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Systemic and pulmonary hemodynamics assessed with a lumped-parameter heart-arterial interaction model

PATRICK SEGERS[1], NIKOS STERGIOPULOS[2], NICO WESTERHOF[3], PATRICK WOUTERS[4], PHILIPPE KOLH[5] and PASCAL VERDONCK[1]
[1]*Hydraulics Laboratory, Institute of Biomedical Technology, RUG Ghent University, B-9000 Gent, Belgium (E-mail: patrick.segers@ugent.be) ;* [2]*Laboratory of Hemodynamics and Cardiovascular Technology, EPFL, PSE-Ecublens, 1015 Lausanne, Switzerland;* [3]*Laboratory for Physiology, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, The Netherlands;* [4]*Centre for Experimental Surgery and Anaesthesiology, KULeuven, Belgium;* [5]*Hemodynamic Research Center, University of Liege, Belgium*

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Abstract. Arterial pressure and flow result from the interaction between the (actively) ejecting ventricle and the (passive) arterial circulation. The main objective was to construct a model, accounting for this interaction, that is simple enough so that (i) model parameters can be derived from data measured in experimental and/or clinical conditions, and (ii) the model can be applied to support the analysis and interpretation of these data. It is demonstrated how an established conceptual model of ventricular function (the time-varying elastance) can be coupled to a four-element windkessel model of the arterial system to yield an elegant model of heart-arterial interaction. The coupling leads to a set of three ordinary differential equations. The model allows the study of the effect of changes in cardiac and/or arterial properties on arterial pressure and flow. As an illustration, cardiac and arterial model parameters are derived from measured experimental data in the systemic circulation of a pig and in the pulmonary circulation of a dog. It is evaluated how well measured cardiac and arterial function actually adhere to their assumed theoretical models (time-varying elastance and four-element windkessel model). It is further assessed how well the simple model of heart-arterial interaction describes systemic and pulmonary hemodynamics by comparing simulated and measured experimental data. The limitations and pitfalls of the model, as well as possible applications in the clinical field, are discussed.

Key words: hemodynamics, lumped-parameter model, modeling, time-varying elastance

1. Introduction

From a biomechanical point of view, it is obvious that arterial pressure and flow result from the interaction between the (actively) ejecting ventricle and the (passive) arterial circulation. As such, pressure and flow depend on the properties of both of these subsystems and, when studying heart-arterial interaction, the inlet boundary condition for the arterial system (either pressure or flow) should not be prescribed, but follow from their interaction. Although the heart is neither a pressure or a flow source [1], the mathematical description of its pumping function can be simple and straightforward, based on a physiological framework elaborated by Suga and co-workers in the early 1970s [2; 3]. Suga and co-workers described the contraction of the ventricle in the pressure-volume plane as an elastance that varies over the cardiac cycle (the time-varying elastance model). Elastance is the ratio of intraventricular pressure and volume, *i.e.*, a measure of cardiac muscle stiffness. In diastole, the muscle is relaxed and stiffness is low; in systole, the muscle contracts and becomes stiffer. They demonstrated that in the left ventricle the elastance function is independent of the load against which the ventricle

ejects. This model includes the effect of ventricular filling (preload) on ventricular contraction. As such, the relation between intraventricular pressure and volume is a basic property of the contracting ventricle and may be used as a constitutive equation for the ventricle. In addition, Suga and co-workers and, later, Senzaki *et al.* [4], demonstrated that, after normalizing the time-varying elastance curve with respect to amplitude and timing of the peak, the intrinsic shape is essentially constant within one species and in a large range of cardiac disease. This normalized curve is easily described mathematically (Fourier series, polynomial description) and therefore suited for computer simulations. The actual elastance curve, describing a specific ventricle, is then fully determined by a small number of parameters.

Models of the (systemic) arterial system have, since long, played an important role in our understanding of cardiovascular hemodynamics [5]. William Harvey in 1733 and later Otto Frank in 1899 made the analog between the heart pumping blood into the arterial tree and the old-fashioned hand-pumped fire engine, where water is pumped into a buffer reservoir (an air chamber or 'windkessel' in German) to provide continuous outflow at the outlet of the water hose[6]. The model, now generally known as the 'windkessel' model, consists of an air chamber termed total arterial compliance, representing the large elastic arteries, and of a linear resistance, termed peripheral resistance, representing the resistance of all small arteries, arterioles and capillaries. Its electrical analog is a parallel connection of a resistance and a capacitance. The windkessel model was the first of a class of models known as lumped-parameter models, where distributed properties of the arterial tree are lumped into a limited number of discrete components, neglecting their spatial distribution. Arterial lumped-parameter models are mainly used for the identification of arterial system parameters and in particular arterial compliance [7]. Using measured arterial flow (or pressure) as an input, one may derive model parameters by minimizing the difference between the measured pressure (or flow) and the pressure (or flow) that is predicted by the model in response to the same flow (or pressure) input.

Numerous extensions of the windkessel model, introducing more elements in different configurations, have been proposed [8]. This generally results in a better description of the relation between arterial pressure and flow (*i.e.*, the model impedance better resembles the actual system impedance) [9]. The addition of model components, however, impedes the straightforward interpretation of the parameters, obscuring their anatomical or physiological counterpart [10]. The characteristic impedance of the proximal aorta was introduced by Westerhof [9, 11], yielding the three-element windkessel model which is a series connection of the aortic Z_c with the classical two-element windkessel model. This third element that connects the windkessel models with transmission-line models, resulted in a close resemblance of input impedance of the total arterial system and the three-element windkessel model. In this work, we will use a lumped-parameter model for the arterial circulation consisting of four elements: two resistances (R and Z_c), one capacitance (C) and one inertance (L). In physiological terms, they represent the total peripheral resistance (R), the total compliance (buffer capacity) of the arterial system (C), the characteristic impedance of the proximal aorta/pulmonary artery (Z_c) and the total inertia of the blood in the arterial system. It was shown by Stergiopulos *et al.* that this model is a correct representation of the systemic arterial circulation [12].

In previous works, we have extensively made use of a lumped-parameter model describing heart-arterial interaction. This paper, to be considered as a review paper, provides a detailed insight into our modelling methodology and a round-up of our work based on this model. In what follows, the (normalized) time-varying elastance concept and the four-element windkessel model are elaborated and it is demonstrated how these two subsystems are coupled math-

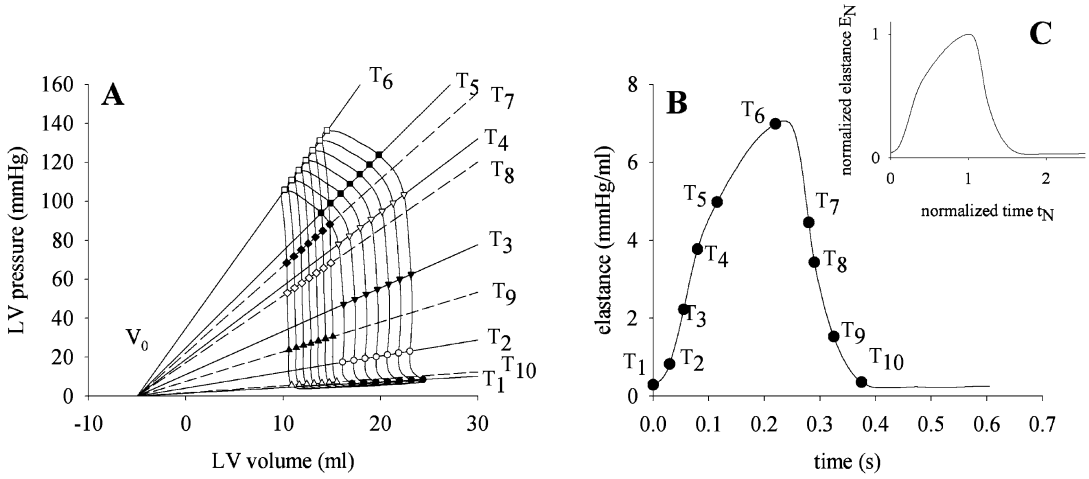

Figure 1. Time-varying elastance concept as elaborated by Suga and Sagawa. The symbols in panel A indicate 'isochronic' points on the different PV-loops, occurring at the moment during the cardiac cycle. These points line up and, stepping through the cardiac cycle (T_1, T_2, ...), the slope of the line (the elastance; panel B) varies in a cyclic way, while the intercept with the volume axis remains constant (V_0). The elastance curve can be normalized with respect to both its amplitude and the time at which the amplitude occurs (panel C).

ematically to a model suited for the study of heart-arterial interaction. It is illustrated how, starting from previously measured and used experimental data in the systemic circulation (left ventricular pressure and volume, aortic pressure and flow) [13] and pulmonary circulation (right ventricular pressure and volume, pulmonary artery pressure and flow) [14], cardiac and arterial model parameters can be derived. It will be evaluated, by comparing the simulations to the experimental data, how well the simple model of heart-arterial interaction describes systemic and pulmonary hemodynamics. We will discuss the limitations and pitfalls of the model, demonstrate possible applications and discuss their position in the spectrum of mathematical and numerical tools for the simulation of cardiovascular problems.

2. Materials and methods

2.1. Modelling ventricular function: the time-varying elastance concept

The time-varying elastance model (Figure 1) is based on work performed in an isolated heart preparation by Suga and Sagawa in the early 1970s, where they analysed cardiac mechanics in the pressure-volume plane [2, 3]. They recorded hemodynamic data measured both from isovolumic (non-ejecting) and ejecting cardiac contractions and found that the 'isochronic' points (*i.e.*, points recorded after a given time from onset of contraction) in the different contractions are located on a single line, characterised by its slope and intercept with the volume axis. The slope is the ratio of the increase in pressure associated with an increase in ventricular volume, and hence has the dimensions of stiffness or elastance (E; mmHg/ml).

The intercept with the volume axis was considered as a 'correction volume' (V_0). Stepping through the cardiac cycle, Suga and co-workers found that the intercept with the volume axis remained quasi-constant, while the slope varies from a low value in diastole to a maximal value reached at the end of ejection, *i.e.*, end-systolic elastance. For a given heart, this time-varying elastance pattern, $E(t)$, appeared independent of cardiac afterload (the pressure or

tension against which the heart has to eject), the most drastic evidence provided by the fact that ejecting and non-ejecting hearts yielded the same time-varying elastance curve. Changes in ventricular filling did not alter $E(t)$. As such, being independent of afterload and inherently containing the effect of preload, ventricular elastance and its maximal ($E_{\max}$) value is considered as the golden standard for the quantification of cardiac contractility.

Given these characteristics, the time-varying elastance model can be considered as a global cardiac muscle property, or as a constitutive equation for the ventricle that linearly relates ventricular volume (V_V) to intracavity pressure (P_V):

$$E(t) = \frac{P_V(t)}{V_V(t) - V_0}, \tag{1}$$

Senzaki *et al.* demonstrated, in human subjects, that when $E(t)$ is normalized with respect to both its maximal amplitude ($E_N = E/E_{\max}$) and the time at which this maximum occurs ($t_N = t/t_{E\max}$), this normalized curve $E_N(t_N)$ has a shape that is surprisingly constant, even in presence of a wide variety of cardiac diseases [4]. For modelling purposes, we further normalize $E_N\,(t_N)$ to peak (1) at $t_N = 1$, but to have a minimal $E_N\,(t_N)$ of 0 (offset correction). This normalized shape is easily described as a finite series of Fourier components (sine waves) where 10 to 12 harmonics are adequate to describe the signal [7].

The actual elastance curve $E(t)$ for a specific case is retrieved from the normalized curve $E_N\,(t_N)$ when the following four parameters are known: heart rate or RR-interval (T), minimal ($E_{\min}$) and maximal elastance, $E_{\max}$, and the time to reach maximal elastance ($t_{E\max}$): $E = E_{\min} + E_N{}^*(E_{\max} - E_{\min})$, while $t = t_N{}^*T/t_{E\max}$. To unequivocally fix the pressure-volume relation, V_0 is the fourth parameter complementing the cardiac parameter set.

A final cardiac parameter is required to quantify the preload or the filling rate of the heart, *i.e.*, the venous filling pressure (P_{venous}) which, in combination with $E_{\min}$, determines the ventricular end-diastolic volume (V_{ed}). When simulating clinical or experimental data, however, V_{ed} is often given, while $E_{\min}$ and/or P_{venous} are unknown. In these cases, it is pragmatic to choose appropriate values for $E_{\min}$ and P_{venous} which yield the correct V_{ed}, since V_{ed}, $E_{\min}$ and P_{venous} are related as $E_{\min} = \frac{P_{\text{venous}}}{V_{\text{ed}} - V_0}$.

In summary, provided that $E_N\,(t_N)$ is considered as a given global property of the ventricular cavity, cardiac function is unequivocally described by 5 (or 6) parameters: $E_{\max}$, V_0, T, $t_{E\max}$, V_{ed} (or $E_{\min}$ and P_{venous}).

2.2. Modelling arterial function: the four-element windkessel model

The lumped-parameter model used in our model is shown in Figure 2 and consists of four elements: total peripheral resistance (R), total arterial compliance, (C), the characteristic impedance of the aorta or pulmonary artery (Z_c), approximated as a (small) simple resistance, and the total inertia of the arterial system (L). In the frequency domain, the model can be described by its impedance which, in the frequency domain, is given as

$$Z = \frac{i\omega L Z_c}{Z_c + i\omega L} + \frac{R}{1 + i\omega RC} \tag{2}$$

with $i = \sqrt{-1}$ and $\omega = 2\pi f$, f being frequency. At 0 Hz (DC component), Z equals the value of total peripheral resistance R. At high frequencies, it reaches the asymptotic value Z_c. Its behaviour at intermediate frequencies depends on the relative values of its system components [7].

The heart and arterial model are, however, coupled in the time domain and we need a time-domain formulation of the four-element windkessel model. Assuming an outlet pressure of 0 mmHg and with P_{art} (which is either aortic or pulmonary artery pressure) the inlet pressure, P_1 the pressure proximal to the RC parallel connection, Q_{art} the total flow in the network and Q_{Zc}, Q_L, Q_C and Q_R the flow through Z_c, L, C and R, respectively (Figure 2), the following constitutive equations of network elements apply:

$$Q_R = \frac{P_1}{R}, \quad Q_C = C\frac{\mathrm{d}P_1}{\mathrm{d}t}, \quad \frac{\mathrm{d}Q_L}{\mathrm{d}t} = \frac{P_{\text{art}} - P_1}{L}, \quad Q_{Zc} = \frac{P_{\text{art}} - P_1}{Z_c}. \tag{3}$$

Since $Q_{\text{art}} = Q_R + Q_C$, it follows that

$$\frac{\mathrm{d}P_1}{\mathrm{d}t} = \frac{Q_{\text{art}}}{C} - \frac{P_1}{RC}. \tag{4}$$

Similarly, $Q_{\text{art}} = Q_L + Q_{Zc}$ and thus $\frac{\mathrm{d}Q_{\text{art}}}{\mathrm{d}t} = \frac{\mathrm{d}Q_L}{\mathrm{d}t} + \frac{\mathrm{d}Q_{Zc}}{\mathrm{d}t}$, yielding $\frac{\mathrm{d}Q_{\text{art}}}{\mathrm{d}t} = \frac{P_{\text{art}}}{L} - \frac{P_1}{L} + \frac{1}{Z_c}\frac{\mathrm{d}P_{\text{art}}}{\mathrm{d}t} - \frac{1}{Z_c}\frac{\mathrm{d}P_1}{\mathrm{d}t}$.

Rearranging as a function of $\frac{\mathrm{d}P_{\text{art}}}{\mathrm{d}t}$ gives

$$\frac{\mathrm{d}P_{\text{art}}}{\mathrm{d}t} = Z_c\frac{\mathrm{d}Q_{\text{art}}}{\mathrm{d}t} + \frac{\mathrm{d}P_1}{\mathrm{d}t} + \frac{Z_c}{L}(P_1 - P_{\text{art}}). \tag{5}$$

If the input into the network, *i.e.*, Q_{art} and its derivative $\mathrm{d}Q_{\text{art}}/\mathrm{d}t$, is known, Equations (3–5) can be used to solve for pressure and flow distribution in the network.

2.3. Modelling heart-arterial interaction

In the complete model of heart-arterial coupling, arterial flow follows from the interaction between the heart and the arterial system. Ventricular volume and arterial flow are related as $\frac{\mathrm{d}V_v}{\mathrm{d}t} = Q_{\text{av}} - Q_{\text{art}}$ with Q_{av} the inflow into the ventricle through the atrio-ventricular valve (AV-valve). Modelling both the AV-valve as the ventriculo-arterial valve as simple resistances ($R_{A\text{-}V}$ and $R_{V_{\text{art}}}$, respectively), pressures and flows through the model compartments relate as $Q_{\text{av}} = \frac{P_{\text{venous}} - P_V}{R_{A\text{-}V}}$ and $Q_{\text{art}} = \frac{P_V - P_{\text{art}}}{R_{V-\text{art}}}$ and thus

$$\frac{\mathrm{d}V_v}{\mathrm{d}t} = \frac{P_{\text{venous}} - P_v}{R_{A\text{-}V}} - \frac{P_v - P_{\text{art}}}{R_{V\text{-art}}}. \tag{6}$$

Note that, given the elastance function, the ventricular pressure, P_v, is related to ventricular volume through ventricular elastance (1). Therefore,

$$Q_{\text{art}} = \frac{E(t)(V_v - V_0) - P_{\text{art}}}{R_{V\text{-art}}} \text{ and } \frac{\mathrm{d}Q_{\text{art}}}{\mathrm{d}t} = \frac{1}{R_{V\text{-art}}}\left(\frac{\mathrm{d}E(t)}{\mathrm{d}t}(V_v - V_0) + E(t)\frac{\mathrm{d}V_v}{\mathrm{d}t} - \frac{\mathrm{d}P_{\text{art}}}{\mathrm{d}t}\right)$$

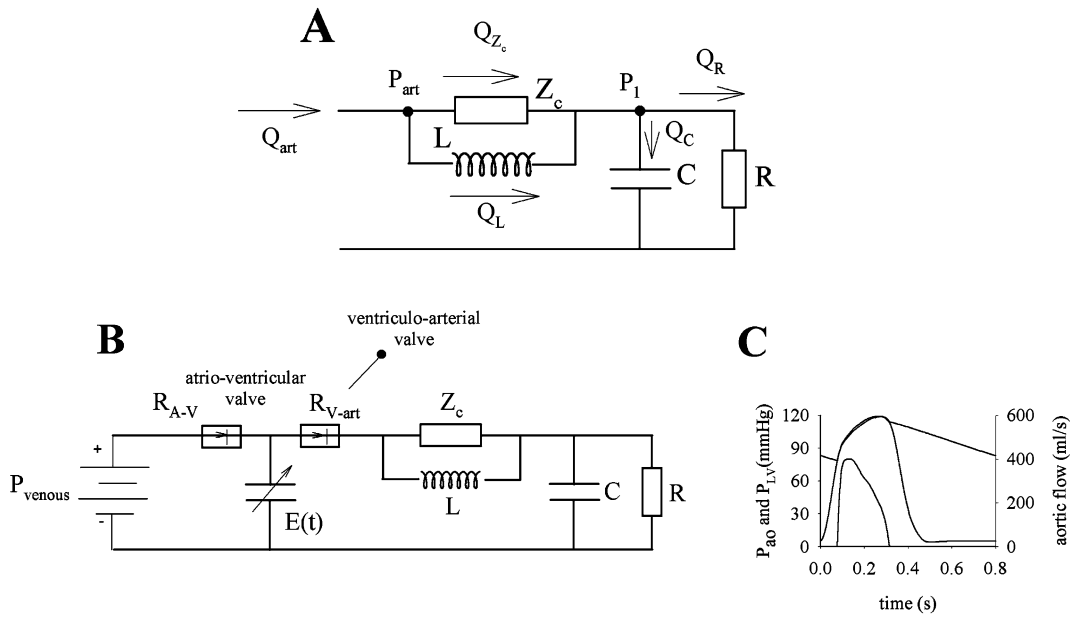

Figure 2. Panel A: four-element windkessel model consisting of total peripheral resistance (R), total arterial compliance (C), total inertance (L) and arterial characteristic impedance (Z_c). See text for further details. Panel B: electrical analog representation of the heart-arterial interaction model. See text for details. Panel C: example of simulated left ventricular and aortic pressure (left axis) and flow (right axis).

and Equations (4–6) can be rewritten as

$$\begin{cases} \dfrac{\mathrm{d}V_v}{\mathrm{d}t} = \dfrac{P_{\text{venous}} - E(t)(V_v - V_0)}{R_{A\text{-}V}} - \dfrac{E(t)(V_v - V_0) - P_{\text{art}}}{R_{A\text{-}V}}, \\ \dfrac{\mathrm{d}P_1}{\mathrm{d}t} = \dfrac{1}{C}\dfrac{E(t)(V_v - V_0) - P_{\text{art}}}{R_{V\text{-art}}} - \dfrac{P_1}{RC}, \\ \dfrac{\mathrm{d}P_{\text{art}}}{\mathrm{d}t} = \dfrac{Z_c}{R_{V\text{-art}}}\left(\dfrac{\mathrm{d}E(t)}{\mathrm{d}t}(V_v - V_0) + E(t)\dfrac{\mathrm{d}V_v}{\mathrm{d}t} - \dfrac{\mathrm{d}P_{\text{art}}}{\mathrm{d}t}\right) + \dfrac{\mathrm{d}P_1}{\mathrm{d}t} + \dfrac{Z_c}{L}(P_1 - P_{\text{art}}). \end{cases} \tag{7}$$

This is a set of ordinary differential equations for the unknowns P_1, V_v and P_{art} that is solved using an ODE solver routine in Matlab 5.3 (Matlab, The Mathworks, Natick, MA). Using the expressions above, P_v can be calculated as well as Q_{art}.

Equations (7) are solved throughout the complete cardiac cycle, but with a variable value of $R_{v\text{-art}}$ and $R_{A\text{-}V}$. As long as P_v-P_{art} and P_{venous}-P_v are positive (positive pressure gradient over the valve, $R_{V\text{-art}}$ and $R_{A\text{-}V}$ are given an appropriate finite value. When the pressure gradient over the valve reverses, $R_{V\text{-art}}$ and $R_{A\text{-}V}$ are assumed infinite (perfectly closing valve). Figure 2 shows an example of simulated left ventricular pressure, aortic pressure and flow.

In what follows, we will use measured experimental data to assess the values of the model parameters, to compare the simulations to the experimental data, and to discuss applications, benefits and limitations of lumped parameter modelling of ventriculo-arterial interaction.

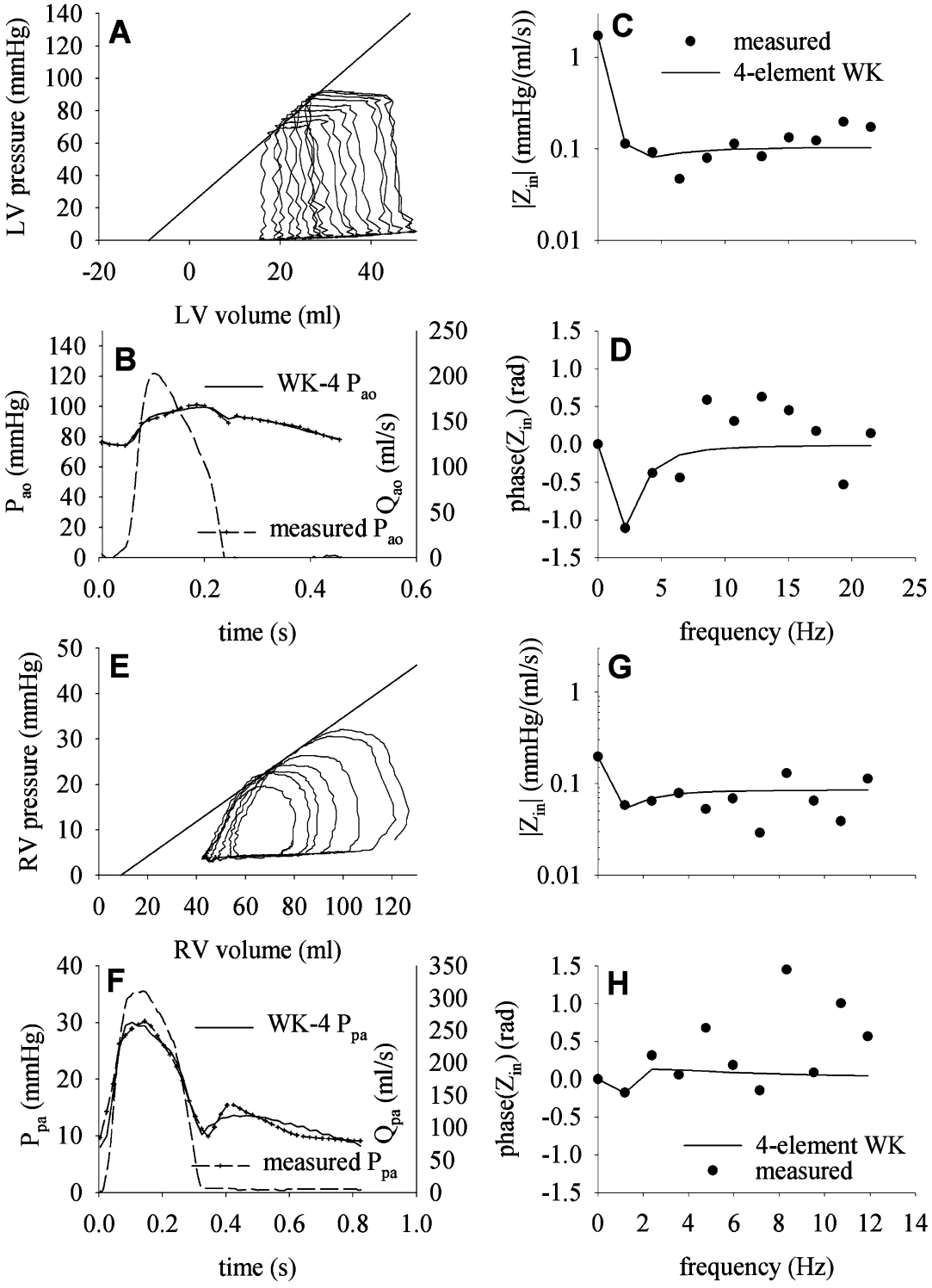

Figure 3. Measured PV-loops in the left ventricle of a pig (panel A) during inferior vena cava occlusion and aortic pressure and flow at steady state (panel B). Panels C and D show modulus and phase, respectively, of measured and fitted (four-element WK model) input impedance. Panels E through G show similar data measured in the right ventricle and pulmonary artery of a dog.

Table 1. Cardiac and arterial model parameters used for the simulations of systemic (pig) and pulmonary (dog) heart-arterial interaction.

	Systemic Circulation (Pig)	Pulmonary Circulation (Dog)
$E_{\max}$ (mmHg/ml)	2·49	0·35
V_0 (ml)	−9·1	7·7
$E_{\min}$ (mmHg/ml)	0·047	0·051
P_v (mmHg)	2·86	5·90
EDV (ml)	51·7	122·6
T (s)	0·465	0·84
$T_{E\max}$ (s)	0·20	0·184
R (mmHg/(ml/s))	1·72	0·196
C (ml/mmHg)	0·48	2·35
Z_c (mmHg/(ml/s))	0·105	0·086
L (mmHg/(ml/s^2))	0·0059	0·010

3. Simulated cases: systemic and pulmonary hemodynamics in mammals

3.1. Parameters for the systemic circulation of a pig

Panel A in Figure 3 shows LV pressure-volume loops in a pig, measured using a conductance catheter (CD Leycom, Zoetermeer, Netherlands) during occlusion of the inferior vena cava to reduce the inflow of the heart. This data-set is representative for the complete set that was used in [13], where details on the experimental protocol of this particular study can be found. Linear regression on the end-systolic points yields $E_{\max}$ (2·49 mmHg/ml) and V_0 (−9·1 ml). End-diastolic volume at steady state was estimated as 51·7 ml, and venous filling pressure 2·86 mmHg. This yields an $E_{\min}$ of 0·047 mmHg/ml.

Measured aortic pressure (Millar pressure transducer, Houston, TX) and flow (Transonic flow probe, Ithaca, NY) during steady state are given in panel B (left axis: pressure; right axis: flow). Fourier analysis on both pressure and flow and calculating the ratio of pressure and flow harmonics yields the measured input impedance, of which modulus and phase are shown in panels C and D, respectively.

To assess the four parameters of the windkessel model, measured Q_{ao} is used as an input to the model. The difference between measured P_{ao} and the calculated response of the windkessel model is then minimized by altering the values of the parameters of the four-element windkessel model until optimal agreement is achieved [10]. This is done using the Matlab 'fminsearch' algorithm (Matlab, The Mathworks, Natick, MA). The obtained parameters are listed in Table 1 and the model response is shown in panel B of Figure 3. The model input impedance as obtained with the model parameters is compared to the measured input impedance (modulus in panel C and the phase in panel D, Figure 3).

Furthermore, the pressure-volume data measured during steady state are used to construct a normalized time-varying elastance. The curve is given in Figure 4.

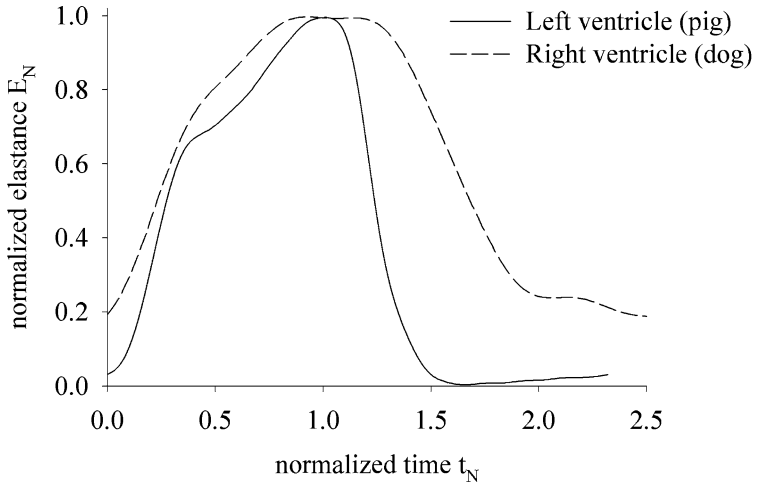

Figure 4. Normalized elastance curve derived from the measured experimental data for the left ventricle of a pig and the right ventricle of a dog.

3.2. Parameters for the pulmonary circulation of a dog

Panels E through F show similar data that were measured in the right ventricle and pulmonary artery of a dog. Again, we use a representative sample from a previously used larger data set, and the reader is referred to this study for details on the experimental set-up [14]. In spite of the markedly different morphology of the PV-loops in the right ventricle, end-systolic points, $E_{\max}$ and V_0 can still be determined (Table 1). Table 1 further lists the values of the remaining cardiac and arterial parameters that were derived from measured pressure (Millar, Houston, Texas) and flow (electromagnetic flow probe, Skalar, Delft, Netherlands). The derived normalized time-varying elastance curve for the right ventricle is shown in Figure 4.

3.3. Agreement between measurements and simulations

The simulations, obtained using the normalized elastance curves shown in Figure 4 and the arterial and cardiac parameter values listed in Table 1 are given in Figure 5 (panels A-C for the systemic circulation of the pig; panels D-E for the dog pulmonary circulation). For the systemic circulation, the agreement is good for aortic and LV pressures (Figure 5, panel A). Simulated PV-loops have the typical rectangular shape (panel B). As we simulated perfectly closing valves, volume remains perfectly constant during the isovolumic contraction and relaxation phases. This is different in the experimental data, where there is a faint skewness in the measured data, which may be due to (mild) valvular insufficiency, measurement errors, or even non-optimal alignment of measured pressure and volume signals. There is some discrepancy between measured and simulated flow (panel C). Peak flow is somewhat higher in the simulations, and the simulated flow profile is also less smooth in the deceleration phase, compared to the measurements.

Concerning the simulations for the pulmonary circulation (Figure 5, panels D–F), qualitative comparison with measured data shows that the morphology of mainly pulmonary artery pressure is less well predicted, although systolic and diastolic pressures are in reasonable agreement (panel D). Both measured and simulated PV-loops (panel E) exhibit the typical

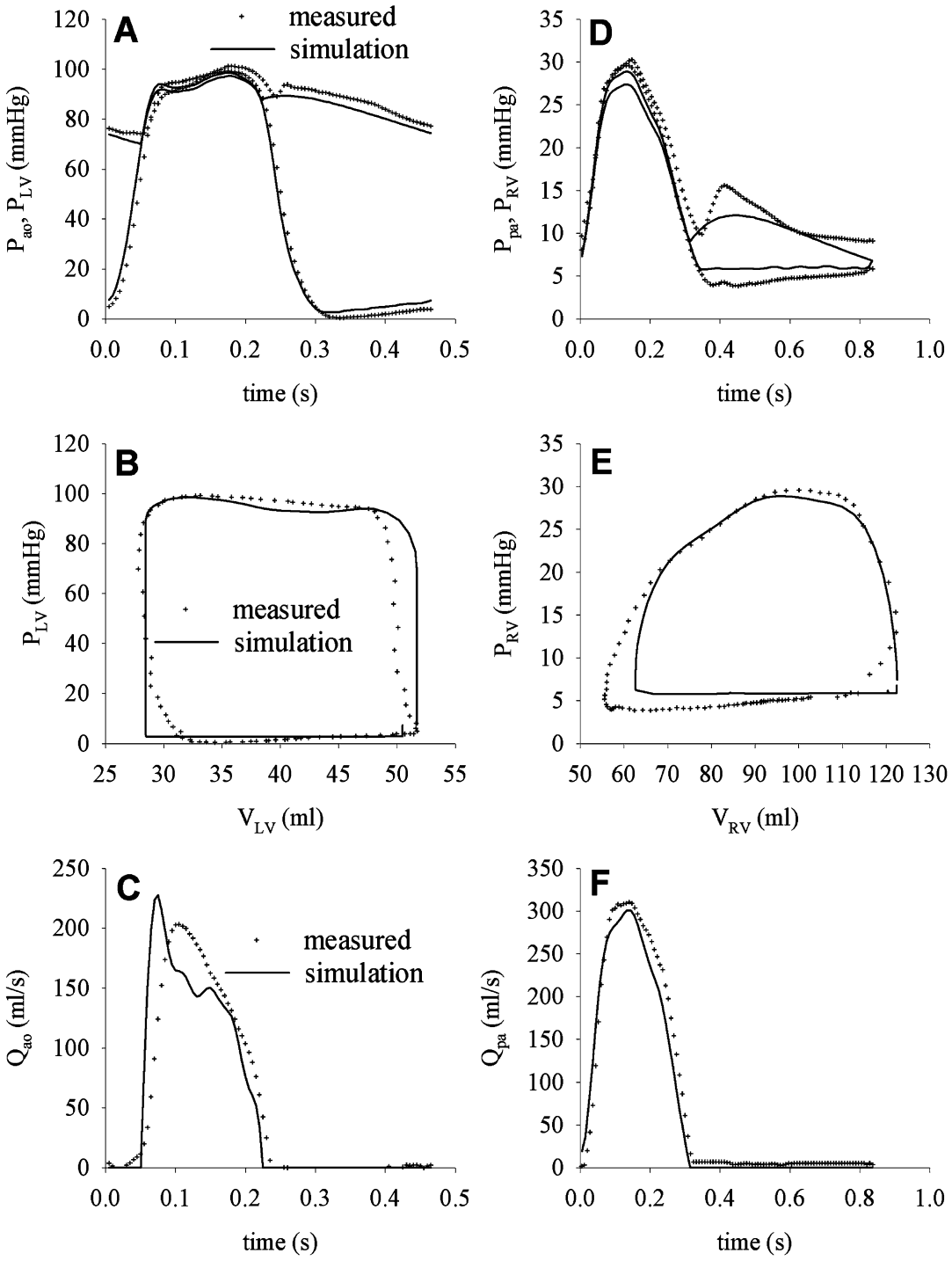

Figure 5. Comparison between measured and simulated ventricular and arterial pressure (A: systemic, D: pulmonary circulation), ventricular pressure-volume loops (B: systemic, E: pulmonary circulation) and arterial flow (C: systemic, F: pulmonary circulation).

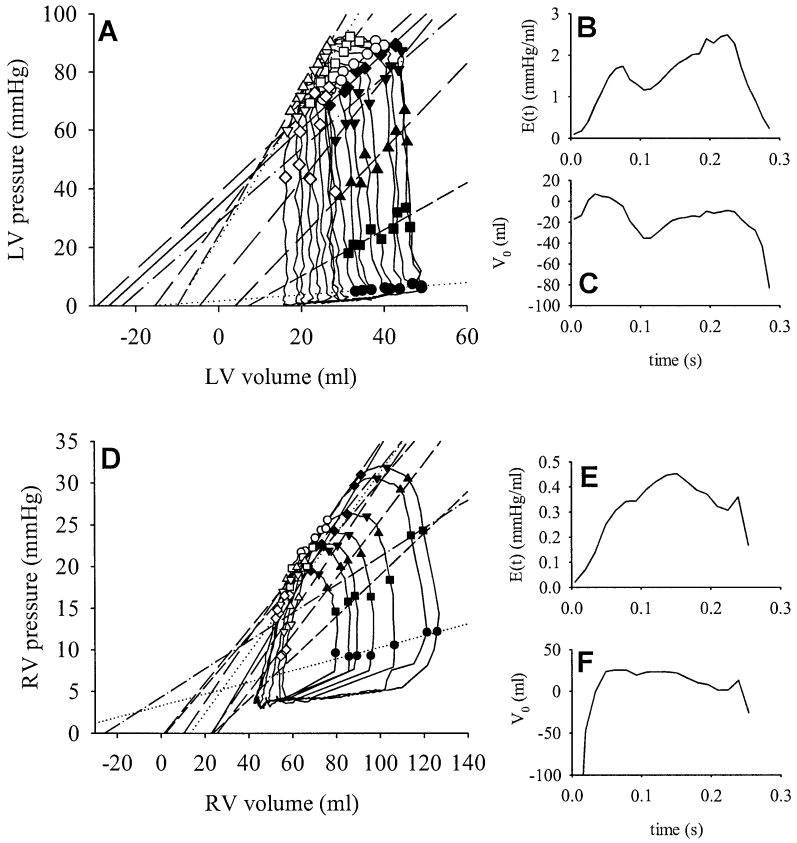

Figure 6. Isochronic lines measured in the left ventricle of a pig (A) and the right ventricle of a dog (D). Panels B, C, E and F show the time course of the slope (elastance; B: left ventricle, E: right ventricle) and intercept with the volume axis (V_0; C: left ventricle, F: right ventricle) during systolic ejection.

'triangular' shape caused by an early opening and late closure of the pulmonary valve, resulting in very short isovolumic contraction and relaxation phases. Simulated pulmonary artery flow, both in morphology and peak value, corresponds well to the measured flow (panel F).

4. Discussion

When constructing the heart-arterial interaction model, it was our main objective to obtain a physiologically relevant model of (systolic) ventricular function that is, however, simple enough so that (i) model parameters can be derived from data measured in experimental and/or clinical conditions, (ii) the model can be applied to support the analysis and interpretation of these data. In this and previous work, we have demonstrated how indeed a simple, conceptual model of ventricular function (the time-varying elastance) can be coupled to a four-element windkessel model of the arterial system to yield an elegant model of heart-arterial interaction. The coupling leads to a set of three ordinary differential equations that needs to be solved, and allows to study the impact of changes in cardiac and/or arterial properties on generated pressure and flow.

Assuming that the normalized time-varying elastance function (which can be described as a Fourier series; we typically use eleven terms) is a given property, the model requires only

ten (or nine) parameters to fully describe ventriculo-arterial coupling: four arterial parameters (R, C, Z_c and L) and six (or five) heart-related parameters: two ventricular systolic-function parameters ($E_{\max}$ and V_0), two parameters that describe the timing of cardiac contraction (T and $t_{\mathrm{E\,max}}$), and two parameters to set diastolic function and preload ($E_{\min}$ and P_{venous}) that can, eventually, be combined into only one preload parameter (V_{ed}). Despite the limited number of parameters, their assessment requires data that is not always available in clinical routine. Especially ventricular contractility ($E_{\max}$ and V_0) are difficult to obtain due to the highly invasive character of the PV-loop measurements and the necessity to acquire these data under at least two different loading conditions of the heart.

The low number of model parameters is due to the incorporation of a normalized time-varying elastance in the model. Senzaki *et al.* showed, in humans, that the intrinsic shape of the elastance function is relatively constant, even independent of many cardiac disease states [4]. This is especially true for the ascending limb describing contraction and ejection, while there is somewhat more scatter for the descending limb (relaxation). Our model, coupling the heart to the arteries, essentially describes the systolic phase of the cardiac cycle, and is therefore mainly determined by the relatively stable ascending limb of the elastance function. With the absence of an atrium and the simple resistive atrio-ventricular valve model, diastolic function is modelled in a minimalistic way. What matters is that at the onset of contraction, a certain end-diastolic volume is reached but it is – at least for our applications – of less importance how it is reached. Therefore, $E_{\min}$ and P_{venous} by themselves are relatively unimportant parameters, as long as their combination yields an appropriate value of the end-diastolic volume. Hence, ventricles (with the same $E_{\max}$ and V_0) with high diastolic stiffness ($E_{\min}$) but with high filling pressures (P_{venous}) will yield similar arterial pressure and flow as a compliant ventricle with low filling pressures, as long as both conditions lead to the same end-diastolic volume.

In this study, we selected representative examples of data that were available from former studies [13, 14] to, qualitatively, demonstrate the applicability of the model to the systemic and pulmonary circulation. As we previously reported [15, 16], the model yields a reasonable correspondence between measured and simulated data, provided that an appropriate time-varying elastance function is implemented, and model parameters are given reasonable values. A factor contributing to dissimilarities between measurement and simulation is the accuracy of the models that are assumed to represent cardiac and arterial function. It is well established that lumped-parameter models in general, and the used four-element windkessel model in particular, are accurate representations of the systemic circulation (as confirmed by our own data; see Figure 3 panels C and D) [12]. For the pulmonary circulation, however, there is quite some discrepancy between the model input impedance and the measured input impedance, especially for the higher frequencies (Figure 3, panels G and H). This may, however, also be due to the fact that there is only little power in the higher-frequency harmonics. As such, it is more difficult to fit the four-element windkessel model in this frequency range. Nevertheless, it is our feeling that it is the discrepancy between measured and model impedance that explains the rather poor simulation of the details of the pulmonary artery pressure wave (Figure 5, panel D), as these details are mainly determined by the higher frequency contents. The four-element windkessel model fairly represents the low-frequency contents (up to fourth harmonic) and the interaction model will therefore well predict the low-frequency features of pulmonary hemodynamics (systolic and diastolic pressures, pulse pressure, stroke volume).

Another important issue is how well measured pressure-volume data adheres to the theoretical concept of a time-varying elastance. To answer this question, we determined isochronic points for the data measured in the left and right ventricle and plotted some of the linear

regression lines to the isochrones in Figure 6. Similar to the theoretical model (Figure 1), the slope increases and decreases over the cardiac cycle. In contrast, however, the intercept shifts substantially over the cycle, an observation that was earlier reported for the right ventricle [17, 18]. To study ventriculo-arterial coupling, only the behaviour during the ejection period is crucial (0·0 to 0·25 s). It can be seen from Figure 6 that, although substantial, the variation of V_0 during this period is less than when considered over the complete cardiac cycle. Nonetheless, this variation of V_0 over the heart cycle will also explain, in part, the differences between measurement and simulations. It is possible that using an average V_0 obtained from the isochronic lines (instead of using the extrapolated V_0 obtained during caval vein occlusion), improves the agreement berween measurements and simulations.

Obviously, the purpose of a model is to use it beyond the validation phase, and to apply it to describe conditions where experimental or clinical data are not directly available or incomplete. In certain situations, it is useful or more convenient to use data generated by a computer model where parameters can be changed one by one in a controlled way, which is not (always) feasible in a clinical or experimental facility. As such, we previously used the model to quantify heart-arterial interaction and to assess analytical relations between systolic and diastolic pressure and stroke volume on the one hand, and dimensionless cardiac and arterial parameters on the other [16, 19]. After validating the model against sheep data, we used the model to generate data over a wider range of cardiovascular parameters (peripheral resistance and compliance, ventricular contractility), than was available from the experimental data [16]. Similarly, we used the model to comprehend the relation between true mechanical arterial properties and arterial elastance, E_a, [20], a parameter that is increasingly used to assess effective arterial stiffness. We demonstrated that E_a is mainly determined by total peripheral resistance and heart rate, rather than by the stiffness of the arterial system [21]. The fact that E_a is often simply termed the arterial stiffness (instead of effective arterial stiffness or elastance) further contributes to the confusion around E_a as an arterial function parameter.

Furthermore, in conditions of aortic regurgitation, the severity of the leak is the most predominant determinant of E_a and of heart-arterial interaction in general [22]. In another study, we used the model to test and confirm the hypothesis that normalization of both systolic and diastolic ventricular wall stress may play a role in the ventricular adaptation process (hypertrophy) to hypertension [15]. Ventricular wall stress was calculated from pressure and volume and assuming a thick-walled sphere and constant ventricular mass throughout the cardiac-cycle. The model can also be extended to study the interaction of the heart with cardiac-assist devices, such as rotary blood pumps [23].

Although the use of this type of model has contributed to the understanding of cardiovascular hemodynamics, the ultimate goal should be to apply models of this kind in clinical conditions and to incorporate them into the assessment of cardiovascular function of the individual patient. In particular, routine clinical diagnosis of ventricular contractility remains difficult. We recently demonstrated, using reported non-invasively measured data in hypertensives, that our model may help to differentiate the contribution of the heart and of the arterial system to blood pressure [24]. Such information is useful to optimise not only the patient's diagnosis (and perhaps to better assess his prognosis), but also to better titrate the pharmacological treatment of the hypertensive patient by selectively administrating blood pressure lowering drugs working via different mechanisms (diuretics, beta-blockers, angiotensine converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockade). Note that the model also helps to guide researchers and doctors to decide what is important to measure. As we demonstrated, measurement of arterial properties alone does not explain hypertension.

Besides 'stand-alone' application of lumped-parameter modelling, the model can also be used in conjunction with more elaborated numerical models and make, for instance, part of a hybrid model. Arterial pressure and/or flow, resulting from the model, can be used as boundary conditions for, for instance, 1-D models describing the propagation of the pressure and/or flow wave over (part of) an arterial network, or as boundary conditions for numerical models aiming to solve the details of the local flow field in a specific part of the circulation.

On the other hand, ventricular pressure and volume may serve as input of more detailed (mechanical) models of the ventricle where the goal may be to, for instance, calculate the distribution of wall stresses.

While the limited number of model parameters is the main strength of our model, it is, at the same time, a serious limitation. At present, the model does not contain a left atrium and can therefore not be used to study ventricular diastolic function or flow problems associated with the atrio-ventricular valve (*e.g.* mitral insufficiency). Although the incorporation of an atrium with an additional time-varying elastance is straightforward, there is, to our knowledge, no generally applicable form of this function. The number of parameters would increase significantly and, most importantly, these parameters would be rather difficult to assess, even in an experimental setting. Furthermore, the valves are modelled as simple linear resistances, causing a pressure drop proportional to the flow through the valve. More appropriately, inertial and nonlinear effects could be taken into account, as well as a resistance that changes in time to account for the progressive opening and closing of the valve. Obviously, this would again increase the number of parameters and impede the clinical applicability of the model. On the other hand, however, the simple valvular model may contribute to the discrepancy between measured and simulated flow as is observed in the simulation of the systemic hemodynamics in the pig.

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