress-free) configurations and material properties of individual constituents within the arterial wall that can turn over at different rates and to different extents during G&R (Baek *et al.*, 2006; Valentín *et al.*, 2009). Hence, let $w(s; t) = \sum_k w^k(s; t)$, where w^k is the energy stored in constituent k (e.g. the elastin, a particular family of collagen fibres or smooth muscle), defined per area, which may include contributions from constituents produced or removed at different times, namely

$$w^k(s; t) = \frac{M^k(0)}{\rho(s)} Q^k(s) \hat{W}^k(\mathbf{F}_{n(0)}^k(s; t)) + \int_0^s \frac{m^k(\tau)}{\rho(s)} q^k(s, \tau) \hat{W}^k(\mathbf{F}_{n(\tau)}^k(s; t)) d\tau, \quad (2.3)$$

where $M^k(0)$ is the mass density, per unit reference area, of constituent k at G&R time $s = 0$, $Q^k(s) \in [0, 1]$ accounts for the fraction of constituent k that was present at time $s = 0$ (the instant when G&R begins) but survives to current time s , $m^k(\tau) \geq 0$ is the so-called true mass density production rate, $q^k(s, \tau) \in [0, 1]$ is the fraction of constituent k that was produced at an intermediate time $\tau \in [0, s]$ but survives to current time s , ρ is a mass density per unit volume for the artery and $\hat{W}^k$ is the strain energy density per unit volume for constituent k , which depends on the finite deformation $\mathbf{F}_{n(\tau)}^k(s; t)$ experienced by that constituent relative to its individual natural configuration defined at the time of production. Similarly, $M(s) = \sum_k M^k(s)$ and, consistent with (2.3),

$$M^k(s) = M^k(0) Q^k(s) + \int_0^s m^k(\tau) q^k(s, \tau) d\tau. \quad (2.4)$$

Observe from (2.3) that three classes of functions (i.e. constitutive relations) must be identified to describe specific cellular and tissue behaviors: constituent stored energy functions $\hat{W}^k(\mathbf{F}_{n(\tau)}^k(s; t))$,

mass density productions $m^k(\tau)$ and survival functions $q^k(s, \tau)$, where $Q^k(s)$ can be prescribed given $q^k(s, \tau)$. Let us consider next the kinematics of G&R with timescales separation and then consider specific forms of the requisite constitutive relations.

Different structurally significant constituents appear to be incorporated within the arterial wall, on the G&R timescale $\tau \in [0, s]$, having individual ‘deposition stretches’ $\mathbf{G}^k(\tau)$ relative to their own natural (i.e. stress-free) configuration, i.e. new constituents appear to be incorporated within extant matrix having a preferred prestress (Valentín & Humphrey, 2009a; Wagenseil & Mecham, 2007). We assume that such constituents are subsequently constrained to deform with the mixture (i.e. motions $\mathbf{x}^k = \mathbf{x}$), which allows deformations of individual constituents to be related to measurable deformations experienced by the wall (cf. Humphrey & Rajagopal, 2002). Let $\mathbf{F}(s)$ denote the gradient of the motion from a given reference configuration for the mixture κ_0 to the ‘current’ configuration of the mixture $\kappa(s)$ at G&R time s and similarly let $\mathbf{F}_s(t)$ denote the gradient of the motion from $\kappa(s)$ to any ‘current’ configuration of the mixture $\kappa_s(t)$ on the cardiac cycle time t (Fig. 1). Thus, at G&R time s and cardiac cycle time t , a constituent k deposited at G&R time $\tau \in [0, s]$ experiences the deformation gradient $\mathbf{F}_{n(\tau)}^k(s; t) = \mathbf{F}_s(t)\mathbf{F}_{n(\tau)}^k(s)$ relative to its individual natural configuration $\kappa_n^k(\tau)$ (hence the subscript notation $n(\tau)$ on $\mathbf{F}^k$), while on the G&R timescale alone, it experiences the deformation gradient $\mathbf{F}_{n(\tau)}^k(s) = \mathbf{F}(s)\mathbf{F}(\tau)^{-1}\mathbf{G}^k(\tau)$ as shown by Baek *et al.* (2006). Consistent with Valentín *et al.* (2009), we assume that constituents are deposited within the configuration of the artery at time τ that corresponds to the mean value of transmural pressure and flow rate over the cardiac cycle (i.e. a specific fixed time

FIG. 1. Relevant configurations in a dynamic G&R framework. Constituents are deposited at a given pre-stretch $\mathbf{G}^k(\tau)$ within *in vivo* (i.e. stressed) configurations $\kappa(\tau)$ on the G&R timescale $\tau \in [0, s]$. The deformation gradient from a common reference configuration κ_0 to this configuration $\kappa(\tau)$ is denoted $\mathbf{F}(\tau)$ for all $\tau \in [0, s]$. The deformation gradient from the *in vivo* configuration $\kappa(s)$ at G&R time s to the *in vivo* configuration $\kappa_s(t)$ corresponding to the cardiac cycle time t (at fixed G&R time s) is denoted $\mathbf{F}_s(t)$. It can be seen, therefore, that the deformation gradient experienced by an individual constituent at any time is $\mathbf{F}_{n(\tau)}^k(s; t) = \mathbf{F}_s(t)\mathbf{F}_{n(\tau)}^k(s)$, where $\mathbf{F}_{n(\tau)}^k(s) = \mathbf{F}(s)\mathbf{F}(\tau)^{-1}\mathbf{G}^k(\tau)$ due to normal G&R.

t); this assumption could be relaxed, however, to account for possible distributions of deposition stretch over the cardiac cycle (cf. [Gleason & Humphrey, 2005](#)). Regardless, these relations allow us to compute constituent deformations needed in the individual strain energy functions given measurable tissue-level deformations and assumed values of deposition stretch (cf. [Valentín & Humphrey, 2009a](#)).

Given the present desire to consider a multiple timescales approach, note that the radial equation of motion over the cardiac cycle timescale can be written as (recall constitutive equation (2.1) and compare with [David & Humphrey, 2003](#))

$$\frac{1}{\lambda_z(s; t)} \frac{\partial w}{\partial \lambda_\vartheta} \bigg|_{s; t} + h(s; t) \sigma_\vartheta^{\text{act}}(s; t) = P(s; t) a(s; t) - \rho h(s; t)^2 \ddot{a}(s; t), \quad (2.5)$$

where P is the luminal pressure and a is the deformed inner radius, with an overdot denoting a time derivative with respect to the cardiac cycle time t . We (see Appendix A) and others have shown, however, that arterial wall mechanics over the cardiac cycle can typically be modelled well by assuming quasi-static motions (e.g. [Humphrey & Na, 2002](#)), and prior models of arterial G&R have similarly been based on equilibrium solutions. When inertial forces are negligible, we recover the usual equilibrium equation (cf. [Valentín et al., 2009](#))

$$\frac{1}{\lambda_z(s; t)} \frac{\partial w}{\partial \lambda_\vartheta} \bigg|_{s; t} + h(s; t) \sigma_\vartheta^{\text{act}}(s; t) = P(s; t) a(s; t), \quad (2.6)$$

which allows one to compute quasi-static motions over the cardiac cycle but is typically defined at the mean arterial pressure $P_m(s)$ and thus yields a single value of radius at each G&R time s . In the absence of inertial forces, the equilibrium equation for the axial direction can be written similarly as

$$\frac{1}{\lambda_\vartheta(s; t)} \frac{\partial w}{\partial \lambda_z} \bigg|_{s; t} + h(s; t) \sigma_z^{\text{act}}(s; t) = \frac{f(s; t)}{\pi h(s; t) (2a(s; t) + h(s; t))}, \quad (2.7)$$

where f is the axial force. Herein, whether dynamic or quasi-static, we account for variations in blood pressure and flow using Fourier series representations over the cardiac timescale t , namely

$$P(s; t) = P_m(s) + \sum_n \left(A_n(s) \cos \left(\frac{2\pi n}{T(s)} t \right) + B_n(s) \sin \left(\frac{2\pi n}{T(s)} t \right) \right), \quad (2.8)$$

$$Q(s; t) = Q_m(s) + \sum_n \left(C_n(s) \cos \left(\frac{2\pi n}{T(s)} t \right) + D_n(s) \sin \left(\frac{2\pi n}{T(s)} t \right) \right), \quad (2.9)$$

where P_m and Q_m are the mean values of transmural pressure and flow rate, A_n , B_n , C_n and D_n are the Fourier coefficients (below we let $n = 1, 2, \dots, 8$; [Milnor, 1989](#)) and T is the cardiac period (which could vary with G&R, as, e.g. in aging). Values of these parameters can be estimated directly from *in vivo* data, and these functions allow one to account for possible changes in mean values, waveform, frequency or relative phase angles as a function of the G&R time variable s .

Finally, based on observations reported in the literature (e.g. [Eberth et al., 2009a](#)), mass production and removal may depend on levels of both stress and stress rate (amplitudes and/or frequency). Consider, therefore, an L^2 -norm over the cardiac period T as a measure of variations of a quantity over the cardiac cycle timescale that is evaluated on the G&R timescale. Given any quantity $y(s; t)$, its rate measure can

be computed at each G&R time as

$$\tilde{y}(s) = \left[\frac{1}{T(s)} \int_0^{T(s)} (\dot{y}(s; t))^2 dt \right]^{\frac{1}{2}}, \quad (2.10)$$

which defines a scalar measure through which the ‘microscale’ time t exerts its influence on the ‘macroscale’ time s . This measure is sensitive to perturbations in frequency as well as variations in the waveform of $y(s; t)$ over the cardiac cycle. Note, too, that $\tilde{y}(s)$ has dimension of the rate of y (i.e. dimensions of $\dot{y} = dy/dt$) and it represents a mean of the speed of variation of the mechanical quantity $y(s; t)$ on the cardiac cycle, a quantity that we hypothesize may influence G&R processes to an extent similar to that by the mean value of $y(s; t)$ itself. In other words, motivated by diverse experimental evidence (e.g. [Na et al., 2008](#); [Eberth et al., 2009a](#)), we assume that cells govern G&R processes based on both a mechanical stimulus and the time rate of change of that stimulus. Because arterial G&R appears to be stimulated by changes in particular mechanical quantities from their preferred (homeostatic) values ([Humphrey, 2008a](#)), it also proves useful to define the difference $\Delta z(s) = (z(s) - z^h)/z^h$, for any value $z(s)$ defined on the G&R timescale, to be the normalized perturbation of z from its homeostatic value z^h at any G&R time s . Hence, $z(s)$ can represent either a mean value over the cardiac cycle or an appropriate rate measure given via (2.10).

2.2 Illustrative constitutive relations

Following [Gleason et al. \(2008\)](#) and [Eberth et al. \(2009b\)](#), mouse common carotid arteries can be modeled mechanically by assuming that they consist primarily of isotropically distributed elastin, four families of collagen fibres (axial, circumferential and symmetric diagonal that are oriented $\pm\alpha_0$ degrees from the longitudinal axes²) and smooth muscle cells that can have circumferential and axial contributions (with elastin denoted by e , collagen fibres denoted by $j = 1, 2, 3, 4$ and smooth muscle denoted by m). Specifically, let the mechanical behaviour of elastin be described by a neo-Hookean form

$$\hat{W}^e = \frac{c_1^e}{2} \left((\lambda_\theta^e)^2 + (\lambda_z^e)^2 + \left(\frac{1}{\lambda_\theta^e \lambda_z^e} \right)^2 - 3 \right), \quad (2.11)$$

and let the behavior of the collagen fibres and passive smooth muscle be described by exponential forms

$$\hat{W}^m = \frac{c_2^m}{4c_3^m} (\exp[c_3^m ((\lambda^m)^2 - 1)^2] - 1) \quad \forall \lambda^m, \quad (2.12)$$

$$\hat{W}^j = \begin{cases} \frac{c_2^j}{4c_3^j} (\exp[c_3^j ((\lambda^j)^2 - 1)^2] - 1) & \text{if } \lambda^j \geq 1, \\ \frac{c_2^j}{4c_{3c}^j} (\exp[c_{3c}^j ((\lambda^j)^2 - 1)^2] - 1) & \text{if } \lambda^j < 1, \end{cases} \quad (2.13)$$

where c_i^k are the material parameters and the stretch experienced by the fibres $\lambda_{n(\tau)}^k(s; t) \equiv \lambda^j$ or λ^m is computed easily, consistent with the aforementioned result $\mathbf{F}_{n(\tau)}^k(s; t) = \mathbf{F}_s(t) \mathbf{F}_{n(\tau)}^k(s)$ (see [Baek et al.,](#)

²One can use different approximations for the collagen orientations, including continuous distributions about two diagonal directions ([Gasser et al., 2006](#)). [Zeinali-Davarani et al. \(2009\)](#) showed further that a six-fibre family model provides an overall best fit to data although residual errors are very similar for the four-fibre family model ([Wicker et al., 2008](#)).

2006). The behaviour for collagen (mainly types I and III) in (2.13) is modelled as bimodular due to its fibrillar structure, expected buckling under compression and compressive resistance by proteoglycans (Cardamone *et al.*, 2009). For simplicity, and due to the lack of complete data, initial behaviours of proteoglycan-supported collagen and smooth muscle were assumed to be the same in compression (i.e. $c_{2c}^j = c_2^m$ and $c_{3c}^j = c_3^m$ at $s = 0$).

Consistent with Baek *et al.* (2007) and Valentín *et al.* (2009), let the active stress generated circumferentially by the smooth muscle be

$$\sigma_{\vartheta}^{\text{act}}(s; t) = T_{\max} \phi^m(s) (1 - \exp[C^2(s)]) \lambda_{\vartheta}^{m(\text{act})}(s; t) \left[1 - \left(\frac{\lambda_M - \lambda_{\vartheta}^{m(\text{act})}(s; t)}{\lambda_M - \lambda_0} \right)^2 \right], \quad (2.14)$$

where $T_{\max}$ is the maximum active stress and λ_M and λ_0 are the circumferential stretches at which the active stress is maximum and zero, respectively. $C(s)$ is the net ratio of vasoconstrictors to vasodilators and the smooth muscle stretch $\lambda_{\vartheta}^{m(\text{act})}(s; t) = a(s; t)/a^{m(\text{act})}(s)$, where inner radius $a^{m(\text{act})}(s)$ evolves on the G&R timescale according to a first-order kinetic relation proposed by Baek *et al.* (2007). Here, we assume the active axial stress to be related to the active circumferential stress via a deformation-dependent scaling, namely

$$\sigma_z^{\text{act}}(s; t) = \chi \lambda_z(s; t)^{\delta} \sigma_{\vartheta}^{\text{act}}(s; t), \quad (2.15)$$

where χ and δ are the dimensionless parameters to be determined via fits to data. Although not well studied, lateral force general by muscle has been measured and modelled (Strumpf *et al.*, 1993; Zahalak, 1996). Finally, note that the mouse carotid does not exhibit a strong myogenic response.

Functional elastin is produced primarily during the perinatal period (Langille, 1993; Wagenseil & Mecham, 2007), hence $m^e(\tau) = 0$ during G&R responses in maturity. In contrast, both fibrillar collagen and smooth muscle turn over continuously on the G&R timescale under both normal and perturbed conditions (Langille, 1993). It appears that altered rates of collagen and smooth muscle production vary with both the local intramural state of stress and the endothelial production of vasoconstrictors and vasodilators, with constrictors (e.g. endothelin-1) tending to promote collagen synthesis and smooth muscle mitosis and dilators (e.g. nitric oxide) tending to inhibit synthesis and mitosis (Humphrey, 2008a). Hence, consider rates of production for $k = j$ and $k = m$ of the form $m^k(\tau) = m^k(\sigma^k(\tau), \tilde{\sigma}^k(\tau), C(\tau))$, where σ^k is a suitable scalar measure of the stress in the k th constituent and $\tilde{\sigma}^k$ is the associated rate measure (cf. (2.10)), both defined on the G&R timescale. Because the ratio of constrictors to dilators C depends in large part on changes in wall shear stress (Humphrey, 2002), we can also write $C(s) = C(\tau_w(s), \tilde{\tau}_w(s))$, where τ_w is the mean wall shear stress and $\tilde{\tau}_w$ its rate measure (e.g. $C(s) = C_s - C_s \Delta \tau_w(s) - C_R \Delta \tilde{\tau}_w(s)$, where C_A are gain-type parameters denoting basal (B), wall shear stress-induced (S) and wall shear stress rate-induced (R) effects). It also appears that the rate of collagen removal (e.g. degradation via proteolysis) depends on local intramural stresses (Willett *et al.*, 2007); hence, let $q^k(s, \tau) = q^k(\sigma^k, \tilde{\sigma}^k)$ in general. Finally, it is possible that stress rate may affect the cross linking of or damage to structural fibres, hence we can let $c_i^k(s) = c_i^k(\tilde{\sigma}_k(s))$, i.e. we assume that the stiffness of a constituent may depend on the stress rate or its history. In particular, this assumption allows one to model fatigue-type damage to elastin, which appears to increase in hypertension and aging wherein pulse pressure and hence stress rates increase (Arribas *et al.*, 2006; Greenwald, 2007; O'Rourke & Hashimoto, 2007), and to capture changes in collagen cross linking in aging due to advanced glycation end products (cf. Pedrighi *et al.* (2007) who suggested that the dimensional constant in exponential relations best captures changes in cross links).

Specifically, for illustrative purposes, let the rate of mass density production of the k th constituent be governed by the linear constitutive function (Valentín *et al.*, 2009)

$$m^k(\tau) = m_0^k[1 + K_\sigma^k \Delta\sigma^k(\tau) + K_{\tilde{\sigma}}^k \Delta\tilde{\sigma}^k(\tau) + K_C^k \Delta C(\tau)], \quad (2.16)$$

where m_0^k is a basal value of the mass production rate and K_α^k (with $\alpha = \sigma^k, \tilde{\sigma}^k, C$) are gain-type sensitivity parameters. Note that a basal rate is recovered, as desired, if normalized perturbations in stress $\Delta\sigma^k$, stress rate $\Delta\tilde{\sigma}^k$ and constrictor concentration ΔC are zero. A scalar metric for stress (or traction) of the k th fibre in the current configuration can be computed using a norm of the Cauchy stress in the direction of the fibre (Valentín *et al.*, 2009), namely

$$\sigma^k(s) = \left| \left(\frac{1}{\det \mathbf{F}} \mathbf{F} \frac{\partial W}{\partial \mathbf{F}^T} + \sigma_\vartheta^{\text{act}} \mathbf{e}_\vartheta \otimes \mathbf{e}_\vartheta + \sigma_z^{\text{act}} \mathbf{e}_z \otimes \mathbf{e}_z \right) \mathbf{m}^k(s) \right|, \quad (2.17)$$

where $\mathbf{m}^k$ is a unit vector in the direction of the k th constituent in the current configuration. That is, one can assume that cells can respond to the overall stress in the tissue and produce new fibres according to the intensity of the stress along a fibre direction. Next, let the survival function for the k th constituent deposited at time τ have the form (Valentín *et al.*, 2009)

$$q^k(s, \tau) = \exp \left[- \int_\tau^s K^k(\eta) d\eta \right], \quad (2.18)$$

where the rate parameters K^k are assumed to be a function of the stress in the fibre σ^k and possibly its rate measure over the cardiac cycle $\tilde{\sigma}^k$. Specifically, for illustrative purposes consider

$$K^k(\eta) = K_h^k + f^k(\Delta\sigma^k(\eta)) + g^k(\Delta\tilde{\sigma}^k(\eta)), \quad (2.19)$$

where

$$f^k(\Delta\sigma^k) = 3K_h^k \left[\frac{2}{\pi} \arctan(\Delta\sigma^k)^4 \right]^2 \quad (2.20)$$

and g^k was chosen similarly for simplicity. This specific functional form was chosen because it is essentially zero in a neighbourhood of zero for its argument, but it grows asymptotically when the argument differs significantly from zero. That is, the removal rate increases up to a limit when the measure of stress or stress rate deviates from its homeostatic value but remains nearly constant near homeostatic values of stress and stress rate (cf. Valentín *et al.*, 2009). If $\Delta\sigma^k = \Delta\tilde{\sigma}^k = 0$, then (2.18) and (2.19) recover the normal half-life of the constituent k consistent with first-order-type kinetics.

As will be seen below, it proved important to assume that collagen deposited at a higher stress rate may be less well cross-linked and more hydrated. A possible consequence of this assumption is that of a net compressive stiffening and tensile softening of the fibrillar network. This possibility was modelled by letting the collagen stiffness parameter depend on a normalized perturbation of the stress rate, namely

$$c_{c2}^j(\tau) = c_{c2}^j(0) \exp[-K_{c2}^j H(\Delta\tilde{\sigma}^j(\tau))], \quad c_{2c}^j(\tau) = c_{2c}^j(0) \exp[K_{2c}^j H(\Delta\tilde{\sigma}^j(\tau))], \quad (2.21)$$

where $H(\cdot)$ denotes the Heaviside step function and K_i^j are sensitivity parameters; the initial values prior to any perturbation in pulsatility are thus recovered as desired. Concerning elastin fragmentation,

we assumed that increased stress rates may accelerate a loss of stiffness suggestive of premature aging (Greenwald, 2007). Hence, let

$$c_1^e(s) = c_1^e(0) \exp \left[- \int_0^s K_{EA} H(\Delta \tilde{\sigma}^e(\tau)) d\tau \right], \quad (2.22)$$

where K_{EA} is a degradation rate parameter having the unit of (time^{-1}) and the elastin stress measure was assumed to be the norm of its Cauchy stress: $\sigma^e = |\sigma| = \sqrt{\sigma_{ij}\sigma_{ij}}$, where repeated indices imply summation per the usual convention.

2.3 Numerical methods

Following Valentín *et al.* (2009), we assumed that the mouse carotid artery is a thin-walled circular cylinder of fixed length subjected to a time-varying internal pressure P and blood flow Q . This assumption of a constant *in vivo* length (not unloaded length, which varies as a consequence of G&R) is reasonable as long as the vessel does not become tortuous (Humphrey *et al.*, 2009), which it does not in the transverse aortic arch banding procedure (Eberth *et al.*, 2009a). Provided that the Womersley number $\alpha = a\sqrt{\rho_f \omega / \mu}$ is small, wall shear stress is generally approximated by the Poiseuille solution

$$\tau_w(s; t) = \frac{4\mu Q(s; t)}{\pi a^3(s; t)}, \quad (2.23)$$

where a is the inner radius of the vessel, $f = \omega/2\pi$ is the frequency of the pressure wave, ρ_f is the density of the fluid and μ is the dynamic viscosity of the blood. Specifically, if $\alpha < 3$, then effects due to inertial forces in the fluid are negligible compared to those due to viscous forces, and the velocity profile of the pulsatile flow is ‘instantaneously’ well approximated by the Poiseuille solution (Zamir, 2000). For the common carotid artery of the mouse, with a reference radius $a = 0.025$ cm, fluid density $\rho_f = 1$ g/cm³, viscosity $\mu = 0.04$ poise and cardiac frequency $f = 1/T \sim 5$ Hz (under experimental conditions for which data are available; Li *et al.*, 2003; Eberth *et al.*, 2009a), $\alpha \sim 0.70$. Similarly, $\alpha \sim 0.99$ for a normal heart rate (i.e. $f = 1/T \sim 10$ Hz) and the steady-state approximation for wall shear stress is again reasonable.

Best-fit values of the material parameters in the constitutive relation for wall stress at G&R time $s = 0$ were determined via non-linear regression of biaxial experimental data from finite extension–inflation tests on normal mouse carotid arteries. Fits were obtained for arteries from three different mice, each represented by two data sets (one for basal muscular tone and one for fully passive behaviour) consisting of 600 stress–stretch points at three different axial stretches (Eberth *et al.*, 2009a). The fitting procedure consisted of two successive steps. First, the objective function (cf. Eberth *et al.*, 2009b)

$$e = \left[\frac{\sum (\sigma_{\vartheta}^{\text{mod}} - \sigma_{\vartheta}^{\text{exp}})^2}{\sum (\sigma_{\vartheta}^{\text{exp}})^2} \right]^{\frac{1}{2}} + \left[\frac{\sum (\sigma_z^{\text{mod}} - \sigma_z^{\text{exp}})^2}{\sum (\sigma_z^{\text{exp}})^2} \right]^{\frac{1}{2}} \quad (2.24)$$

was minimized with respect to the stiffness parameters in (2.11–2.13), the deposition stretches and the diagonal collagen fibre orientation α_o (16 parameters total for the four-fibre family model). Second, once parameters characterizing the passive behaviour of the vessel were known, the error function (2.24) was minimized again with respect to the five parameters of (2.14) and (2.15), with the experimental values (exp) then corresponding to basal smooth muscle activation. *In vivo* waveforms for intramural pressure

and blood flow rate were similarly obtained for the normal carotid artery by fitting eighth-order Fourier series representations, (2.8) and (2.9), using data reported by Eberth *et al.* (2009a) and Li *et al.* (2003) but rescaling for the frequency of a non-anaesthetized mouse.³

Finally, note that all G&R simulations were performed following the flow chart in Appendix B using a nested Newton–Raphson method as reported by Valentín *et al.* (2009) and Baek *et al.* (2007) for the resolution of the equilibrium equation on the G&R timescale. Moreover, note that results are first presented below based on the common assumptions that G&R depends primarily on changes in mean stresses independent of stress rate-dependent changes in elastin and collagen integrity; contrasting results are then presented based on the new constitutive relations proposed herein to account for such effects in the carotid artery of the mouse.

3. Results

3.1 Fitting biaxial mechanical data

Recall that one goal was to model the response of the right common carotid artery of the mouse to perturbations in pressure and flow induced by transverse aortic arch banding, which necessitated that we account for both the passive (i.e. relaxed smooth muscle) and the active (i.e. basal tone) biomechanical behaviours. Constituent mass fractions, typical of a mouse carotid artery, were obtained from Lacolley *et al.* (2001) and are reported in Table 1. Note that the amount of elastin is greater than collagen, which appears to confer important axial mechanical properties (Humphrey *et al.*, 2009). Associated best-fit values of the material parameters are listed in Table 2 for passive and basal behaviours exhibited by all three specimens. Note that axial collagen fibres were, on average, stiffer than circumferential and diagonal fibres (i.e. higher values of c_2^z and c_3^z compared to c_2^θ, c_3^θ and c_2^d, c_3^d , respectively). All collagen fibres were estimated to be deposited at modest pre-stretches, ranging from 0 to 11%, with diagonal fibres oriented slightly towards the axial direction (i.e. $\alpha_0 < 45^\circ$). The estimated stiffness parameter for elastin c_1^e was within the reported range (Fung, 1993). As expected, estimated pre-stretches were much higher for elastin than for collagen, with those in the axial direction higher than those in the circumferential direction. The former finding appears to be consistent with the extreme biological stability of elastin and its production primarily in the perinatal period, prior to subsequent extension as the artery follows the growth of the body during normal maturation (Humphrey *et al.*, 2009). The passive smooth muscle was much softer than the collagen as expected. Overall, the biaxial passive behaviour of the vessel was well approximated in both principal directions as indicated by small values of the objective function (' e passive' in Table 2) and revealed by Fig. 2 (comparison of model to data for specimen #3).

Fitting the basal data revealed that it was necessary to include an axial component of the active stress generated by the smooth muscle (cf. (2.15)). Specifically, when the axial component of active stress was neglected, as is usually the case, the model underestimated the axial force at higher values of axial stretch (e.g. $\lambda_z \sim 1.75$, close to the measured *in vivo* value) and overestimated it for lower values (not shown). Introduction of an axial component of active stress captured the overall axial behaviour well (Fig. 3), thus suggesting a multiaxial effect due to contraction of smooth muscle (cf. Zahalak, 1996). The large values of χ and δ (Table 2) reinforced the importance of the axial component of the active stress. Finally, the computed *in vivo* axial stretches and vasoactive ranges for the three

³Note that, assuming values mentioned above for the mouse carotid, the Womersley number is less than 3 for the first eight harmonics. Thus, the Poiseuille solution is a good approximation for all harmonics of the series considered herein.

TABLE 1 Values of geometric, material, functional and remodelling parameters used to simulate both the normal mechanical behaviour of a mouse carotid artery and its response to transverse aortic arch banding. ‘Observed’ parameters include those reported in literature. ‘Bounded’ parameters are less well known but can be chosen such that the model yields expected biomechanical behaviours. ‘Optimized’ parameters are obtained via minimization of objective functions (i.e. (2.24)) to fit experimental data

Class	Role	Value	Reference
Observed	Initial vessel geometry	$a_h = 250 \mu\text{m}$, $h_h = 26 \mu\text{m}$	Eberth <i>et al.</i> (2009a)
	Initial mass fractions	$\phi_0^e = 0.285$, $\phi_0^j = 0.238$, $\phi_0^m = 0.477$	Lacolley <i>et al.</i> (2001)
	Physical constants	$\rho = 1.050 \text{ g/cm}^3$, $\rho_f = 1.000 \text{ g/cm}^3$, $\mu = 0.04 \text{ Poise}$	Humphrey (2002)
	Homeostatic kinetics	$K^j = K^m = 1/80 \text{ day}^{-1}$	Langille (1993)
	Cardiac frequency	$f = 5\text{--}10 \text{ Hz}$	Valentín <i>et al.</i> (2009)
Bounded	Production kinetics	$K_C^j = K_C^m = 10$, $K_\sigma^j = K_\sigma^m = 1$, $K_\sigma^j, K_\sigma^m \in [1, 100]$	Eberth <i>et al.</i> (2009a)
	Remodeling kinetics	$K_{c2}^j, K_{c2c}^j \in [0, 5.0]$ and $K_{EA} \in [0, 1.0] \text{ day}^{-1}$	
	Shear constrictor	$C_B = 0.68$, $C_S = C_R = 20 C_B$	
Optimized	Elastic parameters	$c_1^e, c_2^j, c_3^j, c_2^m, c_3^m$	see Table 2
	Fibers orientation	α_0	
	Deposition stretches	$G_z^e, G_\phi^e, G^j, G^m$	see Table 3
	Muscle activation	$T_{\max}^z, \lambda_M, \lambda_0, \chi, \delta$	
	Pressure and flow wave form	$P_m, Q_m, A_n, B_n, C_n, D_n$	

TABLE 2 Best-fit values of material parameters for combined pressure–diameter and axial force–length tests on three normal mouse carotid arteries (see (2.11–2.15)), with axial stretch computed relative to the unloaded configuration and active radial contraction–dilation ranges given; e is the minimization error. The *in vivo* axial stretch, active contraction and active dilation reflect experimental findings in Eberth et al. (2009a)

Four families of collagen fibres											
Specimen	c_2^z (kPa)	c_2^θ (kPa)	c_2^d (kPa)	c_3^z	c_3^θ	c_3^d	G^z	G^θ	G^d	α_0 (°)	
#1	2777.6	741.4	2206.5	50.2	4.4	33.6	1.013	1.05	1.03	31.4	
#2	1799.5	2489.6	232.3	16.2	15.6	14.9	1.050	1.00	1.11	37.0	
#3	3066.1	1146.5	582.1	22.1	1.9	11.1	1.035	1.07	1.11	32.3	
Elastin				Passive muscle				Active muscle			
Specimen	c_1^e (kPa)	G_θ^e	G_z^e	c_2^m (kPa)	c_3^m	G^m	$T_{\max}$ (kPa)	λ_M	λ_0	χ	δ
#1	145.3	1.407	1.708	2.6	0.16	1.693	330.2	2.0	0.422	1.23	17.5
#2	87.9	1.628	1.778	33.9	0.95	1.027	243.3	2.0	0.288	1.12	18.6
#3	135.6	1.379	1.847	21.2	1.82	1.029	327.4	2.0	0.481	0.59	26.5
Specimen	e passive	e basal	<i>In vivo</i> axial stretch λ_z^{iv}				Maximum dilation (%)	Maximum contraction (%)			
#1	0.07482	0.15016	1.70				9.0	27.5			
#2	0.07925	0.14856	1.82				7.0	35.4			
#3	0.05134	0.12694	1.86				9.7	23.7

FIG. 2. A best fit by the constrained mixture model (2.11–2.13) to experimental data (Eberth *et al.*, 2009b) from a passive mouse carotid artery: (a) circumferential stress–circumferential stretch and (b) axial stress–circumferential stretch curves at three different fixed axial stretches (1.65, 1.75 and 1.85 relative to the unloaded configuration). Dots represent experimental data and solid lines represent calculated values. The approximation error was $e = 0.05134$ and the model gave an excellent fit to the passive behaviour in both axial and circumferential directions.

specimens (Table 2) were close to reported values (Eberth *et al.*, 2009b), including the bias of the basal state towards passive during the *in vitro* tests. These findings suggested further the overall utility of the model.

3.2 G&R in a mouse carotid subjected to aortic banding

Once the baseline mechanical behaviour of the wall is captured adequately, the equation of motion (2.6) can be solved over the cardiac cycle for a normal artery (i.e. at $s = 0$). The pressure wave for normal conditions (2.8) is depicted by a solid line in Fig. 4(a) and described by Fourier coefficients given in Table 3.

Although mixture models necessarily contain many parameters, Valentín & Humphrey (2009a) showed that many of these parameters can be determined directly from data or are well bounded physically (e.g. mass fractions must range from 0 to 1 and deposition stretches must range from 1 to 2). That is, what is often more important is the basic hypothesis giving rise to a particular constitutive relation or parameter, not the number of associated parameters *per se*. Nevertheless, Valentín & Humphrey (2009b) also performed a parameter sensitivity study on values not known well (e.g. the gain parameters governing the kinetics of production and removal (K_C^k , K_σ^k) and parameters governing shear stress-regulated contractility (C_B , C_S)). Here, we restricted our attention to a complementary sensitivity analysis for the previously unstudied kinetic parameters of Table 1: K_σ^k and the set (K_{c2}^j , K_{c2c}^j , K_{EA}).

FIG. 3. A best fit by the constrained mixture model to experimental data from a mouse carotid artery (specimen #3) at basal muscular tone: (a) circumferential stress–stretch and (b) axial stress–circumferential stretch curves at three different fixed axial stretches (1.65, 1.75 and 1.85 relative to the unloaded configuration). Dots represent experimental data and solid lines the calculated values. The approximation error was $e = 0.12649$; the model thus fit reasonably well both the axial and the circumferential behaviour of the vessel. The best fit without an axial component of active stress (not shown) gave an error $e = 0.27591$, which suggested that an axial component of stress generated by smooth muscle contraction, modelled here via (2.15), was necessary to reproduce accurately the biaxial behaviour of the vessel.

Data were gathered for individual samples before transverse aortic arch banding and compared to mean values 5–8 weeks after banding. Please see Eberth *et al.* (2009a) for the associated data. Accordingly, for subjects used in this paper, there was a 17.7% decrease in cardiac frequency, an $\sim 8.5\%$ decrease in mean pressure (not statistically significant), a 27.4% increase in mean blood flow, a 43% increase in pulse pressure (i.e. $P_{\text{sys}} - P_{\text{dias}}$) and a 57.8% increase in ‘pulse flow’ (i.e. $Q_{\text{max}} - Q_{\text{min}}$) in the right common carotid artery. If G&R were governed by these mean values of pressure and flow rate (cf. Valentín *et al.*, 2009), restoration of the mean circumferential stress $\sigma_\theta = P_m a / h$ and mean wall shear stress $\tau_w = 4\mu Q_m / \pi a^3$ would predict less than a 1.0% decrease in thickness and an $\sim 8\%$ increase in radius. The associated predicted increase in overall volume of the wall, in the absence of matrix turnover, would also suggest an increase in axial force, at a fixed length, and likely a stiffening evidenced by a leftward shift in the pressure–radius curve. Experimental findings were very different, however. For example, a representative artery (see the original paper for histological images) revealed a 218% increase in thickness and 44% increase in radius (well above the vasoactive dilatory capability of the vessel). The dramatic discrepancy between simple model predictions and data suggests, as one possibility, that dynamic features of the pressure and flow patterns over the cardiac cycle may play a fundamental role in the G&R process consistent with many experimental findings. Indeed, comparing the pre-banding specimens studied in this paper to the post-banding group mean further revealed a

FIG. 4. (a) Transmural pressure and (b) blood flow patterns over the cardiac cycle used for the simulations. Normal time courses (solid lines) were obtained by fitting eighth-order Fourier series to experimental data ($\circ$) from Eberth *et al.* (2009a) and Li *et al.* (2003). The perturbed conditions (dotted curves) were calculated from the normal conditions by modifying the mean values and the Fourier coefficients (Table 3) according to experimental findings, i.e. imposing a 17.7% decrease in cardiac frequency, an 8.5% decrease in mean pressure, a 27.4% increase in mean blood flow, a 43% increase in pulse pressure and a 57.8% increase in pulse flow.

5-fold reduction in axial force, a marked reduction of the specimen *in vivo* axial stretch λ_z^{iv} from 1.75 to 1.27, computed relative to the unloaded configuration, a significant increase in axially oriented collagen and a slight rightward shift of the passive pressure–diameter curve. The data also suggested that much of the G&R process reached a steady state 5–8 weeks after the banding surgery, although not with respect to maturation of collagen (e.g. compaction, fibre thickening and cross linking).

The present G&R simulations were performed using material parameters obtained for specimen #3 in Table 2, while investigating possible effects of elastin fragmentation and collagen remodelling. With the exception of the ‘rate parameters’ K_{σ}^k , which were studied parametrically, and the ‘remodelling’ parameters K_{c2}^j , K_{c2c}^j and K_{EA} , whose effect was tested in two separate sets of simulations, the other production and removal parameters were fixed at values reported in Table 1 based on parametric studies reported in Valentín & Humphrey (2009b). Finally, the imposed perturbation in all G&R simulations

TABLE 3 *Fourier coefficients for transmural pressure and volumetric flow rate for mouse carotid arteries under normal conditions. These values were obtained by fitting Fourier expansions (2.8) and (2.9) to measured waveforms in Eberth et al. (2009a) and Li et al. (2003)*

	$P_m = 89.66 \text{ mmHg}$		$Q_m = 13.24 \text{ mm}^3/\text{s}$	
	$A_n \text{ (mmHg)}$	$B_n \text{ (mmHg)}$	$C_n \text{ (mm}^3/\text{s)}$	$D_n \text{ (mm}^3/\text{s)}$
1	-4.83	25.19	2.84	12.88
2	-12.03	3.20	-6.34	-0.04
3	-2.88	-2.19	-1.00	-0.62
4	-2.28	-0.57	-1.34	0.0
5	-0.70	-2.14	-0.75	0.05
6	0.06	-0.79	-0.17	-0.04
7	0.44	0.16	-0.39	0.02
8	0.57	0.0	-0.18	0.02

included a sustained increase in pressure and flow patterns and decrease in frequency consistent with the aforementioned experimental values (from the solid to the dotted curves in Fig. 4).

For purposes of comparison, Figs 5–8 show results for simulations with $K_{c2}^j = K_{c2c}^j = 0.0$ and $K_{EA} = 0.0 \text{ day}^{-1}$, i.e. with the stiffness of the newly deposited collagen independent of stress rate and with the elastin manifesting no fatigue-type fragmentation (essentially null hypotheses). Specifically, Fig. 5 shows the evolution of vessel geometry. The initial increase in radius (panel 5(a)), despite the slight reduction in mean pressure, resulted from muscle relaxation induced by the increased mean and pulsatile blood flow. This initial increase in radius was overcompensated by the deposition of a significant amount of collagen for high values of K_{σ}^k (cf. Fig. 6), while the radius kept increasing, after an initial oscillation, for small values of K_{σ}^k . The initial reduction in thickness (panel 5(b)) was due to an ‘instantaneous’ isochoric motion. For small values of K_{σ}^k , the thickness decreased to a minimum value, but recovered partially (up to 85% of the original value). For higher values of K_{σ}^k , the thickness increased monotonically and the initial reduction was overcompensated by tissue hypertrophy (cf. Fig. 6).

For high values of K_{σ}^k , the copious deposition of stiff and modestly pre-stretched collagen (recall Fig. 6) counteracted the recoiling effect of the elastin and thereby reduced the axial retraction upon ‘numerical excision’ of the artery; this finding explains the slight reduction of the *in vivo* axial stretch reported in Fig. 7. The response was different for small values of K_{σ}^k . The initial atrophy of the vessel and subsequent deposition of collagen in a dilated state (not shown) led to a predicted slight increase of the *in vivo* axial stretch within 5–8 weeks after surgery, a finding not consistent with the experimental findings.

Copious deposition of collagen, as reflected in Fig. 6 for $K_{\sigma}^k = 50$, rendered the artery stiffer and increased the axial force at a given radius (Fig. 8). Both phenomena stand in contrast to the experimental evidence that shows a significant drop in axial force at fixed geometry and a rightward shift in the pressure–radius curves.

Figure 6 also shows the predicted evolution of mass production rate and total mass density of individual constituents. Panel (a) shows that production of circumferential collagen and proliferation of smooth muscle cells were inhibited, while production of axially and diagonally oriented collagen jumped 5- to 7-fold higher than normal and stayed elevated (up to 17-fold higher than normal for axial collagen) for

FIG. 5. (a) Predicted evolution of inner radius normalized with respect to its original value. The initial increase, despite a slight reduction of mean pressure (not statistically significant), resulted from muscle relaxation induced by an increased mean and pulsatile blood flow. This initial increase was overcompensated by the model at high values of K_{σ}^k due to the deposition of a significant amount of collagen (see Fig. 8). (b) Evolving thickness normalized with respect to its original value. Its initial reduction was due to isochoric motion. Panels (a) and (b) show the results for a parametric sensitivity study: $K_{\sigma}^k = 100$ (bold dashed), $K_{\sigma}^k = 50$ (dashed), $K_{\sigma}^k = 30$ (solid), $K_{\sigma}^k = 10$ (dotted) and $K_{\sigma}^k = 1$ (bold dotted). The stiffness of the newly deposited collagen was prescribed to be independent of stress rate ($K_{c2}^j = K_{c2c}^j = 0.0$) and the elastin was not allowed to fragment ($K_{EA} = 0.0 \text{ day}^{-1}$).

the entire process. These variations in mass production rates resulted in a large increase in axial and diagonal collagen and the almost complete loss of circumferential collagen and smooth muscle reported in panel (b).

As evident from Figs 5–8, computational predictions for all the measurable macroscopic quantities (i.e. radius, thickness, *in vivo* axial stretch, passive mechanical behaviour, total mass) did not reach steady state within 8 weeks.

Figures 9–13 show results of simulations with $K_{c2}^j = K_{c2c}^j = 5.0$ and $K_{EA} = 1.0 \text{ day}^{-1}$, i.e. including our postulated dependency of the stiffness of the newly deposited collagen on the current stress rate and the potential for stress rate-induced elastin fragmentation. Figure 9 shows the evolution of the vessel geometry. The instantaneous increase in caliber, despite the reduction of mean pressure, was again due to muscle relaxation induced by increased mean and pulsatile blood flow (panel (a)). The radius increased further for about 4 weeks, then tended to reach steady state (faster for lower values of K_{σ}^k). Values at Week 8, regardless of the value of K_{σ}^k , reflected those observed experimentally. For small values of K_{σ}^k , the radius exhibited a non-monotonic time course and reached a maximum around Week 3. The initial reduction in thickness (panel (b)) was due to the isochoric motion induced by smooth

FIG. 6. Predicted evolution of (a) normalized mass production rate and (b) normalized total mass per unit surface area for axially (solid curves), circumferentially (dashed curves) and diagonally oriented (dotted curves) collagen and for smooth muscle (dash-dotted curves). The boldface solid curve in panel (b) shows the evolution of the total mass of the mixture per unit surface area, which almost doubled at Week 8. Here, $K_{\sigma}^k = 50$. Stiffness of the newly deposited collagen was prescribed to be independent of stress rate ($K_{c2}^j = K_{c2c}^j = 0.0$) and the elastin was not allowed to fragment ($K_{EA} = 0.0 \text{ day}^{-1}$).

FIG. 7. Predicted evolution of the *in vivo* axial pre-stretch (computed relative to the unloaded configuration). The deposition of modestly pre-stretched collagen counteracted the recoiling effect of elastin, thus reducing axial retraction upon excising the vessel from the body. The predicted reduction of the *in vivo* axial stretch is much smaller than that observed experimentally. Results for $K_{\sigma}^k = 100$ (bold dashed), $K_{\sigma}^k = 50$ (dashed), $K_{\sigma}^k = 30$ (solid), $K_{\sigma}^k = 10$ (dotted) and $K_{\sigma}^k = 1$ (bold dotted). The stiffness of the newly deposited collagen was prescribed to be independent of the stress rate ($K_{c2}^j = K_{c2c}^j = 0.0$) and the elastin was not allowed to fragment ($K_{EA} = 0.0 \text{ day}^{-1}$).

FIG. 8. Predicted passive behaviour of the vessel at its *in vivo* length for $K_{\sigma}^k = 50$: (a) transmural pressure and (b) axial force as a function of the inner radius. The copious deposition of collagen rendered the vessel stiffer (a) and increased the axial force at a given radius (b). Both predictions stand in contrast to experimental findings (cf. Fig. 11); hence, note that the stiffness of the newly deposited collagen was prescribed to be independent of stress rate ($K_{c2}^j = K_{c2c}^j = 0.0$) and the elastin was not allowed to fragment ($K_{EA} = 0.0 \text{ day}^{-1}$).

muscle relaxation. The non-monotonic time course of the thickness was more evident for lower values of K_{σ}^k and the final value at Week 8 was higher for smaller values of K_{σ}^k . The thickness also tended towards a steady state during the last 2 weeks of the simulation, following qualitatively the data but still much less than that observed experimentally (Eberth *et al.*, 2009a).

Due to a degradation-induced softening of the elastin (Fig. 10(c)), deposition of collagen having a higher stiffness in compression (Fig. 10(b)) and an increased collagen-to-elastin ratio (Fig. 11(b)), the *in vivo* axial stretch decreased significantly from 1.86, for the normal vessel, to 1.42 to 1.13 depending on the value of K_{σ}^k (Fig. 12). The dependency of the steady-state value of *in vivo* axial stretch on the value of K_{σ}^k was non-monotonic.

Despite the deposition of significant amounts of collagen and increase of total mass (cf. Fig. 11), the overall pressure–radius curve shifted to the right (Fig. 13(a)), suggesting a softening of the vessel. Similarly, the predicted axial force at a given inner radius dropped significantly (Fig. 13(b)), both in agreement with experimental findings (Eberth *et al.*, 2009a). This predicted behaviour resulted, in part, from the lower tensile stiffness of collagen deposited at a higher stress rate (cf. Fig. 10(a)) and from elastin degradation (see Fig. 10(c)). Both the pressure–radius and the axial force–radius curves underwent modest variations from Weeks 5 to 8, which again agreed with experimental findings.

The model also reproduced the abundant deposition of axial collagen (Fig. 11) observed in the experiments (Eberth *et al.*, 2009a), due to the significant increase in the corresponding mass production

FIG. 9. Predicted results for $K_{\sigma}^k = 100$ (bold dashed), $K_{\sigma}^k = 50$ (dashed), $K_{\sigma}^k = 30$ (solid), $K_{\sigma}^k = 10$ (dotted) and $K_{\sigma}^k = 1$ (bold dotted). (a) Inner radius normalized with respect to its original value. The instantaneous increase of the lumen, despite the reduction of mean pressure, was due to muscle relaxation induced by increased mean and pulsatile blood flow. The radius kept increasing and was close to steady state at Week 8, essentially following the time course observed in the experiments. (b) Thickness normalized with respect to its original value. The initial reduction was due to smooth muscle-induced isochoric motion, and recovery was faster for higher values of K_{σ}^k . For $K_{\sigma}^k = 50$, the thickness showed an almost steady-state behaviour in the last 2 weeks of the simulation, but its increase was smaller than observed experimentally (Eberth *et al.*, 2009b). The stiffness of the newly deposited collagen depended on stress rate ($K_{c2}^J = K_{c2c}^J = 5.0$) and the elastin fragmented ($K_{EA} = 1.0 \text{ day}^{-1}$).

rate. Also the diagonal collagen, oriented about 32° from the axial direction (Table 2), increased significantly. The model predicted a reduction of circumferential collagen and an almost complete loss of (functional) smooth muscle, which could explain in part the reduction of vasoactive capability reported experimentally. The predicted evolution of total mass seemed to be more stable compared to the case with no changes in collagen stiffness or elastin fragmentation (compare panels 11(b) to 6(b)).

Collagen stiffness tended to come back towards basal values after a significant initial deviation (Fig. 10(a and b)). The initial increase in stress rate, due to increased pulse pressure, led to the deposition of softer collagen in tension as well as degradation of elastin. These remodelling phenomena reduced both the stress and the stress rate and thereby affected the stiffness of the subsequently deposited collagen, thus limiting the initial divergence and extent of elastin degradation. The model predicted a severe fragmentation of elastin, concentrated within the first 4–5 weeks, with a drop in stiffness to $\sim 5\%$ of the normal value (Fig. 10(c)).

Comparison of Figs 5–8 with Figs 9–13 suggests that allowing the stiffness of newly synthesized collagen to differ and elastin to degrade as a function of stress rate (2.21–2.22) enabled a better agreement with experimental findings for all macroscopically and microscopically measurable quantities. Wall thickness was the only macroscopic quantity whose predicted evolution was quantitatively far from the

FIG. 10. Time courses of normalized stiffness parameters for newly deposited collagen (a) in tension and (b) in compression for axially (solid curves), circumferentially (dashed curves) and helically oriented (dash-dotted curves) collagen. These values tended to return towards original values after a marked initial deviation. (c) Normalized elastin stiffness: the model predicted a severe fragmentation, particularly within the first 3–4 weeks.

experimental finding, though it was in qualitative agreement with the observed time course. Reasons for the quantitative discrepancy in the predicted versus measured thickness could be many. For example, there may have been a change in the apparent mass density due to increased tissue porosity and hydration, or some of the deposited material may not have been mechanically effective and thus did not bear load—these same issues are discussed in Eberth *et al.* (2009a) to address the unexpected experimental finding of such a large increase in wall thickness, due primarily to increased adventitial, axially oriented collagen that appeared loosely organized and to consist of thinner, more fragile fibres.

4. Discussion

Arteries exhibit a remarkable ability to adapt to diverse genetic defects and alterations in mechanical loading, and it will likely be many years before we can reliably predict all such changes within a common mathematical framework. Nevertheless, computational models of arterial G&R have evolved

FIG. 11. Predicted evolution, for $K_{\bar{\sigma}}^k = 50$, of (a) normalized mass production rate and (b) normalized total mass per unit surface area for axially (solid curves), circumferentially (dashed curves) and diagonally oriented (dotted curves) collagen and for smooth muscle (dash-dotted curves). The boldface solid curve in panel (b) shows the evolution of the total mass of the mixture per unit surface area. The stiffness of the newly deposited collagen depended on the stress rate ($K_{c2}^j = K_{c2c}^j = 5.0$) and the elastin fragmented ($K_{EA} = 1.0 \text{ day}^{-1}$). The model reproduced the abundant deposition of axial collagen observed experimentally (Eberth *et al.*, 2009b). Moreover, the helical collagen, oriented about 32° from the axial direction (see Table 2), increased significantly. The model also predicted a significant reduction of smooth muscle, which could explain the reduction of vasoactive capability of the vessel, and an increment of the axially oriented collagen fibres, both observed in the experiments.

FIG. 12. Predicted evolution of the *in vivo* axial stretch (computed from the unloaded configuration) for $K_{\bar{\sigma}}^k = 100$ (bold dashed), $K_{\bar{\sigma}}^k = 50$ (dashed), $K_{\bar{\sigma}}^k = 30$ (solid), $K_{\bar{\sigma}}^k = 10$ (dotted) and $K_{\bar{\sigma}}^k = 1$ (bold dotted). Due to damage- or degradation-induced loss of elastin (Fig. 13(c)) and deposition of collagen having a higher stiffness in compression (Fig. 13(b)), the reduction in *in vivo* axial stress followed well the time course observed experimentally (Eberth *et al.*, 2009b). The stiffness of the newly deposited collagen depended on the stress rate ($K_{c2}^j = K_{c2c}^j = 5.0$) and the elastin fragmented ($K_{EA} = 1.0 \text{ day}^{-1}$).

FIG. 13. Predicted passive behaviour of the vessel at its *in vivo* length for $K_a^k = 50$: (a) transmural pressure and (b) axial force as a function of the inner radius. Despite the deposition of a significant amount of collagen and increase of total mass, the vessel softened (a) and the axial force at a given inner radius dropped significantly (b), both in agreement with experimental findings (Eberth *et al.*, 2009b). This behaviour is related to the lower tensile stiffness of collagen deposited at a higher stress rate (cf. Fig. 13(a)) and to loss of elastin (Fig. 13(c)). The stiffness of the newly deposited collagen depended on the stress rate ($K_{c2}^j = K_{c2c}^j = 5.0$) and the elastin fragmented ($K_{EA} = 1.0 \text{ day}^{-1}$).

quickly over the past decade and many have captured salient features of observed adaptations. In particular, it has long been thought that arteries adapt to sustained alterations in blood pressure and blood flow so as to maintain nearly constant the mean circumferential wall stress and the mean wall shear stress (e.g. Wolinsky, 1970; Kamiya & Togawa, 1980), given, respectively, by Laplace's and Poiseuille's results based on mean values of pressure and flow. These hypotheses lead to simple predictions for changes in radius and wall thickness (Humphrey, 2008b), which have been captured well by different models of arterial G&R. Other experimental evidence suggests, however, that pulsatile characteristics of pressure and flow may also be important determinants of arterial adaptation (e.g. Guyton & Hartley, 1985; Boutouyrie *et al.*, 1999; Eberth *et al.*, 2009a), particularly for large elastic arteries, which appears to support the growing awareness of the importance of central pulse pressure in human disease (Blacher & Safar, 2005; Agabiti-Rosei *et al.*, 2007; O'Rourke & Hashimoto, 2007). In this paper, we presented the first G&R model to consider both the potential effects of stress and stress rate on cell and matrix turnover and the possibility that newly produced collagen may exhibit a lower tensile stiffness while elastin may experience an accelerated loss of structural integrity due to increased stress rates. This work is also the first, to our knowledge, to model specific data from a single experiment rather than merely to describe salient observations from diverse general experiments.

Consistent with prior findings (cf. [Humphrey & Na, 2002](#)), we submit that arterial mechanics over the cardiac cycle is described well by assuming quasi-static rather than dynamic motions, even in the mouse. That is, a simple dimensional analysis reported in Appendix A (and similarly numerical simulations that were not shown) confirmed that inertial forces on the wall are negligible for the mouse carotid artery despite the high heart rate (~ 5 – 10 Hz depending on anaesthesia). Moreover, because of the very different timescales associated with the cardiac cycle and typical periods needed for growth and remodelling, we submit that G&R does not occur over the cardiac cycle (see [Figueroa *et al.*, 2009](#)). These ideas allow one to compute simple rate measures on ‘microscale times’ that can drive adaptive processes on ‘macroscale times’. Our proposed approach, employing a particular choice of rate measures, can also account for effects of phase change between pressure and flow waves on G&R processes.

Development of the present model was driven by the desire to understand and model the response of the mouse right common carotid artery to a transverse aortic arch banding procedure that alters simultaneously the pulse pressure, mean flow and pulsatile flow ([Eberth *et al.*, 2009a](#)). The first step was to model the baseline mechanical properties in both passive and basal states, which was accomplished using a two-step fitting procedure based on a non-linear regression of biaxial data. We found that our basic stress–stretch relations fit the passive data well, but there was a need to introduce an axial contribution of smooth muscle to fit the basal data. There has been some discussion about the likely multiaxial behaviour of contracting muscle (e.g. [Strumpf *et al.*, 1993](#)), but little actual attempt to fit multiaxial data. Because this was not a primary focus of the present work, we introduced a simple scaling method (2.15) that provided an acceptable fit to data (Fig. 3) and allowed us to progress to the primary focus—G&R. There is, therefore, a need for more attention to this potentially very important aspect of arterial mechanics.

The measured evolution of carotid artery geometry, passive behaviour and unloaded length was captured by our constrained mixture model only after multiple constitutive relations were modified appropriately. Note, therefore, that our prior G&R simulations (e.g. [Baek *et al.*, 2006](#); [Valentín *et al.*, 2009](#)) focused on cerebral arteries and aneurysms, which are very different from central elastic (e.g. carotid) arteries—cerebral arteries are muscular arteries and they contain much less intramural elastin. Indeed, it is well known that both hypertension and aging exert very different effects on muscular and elastic arteries ([Benetos *et al.*, 1993](#); [Bortolotto *et al.*, 1999](#)); thus, it is not surprising that our previously developed constitutive relations required some modification. Specifically, comparison of simulations in many different parametric studies against biomechanical data (many results of which were not shown) suggested that there was a need to account for a progressive damage to or degradation of elastin and a diminished stiffness of newly produced collagen. The former is consistent with findings of lost elastic fibre integrity in both hypertension and aging ([Arribas *et al.*, 2006](#); [O’Rourke & Hashimoto, 2007](#)); the latter is consistent with polarized light microscopic images that reveal thinner, and thus possibly less stiff, collagen fibres in the mouse carotid arteries studied by [Eberth *et al.* \(2009b\)](#). Both phenomena were assumed to be driven by suitable measures of stress rate. Although the specific functional forms considered herein provided reasonable predictions, there remains a pressing need for experiments to guide the formulation of improved relations. Indeed, because of the importance of other matrix proteins (e.g. collagen V) and proteoglycans (e.g. biglycan) in collagen fibrillogenesis and the importance of glycoprotein microfibrils in elastic fibre stability (e.g. fibrillin-1), there is similarly a need to correlate associated changes with altered mechanical metrics. So, too, there is a need to quantify better from data the normally slow aging-associated loss of elastic fibres over decades ([O’Rourke & Hashimoto, 2007](#); [Greenwald, 2007](#)) as well as the possible accelerated loss in cases of increased pulse pressure or heart rate ([Avolio *et al.*, 1998](#); [Arribas *et al.*, 2006](#)). Nevertheless, we

found that inclusion, to the best of our knowledge for the first time, of a stress rate-mediated loss of elastin effectiveness and a decreased tensile stiffness of collagen allowed us to match most of the experimental findings of Eberth *et al.* (2009a). For example, the observed overall softening of the artery, despite significant increases in radius and thickness, was understandable only by assuming that the newly deposited collagen was somehow less effective in bearing load (e.g. less cross linked) and/or that original constituents lost some of their mechanical integrity (e.g. elastin degradation or fragmentation). Related to this issue, the one aspect of the model predictions that did not match well the experimental findings was wall thickness. Indeed, the measured increase in wall thickness was also significantly greater than expected based on a mean circumferential stress ($\sigma_\theta = Pa/h$) mediated adaptation that has dominated thinking for decades. There remains a need, therefore, first to understand better the composition of the thickened wall (primarily the adventitia) and second to improve our associated modelling.

Numerous experimental (e.g. Dancu *et al.*, 2004) and theoretical (e.g. Tada & Tarbell, 2005) works suggest that differences in phase between pressure and flow waves can also play an important role in modulating gene expression by endothelial cells and thereby influence overall G&R, at least in coronary arteries. Differences in phase were taken into account herein in an indirect way. First, however, note that the excursion of wall shear stress (and thus its rate) was least for in-phase waveforms because, in this case, the maximum (minimum) of the flow wave was synchronized with the maximum (minimum) of the pressure wave and therefore with the maximal (minimal) radius over the cardiac cycle. That is, in this case the excursion of wall shear stress τ_w induced by variations in flow was mitigated, in part, by the compliance of the vessel. Conversely, in the case of significant differences in phase between pressure and flow, the maximum (minimum) value of flow occurred when the radius was far from its maximum (minimum) value, which increased the excursion of τ_w over the cardiac cycle and therefore the rate measure $\dot{\tau}_w$. Starting with the baseline case, with in-phase pressure and waveforms (always the case in the simulations presented herein), a shift in the flow (or pressure) wave would cause an increase in $\dot{\tau}_w$, a consequent drop in the constrictor concentration and eventually an increase in the luminal radius with effects similar to an increase in mean or pulsatile flow. This mechanism could explain the increase in ET-1 and reduction in NO production by endothelial cells for the increased phase between pressure and flow waves reported in Dancu *et al.* (2004); nevertheless, more simulations and modelling efforts are needed in this case as well.

In summary, we showed that a previously reported constrained mixture model of arterial G&R in cerebral arteries had to be modified via augmented constitutive relations to capture experimental data from a complex *in vivo* model of hypertension in mouse carotid arteries (i.e. data on passive and active biaxial mechanical behaviours as well as the evolution of geometry and structure of the wall in response to altered mean values, amplitudes and frequencies of pulsatile pressure and flow). Moreover, we showed that these modifications suggested interesting new hypotheses that need to be tested experimentally. For example, although data from diverse sources support some of these hypotheses, there is a pressing need for direct measurements of biaxial contractility, stress rate-mediated elastin degradation/damage and stress rate effects on collagen synthesis in arteries under *in vivo* conditions. Although further refinements and validation of constrained mixture models for different types of arteries must await additional data, we submit that the capture so many complex behaviours provides strong motivation to continue to pursue this general approach.

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Appendix A

The numerical finding in [Humphrey & Na \(2002\)](#), that inertial forces are generally negligible in wall mechanics over the cardiac cycle, is supported here for the special case of the mouse common carotid artery via a simple analysis of orders of magnitude of the terms in (2.5). Using the radius a as a reference length, the cardiac period T as a reference time, the mean pressure P_m as a reference pressure and wall density ρ as a reference mass density, the radial equilibrium equation (2.5) can be written in the non-dimensional form as

$$\frac{1}{\lambda_z(s, t)} \left. \frac{\partial w^*}{\partial \lambda_\vartheta} \right|_{s^*, t^*} + h^*(s^*, t^*) \sigma_\vartheta^{\text{act}*}(s^*, t^*) = P^*(s^*, t^*) a^*(s^*, t^*) - \left[\frac{\rho a^2}{P_m T^2} \right] h^*(s^*, t^*)^2 \ddot{a}^*(s^*, t^*), \quad (\text{A.1})$$

where superscript $*$ denotes non-dimensional quantities. Non-dimensionalization of G&R time s would require definition of another reference time S that does not appear explicitly in the equation of motion because it is written over the cardiac cycle timescale and there are no derivatives with respect to s . For a mouse carotid artery, assuming $P_m \sim 100$ mmHg, $a \sim 10^{-1}$ mm, $T \sim 10^{-1}$ s and $\rho \sim 10^3$ kg/m³, the non-dimensional quantity in the square bracket, which represents the ratio between the inertial forces per unit surface $\rho a^2/T^2$ and the pressure P_m , is of order 10^{-7} , suggesting that the inertial force is indeed

FIG. A1. Flow chart of the computational scheme for G&R simulations. N-R denotes the Newton–Raphson method.

negligible. Hence, we used the quasi-static relation (2.6) similar to the one employed previously on the G&R timescale.

Appendix B

Here, we provide a brief description of the numerical scheme used to simulate dynamic arterial G&R (see Fig. A1). We adopt a marching technique in G&R time s , advancing in fixed steps Δs . Before starting the march, we check initial equilibrium and compute homeostatic values of stress and stress rate measures (given values of deposition stretch; Table 1) that will serve as targets through the computation. At each integration time step, we perform a nested loop to satisfy radial equilibrium (2.6) at the mean pressure P_m and to account for the updated turnover of constituents; the loop starts by estimating values of the mass production rates $m_{(i)}^k$ based on previous values and then solves the radial equilibrium (2.6) via a Newton–Raphson method, thus estimating a new value of the radius $a_{(i)}$. It is then possible to compute new values for the stress measures σ^k and thus the mass production $m_{(i+1)}^k$ and removal q^k rates. The nested loop stops when mass production rates are estimated with sufficient resolution (i.e. when $\sum |m_{(i+1)}^k - m_{(i)}^k|$ is smaller than a given tolerance). The solution on the cardiac cycle is computed offline and associated rate measures, which influence the evolution of individual mass productions, removals, remodelling and damaging, are evaluated after the nested loop for computational efficiency.