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Model for post-occlusive reactive hyperemia as measured noninvasively with pressure pulse waveform

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ABSTRACT

Post-occlusive reactive hyperemia is a noninvasive maneuver to assess microvascular reactivity related to the bioavailability and/or bioactivity of endothelial-derived factors. The inability to respond to endogenous vasodilator substances is mostly described by a low peak flow after an event associated with a peak flow. The aim of this study is to propose a model to describe post-occlusive responses observed in the pressure waveforms after occlusion release. Model variables were investigated in search of those representatives of the endothelial response to the ischemic process. Radial pressure pulse waveforms were acquired in the anterior region of the wrist, superficial to the radial artery, using a piezoelectric transducer acquired by a 12 bits acquisition board model at a sampling rate of 1.0 kHz to increase the temporal resolution. The occlusion maneuver was performed using an arm-cuff placed over the brachial artery. A time series of pulse pressure (PP) values, calculated from successive values of beat-to-beat systolic and diastolic pressures, was found to be a useful variable representing blood pressure signal in the model. This data time series of the pulse pressure presents reduced initial values compared with the baseline measurement, and an increasing value until a steady state behavior was sustained after approximately 60 s. This behavior for the pulse pressure series was described by a hyperbolic tangent model with parameters K (rate of change of PP), PP_0 (first value of PP after cuff release), and ΔPP (change in PP). The model was applied to pulse pressure signals from normotensive and hypertensive subjects. The observed responses between groups suggest that PP_0 and ΔPP are 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

Systemic arterial hypertension (SAH) is considered the major risk factor for stroke and myocardial infarction [1]. In subjects with hypertension, target-organ injury may be monitored through the assessment of static (structural) and dynamic (functional) characteristics related to arterial function. Endothelial cells, which compose the inner layer of vessels, are responsible for both partial regulation of arterial stiffness [2] and regulation of blood flow on distal sites through the production of vasodilator substances [3]. The vasomotor response evoked by the endothelium mainly occurs in the skin and muscle microvasculature of the limbs and corresponds to approximately 70% of the regional blood flow [4,5]. At the microcirculatory level (less than 0.1 mm in diameter), the balance of vasodilator/vasoconstrictor factors influences arteriolar diameter and therefore regulates arterial pressure. When the ability to respond to endogenous vasodilator substances – chiefly those derived from endothelium cells – is sufficient, there is both an increase in blood flow and a washout of the metabolic products of cells. However, it has been shown [6] that subjects with hypertension may have their endothelial function blunted, characterized by a low peak flow after the event associated with the peak flow. The reduced vasomotor activity contributes to the physiopathology of SAH.

Post-occlusive reactive hyperemia (PORH) is a noninvasive maneuver to assess microvascular reactivity related to the bioavailability and/or bioactivity of endothelial-derived factors [7]. It consists of occlusion of the blood flow to a distal extremity (lasting 3–5 min) followed by a sudden restoration of arterial circulation [3,4,6,8–10]. Just after the occlusion release, responsive subjects release vasodilator agents produced during ischemia due to increased shear stress over endothelial cells. Although the total reaction time for PORH can last 15 min [6], maximum vasodilation of the forearm vascular bed occurs within the first 30–60 s [10].

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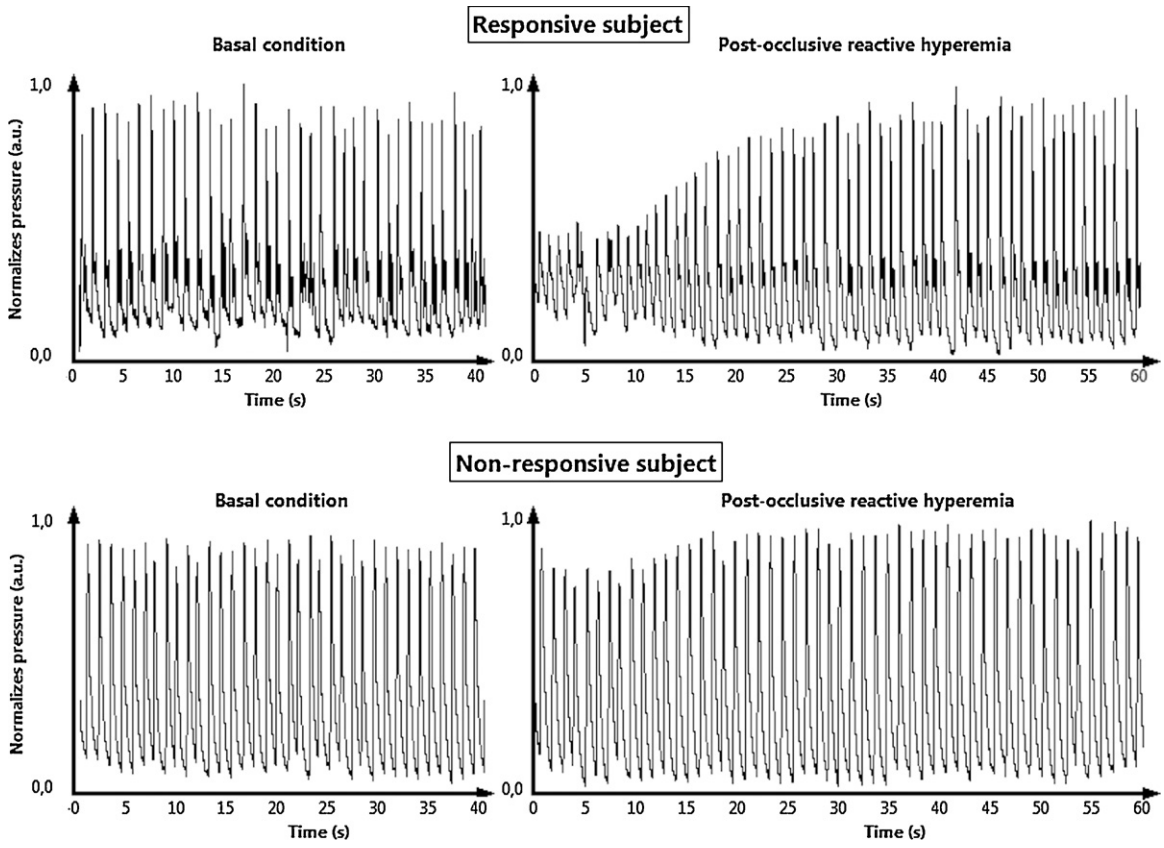

Fig. 1. Typical aspect of the radial artery pressure waveform acquired before, during, and after cuff pressure release from a responsive and non-responsive subject.

PORH has been assessed using ultrasound-based diameter measurement of the radial artery at the wrist [10] and with Laser-Doppler perfusion monitoring [11]. The need for the development of new techniques for the assessment of endothelial function emerges from the limitations of the currently available methods. Invasive protocols using drug infusion [12] are not well suited for longitudinal studies where several measures are required. Moreover, some noninvasive methods, such as ultrasound, need relatively long training times to obtain reproducible and reliable results [13].

Because blood flow is related to arterial pressure by vascular impedance [14], it is expected that hyperemic reactions could be obtained either with flow or pressure waveform signals, but with different signal aspects. Flow signal in peripheral arteries, e.g. radial artery, presents a fast rate of flow and a well-defined peak followed by a quasi-exponential decay to the pre-occlusion value [11]. Such an aspect is explained by the relative changes in radial artery radius compared to the baseline, combined with microvascular vasodilation, both interacting to change the arterial bed impedance.

The aim of this study is to present a model to describe PORH responses in pressure waveforms after blood flow restoration that follows the occlusion release. Model variables were investigated searching for those that represent the endothelial response to the ischemic process and could be used as a clinical tool to assess endothelial-dependent pathogenesis of SAH.

2. Methods

2.1. PORH model

The behavior of the time evolution of pressure waveforms associated with the PORH responses that were considered normal and blunted are depicted in Fig. 1. Since just the relative magnitudes and their temporal behavior are considered, the pressure waveforms values were normalized by its maximum value for each heartbeat series in order to have a unitary maximum. A time series of pulse pressure (PP) values, calculated from successive values of beat-to-beat systolic and diastolic pressures, as described in previous works [15,16]. This procedure beside generates the profile of a pressure pulse (PP) over time also reduces the respiratory variability of the blood pressure. The resulting time evolution of the PP series exhibited reduced initial values compared with the baseline measurement, and increased until a steady value was sustained (maximal response, i.e. a response higher than baseline) after approximately 60 s. A hyperbolic tangent model for the PP series (Eq. (1)) describes this characteristic:

$$PP(t) = PP_0 + \Delta PP \cdot \{0.5[1 + \tanh(K \cdot t - t_0)]\}, \quad (1)$$

where $PP(t)$ represents PP as a function of time, PP_0 corresponds to PP at the first detectable pulse waveform after cuff release, t_0 is the time occurrence of PP_0 (in seconds), ΔPP accounts for PP scaling, and K is a constant related to the rate of change of PP. The model parameters were fitted using an optimization algorithm based on a steepest descent gradient method [17], with initial values of $\Delta PP = (\max(\text{blood pressure signal}) - PP_0)$, and $K = 1.5$.

The rational for the proposed model is as follows. regulatory mechanisms try to stabilize arterial pressure despite local blood flow changes [5]. Hence, higher microvascular vasodilation must be accompanied by a reduced PP_0 and an increased ΔPP. Compared with responsive subjects, subjects with diminished responses show higher PP_0 with consequently smaller ΔPP. Non-responsive subjects present negligible changes in the estimated PP_0 and ΔPP.