Med Biol Eng Comput (2012) 50:419–424
DOI 10.1007/s11517-012-0872-1

ORIGINAL ARTICLE

Arterial reservoir-excess pressure and ventricular work

Kim H. Parker · Jordi Alastruey · Guy-Bart Stan

Received: 5 April 2011 / Accepted: 9 February 2012 / Published online: 26 February 2012

Abstract This study is based on the hypothesis that the pressure within the arterial network can be usefully decomposed as the sum of a reservoir pressure and an excess pressure. The reservoir pressure waveform is defined to be the same in each vessel but delayed by the wave travel time from the root of the aorta. Using calculus of variations and mass conservation, which relates the flow and rates of change of pressure in the vessels, we show that the reservoir pressure waveform minimises the ventricular hydraulic work for any physiologically or clinically reasonable ejection waveform and arterial properties, i.e. vessel compliances and terminal resistances. We conclude that the excess pressure determines the excess work done by the ventricle, which may have clinically important implications.

Keywords Blood flow in cardiovascular system · Differential equations in mathematical aspects of biological physics · Calculus of variations · Time-delay ordinary differential equation

Electronic supplementary material The online version of this article (doi:10.1007/s11517-012-0872-1) contains supplementary material, which is available to authorized users.

K. H. Parker (✉)
Department of Bioengineering, Imperial College,
London SW7 2AZ, UK
e-mail: k.parker@imperial.ac.uk

J. Alastruey
Department of Biomedical Engineering,
King's College, London SE1 7EH, UK
e-mail: jordi.alastruey-arimon@kcl.ac.uk

G.-B. Stan
Department of Bioengineering and Centre for Synthetic Biology and Innovation, Imperial College, London SW7 2AZ, UK
e-mail: g.stan@imperial.ac.uk

1 Introduction

The intermittent pumping of the heart and the anatomical complexity of the arterial system results in very complex haemodynamics. The unsteady, three-dimensional (3-D) flow in individual bifurcations and complexly curved arteries has been partially explored using computational fluid dynamics [8, 10, 11, 16, 20] but full unsteady, 3-D modelling of the complete arterial system is not currently feasible. One-dimensional (1-D) modelling, in which the arteries are treated as 1-D compliant vessels, provides an alternative method for studying arterial blood flow [2, 3, 8, 13, 15].

These 1-D models require detailed knowledge about the connectivity and properties of the individual arteries; information that is not available clinically. Thus, there is a need for more approximate models that can be used to interpret available clinical measurements. Recently, the reservoir-wave hypothesis was proposed which provides such a model [1, 6, 17, 18, 19]. This hypothesis asserts that the measured arterial pressure is the sum of a reservoir pressure, which accounts for the dynamic storage and release of blood by the compliant arteries (the Windkessel effect), and an excess pressure, which is responsible for local changes in the pulse waveform. This paper provides a new, slightly modified definition of the reservoir pressure and explores the relationship between the reservoir pressure and the hydraulic work done by the left ventricle to provide a given volume flow rate. The results may provide a physical explanation for the results of a recent epidemiological study [7].

Additional details of our analysis are given in the supplementary material accompanying this paper.

2 Basic model

We assume that the arterial network is made up of N uniform vessels with a single inlet from the ventricle, denoted as 0, and K terminal vessels through which blood is conducted from the arterial system into the microcirculation. The 1-D conservation equations for each vessel coupled with an elastic tube law relating local pressure to local area are hyperbolic equations that describe the local flow. These equations can be solved exactly by the method of characteristics [4, 12].

A general solution for the instantaneous blood pressure and velocity throughout the network of vessels can be obtained for any conditions applied at the boundaries of the network by applying matching conditions of flow and pressure at the junctions of the vessels. This solution, however, depends upon complete knowledge of the properties of the arterial network that is unavailable clinically. To simplify the problem, we define a spatially averaged pressure P_n for each vessel $n \in N$

$$P_n(t) = \frac{1}{L_n}\int_0^{L_n} P(x,t)dx \qquad n \in N, \tag{1}$$

where $P(x, t)$ is the detailed pressure distribution in the vessel, t is time, $0 \le x \le L_n$ is the axial distance along the vessel and L_n is the length of the considered vessel n. We also assume that the area A_n and distensibility D_n of vessel n are constant so that its volume compliance $C_n = D_n\, A_n\, L_n$. We note that the assumption of uniform properties is not as limiting as it seems since our linear analysis allows us to divide a non-uniform vessel into segments which are effectively uniform. These assumptions are simplistic but are consistent with our goal of developing a model based on clinically accessible measurements.

Overall conservation of mass in the arterial system requires that the instantaneous rate of change of the total volume of the arteries, $V(t)$, is equal to the volume flow rate into the arteries from the ventricle, $Q_{in}(t)$, minus the net flow out of the arteries through the terminal vessels into the microcirculation, $Q_{out}(t)$,

$$\frac{dV(t)}{dt} = Q_{in}(t) - Q_{out}(t), \tag{2}$$

where $V(t) = \sum_{n\in N} V_n(t)$ and $V_n(t) = A_n(t)L_n$ is the volume of vessel n. We denote $Q_0(t)$ as the flow rate at the aortic root, so that $Q_{in}(t) = Q_0(t)$. We assume that the flow through the microcirculation at the end of a terminal vessel is resistive so that the flow is linearly related to the pressure $Q_n(t) = \frac{P_n(t)-P_\infty}{R_n}$, $n \in K$. Here R_n is the resistance for the n^{th} terminal vessel, assumed to be constant in time, and P_∞ is the pressure at which flow through the microcirculation ceases, which is assumed to be uniform throughout the body. In general this pressure will be larger than the venous pressure due to waterfall effects [5].

With these relationships, the overall mass conservation equation can be written

$$\sum_{n\in N} C_n \frac{dP_n(t)}{dt} + \sum_{n\in K} \frac{P_n(t) - P_\infty}{R_n} = Q_0(t). \tag{3}$$

In the rest of this paper, we assume that the input flow waveform $Q_0(t)$ is given and look at different solutions of Eq. 3.

3 Windkessel pressure

The classical Windkessel pressure $P_W(t)$ is obtained by assuming that the pressure in the arterial network is uniform and that it satisfies the mass conservation equation, Eq. 3. With this assumption, $P_n(t) = P_W(t)$ for all n, and the pressures can be taken outside of the summations giving the usual first-order differential equation for the Windkessel pressure

$$C\frac{dP_W(t)}{dt} + \frac{P_W(t) - P_\infty}{R} = Q_0(t), \tag{4}$$

where we define the net compliance of the network $C = \sum_{n\in N} C_n$ and the net resistance out of the terminal vessels, R, using the formula for resistances in parallel, $\frac{1}{R} = \sum_{n\in K} \frac{1}{R_n}$.

This first-order ordinary linear differential equation (ODE) can be solved to give the classical solution for P_W for any given inflow $Q_0(t)$ given the system parameters R, C and P_∞,

$$P_W(t) = \frac{e^{-t/RC}}{C}\int_0^t Q_0(\gamma)e^{\gamma/RC}d\gamma + (P_W(0) - P_\infty)e^{-t/RC} + P_\infty, \tag{5}$$

where $P_W(0)$ is the pressure at $t = 0$, taken to be the start of systole. During diastole $Q_0(t) = 0$ and the solution takes the simple form of an exponentially decreasing pressure with the time constant RC. If we require that the cardiac cycle is periodic with period T, i.e. $P_W(0) = P_W(T)$, we find

$$P_W(0) = P_W(T) = \frac{1}{C(e^{T/RC} - 1)}\int_0^T Q_0(\gamma)e^{\gamma/RC}d\gamma + P_\infty. \tag{6}$$

4 Reservoir pressure

The Windkessel pressure suffers from the limitation that it is assumed to be uniform throughout the arterial system, although the wave nature of flow in the arteries means that

pressure and velocity changes propagate through the arteries at a finite rate. There is, in fact, a basic contradiction in the application of the classical Windkessel theory to real arterial systems: A uniform, time-varying pressure can only be achieved if the wave speed in the arteries is infinite. An infinite wave speed is physically achievable only if the arteries are rigid. But, if the arteries are rigid, there is no compliance to support the Windkessel effect.

We can resolve this problem while maintaining the convenient physical properties and appealing simplicity of the Windkessel model by assuming that the local reservoir pressure varies temporally in the same way throughout the arterial system, but with a time lag that depends on the location and the wave properties of the arteries. Formally, we assume that the reservoir pressure in vessel n is $\bar{P}_n(t) = \bar{P}(t-\tau_n)$, where $\bar{P}(t)$ is the reservoir pressure at the aortic root and τ_n is the time it takes for a wave to travel from the root to vessel n, which is assumed to be constant. As a consequence of these definitions, $\tau_0 = 0$ and $\bar{P}_0(t) = \bar{P}(t)$.

Requiring that the reservoir pressure satisfies the mass conservation equation, Eq. 3, we obtain an equation for the reservoir pressure in vessel n

$$\sum_{n\in N} C_n \frac{d\bar{P}(t-\tau_n)}{dt} + \sum_{n\in K} \frac{\bar{P}(t-\tau_n) - P_\infty}{R_n} = Q_0(t). \tag{7}$$

This is a time-delay ODE for a single variable $\bar{P}$ with coefficients that do not vary in time. This class of ODEs has been studied extensively in the context of control theory and, although there is no straightforward method for obtaining the solution, the existence and uniqueness of a solution is guaranteed [9, 14]. The existence of a unique solution is sufficient for the theory that follows. We chose the integration constant so that $\bar{P}(0) = P(0)$. That is, we require that the reservoir pressure be equal to the averaged pressure at $t = 0$, the start of systole.

The excess pressure in vessel n is defined as the difference between the averaged pressure and the reservoir pressure,

$$p_n(t) = P_n(t) - \bar{P}(t-\tau_n). \tag{8}$$

We now explore the properties of the reservoir and excess pressures; particularly with respect to the hydraulic work done by the left ventricle.

5 Ventricular hydraulic work

The hydraulic work done by the ventricle over a cardiac cycle depends on the volume flow rate from the ventricle $Q_0(t)$ and the averaged pressure measured in the aortic root $P_0(t)$

$$W = \int_0^T P_0(t)Q_0(t)dt, \tag{9}$$

where $T = T_s + T_d$ is the cardiac period with T_s the time of systole and T_d the time of diastole. In the aortic root the time lag is zero so that $p_0(t) = P_0(t) - \bar{P}(t)$. Substituting, the ventricular hydraulic work can be written

$$W = \int_0^T \bar{P}(t)Q_0(t)dt + \int_0^T p_0(t)Q_0(t)dt \equiv \bar{W} + w, \tag{10}$$

where we define the reservoir work $\bar{W}$ as the hydraulic work done by the ventricle against the reservoir pressure and the excess work w as the work done against the excess pressure at the aortic root. Recall that the volume flow rate from the ventricle, $Q_0(t)$, is assumed to be known in this analysis.

We now seek to minimise the excess work w for a given $Q_0(t)$ subject to the constraint that the excess pressure is integrable and periodic. This follows from the assumption that both the averaged pressure, $P_0(t)$, and the reservoir pressure, $\bar{P}(t)$, are integrable and periodic with period T. In order to minimise the excess work with the given constraints, we use the calculus of variations to minimise the function

$$\chi = \int_0^T (p_0(t)Q_0(t) + \lambda p_0(t))dt, \tag{11}$$

where λ is a Lagrange multiplier. We will use the degree of freedom given by λ to impose the periodicity of $p_0(t)$. Following the standard methods of the calculus of variations, we assume that χ attains its non-trivial minimum when $p_0(t) = \hat{p}_0(t)$, and find this minimising function by considering all functions close to $\hat{p}_0(t)$. In particular, we consider the functions $p_0(t) = \hat{p}_0(t) + \epsilon\eta(t)$ where ϵ is a small constant and $\eta(t)$ is an arbitrary function with $\eta(0) = \eta(T) = 0$ in order to satisfy the boundary conditions on p_0, *i.e.* $\hat{p}_0(0) = p_0(0) = 0$ and $\hat{p}_0(T) = p_0(T) = 0$. Similarly, we define $p_n(t) = \hat{p}_n(t) + \epsilon\eta(t)$ for $n \in N$.

The minimising function $\hat{p}_0(t)$ is found by setting the derivative of χ with respect to ϵ equal to zero,

$$0 = \frac{\partial\chi}{\partial\epsilon} = \int_0^T \left[Q_0(t)\eta(t) + \hat{p}_0(t)\left(\sum_{n\in N} C_n \frac{d\eta(t)}{dt} + \sum_{n\in K} \frac{\eta(t)}{R_n} \right) + \lambda\eta(t) \right] dt, \tag{12}$$

where we have used the relationship between Q_0 and P_n from Eq. 3, the definition in Eq. 8 and neglected terms of $\mathcal{O}(\epsilon)$.

The term involving $\frac{d\eta}{dt}$ can be rewritten using integration by parts with $\eta(0) = \eta(T) = 0$ to obtain the variational equation

$$0 = \int_0^T \left[Q_0(t) - \frac{d\hat{p}_0(t)}{dt} \sum_{n\in N} C_n + \hat{p}_0(t) \sum_{n\in K} \frac{1}{R_n} + \lambda \right] \eta(t) dt. \tag{13}$$

Since $\eta(t)$ is an arbitrary function, the terms within the brackets must be equal to zero, so that the minimising $\hat{p}_0(t)$ satisfies the equation

$$C\frac{d\hat{p}_0(t)}{dt} - \frac{\hat{p}_0(t)}{R} = Q_0(t) + \lambda. \tag{14}$$

This equation can be solved by quadrature using the integration factor $e^{-t/RC}$. Using the initial condition $p_0(0) = 0$, the solution can be written as

$$\hat{p}_0(t) = \frac{e^{t/RC}}{C} \int_0^t Q_0(\gamma) e^{-\gamma/RC} d\gamma + \lambda R\left(e^{t/RC} - 1\right). \tag{15}$$

The Lagrange multiplier λ can be evaluated using the periodicity condition $\hat{p}_0(T) = \hat{p}_0(0) = 0$. Substituting, we find the excess pressure that minimizes the excess work

$$\hat{p}_0(t) = \frac{e^{t/RC}}{C} \int_0^t Q_0(\gamma) e^{-\gamma/RC} d\gamma - \frac{e^{T/RC}\left(e^{t/RC} - 1\right)}{C(e^{T/RC} - 1)} \int_0^T Q_0(\sigma) e^{-\sigma/RC} d\sigma. \tag{16}$$

We see that the minimising pressure $\hat{p}_0(t) = f(t; Q_0(t), T, R, C)$.

We are now able to evaluate the minimum excess work that the ventricle can do against the excess pressure in the aortic root, $\hat{w} = \int_0^T \hat{p}_0(t) Q_0(t) dt$,

$$\hat{w} = \frac{1}{C} \int_0^T \left(Q_0(t) e^{t/RC} \int_0^t Q_0(\gamma) e^{-\gamma/RC} d\gamma \right) dt - \frac{e^{T/RC}}{C(e^{T/RC} - 1)} \int_0^T Q_0(\gamma) e^{-\gamma/RC} d\gamma \int_0^T Q_0(\sigma) \left(e^{\sigma/RC} - 1\right) d\sigma. \tag{17}$$

For a given flow rate $Q_0(t)$, this expression can be evaluated, analytically or numerically, to find the minimum excess work.

6 Conditions for which the minimum excess work is positive

Conditions for which $\hat{w}$ is positive are of particular interest because, for these conditions, it follows that the trivial solution $p_0(t) = 0$ is, in fact, the minimising excess pressure. Thus, for these cases the reservoir pressure is the pressure waveform that results in the minimum hydraulic work that the ventricle must do to provide a given flow waveform at given conditions of arterial compliance and resistance. We therefore analyse Eq. 17 to determine the conditions for which $\hat{w} > 0$.

For this analysis, it is most convenient to express $\hat{w}$ in terms of the instantaneous volume ejected by the ventricle, $v(t) = \int_0^t Q_0(\gamma) d\gamma$, instead of the volume flow rate $Q_0(t)$. It is also convenient to nondimensionalise the equation by defining the nondimensional time $t' = t/RC$, the nondimensional ejected volume $v' = v/V_s$, where $V_s = \int_0^T Q_0(t) dt$ is the stroke volume, and the non-dimensional volume flow rate $q(t) = \frac{RCQ_0(t)}{V_s}$. We also define $S' = \frac{T_s}{RC}$ as the non-dimensional time of systole, and the ratio of the cardiac period to the time of systole $k = T/T_s$.

Defining the non-dimensional excess hydraulic work $\hat{w}' = \hat{w}C/V_s^2$, we obtain (dropping the primes)

$$\hat{w} = \int_0^S \dot{v}(t) e^t \int_0^t \dot{v}(\gamma) e^{-\gamma} d\gamma dt - \frac{e^{\kappa S}}{e^{\kappa S} - 1} \int_0^S \dot{v}(\gamma) e^{-\gamma} d\gamma \left(\int_0^S \dot{v}(\sigma) e^{\sigma} d\sigma - 1 \right), \tag{18}$$

where $\dot{v}(t) \equiv \frac{dv}{dt} = q(t)$ and we have assumed that $q(t) = 0$ during diastole, *i.e.* for $S < t < \kappa S$.

In almost all physiological and clinically relevant cases, the time of systole is significantly shorter than the time constant of the arterial system. Typically the duration of systole is $T_s \sim 0.3\ s$ whereas $RC \sim 1.5\ s$. We therefore assume that $S \ll 1$. Expanding the exponential terms in Eq. 18 as power series, we find after some analysis (see supplementary material)

$$\hat{w} = \left[\frac{1}{2} - \frac{1}{\kappa} + \frac{\langle v \rangle}{\kappa}\right] + S\left[-\frac{1}{2}\left(1 - \frac{1}{\kappa}\right) + \left(\frac{3}{2} - \frac{2}{\kappa}\right)\langle v \rangle - \langle v^2 \rangle + \frac{\langle v \rangle^2}{\kappa} + \frac{m}{\kappa}\right] + \mathcal{O}(S^2), \tag{19}$$

where $\langle \cdot \rangle = \frac{1}{S}\int_0^S \cdot dt$ is the average over systole and $m = \frac{\langle vt \rangle}{S}$ is the first moment of v. Note that $\langle v \rangle$ represents the average volume ejected from the ventricle over systole and is always positive in non-surgically assisted conditions.

Neglecting terms of order S^1, we see that $\hat{w} > 0$ if $\kappa \geq 2$, which corresponds to the time of diastole T_d being greater than the time of systole T_s, since $T = T_s + T_d$. As this is true for almost all physiological and clinical heart beats, we conclude to $\mathcal{O}(S^1)$ that the excess work is

positive for all cases where the time of systole is small compared to the arterial time constant.

Neglecting terms of order S^2, we see that the second bracket in the expression for $\hat{w}$ depends on a number of terms describing the shape of the flow rate waveform; $\langle v \rangle$, which depends on the skew of q, $\langle v^2 \rangle$ and m, the first moment of v; as well as the ratio of the cardiac period to the time of systole κ. Although the second term can be negative, the conditions for which it can dominate the first term are highly improbable physically (see supplementary material). We conclude, therefore, that the excess work will be positive for all physiologically reasonable cases. As we have already argued, whenever the excess work $\hat{w}$ is positive, the reservoir pressure waveform yields the minimum hydraulic work required from the ventricle to generate the specified flow waveform given the arterial parameters, R, C, P_∞, T_s and T.

If S is not small, the sign of $\hat{w}$ can be determined for any particular $Q_0(t)$ using Eq. 18. It is difficult, however, to derive the general conditions for which $\hat{w} > 0$ analytically. We have obtained results for several idealised cases; constant, half-sinusoidal and triangular flow during systole (see supplementary material).

7 Discussion and conclusions

The reservoir pressure defined in this work is similar in spirit to that in the reservoir-excess pressure separation described in the papers introducing the reservoir-wave hypothesis [17, 18], but is different in detail. The reservoir pressure is here defined as a waveform that is the same throughout the arterial system, but which is delayed by the wave travel time. As the waveform is uniform, it depends only on the average properties of the system, the total compliance and resistance of the microcirculation, and the input from the heart. Since it is delayed in time, it is also dependent on the wave nature of flow in the arteries. This is an important distinction between the reservoir pressure and the Windkessel pressure, which is assumed to be instantaneously uniform throughout the system, an assumption that can only be realised if the wave speed is infinite.

The relative simplicity of this analysis, compared to the 1-D computer simulations, is based upon the averaging of the pressure within individual vessels. As the wave travel times are small compared to the rates of change of the arterial pressure, this average pressure is very similar to the pressure that would be measured in the vessel in the clinic and is consistent with our goal of finding results that can be applied clinically.

The reservoir pressure is defined as the solution to the time-delay differential equation, Eq. 7. Although the existence and uniqueness of a solution is established [9, 14], analytical solutions to this type of equation are rare and restricted to very simple cases. And, even if the solution was known, it would depend upon the compliances and resistances of all of the arteries, information that is not available clinically. Despite the lack of an analytical solution, we have been able to apply the calculus of variations (and the existence of a solution for the reservoir pressure) to minimise the excess hydraulic work by the ventricle (see supplementary material).

The main result of this work is that for a broad range of flow waveforms from the ventricle, including most physiologically and clinically relevant cases, the reservoir pressure is the pressure waveform that results in the minimum hydraulic work by the ventricle. The excess pressure, which is defined as the difference between the averaged pressure and the reservoir pressure, is therefore linked to the excess work that the heart is doing over and above this minimum work.

The arguments leading to this conclusion are subtle. By definition, the reservoir pressure $\bar{P}(t)$ satisfies overall mass conservation for a given ventricular volume flow rate $Q_0(t)$. The calculus of variations is then used to find the non-trivial excess pressure waveform in the aortic root $\hat{p}_0(t)$ that minimises the excess ventricular hydraulic work $\hat{w}$ for the given $Q_0(t)$. When $\hat{w} > 0$, it follows that the minimum hydraulic work occurs when $p_0(t) = 0$, the trivial solution. That is, when $P(t) = \bar{P}(t)$.

Equation 17 shows that $\hat{w} = f(Q_0(t), T, R, C)$. Since the time of systole, T_s, is generally small compared to the time constant of the exponential decay of pressure during diastole, RC, we non-dimensionalise Eq. 17 and expand in terms of $S = T_s/RC$. The result, Eq. 19, shows that to $\mathcal{O}(S^1)$, $\hat{w} > 0$ for $\kappa \equiv T/T_s \geq 2$. Since $T = T_s + T_d$ and T_d is generally greater than T_s (i.e. the time of filling, a predominantly passive process, is greater than the time of emptying the ventricle, an active process), $\kappa \geq 2$ in almost all cases. Therefore $\hat{w} > 0$ in almost all cases and we therefore conclude that $P(t) = \bar{P}(t)$ is the pressure waveform that produces the minimum hydraulic ventricular work for a given $Q_0(t)$ and global arterial properties R and C in almost all physiological and clinical conditions.

These results do not imply that $\hat{w} > 0$ for all conditions. For example, cardiac assist devices can be programmed to do work on the ventricle. Nor do they imply that it is physiologically possible for the arterial pressure $P(t)$ to equal the reservoir pressure $\bar{P}(t - \tau_n)$ since this would require an exquisite matching between local and global properties throughout the arterial system.

Even if it is not realisable physiologically, the reservoir pressure and the excess pressure associated with it can be useful concepts. The reservoir pressure provides a means of

determining the effects of net arterial compliance and resistance using clinically measurable parameters. The reservoir pressure could also provide a yardstick by which the 'efficiency' of measured pressure waveforms could be calculated. The excess pressure, on the other hand, gives a better indication of local as opposed to global conditions and may help resolve some anomalies in the analysis of wave propagation in the arteries [17]. It could also provide an explanation for the results of a recent analysis of pressure waveforms measured in a prospective epidemiological study, which showed that the excess pressure integrated over a cardiac cycle provided the best indication of the risk for cardiovascular events (death by myocardial infarction or stroke) [7].

Acknowledgements J.A. would like to thank the British Heart Foundation for funding in the form of an Intermediate Basic Science Research Fellowship (FS/09/030/27812).

References

1. Aguado-Sierra J, Alastruey J, Wang J-J, Hadjiloizou N, Davies J, Parker KH (2007) Separation of the reservoir and wave pressure and velocity from measurements at an arbitrary location in arteries. J Eng Med (Proc Inst Mech Eng Part H) 222:403−416. ISSN: 0954-4119
2. Alastruey J, Khir AW, Matthys KS, Segers P, Sherwin SJ, Verdonck PR, Parker KH, Peiró J (2011) Pulse wave propagation in a model human arterial network: assessment of 1-D visco-elastic simulations against in vitro measurements. J Biomech 44:2250–2258. ISSN: 0021-9290
3. Alastruey J (2010) On the mechanics underlying the reservoir-excess separation in systemic arteries and their implications for pulse wave analysis. Cardiovasc Eng 10:176–189
4. Alastruey J, Parker KH, Peiró J, Sherwin SJ (2009) Analysing the pattern of pulse waves in the arterial networks: a time-domain study. J Eng Math 64:331–351
5. Caldini P, Permutt S, Waddell JA, Riley RL (1974) Effect of epinephrine on pressure, flow, and volume relationships in the systemic circulation of dogs. Circ Res 34:606–623
6. Davies JE, Hadjiloizou N, Leibovich D, Malaweera A, Alastruey J, Whinnett ZI, Manisty CH, Francis DP, Aguado-Sierra J, Foale RA, Malik IS, Parker KH, Mayet J, Hughes AD (2007) Importance of the aortic reservoir in determining the shape of the arterial pressure waveform: the forgotten lessons of Frank. Artery Res 1:40–45
7. Davies JE, Lacy PS, Cruickshank K, Stanton A, Collier D, Thurston H, Williams B, Parker KH, Thom SM, Hughes AD (2010) Excess pressure is higher in atenolol-treated individuals and independently predicts cardiovascular events in the CAFE substudy of ASCOT. Eur Heart J 31 (Abstract Supplement):902
8. Formaggia L, Quarteroni A, Veneziani A (eds) (2009) Cardiovascular mathematics: modeling and simulation of the circulatory system. Springer-Verlag, Milan. ISBN: 978-88-470-1151-9
9. Hale J, Verduyn Lunel SM (1933) Introduction to functional differential equations. Applied Mathematical Sciences, vol 99. Springer-Verlag, New York. ISBN: 0-387-94076-6
10. Huberts W, Bosboom EMH, Planken RN, Tordoir JHM, van de Vosse FN (2009) Patient-specific computational modeling to improve the clinical outcome of vascular access creation. In: Tordoir J (ed).EVC textbook: vascular access, Edizioni Minerva Medica. ISBN 10: 88-7711-640-4
11. Karniadakis G, Sherwin SJ (2005) Spectral/hp element methods for computational fluid dynamics. Oxford University Press, Oxford. ISBN: 9780198528692
12. Parker KH, Jones CJH (1990) Forward and backward running waves in the arteries: analysis using the method of characteristics. J Biomech Eng 112:322–326
13. Parker KH (2009) An introduction to wave intensity analysis. Med Biol Eng Comput 47:175–188
14. Richard J-P (2003) Time-delay systems: an overview of some recent advances and open problems. Automatica 39:1667–1694
15. Reymond P, Merenda F, Peren F, Rüfenacht D, Stergiopulos N (2009) Validation of a one-dimensional model of the systemic arterial tree. Am J Physiol Heart Circ Physiol 297:H208–H222
16. Taylor CA (2004) Blood flow. In: Stein E, De Borst R, Hughes TJR (eds). Encyclopedia of computational mechanics. Wiley, UK. ISBN: 9780470846995
17. Tyberg JV, Davies JE, Wang Z, Whitelaw WA, Flewitt JA, Shrive NG, Francis DP, Hughes AD, Parker KH, Wang J-J (2009) Wave intensity analysis and the development of the reservoir-wave approach. Med Biol Eng Comput 47:221–232
18. Wang JJ, O'Brien AB, Shrive NG, Parker KH, Tyberg JV (2003) Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. Am J Physiol Heart Circ Physiol 284:H1358–H1368
19. Wang JJ, Flewitt JA, Shrive NG, Parker KH, Tyberg JV (2006) Systemic venous circulation. Waves propagating on a windkessel: relation of arterial and venous windkessels to systemic vascular resistance. Am J Physiol Heart Circ Physiol 290:H154–H162
20. Yamaguchi T (2000) Clinical application of computational mechanics to the cardiovascualr system. Springer-Verlag, Tokyo. ISBN 4-431-70288-1