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Impact of flow pulsatility on arterial drug distribution in stent-based therapy

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ABSTRACT

Drug-eluting stents reside in a dynamic fluid environment where the extent to which drugs are distributed within the arterial wall is critically modulated by the blood flowing through the arterial lumen. Yet several factors associated with the pulsatile nature of blood flow and their impact on arterial drug deposition have not been fully investigated. We employed an integrated framework comprising bench-top and computational models to explore the factors governing the time-varying fluid dynamic environment within the vasculature and their effects on arterial drug distribution patterns. A custom-designed bench-top framework comprising a model of a single drug-eluting stent strut and a poly-vinyl alcohol-based hydrogel as a model tissue bed simulated fluid flow and drug transport under fully apposed strut settings. Bench-top experiments revealed a relative independence between drug distribution and the factors governing pulsatile flow and these findings were validated with the *in silico* model. Interestingly, computational models simulating suboptimal deployment settings revealed a complex interplay between arterial drug distribution, Womersley number and the extent of malapposition. In particular, for a stent strut offset from the wall, total drug deposition was sensitive to changes in the pulsatile flow environment, with this dependence increasing with greater wall displacement. Our results indicate that factors governing pulsatile luminal flow on arterial drug deposition should be carefully considered in conjunction with device deployment settings for better utilization of drug-eluting stent therapy.

1. Introduction

Drug-eluting stents (DES) are now routinely used for the treatment of coronary artery disease [1] and are increasingly being considered for other vascular beds [2]. The efficacy of these devices is determined based on delivering therapeutic concentrations of drug to the underlying tissue for a sustained period. These desirable drug levels can be achieved by maintaining uniform arterial distribution patterns that are in turn modulated by, amongst other factors [3–6], the hemodynamic environment surrounding the stent [7–9]. Previous work has indicated that stent implantation intervenes with the blood flow milieu by introducing perturbations into the boundary layer of the flow, causing drug-rich recirculating pools proximal and distal to stent struts [7–9]. These regions effectively extend the contact area of drug with the tissue–lumen (or mural) interface and thereby enhance drug uptake into the underlying tissue; flow-mediated transport of drug from non-contacting surfaces of the strut surface accounts for almost 40% of the total drug uptake [7].

As the impact of luminal flow on arterial drug uptake is being increasingly characterized, several aspects associated with blood flow need to be understood. In particular, the time-varying patterns of blood flow caused by the cardiac pulse creates a dynamic flow environment that may influence overall arterial drug distribution patterns. It is now known that net luminal flow governed by mean Reynolds number determines the extent of flow-mediated drug uptake [9], but the mechanisms by which parameters governing the pulsatile nature of blood flow modulate arterial distribution are not completely understood. Given that the transient arterial pressure gradient and the associated fluid flow are dynamically changing and vascular-bed dependent, the question arises as to how one could systematically quantify the flow pulsatility affecting the arterial drug distribution patterns.

Pulsatile flow can be represented by a steady component and its oscillating harmonics that is characterized by an amplitude and a frequency. The properties of the harmonics of blood flow are dependent on the cardiac output and rate, blood viscosity, visco-elastic properties of the arteries and vascular architecture. In his 1955 paper, J. R.

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Womersley numerically derived a solution to the flow harmonics for a short, straight, unbranched rigid vessel under a known driving pressure gradient [10]. Through these pressure–flow relations, Womersley was able to demonstrate sensitivities of instantaneous arterial flow to changes in the frequency of the driving pressure gradient, vessel size, and the viscous properties of the blood. For instance, an increase in the frequency of the driving pressure gradient will yield simultaneously a decrease in the amplitude of the flow rate and a decrease in the timescale of these changes. Conversely, a decrease in frequency will yield large, instantaneous changes in flow over a longer period. Given that flow pulsatility is intricately connected with the frequency of the oscillating pressure harmonics, we sought to understand these frequency-dependent effects on arterial drug distribution. By employing the Womersley's framework, we simulated three distinct scenarios of pulsatile flow patterns wherein the frequency of the oscillating pressure harmonics was varied to quantify the drug distribution patterns under various degrees of strut apposition to the lumen–tissue (or mural) surface.

Our results indicate that model and experimentally derived drug distribution patterns are relatively independent of flow pulsatility when stent struts are fully apposed to the mural surface. Contrastingly, when struts lose contact with the arterial wall, drug uptake is dependent on the dynamic flow environment and varies with the relative amount of malapposition. The finding that pulsatile flow affects arterial drug distribution patterns in a fashion dependent on the deployment settings adds to our understanding of the complex physiological aspects associated with stent-based delivery and paves way for careful consideration of this therapy to several vascular flow regimes.

2. Methods

2.1. A model of flow pulsatility

The relationship between pressure and flow in a single straight arterial segment is given by Womersley's pressure–flow relations, where the nth harmonic of oscillating laminar flow, given a complex oscillating pressure gradient $A_n e^{i\omega_n t}$ [10] is:

$$Q_n(t) = Real\left\{\frac{\pi R^4}{i\mu}\left(\frac{1}{\alpha_n^2} - \frac{2}{\alpha_n^3 i^{\frac{3}{2}}}\frac{J_1\left(\alpha_n i^{\frac{3}{2}}\right)}{J_0\left(\alpha_n i^{\frac{3}{2}}\right)}\right)A_n e^{i\omega_n t}\right\} \quad (1)$$

where, J_0 and J_1 are respectively, the zero and first order Bessel functions of the first kind, R is the radius of the vessel and ρ is the density of blood. Angular frequency is given as $\omega_n = 2\pi f$, where f is the frequency of the nth harmonic. As part of this solution, a dimensionless frequency parameter (α), now referred to as the Womersley number, was introduced, where $\alpha_n = R\sqrt{\omega_n/(\mu/\rho)}$, and μ is the dynamic viscosity.

Consider a realistic pulsatile profile in the renal artery, where the Womersley number at the fundamental frequency is approximately 4 ($\alpha_1 \approx 4$), at basal conditions ($\omega_1 = 2\pi$) (Fig. 1a). We first derive the pressure waveform for the first twelve harmonics using Eq. (1), and then scale the fundamental frequency of the driving pressure gradient, ω and each of its harmonics by the same factor in Eq. (1). Fig. 1b shows that as α increases with frequency, the amplitude of the unsteady flow rate (measured as the ratio of maximum instantaneous flow rate, $\max\left(\sum_{n=1}^{N} Q_n\right)/Q_{mean}$)) decreases, and thus the unsteadiness of the flow decreases as well. A large α implies an inertially driven flow, and so as the frequency of the pressure gradient increases, accelerating the inertia is made more difficult. Increasing frequency and thus α from the nominal renal arterial case shows an instantaneous flow that has a significantly damped flow rate, decreasing the unsteady component of the instantaneous Reynolds number. This implies that in this case, high frequency renal arterial flow reflects a fluid mechanic effect that can serve as a close approximation to steady luminal flow (Fig. 1b). By decreasing α from the nominal renal arterial case *via* this frequency change, the flow becomes highly viscous with large changes in the amplitude of the unsteady flow (Fig. 1b), including periods of reverse flow as the flow moves in phase with the instantaneous pressure gradient.

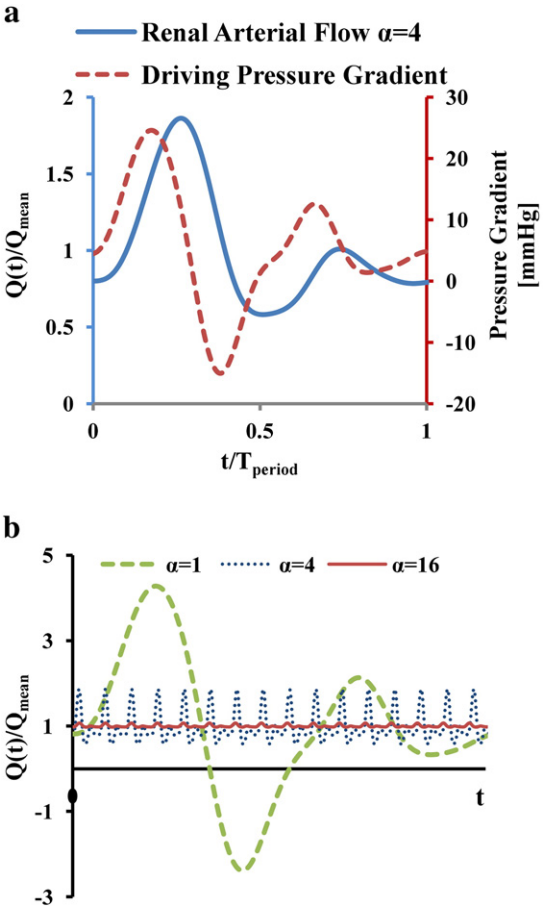

Fig. 1. Effects of Womersley number on different flow regimes. (a) Nominal pressure gradient derived from the renal arterial flow waveform [11] using Womersley's framework. (b) Flow waveforms as a result of varying α *via* frequency of pressure gradient in Eq. (1). Nominal case is shown for the renal artery [11]. As α increases from the nominal case, unsteadiness decreases while a decrease in α acts to increase the amplitude of the unsteady component of flow.

Thus by changing the frequency from the nominal pressure gradient of a renal arterial flow, both the unsteady magnitude ($Q(t)/Q_{mean}$) and the time scale of changes (time period) vary, acting to scale the overall unsteadiness of the system. As α increases to 16 with ω, there is effectively no pulsatility (only steady flow) while as α decreases with ω, we introduce an unsteady component that is far larger than the steady one and is therefore dominantly unsteady, resulting in periods of flow reversal. Taken together, the cases $\alpha = 1$ (truly unsteady), $\alpha = 4$ (physiologic) and $\alpha = 16$ (approximately steady), prescribe a range of dynamic fluid mechanic environments that allowed us to determine the sensitivity in arterial drug to the relative pulsatility of luminal flow. Accordingly, changes in the unsteady flow environment in both our computational and bench-top models were simulated by changing the cardiac frequency (ω) of a nominal renal arterial pressure gradient (Fig. 1a), yielding unsteady flow profiles each characterized in terms of their associated Womersley number.

2.2. In vitro model

A bench-top model was previously constructed, simulating drug release from a model stent strut into compartments housing a