Biomedical Signal Processing and Control 7 (2012) 616–621

Contents lists available at SciVerse ScienceDirect

Biomedical Signal Processing and Control

journal homepage: www.elsevier.com/locate/bspc

Noninvasive pressure pulse waveform analysis of flow-mediated vasodilation evoked by post-occlusive reactive hyperemia maneuver

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ARTICLE INFO

Article history:
Received 19 July 2011
Received in revised form 28 February 2012
Accepted 3 March 2012
Available online 9 April 2012

Keywords:
Hypertension
Reactive hyperemia
Pulse wave analysis

ABSTRACT

Post-occlusive reactive hyperemia (PORH) assesses flow-mediated vasodilation at microvascular level due to bioactivity of endothelial-derived factors. Ordinary augmentation index that quantifies endothelial response is based on an ensemble-averaged waveform that limits its short-time application. This study proposes a mathematical model and two corresponding indices to evaluate arterial pressure response after blood flow restoration. Radial pressure pulse waveforms were acquired by a 12 bits acquisition board at a sampling rate of 1.0 kHz using a piezoelectric transducer. Signals were stored during 30 s at baseline condition and 60 s after 5-min occlusion using an arm-cuff placed over the brachial artery. In both conditions, the pressure pulse waveform presents systolic and diastolic phases with progressive and regressive pulse waveforms, respectively. Changes in pulse wave morphology were also observed and comprised attenuation of the pulse pressure amplitude (markedly first and second systolic peaks). This characteristic of the pulse pressure was described by the time-domain summation of two pairs of Gaussian-like waveforms (representing independent progressive and regressive components) with parameters related to amplitude, time lag, and duration for each component. A steepest descent optimization routine was used to fit the model parameters to experimental data of normotensive and subjects with hypertension. The optimized parameters were used to calculate two indices, $RIx_{1,2}$ (second-to-first systolic peak ratio) and $RIx_{1,3}$ (first diastolic-to-first systolic ratio). The observed responses between groups suggest that $RIx_{1,2}$ is related to an endothelial response to the ischemic process and could be used as a clinical tool to assess endothelial function in hypertension.

1. Introduction

In the beginning of the 21st century hypertension was estimated to occur in 26.4% of the worldwide adult population and 29.2% are projected to have this condition by 2025 [1]. It is also the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life-years [2].

Monitoring the progression of hypertension involves the investigation of target-organ damage through the assessment of static (structural) and dynamic (functional) characteristics of vessels from large arteries to microcirculation. Endothelial cells compose the inner monolayer of all vessels and are involved in production of a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation [3]. At the microcirculatory level (<0.1 mm in diameter), the balance of vasodilator and vasoconstrictor factors influences arteriolar diameter and therefore regulates arterial pressure. It has been shown [4] that subjects with hypertension may have their endothelial function blunted, characterized by a low flow-mediated vasodilation. Also, endothelial dysfunction is associated with large artery stiffness in subjects with coronary heart disease [5] and systemic inflammation in hypertension, which is also related to arterial stiffness [6]. As a consequence, the reduced vasomotor activity contributes to the pathophysiology and progression of hypertension.

Post-occlusive reactive hyperemia (PORH) is a maneuver dedicated to assess flow-mediated vasodilation at microvascular level due to bioavailability and/or bioactivity of endothelial-derived factors [7]. It consists of external occlusion of the blood flow to a distal extremity (commonly, the forearm) lasting 3–5 min followed by a sudden restoration of blood flow [4,8–12]. After cuff deflation, the increased shear stress over endothelial cells release vasodilator agents produced intensively during ischemia period by responsive

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doi:10.1016/j.bspc.2012.03.001

subjects. Although the total reaction time for PORH can last up to 15 min [4], maximum vasodilation of the forearm vascular bed occurs within the first 30–60 s [12].

PORH has been evaluated by invasive protocols using drug infusion [13], which are not well suited for longitudinal studies where several measures are required. Noninvasive assessment is preferred for long-term analysis as well as for specific populations (e.g. pregnant women, children) [7]. It was also performed with ultrasound-based diameter measurement of the radial artery [12] and laser-Doppler perfusion monitoring [14]. However, ultrasound-based measurements need relatively long-time training to obtain reproducible and reliable results [15]. Modeling of pulse pressure (PP) time series during the first 60 s after occlusion release [16] was also performed and is based on the vascular impedance concept that relates regional blood flow to arterial pressure [17]. In Addition, pulse wave analysis (PWA) method – based on the wave reflection phenomenon [18] – was applied to carotid artery pulse [18,19], radial artery pulse [15,18–23] or digital volume pulse [20,21]. Although all those arterial sites are useful for clinical investigation, there are evidences that similar information on central pressure wave reflection can be obtained directly from PWA of the radial artery pulse waveform [21,22].

The augmentation index (AIx) is a PWA-based measure of pulse wave reflections used to assess both endothelial function and arterial stiffness, and it is calculated as the difference between the second and first systolic peaks, expressed as a percentage of the PP [15,19–21,23]. The common method to calculate AIx is the ensemble-average of 6–20 sequential pulse waveforms to generate a peripheral (and possibly corresponding central waveform by using a validated generalized transfer function) [15,18–20,23]. Such approach result in a smooth 'representative' pulse waveform since phase shifts between pulse waveforms would low-pass filter the resulting averaged waveform, as occurred in blood flow signals [24]. This blurring of features is especially pronounced in regions of rapid rate of change, such as the systolic peak and the dicrotic notch (two important regions for calculation of *AIx*). Moreover, the relatively long-time needed to collect 6–20 pulses to calculate the ensemble average (up to 7–24 s based on a heart rate of 72 beats/s) combined with the short-time changes of pressure waveform amplitude observed in patients with hypertension [16] make such a processing not adequate for analysis of immediate vascular effects of the shear stress based on PWA. Hence, the aim of this study is to propose a mathematical model and corresponding indices to evaluate the arterial pressure response during PORH. Such model allows the evaluation of the immediate as well as late effects of the shear stress caused by acute blood flow restoration. It was hypothesized that indices obtained from modeled pulse waveform components are useful for the assessment of transients in flow-mediated vasodilation in subjects with hypertension.

2. Methods

2.1. Physiologic rationale for the derived PWA mathematical model

Considering the wave reflection phenomenon [17,18], the pulse waveform can be interpreted as the time-domain summation of a progressive wave traveling downward to the organs and body segments and a regressive wave traveling backwards to the heart, where the differences between the progressive and regressive components are related to the vascular impedance. The systolic ejection phase of the cardiac cycle is actually a two-stage phenomenon, where the first stage comprises a rapid increase in intraventricular pressure due to the high electric myocardial excitability while the second stage is characterized by a slow decrease in intraventricular pressure due to reduction in excitation [25]. Hence, the complete phase is marked by the presence of two systolic peaks in the ventricular pressure signal, which are transmitted to peripheral arteries of the upper extremities as the progressive waveform shape is dependent on the initial conditions (in this case, left ventricular pressure). Thus, the progressive time-domain pressure waveform $f(t)$ could be empirically modeled as the summation of two Gaussian probability density functions (PDF) where each peak represents its respective stage (Eq. (1)):

$$f(t) = P_1 \cdot e^{[(t-t_{P_1})^2/\sigma_{P_1}^2]} + P_2 \cdot e^{[(t-t_{P_2})^2/\sigma_{P_2}^2]}, \quad (1)$$

where the subscripts represents the stage (1 = rapid pressure transient; 2 = slow pressure transient), P_i (i = 1, 2) stands for the amplitude of the each pulse waveform progressive component, t_{Pi} (i = 1, 2) indicates the location of the forward wave peaks, and σ_{Pi}^2 (i = 1, 2) indicates the width or 'duration' of the forward components (the variance of the Gaussian distribution).

As the regressive wave travels backward to acquisition site of $f(t)$, changes in contour due to the filtering process are reversed and it can be assumed that a very similar contour will be obtained although scaled in amplitude (due to potential and kinetic energy loss) and lagged in time (due to finite pulse wave velocity) [17]. Thus, the regressive component of the traveling waves was also modeled by the summation of the two previous functions (Eq. (2)):

$$g(t) = R_1 \cdot e^{[(t-t_{R_1})^2/\sigma_{R_1}^2]} + R_2 \cdot e^{[(t-t_{R_2})^2/\sigma_{R_2}^2]}, \quad (2)$$

where R_i stands for the amplitude of the each pulse waveform regressive component, t_{R_i} indicates the location of a backward wave peak, and $\sigma_{R_i}^2$ indicates the width or 'duration' of a backward component.

Based on the above hypothesis the time-sampled pressure waveform $P(t)$ at a fixed arterial site is then represented by summation of the progressive and regressive time-domain pressure waveforms $f(t)$ and $g(t)$ (see Fig. 1).

The model parameters were fitted using an optimization algorithm based on a steepest descent gradient method [26] with the following initial values: $P_1 = 0.50$, $P_2 = 0.37$, $R_1 = 0.23$, $R_2 = 0.10$ s; $t_{P_1} = 0.10$ s, $t_{P_2} = 0.23$ s, $t_{R_1} = 0.37$ s, $t_{R_2} = 0.50$ s; $\sigma_{P1}^2 = \sigma_{P2}^2 = \sigma_{R1}^2 = \sigma_{R2}^2 = 0.005$. More specifically, the optimization method was a variable step-size gradient descent. To find a minimum (normally a local minimum) of an error function (proportional to the difference between the experimental data and the theoretical ones computed by the summation of the functions $f(t)$ and $g(t)$) the method takes steps proportional to the negative of the gradient (or approximate gradient) of the function at the current point. The optimization stopped when changes less or equal to 0.1% were observed for all the model parameters. After optimization, the estimated values were used to compute augmentation indices with respect to the second systolic peak ($RIx_{1,2}$) and the first diastolic peak ($RIx_{1,3}$) (Eqs. (3) and (4)):

$$RIx_{1,2} = \frac{P_2}{P_1} \times 100\%, \quad (3)$$

$$RIx_{1,3} = \frac{R_1}{P_1} \times 100\%, \quad (4)$$

2.2. Subjects

Data collection was conducted in the Division of Hypertension of the National Institute of Cardiology (RJ, Brazil), after approval by the Institutional Review Committee. The volunteers were previously informed about the aim of the experiment and they gave their verbal consent. Clinical data of the studied groups are presented in Table 1. The control group (CG) was represented by 63 subjects (30 men, age 29.3 ± 8.6 years), and the