The aim of this study was to investigate which parameters among the ankle brachial index (ABI), toe brachial pressure index (TBI) and transfer function index (TFI) are useful to accurately diagnose PAD in patients with / without arterial calcification, who have undergone some type of diagnostic imaging.

Patients and Methods: A total of 102 patients with 192 limbs (mean age: 72.0 ± 8.4 years) underwent plain radiography, ABI, TBI and TFI. A receiver operating characteristics (ROC) analysis was performed to assess possible threshold values that predict PAD in these patients.

Results: The area under the curve (AUC) of the ABI, TBI and TFI were 83.0%, 87.9%, 93.1% in the all limbs group, respectively. In the non-calcified lesion group, the AUC of the ABI, TBI and TFI were 94.4%, 87.9%, 93.1%, respectively. In the calcified lesion group, the AUC of the ABI, TBI and TFI were 71.4%, 87.9% and 92.9%, respectively.

Conclusions: A cut-off value of TFI ≤ 1.025 exhibits a higher AUC for detecting the presence of PAD than the ABI and TBI. Therefore, the TFI is considered to be useful to estimate the presence of PAD in all types of patients, especially those with arterial calcification.

Key Words: Peripheral arterial disease, Ankle brachial pressure index, Transfer function index, Arterial calcification

Introduction

Peripheral arterial disease (PAD) is a representation of widespread arteriosclerotic disease and to cause range of clinical conditions from asymptomatic disease to critical limb ischemia. It can involve both the upper and lower extremities. Measurements of the ankle brachial pressure index (ABI) are widely used to screen for PAD. However, the ABI should be carefully interpreted in cases with arterial calcification, as arterial calcification in the lower extremities significantly affects the ABI values. Arterial calcification may occur systemically in nearly all vascular beds and in both the medial and intimal layers, which are associated with atherosclerosis and arteriosclerosis. Arterial medial calcification is mostly localized to the femoral and crural arteries. Therefore, this form of calcification has been reported to be associated with increased arterial stiffness and mortality. Furthermore, arterial calcification have previously been shown to reflect advanced occlusive disease including PAD, and patients with calcification of the large arteries have an increased cardiovascular risk compared to similar patients without calcification.

The transfer function index (TFI) is derived from pulse volume recording (PVR) waveforms obtained simultaneously at two sites. The TFI value strongly correlates with the relative patency of the intervening arterial segment. In order to diagnose PAD more accurately, we investigated which parameters among the ABI, toe brachial pressure index (TBI) and TFI exhibit better area under the curve (AUC) in patients undergoing...
any type of diagnostic imaging.

Patients and Methods

Subjects. A total of 102 patients with 192 limbs (86 men, 16 women; age range, 49–90 years; mean age, 72.0 ± 8.4 years), who visited the outpatient clinic or were admitted to Tokyo Medical and Dental University Hospital between February 2011 and March 2013. Twelve out of 204 limbs were amputated in 12 patients. The whole protocol of this study were approved by The Conflict of Interest Committee and Institutional Review Board of Tokyo Medical and Dental University hospital. The study was performed only in patients, who provided their written informed consent was obtained from all participant. All patients were diagnosed with PAD in at least one lower extremity and underwent some type of diagnostic imaging, such as duplex ultrasound, contrast-enhanced computed tomography, magnetic resonance imaging or intra-arterial subtraction angiography, which revealed the presence of >50% vessel stenosis. Patients were excluded for having either cardiac arrhythmia, heart failure. The characteristics of the patients were retrieved from their medical records. Demographic information regarding the clinical symptoms, age, gender, hypertension, dyslipidemia, diabetes mellitus, hemodialysis and smoking was collected. Hypertension (HT) was diagnosed according to a systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 80 mmHg and / or treatment for hypertension. Diabetes mellitus (DM) was diagnosed according to a maintained fasting plasma glucose level of ≥ 7.0 mmol/l (126 mg/dl) or 2-h plasma glucose level of ≥ 11.1 mmol/l (200 mg/dl). Dyslipidemia (DL) was defined as a serum LDL cholesterol level of ≥ 140 mg/dl (3.6 mmol/l), HDL cholesterol level of ≤ 40 mg/dl (1.03 mmol/l) or triglyceride ≥ 150 mg/dl (1.7 mmol/l) and / or treatment for dyslipidemia.

Plain radiography. Soft-tissue native radiograms of the thigh and calf were taken with the patient in a recumbent position. The radiological findings of the femoral artery were analyzed by a vascular technologist and a surgeon, who were blinded to the noninvasive examination data. The degrees of lower-limb artery calcification were divided into intimal type and medial type. (Fig. 1).

Measurement of ABI, TBI and TFI. The ABI, TBI and TFI values were measured in 102 patients. After each patient rested in the supine position for at least 10 minutes, the ABI and TBI values were measured using a commercially available multi-cuff unit (VasoGuard™; Nicole Vascular Inc, Madison, WI, USA), which automatically recorded the parameters. The TFI was calculated according to PVR waveforms obtained simultaneously at two sites: (1) an inflow PVR waveform was obtained from the arm, which served as a surrogate; and (2) outflow PVR waveforms were obtained from the calf and ankle. The outflow PVR was divided by the inflow PVR, which yielded the TFI. A commercially available multi-cuff unit (VasoGuard™) was run automatically.

Statistical analysis. The data are presented as the mean ± SD. Comparisons of unpaired data were performed using Student’s t-test for parametric data. Categorical clinical data (e.g., peripheral arterial disease risk factors, gender) were compared between the study groups using chi-square test depending on sample size. Statistical significance was considered to exist at a P value < 0.05. A receiver operating characteristic (ROC) curve analysis was performed to assess the sensitivity and specificity. Statistical analysis for ROC was not performed, which was executed by manual operation. The sensitivity and specificity of the ABI, TBI and TFI (112 of the 192 limbs) in diagnosing PAD could be assessed only in limbs, which were not treated with endovascular therapy and / or bypass surgery because the TFI values

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Fig. 1: X-ray photography at the crural region
The roentgenogram shows arterial calcification (depicted in white). Discrete intimal type (A) and medial type (B).
are influenced by vascular reconstruction. Therefore, ROC analyses were performed for the all limbs group (112 limbs), non-calciﬁed lesion group (63 limbs) and calcified lesion group (49 limbs), respectively. The ROC curves were depicted based on the true positive being deﬁned as the presence of limb stenosis. The AUC and cut-off values were calculated using the ROC curves, and the AUC was deﬁned as the area between the curve and the x-axis. The closer the left corner and the top border of the ROC space, the more accurate the test. All statistical analysis were performed with Stat View version 5 software program (Abacus Concept Inc., Berkley, CA).

**Results**

**Patient Characteristics.** According to the Rutherford classification⁹, there were 68 limbs with Rutherford I, 115 limbs with Rutherford II, 5 limbs with Rutherford III, and 4 limbs with Rutherford IV. Crural arterial lesions were present in 52 limbs (27.1%) out of 192 limbs. All patients were divided non-calciﬁed lesion (61 patients, 59.8%) and calcified lesion group (41 patients, 40.2%), and compared their characteristics. The incidences of DM were 34.4% and 68.3% in the non-calciﬁed lesion and calciﬁed lesion groups, respectively, and a signiﬁcant difference was observed (p<0.01). There were signiﬁcant differences between the non-calciﬁed lesion (4.9%) and calciﬁed lesion (19.5%) groups in terms of hemodialysis (HD) (p<0.05). However, no differences were observed in the incidence of HT, DL, or smoking habits between the two groups. Additionally, the ABI was not signiﬁcantly different between the two groups (calciﬁed lesion: 0.89 ± 0.31 versus non-calciﬁed lesion: 0.86 ± 0.24, P=0.54, p<0.01). However, the TBI and TFI were lower in the calcified lesion group than in the non-calciﬁed lesion group (TBI: 0.49 ± 0.23 versus 0.62 ± 0.24; TFI: 0.89 ± 0.21 versus 1.01 ± 0.26, p<0.01) (Table 1).

**The Accuracy of the Diagnosis of PAD with and without calcification.** In the all limbs group (112 limbs), the ROC analysis revealed the sensitivity and speciﬁcity of an ABI≤ 0.90 to be 70.0% and 96.9%, respectively, to diagnose PAD (AUC: 83.0%). The sensitivity and speciﬁcity of the TBI set at 0.65 for detecting PAD were 80.0% and 84.4% (AUC: 87.9%), respectively. In contrast, ROC curve showed that the best cutoff to differentiate between normal and abnormal limbs was a TFI of 1.025, with a sensitivity of 86.3% and speciﬁcity of 93.8%, respectively. (AUC: 93.1%) (Fig. 2a).

<table>
<thead>
<tr>
<th>Table 1 Comparison of patient characteristics and parameters</th>
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<td>Patients</td>
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<td>N = 61</td>
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<td>Age (years)</td>
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<td>Male / female</td>
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<td>Diabetes mellitus (%)</td>
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**Fig. 2a:** Receiver operating characteristic curves to assess the ability of the ABI, TBI and TFI in the all limbs group (112 limbs). Sensitivity: is the proportion of true positives that are correctly identified by a diagnostic test; Specificity: is the proportion of the true negatives correctly identified by a diagnostic test; The false-positive rate is also known as the fall-out and can be calculated as (1 – specificity); ABI: ankle brachial pressure index; TBI: toe brachial pressure index; TFI: transfer function index.
In the non-calcified lesion group (63 limbs), the sensitivity, specificity and AUC value for the detection of PAD with an ABI $\leq 0.90$ were 80.0%, 95.7% and 94.4%, respectively. The sensitivity and specificity to detect PAD with a TBI $\leq 0.65$ were 77.5% and 82.6%, whereas the AUC value remained at 87.9%. The sensitivity, specificity and AUC value for detecting PAD with a TFI $\leq 1.025$ were 82.5%, 95.7% and 93.1%, respectively (Fig. 2b).

In the calcified lesion group (49 limbs), the diagnostic accuracy of an ABI of $\leq 0.90$ exhibited a low sensitivity of 60.0% with a specificity of 100%, respectively (AUC: 71.4%). The sensitivity and specificity to detect PAD with a TBI $\leq 0.65$ were 77.5% and 82.6%, whereas the AUC value remained at 87.9%. The sensitivity, specificity and AUC value for detecting PAD with a TFI $\leq 1.025$ were 82.5%, 95.7% and 93.1%, respectively (Fig. 2b).

In the calcified lesion group (63 limbs), the sensitivity, specificity and AUC value for the detection of PAD with an ABI $\leq 0.90$ were 80.0%, 95.7% and 94.4%, respectively. The sensitivity and specificity to detect PAD with a TBI $\leq 0.65$ were 77.5% and 82.6%, whereas the AUC value remained at 87.9%. The sensitivity, specificity and AUC value for detecting PAD with a TFI $\leq 1.025$ were 82.5%, 95.7% and 93.1%, respectively (Fig. 2c).

**Fig. 2b:** Receiver operating characteristic curves to assess the ability of the ABI, TBI and TFI in the non-calcified lesion group (63 limbs). Sensitivity: is the proportion of true positives that are correctly identified by a diagnostic test; Specificity: is the proportion of the true negatives correctly identified by a diagnostic test; The false-positive rate is also known as the fall-out and can be calculated as (1 – specificity); ABI: ankle brachial pressure index; TBI: toe brachial pressure index; TFI: transfer function index.

**Fig. 2c:** Receiver operating characteristic curves to assess the ability of the ABI, TBI and TFI in the calcified lesion group (49 limbs). Sensitivity: is the proportion of true positives that are correctly identified by a diagnostic test; Specificity: is the proportion of the true negatives correctly identified by a diagnostic test; The false-positive rate is also known as the fall-out and can be calculated as (1 – specificity); ABI: ankle brachial pressure index; TBI: toe brachial pressure index; TFI: transfer function index.

**Discussion**

Arterial calcification is associated with most conventional cardiovascular risk factors, including obesity, HT, DL, and DM. DM and calcification were found to have a close relationship in the present study. Because diabetic patients with medial calcification have a significantly higher incidence of lower extremity amputations, the early detection of calcification may provide information predicting critical limb ischemia in diabetic patients. Nevertheless, atherosclerotic calcification contributes to intimal arterial calcification in the lower extremities in cases of PAD. Intimal and medial calcification cannot be differentiated using non-contrast multidetector row computed tomography (MDCT) images. Plain radiological findings and/or the pathological diagnosis can be used to identify the classification of calcification, and plain radiography is recommended to assess the degree and type of calcification, which may be helpful for predicting the status of calcification and progression of arterial disease in diabetic patients.

PAD is highly prevalent in HD patients, although it is frequently underdiagnosed. In patients with HD, a
high age, DM, hypercalcemia and hyperphosphatemia have been described to be associated with a higher risk of amputation, which may contribute to arterial calcification for the onset of PAD in this population. In the current study, there were significant differences in the incidence of arterial calcification according to the use of HD. Moreover, the prevalence of PAD is higher among dialysis patients than in the general population. In the comparison of MDCT findings, the sensitivity of an ABI ≤ 0.90 for appraising PAD was only 29.9%, whereas the specificity was 100%. Furthermore, arterial calcification in the lower extremities is associated with PAD. Amputation was associated with the presence of PAD in 85% of the patients, which was a frequent condition in HD patients. The early detection of PAD is also considered to be very important in order to prevent major amputation.

The ABI is a useful objective parameter to document the presence of lower-extremity PAD. Generally, an ABI of less than 0.90 has been shown to have a sensitivity of 90% and specificity of 98% to detect significant arterial stenosis (luminal stenosis ≥ 75%). A high ABI value (≥ 1.30) reflects non-compressible arteries in the ankle, which may be related to distal arterial calcification. The ABI can be used and it may be valuable to evaluate the presence or severity of PAD in the lower extremities because digital arteries are much less susceptible to medial calcification. The digital arterial pressures are normally lower than brachial pressures; a normal TBI is 0.70. A patient with a TBI of ≤ 0.7 may complain of claudication, and rest pain typically occurs at a TBI of less than 0.2.

It is therefore important to estimate the presence of PAD associated with calcification using noninvasive methods to reduce the risk, time and costs associated with invasive modalities, such as angiography. We thus attempted to elucidate whether resting parameters, such as the ABI, TBI or TFI, are more useful for assessing PAD in patients with calcification. Conventionally, ABI ≤ 0.9 is used as standard cut-off value for diagnosing PAD. In our study, the AUC of an ABI ≤ 0.9, was 83.0%, 94.4% and 71.4% in the all limbs group (112 limbs), non-calcified lesion group (63 limbs) and calcified lesion group (49 limbs), respectively. Furthermore, a cut-off value for TFI of ≤ 1.025 for a potential diagnosis of PAD showed sufficient AUC values at 93.1%, 93.1% and 92.9% in the all limbs, non-calcified lesion and calcified lesion groups, in our study, respectively. The AUC for the ABI may be poor because the ABI values often provide false-negative results for diagnosing PAD due to the presence of arterial calcification in the calcified lesion group. Hence, current study result is consistent with the statement of Stein et al. that the ABI is not useful for appraising the ischemic status in patients with arterial calcification. The TBI should be used to establish the diagnosis of PAD in patients when the ABI value is not reliable. In our study, we defined a cut-off value for the TBI of ≤ 0.65, and the AUC values were 87.9%, 87.9% and 87.9% in the all limbs, non-calcified lesion and calcified lesion groups, respectively. Although the specificity of the TBI and TFI were similar in the calcified lesion group, the sensitivity and AUC of the TFI were superior to that of the TBI, in the current study. Furthermore, the sensitivity and AUC of the TBI value were lower than the TFI value in all three groups. Therefore, our study demonstrated that TFI is a more reliable, definitive screening test to diagnose the prevalence of PAD, especially in patients with calcification.

The TFI is also an efficient parameter for executing infragluteal vein graft surveillance because vein grafts remain compliant, similar to native arteries. Similar results were obtained which demonstrated that the TFI calf was a more useful parameter than the ABI or TFI ankle to diagnose claudicants (recovery ability index > 0.6) even in diabetic patients. If there are no crural arterial lesions in these patients, then the TFI calf and TFI ankle should equal. The lower limbs TFI ankle is considered to be smaller than TFI calf when there are crural arterial lesions. The crural arterial lesions were determined as 27.1% in the present study which is slightly higher than that of Nakashima’s report. The TFI ankle was more efficient to diagnose PAD because crural arterial lesions were diagnosed more frequently in this study than in the previous study.

PVR was first introduced as an accurate modality for documenting lower extremity PAD in the 1970s. Plethysmography is also an excellent modality for diagnosing PAD, even in patients with DM and / or HD; however, it is not widely used in the clinical setting. The pulsatile pressure and blood flow must be calculated in order to determine the impedance in the arterial segment, which is associated with theoretical and practical problems. The blood flow is calculated based on the Doppler flow wave and cross-sectional diameter, both
of which depend on local hemodynamics. In the current study, the multi-cuff unit simultaneously recorded pulse volume waveforms at 10 sites, which were subsequently analyzed using Fourier and Laplace transformation to produce the TFI automatically, without examiner dependency or technical demands. This is why the TFIs were more resistant to the effects of arterial calcification than the ABI. PVR can evaluate the ischemic severity even in patients with arterial calcification which cannot be compressed by a cuff. The TFI measurement using PVR is a promising method for appraising arterial disease due to its noninvasiveness, as well as its simplicity, painlessness and operator independency. Simple assessments of PAD using the TFI in patients with arterial calcification may play an important role in more accurately assessing the prevalence of PAD, particularly in subjects with calcification.

In conclusion, arterial calcification was detected in all patients with/without DM and HD in the present study. A cut-off value for a TFI of $\leq 1.025$ has a higher AUC for detecting the presence of PAD than an ABI of $\leq 0.90$ and TBI of $\leq 0.65$. Therefore, the TFI measurement is considered to be a useful method for diagnosing PAD more accurately in all types of patients, especially in those with arterial calcification.

References

TFI is useful to detect PAD with artery calcification


