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EXERCISE DIASTOLIC BLOOD PRESSURE AS AN INDICATOR OF ENDOTHELIAL FUNCTION AMONG SUBJECTS WITH NORMAL AND LOW ANKLE-BRACHIAL INDEX

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ABSTRACT

Clinically, endothelium dysfunction in atherosclerosis has primarily been defined by impairment of endothelial-dependent vasodilatation. It becomes a targeted catalyst, ultimately promoting and perpetuating atherosclerosis in the lower-extremity arteries. Peripheral arterial disease (PAD) can be determined by a simple non-invasive method (Ankle-brachial index). The low ABI (<0.9) indicates that PAD exists and reflects the systemic atherosclerosis process seemingly to be involved at all vascular beds. Hence, to reduce the heavy burden of cardiovascular disease, early identification of endothelial dysfunction should be routinely taken place. We assume that a simple mode of exercise test/treadmill could be used to predict the existing of endothelial dysfunction. Effects of acute dynamic exercise are net vasodilatation and leads to a reduction in muscular vessel resistance, with a fall in diastolic pressure. These effects are affected by intrinsic circumstances, such as an endothelial dysfunction in atherosclerotic vessels. Unfortunately, the current method of assessing the endothelial function is techniquely invasive, costly and complicated, making them unsuitable for routine clinical application. We evaluated the endothelial function with simple mode of treadmill test on atherosclerotic subject which was determined by existing PAD. The objective of this study was to assess the difference of diastolic blood pressure response to exercise (ExDBP) between subject with normal and low ABI. This was a cross-sectional study at Dr. Soetomo General Hospital Surabaya, February 2006 - May 2006. A total of 35 subjects aged 50 years or older with 1 or more risk factors of atherosclerosis were evaluated by measurement of ABI and followed by treadmill test on phase I of Bruce Protocol. Results showed that a number of 18 men and 17 women were studied, the mean age was 59.3 ± 6.39 years, and the mean BMI was 24.8 ± 3.27. The presence of low ABI was found in 15 (42.86%) patients. The mean of ExDBP of these patients were found to be higher than in subjects with normal ABI (92.67 ± 13.34 mmHg versus 78.0 ± 11.52 mmHg; p=0.001). The mean increase of ExDBP during 3 minutes treadmill among subject with Low ABI was 11.34 mmHg. The ExDBP during 3 minutes treadmill among subjects with normal ABI decreased as much as 2.5 mmHg. The ExDBP between subject with low and normal ABI was significantly different (p < 0.002). In conclusions, response of diastolic blood pressure during acute exercise is strongly different between subjects with normal and low ABI. This difference probably reflects an impairment of endothelial-dependent vasodilatation in atherosclerotic subjects.

Keywords: *endothelial function, ABI, and exercise diastolic blood pressure*

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INTRODUCTION

The manifestation of atherosclerosis is different among the population in Asia and the West. In Asia, there is an increase of cardiovascular disease incidence as the primary cause of death related to lifestyle change, which has effect on cardiovascular risk factor (Teoh 2002). The increase has much lead preventive efforts to reduce cardiovascular mortality rate. An important first step in those preventive efforts is to improve the identification capability of individuals with subclinical atherosclerosis (asymptomatic), which naturally have an increase of complication risks. Risk assessment can be carried out by determining risk score, such as Framingham score and examination of various atherosclerotic markers. One of these is the assessment of endothelial function. Vogel (2004) wrote that endothelial function has a high predictive value in determining the risk of cardiovascular events. Endothelial function assessment, therefore, becomes an important fact and target in primary and secondary prevention of cardiovascular disease (Vanhoutte 1999; Viles-Gonzalez 2004). Endothelial-related vasodilatation can be assessed in coronary as well as peripheral circulation. In coronary

circulation, we may accomplish quantitative coronary angiography, intra-coronary Doppler technique, and several non-invasive methods use Doppler echocardiography, positron emission tomography, and phase-contrast magnetic resonance imaging. In peripheral circulation we may conduct non-invasive measurement to brachial artery using ultrasonography for measuring flow-mediated dilatation. Another examination was done using venous plethysmography. Several measurements of endothelial dysfunction markers in blood circulation can be carried out as C-reactive protein (CRP) and soluble cellular adhesion molecules (CAMs) examinations (Shimokawa 2000; Verna 2002). Examination for assessing endothelial function still use invasive, expensive, and complicated method, which is unsuitable for routine clinical application. There has been no adequate examination that is declared as standard (Vogel 2004), while more simple examination remains under study, so that it is challenging to find a more simple non-invasive examination that can be easily undertaken in routine clinical practice (Tzemos 2002). The objective of this study was to prove the presence of different diastolic blood pressure response during treadmill in individuals with low and normal ABI values, so hat diastolic blood pressure during treadmill can be regarded as an indicator of endothelial function related with the capability of vasodilatation regulation.

MATERIALS AND METHODS

This study used cross-sectional design, undertaken at Cardiology Outpatient Clinic, Dr Soetomo Hospital, Surabaya, for 6 months. Samples were taken using purposive consecutive sampling. Samples consisted of patients with heart disease who met the criteria of aged 50 years or more, willing to participate in this study, ABI value not more than 1.50, no atrial fibrillation, no regular exercise, capable in exercising, and no severe disease, such as COPD, congestive heart failure, renal failure, and decompensated hepatic cirrhosis. The patients were excluded if they showed hypertensive response during treadmill. After informed consent was given, ABI value was examined and the patients were divided into two groups with low and normal ABI values. Each patient subsequently underwent diastolic blood pressure measurement after 3 minutes treadmill using Bruce protocol, first stage only.

RESULTS

The response of mean systolic, diastolic, blood pressure and pulse increase related to activity from resting standing position with 3 minutes treadmill was significantly different in group with low ABI. The response of mean systolic blood pressure and pulse increase related to activity from resting standing position with 3 minutes treadmill was significantly different in groups with normal ABI, while mean diastolic blood pressure related to activity from resting standing position with 3 minutes treadmill inclined to be constant or reduced insignificantly in group with normal ABI (Table 6). There was an increase of diastolic blood pressure during 3 minutes treadmill in group with lower ABI, reaching a mean of 11.34 mmHg, while in group with normal ABI there was a mean reduction of 2.5 mmHg. Between groups with low and normal ABI, it could be observed that in almost all observed hemodynamic parameters, in this case the diastolic pressure during sitting, standing, and 3 minutes treadmill, the pulse and recovery time were not significantly different. In diastolic blood pressure, the sitting and standing position were not significantly different in both groups (Table 7).

Table 1. Patients' characteristics

Data	Values
Age (year)	59.3 ± 6.39*
Sex: Male	18 (51.4)**
Female	17 (48.6)**
BMI	24.8 ± 3.27*
Cigarette smoking	8 (22.8)**
DM	9 (25.7)**
Hypertension	22 (62.9)**
Hyperlipidemia	15 (42.9)**
Clinical CHD	6 (17.1)**
CHD history in family	8 (22.9)**

* Mean ± SD
** n (%)

From group with lower ABI value, 12 patients (80.0%) showed abnormal response in diastolic blood pressure during treadmill. Contrastingly, in group with normal ABI, 15 patients (75.0%) showed normal response in diastolic blood pressure during treadmill. The difference of diastolic blood pressure response during 3 minutes treadmill between both groups can be clearly observed in Figure 8. The mean of diastolic blood pressure during treadmill in patients with low ABI value appeared to be significantly higher than the mean in group with normal ABI value (92.67 ± 13.3 mmHg vs 78.0 ± 11.5 mmHg, $p = 0.002$).

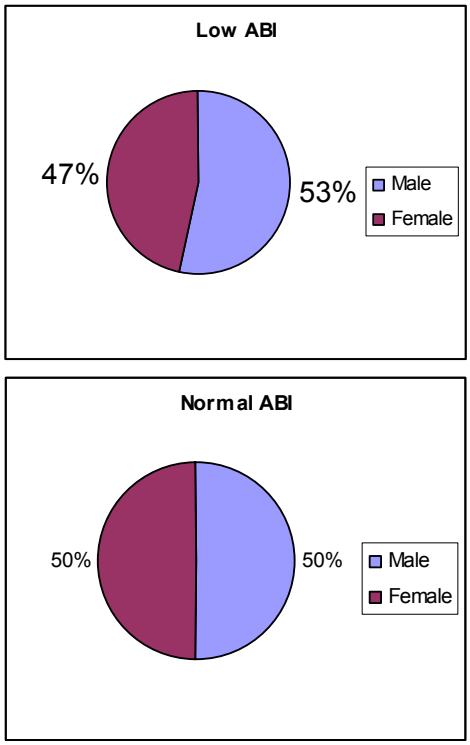

Figure 1. Patients proportion, according to sex and ABI value.

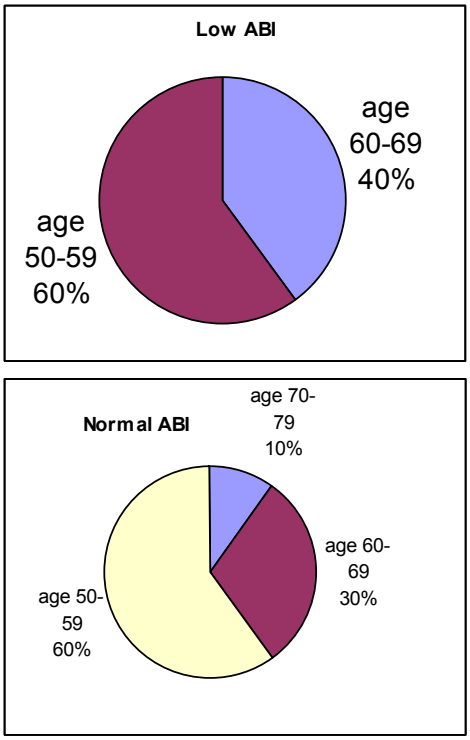

Figure 2. Patients proportion, according to age and ABI value.

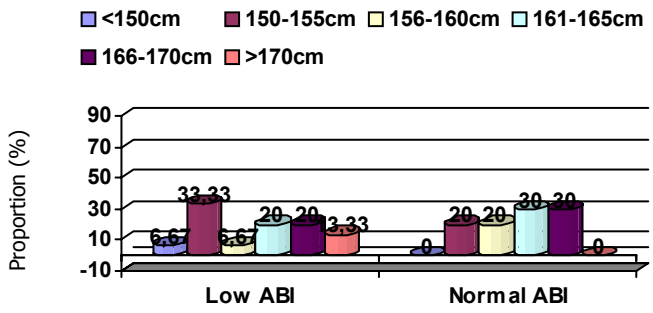

Figure 3. Patients proportion, according to body height and ABI value.

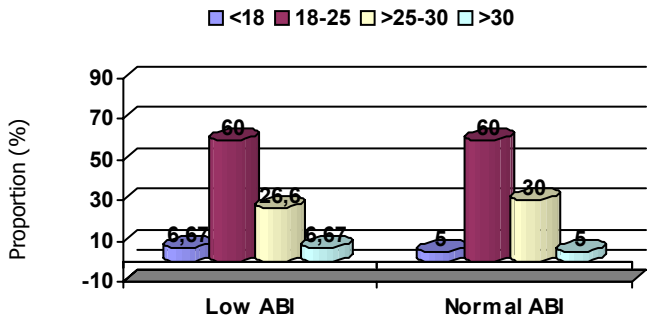

Figure 4. Patients proportion, according to BMI and ABI value.

Table 2. Correlation between age, BMI and body height with ABI value.

Data	Low ABI	Normal ABI	P	95%CI Lower : Upper
Age (year)	58.07 ± 6.22	60.30 ± 6.51	.314 (ns)	-2.21 : 6.67
BMI	24.82 ± 3.2	24.78 ± 4.0	.973 (ns)	-2.52 : 2.43
Body height (cm)	161.8 ± 9.52	162.35 ± 6.3	.838 (ns)	-4.89 : 5.99

Statistical analysis with T-test; ns: *non significant*

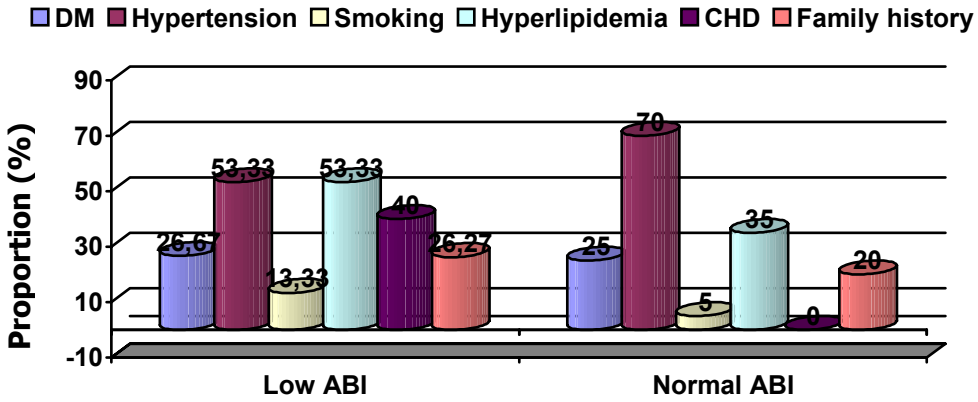

Figure 5. Patients proportion according to atherosclerotic risk factor and ABI value.

Table 3. Correlation between atherosclerotic risk factor and ABI value.

Data	Low ABI	Normal ABI	P	95%CI Lower : Upper
Smoker	4	4	0.700*	0.14 : 3.352
Non-smoker	11	16		
Hypertension	8	14	0.481*	0.506 : 8.231
Non-hypertension	7	6		
DM	4	5	0.911*	0.199 : 4.224
Non-DM	11	15		
Hyperlipidemia	8	7	0.460*	0.120 : 1.852
Non- Hyperlipidemia	7	13		
CHD history in family	4	4	0.700*	0.141 : 3.352
No history	11	16		
Lipid profile:				
- Total cholesterol	241.58 ± 30.1	211.39 ±36.7	.025 **	
- TG	102.58 ± 19.1	114.56 ±41.7	.361** (ns)	-56.4 : -4.02
- LDL	151.25 ± 27.3	129.22 ±29.2	.047**	
- HDL	51.25 ± 7.3	53.61 ±13.63	.588** (ns)	-43.7 : -.2967

*Statistical analysis with X^2 test;
** Statistical analysis with T-test; ns: *non significant*

Table 4. Correlation between coronary heart disease and ABI value.

Data	Low ABI	Normal ABI	P	95%CI Lower : Upper
Clinical CHD	6	0	0.003	1.873 : 5.543
No Clinical CHD	9	20		
*Statistical analysis with X^2 test;				

Table 5. Mean blood pressure related with measurement position.

Data	Sitting	Standing	P*	95%CI Lower : Upper
Low ABI				
Systolic BP	138.67 ± 14.1	138.67 ± 15.1	.10 (ns)	-2.96 : 2.96
Diastolic BP	82.00 ± 5.6	81.33 ± 5.2	.582 (ns)	-1.87 : 3.201
Normal ABI				
TD Systolic	141.5 ± 16.6	141.0 ± 16.5	.577 (ns)	-1.34 : 2.344
TD Diastolic	79.50 ± 6.0	80.50 ± 7.6	.330 (ns)	-3.09 : 1.09
*Statistical analysis with T-test; ns: non significant				

Table 6. Mean blood pressure and pulse rate related to activity

Data	Resting (standing)	Treadmill	P*	95%CI Lower : Upper
Low ABI				
Systolic BP	138.67 ± 15.1	176.00 ± 19.2	.000	-30.24: -11.297
Diastolic BP	81.33 ± 5.2	92.67 ± 13.3	.002	-17.56: -5.1007
Pulse	87.07 ± 11.3	129.2 ± 16.5	.000	-49.65: -34.62
Normal ABI				
Systolic BP	141.0 ± 16.5	179.00 ± 21.5	.000	-44.72: -31.277
Diastolic BP	80.50 ± 7.6	78.00 ± 11.5	.330 (ns)	-2.73 : 7.73
Pulse	84.15 ± 12.6	127.9 ± 17.3	.000	-51.10 : -36.40
*Statistical analysis with T-test; ns: non significant				

Table 7. Blood pressure and pulse response during resting and 3 minutes treadmill

Data	Low ABI	Normal ABI	P*	95%CI Lower : Upper
BP (resting):				
Systolic (sitting)	138.67 ± 14.1	141.5 ± 16.6	.598 (ns)	-8.00 : 13.67
Systolic (standing)	138.67 ± 15.1	141.0 ± 16.5	.670 (ns)	-8.72 : 13.39
Diastolic (sitting)	82.00 ± 5.6	79.50 ± 6.0	.221 (ns)	-6.58 : 1.58
Diastolic (standing)	81.33 ± 5.2	80.50 ± 7.6	.717 (ns)	-5.47 : 3.80
TD (treadmill):				
Systolic	176.00 ± 19.2	179.00 ± 21.5	.672 (ns)	-11.28 : 17.28
Diastolic	92.67 ± 13.3	78.00 ± 11.5	.002	-23.5 : -5.85
Pulse (resting)	87.07 ± 11.3	84.15 ± 12.6	.484 (ns)	-11.29 : 5.46
Pulse (treadmill)	129.2 ± 16.5	127.9 ± 17.3	.824 (ns)	-13.09 : 10.49
Recovery(minutes)	4.0 ± 1.5	3.9 ± 1.4	.839 (ns)	-1.09 : 0.89
*Statistical analysis with T-test; ns: non significant				

DISCUSSION

In this study, peripheral circulation of atherosclerotic patients was examined for determining those with low ABI value. Although ABI examination is simple, inexpensive, and non-invasive for peripheral atherosclerotic disease (Mohler 2001), it has several shortcomings, including: probability of normality in well-collateralized and resting patients, probability of normality or "supernormality" in patients with arterial calcification (DM, end-stage renal disease), not determining location of disease or stenosis vs. occlusion. ABI value more than 1.50 or "supernormal" indicates high severity of compression in leg arteries, and this affects the accuracy of arterial obstruction measurement (Jaff 2002). However, there were no patients with ABI value more than 1.50.

There are several risk factors affecting the occurrence of atherosclerotic process, such as age, genetic, smoking, hypertension, hyperlipidemia, DM, and obesity (Ross 1999). In the course of time, those factors may lead to the manifestation of atherosclerosis, including in peripheral circulation. The patients in this study was limited to those aged more than 50 years since in these patients we commonly find abnormal ABI value, although it does not necessarily occur all the time (Greenland 2000). The consideration of ABI examination for assessing risk level remains limited to individuals aged $\geq$ 50 years. Cross-sectional analysis in Atherosclerosis Risk in Communities Study (ARIC) showed that ABI prevalence < 0.9 (low ABI) is rare in young individuals (Zheng 1997). Therefore, ABI may have additional value for atherosclerotic risk assessment in certain population, particularly in individuals aged $\geq$ 50 years or those with moderate or high atherothrombotic risk based on traditional risk factors. If the patient has low ABI value, he may have an increase of risk category (Greenland 2000).

Chenzbraun (2001) reported that patients with atherosclerotic risk factors may experience disturbance in peripheral response against exercise. This author did not investigate direct correlation between atherosclerotic risk factors and the occurrence of PAD. However, he assumed that vascular behavior in patients with atherosclerotic risk factors is related to endothelial dysfunction. In this study, we tried to observe correlation between atherosclerotic risk factors and ABI value. We found that, apparently, several atherosclerotic risk factors, including cigarette smoking, hyperlipidemia, CHD history in the family, were related with lower ABI value, although the correlation was statistically not significant, which was likely due to smaller size of the sample. In hypertensive patients such pattern was not found, and this was presumably due its high prevalence among elderly, so that, with the smaller size of the sample, correlation between hypertension as atherosclerotic risk factor and lower ABI value was not apparent. CHD clinical occurrence was found in group with low ABI value. Statistical analysis also showed positive correlation between low ABI value and CHD clinical occurrence. The correlation was significant, with $p = 0.003$. The result was consistent with the report of Soemantri in 2004.

Bruce Protocol in treadmill is the most commonly used procedure and has been highly validated. It has seven stages, each stage lasts for 3 minutes, resulting in 21 minutes exercise as complete test. In stage 1, the patient walks in 1.7 mph (2.7 km) with inclination of 10% and the estimated energy expense was 4.8 METs (metabolic equivalents). Speed and inclination was increased in the subsequent stages. Modified Bruce Protocol was used for testing exercise load in acute myocardial infarct patients after 1 week (Fletcher 2001; Hill 2002). In this study, a simple method was modified to assess blood pressure soon after exercise using Bruce Protocol stage I only. The considerations were as follows: immediate effect of dynamic of dynamic exercise has already emerged during the first minutes (Fletcher 2001; Rohan 2003), low exercise intensity is approximately similar to daily activities and has been used in larger study (Fletcher 2001; Tzemos 2002). The exercise load test can be accomplished in most of the subjects in the existing cardiovascular condition, so that it can be practically applied in outpatient setting.

Most of the studies observing blood pressure during exercise emphasize the diastolic blood pressure. Abnormal response of systolic blood pressure has been studies and promised an alternative of simple examination for assessing the endothelial function (Tzemos 2002). The interpretation of systolic blood pressure measured in brachial artery during exercise is quite complicated since during exercise systolic blood pressure is higher than aortic central blood pressure with $\leq$ 80 mmHg as a result of frequency-dependent transmission, which is the characteristic of upper extremity (Rowell 1968). In contrast to systolic blood pressure, diastolic blood pressure remains constant in brachial artery and central artery during exercise. Diastolic blood pressure measurement during exercise is rarely reported, possibly due to its level of accuracy. We tried to create simple verification test by comparing manual measurement method in 4th phase Korotkoff sound with automatic measurement by skilled personnel (nurse) and it was acceptable.

Diastolic blood pressure is determined primarily by cardiac output and peripheral vascular resistance. During exercise, cardiac output increases and peripheral

vascular resistance reduce as a response against vasodilatation of blood vessels in skeletal muscles that are contracting during the exercise (Concu 2000; Rohan 2003), so that the immediate increase in diastolic blood pressure during exercise can be regarded as a result of imbalance cardiac output or vasodilatation failure of the blood pressure in skeletal muscle system. Vasodilatation of blood vessels in contracting muscle is affected by several mediators, either those related to endothelium or not, including nitric oxide (NO) (Gilligan 1994; Griendling 2001). Previous study reported that there is endothelial-dependent vasodilatation failure in patients with PAD. PAD severity is related to the severity of endothelial dysfunction (Oka 2001). The observation in this study, which revealed positive correlation between low ABI values, indicating the presence of PAD with abnormal response from diastolic blood pressure during 3 minutes treadmill, was consistent with that report.

To our knowledge, there have been no studies observing diastolic blood pressure during exercise in PAD patients. Akhras in 1985 observed the response of increased diastolic blood pressure during exercise in Coronary Artery Disease (CAD) patients, and concluded that the increase of diastolic blood pressure response during exercise is an indication of CAD severity. Brett (2000) reported that the response of diastolic blood pressure increase during exercise has positive correlation with serum cholesterol level and insulin resistance. The study investigating endothelial function with novel non-invasive technique conducted by Tzemos in 2002 had several similarities and differences from this study. For example, in Dundee step test uses step test of 17.5 cm height and this study used treadmill test with 10% inclination. The indicator of Dundee step test was systolic blood pressure, while this study used diastolic blood pressure, and the working load in the first study was 5 metz, and in the latter was 4.5 metz. Subjects in Dundee step test (1998) were hypertensive and non-hypertensive patients, while in this study we involved those with normal and low ABI. In subjects with PAD, Brevetti in 2003 found endothelial dysfunction using flow-mediated dilation (FMD) technique in brachial artery and concluded that FMD examination can provide added value in ABI examination for predicting cardiovascular events. In this study we used more simple examination, i.e., diastolic blood pressure during treadmill for assessing endothelial dysfunction.

CONCLUSION

In this study that observing patients aged more than 50 years, in 42.86% of the patients we found a low ABI value, which is recently regarded as a marker for identifying patients with increased risk of atherothrombosis, particularly in peripheral circulation, and related to the increased risk of atherothrombosis in coronary and brain circulation. The increase of diastolic blood pressure response during 3 minutes treadmill in group with low ABI is averagely 11.34 mmHg, while in those with normal ABI there is a mean reduction of 2.5 mm Hg. Statistical analysis demonstrated significant difference in diastolic blood pressure response during 3 minutes treadmill between individuals with low and normal ABI, with $p = 0.002$. The difference probably shows the failure of endothelial-dependent vaso-dilatation in atherosclerotic individuals. A confirmative study with better design is needed for the results obtained in this study. Since ABI is a non-invasive, cheap, quick, and simple examination that can be carried out in cardiovascular outpatient setting, this examination is necessary to complete the basic data of certain patients. The establishment of PAD diagnosis in ABI examination may lead to a conclusion that the patient has atherosclerotic condition with an increase of atherothrombotic event. For preventive and promotion purposes, the identification of patients with increased risk is necessary. Patients selected for routine ABI screening examination are those with age of more than 50 years, or less than 50 years as an additional value for the existing traditional risk factor assessment. By taking into attention that the response of diastolic pressure during treadmill in atherosclerotic patients (low ABI) is abnormal, which is very likely due to endothelial dysfunction, the monitoring of the pattern of diastolic pressure change during any treadmill exercise should be improved more. The finding of abnormal diastolic pressure response in each treadmill exercise has not provided definitive value of the presence of endothelial dysfunction. However, the data can be used as a basis for confirmation in subsequent examination, and, if necessary, can be used a confirmation with other more sophisticated or invasive examinations, such as flow-mediated dilation, response against vasodilator intra-arterial (adenosine, sodium nitroprusside, acetyl-choline), Positron-Emission Tomography Scanning, and phase-contrast MRI.

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