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Non-invasive aortic systolic pressure and pulse wave velocity estimation in a primary care setting: An *in silico* study

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ABSTRACT

Everyday clinical cardiovascular evaluation is still largely based on brachial systolic and diastolic pressures. However, several clinical studies have demonstrated the higher diagnostic capacities of the aortic pressure, as well as the need to assess the aortic mechanical properties (e.g., by measuring the aortic pulse wave velocity). In order to fill this gap, we propose to exploit a set of easy-to-obtain physical characteristics to estimate the aortic pressure and pulse wave velocity. To this aim, a large population of virtual subjects is created by a validated mathematical model of the cardiovascular system. Quadratic regressive models are then fitted and statistically selected in order to obtain reliable estimations of the aortic pressure and pulse wave velocity starting from the knowledge of the subject age, height, weight, brachial pressure, photoplethysmographic measures and either electrocardiogram or phonocardiogram. The results are very encouraging and foster clinical studies aiming to apply a similar technique to a real population.

1. Introduction

The use of arterial blood pressure as a prognostic quantity in cardiovascular care has a long history, which started in 1896 when Riva-Rocci proposed the sphygmomanometer [1]. At the very beginning this instrument was able to give only maximum systolic absolute pressure, but soon after, in 1905, the Russian physician Korotkoff discovered the heart sounds (now holding his name) allowing both systolic and diastolic brachial pressures to be measured [1]. Because of the ease of use and low cost, current ambulatory and clinical cardiovascular evaluation is still largely based on these two quantities. However, in the last years an increasing number of clinical studies has demonstrated that aortic pressure strongly differs from its brachial counterpart and it has a greater diagnostic value [2,3]. Different non-invasive methods for the estimation of central pressure were explored [4,5] and patented [6]. Unfortunately, although new, promising technique are being proposed [5], to date central pressure can still be measured accurately only through invasive techniques [7], which are limited to serious pathological conditions. As a reference, a large meta-analysis showed that the most common non-invasive technique (namely based on a generalized transfer function to the radial tonometric waveform) is affected by a noisy underestimation of systolic (-8.2± 10.3 mmHg (mean± *SD*)) and overestimation of diastolic (7.6± 8.7 mmHg) aortic pressure. It follows that easy-to-use and cheap methods would be important to improve the central pressure assessment in primary care.

Many recent studies have also highlighted the high prognostic value of the aortic pulse wave velocity (aoPWV), recognizing the impact of the pressure/flow wave propagation (and hence the mechanical and geometrical properties of vessel walls) on the arterial function and cardiovascular risk [8]. Due to the long-standing difficulties in measuring aoPWV non-invasively, scientific community usually uses the carotid-femoral pulse wave velocity (cfPWV), i.e. the average celerity of propagation between carotid and femoral arteries, being both locations accessible to tonometric inspection [9]. However, despite the high correlation between aoPWV and cfPWV [9], even cfPWV is not entered in the everyday clinical practice, mainly because of the uncertainties in the carotid-femoral distance evaluation [9], the operator dependence of the tonometric technique [7], and the large time consumed for its evaluation.

A possible, low-cost alternative for the quantification of the mechanical characteristics of vessels relies on the use of photoplethysmography (PPG) [10]. Indeed, this simple technology, suitably coupled with an electrocardiogram (ECG), has proven to reliably predict aoPWV through the measurement of the pulse transit time

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(PTT), i.e. the delay between the R peak in the ECG and the onset of the PPG waveform at, for example, a hand finger [11]. An estimate of aoPWV could be obtained by the ratio of the distance between the aortic and the finger locations and the PTT: this estimate is here indicated by pttPWV. Moreover, PPG technology was also used to track beat-to-beat changes in the central [6] and peripheral blood pressure [12–14]. The aoPWV and blood pressure assessment can be improved if the pre-ejection time (PET) is removed from the PTT obtaining the so-called vascular transit time (VTT) [15,16]. This could be done by using the phonocardiogram (PCG) instead of the ECG to measure the heartbeat [15]. The PCG allows the time of the aortic valve opening to be detected by analysing the heart murmurs. The part of the PTT corresponding to the isovolumetric compression is thus excluded, leaving a better estimate of the propagation time. The estimation of aoPWV by the ratio of the distance between the aortic and the finger locations and the VTT is indicated by vttPWV in the following.

The medical community is thus facing an intriguing problem: on one hand, clinical and epidemiological studies highlight the need to include both the aortic blood pressure and aoPWV in the clinical setting [8]; on the other hand, the limitations inherent to the non-invasive evaluation of these quantities still represent a significant hindrance for the common clinical practice [9].

In this work, we adopt a multivariate regressive approach to simultaneously exploit the information contained in different quantities that can be readily measured in clinical practice. We focus on age, height, weight, brachial systolic and diastolic pressure, and either PTT or VTT obtained via photoplethysmography (coupled with either ECG or PCG, respectively). By using a large data set of virtual subjects obtained by a validated cardiovascular mathematical model [17], our aim is to select the best regressive models able to estimate aortic systolic blood pressure (aoSBP) and aoPWV from easy-to-obtain and cheap data. Specifically, the mathematical model is based on a one-dimensional formulation of wave propagation, which have already proven to compare well in experimental [18,19] and *in vivo* [17,20-22], setup as well as being a useful tool for cardiovascular investigations [23–25]. The choice of using a virtual population has the advantage of avoiding the non homogeneity of the characteristics of a real population, thus allowing a clean investigation of the relative dependencies. On the other hand, a clinical validation of our results is needed.

2. Methods

In this section, the validated mathematical model for the simulation of cardiovascular dynamics of virtual subjects is recalled (the complete description is given in [17]), the criteria used to design the virtual population are presented and the regression strategy is detailed.

2.1. Heart-arterial model

The network of large arteries is modeled by assuming axisymmetric, impermeable, tapered, and longitudinally-tethered vessels, subjected to small and radial deformations in the absence of gravitational effects. Flow is laminar and the pressure (P) is considered uniform across the transversal section. Blood is assumed Newtonian, incompressible, and characterized by constant density (ρ) and kinematic viscosity (ν).

Under these hypotheses, the one-dimensional mass and momentum balance equations read

$$\frac{\partial A}{\partial t}+\frac{\partial Q}{\partial x}=0$$
$$\frac{\partial Q}{\partial t}+\frac{\partial}{\partial x}\left(2\pi\int_0^R u^2 r\mathrm{dr}\right)=-\frac{\mathrm{A}}{\rho}\frac{\partial \mathrm{P}}{\partial x}+2\pi\nu\left[\mathrm{r}\frac{\partial \mathrm{u}}{\partial \mathrm{r}}\right]_{\mathrm{r=R}} \quad (1)$$

Table 1
Values of characteristic quantities chosen to create a heterogeneous population.

Quantity	Reference value	Other values
Age [years]	20	35 , 50, 65, 80
Height [m]	1.75	1.60, 1.90
BMI	22	19, 25
HR [bpm]	70	60, 80
EDV [ml]	120	110, 130
η_W	1	0.75, 0.875, 1.125, 1.25
η_E	1	0.7 , 1.3
η_R	1	0.9, 1.1

where x and r are the longitudinal and radial coordinates, respectively, t is time and u is the longitudinal velocity. A and R are the vessel cross-sectional area and radius, respectively, and $Q=2\pi\int_0^R u\mathrm{dr}$ is the flow rate. The velocity profile is modeled as a central flat profile joined to a parabolic boundary layer of fixed thickness [17]. By assuming that the arterial wall exhibits a radius-dependent nonlinear viscoelastic behavior [26], the constitutive equation is written as

$$P=B_1+B_2A+B_3A^2+B_4A^3-B_5\frac{1}{\sqrt{A}}\frac{\partial Q}{\partial x} \quad (2)$$

where the coefficients B_i $(i=1,\ldots,5)$ contain the information about the local viscoelastic mechanical properties [17].

The inlet boundary condition of the arterial system corresponds to the left ventricle (LV) and it is described by a lumped time-varying elastance model. The ventricle-aorta connection is mediated by the aortic valve, whose leaflets are modeled to freely move (between a minimum and a maximum opening angle) under the actions of a number of mechanical and fluid dynamical forces [23,27].

Distal boundary conditions are set by three-element Windkessel models [26]. The conservation of mass and total pressure at arterial bifurcations is set as boundary conditions. The well-posedness of the problem at bifurcation is obtained through the use of pseudo-characteristics, which neglect the local effect of arterial wall viscoelasticity [17].

The system of hyperbolic partial differential equations was solved by the Runge–Kutta Discontinuous-Galerkin method, by adopting the geometrical and mechanical characterization of the arterial tree and distal models described in the benchmark data set reported by Reymond et al. [21]. By numerically exploiting the symmetry of the legs of the benchmark data set [21], we can avoid to simulate one leg, thus reducing the number of arteries from 55 to 48. The simulations were done with a temporal step of 10^{-4} s, and the arterial network was discretized in 408 non uniform segments. Smaller and more rigid arteries were discretized with a finer mesh, while larger and softer arteries with larger elements. This was done in order to maintain the CFL number as uniform as possible throughout the network. Maximum CFL ranged from 0.1 to 0.27, depending on the coupling between height, age and pulse wave velocity, with a mean value of 0.17.

2.2. Population design

The mathematical model was used to obtain a large population of virtual subjects. To this aim, a set of variables was chosen and the corresponding benchmark values were varied in suitable ranges. The variables focused are the following (see Table 1): age, height, body mass index (BMI), heart rate (HR) (and coherently ejection time [28]), end-diastolic left-ventricular volume, mechanical properties of the arteries, maximum left-ventricular force of contraction, and resistance of the peripheral Windkessel models. Peripheral compliances were not changed as *in silico* studies

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