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The Windkessel model revisited: A qualitative analysis of the circulatory system

Athanasios Tsanas[a], John Y. Goulermas[a,*], Vassiliki Vartela[b], Dimitrios Tsiapras[b], Georgios Theodorakis[b], Antony C. Fisher[d], Petros Sfirakis[c]

[a] Department of Electrical Engineering and Electronics, Brownlow Hill, University of Liverpool, Liverpool L69 3GJ, UK
[b] B' Cardiologic Department of Onassis Cardiac Surgery Centre, 356 Syggrou Avenue, 176 74 Athens, Greece
[c] Transplantation and Mechanical Circulatory Support, 1st Division of Cardiothoracic Surgery, Onassis Cardiac Surgery Centre, Greece
[d] Department of Clinical Engineering, Liverpool University Hospital, Liverpool L7 8XP, UK

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ABSTRACT

In this paper, we derive a comprehensive computational model to estimate the arterial pressure and the cardiac output of humans, by refining and adapting the well-established equations of the Windkessel theory. The model inputs are based on patient specific factors such as age, sex, smoking and fitness habits as well as the use of specific drugs. The model's outputs correlate very strongly with physiological observations, with a low error of ~5% for the arterial pressure.

1. Introduction

The accurate measurement of the arterial pressure is known to have great diagnostic and prognostic value [1] and has inspired numerous attempts of modeling the circulatory system. The main focus of research for a very accurate description of the circulatory system is undoubtedly the Navier–Stokes equations [2]; however its enormous complexities make its practical implementation for the whole body impossible [3]. Although attempts have been made to combine it with the Windkessel model (WM) [4] in order to achieve both accurate circulatory representation as well as reduction of the inherent complexities [3], the WM is widely adopted in applications relating blood pressure, flow and heart load [5].

Most researchers focus on parts of the cardiovascular system and in particular either the systemic [6,7] or pulmonary arterial tree [5,8]. The model proposed in this paper, expands on these equations to encompass the whole circulation in a similar way to Keener and Sneyd's work [9] where they suggest a similar variation of WM layout but without attempting to solve the resulting systems of equations. The significance of this *closed loop* approach is that it offers a functional insight in the complicated cardiovascular system in terms of directly providing estimates of the blood pressures, flows and volumes in various parts of the cardiovascular system. Moreover, this paper relates the measurements and patient specific factors of age, sex, smoking/fitness habits and drug use with the lumped parameters of the Windkessel theory in a simple way, and allows even a non-expert to compare the measured arterial pressure with the expected pressure of the model by simply altering the model inputs. Additionally, the cardiac output (CO) is estimated, building on a previous study which proved that the simpler WM method outperforms alternative sophisticated attempts of CO estimation, providing near optimal evaluation performance [15]. This saves the patient from invasive methods and costly tests (intensive care unit and echocardiography).

In general, there is a very high potential and wide applicability for such virtual environments of the circulation. For instance, they can allow interactive experimental simulations of the physiology of the circulatory system, allowing for a deeper understanding of the interaction between the model inputs and parameters. These relationships of pressures, volumes and flows could be directly implemented in mechanical circulatory support systems. Their benefit in diagnosis and treatment can also be high, as the symptoms of pathologies incorrectly assessed by the clinicians, could be traced down to the associated causative model parameters introduced in respective parts of the circulation.

2. Data collection

The study population consisted of 208 patients (154 men and 54 women) aged 30–80 years old (mean age 53.5 ± 11.7 years) who

* Corresponding author.
E-mail addresses: tsanasthanasis@gmail.com (A. Tsanas), j.y.goulermas@liverpool.ac.uk (J.Y. Goulermas), a.c.fisher@liverpool.ac.uk (A.C. Fisher).

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Nomenclature

Terms

C	compliance
CO	cardiac output
F	heart rate
P	pressure
Q	flow
R	resistance
SV	stroke volume
S	sympathetic innervation
T	period
V	volume

Subscripts

a	arterial
s	systemic
p	pulmonary
v	venous
AV	aortic valve
LA	left atrium
LV	left ventricle
MV	mitral valve
PV	pulmonary valve
RA	right atrium
RV	right ventricle
TV	tricuspid valve
0	residual (volume)

referred to Onassis Cardiac Surgery Center for an exercise treadmill test (ETT) from March to September 2006, 70 of whom had coronary artery disease (CAD). Eighty-three of them were smokers, 62 had systemic hypertension and/or high cholesterol, and 26 were without known heart disease or any risk factor for cardiovascular disease. Patients who had implanted devices (pacemakers, defibrillators) were excluded. The measurements were recorded and provided by the same cardiologist and nursing staff using armmanometer. The study protocol was reviewed and approved by the local ethics committee.

3. The Windkessel model

The term WM was introduced by Otto Frank in his milestone work in 1899 [4]. In its simplest form, it consists of two lumped parameters: the resistance R and the compliance (often, simply referred to as capacitance) C which are attributed to blood vessels. The attraction of the WM is that these electric elements have explicit physiological sense: the resistance depends on the radius (following Poiseuille's law) and the compliance corresponds to the elasticity of the vessel. Large vessels are treated as compliances whereas smaller vessels are resistances. Although this distinction is idealistic, it works well in practice. Fig. 1 shows the representation of a blood vessel.

The modeling equation for the resistive vessel is

$$Q_2 = \frac{P_1 - P_2}{R} \tag{1}$$

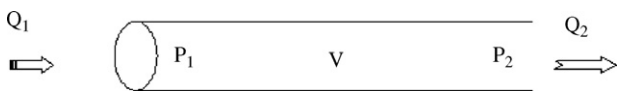

Fig. 1. Representation of a blood vessel, where P_1 and P_2 are the upstream and downstream pressures, and Q_1 and Q_2 the inflow and outflow, respectively.

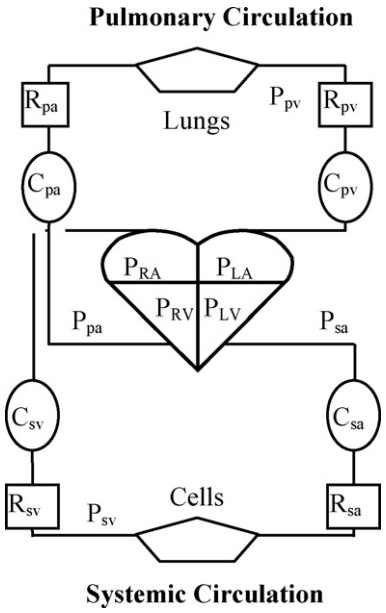

Fig. 2. Schematic diagram of the modeled circulation.

and for the compliant vessel we have

$$V = V_0 + C \times P \tag{2}$$

$$\frac{dV(t)}{dt} = Q_1 - Q_2 \tag{3}$$

where Q represents the flow, P the pressure, R the resistance, C the compliance and V the volume of blood. V_0 is the residual volume, which is defined as the hypothetical volume of blood in zero pressure. Combining Eqs. (2) and (3) we derive the equation which will be later used in the model analysis:

$$C \times \frac{dP(t)}{dt} = Q_1 - Q_2 \tag{4}$$

It is possible to incrementally include more elements of R and C, to make up for a more realistic model at the cost of greater complexity [10]. Additional elements may also be integrated, providing the framework for a more comprehensive study. For example, a fundamental deficiency of the WM is the assumption that the pulse wave travels at infinite speed. The effect of inertia can be introduced in the form of the inductor (L) equivalent electrical component, which has been incorporated to construct a 4-element WM in [10]. That paper is primarily concerned with the accurate estimation of lumped parameters and pressure waveforms. For the purpose of monitoring pressures and flows, we endeavor to prove the 2-element WM is sufficiently adequate. In this paper we are interested only in 'steady state' results (systolic/diastolic pressures) at rest; transient analysis (i.e. to monitor the pressure pulse shape) is feasible by expanding the current approach (introducing inertance elements). Furthermore, multiple distributed parameter models can be used to refine specific vascular regions, e.g. the aorta, the pulmonary artery, etc.

4. Model analysis

In this study, the simplest case for the entire circulatory system is used: one resistive and one compliant element are introduced in each of the four large parts of the system shown in Fig. 2. Bridging this with the Nomenclature presented above, the subscripts are interchangeably used with the terms. Thus, C_{pv} stands for 'compliance of pulmonary veins', P_{LV} for 'pressure of left ventricle' (by convention, all capital subscripts refer to the heart).

The derivation of our model starts by applying the fundamental equations of the WM for the resistance and compliance vessels. Since a closed loop is formed, the output of one part consists of the input of the next and the approach is similar to an equivalent Kirchhoff electrical circuit. Electrical problems are primarily concerned with voltage and current; these amount to pressure and flow in physiology. Thus, it is desirable to reach equations where the pressures are determined, and subsequently used to calculate the blood flows and volumes.

Our approach has been to merge and solve the resulting differential equations from Eqs. ((1) to (4)) via Euler approximations, which significantly reduces complexity. Although this old simple method is known to be potentially unstable, we did not encounter any problems in the numerous simulations of the interactive program developed. We present below the derivation of the resulting equations for the systemic circulation; the analysis for the pulmonary circulation is identical, provided that the systemic subscripts are converted into pulmonary ones (i.e. '*s*' becomes '*p*', 'LV' becomes 'RV', and so on). Firstly, the pressure for the systemic veins is calculated:

From Eq. (1) we deduce: $Q_{sa} = (P_{sa} - P_{sv})/R_{sa}$ and $Q_{sv} = (P_{sv} - P_{RA})/R_{sv}$ which are implemented in Eq. (4):

$$\begin{aligned}&\frac{C_{sv}[P_{sv}(t) - P_{sv}(t-\Delta t)]}{\Delta t}\\ &= \frac{P_{sa} - P_{sv}}{R_{sa}} - \frac{P_{sv} - P_{RA}}{R_{sv}} \Leftrightarrow P_{sv}(t)\\ &= \frac{P_{sv}(t-\Delta t) + (P_{sa}\Delta t/C_{sv}R_{sa}) + (P_{RA}\Delta t/C_{sv}R_{sv})}{1 + (\Delta t/C_{sv}R_{sv}) + (\Delta t/C_{sv}R_{sa})}\end{aligned} \tag{5}$$

Following the same pattern, the pressure for the left ventricle and the systemic arteries are determined. The flows from the atria to the ventricles and from the ventricles to the arteries are conditional on the pertinent valves being open. In the study of the systemic circulation this is integrated in the form of MV_{state} (mitral valve) and AV_{state} (aortic valve), which take Boolean values and determine whether the valves allow blood flow through them. Modifying Eq. (1) to incorporate the valves of the heart gives: $Q_{LA}(t) = MV_{state}\frac{P_{LA}(t)-P_{LV}(t)}{R_{MV}}$ and $Q_{LV}(t) = AV_{state}(P_{LV}(t) - P_{sa}(t))/(R_{AV})$ which are then inserted in Eq. (4):

$$\begin{aligned}&\frac{C_{LV}(t)P_{LV}(t) - C_{LV}(t-\Delta t)P_{LV}(t-\Delta t)}{\Delta t}\\ &= \frac{MV_{state}[P_{LA}(t) - P_{LV}(t)]}{R_{MV}} - \frac{AV_{state}[P_{LV}(t) - P_{sa}(t)]}{R_{AV}}\end{aligned} \tag{6}$$

Similarly,

$$C_{sa}\frac{P_{sa}(t) - P_{sa}(t-\Delta t)}{\Delta t} = \frac{AV_{state}[P_{LV}(t) - P_{sa}(t)]}{R_{AV}} - \frac{P_{sa}(t) - P_{sv}}{R_{sa}} \tag{7}$$

is derived.

Merging Eqs. (6) and (7), the pressures of the left ventricle and the systemic arteries are deduced:

$$\begin{aligned}&\underbrace{P_{LV}(t)}_{x}\underbrace{\left[\frac{C_{LV}(t)}{\Delta t} + \frac{MV_{state}}{R_{MV}} + \frac{AV_{state}}{R_{AV}}\right]}_{a_1} + \underbrace{P_{sa}(t)}_{y}\underbrace{\left[-\frac{AV_{state}}{R_{AV}}\right]}_{b_1}\\ &= \underbrace{\left[\frac{C_{LV}(t-\Delta t)P_{LV}(t-\Delta t)}{\Delta t} + \frac{P_{LA}(t)MV_{state}}{R_{MV}}\right]}_{c_1}\\ &\underbrace{P_{LV}(t)}_{x}\underbrace{\left[-\frac{AV_{state}}{R_{AV}}\right]}_{a_2} + \underbrace{P_{sa}(t)}_{y}\underbrace{\left[\frac{C_{sa}}{\Delta t} + \frac{AV_{state}}{R_{AV}} + \frac{1}{R_{sa}}\right]}_{b_2}\\ &= \underbrace{\left[\frac{C_{sa}P_{sa}(t-\Delta t)}{\Delta t} + \frac{P_{sv}}{R_{sa}}\right]}_{c_2}\end{aligned} \tag{8}$$

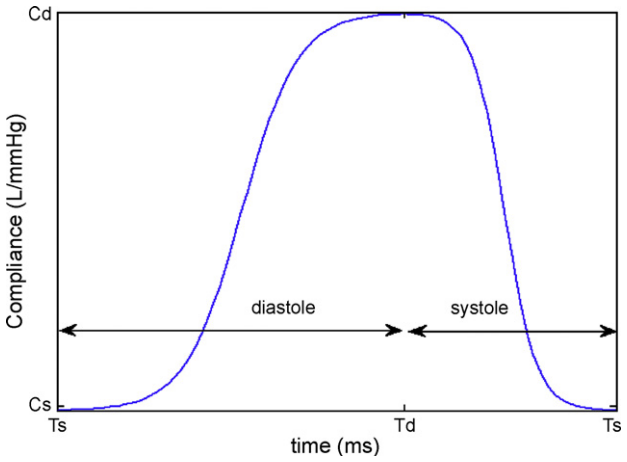

Fig. 3. The proposed time-dependent variation compliance of the ventricles.

A similar system of equations is then developed for the pulmonary circulation. It can be seen, that these systems are linear of the form, $AX = B$ with the components of $A = \begin{bmatrix} a_1 & b_1 \\ a_2 & b_2 \end{bmatrix}$, $X = \begin{bmatrix} x \\ y \end{bmatrix}$ and $B = \begin{bmatrix} c_1 \\ c_2 \end{bmatrix}$ participating in Eq. (8). Hence, the solution is simply provided by means of $X = A^{-1}B$. This system of equations allows some interesting remarks. The valve states (AV_{state}, etc.) are dependent upon the pressures before and after each valve (e.g. AV_{state} depends on P_{LV} and P_{sa}). Since the pressures themselves depend on the state of the valves, the system needs a random initial guess of the pressures at time $t = 0$ so that the valve states are set and the iterative calculations can begin. This is a common theme to various optimisation problems, where random initial values are required to start the iterative procedure. For example setting $P_{sa} = 100$ mmHg and $P_{LV} = 10$ mmHg results in AV_{state} becoming 0 (posterior pressure is larger than the prior pressure of the valve). Using physiological values of pressures for adults [12] facilitates the whole process. Any initial values would allow the system to converge but using normal physiological values allows the system to converge fast, normally after 4–5 periods. The time-step Δt was set to be $0.01 \times T$ where T is the period (see Fig. 3 for the contraction and dilation of the heart). The resistance of the valves is physiologically considered negligible and was assumed to be 0.0001 mmHg × min/L. Pathological problems associated with one or more valves (such as stenosis) could be modeled by increasing the corresponding resistances. This study was conducted on the assumption of healthy valve resistances. The value of the resistance of the systemic arteries R_{sa} is determined in Table 2 and depends on the inputs of the model (the procedure for optimising these model parameters is thoroughly described in Section 5). $C_{LV}(t)$ (and $C_{RV}(t)$ for the pulmonary circulation) is addressed to the time-dependent compliance of the ventricles.

We model the contraction and dilation of the heart as two time-variant compliant vessels, and introduce a double sigmoid function $f(x, z_1, q_1) - f(x, z_2, q_2)$ shown in Fig. 3 to model the compliance of the ventricles. This is based on the sigmoid $f(x, z, q) = \left(1 + e^{-z(x-q)}\right)^{-1}$ (where z and q are shape control parameters), and use it twice for the time intervals $[T_s, T_d]$ and $[T_d, T_s]$, that correspond to the diastolic and systolic responses of the ventricles, respectively. The interval durations were correspondingly set to 550 and 300 ms following physiological observations of the cardiac cycle [11]. The minimum compliance of the ventricles C_s, which is the systolic ventricular compliance, was assumed to be practically zero ($C_{LV,systole} = 0.00003$ L/mmHg and $C_{RV,systole} = 0.0003$ L/mmHg for the needs of the simulation). The difference between the pro-

Table 1
Residual and normal volumes of blood.

Part of circulation	Residual blood volume (L)	Normal blood volume (L)
Systemic arteries	$V_{0\_sa} = 0.65$	$V_{sa} = 1.00$
Systemic veins	$V_{0\_sv} = 3.35$	$V_{sv} = 3.50$
Pulmonary arteries	$V_{0\_pa} = 0.03$	$V_{pa} = 0.10$
Pulmonary veins	$V_{0\_pv} = 0.06$	$V_{pv} = 0.40$
Left ventricle	$V_{0\_LV} = 0.03$	$V_{LV} = 0.07–0.14$
Right ventricle	$V_{0\_RV} = 0.03$	$V_{RV} = 0.07–0.14$

posed variation of left and right ventricular compliance is in the maximum value C_d, which corresponds to $C_{LV,diastole}$ and $C_{RV,diastole}$. These values are determined at the end of this section.

Having determined the pressures for the respective parts of the circulation, we move on to calculate the stroke volume and the cardiac output as well as the volumes of blood in the whole circulation. Applying Eq. (2) for the left ventricle, the end-diastolic and end-systolic volumes are

$$V_{\text{end-diastolic}} = V_0 + C_{LV,diastole} P_{pv} \tag{9}$$

$$V_{\text{end-systolic}} = V_0 + C_{LV,systole} P_{pa} \tag{10}$$

and, similarly, we calculate the equations for the right ventricle. The stroke volume (SV) and the cardiac output (CO) are found from the well known physiological relationships [9].

$$\begin{aligned} SV_{LV} &= V_{\text{end-diastolic}} - V_{\text{end-systolic}} \\ &= C_{LV,diastole} P_{pv} - C_{LV,systole} P_{pa} \cong C_{LV,diastole} P_{pv} \end{aligned} \tag{11}$$

$$CO_{LV} = F SV_{LV} \tag{12}$$

The approximation employed for the stroke volume in Eq. (11) is physiologically justified since $C_{LV,systole}$ is approximately zero (see also Fig. 3). The volume and flow of blood in the respective parts of the circulation is calculated by direct application of Eqs. (1)–(3). The residual volumes of the circulation were set so that the corresponding volumes of blood would coincide with normal physiological values, which are summarised in Table 1. The initial estimation of the values for the model parameters was by using physiological values of volumes and pressures [12] when applied in Eqs. (1)–(3). Further refinement by trial and error was dictated by the desired expected arterial pressure outputs which had to be in the proximity of 120/80 and 25/9 mmHg for the systemic and pulmonary arteries, respectively. The CO should also be in the range 5–6 L/min and ideally the stroke volume of the two ventricles should be identical (in real life it is axiomatically identical; a deviation of 1 mL was considered acceptable in the model). C_{LV} and C_{RV} were set to be in phase (see also Fig. 5a and b). Numerous simulations show the corresponding valves (mitral and tricuspid valve; aortic and pulmonary valve) are almost always in phase (opening and closing at the same time step). In some of the simulations there is a delay of 1 Δt in certain cardiac cycles regarding the opening and closure of the analogous valves, but this is also true in real life.

The maximum ventricular compliance was determined by applying Eq. (11) ($C_{LV,diastole} = 0.014$ L/mmHg and $C_{RV,diastole} = 0.035$ L/mmHg) and subsequently refined to produce an output of 120/80 mmHg for the arterial pressure and CO = 5.2 L/min (the final values were $C_{LV,diastole} = 0.0145$ L/mmHg and $C_{RV,diastole} = 0.03436$ L/mmHg). The refinement is dictated from the fact that the minimum ventricular compliances and the valve resistances are not zero (which affects pressures and in turn the cardiac output).

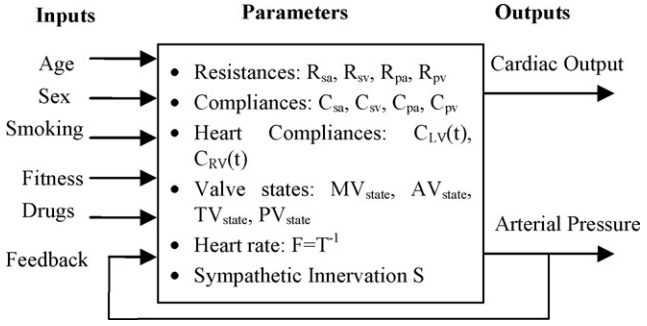

Fig. 4. Schematic representation of the model. The valve states take Boolean values.

5. Optimising the model parameters

The model developed so far explains the relationship between the model parameters and outputs in Fig. 4. Nevertheless, the aim here is to provide a full clinically interpretable model that takes as input the patient specific factors (age, sex, etc.) and habitual measurements of one human subject (left side of Fig. 4) and estimates the cardiac output and the arterial pressure. Ultimately, Sections 5 and 6 seek to develop appropriate relationships between the patient specific factors (inputs) with the model parameters in order to provide realistic estimates of resistances and compliances. The significance of the proposed model (apart from offering simple relationships between model parameters and outputs for the whole circulation) is to try and identify the effect of each input to the model parameters. Thus, it could potentially identify underlying vascular problems (e.g. high resistance possibly corresponds to stenosis), which are not easily discernible when only considering the pressures, cardiac output, etc.

For modeling simplicity, we assume that the six unknown model parameters R_{sa}, R_{pa}, C_{sa}, C_{pa}, $C_{LV,diastole}$ and $C_{RV,diastole}$ follow a polynomial relationship with the patient specific factors (the venous parameters are discussed at the end of this section). A low-order, linear relationship worked effectively for the current problem. Since there are seven inputs: age, sex, smoking, fitness, and three types of commonly used drugs known to affect the circulatory system (beta-adrenergic blocking (beta-blockers), angiotensin-converting enzyme (ACE) inhibitors and anti-arrhythmic drugs), there are 8 polynomial coefficients $a_0,\ldots,a_7$ for each parameter that need evaluation to complete the model. Specifically, each of the 6 model parameters was implemented in the form of Eq. (13):

$$\begin{aligned} \text{Parameter}_i = {} & a_{0,i} + a_{1,i}\text{Age} + a_{2,i}\text{Sex} + a_{3,i}\text{Smoking} + a_{4,i}\text{Fitness} \\ & + a_{5,i}\text{Drugs}_1 + a_{6,i}\text{Drugs}_2 + a_{7,i}\text{Drugs}_3 \end{aligned} \tag{13}$$

where Drugs_1, Drugs_2 and Drugs_3 refer to beta-blockers, ACE inhibitors and anti-arrhythmic drugs, respectively. With Eq. (13) we represent the part of the model relating the *inputs* with the *model parameters* (see left side of Fig. 4 for a diagrammatic representation of this). Then, the model parameters form the relationships devel-

Table 2
Polynomial coefficients for each of the six model parameters calculated for the entire patient dataset.

	R_{sa}	R_{pa}	C_{sa}	C_{pa}	$C_{LV,max}$	$C_{RV,max}$
a_0	5.8946	1.1125	4.310E−3	6.808E−3	1.466E−2	3.476E−2
a_1	0.0599	0.0105	−2.170E−5	−1.974E−5	−7.979E−6	−2.110E−5
a_2	−0.4196	−0.0220	1.848E−4	4.269E−5	4.908E−6	1.553E−6
a_3	0.0493	0.0492	−6.322E−5	−3.797E−5	−9.732E−6	−2.252E−5
a_4	−0.0182	−0.0091	7.107E−5	2.728E−5	1.432E−5	3.087E−5
a_5	0.0719	0.0080	−5.397E−5	−2.189E−5	−1.518E−5	−2.376E−5
a_6	0.0992	0.0234	−1.666E−4	−2.412E−6	−2.263E−5	−4.000E−5
a_7	−0.0354	−0.0488	−1.376E−4	4.487E−5	−5.302E−6	3.432E−5

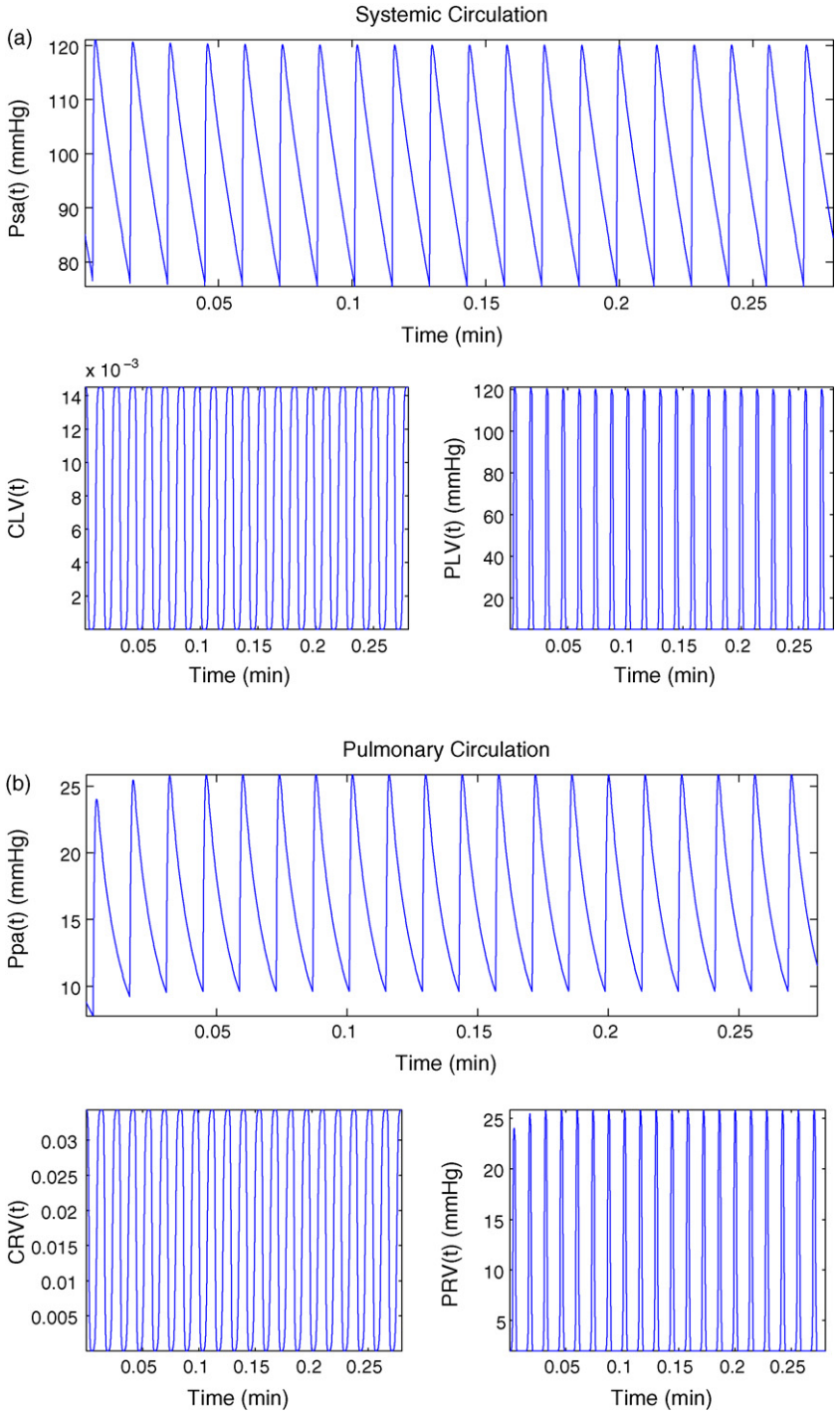

Fig. 5. (a) Typical output of the model: systemic circulation results for a man aged 20, non-smoker, fit and not under drugs. (predicted CO = 5.18 L/min). (b) Pulmonary circulation results for a man aged 20, non-smoker, fit and not under drugs.

Table 3
Typical numeric model responses for people not taking any drugs. The systemic arterial pressure is given in the form X/Y where X is the systolic and Y the diastolic pressure. The heart rate F is rounded to the nearest integer value.

	Age	Sex	Fitness	Smoking	$C_{LV,diastole}$ (L/mmHg)	P_{pv} (mmHg)	F (bpm)	P_{sa} (mmHg)	CO (L/min)
H_1	30	M	Yes	No	0.014438	5.0010	70	127/79	5.0377
H_2	65	M	Yes	No	0.014159	5.0013	65	139/84	4.5687
H_3	45	M	Yes	No	0.014319	5.0012	67	133/81	4.8277
H_4	45	F	Yes	No	0.014324	5.0010	67	126/79	4.8291
H_5	50	F	No	No	0.014269	5.0011	67	127/79	4.7575
H_6	50	F	Yes	No	0.014284	5.0011	67	127/78	4.7623
H_7	35	M	Yes	Yes	0.014389	5.0011	69	129/81	4.9627
H_8	35	M	Yes	No	0.014399	5.0011	69	128/81	4.9661

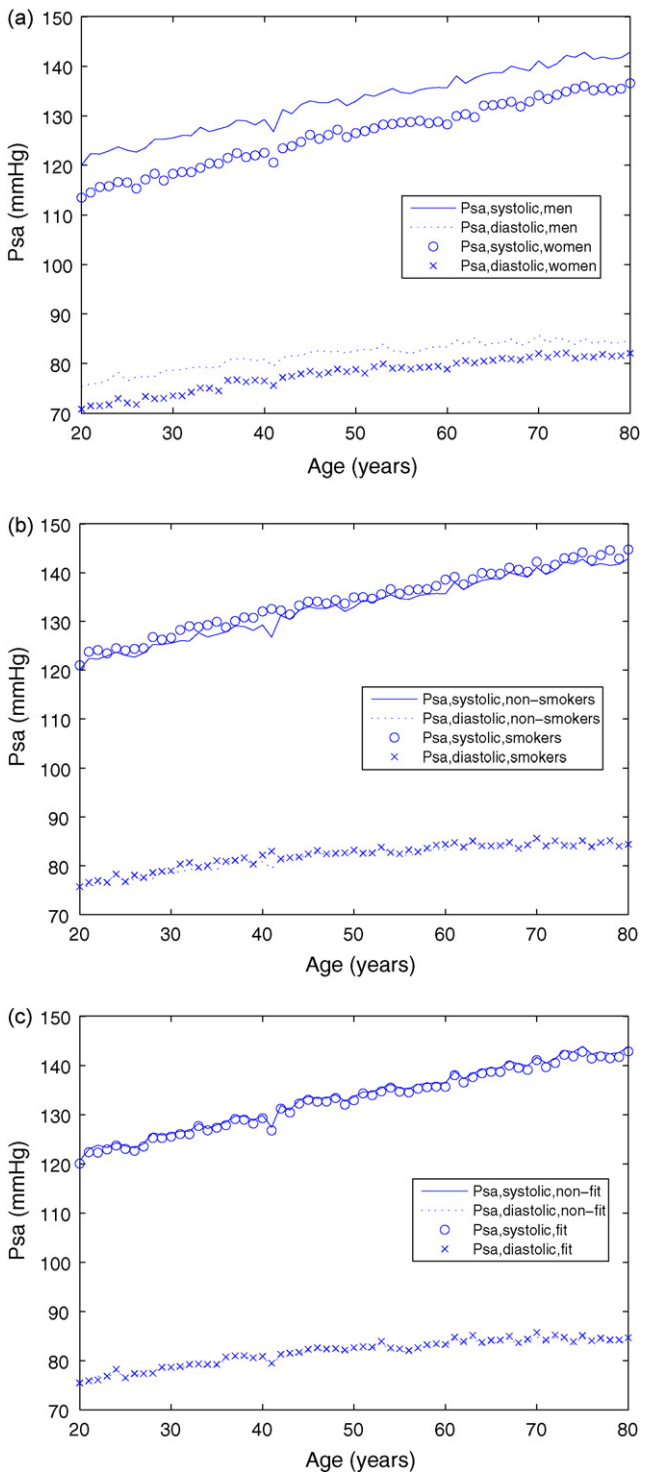

Fig. 6. (a) Model's prediction for the effect of aging in the systemic pressure for men and women. (b) Model's prediction for the effect of smoking in the systemic arterial pressure for healthy men. Both the systolic and diastolic systemic arterial pressures are elevated. (c) Model's prediction for the effect of fitness in the systemic arterial pressure for healthy men. There is a slight improvement in the systolic arterial pressure.

oped in the manuscript to derive the *model's outputs* (right side of Fig. 4).

The patient specific factors, with the exception of age, are assigned Boolean values. This forced simplifying approach due to lack of more precise data, steals quantitative accuracy; nonetheless it seems to provide effective results. Presumably the induced error by the Boolean assignment is sufficiently small, making it a fine approximation. Further research could elaborate on this issue, to refine the determination of the coefficients. For example it is sensible to assume that the amount of smoking ought to have an effect on the parameters, in which case the input 'smoking' could have a percentage value based on the number of cigarettes smoked, etc. A patient was classified as 'fit' when the ETT protocol (given his/her age and gender) was completed. With the aid of physicians this input could also be expressed as a percentage of fitness. Additionally, each of the 'Drug' inputs ought to depend on drug dosage with possible further elaboration on specific drugs, etc.

The initial parameter values of [12] were modified by trial and error in order to obtain meaningful physiological outputs of the model (providing a reference point for a 20-year-old healthy man, i.e. these parameter values will be the standard against which to compare changes in the model parameters for future reference). Subsequently, we aimed to determine the values of the 6 model parameters (R_{sa}, R_{pa}, C_{sa}, C_{pa}, $C_{LV,diastole}$ and $C_{RV,diastole}$) for each patient, so that the model output of the arterial pressure and the actual measured pressure in the provided patient dataset coincide. Furthermore, the remaining outputs (pressures, CO) ought to result in the physiologically expected values, in the opinion of the clinicians. These 6 parameters were estimated by trial and error for each patient, regarding their qualitative trend with respect to the inputs and the standard reference parameter values. For example, as age increases, $C_{LV,diastole}$ and $C_{RV,diastole}$ are expected to decrease to some extent in order to make up for the reduced cardiac output. The parameter values were assumed correct when the resulting model systolic and diastolic pressure outputs would converge within 1 mmHg from the corresponding measured pressures. Care was taken to make sure all the results were reasonably related (cross-referencing the parameter values between all of them, whilst taking into account the respective inputs). This is deemed necessary due to lack of further specific data (i.e. all the pressure values and CO). For simplicity, the heart rate F was set to depend only on age with a linear relationship (imposed in the model through the reciprocal of heart rate, the period T). We have used the values of $T = 0.014$ min and $T = 0.016$ min for the ages of 20 and 80, respectively. The ratio of the systolic time over the period T of each pulse was presumed constant, following the pattern of Fig. 3 (systolic time $= 0.353T$). The venous lumped parameters (see Fig. 2), introduced in the model were assumed to have a linear relationship depending only on age, which was determined by the normal physiological values of pressure for the ages of 20 and 80 years old. This is justified due to the fact that the sensitivity of the outputs on

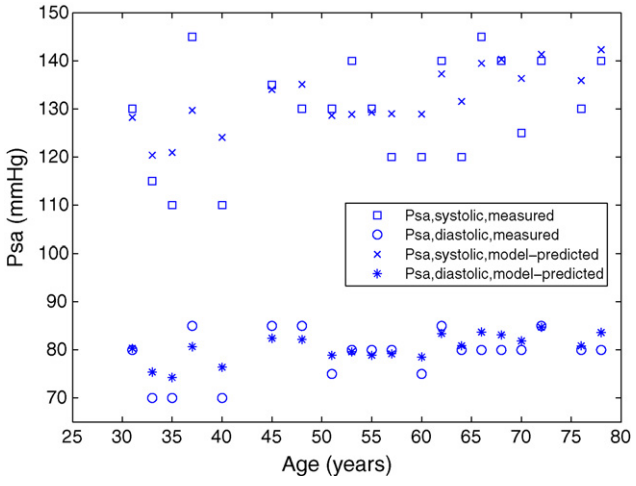

Fig. 7. Graphical demonstration of the predictive ability of the model.

the venous parameters is generally larger [9]. This amounts to very small comparative changes on the venous parts of the circulation, which can be conveniently attributed only to age. Finally, the polynomial coefficients for each of the parameters were determined through least-squares fitting procedures. Table 2 presents the coefficients using the entire dataset, but very similar coefficients were obtained in each run of the validation scheme explained in Section 6.

6. Numerical experiments and discussion

The proposed model relates age, sex and measurements involving smoking/fitness habits as well as use of specific drugs to estimate the cardiac output and the arterial pressure. The aim is to establish physiologically valid and realistic predictions of the outputs dependent on the inputs.

The results of the least-squares regression applied to the coefficients a_0,. . .,a_7 show that age and smoking contribute to increasing arterial pressure. Conversely, fitness has a positive effect on every major part involved in the circulation. These trends are clearly identified by the sign of the coefficient associated with the corresponding input—see Table 2. Reflecting on these, the increase of resistance (physiologically translated as decrease of the vessel radius) contributes to an increase in pressure whereas the decrease of compliance (physiologically addressed to a decrease in elasticity) leads to an increase of the pulse pressure. The problem in this analysis is the effect of drugs, since the beta-blockers and ACE inhibitors seem to increase the arterial pressure, whereas it is known that the opposite is true. This is partly explained by the aggravated cardiovascular health of the individuals in need of those drugs. Perhaps more importantly, it indicates that the suggested layout with only two lumped components for each section of the circulation may be inadequate to qualitatively and quantitatively assess the effects of drugs on the circulation. Despite this shortcoming, since the quantitative effect of the drugs appears very small, the insight offered by the model is still numerically valid. Another observation from the model outputs was the confirmation of the established medical knowledge that men and women have similar hemodynamic responses but women tend to have lower blood pressure. We achieved that by separating men and women in two large categories: the control group and patients with similar heart-related problems. The hemodynamic output of the model (stroke volume, cardiac output) was very similar for both sexes, provided there was no significant difference in age. The validity of the proposed model can be ascertained in that attributing the corresponding pressure to the appropriate combination of the lumped parameters of resistances and compliances leads to physiologically valid and clinically interpretable conclusions. A typical output of the model is presented for a healthy individual aged 20 in Fig. 5. In Fig. 6 we compare the systemic arterial pressure for men and women and see the effects of fitness and smoking with respect to age. In Table 3 some typical numeric responses of the model for the systemic arterial pressure and the CO are presented. The model parameter values for $C_{\mathrm{LV,diastole}}$ and P_{pv} are derived from their relationship to the patient specific factors and are related to the CO estimation via Eqs. ((11)–(12)). The results in Fig. 6 and Table 3 demonstrate that the model's outputs are realistic and predict 'normal' CO and hypertension in advanced age. Fig. 7 graphically demonstrates the predictive ability of the model for 20 patients (who did not take drugs) chosen randomly over the age range.

To objectively test the ability of the proposed model in estimating arterial pressure we used cross-validation, a statistical resampling technique typically used for model assessment [13]. Specifically, the 208 subject dataset was split into 4 subsets, of which 3 were used for training and 1 for testing. The *training* dataset was used to determine the coefficients a_0,. . .,a_7 by linear regression as explained above; the *testing* dataset was applied in the final form of the equation to evaluate the model's generalization. This was done for all 4 splits, and was further repeated for the data reshuffled a total of 30 times, in order to increase the objectivity of the assessment, giving thus 120 runs. For each run we recorded and accumulated the relative absolute error for each ith subject in the test set defined as

$$\text{error in } P = \sum_{i \in \text{test set}} \left| \frac{P_i - \hat{P}_i}{P_i} \right|$$

where P_i is the true pressure value as provided by the dataset and $\hat{P}_i$ the model's estimate. Errors from all runs were averaged. The testing errors (mean ± S.D.) were for $P_{\mathrm{sa,max}}$ 0.0596 ± 0.042 and for $P_{\mathrm{sa,min}}$ 0.0515 ± 0.037. The maximum $P_{\mathrm{sa,max}}$ and the minimum arterial pressure $P_{\mathrm{sa,min}}$ amount to the diastolic and systolic systemic pressure, respectively. In the vast majority of cases this error is acceptable providing accurate information whether someone may be in danger of hypertension. The fact that the error in unseen data remains relatively low indicates that the model has achieved globalization.

7. Conclusion

We have constructed a comprehensive computational model of the cardiovascular system, which incorporates the patient specific factors and models questions posed by clinicians in order to create an effective algorithm with physiological interpretability. The model is simple enough to offer an insight in the interrelations of the circulatory system between inputs, physiological parameters and outputs. The validity of the model was qualitatively ascertained by the fact that it complies with the expected detrimental/beneficial effects of smoking/fitness on the circulatory system [14], and realistic hemodynamic responses. Additionally, the model was quantitatively verified by the low errors between estimated and actual systemic arterial pressures. The remaining vascular region pressures, cardiac output and volumes of blood, although physiologically reasonable, will have to be quantitatively evaluated by future studies (a simple case is by refining the linear coefficients with respect to the inputs or suggesting a more complex non-linear relationship of inputs and model parameters). We propose the suggested 2-element WM is used in healthy individuals for understanding and evaluating the quantitative relationships between age, sex, fitness and smoking with the pressures and flows. The major drawback of the suggested model is its failure to predict the consequences of drugs. In order to account for pathological cases a disease state affecting the resistance and/or compliance of one or more vascular regions should be imposed leading to hypertension. Then the drugs could be shown to have a positive effect, lowering the arterial pressure. Ongoing research by our group is focused on expanding and refining the relatively simple and well-established Windkessel theory to remedy this shortcoming by the 4-element WM which also deals with transient results as part of the diagnostic process. The proposed model is useful for providing an easy, cost-effective estimation of the arterial pressure serving non-experts, in order to compare with their measured values. It can also be used for instructing purposes offering an insight to the causative and quantitative relation of inputs/outputs, and for clinical monitoring taking advantage of all the pressures and CO evaluation.

Conflict of interest statement

No conflicts related to this submission exist.

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