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Review

Evaluation of endothelial function by peripheral arterial tonometry and relation with the nitric oxide pathway

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ABSTRACT

Endothelial dysfunction is an important component in the development of cardiovascular diseases. Endothelial function may be evaluated by peripheral arterial tonometry (PAT) which measures the vasodilator function in the microvasculature of the fingertip during reactive hyperaemia. The reactive hyperaemia index (RHI) is decreased in the presence of cardiovascular risk factors and thus far several studies have shown that PAT-RHI may provide reliable prediction of outcome. The technique is operator independent and easy to perform. Abnormalities measured by PAT follow the same trend as those measured by flow-mediated dilation in the brachial artery, but the two methods are not interchangeable. We have reviewed the recent literature in an effort to evaluate peripheral arterial tonometry as a method to assess the function of the endothelium and additionally suggest directions for future research. Special attention will be directed to the nitric oxide dependency of the reactive hyperaemia index obtained by peripheral arterial tonometry.

1. Introduction

The endothelium layer produces factors responsible for maintaining vascular tone, blood fluidity and coagulation. It is crucial for the production of cytokines and cellular adhesion molecules, which are primary factors for initiating and upholding an inflammatory process. In blood vessels with intact endothelium acetylcholine evokes dilation [1]. However, patients with advanced coronary stenosis have abnormal vascular response to acetylcholine [2]. This indicated that defects in the endothelium layer may be an important factor in the pathogenesis of vascular diseases [2]. Numerous studies have evaluated the prognostic value of assessing the function of the endothelium [3–7]. In summary, the studies demonstrate that patients in risk of short and long-term cardiovascular events can be identified by an impaired endothelium function.

Vascular tests are the most used methods in assessment of the endothelium function [8]. Flow-mediated dilation (FMD) of the brachial artery measured by ultrasound is a widely used method to evaluate function of the endothelium. This review highlights a new non-invasive technique for analysing information about the endothelium layer based on amplitude tonometry in the fingertip (peripheral arterial tonometry, PAT). Special attention will be directed to the nitric oxide (NO) dependency of the reactive hyperaemia index obtained by PAT.

2. Peripheral arterial tonometry (PAT)

A peripheral arterial tonometer consists of a finger-mounted probe plethysmograph capable of sensing volume changes in the vessels of the index finger during each pulsation. The index finger is well perfused and the lack of major muscle mass makes it a suitable object for measuring changes in the blood volume [9]. The finger-mounted probe has a stiff external covering containing the electronically controlled inflatable chambers, which apply a significant pressure (70 mmHg) across the finger (Fig. 1). This prevents venous pooling and blood stasis which otherwise can provoke a vasoconstrictor reflex [10,11]. The recorded PAT signal is transmitted to a computer where the signal undergoes filtration, amplification, algorithm processing and finally is displayed and stored for further analysis.

PAT examination includes three phases: baseline, occlusion and reactive hyperaemia. A PAT probe is attached to the index finger on each hand (control and test). The test finger is exposed to all three phases, each lasting for 5 minutes. Data obtained in the control finger are used in the computer algorithm to adjust for systemic effects. After 5 minutes of baseline recording, a blood pressure cuff is inflated to suprasystolic pressure for 5 minutes [12]. Once the cuff is released reactive hyperaemia is obtained in the test arm and the signal is recorded for a further 5 minutes. Reactive hyperaemia is considered an important haemodynamic response to a period of ischaemia. Reactive hyperaemia increases blood flow and thereby the delivery of oxygen and removal of metabolic products.

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Fig. 1. **(Top left)** Examination settings; finger probes are placed on the index finger of each hand. A foam rubber ring disperses the index finger and middle finger, allowing the probe not to be touched which otherwise can result in artefacts. **(Bottom left)** A cuff is placed on the forearm and is inflated to induce reactive hyperaemia. **(Top right and bottom right)** The examination probe consists of a stiff external covering containing the electronically controlled inflatable chambers.

After cuff deflation (phase 3), the pulse amplitude of a healthy individual will rise rapidly, whereas a low response is observed in individuals with endothelial dysfunction (Figs. 2 and 3). Any observed change in amplitude on the control finger after cuff deflation may be a response to a systemic effect of the cuff inflation. The key outcome of a PAT examination is the reactive hyperaemia index (RHI), which describes the ratio of average amplitude during reactive hyperaemia compared with the pre-occlusion baseline period (Fig. 2). The final result is multiplied by the baseline correction factor (0.2276 × ln(mean occluded baseline amplitude) – 0.2) [13].

RHI is calculated on the basis of the following equation:

$$\mathrm{RHI} = \frac{A}{B} \Big/ \frac{C}{D} \times \text{Baseline Correction Factor}$$

A: Mean PAT amplitude between 90 s–150 s post occlusion of the occluded arm
B: Mean PAT amplitude from the baseline period of the occluded arm

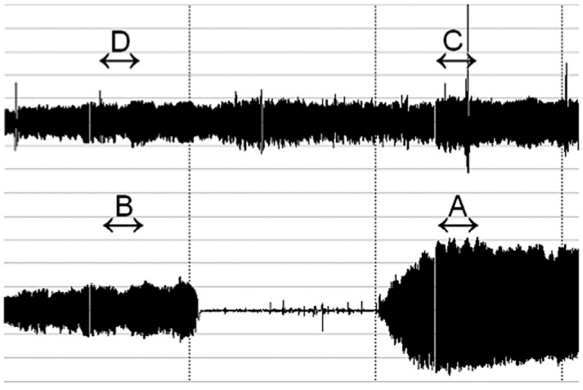

Fig. 2. Result from a PAT examination in a healthy male individual. Letters visualise the calculation of the reactive hyperaemia index (see text).

C: Mean PAT amplitude between 90 s–150 s post occlusion of the control arm
D: Mean PAT amplitude from the baseline period of the control arm

Following cuff release, RHI can be calculated by the computer in intervals of 30 seconds. The hyperaemia response is maximal between 90 and 120 seconds after cuff release [14]. Reference values for RHI from the manufacturer suggest that an index of 1.67 and below indicates endothelial dysfunction [15], but in general an RHI below 2.0 is considered as dysfunction, whereas a higher index is categorised to reflect normal endothelial function [16]. An alternative method when calculating the reactive hyperaemia response has been proposed by researchers in the Framingham Heart Study [14]. The Framingham reactive hyperaemia index (fRHI) has shown to have stronger overall association with cardiovascular risk factors. fRHI is calculated from the 90 to 120-second interval after cuff deflation and applies natural logarithmic transformation to the final ratio [14,17]. Furthermore, this model does not include the baseline correction factor. However, the original PAT-RHI is still the most used method when calculating the hyperaemic response.

Another outcome when assessing endothelial function by PAT is the augmentation index (AI) that measures arterial stiffness. This parameter is calculated via pulse waveform analysis from the PAT signal collected. The software identifies the systolic peak (P_1) and the reflected wave's peak (P_2) (Fig. 4). The peak points are incorporated into the final formula: AI = (P2 – P1)/P1 × 100. The difference between the peaks characterise the degree to which arterial stiffness increases central systolic blood pressure [17]. Lower AI reflects better arterial elasticity. The AI is further standardised to a heart rate of 75 bpm since heart rate can influence the pulse waveform [17].

3. Reproducibility and carry-over effect

In a cohort of adult patients with diabetes and vascular diseases (n = 123), PAT examination was performed twice a day with an interval of 2–6 hours between measurements [18]. Mean RHI