Mechanical events within the arterial wall: The dynamic context for elastin fatigue

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Abstract

Change in arterial stiffness is generally considered a risk factor for cardiovascular disease and, in various ways, has been associated with hypertension, diabetes, hyperlipidemia, atherosclerosis, and heart failure, likely because of altered dynamics of the wall and of the fluid–wall interplay in pulsatile flow. We present a comprehensive analytical study of longitudinal displacements and stresses within the thickness of the vessel wall induced by pulsatile flow at different times within the cardiac cycle, using the fractional derivative model which has been found to provide a good descriptor of the rheological material’s response to frequency. The results indicate that the extent of displacement and shear stress within the depth of the vessel wall depend critically on the degree to which the wall is tethered to surrounding tissue and on the mechanical consistency of the wall material, particularly on the relative proportions of viscous and elastic content within the wall. In particular, loss of viscous consistency leads to higher shear stresses within the wall thus putting higher loading on elastin and may ultimately lead to elastin fatigue and, as elastin gradually fails, its load bearing function is presumably taken over by collagen which renders the vessel wall less elastic and more rigid as is indeed observed in the aging process. It is thus concluded that loss of viscous content within the vessel wall, whether by disease or aging, may be a prelude to elastin fatigue and elastin failure within the vessel wall.

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1. Introduction

Mechanical properties of the arterial wall play an important role in blood pressure regulation, in the determination of cardiac load, and in a number of clinical conditions. The change in arterial stiffness seen in arteriosclerosis is generally considered a risk factor for cardiovascular disease and, in various ways, has been associated with hypertension, diabetes, hyperlipidemia, atherosclerosis, and heart failure (Benetos, 1993). The mechanisms involved or indeed the cause and effect in each case are not fully established but are likely related to altered dynamics of the wall and of the fluid–wall interplay in pulsatile flow.

In the case of atherosclerosis, patchy lesions may typically affect the intima at first but eventually progress to the entire wall. Here the mechanical properties of the wall as well as its geometry are affected in a rather non-uniform way, and over the course of the disease the mechanical properties of the lesions may range from those of soft tissue to those of highly rigid calcium deposits.

In aging and arteriosclerosis, arterial stiffening is suspected to be due to a deterioration in the elastic properties of elastin within the arterial wall or, more specifically, to “elastin fatigue” caused by the oscillatory motion induced by pulsatile flow (O’Rourke, 2007; Lillie and Gosline, 2007; Versluis et al., 2006).

A study of the dynamics of the vessel wall in pulsatile flow may therefore improve our understanding of how these dynamics, including displacements and stresses within the wall, are altered by disease affecting the mechanical properties of the wall or, conversely, how displacements and stresses within the vessel wall created by the constant oscillatory pull of pulsatile flow may actually contribute to damage and disease processes within the wall and hence to a change in its mechanical properties.

In particular, the concept of elastin fatigue is based on the notion that many millions of repetitive oscillations within the arterial wall may degrade the elasticity of elastin and cause a stiffening of the arterial wall due to the transfer of load bearing from elastin to collagen. While this notion has a good basis in mechanics, the nature of stresses that may lead to elastin failure received little attention (Lillie and Gosline, 2007; Avolio et al., 1998; Greenwald, 2007) and requires further study.

Early studies were focused largely on effects at the endothelial layer of the vessel wall, but more recently dynamics within the thickness of the wall have been considered using viscoelastic
models (Holzapfel et al., 2002; Humphrey and Na, 2002; Hodis and Zamir, 2008). Effects of the pressure-induced normal stress were considered at first, with the flow-induced shear stress being neglected on the grounds that it is less significant. However, advances in imaging technology have shown recently that there is considerable longitudinal motion within the vessel wall (Cinthio et al., 2006; Persson et al., 2003). In a remarkable study Cinthio et al. (2006) measured the longitudinal displacement of the intima-media, adventitia and surrounding tissue and demonstrated for the first time that axial displacements are of the same order of magnitude as the pressure-induced diameter change. Axial displacements within the vessel wall have also been implicated in the investigation of clutter in Doppler ultrasound flow measurements (Warriner et al., 2008) and in the study of stent migration in abdominal aortic aneurysms (Morris et al., 2004). The technique of Wagensell et al. (2005), using carbon markers, can be very valuable in producing much needed data on this subject.

The purpose of the present paper is to present a comprehensive analytical study of longitudinal displacements and stresses within the thickness of the vessel wall induced by pulsatile flow at different times within the cardiac cycle, as illustrated schematically in Fig. 1. A range of viscoelastic properties of the vessel wall are used, representing the known range of these properties in health and disease. We also examine the effect of tethering in its full range, from one extreme in which the vessel is free to the other extreme in which the vessel is fully tethered to surrounding tissue.

2. Methods

In pulsatile flow the vessel wall is exposed to two oscillatory forces at the endothelial layer: shear stress τa acting tangential to the wall and pressure pwa acting normal to it as shown in Fig. 1. These two forces, in conjunction with any tethering at the outer layer of the wall, produce displacements and stresses within the thickness of the wall which are the subject of our study. In general, τa and pwa are functions of time t, radial and axial coordinates, r, x, respectively. The x variations are of the order of magnitude of the propagating wave length L, which in the systemic circulation at a frequency of 1 Hz is about 10 m. For a vessel segment of length l which is typically much less than L, therefore, the x variations can be neglected compared with the time variations as has been the practice in the past (Humphrey and Na, 2002) and, on this basis, we consider τa and pwa to be functions of t and r only. Under these assumptions, longitudinal displacement z(t, r) and shear stress τ(t, r) within the thickness of the wall are governed by the equation (Hodis and Zamir, 2008)

\[
\frac{\partial^2 z(t, r)}{\partial t^2} - \frac{\partial z(t, r)}{\partial t} + \frac{\tau(t, r)}{\rho} = 0
\]

(1)

where \(\rho\) is density of the wall material.

![Fig. 1. Longitudinal cross section of the arterial wall being considered in the r, x plane (light shading) where \(r, x\) are radial and axial coordinates, respectively. Curves show a sample of displacements within the wall thickness, \(h\), which is here exaggerated for the purpose of illustration.](image)

A solution of Eq. (1) requires a prescribed relation between \(\xi\) and \(\tau\), of the form

\[
\tau = E' \frac{\partial^2 \zeta}{\partial t^2}
\]

(2)

where \(E'\) is generally a complex modulus which depends on the mechanical properties of the wall material. It is generally accepted that in the absence of disease, mechanical properties of the arterial wall are determined largely by the media which behaves as a homogeneous material (Nichols and O'Rourke, 2005; Fung, 1993; Lasheras, 2007). In this paper we follow this practice and use the fractional derivative model introduced recently by Craiem and Armentano (2007) to describe the viscoelasticity of the arterial wall. This model has been found to provide a good descriptor of the rheological material's response to frequency, based on in vivo measured data from the descending thoracic aorta of the sheep (Craiem and Armentano, 2007).

The complex modulus in the fractional derivative model is given by (Craiem and Armentano, 2007)

\[
E' = E_0 + \eta_1 e^{i\omega t} e^{i\omega t} + \eta_2 e^{i\omega t} e^{i\omega t}
\]

(3)

where \(\omega\) is the fundamental frequency of the oscillatory flow (and hence of longitudinal displacements and stresses within the vessel wall), \(E_0\) is the static elastic modulus of the wall material, and \(\eta_1\) and \(\eta_2\) are the derivative orders of the "spring-pots" whose viscosity parameters are \(\eta_1\) and \(\eta_2\), respectively.

Eqs. (1) and (2) together provide the governing equation for the displacement field \(z(t, r)\) within the arterial wall, namely

\[
\frac{\partial^2 z}{\partial t^2} - \frac{\partial z}{\partial t} + \frac{\tau}{\rho} = E' \frac{\partial^2 \zeta}{\partial t^2}
\]

(4)

Solution of the above equation depends on the form of the driving force at the endothelial layer of the wall and on the degree of tethering at the outer layer. We shall assume that the driving force is the drag force \(\tau_a\) exerted by the oscillatory blood flow. Initially we take \(\tau_a\) as a single harmonic, so the displacement induced by this drag force at the endothelial layer \((r = a, \text{ where } a\text{ is the neutral radius})\) will have the same form (Zamir, 2000)

\[
z(a, t) = \zeta_0 e^{i\omega t}
\]

(5)

but later we add more harmonics so as to give \(\tau_a\) the form of a cardiac pressure wave.

The general solution of Eq. (4) with the boundary condition in Eq. (5) can be obtained in terms of Bessel functions:

\[
z(r, t) = [A_0(I_0) + BK_0(z_0)] e^{i\omega t}
\]

(6)

where \(A\) and \(B\) are constants of integration whose values depend on the wall material and the outer layer boundary condition, \(I_0, K_0\) are modified Bessel functions of order zero of first and second kind, respectively, and

\[
\begin{align*}
\zeta_0 &= -\frac{\zeta_0}{c_0} \\
\zeta_0 &= A(1 + d) \\
\zeta_0 &= \frac{r - a}{a} \\
A &= c_0 \sqrt{\rho/\bar{E}}
\end{align*}
\]

(7)

2.1. Fully tethered wall

When the outer layer of the vessel wall is fully tethered, meaning that there is sufficient perivascular tissue to prevent any movement of the outer layer of the vessel wall, the outer boundary condition is

\[
z(a + h, t) = 0
\]

(8)

and with this boundary condition the constants of integration in Eq. (6) are given by

\[
\begin{align*}
A &= A_1 = \frac{K_0(z_0)}{I_0(z_0)} - \frac{\xi_0 K_0(z_0)}{\xi_0 I_0(z_0)} \\
B &= B_1 = K_0(z_0)/I_0(z_0) - \frac{\xi_0 K_0(z_0)}{\xi_0 I_0(z_0)}
\end{align*}
\]

(9)

where

\[
\begin{align*}
\zeta_0 &= A0/h \\
\zeta_0 &= A0/(b + h)/h
\end{align*}
\]

(10)

The stress distribution within the wall thickness corresponding to the displacement in Eq. (6), then follows by using Eqs. (2) and (6) to get, in nondimensional form again

\[
\begin{align*}
\zeta(t, r) &= A_1 \zeta_1(t) - B_1 K_1(z) e^{i\omega t} \\
\ell &= \frac{\ell_1}{\ell_1 E_1}
\end{align*}
\]

(11)

where \(\ell_1, K_1\) are modified Bessel functions of order one of first and second kind, respectively, and

\[
\begin{align*}
\tau(t, r) &= \frac{\ell_1 E_1}{E_1}
\end{align*}
\]

(12)
Viscous, viscoelastic, and stiff materials, and of vessel wall material

where $E_1$ represents only the static elastic modulus. The more important parameter in this model is the dynamic modulus $E'$ whose value depends on frequency. In this study we follow other authors (Muir and Choudhury, 1984; Mirsky, 1967; Bulanowsky and Yeh, 1971) in making use of the theoretical relationship between the circumferential and the longitudinal moduli, the latter being one-third of the former. Thus, taking the circumferential dynamic modulus as 4 MPa (Mirsky, 1967), we consider values of the corresponding longitudinal modulus in the range of 1.3–2.0 MPa (Learoyd and Taylor, 1966; Faury, 2001).

2.2. Free wall

When the vessel wall is free from surrounding tissue, there will be some longitudinal displacement at the outer layer of the wall which is not known but is required as a boundary condition. We deal with this by writing

$$\zeta(0 + h, t) = \zeta_1 e^{\omega t}$$

where $\zeta_1$ is the amplitude of the unknown displacement at the outer layer. The value of $\zeta_1$ is then found from a solution of the limiting problem of a wall fully tethered at infinity in which the displacement at a small finite distance from the inner boundary is the same as the displacement at the outer layer of a finite free wall (Hodis and Zamir, 2008). In this way we find

$$\begin{cases}
A = A_1 = 0 \\
B = B_2 = 1/K_0(\omega)
\end{cases}$$

The corresponding stress distribution within the free wall then follows by using Eqs. (2), (6), and (14) to get, in nondimensional form again

$$\tau(t) = -A_1 B_2 K_0(\omega) \zeta_1 e^{\omega t}$$

where $K_1$ is modified Bessel function of order one of second kind.

To generalize these results to the physiological form of pulsatile blood flow where the displacement at the inner wall is a composite waveform, we take

$$\zeta(a,t) = \sum_{n=0}^{n_{10}} M_n \cos(n \omega t) + N_n \sin(n \omega t)$$

where $M_n$, $N_n$ are Fourier coefficients. Details are given in Appendix.

3. Results

The results to follow are based on Eq. (3) and on values of $\alpha$, $\beta$, $\eta_1$, $\eta_2$, and $E_0$, shown in Table 1, chosen as representative values of viscous, viscoelastic, and stiff materials, and of vessel wall material (VWM) taken from Craiem and Armentano (2007). In general, in the viscoelastic case where the modulus of elasticity $E'$ is complex, its real part represents the elastic content while its imaginary part represents the viscous content within the material of the vessel wall, and both are increasing functions of frequency. The imaginary part is zero when the wall material is purely elastic ($\alpha = \beta = 0$) and the real part is zero in the purely viscous case ($E_0 = 0$ and $\alpha = \beta = 1$). As a reference, we used particular values provided by Craiem and Armentano (2007), namely $\alpha = 0.11$ and $\beta = 0.8$, which agrees with experimental data obtained by Learoyd and Taylor (1966).

Longitudinal displacements at different depths within the arterial wall are shown in Figs. 2–4 for viscous, viscoelastic and stiff materials, respectively, for fully tethered or free wall conditions, and at four key points within the cardiac cycle. For the purpose of comparison, the displacements are normalized in terms of the maximum displacement at the inner boundary. In general, viscous content within the wall material causes the displacements to be confined to the inner layers of the wall while the outer layers are spared. As the viscous content declines and elastic content increases, more of the outer layers of the wall become involved in the back and forth longitudinal displacements.

Figs. 5 and 6 show the maximum axial displacement within one cardiac cycle at different layers of the wall for a fully tethered and a free vessel wall, respectively. Maximum displacements at the outer layer of the wall are compared in Table 2 for different wall material categories. Again, maximum displacements within the cardiac cycle are lower with higher viscous content and higher with higher elastic content.

Figs. 7 and 8 show the maximum shear stress within one cardiac cycle at different layers of the wall for a fully tethered and a free vessel wall, respectively. In general, maximum shear stresses within the wall are considerably higher when the wall is tethered than they are when the wall is free. Also, higher maximum stresses are reached when the wall material has higher elastic than viscous content. It is important to note that the shear $\tau$ depends not only on the displacement gradient $\partial \zeta / \partial r$ but on the complex form of $E'$ (Eqs. (2) and (3)), thus the relation between the displacement results (Figs. 5 and 6) and stress results (Figs. 7 and 8) is not a simple one. In particular, the differences between the maximum stresses in the four material categories derive more from the differences in their complex moduli than from the corresponding differences in their displacement gradients. The maximum stresses at the inner and outer layers of the fully tethered and the free wall are summarized in Tables 3 and 4.

4. Discussion and conclusions

Elastin fatigue may result from repeated stretching of elastin fibers, as in the stretching and relaxing of an elastic band, or from repeated shear stress within and between the elastin fibers, as in the shear stress between the layers of a tire on the road. Our study has focused on the latter. The results show that the extent of longitudinal displacement and shear stress within the thickness of the vessel wall depend critically on the degree to which the wall is tethered to surrounding tissue and on the mechanical consistency of the wall material, particularly on the relative proportions of viscous and elastic content within the wall. These findings may clearly be relevant in aging and in various vascular disease states.

The fractional derivative model which we have chosen to examine the dynamics of the wall under different consistencies has three parallel elements: a spring of modulus $E_0$ and two “spring-pots” with viscoelastic parameters $\eta_1$, $\eta_2$ whose fractional derivative orders are $\alpha$ and $\beta$, respectively ($0 < \alpha, \beta < 1$). The behavior of the spring-pot in the frequency domain is intermediate between a constant elastic response and a linear viscous one and is intended to mimic the natural response of the arterial wall (Craiem and Armentano, 2007). The structural elasticity of the wall, in the absence of muscle activation, is represented by the ideal spring $E_0$. The first spring-pot ($\eta_1, \alpha$) with $\alpha = 0.2$ is predominantly elastic and is associated with the elastic contribution of vascular smooth muscle, and the second spring-pot ($\eta_2, \beta$) with $\beta = 0.8$ is predominantly viscous and is associated with the
dissipative viscous element of the arterial wall (Craiem and Armentano, 2007). In general, an artery contains proportionally more elastin the closer it is to the heart and more smooth muscle the farther away it is from the heart (Lasheras, 2007; Learoyd and Taylor, 1966). The choice of parameter values is difficult because they are not easily measured. The first measurements of the

Fig. 2. Normalized axial displacements $\tilde{\gamma}$ within the thickness of the vessel wall (left panels) at specific times within the cardiac cycle (shown by $\blacktriangle$, right panels) for a viscous wall material, fully tethered (line) and free vessel (dashed), with $\tilde{\gamma}$ as defined in Eq. (24).

Fig. 3. Normalized axial displacements $\tilde{\zeta}$ within the thickness of the vessel wall (left panels) at specific times within the cardiac cycle (shown by $\blacktriangle$, right panels) for a viscoelastic wall material, fully tethered (line) and free vessel (dashed), with $\tilde{\zeta}$ as defined in Eq. (24).
storage ($\mathcal{R}(E')$) and dissipative ($\mathcal{X}(E')$) moduli of vessel wall were made by Bergel (1961) in dog arteries and by Learoyd and Taylor (1966) in human arteries and it was found that the complex modulus is frequency independent over the frequency range (2–20 Hz). The measurements of Craiem and Armentano (2007) from the descending thoracic aorta of an adult sheep in controlled state is in agreement with this, but in a state of smooth muscle activation it was found that there was partial frequency dependence. The advantage of the fractional derivative model is that the fractional order can be chosen anywhere between 0 (elastic) and 1 (viscous) to capture different degrees of wall viscoelasticity.

In conclusion, our results suggest a possible scenario in which the vessel wall material may, with age or disease, lose some of its viscous consistency thus leading to higher stresses within the wall which put higher loading on elastin and ultimately lead to elastin fatigue. As elastin gradually fails (Lillie and Gosline, 2007; Versluis et al., 2006), its load bearing function is taken over by collagen which renders the vessel wall less elastic and more rigid as is indeed observed in the aging process (Benetos, 1993; O’Rourke, 2007; Learoyd and Taylor, 1966; McDonald, 1974; Nichols and O’Rourke, 2005; Versluis et al., 2006).

Loss of vessel compliance due to elastin failure, because of its effect on wave reflections, may have far reaching consequences in arterial pressure regulation and hence in the pathogenesis of hypertension. In atherosclerosis, because of the patchy nature of the disease and because of its destruction of the mechanical properties of the wall, there may be local consequences whereby the loss of elasticity may be part of the cause or effect of the disease. While a direct link between loss of viscous content and elastin fatigue cannot be made at this time, perhaps the most important conclusion of our study is that loss of viscous content within the vessel wall, by whatever means, may be a prelude to elastin fatigue and elastin failure within the vessel wall.

**Conflict of interest statement**

The authors have no conflict of interest to report.
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Appendix

In pulsatile flow driven by a composite cardiac pressure wave, the solution for displacements and stresses within a fully tethered vessel wall, using the boundary condition in Eq. (16), is given by

$$\tilde{\xi}(r, t) = \sum_{n=1}^{10} M_n \Re \left[ (A_{1n} I_0(\zeta_n) + B_{1n} K_0(\zeta_n))e^{i\omega n t} \right] + \sum_{n=1}^{10} N_n \Im \left[ (A_{1n} I_0(\zeta_n) + B_{1n} K_0(\zeta_n))e^{i\omega n t} \right]$$  \hspace{1cm} (17)
where $M_n, N_n (n = 1–10)$ are Fourier coefficients and $A_{1n}$ and $B_{1n} (n = 1–10)$ are given by

$$
A_{1n} = \frac{K_{0}(s_{1n})h_{0}(s_{0n})}{K_{0}(s_{1n})h_{0}(s_{0n}) - h_{0}(s_{1n})K_{0}(s_{0n})}
$$

$$
B_{1n} = \frac{1}{K_{0}(s_{1n})h_{0}(s_{0n}) - h_{0}(s_{1n})K_{0}(s_{0n})}
$$

where

$$
\zeta_{n} = A_{1n} \frac{t}{h}
$$

$$
\zeta_{0n} = A_{2n} \frac{a}{h}
$$

$$
\zeta_{1n} = A_{4n} (a + h) / h
$$

$$
A_{n} = n\rho h \sqrt{\varepsilon / E_{n}}
$$

$$
A_{n} = E_{n}^B / E_{1}
$$

The corresponding expressions in the case of a free wall are

$$
\zeta(t, r) = \sum_{n=1}^{10} M_{n} \Re \left[ B_{2n} K_{1}(\zeta_{n}) e^{i\omega t} \right] + N_{n} \Im \left[ B_{2n} K_{1}(\zeta_{n}) e^{i\omega t} \right]
$$

$$
\zeta(t, r) = \sum_{n=1}^{10} \left( A_{2n} \frac{t}{h} \right) M_{n} \Re \left[ B_{2n} K_{1}(\zeta_{n}) e^{i\omega t} \right] + N_{n} \Im \left[ B_{2n} K_{1}(\zeta_{n}) e^{i\omega t} \right]
$$

where

$$
B_{2n} = 1 / K_{0}(\zeta_{0n})
$$

The solutions are normalized as

$$
\zeta(t, r) = \zeta / \max_{t} \zeta(t, t)
$$

$$
\tau(t, r) = \tau(t, r) h / \max_{t} |\zeta(t, t)| E_{1}
$$

where $\max_{t}$ denotes the maximum value in time within one cardiac cycle.

References


