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What is needed to make low-density lipoprotein transport in human aorta computational models suitable to explore links to atherosclerosis? Impact of initial and inflow boundary conditions

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ABSTRACT

Personalized computational hemodynamics (CH) is a promising tool to clarify/predict the link between low density lipoproteins (LDL) transport in aorta, disturbed shear and atherogenesis. However, CH uses simplifying assumptions that represent sources of uncertainty. In particular, modelling blood-side to wall LDL transfer is challenged by the cumbersomeness of protocols needed to obtain reliable LDL concentration profile estimations. This paucity of data is limiting the establishment of rigorous CH protocols able to balance the trade-offs among the variety of in vivo data to be acquired, and the accuracy required by biological/clinical applications.

In this study, we analyze the impact of LDL concentration initialization (initial conditions, ICs) and inflow boundary conditions (BCs) on CH models of LDL blood-to-wall transfer in aorta. Technically, in an image-based model of human aorta, two different inflow BCs are generated imposing subject-specific inflow 3D PC-MRI measured or idealized (flat) velocity profiles. For each simulated BC, four different ICs for LDL concentration are applied, imposing as IC the LDL distribution resulting from steady-state simulations with average conditions, or constant LDL concentration values.

Based on CH results, we conclude that: (1) the imposition of realistic 3D velocity profiles as inflow BC reduces the uncertainty affecting the representation of LDL transfer; (2) different LDL concentration ICs lead to markedly different patterns of LDL transfer.

Given that it is not possible to verify in vivo the proper LDL concentration initialization to be applied, we suggest to carefully set and unambiguously declare the imposed BCs and LDL concentration IC when modelling LDL transfer in aorta, in order to obtain reproducible and ultimately comparable results among different laboratories.

1. Introduction

Circumstantial evidence suggests a key role for mass transport in atherogenesis, with the accumulation process of high molecular weight solutes in the arterial intima considered as an hallmark of early atherosclerosis (Caro et al., 1971; Getz, 1990; Stary et al., 1994). In particular, it has been observed that high plasma levels of low-density lipoproteins (LDL) are causally related to the development of lesions (Nielsen, 1996). The LDL delivery from streaming blood to the artery wall has been proposed to be mainly consequence of a convective transport rate process (promoted by an arterial pressure-driven transmural flux of water in the lumen-to-wall direction), that ultimately results in a LDL concentration polarization at the surface of the endothelial barrier (Deng et al., 1993, 1995; Lever et al., 1992; Wada and Karino, 1999). This boundary layer, giving rise to near-wall local elevated LDL concentrations, promotes LDL transfer into the arterial wall in disturbed shear regions (see, e.g., Ethier, 2002; Sill et al., 1995; Sun et al., 2006; Wada and Karino, 2002; and references therein).

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However, (1) the general picture that regions at the lumen with elevated LDL polarization tend to co-localize with regions where atherosclerotic lesions develop, and (2) the observed tendency of such regions to co-localize with atherogenic wall shear stress (WSS) phenotypes, suggest but do not definitively prove that blood-to-wall LDL transfer is a primary factor promoting atherogenesis (Ethier, 2002). The fact that mass transfer to the arterial wall is regulated by complex and nonlinear mechanisms (Tarbell, 2003; Vincent and Weinberg, 2014), including WSS-related effects (Kang et al., 2014), markedly contributes to complicate the picture.

Advanced computational fluid dynamics coupled with medical imaging allows to combine the anatomical and hemodynamic inputs to realistic, fully personalized flow simulations to study local hemodynamics in arteries. Such an approach represents an effective way when addressing the still open questions about the role of blood-side LDL transfer to the arterial wall in atherogenesis (Ethier, 2002). In particular, personalized computational models have been proposed to study LDL blood-to-wall transfer in the aorta (Alimohammadi et al., 2016; Chen et al., 2014; Lantz and Karlsson, 2012; Lei et al., 2015; Li et al., 2017; Liu et al., 2009, 2011; Soulis et al., 2016), a district of election for the study of the relationships between the intricate local hemodynamics (Kilner et al., 1993; Morbiducci et al., 2011), LDL transport and disease.

However, computational hemodynamics (CH) requires some assumptions that could affect the solutions of the equations governing blood flow and the aortic convective LDL transport. In previous studies, the Authors have demonstrated that different strategies in applying boundary conditions (BCs) derived from phase-contrast MRI (PC-MRI) measurements could lead to different results in terms of distribution of near-wall and intravascular flow quantities (Gallo et al., 2012; Morbiducci et al., 2013). In particular, it has been reported that idealized velocity profiles as aortic inflow BCs could not be sufficiently representative of the aortic hemodynamics (Morbiducci et al., 2013). Additionally, a paucity of data characterize the literature concerning the BCs and initial conditions (ICs) adopted to model LDL transport.

In this study, we analyze the impact that different possible strategies of applying (1) PC-MRI measured data as inflow BC, and (2) LDL concentration profiles as IC, have on LDL blood-to-wall transfer modelling in the human aorta. Technically, two different inflow BCs are generated, by imposing at the ascending aorta inflow PC-MRI measured 3D velocity profiles or idealized (flat) velocity profiles. In this way, the sensitivity of blood-to-wall LDL transfer to the inflow BC is explored, as the inflow BC influences LDL advective transport. Moreover, for each simulated BC, four different ICs for LDL concentration profiles are applied. In this regard, here for the first time the problem of the unavailability of in vivo data to properly set concentration profile ICs in computational modelling of LDL transfer in aorta is faced up.

The impact of applied BC-IC strategies on LDL blood-to-wall transfer is evaluated in terms of computational costs and LDL polarization profiles at the luminal surface. Moreover, by virtue of the reported high LDL concentration in correspondence of disturbed shear regions (Ethier, 2002; Sill et al., 1995; Sun et al., 2006), here a co-localization analysis with areas exposed to atheroprone WSS phenotype is proposed as a "physics consistency check".

The study here presented would contribute to clarify which is (1) the level of detail obtained from measured flow data to be used as inflow BC, and (2) the plausibility of hypotheses on LDL concentration to be used as IC strategy, to satisfactorily simulate mass transport/transfer in personalized CH models of human aorta.

2. Materials and methods

An overview of the study method is provided in Fig. 1. Details on the 3D Cine PC-MRI image acquisition of the healthy human aorta and geometry reconstruction (Fig. 2) are provided in the Supplementary Material and in previous studies (Gallo et al., 2012; Morbiducci et al., 2009).

Transport of LDL in the streaming blood was modelled by coupling the governing (Navier-Stokes) equations of fluid motion with the advection-diffusion equation under unsteady flow conditions. Blood was modelled as an isotropic, incompressible, Newtonian fluid (specific mass 1060 kg m^{-3}, dynamic viscosity 0.0035 Pa s). LDL was assumed to be present in dissolved form in blood and it was modelled as a passive non-reacting scalar, transported in the streaming blood according to the advection-diffusion equation:

$$\frac{\partial C}{\partial t} + \mathbf{u} \cdot \nabla C - D_{LDL} \nabla^2 C = 0 \quad (1)$$

where C is the LDL concentration, **u** is the velocity vector obtained from the solution of the Navier-Stokes equations, and D_{LDL} is the diffusivity of LDL in flowing blood, set to a constant value of $5.983 \cdot 10^{-12}$ m^2 s^{-1} (Wada and Karino, 2002). At the inlet section, the average Peclet number (*Pe*), indicating the relative importance of advective *vs.* diffusive transport, is equal to $6.5 \cdot 10^8$.

The finite volume method was adopted to solve the coupled discretized Navier-Stokes and advection-diffusion equations. The adopted discretization schemes are detailed in the Supplementary Material. In particular, for the advection-diffusion equation here we applied the same scheme for modelling biological mass transport proposed and experimentally validated elsewhere (Carroll et al., 2010).

2.1. Conditions at boundaries

Two different inflow BC strategies were applied (Fig. 1). In the first strategy, measured 3D phase-contrast flow maps were extracted along the cardiac cycle and used to generate Dirichlet inflow BCs, applied in terms of 3D velocity profiles (BC_{3D}) at the ascending aorta (AAo) inlet section (as detailed in Morbiducci et al., 2013). The second strategy consists in the application of idealized flat velocity profiles (BC_F) derived from the measured flow rate waveform at the AAo inlet section. Such an assumption is in general consequence of the clinical availability of a measured flow rate waveform but a lack of knowledge on the associated realistic velocity profiles.

As regards outflow BCs, PC-MRI measured flow rates (Fig. 2) were prescribed at the supra-aortic vessels (Gallo et al., 2012). The aorta was assumed to be rigid with no-slip condition at the wall.

To solve Eq. (1), a uniform LDL concentration profile C_0 equal to $2.86 \cdot 10^{-9}$ mol m^{-3}, corresponding to the physiological LDL concentration in whole blood (Yang and Vafai, 2006), was prescribed at the AAo inflow section. At each outflow section of the aorta, a zero flux condition for LDL was applied. The LDL blood-to-wall transfer was modelled imposing the following equation at the luminal surface:

$$C_W V_W - D_{LDL} \left.\frac{\partial C}{\partial n}\right|_W = K_W C_W \quad (2)$$

where C_W is the LDL concentration at the vessel wall, V_W the water filtration velocity at the wall (set equal to $4 \cdot 10^{-8}$ m/s as in previous studies (Wada and Karino, 2002)), $\partial C/\partial n$ is the concentration gradient normal to the wall (with n indicating the direction normal to the luminal surface), and K_W the overall mass transfer coefficient of LDL at the vessel wall ($K_W = 2 \cdot 10^{-10}$ m s^{-1} (Wada and Karino, 2002)).

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