Original Article

Relationship between Augmentation Index and Flow-Mediated Vasodilation in the Brachial Artery

Junko SOGA¹⁾, Shuji NAKAMURA²⁾, Kenji NISHIOKA²⁾, Takashi UMEMURA²⁾,
Daisuke JITSUIKI²⁾, Takayuki HIDAKA¹⁾, Hiroki TERAGAWA¹⁾, Hiroaki TAKEMOTO¹⁾,
Chikara GOTO²⁾, Masao YOSHIKUMI²⁾, Kazuaki CHAYAMA¹⁾, and Yukihiro HIGASHI²⁾

Recent studies have shown that the augmentation index (AI) is a predictor of cardiovascular complications. Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis, which in turn can lead to cardiovascular complications. Endothelial function assessed by flow-mediated dilation (FMD) can serve as an independent predictor of cardiovascular events. However, there is little information on the relationship between AI and FMD in the human vasculature, and we therefore investigated this relationship in the present study. A total of 100 subjects (71 males and 29 females; age range, 22–88 years; mean age, 59±17 years), including 83 patients with cardiovascular diseases (e.g., atherosclerosis, hypertension, coronary heart disease, stroke and peripheral arterial disease) and 17 healthy subjects were enrolled. High-resolution ultrasonography (automated vessel-diameter measurements; eTRACKING system), a linear array transducer (13 MHz) and an arm holding device were used to measure the arterial diameter response to reactive hyperemia and sublingual nitroglycerine (NTG, 75 µg) in all subjects. AI measured using an automated device was significantly correlated with FMD ($r=-0.38$, $p<0.0001$). There was no significant correlation between AI and vascular response to NTG. Multiple regression analysis showed that FMD was a significant independent predictor of AI ($p<0.05$). These findings suggest that increase in arterial stiffness may be associated with grade of endothelial dysfunction and that AI may be an index of not only arterial stiffness but also endothelial function. (*Hypertens Res* 2008; 31: 1293–1298)

Key Words: augmentation index, arterial stiffness, flow-mediated vasodilation, endothelial function

Introduction

Recent studies have shown that the augmentation index (AI) is a predictor of cardiovascular complications (1, 2). AI is a measure of the contribution of wave reflection to the arterial pressure waveform. The amplitude and timing of the reflected wave ultimately depend on the stiffness of small vessels and large arteries. Therefore, AI provides a measure of systemic arterial stiffness and is a parameter of vascular structure (3). In addition, AI may reflect vascular function.

Previous reports on cardiovascular assessment have dealt

mainly with aortic AI (A_{Ia}), but recently there has been increasing evidence that not only A_{Ia} but also radial AI (A_{Ir}) is a marker or predictor of cardiovascular complications (4, 5). Measurement of A_{Ir} is safe and feasible. We therefore substituted A_{Ir} for A_{Ia} in this study.

Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis, which in turn can lead to cardiovascular complications (6). The vascular endothelium is involved in the release of various vasodilators, including nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarizing factor, as well as vasoconstrictors (7, 8). NO plays an important role in the regulation of vascular tone, inhibition of plate-

From the ¹⁾Department of Medicine and Molecular Science and ²⁾Department of Cardiovascular Physiology and Medicine, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan.

Address for Reprints: Yukihiro Higashi, M.D., Ph.D., Department of Cardiovascular Physiology and Medicine, Hiroshima University Graduate School of Biomedical Sciences, 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan. E-mail: yhigashi@hiroshima-u.ac.jp

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let aggregation, and suppression of smooth muscle cell proliferation (9, 10). Impaired endothelium-dependent vasodilation has been found in the forearm, coronary, and renal vasculatures in patients with hypertension (11–16), hypercholesterolemia (17, 18), diabetes mellitus (19, 20), and coronary artery diseases (21–23). Measurement of flow-mediated vasodilation (FMD) in the brachial artery using ultrasound is noninvasive and is an accurate indicator of NO production (6, 24–28). It is accepted that measurement of FMD is an index of conduit artery endothelial function. Endothelial function assessed by FMD can serve as an independent predictor of cardiovascular events (8, 29).

It has long been suspected that there is a relationship between AI and endothelial function, and indeed, several recent studies using human subjects seem to confirm that such a relation exists. In those studies, endothelial function was assessed using pulse wave analysis by calculating AIa from derived aortic waveforms. There is little information on the relationship between AIr and FMD in the human vasculature and we therefore investigated this relationship in the present study.

Methods

Subjects

One hundred subjects (71 males and 29 females; age range, 22–88 years; mean age, 59 ± 17 years), including 83 patients with cardiovascular diseases or risk factors of atherosclerosis, including hypertension ($n=53$), hyperlipidemia ($n=51$), diabetes mellitus ($n=22$), coronary heart disease ($n=39$), stroke ($n=8$) and peripheral arterial disease ($n=8$), and 17 healthy subjects were enrolled. A series of inpatients who agreed to participate in this study and healthy volunteers were recruited in Hiroshima University Hospital during the period from June 2005 to April 2007. The Ethics Committee of Hiroshima University Graduate School of Biomedical Sciences approved the study protocol. Informed consent for participation in the study was obtained from all subjects.

Measurement of AIr

All studies were performed in the morning, after overnight fasting, in a dark, quiet air-conditioned room (constant temperature of 22–25°C). Subjects rested quietly in the sitting position for 15 min before examinations.

Arterial stiffness was assessed by noninvasive measurement of AIr. The measurement was carried out using an automated applanation tonometer coupled to computer-assisted analysis software (HEM9000AI; Omron Healthcare Co., Kyoto, Japan). The details of this device have been described previously (5). Briefly, the device consists of three units: a sensor unit, a pulse measurement unit, and an expression unit that has an automatic cuff oscillometric device to measure brachial blood pressure. The sensor unit has a pressure sensor

Table 1. Clinical Characteristics of Subjects

Variables	
Gender, male/female	71/29
Age, years	59 ± 17
Body mass index, kg/m ²	24.2 ± 3.7
Systolic blood pressure, mmHg	131.0 ± 15.0
Diastolic blood pressure, mmHg	74.2 ± 13.3
Heart rate, bpm	70.3 ± 10.6
Glucose, mmol/L	6.0 ± 2.1
Total cholesterol, mmol/L	5.20 ± 0.94
Triglyceride, mmol/L	1.70 ± 0.91
HDL cholesterol, mmol/L	1.44 ± 0.43
LDL cholesterol, mmol/L	3.02 ± 0.86
Hypertension, <i>n</i>	53
Hyperlipidemia, <i>n</i>	51
Diabetes mellitus, <i>n</i>	22
Coronary heart disease, <i>n</i>	39
Stroke, <i>n</i>	8
Peripheral arterial disease, <i>n</i>	8
Smoker, <i>n</i>	44

$n=100$. All results are presented as mean $\pm$ SD. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

with an array of forty microtransducer elements on its inner surface. The sensor is placed on the left wrist over the radial artery, and the device automatically flattens the artery, adjusts the applanation hold-down pressure, and selects an optimal sensing element to record the pulse wave appropriately. Continuous steady-state data are recorded over a period of 30 s. AI was defined as the ratio of the amplitude of the second systolic peak to the amplitude of the first systolic peak. AI was determined for each pulse, and the mean value for all pulses assessed over a period of 30 s was used for analysis. Because the heart rate has been shown to be a possible confounder in the determination of AI, we normalized the obtained AIr values for a heart rate of 75 bpm (2, 30).

Measurement of FMD

Following the measurement of AI, the subjects rested in the supine position quietly for 15 min before examinations and remained in the supine position throughout the study.

The vascular response to reactive hyperemia in the brachial artery was assessed in accordance with the guidelines for ultrasound assessment of endothelium-dependent FMD (31). The details of FMD measurement have been described previously (28). Briefly, the subjects underwent a study of vascular function using ultrasound equipment and a high-resolution linear artery transducer (13 MHz) coupled to computer-assisted analysis software (e-TRACKING system; Aloka Co., Tokyo, Japan) that used an automated edge detection system for measurement of the brachial artery diameter. To ensure consistency of the image, the right arm of the subject was

Table 2. Vascular Studies

Variables	
Baseline brachial artery diameter, mm	4.2±0.6
FMD, %	6.1±4.2
NTG, %	11.0±6.7
Increased hyperemic flow, %	325±183
Radial augmentation index, %	79.5±15.9

n=100. All results are presented as mean±SD. FMD, flow-mediated vasodilation; NTG, nitroglycerin-induced vasodilation.

fixed by a special arm-holding device (MIST-100; Saraya Co., Osaka, Japan), and the transducer was held at the same point throughout the scan by a special probe holder (MP-PH0001; Aloka Co.)

The response to nitroglycerine (NTG) was used for assessment of endothelium-independent vasodilation. After acquiring a baseline resting image for 30 s, a sublingual tablet (NTG 75 µg) was given, and an image of the artery was recorded continuously for 5 min. The response of the brachial artery diameter to NTG was immediately expressed as a percent change relative to the vessel diameter. NTG-induced vasodilation was automatically calculated as a percent change in the peak vessel diameter from the baseline value. The %NTG [(peak diameter – baseline diameter)/baseline diameter] was used for analysis.

The coefficient of variation for the baseline diameter was 2.8 % in our laboratory.

Statistical Analysis

Results were presented as the mean±SD. Pearson's correlation analysis was carried out to determine the correlation between clinical variables. Multiple regression analysis was performed to determine the relationships between AIr and age, gender, body mass index, systolic and diastolic blood pressure, serum concentrations of cholesterol and glucose, smoking habits, FMD, and NTG-induced vasodilation. A value of *p*<0.05 was considered to be statistically significant. Multivariate analysis was performed with the SAS program package.

Results

Table 1 shows the baseline clinical characteristics of the subjects. Basal brachial artery diameter, hyperemic blood flow, FMD, vascular response to NTG and AIr are summarized in Table 2. The results of univariate analysis revealed that AI was significantly correlated with FMD and age but not with other clinical variables in all subjects (Table 3). AIr was significantly correlated with FMD (*r*=−0.38, *p*<0.0001), but there was no significant correlation between AIr and vascular response to NTG in all subjects (Fig. 1). AIr tended to be, but not significantly, correlated with FMD in the healthy subjects

Table 3. Correlations of Radial Augmentation Index with Clinical Variables

Variables	<i>r</i>	<i>p</i> value
Age, years	0.57	<0.0001
Body mass index, kg/m ²	0.02	0.87
Systolic blood pressure, mmHg	0.14	0.16
Diastolic blood pressure, mmHg	0.11	0.27
Glucose, mmol/L	0.07	0.59
Total cholesterol, mmol/L	0.04	0.68
Triglyceride, mmol/L	0.05	0.62
HDL cholesterol, mmol/L	0.18	0.12
LDL cholesterol, mmol/L	0.09	0.36
FMD, %	−0.38	<0.0001
NTG, %	−0.19	0.10

All results are presented as mean±SD. HDL, high-density lipoprotein; LDL, low-density lipoprotein; FMD, flow mediated vasodilation; NTG, nitroglycerine.

(*n*=17, *r*=−0.42, *p*=0.07) and in patients with cardiovascular diseases (*n*=40, *r*=−0.28, *p*=0.06). Stepwise multiple regression analysis showed that male gender (*β*=0.309, *p*=0.010) and FMD (*β*=−0.242, *p*=0.040) were independent predictors of AIr in all subjects (Table 4).

Discussion

Recent studies have shown that AI is a predictor of cardiovascular and cerebrovascular complications. AI is a measure of the contribution of wave reflection to the arterial pressure waveform. The amplitude and timing of the reflected wave ultimately depend on the stiffness of small vessels and large arteries. Applanation tonometry is a noninvasive and reproducible method for pulse wave analysis. The technique involves partial flattening of a superficial artery against an underlying bone using a handheld external pressure sensor; the sensor automatically flattens the artery, adjusts the applanation hold-down pressure, and determines the pressure within the artery. The pressure waveform obtained noninvasively by using the sensor is almost identical to the waveform obtained by using an intra-arterial transducer. The most widely used approach is to perform radial artery tonometry. The AI was defined as an index of the augmentation of central blood pressure in systole derived from the return of pressure waves reflected from the periphery. The radial artery pressure waveform is used to derive a central aortic pressure waveform using a mathematical transfer function that has been validated under several different conditions. Several investigators have shown that AI obtained directly from the radial artery pressure waveform provides information similar to that provided by A1a (32–34). Finally, measurement of AIr has been shown to be safe and feasible.

Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis, which in turn can lead to cardiovascular

Fig. 1. Scatter plots showing the relationship between the augmentation index and flow-mediated vasodilation (FMD) and nitroglycerine (NTG)-induced vasodilation in all subjects.

complications (6). Measurement of FMD in the brachial artery is an appropriate method to assess endothelial function in humans, since measurement of FMD is noninvasive and reflects NO production. Several clinical studies have shown that endothelial function assessed by FMD can serve as an independent predictor of cardiovascular events (8, 29). In addition, some interventions, including treatment with antihypertensive agents, treatment with statins, supplementation therapy, treatment with antioxidant vitamins, and lifestyle modifications, have been shown to improve endothelial function and prevent cardiovascular complications (24–26, 35, 36). Therefore, from a clinical perspective, it is important to estimate the grade of the basal condition of endothelial function and of the improvement in endothelial function.

Previous studies have already shown that AI is related to endothelial function in humans. However, endothelial function was assessed as global endothelial function using pulse wave analysis in those studies (37–39). Global endothelial function is obtained by calculating the ratio of changes in pulse wave in response to NTG and albuterol. This method is not a gold standard for assessment of conduit endothelial function and is a burden for subjects. In the present study, we assessed endothelial function by measurement of FMD, which is an index of conduit artery endothelial function. In addition, in previous studies, AI was assessed as AIa (1, 2). Both AIr and AIa are markers or predictors of cardiovascular

Table 4. Multiple Regression Analysis on the Predictor of Radial Augmentation Index

Independent variables	β	p value
Male gender	0.309	0.010
%FMD	−0.242	0.040

FMD, flow mediated vasodilation.

complications. In the present study, we measured AIr using a recently developed device, the usefulness of which has been confirmed in previous studies (4, 5).

In this study we demonstrated that AIr was significantly correlated with FMD, whereas there was no significant correlation between AIr and vascular response to NTG. In addition, multiple regression analysis showed that FMD was a significant independent predictor of AIr. These findings suggest that increase in arterial stiffness may be associated with the grade of endothelial dysfunction and that AIr may be an index of not only arterial stiffness but also endothelial function.

Study Limitations

It is well known that certain antihypertensive agents and statins influence AI or FMD. In the present study, we analyzed the relationship between AIr and FMD in general populations, including healthy subjects and patients receiving pharmacological therapy. We cannot deny the possibility that pharmacological therapy has different effects on the changes in AIr and FMD.

In conclusion, our results suggest that both AI and FMD are surrogate endpoints for cardiovascular outcomes. Measurement of AIr can be more easily performed than measurement of FMD and enables simultaneous assessment of arterial stiffness and endothelial function.

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