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Remodeling of conduit arteries in hypertension and flow-overload obeys a minimum energy principle

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Abstract

Arterial remodeling is an important process in physiology and pathophysiology. Based on an energy minimization method, Murray's law predicts the optimal inner radius. Application of Darcy's law in the wall results in an optimal outer radius. The average wall stress is computed by the Laplace's law. Using these formulas, a large porcine coronary artery in hypertension is studied. The results reveal how wall thickness and average circumferential stress change after increasing blood pressure and volume flow rate. The theoretical predictions are in good qualitative agreement with experimental observations. The advantage and limitation of the current approach are discussed.

Keywords

Blood vessel; Remodeling; Optimal design

1. Introduction

Arterial remodeling has been studied experimentally (Fung and Liu, 1989; Lu et al., 2001; Kassab et al., 2002; Gruionu et al., 2005) and theoretically (Rachev et al., 1996; Rachev, 2000; Taber and Humphrey, 2001; Gleason and Humphrey, 2005).

To predict the remodeling process, rate equations (evolution laws) are typically considered; e.g., Rachev et al. (1996) and Taber and Humphrey (2001). Although these models predict the general trends, complex calculations are necessary. In this work, we simplify this task for a loaded artery.

2. Methods

It is assumed that the artery is an axisymmetric poroelastic medium under blood pressure $p_i(r, z)$. In the lumen, the radial (r) flow is neglected and an axial (z) flow exists. In the wall,

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Conflict of interest
None.

only a radial flow exists. The blood is treated as incompressible Newtonian fluid and the flow is viewed as a steady-state process.

2.1. Optimal inner and outer radii

To establish the formulations, we need to consider some physiological facts. First, the wall shear stress τ can be expressed by (Fung, 1997):

$$\tau = -\mu \left. \frac{du_z}{dr} \right|_{r=r_i} = \frac{4\mu Q_z}{\pi r_i^3} \quad (1)$$

where $u_z(r)$ is axial flow velocity, μ is coefficient of dynamic viscosity, Q_z is axial volume flow rate, and r_i denotes inner radius.

At physiological state, r_i can be viewed as an optimized constant. If blood pressure perturbs, the first-order approximation of remodeled r_i depends linearly on p_i :

$$r_i = a_0 + \eta(p_i - p_c) \quad (2)$$

where a_0 and η are constants, and p_c is physiological (control) pressure.

If τ is regulated, it should be restored after remodeling. Thus, hypertension would result in a change of Q_z to compensate for the change of r_i . Considering Eqs. (1) and (2), Q_z is a function of p_i :

$$Q_z(p_i) = \frac{\pi \tau}{4\mu} [a_0 + \eta(p_i - p_c)]^3 \quad (3)$$

It is noted that Q_z (depending on τ) is also a function of pressure gradient.

Considering the energy balance, Murray (1926) proposed a cost function to predict the optimal r_i . The cost function per unit length c_b is (Fung, 1997):

$$c_b = \frac{8\mu Q_z^2}{\pi r_i^4} + K_b \pi r_i^2 \quad (4)$$

where K_b is the metabolic constant of the blood. Substitution of Eq. (3) into Eq. (4) results in

$$c_b = \frac{\pi \tau^2}{2\mu r_i^4} [a_0 + \eta(p_i - p_c)]^6 + K_b \pi r_i^2 \quad (5)$$

The optimal r_i from $\partial c_b / \partial r_i = 0$ (Murray's law) is Eq. (2) since $\tau = (\mu K_b)^{1/2}$ (Kassab and Fung, 1995).

Another physiological fact is that the wall tissue consumes energy from blood. For simplicity, we lump the net result of energy supply (diffusion, convection, and fluid flow) into a virtual radial flow described by the Darcy's law (Klanchar and Tarbell, 1987; Khaled and Vafai,

2003). The filtration velocity u_r (i.e., flow relative to solid per unit bulk area) is given by (Kenyon, 1976; Klanchar and Tarbell, 1987):

$$u_r(r) = \frac{\kappa_0 p_i}{\mu r \ln(r_o/r_i)} \quad (6)$$

where κ_0 is permeability (a measure of the pore area) and r_o is the vessel outer radius.

The radial volume flow rate Q_r through a vessel segment with length $L \approx 0$ can be calculated by

$$Q_r = 2\pi \int_0^L u_r r dz \approx \frac{2\pi \kappa_0 p_i L}{\mu \ln(r_o/r_i)} \quad (7)$$

The power (rate of work) done to the wall is

$$\begin{aligned} P_w &= 2\pi \int_0^L [p_i u_r(r_i) r_i - p_o u_r(r_o) r_o] dz \\ &\approx p_i Q_r \approx \frac{2\pi \kappa_0 p_i^2 L}{\mu \ln(r_o/r_i)} \end{aligned} \quad (8)$$

where $p_o = 0$ is the reference pressure at $r = r_o$.

Analogous to Murray's method, a cost function per unit length c_w ($L \rightarrow 0$) for the wall can be constructed as

$$c_w = P_w/L + K_w \pi (r_o^2 - r_i^2) = \frac{2\pi \kappa_0 p_i^2}{\mu \ln(r_o/r_i)} + K_w \pi (r_o^2 - r_i^2) \quad (9)$$

where K_w is the metabolic constant of the wall. For a given r_i , the $\partial c_w / \partial r_o = 0$ gives the optimal r_o :

$$r_o = \sqrt{\frac{\kappa_0}{\mu K_w}} p_i / W \left(\sqrt{\frac{\kappa_0}{\mu K_w}} \frac{p_i}{r_i} \right) \quad (10)$$

where W is the Lambert W function (Corless et al., 1996). Note that $r_o \rightarrow r_i$ when $p_i \rightarrow 0$ or $\kappa_0 \rightarrow 0$.

2.2. Average circumferential stress

At a given pressure the loaded radii r_i and r_o are known according to Eqs. (2) and (10). The average circumferential Cauchy stress σ_a can be calculated with the Laplace's law:

$$\sigma_a = \frac{p_i r_i}{r_o - r_i} = \frac{p_i r_i}{h} \quad (11)$$

2.3. Modeling parameters

We select parameters typical for a porcine coronary artery (Kassab and Fung, 1995; Taber, 1998; Humphrey and Na, 2002): $\tau = 1.5$ Pa, $\mu = 4.0$ mPa s (0.04 poise), $K_b = \tau^2/\mu = 0.5625$ kW m⁻³, $K_w = 1.531$ kW m⁻³ (using $\sigma_a = 88$ kPa in the equation by Taber, 1998), $a_0 = 2.46$ mm is computed from the equilibrium equation (Wang et al., 2008), $\eta = 0.004$ mm kPa⁻¹ is an estimated value, and $\kappa_0 = 0.00543$ μm^2 is derived from Eq. (10) for known $r_o = 2.81$ mm.

We describe hypertension by a pressure change from $p_c = 12.32$ kPa (92.4 mmHg) to $p_h = 18.48$ kPa (138.6 mmHg). The remodeled radii and wall stress are computed by Eqs. (2), (10) and (11).

3. Results

Eq. (5) is plotted in Fig. 1A to show the optimal $r_i = 2.46$ mm at $p_i = p_c$ and $r_i = 2.49$ mm at $p_i = p_h$, respectively. Similarly, a plot of Eq. (9) in Fig. 1B shows optimal $r_o = 2.81$ and 2.99 mm.

Fig. 2A shows the plots of Eqs. (2) and (10), where r_o changes with p_i almost linearly although Eq. (10) is nonlinear. Fig. 2B shows that the remodeled σ_a increases with the hypertensive pressure. It is shown that the effect of parameter η is marginal on wall thickness $h = r_o - r_i$ (Fig. 3A) but significant on σ_a (Fig. 3B).

4. Discussion

Some parameters are interrelated: $\tau = (\mu K_b)^{1/2}$, η is related to Q_z (Eq. (3)), $a_0 = r_i$ when $p_i = p_c$, and Eq. (10) connects r_o with $\kappa_0/(\mu K_w)$ for $p_i = p_c$. It is noted that negative η implies that r_i (and Q_z) decreases under hypertension, which may be useful for modeling active contraction. Also note that K_b and K_w represent the consumption rates of energy per volume. The larger the metabolic constant and the volume, the more energy is needed to sustain the cells. Thus, the optimal radii depend on K_b and K_w as well as other parameters.

4.1. Arterial wall thickness

Eq. (10) predicts $h = 0$ if $\kappa_0 = 0$, which means that the wall will eventually disappear without an equivalent radial flow (including other transport mechanisms) that supplies energy from blood. The pressure p_i ($p_o = 0$) is the driving force for radial flow and the permeability κ_0 is inversely proportional to the flow resistance, and thus the larger the p_i and κ_0 , the larger the h . Parameters μ and K_w represent energy consumption mechanisms and have opposite effect on h .

The current results predict a 1% increase of r_i , 6% increase of r_o , 46% increase of h , and 52% increase of the wall area after remodeling, which agree qualitatively with the results of Fung and Liu (1989), Rachev et al. (1996), and Kassab et al. (2002).

4.2. Wall stress after remodeling

The remodeled wall stress depends on some parameters (Figs. 2B and 3B). Kassab et al. (2002) found that a significant flow increase results in a larger σ_a , though τ is restored to its normal level. We considered the flow overload and a uniform shear hypothesis (Eq. (3)). The result shows a 4% increase of σ_a when p_i increases from 12.32 to 18.48 kPa (Fig. 2B), which is in qualitative agreement with the findings of Kassab et al. (2002).

4.3. Comparison with other studies

Murray's law was proposed for the blood (Murray, 1926). Taber (1998) generalized it to include the vessel wall and the active contraction of smooth muscles. We further separated the cost functions for the blood and the vessel wall. In our model, the ratio r_i/h is allowed to vary with the flow rate. Therefore, the predicted σ_a may differ from Taber's result where r_i/h was kept constant.

Several authors postulated rate equations for the zero-stress state (e.g., Rachev et al., 1996), where the loaded radii r_i and r_o can be obtained only by solving a set of nonlinear control equations. The present model directly predicts the loaded state. This is more convenient for assessing the in vivo structural change of remodeled arteries. In fact, evolution laws can be proposed based on the gradient flow method (Garcke et al., 2001) for the temporal remodeling process.

4.4. Limitation of approach

We made several assumptions and did not consider the cellular details of remodeling mechanisms (Pries et al., 2005). These simplifications may be responsible for possible quantitative differences between modeling and experimental data; e.g., considering non-Newtonian (viscosity depends on shear rate) blood may improve the model predictions.

The above issues can be viewed as secondary factors, however, that should not significantly influence the essence of the model predictions; e.g., the radial flow (leakage due to the porosity) is negligible as compared to the axial flow in the lumen because permeability is low.

5. Concluding remarks

Murray's law was used to compute the optimal inner radius of large arteries. The radial flow in the wall and the minimum energy principle were considered to predict the optimal outer radius. This method has not been previously explored in a similar way. The advantage of the model is that it can predict the in vivo wall thickness and the average circumferential wall stress without simulating the remodeling process.

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References

- Corless RM, Gonnet GH, Hare DEG, Jeffrey DJ, Knuth DE. On the Lambert W function. *Advances in Computational Mathematics* 1996;5:329–359.
- Fung YC. *Biomechanics: Circulation*. Vol. 2. Springer; New York: 1997.
- Fung YC, Liu SQ. Change of residual strains in arteries due to hypertrophy caused by aortic constriction. *Circulation Research* 1989;65:1340–1349. [PubMed: 2805247]
- Garcke H, Preusser T, Rumpf M, Telea AC, Weikard U, van Wijk JJ. A phase field model for continuous clustering on vector fields. *IEEE Transactions on Visualization and Computer Graphics* 2001;7:230–241.
- Gleason RL, Humphrey JD. A 2D constrained mixture model for arterial adaptations to large changes in flow, pressure and axial stretch. *Mathematical Medicine and Biology* 2005;22:347–369. [PubMed: 16319121]
- Gruionu G, Hoying JB, Pries AR, Secomb TW. Structural remodeling of mouse gracilis artery after chronic alteration in blood supply. *American Journal of Physiology—Heart and Circulatory Physiology* 2005;288:H2047–H2054. [PubMed: 15604133]

- Humphrey JD, Na S. Elastodynamics and arterial wall stress. *Annals of Biomedical Engineering* 2002;30:509–523. [PubMed: 12086002]
- Kassab GS, Fung YCB. The pattern of coronary arteriolar bifurcations and the uniform shear hypothesis. *Annals of Biomedical Engineering* 1995;23:13–20. [PubMed: 7762878]
- Kassab GS, Gregersen H, Nielsen SL, Lu X, Tanko LB, Falk E. Remodelling of the left anterior descending artery in a porcine model of supraaortic stenosis. *Journal of Hypertension* 2002;20:2429–2437. [PubMed: 12473868]
- Kenyon DE. Transient filtration in a porous elastic cylinder. *Journal of Applied Mechanics* 1976;98:594–598.
- Khaled ARA, Vafai K. The role of porous media in modeling flow and heat transfer in biological tissues. *International Journal of Heat and Mass Transfer* 2003;46:4989–5003.
- Klanchar M, Tarbell JM. Modeling water flow through arterial tissue. *Bulletin of Mathematical Biology* 1987;49:651–669. [PubMed: 3442711]
- Lu X, Zhao JB, Wang GR, Gregersen H, Kassab GS. Remodeling of the zero-stress state of femoral arteries in response to flow overload. *American Journal of Physiology—Heart and Circulatory Physiology* 2001;280:H1547–H1559. [PubMed: 11247765]
- Murray CD. The physiological principle of minimum work. I. The vascular system and the cost of blood volume. *Proceedings of the National Academy of Sciences of the United States of America* 1926;12:207–214. [PubMed: 16576980]
- Pries AR, Reglin B, Secomb TW. Remodeling of blood vessels—responses of diameter and wall thickness to hemodynamic and metabolic stimuli. *Hypertension* 2005;46:725–731. [PubMed: 16172421]
- Rachev A. A model of arterial adaptation to alterations in blood flow. *Journal of Elasticity* 2000;61:83–111.
- Rachev A, Stergiopoulos N, Meister JJ. Theoretical study of dynamics of arterial wall remodeling in response to changes in blood pressure. *Journal of Biomechanics* 1996;29:635–642. [PubMed: 8707790]
- Taber LA. An optimization principle for vascular radius including the effects of smooth muscle tone. *Biophysical Journal* 1998;74:109–114. [PubMed: 9449315]
- Taber LA, Humphrey JD. Stress-modulated growth, residual stress, and vascular heterogeneity. *Journal of Biomechanical Engineering* 2001;123:528–535. [PubMed: 11783722]
- Wang C, Zhang W, Kassab GS. The validation of a generalized Hooke's law for coronary arteries. *American Journal of Physiology—Heart and Circulatory Physiology* 2008;294:H66–H73. [PubMed: 17933971]

Fig. 1. Cost functions for (A) blood and (B) arterial wall at control pressure $p_i = p_c$ and hypertensive pressure $p_i = p_h$. The corresponding optimal inner radius has been substituted in (B) for outer radius.

Fig. 2. (A) Relations between optimal radii and blood pressure and (B) dependence of remodeled stress on blood pressure for the chosen $\eta = 0.004 \text{ mm kPa}^{-1}$.

Fig. 3. Dependence of remodeled (A) wall thickness and (B) stress on parameter η when $p_i = p_h$ (reflecting influence of flow overload).