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Strain-Blood Pressure Index for Evaluation of Early Changes in Elasticity of Anterior Tibial Artery in Patients with Type 2 Diabetes Mellitus

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Background: The aim of this study was to investigate the feasibility and value of strain-blood pressure index (SBPI) to assess early changes in elasticity of anterior tibial artery in patients with type 2 diabetes mellitus (T2DM).





Material/Methods: Eighty-one randomly selected in-patients with T2DM were divided into 2 groups – a vascular complication negative group (n=42) and a vascular complication positive group (n=39). Forty healthy volunteers were enrolled in a control group. Ultrasonographic scans using Xstrain™ technique were conducted for every patient to obtain the maximum circumferential strain (CS_{max}) of anterior tibial artery; patient blood pressure was also measured for calculating strain-blood pressure index (SBPI=CS_{max} / [(local pulse pressure) / local diastolic blood pressure] ×100%. Afterwards, SBPIs of various groups were comparatively analyzed.

Results: Differences in SBPIs among the 3 groups were statistically significant (control group > negative group > positive group, P<0.05).

Conclusions: SBPI could be used as a new indicator for the evaluation on the anterior tibial arterial elasticity of T2DM patients and it was able to reflect the early elasticity changes in anterior tibial arteries in T2DM patients with atherosclerosis.

MeSH Keywords: **Arterial Pressure • Diabetes Mellitus, Type 2 • Elasticity • Tibial Arteries**

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Background

Lower extremity atherosclerosis and occlusive arterial diseases are the major risk factors causing diabetic foot disease; hence, early evaluation of the lower extremity arterial lesions has significant implications in guiding early clinical interventions and preventing/ delaying development and progression of diabetic foot [1]. On the other hand, during the formation of atherosclerotic plaques, the anterior tibial artery lumen, which is relatively smaller than that of femoral and popliteal arteries, is more likely to be narrowed and occluded, resulting in ischemic necrosis of distal tissues; therefore, early evaluation of atherosclerosis in the anterior tibial artery is particularly important. Ankle-brachial index is the most commonly used clinical indicator reflecting the degree of arterial stenosis of lower limbs, but when lower limb arterial wall calcification is widespread, or when the patients also has upper limb arterial lesion, elevated or normal ankle-brachial index can be caused; thus, the index cannot accurately reflect the degree of lower limb arterial disease. Moreover, whether ankle-brachial index can reflect early elasticity changes in the anterior tibial artery is unknown, so it has very important limitations.

Although decreased arterial elasticity is the early change prior to increase of intima-media thickness (IMT) and formation of atherosclerotic plaques [2], studies of anterior tibial artery elasticity evaluation have rarely been reported. Hence, in the present study, strain-blood pressure index was selected to assess anterior tibial artery elasticity.

Material and Methods

Subjects

Based on the etiological classification and diagnostic criteria recommended by the American Diabetes Association (ADA) [3], 81 in-patients, who were diagnosed with type 2 diabetes mellitus (T2DM), and were admitted in the Department of Endocrinology at our hospital between May 2013 and April 2014, were enrolled in the present study and divided into 2 groups according to the presence of vascular complications (including both macroangiopathy and microangiopathy): 42 patients (20 males and 22 females, aged 33 to 65 years with a mean age of 49.62 ± 12.03 years) without any vascular complications were included in the negative group, and 39 patients (18 males and 21 females, aged 36 to 68 years with a mean of 52.42 ± 12.26 years) with vascular complication were included in the positive group. Diabetic vascular complications included macrovascular and microvascular lesions; macrovascular lesions included cerebral infarction, myocardial infarction, and peripheral atherosclerosis; and microvascular lesions included retinopathy and kidney lesion [4,5]. In cerebral infarction,

the necrosis focus in brain tissue was confirmed by CT or MRI; in myocardial infarction, non-perfused areas in the myocardium were confirmed by DSA examination. In peripheral atherosclerosis, the atherosclerotic plaque within the artery was confirmed by color Doppler ultrasound examination. In retinopathy, microaneurysm or small hemorrhage focus was confirmed by ophthalmofundoscopy. Diabetic nephropathy was confirmed by urine examination and the clinical diagnosis criterion was that urinary protein excretion was greater than 300 mg/24h. Among the 39 patients in the positive group, 11 had retinopathies, 8 had nephropathies, 9 had coronary heart disease, 7 had carotid atherosclerosis, and 4 had cerebral infarction. Hypertension, heart failure, or any other endocrine diseases associated vascular diseases were excluded in all the patients. Forty healthy volunteers (24 males and 26 females, aged 31 to 68 years, mean 47.89 ± 11.92 years) were enrolled during the same period as the control group. Ankle-brachial indexes were recorded and all subjects abstained from caffeine- or alcohol-containing products during the 24 hours prior to the test.

General examinations

A team from the Department of Endocrinology at our hospital was assigned to review medical histories and conduct physical examinations for all patients, to collect the data on age [6], sex [7], BMI [8], and blood pressure [9], as well as occurrence of diabetic foot symptoms such as rest pain, abnormal cold perception in lower limbs, intermittent claudication, and lack of dorsalis pedis artery pulse [10–13]. Blood samples were collected from all patients within 24 h before ultrasonography to test for fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), fibrinogen (FiB), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol [14,15]. Before ultrasound examination, no drugs including anti-coagulants or vasodilators, except for anti-diabetic drugs, were given to any patient.

Instrument and methods

Ultrasonography was conducted using the Mylab 90 Ultrasound Imaging System (Esaote Co.), which was equipped with an LA523 transducer (frequency 4 to 13 MHz) and integrated with Xstrain™ technology.

The subjects were held in supine position for 10 min, before their blood pressures in bilateral anterior tibial arteries were measured. Next, right ankle artery and brachial artery systolic pressures were measured. The pressures recorded when the first and the fifth Korotkoff sounds were heard were taken as the systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. While holding the patient's bilateral lower extremities fully exposed, the ECG was connected. The

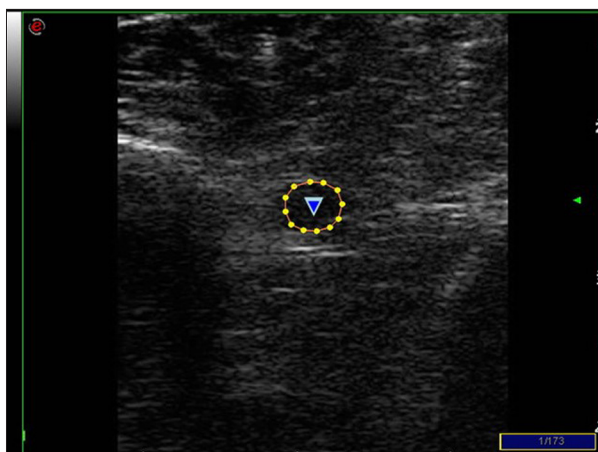


Figure 1. By using the semi-automatic tracings method, the arterial intima was evenly divided into 12 small segments and the reference point was set at the center of the lumen.

bilateral anterior tibial arteries were taken as the target artery, on which horizontal and vertical scanning were performed towards the inferior end to confirm the absence of plaque formation. If plaques were revealed, the patient was excluded from the trial. Presence of plaque was judged according to the criteria proposed by Salcumi et al. [16], by which plaque was defined as any local thickening of intima-media thickness (IMT) local thickening >1.2 mm. For measurement of the maximum circumferential strain, the short-axis view of the anterior tibial artery at the level 5 cm inferior to the lower edge of the patella was selected and the probe was held perpendicular to the skin for a clear display of endometrium; the 2-dimensional dynamic gray scale short axis images of the anterior tibial artery during 3 consecutive cardiac cycles were collected and documented for later analysis. The left ventricular ejection fraction (LVEF) and stroke volume (SV) were calculated by using biplane Simpson's method, and heart rate (HR) was recorded.

Image analysis: From playback of the recorded video, analysis of anterior tibial artery was conducted by using the Xstrain™ automatic analysis tool. The image was frozen on the frame of the ECG T-wave; by using the semi-automatic tracings method, the arterial intima was evenly divided into 12 small segments and the reference point was set at the center of the lumen (Figure 1). Afterwards, automatic analysis and calculation were conducted by taking the average maximum circumferential strains experienced by the various segments of the arterial wall as the maximum circumferential strain (CS_{max}) (Figure 2).

Strain-blood pressure index (SBPI) was calculated according to the following equation:

$$SBPI = CS_{max} / [(LSBP - LDBP) / LDBP] \times 100\%$$

Ankle Brachial Index (ABI) – right ankle artery systolic blood pressure/right brachial artery systolic blood pressure.

Statistical analysis

All measurements are expressed as mean ± standard deviation. All the original data were statistically processed by using SPSS 18.0 software package. The inter-group parameters were subjected to ANOVA and t-test, while the intra-group parameters were tested by paired t-test; any P value <0.05 was considered as statistically significant.

Results

Comparisons of general clinical data and hematologic biochemical parameters

The differences in age, BMI, HDL-cholesterol and Fib among the 3 groups were all not statistically significant (P>0.05). Pairwise

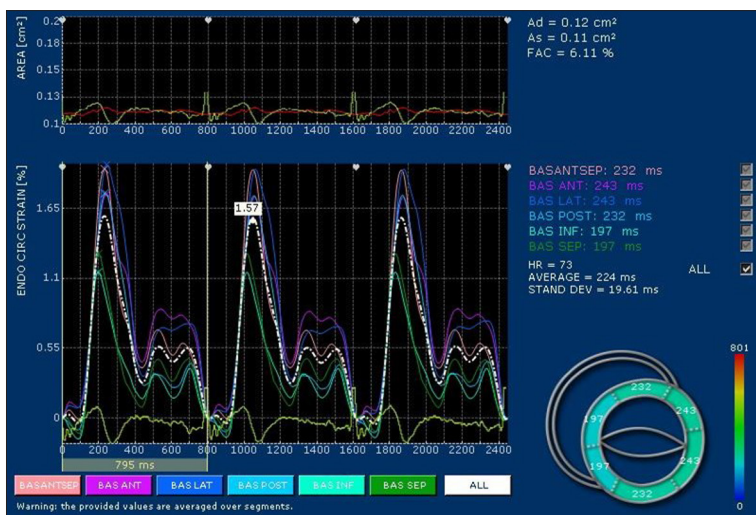


Figure 2. The maximum circumferential strain on the anterior tibial artery of 1 diabetic patient was 1.57%.

Table 1. Comparisons of general clinical data and hematologic biochemical parameters ($\bar{x}\pm s$).

Group	Cases (n)	Age (years)	BMI (kg/m ²)	FBG (mmol/L)	HbA1c (%)	FIB (g/L)	TC (mmol/L)	TG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
Control	40	47.89 ±11.92	21.56 ±2.62	5.01 ±0.51	5.45 ±0.44	3.85 ±1.05	3.39 ±0.58	1.423 ±0.513	0.988 ±0.271	2.137 ±0.370
Negative group	42	48.16 ±12.38	22.31 ±2.56	7.57 ±1.42*	6.84 ±2.06*	3.96 ±1.03	5.14 ±1.11*	1.982 ±0.653*	1.022 ±0.255	3.221 ±0.402*
Positive group	39	49.02 ±11.26	22.66 ±2.82	9.63 ±1.51***	8.04 ±2.46***	4.17 ±1.10	6.87 ±1.24***	2.483 ±0.675***	1.103 ±0.675	5.238 ±0.575***

Comparisons between negative/positive group and the control group, * $P<0.05$; comparison between negative group and positive groups, ** $P<0.05$. SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; FBG – fasting blood glucose; HbA1c – glycosylated hemoglobin; TC – total cholesterol; TG – triglyceride; FIB – fibrinogen; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol.

Table 2. Comparisons of direct measurements ($\bar{x}\pm s$).

Group	Cases (n)	SBP (mmHg)		DBP (mmHg)		CS _{max} (%)		HR (bpm)	LVEF (%)	SV (ml)
		Left	Right	Left	Right	Left	Right			
Control	40	128.69 ±17.14	130.92 ±21.43	85.15 ±11.23	84.78 ±10.72	2.59 ±0.32	2.64 ±0.36	75.36 ±12.08	70.32 ±8.14	80.16 ±9.37
Negative group	42	131.12 ±20.05	129.52 ±18.65	83.84 ±10.79	83.15 ±9.98	2.43 ±0.30*	2.45 ±0.29*	72.98 ±11.92	68.69 ±8.38	78.56 ±9.01
Positive group	39	127.11 ±18.73	130.15 ±19.52	82.96 ±12.68	83.95 ±10.59	2.21 ±0.28***	2.28 ±0.31***	74.06 ±12.17	68.93 ±8.25	78.95 ±9.68

Comparisons between negative/positive group and the control group, * $P<0.05$; comparison between negative group and positive groups, ** $P<0.05$. 1 mmHg=0.133 kpa. CS_{max} – maximum circumferential strain; HR – heart rate; LVEF – left ventricular ejection fraction; SV – stroke volume.

comparisons of FBG, HbA1c, TC, TG, and LDL-cholesterol revealed statistically significant differences among the groups and a trend of the positive group > negative group > control group ($P<0.05$), (Table 1).

Comparison of direct measurements

Xstrain™ automatic analysis tool was used for analyzing the collected dynamic image of the anterior tibial artery, and time-circumferential strain curves of various segments of the anterior tibial artery wall were obtained; curves with different colors represented different segments, and the curves were all shown as regular waveform; movement time of various segments were synchronous, but circumferential strain values were different. Amplitudes of waveform types were different; white curve represented the average of circumferential strain in various segments, and its peak value was the maximum circumferential strain value (Figure 2). The difference in the maximum circumferential strain on bilateral anterior tibial arteries among the 3 groups were statistically significant (the control group > negative group > positive group,

$P<0.05$). The differences in other anterior tibial artery parameters (including SBP, DBP, HR, LVEF, and SV) were not statistically significant ($P>0.05$), and the intra-group differences in various anterior tibial artery parameters (including SBP, DBP, and CS_{max}) within each of the 3 groups were statistically insignificant ($P>0.05$) (Table 2).

Comparison of the calculated results

SBPI of the anterior tibial artery was calculated by obtaining the anterior tibial artery maximum circumferential strain, blood pressure, and other parameters, according to the formula $SBPI=CS_{max} / [(LSBP-LDBP)/LDBP] \times 100\%$. ABI was calculated through obtaining systolic blood pressures of the right ankle artery and right brachial artery, according to the formula: ankle brachial index (ABI) – right ankle artery systolic blood pressure/right brachial artery systolic blood pressure. The differences in SBPI of bilateral anterior tibial artery among the 3 groups were statistically significant (the control group > negative group > positive group, $P<0.05$); while the differences in ankle brachial index among the 3 groups were statistically

Table 3. Comparisons of calculations ($\bar{x}\pm s$).

Group	Cases (n)	Left SBPI (%)	Right SBPI (%)	ABI
Control group	40	5.98±0.49	6.06±0.51	1.11±0.13
Negative group	42	5.12±0.46*	5.23±0.47*	1.09±0.11
Positive group	39	4.18±0.53***	4.04±0.55***	1.08±0.15

Comparisons between negative/positive group and the control group, * $P<0.05$; comparison between negative group and positive groups, ** $P<0.05$.

insignificant ($P>0.05$) and the intra-group differences in SBPI within each of the 3 groups were also statistically insignificant ($P>0.05$) (Table 3)

Discussion

Lower extremity atherosclerosis and occlusive arterial diseases in T2DM patients may cause ischemic necrosis of the distal tissues and seriously affect patient prognoses. Being attributed to the smaller lumen, anterior tibial artery is more susceptible to atherosclerotic occlusion [17]; therefore, prompt observation and evaluation of anterior tibial arterial lesions is particularly important. Color Doppler ultrasound scanning allows clear observation of the anterior tibial arterial wall, lumen, and blood perfusion, and thus is becoming widely accepted and applied in clinical practice [18–20]. However, when conventional color Doppler sonographic technique reveals the findings of the anterior tibial artery atherosclerosis, anterior tibial artery has mostly experienced significant structural changes and almost irreversible conditions; therefore, early detection of changes in elasticity at the early stage of anterior tibial arterial atherosclerosis are believed to have important clinical implications.

In the present study, blood pressure index (SBPI) was used to reflect the deformation ability of a local artery when blood pressure changes. Based on the theory of elasticity, the rate of blood pressure change was used to represent the overall changes in blood pressure, and circumferential strain exerted on the wall of the anterior tibial artery was used to reflect arterial deformation. In other words, when the rate of blood pressure change remains constant, SBPI increases as circumferential strain increases, implying higher elasticity, and vice versa. From the results of the present study, the maximum circumferential strain and SBPIs of the anterior tibial artery among the 3 groups significantly differed, with the control group > negative group > positive group, whereas the differences in other factors affecting SBPI, including age, bilateral anterior tibial arterial SBP and DBP, heart rate, left ventricular ejection fraction, and stroke volume, were statistically insignificant among the 3 groups, indicating that decreased arterial elasticity was still the main cause of decreased maximum circumferential strain and

SBPI in patients with T2DM. In T2DM patients, arterial elasticity may have markedly changed before the formation of atherosclerotic plaques. This decreased elasticity of the anterior tibial artery was more prominent in the patients with vascular complications than in those without vascular complications.

Ankle-brachial index (ABI) is a commonly used clinical indicator to assess lower extremity arterial disease in diabetic patients [21]. In the present study, comparative analysis of ABI among the 3 groups did not reveal any significant difference, probably because the abnormal change in ABI was only observable when atherosclerosis of the anterior tibial artery has become severe; thus, it was inappropriate to use the index to reflect the changes in anterior tibial arterial elasticity during the early stage of atherosclerosis. In addition, when lower limb arterial wall calcification is extensive, the arterial lumen is still open when pressure within the balloon cuff exceeds arterial pressure; therefore, the measured pressure significantly increases and ankle-brachial index increases or is normal, accordingly, causing an inaccurate assessment. In some patients with concomitant upper limb arterial disease, brachial artery pressure may decrease, possibly causing elevated or normal ankle-brachial index; therefore the extent of lower limb arterial lesions cannot be accurately reflected. SBPI, the indicator, is not affected by upper limb arterial conditions, and reflects elasticity of the anterior tibial artery through evaluating mechanical movement of its wall. Compared with ABI, SBPI is more objective and direct, and is conducive to finding early elasticity change of the anterior tibial artery and thus is conducive to early clinical intervention. The advantage of this and its clinical value are obvious.

From clinical data collected in the present study, we show that the differences in fasting blood glucose and glycosylated hemoglobin (HbA1c) among the 3 groups were significant ($P<0.01$, positive group > negative group > control group). HbA1c reflected blood glucose level at 8–12 weeks. An increased HbA1c level indicated poor glycemic control and was highly correlated with postprandial blood glucose. Hyperglycemia may cause glycosylation of blood proteins and result in generation of advanced glycation end product (AGE), which could readily penetrate blood vessel walls and accumulate to gradually induce a variety of pathological effects causing proliferation and smooth muscle

cell fibrosis, resulting in decreased blood vessel wall elasticity and increased stiffness [22,23]. The patients in the 3 groups also had significantly different levels of serum triglyceride (TG) and low-density lipoprotein (LDL) cholesterol ($P < 0.01$, positive group > negative group > control group), suggesting the occurrence of dyslipidemia in T2DM patients. Hyperlipidemia may facilitate blood coagulation, inhibit fibrinolysis, facilitate aggregation and release of blood platelets, reduce synthesis of prostacyclin, and damage the structure and function of endothelial cells [24]. The results of the present study also show a significant increase in total cholesterol in the control group compared with patients with T2DM ($P < 0.01$). The results of most studies show that total cholesterol level is an independent risk factor for lower extremity vascular disease [25,26], and that elevated total cholesterol may inhibit the secretion of vasodilator prostacyclin (PGI₂) by blood vessel endothelium, affecting the response of vasodilator substance to acetylcholine, and thus significantly reducing the response ability of blood microcirculation in toes of T2DM patients.

Furthermore, the differences in other anterior tibial arterial parameters (including SBP, DBP, and maximum SBPI) among the 3 groups were statistically insignificant, suggesting that the normal controls had similar anterior tibial arterial elasticity when compared with T2DM patients. Although the association between the pressures on muscular arteries and the changes in cross sectional area are complicated [27], the approach of using SBPI and its actual implications are consistent

with the theory of elasticity, and thus are able to reflect arterial elasticity.

There are 3 main limitations of this study. First, image analysis requires a clear dynamic image of the anterior tibial artery. During the examination process, probe pressure must be moderate, otherwise it affects the real wall mechanical movement, causing inaccurate analysis results and requiring high-quality image acquisition and needing an experienced physician to perform the ultrasound examination. Second, the image analysis methods were comparable only with strict and uniform standards to avoid relatively large deviations. Third, the examination time was longer than conventional ultrasound examination time. We hope that these limitations are offset by the potential clinical importance of detecting early changes in anterior tibial artery elasticity, which would aid in early diagnosis and treatment and thus prevent or delay distal tissue ischemic necrosis in patients with T2DM.

Conclusions

We have demonstrated that SBPI is a valuable new indicator for evaluating anterior tibial artery elasticity, allowing detection of early elasticity changes in the anterior tibial artery. SBPI is significantly better than the now commonly used ABI and may become preferred method and new index for evaluating elasticity of medium-sized muscular arteries.

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