A Model-Based Study of the Influence of Vaso-Active Drugs on Pulse Delays Measured from the Electrocardiogram

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Abstract

The use of ECG-based pulse delays as a surrogate of the arterial blood pressure has long been questioned, especially when the subject is given vaso-active drugs altering the vascular resistance. When measured from the ECG, pulse delays include two components: the vascular pulse transit time and cardiac pre-ejection period (PEP).

This paper analyses the relationships of both vascular and cardiac components with the blood pressure. As there is no known equation ruling PEP, a lumped model of arterial circulation is used to study the dependencies between blood pressure and PEP. When the peripheral resistance varies PEP shows a direct correlation with the blood pressure, opposite to the inverse pulse transit time dependency. Real-life signal examples from intensive care unit patients are presented and discussed.

1. Introduction

Non-invasive measurements of pulse wave velocity (PWV) or pulse transit time (PTT) have been studied for more than 30 years [1] as possible surrogate of the arterial blood pressure (ABP), with the aim of replacing the uncomfortable and intermittent cuff method. A number of papers have questioned the usefulness of pulse delays measured from the ECG as a marker of ABP, especially when the subject has been administered vaso-active drugs [2-6]. In this paper, elements of explanation are proposed, based on mathematical models of the arterial circulation and pulse wave propagation.

Vaso-active drugs (VAD) are widely used in the management of cardio-vascular diseases, especially during decompensation phases. Their main effect is to alter the systemic vascular resistance (SVR) with little impact on the frequency and intensity of cardiac contractions, depending on the type and dosage of the used VAD.

When measuring the delay of pulse arrival time (PAT) at periphery from the ECG QRS complex, two distinct time intervals are actually summed up: the pre-ejection period (PEP) and the vascular PTT. The PEP covers the iso-volumic contraction phase up to the aortic valve opening while PTT represents the pulse propagation time along the arterial wall up to the chosen peripheral site. Both terms do carry significant beat-to-beat information about the ABP, however, of quite different nature and time dynamics [2, 7] while the observed PAT values consist of their *sum* only.

The inverse dependency of PTT on the transmural pressure is established by the Moens-Korteweg equation coupled with Hughes' non-linear elasticity-pressure relationship [8]. However, there is a lack of knowledge about the inter-dependencies of PEP and ABP [9]. In this work, a lumped model of the arterial circulation is exploited to compute dependence curves of PEP on ABP when varying hemodynamic parameters like the peripheral resistance and left-ventricular (LV) contractility [10]. Simulation results indicate that PEP varies either directly or inversely with the ABP, depending on the changes occurring to the cardio-vascular status. When the peripheral resistance changes, the PEP shows a direct correlation with the ABP, opposite to the inverse PTT dependency. Hence, PAT becomes an unreliable marker of ABP because the changes of PTT may be offset or even largely obliterated by opposite PEP variations.

In section 2 previous work having addressed the impact of VAD on pulse delays is briefly reviewed. Section 3 explains the main equations and model used to derive the relationships of either PTT or PEP with the ABP. Section 4 presents the computed dependence curves of PEP on the ABP as well as examples of systolic blood pressure (SBP) predictions for real-life recordings in the intensive care unit (ICU), drawn from the MIMIC database. These results and their limitations are discussed in section 5.

2. Brief overview of previous work

Four papers published from 1983 to 2006 are examined, each one dealing with the influence of vaso-active drugs on pulse delays measured from the ECG [2-5]. Human measurements from young volunteers are studied in [2, 5] and from ICU patients in [3] while anesthetized dogs are investigated in [4]. In all four studies, an invasive catheter line provides the ABP (radial for humans, aortic for dogs). Beat-to-beat PEP and PTT durations are

measured separately in [2, 4, 5]. PEP could not be estimated from the ICU data, hence only the PAT values are available in [3]. Various drugs have been injected to provoke hypotension (amyl-nitrite [2], nitroglycerin [3, 4] and glyceril trinitrate [5], as vaso-dilators) or hypertension (neo-synephrine [3], phenylephrine [4], angiotensin and norepinephrine [5], as vaso-constrictors).

The main conclusions can be summarized as follows. When available, PEP appeared to contribute substantially to the PAT variations. Thus PAT cannot be regarded as a purely vascular index. In general, PAT correlations with SBP remained negative, however, to a variable extent such that PAT proved to be an unreliable SBP predictor. More specifically, strong correlations have been observed for PEP and PTT separately with the SBP, but these were always negative for PTT while PEP correlations appeared well positive in case of VAD induced hypotension [2, 4] and negative for cardiac inotropic stimulation [4]. The physical properties of arterial walls seemed unaffected in [4]. VAD dosages in ICU appeared too small to modify the smooth muscle tone although they did affect SVR [3].

3. Methods

As introduced above, when measured from the ECG R-peak, the pulse arrival time is ruled by the equation:

$$PAT = PEP + PTT\ ,$$

involving the sum of a cardiac and a vascular component. The links of the ABP with each of these components will be derived separately, either from equations for the PTT or based on a lumped model for PEP, as explained below.

3.1. Relationship between ABP and PTT

According to the Moens-Korteweg equation, PWV is basically an indicator of vessel wall elasticity through

$$PWV = \frac{distance}{PTT} = \sqrt{\frac{Eh}{\rho 2r}}\ ,$$

ρ being the blood density, r the vessel radius, h the wall thickness and E the Young elasticity modulus of the wall. Indeed, assuming that ρ, r and h undergo small changes, the main variation is expected to come from the elasticity modulus only, through the experimental relation [8]:

$$E(P) = E_0 e^{\alpha P}, \alpha \approx 0.017 mmHg^{-1}$$

This provides a link between the transmural pressure P and either PWV or PTT measurements. Parameters of the resulting ABP prediction rule are tuned with a calibration step. For $\alpha > 0$, pressure estimates depend inversely on PTT. In practice, strong negative correlations are generally observed between PTT and systolic blood pressure (SBP) values and, to a weaker extent, also for the diastolic BP [1, 2, 4, 5, 7].

3.2. Relationship between ABP and PEP

As there is no known equation in closed form for PEP, the avenue of numerical simulation has been investigated, based on a lumped model of the arterial circulation. A compact presentation is given below, the whole model having been explained in details in a previous paper [10].

3.2.1. Description of the cardiac-arterial model

Figure 1 shows the arterial circulation model made of two parts, the LV pump and the arterial system analog circuit.

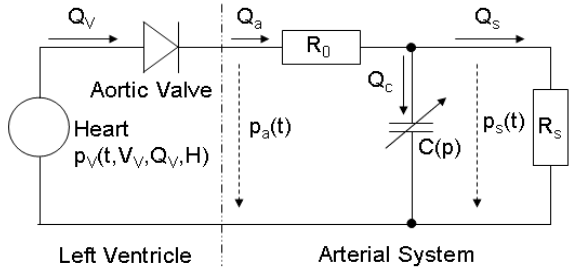

Figure 1. Lumped analog model of the arterial circulation
p = pressure, t = time, V_v = LV volume, Q_v = LV outflow, H = heart rate
R_0 = aortic impedance, Rs = peripheral resistance, C = total compliance

The left ventricle (LV) is handled as a pressure source that depends on time (t), ventricular volume (V_v), outflow (Q_v) and heart rate (H), which provides a direct coupling with the varying vascular conditions [11,12]. By coupling this ventricular pump model with a Windkessel afterload, the main variables of the arterial circulation can be numerically simulated, including the aortic valve opening and closure times. The basic LV model equation is

$$p_v(t,V_v,Q_v,H) = a(V_v - b)^2 + (cV_v - d)F(t,Q_v,H),$$

where the activation function $F(t,Q_v,H)$ includes specific ejection effects depending on the outflow Q_v [11] and a cardiac force-frequency relation derived from experimental canine data [12]. All LV model parameters have a physiological meaning e.g., c is the main contractility parameter. The arterial tree is modeled with a three-element Windkessel analog involving two resistive terms R_0, R_s and a non-linear pressure-dependent compliance: $C(p) = C_0 \cdot e^{C_e p}, C_e < 0$. The equation relating the root aortic pressure $p_a(t)$ and flow $Q_a(t)$ is given by

$$Q_a(t) = \frac{p_a(t) - p_s(t)}{R_0} = \frac{1}{R_0 + R_s}\left[p_a(t) + R_s \cdot C_s(p_s)\frac{dp_s}{dt} \right]$$

After prescribing the appropriate boundary conditions along one cardiac cycle [10], the model equations can be solved numerically. More information is given in [10-12].

3.2.2. Derivation of model parameter dependencies

Relationships between the arterial blood pressure and the PEP duration have been investigated by varying *one* parameter at a time in the baseline model. Two effects are shown here, regarding the influence of the peripheral resistance (parameter Rs) and of the LV contractility (c). More parameter dependencies have been included in [10]. Dependence curves of the systolic and diastolic pressure on PEP durations are obtained by running multiple model simulations for distinct parameter values.

4. Results

The outcome of the lumped model simulations are first presented in terms of two selected dependence curves and next, examples of beat-to-beat prediction of systolic blood pressure are shown for ICU signal data.

4.1. Computed ABP-PEP dependence curves

When varying the R_s parameter from 1 to 12 mmHg sec ml^{-1}, PEP shows a direct almost-linear correlation with BP as seen in figure 2a, on the left side. By contrast, when varying the LV contractility parameter c from 1.5 to 5.5 mmHg ml^{-1}, the ABP-PEP inter-dependencies exhibit an inverse relationship shown in figure 2b. Both cases correspond to the same BP range. However, the overall PEP variations achieved by changing the peripheral resistance are about twice as large as those induced by varying the LV contractility parameter.

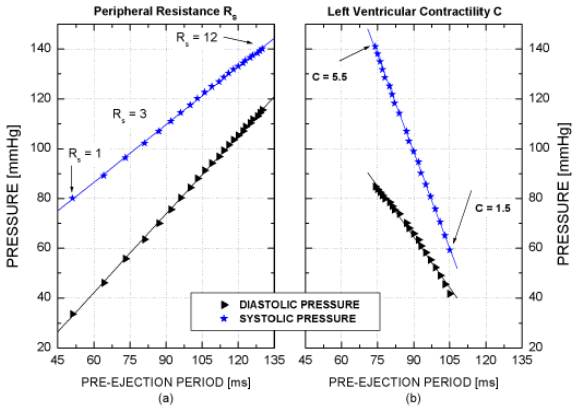

Figure 2. Dependence curves of the PEP with the ABP

These simulation results are in good qualitative agreement with observations reported by Ochiai et al. in [4].

4.2. SBP prediction for ICU data

The MIMIC Physionet database provides real signals recorded from ICU patients [3]. PAT values have been computed from the ECG and PPG signal pair with own algorithms. The available continuous ABP waves serve as "golden" reference to evaluate the accuracy of predicted BP at a beat-to-beat level. An initial calibration is carried out using the first 5 regular beats of each patient record. Systolic BP values are displayed over time in the plots below: the blue continuous curve is derived from the reference ABP waves while the green dashed curve shows the predicted values.

Figure 3 zooms on a short interval taken from a record during which the patient' hemodynamic status remained stable up to that time. The predicted SBP values closely follow the reference values at a beat-to-beat level. Sinus-rhythm oscillations reveal the (forced) respiration cycles.

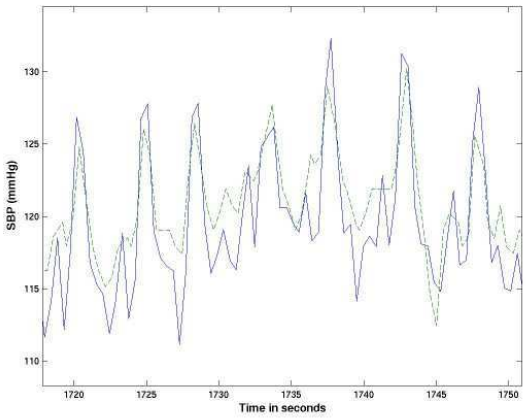

Figure 3. Systolic BP prediction for stable hemod. status
Reference SBP: continuous blue; Predicted: dashed green

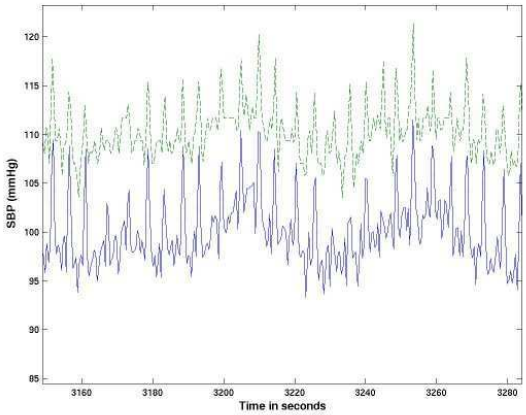

Figure 4. Systolic BP prediction after hemodyn. change
Reference SBP: continuous blue; Predicted: dashed green

By contrast, figure 4 above shows a short interval of the same record taken 20 minutes after the previous snapshot, following some change of the patient' hemodynamic status. Close inspection of the ABP and PPG signals reveal clear changes in reflected waves that may have been caused by drug injection or by some other medical intervention. Note that this hemodynamic transition takes about a quarter to settle down to a new "stable" status. An almost constant prediction error of more than 10mmHg is visible. The relative SBP variations are still fairly well predicted in spite of a large offset between the two curves.

5. Discussion and conclusion

The presented analysis provides a number of elements explaining why PAT " per se" is not a reliable predictor of the ABP when subjects are given vaso-active drugs altering their peripheral vascular resistance. Some caveats have to be made clear, however.

- First, the lumped model setup is based on canine data [10] and has not been systematically validated.
- Next, no regulation feedback has been included, which would have allowed multiple parameters to be jointly varied in a more realistic way.
- The Moens-Korteweg equation relies on ideal and quite restrictive assumptions, especially concerning the physics of vessel wall (Perfect linear elastic material, internal radius variations neglected).
- The MIMIC-I database does not provide access to information on drugs and medications given in the ICU, making impossible to associate signal wave changes with medical intervention or health status evolution.
- Signal streams available in MIMIC-I do not allow for directly estimating the PEP, which prevents from monitoring separately the vascular (PTT) and cardiac (PEP) components of the PAT.
- The observation that the prediction error mainly consists of an additive offset (see Figure 4) supports the hypothesis that the vascular tone is not significantly affected in this example.

To conclude, the relevance of this model-based study is essentially qualitative. Signal examples were only given to illustrate one typical "problematic" situation. An extensive evaluation is currently under way regarding possible solutions in the monitoring context of ICU.

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