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Global sensitivity analysis of a model for venous valve dynamics

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ABSTRACT

Chronic venous disease is defined as dysfunction of the venous system caused by incompetent venous valves with or without a proximal venous obstruction. Assessing the severity of the disease is challenging, since venous function is determined by various interacting hemodynamic factors. Mathematical models can relate these factors using physical laws and can thereby aid understanding of venous (patho-) physiology. To eventually use a mathematical model to support clinical decision making, first the model sensitivity needs to be determined. Therefore, the aim of this study is to assess the sensitivity of the venous valve model outputs to the relevant input parameters. Using a 1D pulse wave propagation model of the tibial vein including a venous valve, valve dynamics under head up tilt are simulated. A variance-based sensitivity analysis is performed based on generalized polynomial chaos expansion. Taking a global approach, individual parameter importance on the valve dynamics as well as importance of their interactions is determined. For the output related to opening state of the valve, the opening/closing pressure drop ($dp_{\mathrm{valve},0}$) is found to be the most important parameter. The venous radius ($r_{\mathrm{vein},0}$) is related to venous filling volume and is consequently most important for the output describing venous filling time. Finally, it is concluded that improved assessment of $r_{\mathrm{vein},0}$ and $dp_{\mathrm{valve},0}$ is most rewarding when simulating valve dynamics, as this results in the largest reduction in output uncertainty. In practice, this could be achieved using ultrasound imaging of the veins and fluid structure interaction simulations to characterize detailed valve dynamics, respectively.

1. Introduction

Chronic venous disease is defined as dysfunction of the venous system caused by incompetent venous valves either with or without a proximal venous obstruction (international consensus committee on chronic venous disease (Porter and Moneta, 1995)). As a result of venous valve incompetence, the muscle pump efficiency is significantly reduced, which has a negative effect on venous return, especially in upright position (Laughlin, 1987). Additionally, chronic venous disease results in increased venous pressure and blood accumulation in the leg (Bergan et al., 2006). Venous hypertension, in turn, may contribute to the development of varicose veins (affecting one third of the Western population (Evans et al., 1999)) and in the long term to skin changes including pigmentation, venous eczema and even venous ulcers (chronic venous insufficiency) (Eberhardt and Raffetto, 2005).

For diagnosis of chronic venous disease Doppler ultrasound or phlebography (venous X-ray with contrast-agents) are often used to assess the location of leaking valves and varicose veins (Coleridge-Smith et al., 2006; Eberhardt and Raffetto, 2005; Nicolaides, 2000). Although these methods can adequately detect local defects, they cannot determine the hemodynamic consequences of the disease, such as increased venous pressure and muscle pump inefficiency. Therefore, global measures such as venous pressure or venous calf volume (using air plethysmography (Criado et al., 1998; Eberhardt and Raffetto, 2005)) should be examined after calf muscle contractions or under head up tilt (i.e. going from supine to upright position without putting weight on the limb being measured). With these methods global diagnostic parameters, related to either venous refilling speed following tilt or ejection fraction after muscle contraction, can be assessed (Katz et al., 1991); e.g. venous filling index $\left(VFI = \frac{\Delta V}{\Delta t}\big|_{90\%\mathrm{refilling}}\right)$, which is

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measured after tilt. However, measuring venous pressure is invasive and air plethysmography is not available in every vascular laboratory.

An alternative approach to assess the global severity of chronic venous disease is the use of mathematical models based on physical laws and physiological mechanisms. These models can quantitatively predict hemodynamic parameters, that are important for the development of chronic venous disease and are difficult to measure. In the last decade, reduced order models of arterial hemodynamics have developed to a stage where they not only aid understanding cardiovascular (patho-)physiology (Boileau et al., 2015; Shi et al., 2011; van de Vosse and Stergiopulos, 2011), but are also being validated to support clinical decision making (Caroli et al., 2013; Marchandise et al., 2009). For the venous system relatively few reduced order models have been developed to examine hemodynamics (Müller and Toro, 2014; Mynard and Smolich, 2015), regulation (Simakov et al., 2013) and valve dynamics (Keijsers et al., 2015), but these do include sufficient detail to capture generic venous function and the interplay between the various valves and veins. Although these models are suitable for assessment of the hemodynamic significance of chronic venous disease, they have not yet been applied in this context. Most models used to represent venous valve dynamics are generally only able to represent the open and closed state (diode) (Fullana and Zaleski, 2008; Müller and Toro, 2014; Zervides et al., 2008), whereas reduced order heart valve models provide more detail (Werner et al., 2002; Zacek and Krause, 1996). More sophisticated reduced-order valve models have been developed by Korakianitis and Shi, 2006, who included valve leaflet motion based on a force balance and Mynard et al., 2012, who related valve opening state to the pressure drop over the valve. The latter model was extended by Pant et al. (2015) to include valve regurgitation due to valve prolapse. These versatile valve models are also preferred for the venous system as they can model regurgitation in leaking valves and allow more detailed studies of venous valve dynamics, such as capturing venous valve dynamics under head up tilt. Unfortunately, these models require the introduction of more model parameters, which may increase the resulting uncertainty of the model output.

To eventually use such models to support clinical decision making, it is essential to assess the influence of the input parameters on the model output, which can be addressed through a sensitivity analysis. Using a global method both the importance of individual parameters and their interactions can be assessed (Eck et al., 2015). Furthermore, knowing which parameters are most important, allows for refinement of clinical measurement protocols when using these models to support clinical decision making. Additionally, parameters that are difficult to measure can be assessed by using fluid structure interaction simulations.

The aim of this study is to investigate the sensitivity of a mathematical model of a tibial vein simulating venous valve dynamics under head up tilt. Our previously presented venous model (Keijsers et al., 2015) is extended with the versatile valve model of Mynard et al. (2012). The influence of venous filling and valve input parameters on the valve dynamics in a healthy subject is assessed via a sensitivity analysis based on generalized polynomial chaos expansion (gPCE). Finally, it is investigated whether more detailed fluid structure interaction simulations are necessary to inform the reduced order model.

2. Methods

To examine the dynamics of a healthy venous valve under head up tilt, a pulse wave propagation model of a vein including a single valve was developed (Fig. 1). The pulse wave propagation model enables a continuous distribution of gravity, allows an easy extension of the model configuration to a larger domain and includes non-linear effects.

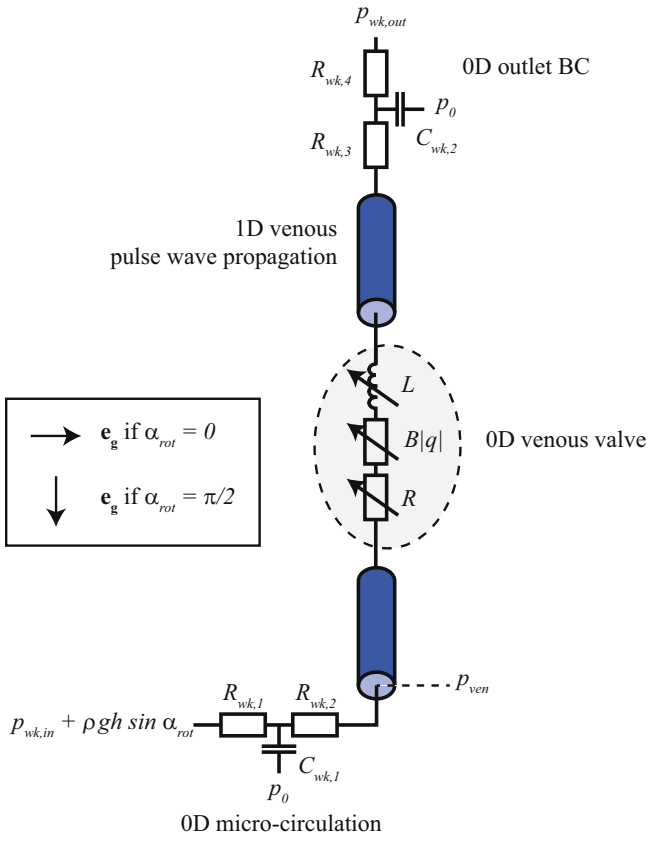

Fig. 1. Model configuration consisting of a 0D venous valve, 1D venous pulse wave propagation elements, a 0D micro-circulation and a 0D outlet boundary condition (BC). Furthermore, the gravity vector $\mathbf{e_g}$ is shown together with the rotation angle in both supine and tilted position. The 1D vein is split into a distal ($l_{dist} = 10$ cm) and a proximal ($l_{prox} = 20$ cm) part by a 0D valve (zero length). p_{ven} indicates the location of distal venous pressure as reported in the Results Section in Fig. 4E.

2.1. Model

The governing model equations are described in this section. This includes the 1D venous pulse wave propagation model, the 0D venous valve model and the boundary conditions. The baseline values of the model parameters can be found in Table 1.

2.1.1. 1D Venous pulse wave propagation

The hemodynamics in the large veins are captured using one-dimensional equations for mass and momentum balance. In this formulation, blood is assumed to be an incompressible, Newtonian fluid. This gives:

$$C\frac{\partial p_{tr}}{\partial t} + \frac{\partial q}{\partial z} = 0, \tag{1}$$

$$\frac{\partial q}{\partial t} + \frac{\partial A\bar{v}_z^2}{\partial z} + \frac{A}{\rho}\frac{\partial p}{\partial z} = \frac{2\pi a}{\rho}\tau_w + Ag_z, \tag{2}$$

where C, compliance per unit length, is a function of transmural pressure $p_{tr} = p - p_{ex}$, where p and p_{ex} are the intra- and extra-vascular pressure respectively, q is the flow, t is the time and z is the axial coordinate. Furthermore, A is the cross-sectional area, $\bar{v}_z$ is the mean velocity in the axial direction, ρ is the blood density, $a = \sqrt{A/\pi}$ is the equivalent radius for equal area, τ_w is the wall shear stress and $g_z = g\,\mathbf{e_g}\cdot\mathbf{e_z}$ is the contribution of gravitational acceleration in the axial direction. Additionally, g is the gravitational acceleration on earth, $\mathbf{e_g}$ is the unit vector in the direction of gravity and $\mathbf{e_z}$ is the unit vector in the axial direction along the vessel.

To obtain an estimate of the wall shear stress τ_w and the advection term $\frac{\partial A\bar{v}_z^2}{\partial z}$ the approximate velocity profile of Bessems et al. (2007) is used. The pressure gradient and gravitational forces are assumed to be in balance with viscous forces in the unsteady boundary layer (Stokes layer) close to the vessel wall, whereas inertia