OPTIMIZING VENTRICULAR WORK: A MATTER OF CONSTRAINTS

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ABSTRACT
The analysis of aortic blood pressure and flow represent an important tool to predict cardiovascular risk. A Windkessel model relating pressure and flow, together with an optimal performance criterion of left-ventricular work, is used to generate the aortic flow pattern for a given central pressure curve. For the corresponding optimization problem, different physiologically relevant constraints are specified, but due to the limited number of degrees of freedom not all of them can be included at once. The optimization problem is solved with every possible combination of constraints and the resulting flow and pressure curves are analyzed. These waveforms show that the choice of constraints strongly affects the accuracy of the generated curves. Constraining aortic flow during diastole appears to be the best choice, but a physiologically shaped flow and pressure pattern cannot be achieved simultaneously with the applied objective function and constraints.

Keywords: pulse wave analysis, blood flow model, cardiovascular system, aortic pressure waveform

1. INTRODUCTION
The circulation of blood in the human cardiovascular system is determined by pressure and flow. Both state variables depend on the mechanisms of the heart and the properties of the vessels. Therefore they can be used to characterize the status of the cardiovascular system of a specific person, and several methods and parameters have been developed for this purpose, which are often subsumed as pulse wave analysis (PWA).

Beside systolic and diastolic blood pressure levels obtained from brachial pressure readings, also parameters reflecting arterial stiffness and wave reflection in the aorta are supposed to yield important information about cardiovascular risk. Their computation is based on analysis of central arterial waveforms of pressure and/or flow and thus require measurements thereof (Chirinos and Segers 2010b, Laurent et al. 2006, Mitchell 2009). See Fig. 1 for a stylized example of aortic pressure and flow waveforms.

Arterial pressure can be measured rather easily by non-invasive oscillometric or tonometric techniques on peripheral sites, and validated transfer functions provide an aortic pressure curve (Karamanoglu et al. 1993, Wassertheurer et al. 2010b, Weber et al. 2011). A non-invasive measurement of aortic flow on the other hand is more cumbersome and consequently not convenient for clinical applications (Chirinos and Segers 2010a).

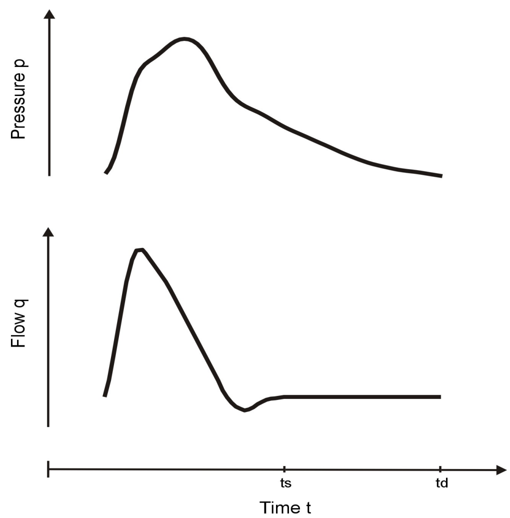

Figure 1: Exemplary waveforms of aortic blood pressure (upper panel) and flow (lower panel)

Different models for generating blood flow patterns based solely on information from pressure readings have been developed to overcome this limitation. One approach is to replace the unknown flow wave by an estimate, e.g. a triangular approximation, generated with the help of parameters derived from the (known) aortic pressure wave.

Westerhof et al. (2006) studied the accuracy of a triangular waveform to determine parameters of wave reflection in the aorta by the means of wave separation analysis. They achieved results close to those obtained with measured flows, whereas Kips et al. (2009) found substantial differences in a similar study. They again tested a triangular approximation of the blood flow for the application in pulse wave separation, but in contrast to the other study, they used a pressure waveform derived from non-invasively measured data to base their approximation on. They outlined this fact as their main limitation and as a probable explanation for the differing results. Therefore, since non-invasive techniques are preferable for clinical application, this method might be disadvantageous. Along with the triangular waveform, they also examined the qualities of a newly proposed estimate with a more physiological form, which is obtained by averaging the normalized measured flow waves of various patients. Even though thereby the same waveform (except for an individualized timing) is used for every patient, the results were improved in comparison to the triangular form. Yet for the reflection parameters determined with the use of this curve, the deviations from measured values were still considerable.

Another approach is to use a Windkessel equation to establish a functional relation between pressure and flow. The assumption that the heart works in an optimal manner, i.e. that the power dissipation is minimized under given constraints, enables the computation of an aortic root flow and the corresponding pressure contour (Pfeiffer and Kenner 1978; Yamashiro, Daubenspeck, and Bennett 1979). Subsequently, the parameters of the Windkessel model can be identified by fitting the calculated to the measured pressure wave to finally obtain the left ventricular ejection pattern (Estelberger 1977).

One advantage of this method is that the flow curve is modeled with physiological significant parameters (Westerhof et al. 2009). Hence establishing the model itself already yields information about the arterial system without further analysis. Its main drawback is that the number of constraints that should be taken into account exceeds the degrees of freedom in the optimization problem. Therefore certain constraints have to be omitted.

A specific choice of constraints to generate a flow curve is currently used in the ARCSolver algorithms for PWA (Hametner 2011b, Mayer 2007, Wassertheurer et al. 2010a). Cardiac output determined in this way, i.e. by using the modeled aortic root flow, showed a good correlation with the one obtained from invasively measured data (Wassertheurer et al. 2008). Furthermore this model is part of algorithms that provide accurate and clinically relevant estimates of wave reflection parameters which are capable of predicting cardiovascular risk. (Hametner et al. 2011a, Hametner et al. 2012, Weber et al. 2012). This indicates that even without including all constraints a reliable description of the hemodynamics in the arterial system can be achieved with this method.

The aim of this study is to solve the optimization problem with different combinations of constraints and characterize the resulting pressure and flow curves, which should bring further insights in the dynamical behavior of the underlying model.

2. METHODS

To generate a central flow curve, first of all pressure and flow are related over a Windkessel equation. Then the considered constraints are formulated and subsequently the resulting optimization problem is solved by the means of calculus of variations.

2.1. Windkessel Models

Windkessel models describe a dynamic relation between pressure and flow in the arterial system. The pressure is thereby assumed to be the same all over the arterial tree, because the whole system is modeled as one compartment, which makes spatial distributions impossible. The idea is based on the comparison of the volume elasticity of the large arteries with the air chambers in old-fashioned fire-engine pumps. During systole, the blood is ejected from the left ventricle with high pressure whereby the elastic arteries close to the heart expand. After closing of the valves, the pressure drops and thus the arteries relax again. By doing so, the contained blood is discharged, providing a continued blood flow during diastole (Westerhof et al. 2009).

In 1899 Otto Frank formulated the mathematical equations to relate pressure and flow in terms of a compliant and a resistant element (Hametner 2011b). The arterial compliance C_a is defined as the change in blood volume V caused by a change in blood pressure p

$$C_a = \frac{dV}{dp} \tag{1}$$

and thus gives a measure of the elasticity of the arteries, i.e. their capacity to store blood. It is assumed to be constant.

The peripheral resistance R_p characterizes the power dissipation in the area of the arterioles and capillaries and describes the proportionality between mean blood pressure $\overline{P}$ and mean peripheral blood flow $\overline{X}$:

$$R_p = \frac{\overline{P}}{\overline{X}} \tag{2}$$

As mass has to be conserved, the change in blood volume over time corresponds to the difference of inflow and outflow, see Eq. 3.

$$\frac{dV}{dt} = q(t) - x(t) \tag{3}$$

Thereby q denotes the aortic root flow, i.e. the blood ejected from the left ventricle. Combining Eqs. (1) to (3) yields the model equations of the two-element Windkessel:

$$\begin{aligned} q(t) &= C_a R_p \dot{x}(t) + x(t) \\ p(t) &= R_p x(t) \end{aligned} \tag{4}$$

During diastole, when the aortic valve is closed and thus q equals zero, the system becomes a linear homogeneous differential equation in x with the following solution (t_d denotes the length of a heartbeat):

$$x_d(t)=x_{t_d} e^{\frac{t_d-t}{R_p C_a}}, \quad x_{t_d}=x(t_d) \tag{5}$$

Hence the model predicts an exponential decay for the diastolic peripheral flow and consequently the blood pressure with time constant R_pC_a, which coincides approximately with the physiological form. But with the development of improved measurement methods enabling recording of the aortic root flow, the shortcomings of the model during systole became clear (Westerhof et al. 2009).

Therefore a third element was added to improve the predicted behavior during left ventricular contraction. The resulting three-element Windkessel consists, like Frank's model, of the arterial compliance C_a, the peripheral resistance R_p, plus an additional resistor R_c (Estelberger 1977).

The characteristic resistance R_c includes the power dissipation in the area of the large arteries due to the viscoelastic properties of blood and vessel walls. It affects the aortic root flow q and thus only the behavior of the model during systole. Figure 2 shows an electrical analog of the three-element Windkessel used in this study.

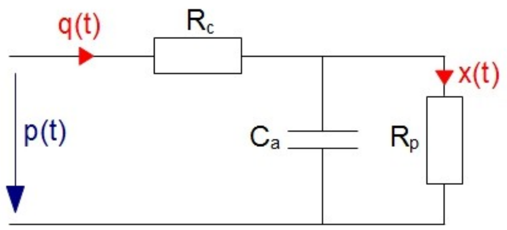

Figure 2: Electrical analog of the three-element arterial Windkessel model

Application of Ohm's law as well as Kirchhoff's circuit laws yields a differential system for pressure and flow, that constitute the model equations:

$$\begin{aligned} q(t)&=R_p C_a \dot{x}(t)+x(t) \\ p(t)&=R_c q(t)+R_p x(t) \end{aligned} \tag{6}$$

Even though the model still has its weaknesses at capturing high frequency details, the overall predicted waveform of the aortic pressure p is close to the physiological one for a given root flow q (Westerhof et al. 2009).

2.2. Optimization of Left Ventricular Work

The Windkessel model characterizes an open dynamical system that takes the flow q as input and returns the pressure p as output. Hence the established relation is unidirectional, i.e. blood pressure depends on blood flow (and the properties of the system), but not vice versa. Therefore, in order to generate an aortic root flow (the input) from a given pressure curve (the output) a feedback mechanism has to be included to couple flow with pressure (the input with the output) (Estelberger 1977). This is done by assuming that the work of the heart is subject to an optimization principle, i.e. that it works with minimal effort to provide a certain outflow.

This approach is based on the hypothesis, that biological systems have evolved to operate on minimal energy requirements. For the major breathing pattern characteristics in man this was found to be true, as the concept of minimal power dissipation made their explanation possible. Since the energy expenditure of the heart exceeds that of breathing, it seems convincing that similar regulation mechanisms also occur in the heart (Hämäläinen and Hämäläinen 1985; Yamashiro, Daubenspeck, and Bennett 1979).

The ventricular work over one heartbeat can be calculated as (t_s denotes the ejection time):

$$W=\int_0^{t_s} p(t)q(t)\,dt \tag{7}$$

Optimal performance of the heart is achieved when the cardiac output required by the body is produced with the lowest energy consumption possible, i.e. with the least work done by the left ventricle. Thus an optimal flow should minimize the integral in Eq. 7 under the constraint that a specific stroke volume V_s

$$V_s=\int_0^{t_s} q(t)\,dt \tag{8}$$

has to be reached. By introducing a Lagrange multiplier μ, this problem can be formulated as:

$$\int_0^{t_s} p(t)q(t)+\mu\, q(t)\,dt \rightarrow min \tag{9}$$

With the use of the Windkessel model (see Eq. 6), Eq. 9 can be expressed in terms of the peripheral flow x together with its derivative. Thereby an isoperimetric problem is obtained, which is solved by calculus of variations, resulting in a second order differential equation for x with the following general solution (λ denotes the eigenvalue of the differential equation):

$$x(t)=Ae^{\lambda t}+Be^{-\lambda t}+C \tag{10}$$

Thus additional constraints are needed to determine the three unknowns (A, B, C).

Beside V_s, another obvious constraint is the periodicity of the peripheral flow over one cardiac cycle:

$$x(0)=x(t_d)=x_0, \tag{11}$$

or equivalently (see Eq. 5):

$$x(0)=x_0, \quad x(t_s)=x_0 e^{\frac{t_d-t_s}{R_p C_a}} \tag{12}$$

Furthermore the aortic flow should be zero at the beginning of the heartbeat and during diastole when the cardiac valve is closed:

$$q(0)=q(t_s)=0 \qquad (13)$$

Altogether five constraints have been formulated (Eq. 8 and Eqs. 11-13) but the general solution of the optimization problem has only three degrees of freedom. Therefore only three conditions can be chosen to solve the problem exactly.

To analyze the behavior of the formulated model, the problem is implemented in Matlab (MathWorks, Natick, MA, USA) and all possible combinations of constraints are studied. The parameters in the Windkessel equation as well as ejection time, heart rate and stroke volume are fixed within the physiological range, see table 1 (Estelberger 1977).

Table 1: Parameter values

NAME	NOTATION	VALUE	UNIT
stroke volume	V_s	71	ml
peripheral resistance	R_p	0.82	$mmHg{\cdot}ml^{-1}{\cdot}s$
characteristic resistance	R_c	0.015	$mmHg{\cdot}ml^{-1}{\cdot}s$
arterial compliance	C_a	1	$ml{\cdot}mmHg^{-1}$
length of cardiac cycle	t_d	0.664	s
ejection time	t_s	0.26	s

3. RESULTS

There are ten possible combinations of the five constraints described above.

Inclusion of both boundary conditions for the arotic flow, i.e. $q(0)=q(t_s)=0$, gives a concave aortic flow and a decreasing peripheral flow x and pressure p. The quantitative outcome differs strongly depending on the third constraint.

When solely the initial value of q is taken into account, the aortic flow is increasing and peripheral flow x as well as pressure p become convex during systole. Quantitatively, the results are very similar in all three cases.

Considering the boundary condition $q(t_s)=0$ for the aortic flow without constraining $q(0)$, the results show the same qualitative and quantitative behavior for all choices of the two other constraints: a decreasing aortic flow q, a concave peripheral flow x as well as a concave pressure p.

The last possible combination excludes the boundary conditions for q, thus the stroke volume V_s and the periodicity of the peripheral flow, $x(0) = x(t_d) = x_0$, are considered as constraints. With the fixed parametrization this results qualitatively and quantitatively in almost exactly the same pressure and flow as in the previous case.. But depending on the initial value of the peripheral flow x_0, q can vary from decreasing to increasing, x and p from concave to convex, whereas for the other combinations of constraints no change in the qualitative behavior occurs.

All qualitative shapes are shown in Fig. 3 for central and peripheral flow as well as pressure.

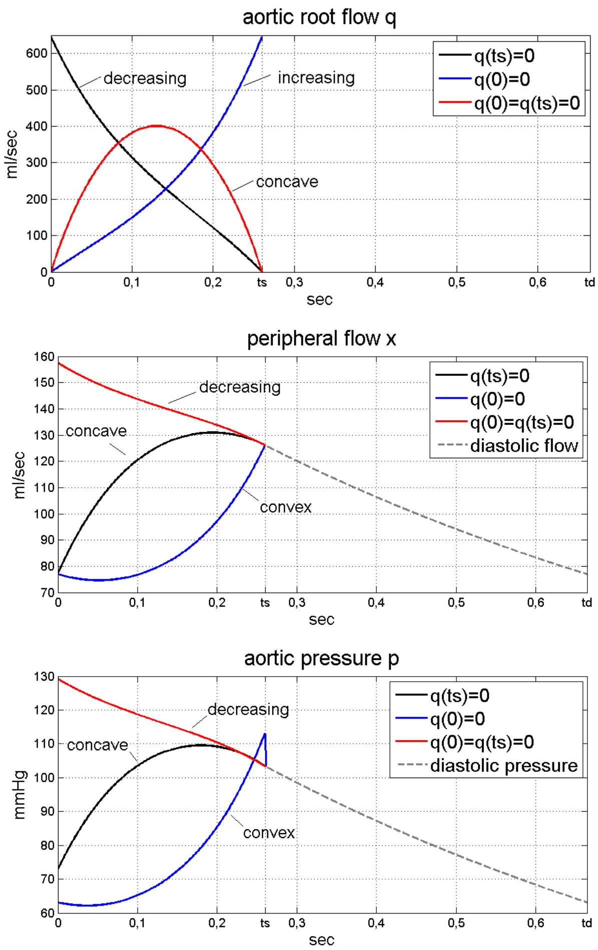

Figure 3: Examples of aortic root flow (upper panel), peripheral flow (middle panel) and aortic pressure (lower panel) for the three different types of qualitative behavior

4. DISCUSSION

The results clearly show that the choice of constraints strongly affects pressure and flow when optimizing left ventricular work. In total, three types of qualitative behavior can be distinguished, which will be discussed separately.

A first type of qualitative behavior occurs when the aortic flow is supposed to be zero at the beginning and the end of systole, i.e. $q(0)=q(t_s)=0$. This type is characterized by a concave aortic flow and a decreasing aortic pressure. Even though the shape of q seems reasonable, that of p is inaccurate, since firstly, it is not periodic and secondly, it implies that the increase in volume during blood ejection causes a decrease in pressure. Furthermore the quantitative outcomes are not in a physiological range. The combination including the stroke volume as third constraint, i.e. the constraints described in Eqs. 8 and 13, might seem to be a natural choice for generating an ejection pattern, as all constraints including q are considered**.** But for this combination, the predicted pressure reaches values of more than 800 mmHg, which is a multiple of the normal maximum. The other two possible choices for the third condition required are to restrain initial systolic or end diastolic peripheral flow. In the first case, pressure as well as stroke volume are greatly underestimated (the computed stroke volume is 5.3 ml, the maximal pressure 63 mmHg). In the second case, although pressure varies in a more realistic range, the predicted stroke volume is still far too low (10.85 ml).

In conclusion, these combinations of constraints show weaknesses in both the qualitative and the quantitative results.

Another type of behavior can be observed when the constraint $q(0)=0$ is used without $q(t_s)=0$. In this case, the results show an increasing aortic flow and a convex systolic pressure. Again, the qualitative agreement of both pressure and flow with observed patterns is poor. The peak pressure as well as the maximal flow are not reached until the end of systole, which differs substantially from the physiological form. Especially with regards to the identification of system parameters by fitting of the modeled to the measured pressure wave, this could create difficulties. Therefore, also this second type does not provide appropriate waveforms for further analysis.

Finally, a decreasing aortic flow and a concave pressure characterize the third class of results. This situation arises from the specification of q being zero after the valves have closed, i.e. $q(t_s)=0$. With the chosen parametrization, the results are almost exactly the same for all three possible combinations of constraints. Therefore, when V_s remains unconstrained (this would correspond to the case, where the periodicity of the peripheral flow x is in focus), the obtained patterns can be used for stroke volume determination (Estelberger 1977). For the parameter values specified in Table 1, the area enclosed by the modeled aortic flow gives 70.9674 ml compared with the demanded 71 ml. On the other hand, also the periodicity of x can be achieved without including it explicitly.

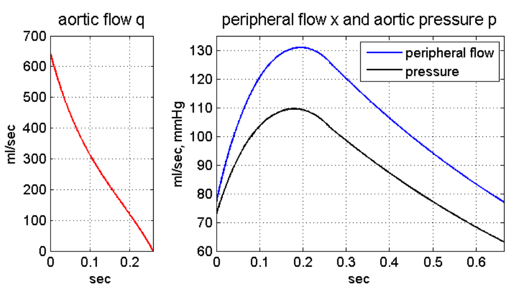

Figure 4: Pressure and flow shapes from an optimization with $q(t_s)=0$

Figure 4 depicts a set of computed curves representative for all three combinations with $q(t_s)=0$. Although the aortic flow wave is physiologically incorrect, as it shows an infinite slope at the beginning of blood ejection, the pressure curve is in qualitative accordance with human measurements. Waveforms of this type are also used in the ARCSolver. There, a combination of constraints including the stroke volume in addition to $q(t_s)=0$ is used.

With the chosen parametrization, also the results obtained by leaving the aortic flow unconstrained belong to this type. For these patterns, the major shape predictions were shown to be consistent with measured ones in a dog, both for varying cardiac output and heart rate (Yamashiro, Daubenspeck, and Bennett 1979). Yet, in this case, flow as well as pressure react sensitively on changes in x_0, see Fig. 5. An increase of 5 ml/sec (6.5%) already results in a completely different shape of the curves. For practical applications, this might be disadvantageous as x_0 is determined by the diastolic aortic blood pressure obtained from measurements and/or further computations thereof.

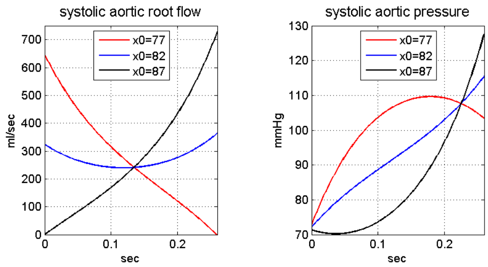

Figure 5: Results for aortic flow q (left) and pressure p (right) with an unconstrained aortic flow for different values of x_0

In summary, the variants based on a combination of constraints including $q(t_s)$ but not $q(0)$ provide the best results with regards to both the quantitative and qualitative behavior. Furthermore it can be seen that the condition $q(0)=0$, which is needed for a physiological shape of the aortic flow, causes a qualitative deterioration of the results whenever included.

4.1. Conclusions and Perspectives

The analysis of different combinations of constraints revealed that a physiological waveform of both pressure and flow cannot be achieved simultaneously with the presented method and the corresponding choices for the objective function and constraints.

Comparing the combinations of constraints which lead to the same type of behavior indicates that the boundary conditions of the aortic flow q are the key determinants for the shape of the curves. Except for the case where no boundary value of q is taken into account, the qualitative behavior is fully determined by whether $q(0)$ or $q(t_s)$ or both are set to zero. The choice of additional constraints as well as initial-systolic or end-diastolic peripheral blood flow x_0 thereby only influence the quantitative outcome. This does not apply when the boundaries of q are not constrained. In this case, the qualitative properties of pressure and flow are indeed affected by changes in x_0 and thus by the diastolic pressure.

A description of the system that is closest to reality is achieved when the aortic root flow is decreasing. To improve the shape of the ejection pattern, the outflow has to be forced to start at zero, but by doing so the existing benefits of the current solution should not be lost. The aim of future work will be to extend the method in a way that allows the inclusion of additional conditions, in particular the zero initial aortic flow. This could be done by modifying the performance criterion or by using more than three constraints and searching for approximate solutions for such an overdetermined problem.

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