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Disparity between EndoPAT measurement and brachial artery flow-mediated vasodilatation in hypertensive patients

Bonpei Takase, MD, Yuko Higashimura, MS and Kenichi Hashimoto, MD

Abstract:

Background: EndoPAT measurement has been reported to be well correlated with brachial artery flow-mediated vasodilatation (FMD) in coronary artery disease. However, this relation is still controversial in hypertensive patients or normal subjects and the pathophysiological mechanisms of EndoPAT index is still not completely clarified. **Purpose:** The purpose of this study is to investigate the correlation of EndoPAT index with FMD and the physiological role of EndoPAT index in hypertension. **Methods:** To study this aim, we simultaneously measured EndoPAT index (RHI) and FMD by forearm occlusion technique, that is reported to be nitric oxide (NO) dependent, in 47 hypertensive patients without hypertensive complication (62±11 years old). BaPWV and augmentation index (AI@75bpm) by EndoPAT were also measured at the same time. **Results:** RHI did not correlate with FMD nor baPWV (r= 0.17, NS) while FMD also did not correlate with baPWV (r=0.08, NS). However, baPWV significantly correlated with AI@75bpm by EndoPAT (r=0.50, p<0.01). **In conclusion:** Augmentation index expressed as AI@75bpm by EndoPAT was associated with arterial stiffness measured by baPWV. However, there is no correlation between EndoPAT index of RHI and FMD in hypertensive patients, suggesting that the indexes reflect partially different vascular functions.

Key words:

FMD, EndoPAT2000, PWV, Hypertension

Introduction

Brachial artery (BA) flow-mediated vasodilatation (FMD) and nitroglycerin-induced dilation (NMD) in brachial artery (BA) is well known indices for evaluating endothelial function. However, especially FMD measurements are sometimes difficult and the reproducibility is limited despite well-established guideline[1-3]. Well-equipped UNEXEF18G system in Japan, that has recently been developed, as the semi-automatic image chasing measurement system, can precisely measure BA FMD[4]. In contrast to FMD, EndoPAT measurement has less bias for measurement and has excellent reproducibility[5,6]. In addition, hypertension is well known and common disorder to impair endothelial function[7]. For measuring the aortic stiffness caused by atherosclerosis, brachial-ankle pulse wave velocity (baPWV) an arterial augmentation index also has been utilized as the prognostic and diagnostic modality in the routine clinical practice[8]. The latter could be partly assessed by EndoPAT measurement.

In the previous report[9], EndoPAT measurement has been reported to be well correlated with BA FMD in coronary artery disease. However, this relation is still controversial in hypertensive patients or normal subjects and the pathophysiological measure of EndoPAT index is still not completely clarified.

Thus, to investigate the physiological role of EndoPAT index in hypertension, we simultaneously measured EndoPAT index (RHI) and FMD by forearm occlusion technique, that is reported to be nitric oxide (NO) dependent, in hypertensive patients without complication. In addition, baPWV and augmentation index (AI@75bpm) by EndoPAT were measured at the same time.

Methods

Study population and protocol

The study population consisted of 47 patients (27 men

Department of Intensive Care Medicine, National Defense Medical College, Japan
Corresponding author: Bonpei Takase, dui1577@db3.so-net.ne.jp
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and 20 women; age, 63.2±10.6 years) who have visited our outpatient clinic of cardiology department in National Defense Medical College hospital under the diagnosis of hypertension without any complications. FMD and RHI have been approved by public insurance in Japan, and recommended in the guideline of Japanese Circulation Society for patient care[10]. The 37 subjects were also registered in FMD-J multi-center observational study[11], whereas the rest of 10 subjects were enrolled only for this investigation. Secondary hypertension such as primary aldosteronism and the patients with either renal artery stenosis or chronic renal failure had been worked out and excluded from the selection for study population. Additional exclusion criteria were as follows: 1) the presence of atrial fibrillation or diabetes mellitus; 2) advanced heart block; 3) any malignant disorders; 5) any other acute disorders; or 6) severe hypertensive patients who experienced hypertensive crisis. To use the patient's any information for this study, written informed consent was obtained from each patient and this clinical study was approved by institutional review board.

Blood pressure (BP), heart rate (HR) and body weight measurement

BP measurements were followed by the guideline of American Heart Association Scientific Statement[12]. The patients were asked to take away all clothing that covered the position of the cuff placement. And they were comfortably seated and the cuff on the upper arm was placed at the level of right atrium. The patients were instructed to relax, and at least 5 min passed before the BP measurement was carried out. All study patients had systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg when BP was obtained in the sitting position at outpatient clinics. BP was measured by Korotkoff's method using a sphygmomanometer. HR was directly obtained by stethoscope attached on the precordial region of the chest wall. Body weight was also measured at outpatient clinic.

Measurement of baPWV

The brachial-ankle PWV was measured using a volume plethysmographic apparatus (Form/ABI, Colin Co. Ltd., Komaki, Japan), in accordance with a previously described methodology[13,14]. In brief, occlusion cuffs, which were connected to both the plethysmographic and oscillometric sensors, were positioned around both the upper arms and ankles of the subjects lying in the supine position. The brachial and post-tibial arterial pressures were measured using the oscillometric sensor. The measurements were performed after the subjects had rested for at least 5 min in the supine position, in a temperature-controlled room (25℃) designed exclusively for this purpose.

Ultrasound FMD and RHI measurements in the brachial artery

All ultrasound studies were done in a temperature-controlled room (25℃) with the subject in a fasting, resting, and supine state from approximately 14:00 to 17:00. Heavy meals, including a high fat diet and caffeine-containing beverages, were prohibited beginning the night before the study. Patients were not allowed to have lunch on the day of ultrasound study. BP and HR were recorded from the left arm every 3 min with an automatic sphygmomanometer (Nihon Korin, BP-203, Tokyo, Japan) during the ultrasound procedure. Vasodilatation responses of the brachial artery were determined by the ultrasound technique using a semi-automatic device (EF18G; UNEX, Nagoya, Japan). Briefly, the diameter of the brachial artery was measured from B-mode ultrasound images using a 10-MHz linear array transducer. Then, a BP cuff was inflated to 50 mmHg above the systolic BP over the proximal portion of the right forearm for 5 min. The diastolic diameter of the brachial artery was determined semi-automatically using an instrument equipped with software for monitoring the brachial artery diameter. The changes in the diastolic diameter were continuously recorded. Then, FMD was determined as the maximum change in diameter after cuff release normalized to the baseline diameter (% of baseline diameter). Calculation of these values by the EF18G in our laboratory showed that both the intra- and inter-observer variability (coefficient of variation) for repeated measures of diameter before and after reactive hyperemia in the brachial artery were < 3%[15,16].

Assessment of endothelial function by reactive hyperemia peripheral arterial tonometry (RHI measure) was simultaneously assessed by reactive hyperemia peripheral arterial tonometry using the EndoPAT2000 system (Itamar Medical, Caesarea, Israel) with FMD. As described previously[17], RHI was automatically calculated, and there is minimal inter-operator and intra-operator variability. Since FMD and RHI was measured simultaneously, RHI studies were performed when patients were in stable as described above. The RHI value that reflected the extent of reactive hyperemia was calculated as the ratio of the average pulse amplitude of EndoPAT2000 system signal over a 1-minute time interval starting 1.5 min after cuff deflation to the average pulse amplitude of EndoPAT2000 system signal of the 2.5-minute time period before cuff inflation (baseline). The RHI value was calculated by the EndoPAT2000 system. In addition, augmentation index (AI@75bpm) by EndoPAT was measured as arterial augmentation index. As mentioned earlier, previous studies have demonstrated that RHI has excellent reproducibility[17,18].

Statistical Analysis

Data are expressed as the mean ± SD. Even if the sample size was small, the histogram of each sample were not skewed (data not shown) so that we presumed each samples in this study were drawn from normally distributed data. Parametric statistical methods were subsequently utilized. Pearson product-moment correlation was performed between RHI, FMD, baPWV or augmentation index (AI@75bpm) by EndoPAT. Differences or statistical values were considered significant at $p<0.05$.

Table 1. Summarized clinical characteristics of the study population

	Study patients (n=47)
Age, years	63.2±10.6
Male/Female	27/20
Complications or comorbidities	
Hypercholesterolemia, %	11 (23%)
Hyperuricemia, %	4 (9%)
Combination treatment	
ARB , %	23 (48%)
CCB, %	38 (81%)
β blocker, %	5 (11%)
Statin, %	11 (23%)

Hypercholesterolemia, total cholesterol>220 mg/dl; Hyperuricemia, >7.0 ml/dl; ARB, Angiotensin II Receptor Blocker; CCB, calcium channel blocker; data are expressed as mean±SD or % in parenthesis

Table 2. Summary of body weight and ultrasound measurements of flow-mediated dilation in the brachial artery, brachial-ankle pulse wave velocity and indices in EndoPAT2000 system

Body weight, kg	64±16
Systolic BP, mmHg	136±12
Diastolic BP, mmHg	84±12
Heart rate, beats/min	69±11
Brachial artery diameter at baseline, mm	4.32±0.64
FMD, %	6.23±2.79
RHI	1.95±0.52
baPWV (cm/s)	1697±0.52
Augmentation index by EndoPAT	27±20

Data are expressed as mean±SD; BP, blood pressure; FMD, flow-mediated dilation; RHI, reactive hyperemic index; baPWV , brachial-ankle pulse wave velocity

Results

Patient Profile

The present study population consisted of 47 patients and the clinical characteristics are shown in **Table 1**. Mean age in study group was approximately 63 years. All patients had a clinically diagnosed hypertension. Approximately 23% of patients had hypercholesterolemia, and 4% had hyperuricemia. Combination medical treatment is also described in **Table 1**. As shown in the **Table 1**, 48% of patients have angiotensin II receptor blocker, 11% β blocker, and 23% statin treatment, and 81% patients had calcium channel blocker therapy. Hemodynamic and brachial artery diameter as well as the values of RHI, FMD, baPWV and augmentation index (AI@75bpm) by EndoPAT were listed in **Table 2**.

Correlation among RHI, FMD, and baPWV and augmentation index (AI@75bpm) by EndoPAT

Correlation between FMD and RHI, that between RHI and baPWV, that between FMD and baPWV and that between FMD and augmentation index (AI@75bpm) by EndoPAT were not significantly observed as shown in **Figure 1-4**. However, baPWV significantly correlated with augmentation index (AI@75bpm) by EndoPAT (**Figure 5**).

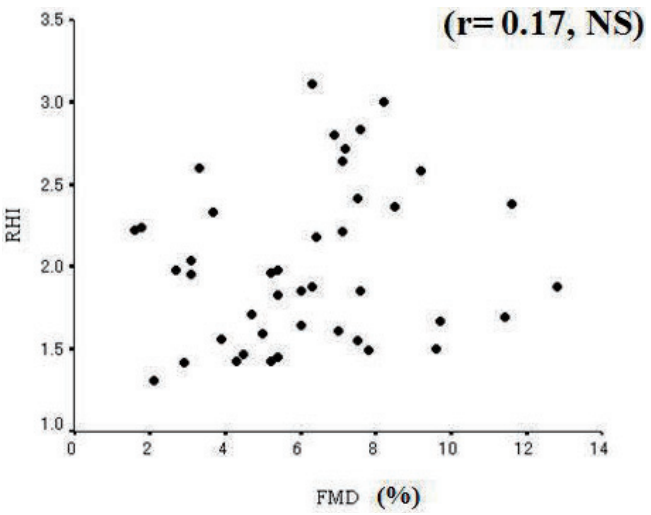

Figure 1. Relation between FMD and RHI
There was no significant correlation between them. FMD, flow-mediated vasodilatation; RHI, reactive hyperemic index assessed by EndoPAT.

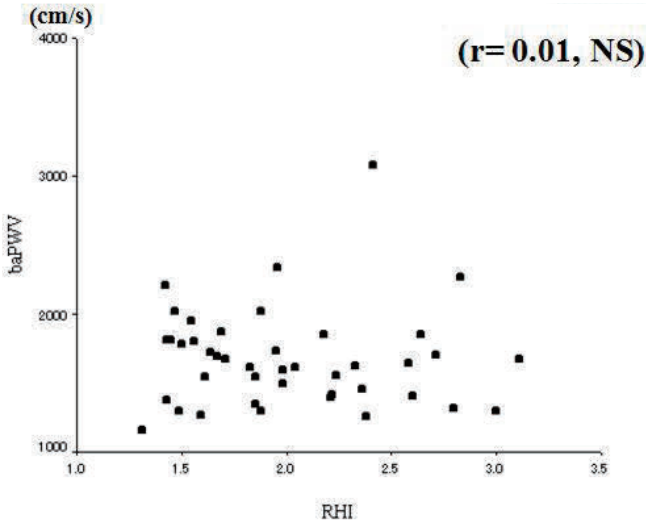

Figure 2. Relation between RHI and baPWV
There was no significant correlation between them. RHI, reactive hyperemic index assessed by EndoPAT; baPWV, brachial-ankle pulse wave velocity.

Discussion

The present study demonstrated that EndoPAT index of RHI might have different physiological property from FMD mainly reflecting NO metabolism, because the correlation between RHI and FMD was poor. Moreover, EndoPAT index of AI@75bpm was significantly correlated with baPWV in the hypertensive patients, suggesting AI@75bpm can be a useful index for arterial atherosclerotic changes as well as

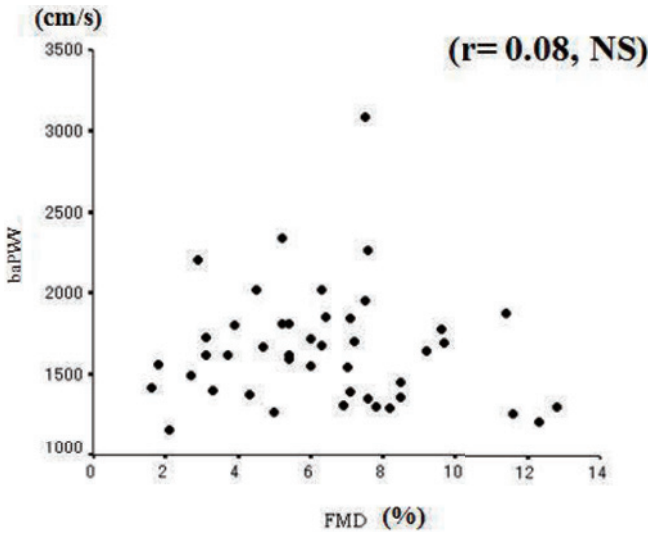

Figure 3. Relation between FMD and baPWV
There was no significant correlation between them. FMD, flow-mediated vasodilatation; baPWV, brachial-ankle pulse wave velocity.

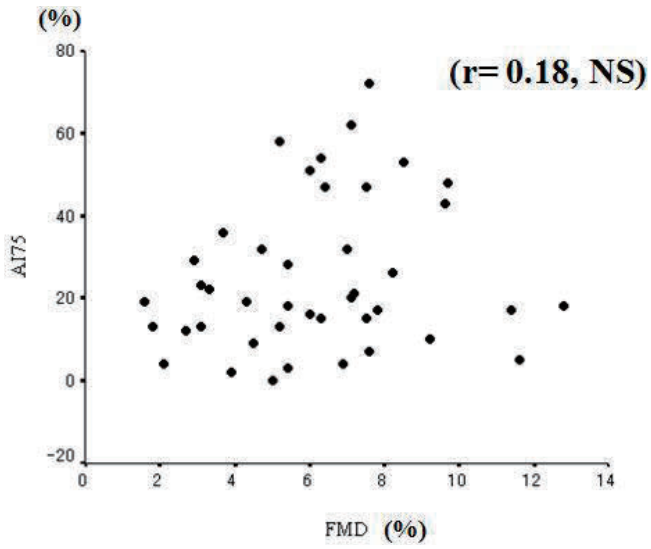

Figure 4. Relation between FMD and AI75
There was no significant correlation between them. FMD, flow-mediated vasodilatation; AI75, augmentation index (AI@75 bpm) by EndoPAT.

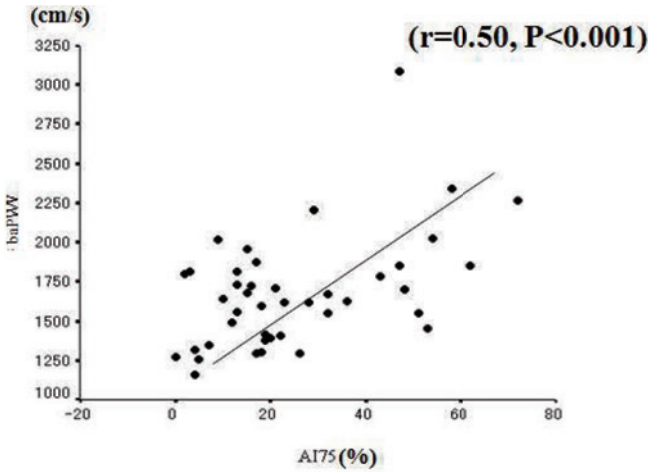

Figure 5. Relation between baPWV and AI75
There was significant correlation between them. baPWV, brachial-ankle pulse wave velocity; AI75, augmentation index (AI@75 bpm) by EndoPAT.

baPWV. EndoPAT index of RHI could reflect not only NO, but also endothelial derived prostaglandin I_2 (PGI_2) or endothelium-derived hyperpolarization factor (EDHF) in hypertensive patients. In contrast, AI@75bpm by EndoPAT could measure arterial elasticity and/or stiffness because baPWV reflects arterial elasticity while augmentation index expressed as AI@75bpm by EndoPAT can associate with arterial stiffness.

The relation among the indices measured in this hypertensive cohort was weak and these results support the above suggested conclusions. A shown in **Figure 1** to **Figure 3**, there were no correlation between RHI and FMD and between baPWV and either RHI or FMD. The correlation between AI@75bpm by EndoPAT and FMD was also not significant. Only significant correlation was observed between baPWV and AI@75bpm by EndoPAT. Since our hypertensive population was relatively homogeneous, these correlations are suggested to be significantly consistent findings for considering the relations among these indices in hypertensive patient. The results in this study are significant for these indices to be applied to the clinical practice.

The results in this study might not agree with the previous report[9,19], however, the study population is different between the studies. In the patients with coronary artery disease, RHI is reported to be significantly correlated with FMD. The reason why the concordant result was not obtained is not clarified by our study, however, the difference in patient population could be one of the explanation for this difference.

Even if the physiological backgrounds are different among the non-invasive vascular assessment indices of RHI by EndoPAT, FMD, baPWV, and augmentation index (expressed as AI@75bpm by EndoPAT), these parameters have separately been reported to predict the prognosis of cardiovascular diseases[20-23]. Any of these indices are thought to be useful in the clinical settings. However, some of these indices seem to be independent. The combination assessment such as RHI with FMD, baPWV or augmentation index could have a potential benefit for predicting untoward outcome of the patients with any significant atherosclerotic risk factors or the patients with overt cardiovascular disorders. Therefore, these evaluations are preserved as the further investigation of these indices.

Study Limitations

First, this study is cross sectional retrospective single center study and the numbers of study patients are small so that the power of the study is limited. In order to confirm our re-

sults and speculation, the results of FMD-J multi-center clinical trial[11] should be obtained and reviewed. Second, we performed endothelial function tests using simultaneous measures of FMD and RHI. However, we did not measure NMD, which is independent measure of endothelial function. To precisely measure endothelial function by FMD method, NMD should be measured. However, NMD measurement is out of our scope of purpose. In general, when endothelial function is preserved by FMD technique, NMD, that is the reflection of vascular smooth muscle function, is also well preserved so that NMD is presumed to be considered near normal in the present study.

Conflicts of Interest

The authors declare that we have no conflicts of interest.

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