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Reactive hyperemia-peripheral arterial tonometry is useful for assessment of not only endothelial function but also stenosis of the digital artery

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ABSTRACT

Background: Although reactive hyperemia-peripheral arterial tonometry (RH-PAT) is widely used for assessment of endothelial function, RH index (RHI) cannot be measured in some cases when pulse wave amplitude (PWA) is very low. Decrease in PWA is mainly caused by proper palmar digital artery (PPDA) stenosis. The purpose of this study was to evaluate the relationship between PWA measured by RH-PAT and stenosis of the PPDA measured by digital subtraction angiography and to evaluate the limitation of assessment of endothelial function measured by RHI in patients with PPDA stenosis.
Methods: We measured baseline PWA in 51 fingers including the first to third fingers of both hands in 10 patients who had PPDA stenosis and in 66 fingers that were the first fingers of both hands in 33 subjects who had no PPDA stenosis. Severe stenosis was defined as over 75% by lower percent diameter stenosis between two PPDAs in a finger.
Results: PWA was significantly correlated with stenosis of the digital artery ($r = -0.55$; $P < 0.0001$). A PWV value of 300 mV was the optimal cut-off value for severe stenosis (sensitivity, 84.0%; specificity, 88.5%). Log RHI was significantly lower in patients with PPDA stenosis than in subjects without PPDA stenosis (0.33 ± 0.27 versus 0.73 ± 0.27, $P = 0.007$).
Conclusions: RH-PAT may be useful for assessment of not only endothelial function but also PPDA stenosis. RHI may be underestimated in patients with PPDA stenosis. We should pay attention to low baseline PWA when measuring RHI.
Clinical trial registration information: URL for clinical trial: http://UMIN; registration number for clinical trial: UMIN000003409.

1. Introduction

It is well established that reactive hyperemia index (RHI) measured by RH-peripheral arterial tonometry (RH-PAT) is used for assessment of endothelial function. Endothelial dysfunction is the early stage in the pathogenesis of atherosclerosis [1]. Measurement of RHI is noninvasive and is mediated by nitric oxide (NO) release. Several investigators have shown that endothelial function assessed by RHI is a prognostic predictor of cardiovascular events [2–5]. RHI measured by RH-PAT offers an easy and rapid assessment of endothelial function.

In some cases, we cannot measure RHI. In general, a small finger size or long fingernails interfere with the measurement of RHI due to low pulse wave amplitude (PWA) [6]. Decrease in PWA when measuring RHI is mainly caused by proper palmar digital artery (PPDA) stenosis. Therefore, it is thought that PPDA stenosis caused by Buerger disease, atherosclerotic peripheral artery disease, and collagen diseases contributes to the decrease in PWA and that baseline PWA measured by RH-PAT may

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enable an assessment of stenosis of PPDA. The purpose of this study was to 1) evaluate the relationship between baseline PWA measured by RH-PAT and grade of PPDA stenosis measured by angiography in patients with PPDA stenosis, to 2) evaluate the limitation of assessment of endothelial function measured by RH-PAT in patients with PPDA stenosis and to 3) evaluate the effect of vasodilator on PWA.

2. Methods

2.1. Study protocol 1: relationship between baseline PWA and PPDA stenosis

We studied 60 fingers including the first to third fingers of both hands in 10 consecutive patients with PPDA stenosis (9 men and 1 woman; mean age, 45 ± 17 yr) and 66 fingers that were the first fingers of both hands in 33 consecutive patients without PPDA stenosis (20 men and 13 women; mean age, 52 ± 16 yr). Nine of the 60 fingers in patients with PPDA stenosis, including 2 amputated fingers, 2 fingers with amputated fingers on the other side, 2 fingers with ulcers, and 3 fingers with noisy signal quality of PWA were excluded. Finally, 10 patients with PPDA stenosis (51 fingers) and 33 patients without PPDA stenosis (66 fingers) were enrolled from Hiroshima University Hospital. The patients with PPDA stenosis included 8 patients with Buerger disease and 2 patients with atherosclerotic peripheral artery disease. Patients with PPDA stenosis underwent hand angiography to evaluate stenosis of digital arteries. Buerger disease was diagnosed by previous criteria [7], including results of physical examinations, clinical symptoms, angiographic findings, and results of arterial duplex scanning. To rule out other vasculitis and hypercoagulable states, rheumatoid factor, lupus anticoagulants, and serologic investigations were evaluated. Patients without stenosis of digital arteries underwent digital artery ultrasonography to evaluate a normal artery. We defined a normal artery according to the diagnostic criteria in guidelines of noninvasive vascular laboratory testing from the American Society of Echocardiography and the Society of Vascular Medicine and Biology [8]. The diagnostic criteria used for a normal artery were no change in peak systolic velocity ratios from the common PPDA to distal PPDA and a triphasic waveform. Subjects with Raynaud's were excluded. Hypertension was defined as systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg, in a sitting position, on at least three different occasions. Normotension was defined as systolic blood pressure of <140 mm Hg and diastolic blood pressure of <90 mm Hg. Diabetes was defined according to the American Diabetes Association or a previous diagnosis of diabetes [9]. Dyslipidemia was defined according to the third report of the National Cholesterol Education Program [10]. The ethical committees of our institutions approved the study protocol. Written informed consent for participation in the study was obtained from all of the subjects.

The subjects fasted and refrained from smoking the previous night for at least 12 h. The study began at 8:30 AM. The subjects were kept in the supine position in a quiet, dark, air-conditioned room (constant temperature of 22 °C–25 °C) throughout the study. A 23-gauge polyethylene catheter was inserted into the left deep antecubital vein to obtain blood samples. Thirty minutes after maintaining the supine position, RHI was measured and digital arterial ultrasonography was performed.

2.2. Study protocol 2: relationship between RHI and PPDA stenosis

RHI was evaluated in the same manner as that in study 1 in 9 of the 10 patients with PPDA stenosis (8 men and 1 women; mean age, 48 ± 14 yr) and in 9 age-, sex-, prevalence of hypertension-, prevalence of dyslipidemia-, prevalence of diabetes mellitus-, and smoking status-matched patients without PPDA stenosis (8 men and 1 women; mean age, 48 ± 20 yr). The definition of RHI in patients with PPDA stenosis was the highest value of RHI among the first to third fingers including 25% to 74% stenosis of the finger's artery, excluding over 75% stenosis of finger arteries. One of the 10 patients with PPDA stenosis who had >75% stenosis of the PPDA was excluded.

2.3. Study protocol 3: effect of nitroglycerine on PWA

We studied 14 fingers including the first fingers of both hands in 7 consecutive patients with PPDA stenosis (6 men and 1 woman; mean age, 53 ± 13 yr) and 66 fingers that were the first fingers of both hands in 33 consecutive patients without PPDA stenosis (20 men and 13 women; mean age, 52 ± 16 yr). PWA was assessed before and after administration of a sublingual tablet (75 μg nitroglycerine) to evaluate nitroglycerine-induced vasodilation. Images of PWA were recorded continuously for a period of 210 s beginning exactly 3 min after administration of sublingual nitroglycerine.

2.4. Measurements of PWA and RHI

Peripheral arterial PWA was measured using a PAT device that was placed on each first finger (Endo-PAT2000, Itamar Medical, Caesarea, Israel). The inflation pressure of the PAT device was set to 10 mm Hg below diastolic blood pressure or at least 70 mm Hg. After baseline PWA had been recorded from each finger for 3 min, the blood pressure cuff was inflated in the test arm for 5 min to whichever inflated pressure would be higher: 200 mm Hg or 60 mm Hg plus systolic blood pressure. PWA was recorded simultaneously from both fingers. After the cuff had been deflated, PWA was recorded for up to 5 min. Baseline PWA and the ratio of PAT were calculated automatically through a computer algorithm (Itamar Medical). Log-transformed RHI (Log RHI) was calculated for subsequent analysis. In patients with PPDA stenosis, baseline PWA and RHI on each first finger to third finger were evaluated. The examination interval of each finger was over 30 min after the previous examination. We only calculated semi-automatically baseline PWA by selecting a baseline segment and a test segment when PWA was very low. Intra-coefficient of variation for baseline PWA was 6.0% in our laboratory.

2.5. Digital subtraction angiography and quantitative angiography

All of the 10 patients with PPDA stenosis underwent intra-arterial digital subtraction angiography (DSA). Conventional DSA was performed with a 4 French sheath via brachial artery access using a DSA unit (Siemens-Asahi Medical, Tokyo, Japan). Five mL of iopromidum was injected at a rate of 1 mL/s using a power injector. Analysis of DSA studies by quantitative vascular analysis (QVA) (QVA-CMS, Medis, Leiden, The Netherlands) was performed for the common PDA to PPDA. Percent diameter stenosis (%DS) was defined as the narrowest diameter of the residual lumen compared with the lumen diameter of the common PPDA. Stenosis of each finger's artery was defined in two ways: 1) by better %DS of PPDAs in a finger and 2) by mean %DS of the radialis PPDA and %DS of the ulnaris PPDA. The following classification was used: 0% stenosis, 0% to 10% stenosis; 25% stenosis, 10% to 25%; 50% stenosis, 25% to 49% stenosis; 75% stenosis, 50% to 74% stenosis; 90% stenosis, 75% to 89% stenosis; 99% stenosis, 90% to 99% stenosis; 100% stenosis, 100%. The definition of severe stenosis of each finger's artery was 75% or over.

2.6. Evaluation of PPDA ultrasonography

The ultrasonography unit Aloka-α7 (Aloka Co, Tokyo, Japan) equipped with a linear, phased-array high-frequency (13-MHz) transducer was used for scanning the PPDA. Digital arterial ultrasonography was evaluated according to standard techniques [8]. The duplex scanner simultaneously provides a B mode ultrasound image and a pulsed Doppler flow to detect velocity changes at specific locations along visualized arteries. Digital arterial ultrasonographic parameters were evaluated by peak systolic ratios from the common PPDA to distal PPDA and waveform [11]. A normal artery was defined as no change of peak systolic ratios and triphasic waveform or color Doppler ultrasound longitudinal images without artery diameter narrowing [12].

2.7. Statistical analysis

Results are presented as means ± SD for continuous variables and as percentages for categorical variables. Statistical significance was set at a level of $P < 0.05$. Continuous variables were compared by using ANOVA multiple groups. Categorical variables were compared by means of the χ^2 test. Relationships between variables were determined by Spearman correlation coefficients analysis. Baseline PWA cutoff values were evaluated on the basis of receiver-operating characteristic curve analysis using the Youden index. We created matched pairs (1 patient with stenosis of the PPDA to 1 patient without stenosis of the PPDA). The effects of nitroglycerine on PWA was analyzed by the paired Student's *t*-test. The data were processed using the software package Stata, version 9 (Stata Co, College Station, TX).

3. Results

3.1. Study protocol 1: relationship between baseline PWA and PPDA stenosis

The baseline clinical characteristics of the 10 patients with PPDA stenosis and 33 patients without PPDA stenosis are summarized in Table 1. eGFR, proportion of past smokers and proportion of patients taking antiplatelets were significantly higher in patients with PPDA stenosis than in patients without PPDA stenosis. Total cholesterol, low-density lipoprotein cholesterol, prevalence of hypertension and prevalence of dyslipidemia were significantly lower in patients with PPDA stenosis than in patients without PPDA stenosis. There were no significant differences in other parameters between patients with PPDA stenosis and patients without PPDA stenosis.

The baseline clinical characteristics of the 10 healthy subjects and 23 patients without PPDA stenosis are summarized in Supplemental Table S1. Age, body mass index, systolic blood pressure, diastolic blood pressure, prevalence of hypertension, prevalence of dyslipidemia, proportion of smokers, proportions of patients taking calcium channel blockers, angiotensin II receptor blockers and statins, and proportion of patients with medically treated diabetes mellitus were significantly higher in patients without PPDA stenosis than in healthy subjects. There were no significant differences in other parameters between patients without PPDA stenosis and healthy subjects. Fig. 1 shows representative data for the classification of stenosis, DSA of PPDA and baseline PWA.