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Elevated plasma B-type natriuretic peptide concentration and resistive index, but not decreased aortic distensibility, associate with impaired blood flow at popliteal artery in type 2 diabetic patients

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Abstract. Blood flow in lower extremity arteries is frequently impaired in diabetic patients even though they have a normal ankle-brachial index (ABI 1.0-1.4). Risk factors contributing to this lower extremity arterial disease have not been fully elucidated. We enrolled 52 type 2 diabetic patients with normal ABI and 30 age-matched nondiabetic subjects consecutively admitted to our hospital. Plasma B-type natriuretic peptide (BNP) concentrations were measured. Distensibility in ascending thoracic and abdominal aortas as well as total flow volume and resistive index at popliteal artery were evaluated by gated magnetic resonance imaging. An automatic device was used to measure ABI and brachial-ankle pulse-wave velocity (baPWV). Diabetic patients showed lower distensibility in ascending thoracic aorta (p<0.001) and total flow volume (p<0.001) and higher baPWV (p<0.001) and resistive index (p=0.005) and similar BNP and distensibility in abdominal aorta compared to nondiabetic subjects. Simple linear regression analyses revealed that distensibility in ascending thoracic (p=0.019) and abdominal (p=0.030) aortas positively as well as baPWV (p=0.020), resistive index (p<0.001) and BNP (p<0.001) negatively correlated with total flow volume. Stepwise multiple regression analysis demonstrated that increased BNP and resistive index were independent risk factors for total flow volume in diabetic patients (r^2=0.639, p<0.001). These results indicate that increased plasma BNP levels and peripheral vascular resistance, but not decreased aortic distensibility, associate with impaired blood flow in lower extremity arteries in diabetic patients.

Key words: Lower extremity arterial disease, B-type natriuretic peptide, Aortic distensibility, Peripheral vascular resistance

LOWER EXTREMITY arterial disease is an important cause of ischemic limb, delayed wound healing, lower extremity amputation [1] and subsequent cardiovascular mortality in diabetic patients [2]. Diabetic patients have two types of lower extremity arterial disease associated with changes in vessel wall properties. The diabetic condition is likely to promote atherosclerotic plaque formation in the vessel wall and lead to occlusive peripheral artery disease (PAD). To help identify high risk patients with PAD, ankle-brachial index (ABI) is generally used [3]. The diabetic condition also causes higher arterial rigidity and greater peripheral vascular resistance, resulting in reduced blood flow in the lower-leg arteries even though the individual has no apparent PAD [4]. These patients are characterized by higher incidence of cardiovascular disease events [5]. In Japan, the frequency of diabetic patients with low ABI is 7.6% [6], which is 3-fold higher than that in the general population [7]. The prevalence of diabetic patients with normal ABI accompanied by impaired blood flow in lower-leg arteries is similar to that of diabetic patients with low ABI [8]. Although this lower extremity arterial disease may be one of the major causes of ischemic limb, the contributing risk factors have not been fully elucidated.

Left ventricular function, large artery stiffness and peripheral vascular resistance contribute to arterial blood supply to the lower extremity and these are fre-

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quently impaired in diabetic patients. Plasma B-type natriuretic peptide (BNP) is secreted predominantly from left ventricle in response to ventricular volume expansion and pressure overload. Individuals with type 2 diabetes are at increased risk of heart failure [9] and show elevated plasma BNP levels [10]. The diabetic condition affects the vasculature through a glycation process of the arterial wall and accelerates aortic stiffness [11]. Biopsy specimen from subcutaneous fat demonstrates that diabetic patients have greater peripheral vascular resistance due to endothelial dysfunction or structural alteration in small resistance arteries [12, 13]. In the present study, we attempted to clarify associations of plasma BNP concentration, aortic distensibility and resistive index with total flow volume at popliteal artery in type 2 diabetic patients using gated magnetic resonance imaging.

Material and Methods

Subjects

We considered patients eligible if they fulfilled the following criteria: diagnosis of type 2 diabetes based on Japan Diabetes Society (JDS) criteria, age ranging from 45 to 75 years at the time of enrollment, no history of transient cerebral ischemic attack, cerebral infarction, stable or unstable angina, percutaneous coronary intervention, coronary artery bypass surgery, myocardial infarction or abnormal ABI (<1.0 or >1.4 in either leg) [3]. Screening of the study patients consecutively admitted to our hospital between September 2010 and March 2013 was performed. All patients who met eligibility criteria were asked whether they could participate in the current study and all of the patients who agreed to participate were registered. Of a total of 57 eligible participants, 5 were excluded for the following reasons: high plasma BNP level (n=1) (>62 pg/mL for detecting left ventricular diastolic dysfunction assessed by ratio of peak early to late mitral inflow velocity (E/A) [14] as well as >80 pg/mL for suggesting congestive heart failure [15]), atrial fibrillation (n=2), history of valvular heart disease (n=1) and severe chronic kidney disease having estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2 (n=1). A total of 52 asymptomatic diabetic patients were consecutively recruited for the study. No participants had pacemaker or defibrillator implantation, dyspnea precluding 12 second breath hold and claustrophobia, alcohol abuse or liver cirrhosis. Statins were used for the treatment of low-density lipoprotein (LDL) cholesterol ≥120 mg/dL. Angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) was used for the management of high blood pressure ≥130/80 mmHg. We also enrolled age-matched healthy volunteers who were interested in taking part in this research. A 75-g glucose tolerance test was performed for the diagnosis of patients with normal glucose regulation, impaired glucose tolerance and diabetes mellitus. Thirty individuals with normal glucose tolerance were used as nondiabetic subjects in this study.

This study was conducted after approval by the ethics committee of our institution, and signed informed consent was obtained from all patients or volunteers before the examinations done.

Clinical assessment

Blood samples were drawn before breakfast in the morning after a 12-hour overnight fast. Hemoglobin A1c (HbA1c) was measured by high performance liquid chromatography (HPLC) and expressed as the National Glycohemoglobin Standardization Program (NGSP) value, as defined by JDS [16]. Plasma B-type natriuretic peptide (BNP) concentrations were determined using a chemiluminescent enzyme immunoassay kit (MIO2 Shionogi BNP, Shionogi & Co., Ltd., Osaka, Japan). Serum high-sensitivity C-reactive protein (hsCRP) levels were measured by a microparticle-enhanced immunonephelometric assay (CardioPhase hsCRP, Dade Behring, Newark, DE). Plasma von Willebrand factor ristocetin cofactor activity (VWF) was tested using reagents (BC von Willebrand Reagent, Dade Behring, Marburg, Germany). Plasma 5-hydroxyindole acetic acid (5-HIAA) concentrations were measured by the HPLC system using a Model L-7100 pump (Hitachi, Tokyo, Japan) and a Model ECD-300 electrochemical detector (Eicom, Kyoto, Japan). Serum tumor necrosis factor-alpha (TNF-α) concentrations were measured by an enzyme immunoassay kit (Quantikine HS Human TNF-α Immunoassay kit, R&D Systems, Minneapolis, MN). Blood pressure was measured by a sphygmomanometer with the patients in the sitting position after 5 min of rest. Three readings separated by 2 minutes were taken, and the average was used for analysis. An automatic device (BP-203RPE; Colin, Komaki, Japan) was used to measure ABI and brachial-ankle pulse wave velocity (baPWV). After patients were at rest in the supine position for 5 minutes, single measurement of these parameters was carefully performed by trained

operators. ABI and baPWV were obtained bilaterally and averages of each parameters were used for the analysis. A trained ophthalmologist carried out fundus ophthalmoscopies and classified diabetic patients as without retinopathy or as having simple, preproliferative, or proliferative retinopathy. Diabetic patients were classified by the measurement of urinary albumin excretion in 24-h urine collection as having normo-, micro-, or macroalbuminuria when at least two of three specimens were at diagnostic threshold of <30, 30-299 or ≥300 mg/24 h, respectively. eGFR was calculated using the simplified prediction equation proposed by the Japanese Society of Nephrology: eGFR (mL/min per 1.73 m^2) = 194 x $Age^{-0.287}$ x $SCr^{-1.094}$ (if female x 0.739), where SCr is serum creatinine (mg/dL) [17]. Diabetic patients were screened for distal symmetric polyneuropathy using a 128-Hz tuning fork applied to the bony prominence at the dorsal surface of both great toes, just proximal to the nail bed. If the patient felt vibration for more than 10 seconds, vibration perception was regarded as a normal response. Autonomic function was evaluated from the coefficient variation of the R-R interval (CV_{R-R}) during deep breathing monitored on an electrocardiogram (Cardio Star FCP-7541, Fukuda Denshi, Tokyo, Japan). Each subject was also classified based on smoking habits as being a current smoker or nonsmoker. Nonsmokers were defined as not having consumed tobacco for at least the previous 3 years.

Magnetic resonance imaging (MRI)

An MRI scanner operating at 1.5-Tesla (Signa Horizon-LX; GE Medical Systems, Milwaukee, WI) was used with phased array cardiac coil or birdcage coil. Electrocardiogram-gated three-dimensional fast imaging employing steady-state acquisition (3D-FIESTA) pulse sequence during 12 second single-breath hold with a temporal resolution of 20 frames per cardiac cycle was used. All patients were at rest in the supine position during examinations, which were done in a temperature-controlled room at 25°C. Ten mm slice thickness and two locations of short axis images in ascending thoracic aorta distal to the sinutubular junction and abdominal aorta proximal to the origin of renal arteries were obtained. A series of short axis images with 5 mm slice thickness at the popliteal artery was obtained using two-dimensional cine-mode phase-contrast (2D-cine-PC) MRI with 80-cm/s velocity encoding triggered by peripheral gating. Systolic and diastolic blood pressures were measured at the end of MRI examinations, using an automated brachial artery sphygmomanometer cuff placed around the right arm. Average blood pressure of three measurements was used for data analysis.

Image analysis and calculations

Obtained images were analyzed with commercial software (MASS analysis and CV flow) on an Advantage Windows version 4.3 workstation (GE Medical Systems, Milwaukee, WI). Contours of ascending thoracic and abdominal aortas and popliteal artery were manually drawn on each of the short-axis images of all cardiac phases. All tracing was performed by a single experienced observer, blinded to subject identity. Maximal systolic and minimal diastolic cross-sectional areas and distensibility at two separate locations, ascending thoracic and abdominal aortas, were obtained. Aortic distensibility was calculated from the following equation: D = (Amax – Amin) ÷ [Amin x (Pmax – Pmin)], where D is distensibility (10^{-3}/mmHg), Amax is the maximal systolic cross-sectional area (mm^2), Amin is the minimal diastolic cross-sectional area (mm^2), Pmax is the systolic blood pressure (mmHg), and Pmin is the diastolic blood pressure (mmHg) [11]. Total flow volume and flow components during the cardiac cycle at the popliteal artery were obtained. The instantaneous flow volume at 20 equally spaced time points through the cardiac cycle was calculated from the individual velocity images by integrating the velocity across the area of the vessel [4, 5]. A resistive index, which reflects peripheral vascular resistance, has been defined as (A-B)/A, where A is the systolic peak velocity and B is the end-diastolic velocity [18]. The resistive index was calculated from the 20 velocity images originally obtained. These vascular parameters were obtained bilaterally and averages of both lower limbs were used for the analysis.

Statistical analyses

Statistical evaluation was done on SPSS software version 11.0 for Windows (SPSS Inc., Chicago, IL, USA). Normality of distribution of each variable was assessed with the Kolmogorov-Smirnov test. Comparison between the two groups was performed using the unpaired Student's t-test. The chi-squared test for 2-by-2 contingency table was used to compare frequencies between the two groups. To analyze the effect of variables on blood flow at popliteal artery,

simple linear regression analysis or stepwise multiple regression analysis was performed. In the stepwise multiple regression analysis, F value for the inclusion of variables was set at 4.0 at each step. Values were expressed as the means±SD. *p* values of <0.05 were considered to be statistically significant.

Results

Clinical characteristics in all subjects are shown in Table 1. There were no significant differences between the groups for prevalence of male gender, age, LDL-cholesterol and systolic and diastolic blood pressures, frequency of smokers and eGFR. However, diabetic patients had higher body mass index (p=0.010), fasting plasma glucose (p<0.001), HbA1c (p<0.001), triglycerides (p=0.025), frequency of statins use (p=0.006) and frequency of ACEI or ARB use (p=0.024) and lower high-density lipoprotein (HDL) cholesterol (p=0.024) and CV_{R-R} (p<0.001) than nondiabetic subjects.

Vascular parameters in aortas and popliteal artery as well as circulating biomarkers in all subjects are shown in Table 2. Diabetic patients had higher minimal diastolic cross-sectional area in ascending thoracic aorta (p=0.015), resistive index (p=0.005) and baPWV (p<0.001) as well as lower distensibility in ascending thoracic aorta (p<0.001), systolic (p=0.014), late diastolic (p<0.001) and total (p<0.001) flow volumes at popliteal artery than nondiabetic subjects. However, maximal systolic cross-sectional area in ascending thoracic aorta and maximal systolic and minimal diastolic cross-sectional areas and distensibility in abdominal aorta, heart rate, early diastolic flow volume at popliteal artery and ABI were similar between the groups. Diabetic patients showed higher TNF-α (p=0.032), log hsCRP (p<0.001), VWF (p<0.001) and 5-HIAA (p=0.004) and similar BNP compared to nondiabetic subjects.

To clarify influences of vascular parameters and circulating biomarkers on flow volumes during the cardiac cycle at popliteal artery among diabetic patients, simple linear regression analyses were performed, as shown in Table 3. Resistive index (p<0.001) and BNP (p=0.006) negatively correlated with systolic flow volume. There was no significant correlation between early diastolic flow volume and vascular parameters as well as circulating biomarkers. Distensibility in ascending thoracic (p<0.001) and abdominal (p<0.001) aortas positively and baPWV (p=0.001), resistive index (p<0.001), BNP (p<0.001) and log hsCRP (p=0.048) negatively correlated with late diastolic flow volume. Distensibility in ascending thoracic (p=0.019) and abdominal (p=0.030) aortas positively and baPWV (p=0.020), resistive index

Table 1 Clinical characteristics in type 2 diabetic patients and age-matched nondiabetic subjects

Group	Nondiabetic subjects	Diabetic patients	*p* value
Number	30	52	
Male gender (%)	15 (50.0)	28 (53.8)	0.737
Age (years)	60.3±4.8	62.2±8.0	0.252
Body mass index (kg/m^2)	22.8±2.4	25.1±4.4	0.010
Duration of diabetes (years)	-	10.8±7.2	-
Treatment (diet/OHA/insulin)	-	11/23/18	-
Fasting plasma glucose (mg/dL)	98±9	153±37	<0.001
Hemoglobin A1c (%)	5.6±0.3	8.9±1.5	<0.001
LDL-cholesterol (mg/dL)	129±29	123±32	0.364
HDL-cholesterol (mg/dL)	60±18	51±16	0.024
Triglycerides (mg/dL)	126±51	165±85	0.025
Statins (%)	3 (10.0)	20 (38.5)	0.006
Systolic blood pressure (mmHg)	125±12	129±11	0.082
Diastolic blood pressure (mmHg)	79±10	76±9	0.169
ACEI or ARB (%)	4 (13.3)	19 (36.5)	0.024
Smokers (%)	8 (26.7)	11 (21.2)	0.569
Retinopathy (%)	-	19 (36.5)	-
Micro- or macroalbuminuria (%)	-	24 (46.2)	
eGFR (mL/min/1.73m^2)	71.5±7.4	76.6±17.2	0.123
Neuropathy (%)	-	26 (50.0)	-
CV_{R-R} (%)	3.31±1.17	2.17±1.13	<0.001

Data are expressed as n (%) or means±SD. OHA, oral hypoglycemic agent.

Table 2 Vascular parameters in aortas and popliteal artery as well as circulating biomarkers in type 2 diabetic patients and age-matched nondiabetic subjects

Group Number	Nondiabetic subjects 30	Diabetic patients 52	*p* value
Ascending thoracic aorta			
Cross-sectional area (mm^2)			
Maximal systolic	764±111	791±129	0.335
Minimal diastolic	637±100	705±128	0.015
Distensibility (10^{-3}/mmHg)	3.74±1.67	2.47±1.18	<0.001
Abdominal aorta			
Cross-sectional area (mm^2)			
Maximal systolic	359±58	365±88	0.752
Minimal diastolic	291±49	309±79	0.262
Distensibility (10^{-3}/mmHg)	3.40±0.52	3.63±1.45	0.419
Popliteal artery			
Flow volume (mL/min)			
Systolic	98.2±20.3	84.6±25.4	0.014
Early diastolic	-20.7±13.2	-17.5±9.9	0.216
Late diastolic	19.7±9.1	5.5±10.7	<0.001
Total	97.2±23.3	72.6±29.9	<0.001
Other parameters			
Heart rate (bpm)	72±12	69±10	0.337
ABI	1.14±0.03	1.12±0.07	0.187
baPWV (cm/sec)	1405±188	1600±253	<0.001
Resistive index	1.007±0.034	1.035±0.045	0.005
Circulating biomarkers			
BNP (pg/mL)	15.4±17.4	17.0±16.8	0.683
TNF-α (pg/mL)	1.28±0.57	1.53±0.46	0.032
Log hsCRP	2.21±0.38	2.94±0.63	<0.001
VWF (%)	36.5±16.0	136.9±60.9	<0.001
5-HIAA (ng/mL)	4.08±1.13	5.18±1.84	0.004

Data are expressed as n (%) or means±SD.

Table 3 Simple linear regression analyses between vascular parameters as well as circulating biomarkers and flow volumes during the cardiac cycle at popliteal artery in type 2 diabetic patients

Flow volume	Systolic		Early diastolic		Late diastolic		Total	
	β value	*p* value	β value	*p* value	β value	*p* value	β value	*p* value
Distensibility in ascending thoracic aorta	2.451	0.459	2.011	0.102	5.013	<0.001	9.474	0.019
Distensibility in abdominal aorta	2.538	0.321	0.308	0.750	3.953	<0.001	6.799	0.030
ABI	65.061	0.224	-12.215	0.546	45.876	0.061	98.722	0.138
baPWV	-0.024	0.097	0.003	0.533	-0.021	0.001	-0.041	0.020
Resistive index	-270.977	<0.001	-51.023	0.078	-205.771	<0.001	-527.772	<0.001
Heart rate	0.771	0.053	-0.137	0.367	0.285	0.125	0.919	0.065
BNP	-0.592	0.006	0.037	0.658	-0.325	<0.001	-0.880	<0.001
TNF-α	9.036	0.269	0.266	0.931	5.216	0.167	14.518	0.153
Log hsCRP	-8.664	0.134	2.425	0.267	-5.248	0.048	-11.487	0.112
VWF	-0.110	0.069	0.025	0.282	-0.035	0.216	-0.121	0.113
5-HIAA	-2.399	0.240	0.186	0.809	-1.411	0.134	-3.624	0.154

Table 4 Stepwise multiple regression analyses between vascular parameters as well as circulating biomarkers and flow volumes during the cardiac cycle at popliteal artery in type 2 diabetic patients

Flow volume	Systolic		Early diastolic		Late diastolic		Total	
	β value	F value	β value	F value	β value	F value	β value	F value
Distensibility in ascending thoracic aorta	-0.145	0.854	0.182	1.053	0.048	0.247	-0.044	0.148
Distensibility in abdominal aorta	0.019	0.015	-0.041	0.052	0.186	3.573	0.072	0.387
baPWV	0.013	0.007	0.151	0.837	-0.064	0.507	0.032	0.090
Resistive index	-0.472	10.691	-0.271	2.772	-0.663	55.904	-0.705	45.455
BNP	-0.252	3.435	0.112	0.537	-0.152	3.305	-0.225	5.181
	r^2=0.312 (p=0.003)		r^2=0.127 (p=0.265)		r^2=0.740 (p<0.001)		r^2=0.639 (p<0.001)	

(p<0.001) and BNP (p<0.001) negatively correlated with total flow volume. Stepwise multiple regression analyses were performed to examine the associations of possible risk factors (BNP, distensibility in ascending thoracic and abdominal aortas, baPWV and resistive index) with flow volumes during the cardiac cycle at popliteal artery in diabetic patients, as shown in Table 4. The significant independent determinant was resistive index for systolic flow volume (β= -0.472, F=10.691) (r^2=0.312, p=0.003) and for late diastolic flow volume (β=-0.663, F=55.904) (r^2=0.740, p<0.001). There was no significant independent determinant for early diastolic flow volume. The significant independent variables determined for total flow volume were BNP (β=-0.225, F=5.181) and resistive index (β= -0.705, F=45.455) (r^2=0.639, p<0.001).

Discussion

It has been reported that nondiabetic subjects had a typically triphasic waveform, which could be clearly separated into systolic and early and late diastolic phases of the cardiac cycle at popliteal artery [4, 5]. Our waveform analyses showed diabetic patients to have lower systolic, late diastolic and total flow volumes at popliteal artery than those in nondiabetic subjects. Diabetic patients also had increased circulating biomarkers of VWF, 5-HIAA, TNF-α and log hsCRP compared to nondiabetic subjects. These findings suggest that the diabetic condition may result in endothelial impairment [19] and peripheral circulatory disorder.

In this study, diabetic patients had higher baPWV and lower distensibility in ascending thoracic aorta and similar distensibility in abdominal aorta compared to nondiabetic subjects. These results suggest that diabetic patients have heterogeneous stiffening in different arterial regions. Diabetic patients show greater impact on pulse wave velocity of elastic central arteries as compared to muscular peripheral arteries [20]. Aging-caused degenerative changes in the vessel wall of large arteries and aortic stiffening may be more likely to occur in the proximal rather than the distal segment [21, 22]. Glycation of extracellular matrix in the vessel wall contributes to the development of aortic stiffness that is accelerated in diabetic patients [11, 23]. Other risk factors for aortic stiffness in diabetic patients include endothelial dysfunction [24], increased intima-media thickness [25] and arterial calcification [26] in the vessel wall. Simple linear regression analyses revealed that distensibility in ascending thoracic and abdominal aortas positively and baPWV negatively correlated with late diastolic and total flow volumes at popliteal artery among diabetic patients. The large arteries serve a conduit function to deliver adequate blood supply from the heart to peripheral tissues. Aorta also transforms the pulsatile flow generated by left ventricular contraction into steady flow at the peripheral arteries. Under normal condition during systole, roughly 40% of stroke volume is forwarded directly to arterioles and capillaries in the periphery, whereas the remainder is stored in aorta and proximal large vessels [27]. In diastole, elastic forces of the aortic wall drain it antegrade through arterioles into venous circulation, creating a nearly continuous peripheral blood flow. In case of decreased aortic elasticity, a greater proportion of the stroke volume is forwarded to the peripheral circulation, and less blood can be stored in the aorta, resulting in reduced late diastolic forward flow in lower-leg arteries.

Our data demonstrated that diabetic patients had higher resistive index than nondiabetic subjects although plasma BNP levels were similar between

the groups. An epidemiologic study has reported that plasma BNP geometric mean was 13.7 pg/mL in a general population with mean age of 56.1±9.7 years in Japan [28]. These findings indicated that our nondiabetic subjects (15.4±17.4 pg/mL) have higher plasma BNP level than the general population and consequently a similar value to diabetic patients (17.0±16.8 pg/mL). Although nondiabetic subjects had only negative correlation between total flow volume and resistive index ($p<0.001$), no significant correlation was found between total flow volume and distensibility in ascending thoracic and abdominal aortas, ABI, baPWV, heart rate, BNP, TNF-α, log hsCRP, VWF or 5-HIAA. These data suggest that association of plasma BNP level with total flow volume at popliteal artery is a specific finding in diabetic patients.

Multivariate analysis demonstrated that increased plasma BNP concentration and resistive index, but not decreased aortic distensibility, were independent risk factors of impaired total blood flow in popliteal artery among diabetic patients. It has been reported that left ventricular diastolic dysfunction is prevalent [9] and is associated with aortic stiffness in diabetic patients [29]. Echocardiographic measurements show that increased plasma BNP level reflects left ventricular diastolic dysfunction in asymptomatic diabetic patients [30]. Cardiac MRI in left ventricle demonstrates that diabetic patients at rest have smaller end-diastolic volume (EDV), E/A ratio and stroke volume than nondiabetic individuals [31]. This literature suggests the possibility that elevated plasma BNP levels associate with impaired blood flow at popliteal artery in diabetic patients. The small-caliber arteries and arterioles act as resistance vessels that regulate blood flow to the capillaries [27]. Diabetic patients had endothelial dysfunction and reduced caliber and number of small arteries and arterioles [12, 13], resulting in increased peripheral vascular resistance.

In this study, we did not perform ultrasound examination in lower extremity arteries. We used 2D-cine-PC MRI to evaluate blood flow in popliteal artery. All patients were at rest in the supine position during examination, which were done in a temperature-controlled room at 25°C. The accuracy and reproducibility of 2D-cine-PC MRI to measure flow volume for both triphasic and monophasic waveforms created from a pulsatile pump has been reported [32]. 2D-cine-PC MRI is analogous to Doppler sonographic evaluation because both methods measure the vector component of flow along an axis. When the feasibility of 2D-cine-PC MRI was compared with color-coded Doppler sonography, the velocity waveforms acquired using both methods correlated well [33]. The present examination time using 2D-cine-PC MRI was similar to Doppler sonography. Some characteristics of 2D-cine-PC imaging could be superior to those of Doppler sonography. High frequency at 63.9 MHz provided excellent resolution of deep vasculatures through thick body tissue or calcified plaque of the vessel. The large size of quadrature coil with 20 cm field of view simultaneously covers both sides of the popliteal arteries as well as different locations along the same vessel. The angle of view is perpendicular to the flow direction with no operator dependency in selection of angle correction between the transducer axis and the vessel.

This study has several limitations. Although increased plasma BNP level was one of the independent risk factors for impaired total flow volume in lower leg arteries, we did not measure EDV, E/A ratio and stroke volume in left ventricle by echocardiography or cardiac MRI. Therefore, further study is necessary to confirm our findings. Furthermore, we enrolled diabetic patients with normal ABI. We did not measure toe systolic pressure, which is less affected by medial arterial calcification and generally considered a more reliable tool to assess PAD in diabetic patients [34]. Thus, our study includes the possibility of undetected PAD. Our cross-sectional study design cannot assess temporality or prove causality and further prospective study is required to clarify these results.

In conclusion, consistent with our previous reports, diabetic patients were found to have impaired blood flow at popliteal artery even though they have a normal ABI. Elevated plasma BNP level and resistive index, but not decreased aortic distensibility, were independently associated with impaired total flow volume at popliteal artery. These findings contribute to understanding the mechanism of critical limb ischemia in diabetic patients.

Conflicts of Interest

The authors declare no conflict of interest relevant to this manuscript.

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