Open Access

Arterial Stiffness, But Not Endothelium-Dependent Vasodilation, is Related to a Low Ankle-Brachial Index in the Elderly - The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study

Lars Lind*

Department of Medicine, Uppsala University Hospital, Sweden

Abstract: *Background*: Arterial compliance and endothelium-dependent vasodilation are two characteristics of the vessel wall. In the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study we studied the relationships between arterial compliance and endothelium-dependent vasodilation *vs* the ankle-brachial index, a clinically used index of peripheral artery disease.

Methods: In the population-based PIVUS study (all aged 70), arterial compliance was determined by ultrasound as the distensibility of the carotid artery and the stroke volume to pulse pressure (SV/PP) ratio by echocardiography, while endothelium-dependent vasodilation was assessed by the invasive forearm technique with acetylcholine (EDV) and brachial artery ultrasound (FMD) in 519 subjects in whom the ankle-brachial index (ABI) was investigated.

Results: After adjustments for gender and Framingham risk score, distensibility in the carotid artery and the SV/PP ratio were significantly reduced in subjects with a reduced ABI (<0.9) in both legs (n=15, p=0.0006 and p= 0.0003, respectively). Endothelium-dependent vasodilation was not significantly related to a reduced ABI.

Conclusion: An impaired arterial compliance, but not endothelium-dependent vasodilation, was related to a low ABI in both legs after adjustment for major risk factors, suggesting that atherosclerosis in the leg arteries is associated with arterial compliance also in other parts of the vasculature.

Keywords: Atherosclerosis, artery, compliance, endothelium, vasodilation.

INTRODUCTION

Peripheral vascular disease (PVD) is a common disorder of the elderly. In the epidemiological setting it is most often defined either according to a history of claudicatio intermittens or by a low ankle-brachial index (ABI) [1-5]. The underlying cause is in the majority of cases a stenosis in the lower limb arteries due to atherosclerotic lesions, and it has repeatedly been shown that a low ABI could predict the major cardiovascular disorders in prospective cohort studies [1-5].

Arterial compliance and endothelium-dependent vasodilation are two other major characteristics of the arteries. These two vascular features are both related to the main cardiovascular risk factors [6-12], and have both the ability to predict future cardiovascular outcomes in prospective studies [13-17].

Both a reduced arterial compliance and an impaired endothelium-dependent vasodilation have previously been described in patients with overt PVD [18-22]. However, there are sparse data on how these two indices of vascular function relates to ABI in a general population. In the present study, we investigated the relationships between arterial compliance and endothelium-dependent vasodilation *vs* ABI, using data from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study [23], with the hypothesis that both arterial compliance and endothelium-dependent vasodilation were impaired in those with a low ABI.

MATERIAL AND METHODS

This section has previously been given in detail [23, 24].

Subjects

Eligible were all subjects aged 70 living in the community of Uppsala, Sweden. The subjects were randomly chosen from the register of community living. 1016 subjects participated giving a participation rate of 50.1%. In the last consecutive 519 subjects of the sample, ABI was measured. The study was approved by the Ethics Committee of the University of Uppsala. Signed informed consent was given by all subjects.

All subjects were investigated in the morning after an over-night fast. No medication or smoking was allowed after midnight. An arterial cannula was inserted in the brachial artery for blood sampling and later regional infusions of vasodilators. Blood pressure was measured by a calibrated mercury sphygmomanometer. Fasting blood glucose and lipids were measured by standard techniques and from these values the Framingham risk score was calculated [25]. Basic characteristics of the total sample are given in Table **1**, since the ABI subsample did not differ from the total sample in terms of the major characteristics.

Approximately 10% of the cohort reported a history of coronary heart disease, 4% reported stroke and 9% diabetes

*Address correspondence to this author at the Department of Medicine, University Hospital, 751 85 Uppsala, Sweden; Tel: +46709726805; E-mail: lars.lind@medsci.uu.se

Table 1. Major Cardiovascular Risk Factors, Prevalence of Cardiovascular Medication and Disorders in Subjects with a Normal Ankle-Brachial Index (ABI>0.9), and in Subjects with a Low ABI in One or Both Legs

	Normal ABI	Low ABI in One Leg	Low ABI in Both Legs	p-Value
n	482	22	15	
Females (%)	48	50	40	0.81
BMI (kg/m2)	27.0 ±4.3	26.1 ±4.2	27.9 ±4.8	0.43
SBP (mmHg)	149 ±22	157±25	172±23**	0.0001
DBP (mmHg)	79 ±10	78 ±10	82 ±9	0.41
LDL-cholesterol (mmol/l)	3.2 ±0.8	3.4 ±1.0	3.4 ±0.9	0.53
HDL-cholesterol (mmol/l)	1.5 ±0.4	1.5 ±0.3	1.3 ±0.2	0.27
Serum triglycerides (mmol/l)	1.3 ±0.6	1.4 ±0.7	1.6 ±0.4	0.070
Fasting blood glucose (mmol/l)	5.4 ±1.5	6.5 ±3,7**	5.8 ±1.9	0.011
Current smoking (%)	7	32**	33**	0.0001
Framingham risk score	11.1±3.3	12.7±3.5**	13.9±3.0**	0.0001
Antihypertensive medication (%)	32	41	60	0.07
Statin use (%)	16	9	27	0.37
Antidiabetic treatment (%)	6	18	13	0.15
History of myocardial infarction (%)	8	9	20	0.22
History of stroke (%)	5	4	0	0.65

**Means are given ± SD or %. SBP= Systolic blood pressure. DBP= Diastolic blood pressure. BMI= Body mass index.

mellitus. Almost half the cohort reported any cardiovascular medication (45%), with antihypertensive medication being the most prevalent (32%). Fifteen percent reported use of statins, while insulin and oral antiglycemic drugs were reported in 2 and 6%, respectively.

Ankle-Brachial Index

Systolic blood pressure was measured in the brachial artery using the arm with the highest value and in both anterior tibial arteries with Doppler after at least 30 min rest in the supine position. The ABI was calculated for each leg separately.

The Invasive Forearm Technique

Forearm blood flow (FBF) was measured by venous occlusion plethysmography (Elektromedicin, Kullavik, Sweden). After evaluation of resting FBF, local intra-arterial drug-infusions were given during 5 minutes for each dose. The infused dosages were 25 and 50 ug/minute for Acetylcholine (Clin-Alpha, Switzerland) to evaluate endothelium-dependent vasodilation (EDV) and 5 and 10 ug/minute for SNP (Nitropress, Abbot, UK) to evaluate endothelium-dependent vasodilation (EIDV).

EDV was defined as FBF during infusion of 50 ug/min of Acetylcholine minus resting FBF divided by resting FBF. EIDV was defined as FBF during infusion of 10 ug/min of SNP minus resting FBF divided by resting FBF.

The Brachial Artery Ultrasound Technique

The brachial artery was assessed by external B-mode ultrasound imaging 2 – 3 cm above the elbow (Acuson XP128 with a 10 MHz linear transducer, Acuson Mountain View, California, USA). Blood flow increase was induced by inflation of a pneumatic cuff placed around the forearm to a pressure at least 50 mmHg above systolic blood pressure for 5 min. FMD was defined as the maximal brachial artery diameter recorded between 30 and 90 sec following cuff release minus diameter at rest divided by the diameter at rest.

Pulse Wave Analysis for Arterial Compliance and Vasoreactivity

The pulse wave in the radial artery was captured by aplanation tonometry (Sphygmocor, Pulse Wave Medical Ltd, Australia) [24]. Based on transfer functions, aortic systolic and diastolic blood pressures were calculated. Central pulse pressure (PP) was defined as central systolic minus central diastolic blood pressure.

Carotid Artery Compliance

The diameter of the common carotid artery (CCA) of the right side 1-2cm proximal of the bifurcation was measured at its maximal diameter in systole and the minimal diameter in diastole. The distensibility of the CCA was calculated as the change in diameter maximum to minimum in relation to the minimal diameter in diastole divided by the central PP obtained by pulse wave analysis.

Stroke Volume to Pulse Pressure Ratio

Echocardiography was performed (2.5 MHz transducer, Acuson XP124, California, USA) and using Teichholz formula ejection fraction (EF) and stroke volume (SV) were calculated. The SV/PP ratio was calculated as SV divided by central PP (achieved by pulse wave analysis) [24].

Statistics

Non-normally distributed variables (such as EDV, EIDV and FMD) were log-transformed to achieve a normal distribution. ANOVA and ANCOVA were used to compare means between groups. The Bonferroni correction was used for post-hoc analysis. The chi-square test was used to evaluate differences in proportions. Two-tailed significance values were given with p< 0.05 regarded as significant. The statistical programme package StatView (SAS inc, NC; USA) was used.

RESULTS

The mean ABI in the population was 1.15 (0.16 SD) in the right leg and 1.14 (0.16) in the left leg.

When a reduced ABI was defined as <0.90, twenty-two subjects showed a reduced ABI in one of the legs and another 15 subjects showed an impaired ABI in both legs.

If the sample was divided into these two groups together with a group with a normal ABI in both legs, the two groups with a reduced ABI showed higher SBP and Framingham risk score and an increased prevalence of smoking compared with subjects with a normal ABI. Levels of DBP, BMI, LDL or HDL-cholesterol, triglycerides were not different between the groups, while fasting glucose was significantly increased in the group with a low ABI in one leg only (see Table **1** for details).

The prevalences of antihypertensive medication, statin use and antidiabetic treatment were not significantly between the groups. Neither were any significant differences between the groups seen regarding history of myocardial infarction and stroke (Table **1**).

When the sample was divided into these three groups, a significant difference in EIDV was seen between the groups (p=0.013) after adjustment for gender, with similarly reduced levels in both groups with a reduced ABI compared to the normal group. EDV and FMD were not different between the three groups (see Table **2** for details).

Both of the arterial compliance measurements were significantly different between the groups (p<0.004 for both) after adjustment for gender. In both the case of CCA distensibility and the SV/PP ratio, reductions were only seen in the group with a reduced ABI in both legs when compared to the normal group (p=0.0006 and 0.0003, respectively, Fig. **1**). The differences between the groups were still significant also after addition of the Framingham score as independent variable to the models (p=0.02 for CCA distensibility and p=0.01 for the SV/PP ratio).

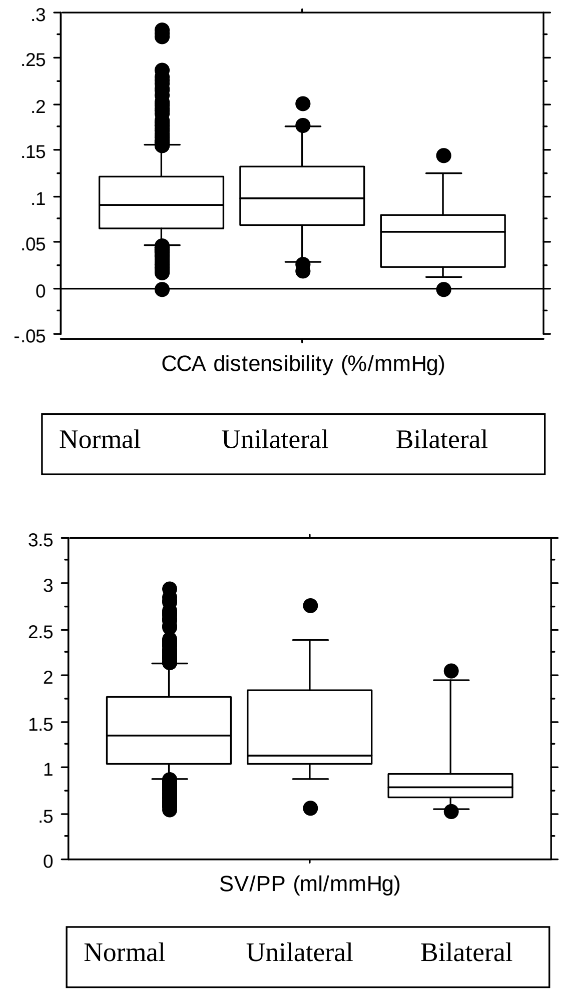

Fig. (1). Common carotid artery (CCA) distensibility (upper panel) and the stroke to pulse pressure ratio (SV/PP, lower panel) given as median, 10 th, 25 th, 57 th and 90th percentiles in subjects with unilateral or bilateral reduction in ankle-brachial index (ABI<0.90) and in those with a normal ABI. p<0.005 for bilateral *vs* normal and p<0.05 for bilateral *vs* unilateral for both markers of arterial compliance.

DISCUSSION

The present study showed two measurements of arterial compliance to be reduced in subjects with a low ABI in both

Table 2. Measures of Endothelium-Dependent Vasodilation in Subjects with no Leg with an Ankle-Brachial Index (ABI) >0.90 (Normal) or with ABI <0.90 in One or Two Legs (Unilateral and Bilateral, Respectively)

	Normal	Unilateral	Bilateral	ANOVA p-Value
n	482	22	15	
EDV (%)	476 (201-919)	454 (156-751)	262 (191-618)	0.10
EIDV (%)	321 (144-627)	240 (84-443)	221 (103-454)	0.013
FMD (%)	4.7 (0-10)	3.2 (0.7-7.5)	4.5 (0-13.3)	0.13

Median and 10th and 90th percentiles are given. EDV= endothelium-dependent vasodilation (invasive forearm technique). EIDV= endothelium-independent vasodilation (invasive forearm technique). FMD= flow mediated dilatation of the brachial artery.

legs after adjustment for major cardiovascular risk factors, while endothelium-dependent vasodilation was not altered in subjects with a low ABI.

Arterial Compliance

The ABI is a commonly used variable to asses the occurrence of peripheral artery disease in epidemiological studies, as well as in the clinical setting. A low ABI has repeatedly been shown to predict future cardiovascular events and 0.90 is usually used as a cut-off limit [5, 21]. In the present study, a reduced arterial compliance was mainly seen in those with a low value in both legs.

A reduced arterial compliance has previously been recorded in patients with overt PVD, as evaluated by compliance in the carotid or femoral artery [21, 22]. However, no clear effect of PVD on arterial compliance was seen when evaluated by pulse wave analysis [26, 27]. This is the first study evaluating two indices of arterial compliance *vs* the ABI in a population-based sample.

The major risk factors included in the Framingham risk score, blood pressure, smoking, LDL- and HDL-cholesterol and diabetes, have all been associated with both atherosclerosis as well as reduced arterial compliance [10-12, 17]. It was therefore of importance to investigate if any relationship between a low ABI and a reduced arterial compliance was present also after adjustment for the Framingham score, although it was mainly SBP and smoking that was related to a low ABI in the present study. Using adjustment for the Framingham score, PVD was associated with arterial stiffness independently of the major risk factors.

The fact that the measures of arterial compliance was mainly impaired in subjects with a low ABI in both legs might indicate that these subjects were having a more profound atherosclerotic disease that those subjects with a reduced ABI in one of the legs only. This assumption is further validated by the finding that the Framingham score was higher in subjects with a low ABI in both legs as compared to those with a reduced ABI in one of the legs only.

A clinical usefulness of this finding is that if a reduced arterial compliance is found ABI should be evaluated since the likelihood of PAD in those subjects are increased.

Endothelium-Dependent Vasodilation

In the present study endothelium-dependent vasodilation was not related to ABI, neither when measured in the brachial artery, nor when evaluated in the forearm resistance arteries.

This in contradiction to previous studies showing a reduced FMD in patients with overt PVD [18-20]. It has recently been shown that FMD is of limited value in subjects with reduced arterial compliance [28, 29], and the fact that arterial compliance as such was related to a low ABI limits the power to detect an effects of a low ABI on FMD. Previous studies using FMD were performed in subjects with overt PVD possibly representing profoundly more severe cases of PVD than found in the present population-based study, in which only a minority of those with a low ABI reported any claudication symptoms. In these claudication patients FMD measurements seem to be of value, as they predict future cardiovascular events [30, 31].

No previous study has reported acetlycholine-mediated dilation in the forearm vessels in subjects with low ABI. Since one study reported a reduced endothelium-dependent vasodilation in the leg resistance vessels in PVD patients [32], it may be that only the affected vascular bed is influenced by the atherosclerotic process.

Contrary to the finding with EDV, EIDV was reduced in subjects with a low ABI. This indicates that the vasodilatory mechanisms not influenced by the endothelium, such as the vascular smooth muscle cells in the forearm resistance arteries are impaired in subjects with a low ABI. Thus, vasodilation in resistance arteries is a problem in subjects with a low ABI and might contribute to the symptoms seen in peripheral artery disease.

Limitations

The present sample is limited to Caucasians aged 70. Caution should therefore be made to draw conclusions to other ethnic and age groups.

The PIVUS study had a moderate participation rate. However, an analysis of non-participants showed the present sample to be fairly representative of the total population regarding most cardiovascular disorders and drug intake.

EIDV was only assessed by one of the methods for practical and ethical reasons not to prolong the investigation procedure. We have previously shown that EIDV evaluated by SNP infusion in the brachial artery and GNT provoked change in brachial artery diameter are closely related [33], so additional measurements of EIDV would probably not add substantial information to the study.

It must furthermore be pointed out that none of the measurements of arterial compliance or endothelium-dependent vasodilation were carried out in the leg vessels.

Thus, we evaluated vascular characteristics in vascular beds being remote from those being the basis for the measurement of the low ABI. Other results may have emerged if arterial compliance or endothelium-dependent vasodilation had been evaluated in the vasculature of the legs.

Another limitation is that aortic pulse wave velocity, the most commonly used index of arterial compliance, was not evaluated in the present cohort.

Only six subjects reported claudication, and due to the small number no statistical evaluation of vascular function in subjects with overt claudication could be performed.

In conclusion, an impaired arterial compliance, but not endothelium-dependent vasodilation, was related to a low ABI in both legs after adjustment for major risk factors, suggesting that atherosclerosis in the leg arteries influences arterial compliance also in other parts of the vasculature.

ACKNOWLEDGEMENT

The outstanding work at the endothelium laboratory performed by Nilla Fors, Jan Hall, Kerstin Marttala and Anna Stenborg in the collection and processing of the data is highly acknowledged.

REFERENCES

[1] Feringa HH, Bax JJ, van Waning VH, *et al*. The long-term prognostic value of the resting and postexercise ankle-brachial index. Arch Intern Med 2006; 166: 529-35.

[2] Guerrero M, Harjai K, Stone GW, *et al.* Usefulness of the presence of peripheral vascular disease in predicting mortality in acute myocardial infarction patients treated with primary angioplasty (from the Primary Angioplasty in Myocardial Infarction Database). Am J Cardiol 2005; 96: 649-54.

[3] Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW. Framingham Study.The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. Arch Intern Med 2003; 163: 1939-42.

[4] Tsai AW, Folsom AR, Rosamond WD, Jones DW. Ankle-brachial index and 7-year ischemic stroke incidence: the ARIC study. Stroke 2001; 32: 1721-4.

[5] Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation 2004; 110: 3075-80.

[6] Linder L, Kiowski W, Buhler FR, Lüscer TF. Indirect evidence for the release of endothelium-derived relaxing factor in the human forearm circulation *in vivo*: Blunted response in essential hypertension. Circulation 1990; 81: 1762-7.

[7] Creager MA, Cooke JP, Mendelsohn ME, *et al*. Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. J Clin Invest 1990; 86: 228-34.

[8] Johnstone MT, Creager SJ, Scales KM, Cusco JA, Lee BK, Creager MA. Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. Circulation 1993; 88: 2510-6.

[9] Celermajer DS, Sorensen KE, Gooch VM, *et al.* Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992; 340: 1111-5.

[10] Lehmann ED, Hopkins KD, Rawesh A, *et al*. Relation between number of cardiovascular risk factors/events and noninvasive Doppler ultrasound assessments of aortic compliance. Hypertension. 1998; 32: 565-9.

[11] Laurent S, Caviezel B, Beck L, *et al*. Carotid artery distensibility and distending pressure in hypertensive humans. Hypertension 1994; 2: 878-83.

[12] Roman MJ, Pini R, Pickering TG, Devereux RB. Non-invasive measurements of arterial compliance in hypertensive compared with normotensive adults. J Hypertens 1992; 10: S115-8.

[13] Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000; 101: 1899-906.

[14] Perticone F, Ceravolo R, Pujia A, *et al*. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation 2001; 104: 191-6.

[15] Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. Hypertension 1998; 32: 570-4.

[16] London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. Hypertension 2001; 38: 434-8.

[17] Lind L, Andren B, Sundstrom J. The stroke volume/pulse pressure ratio predicts coronary heart disease mortality in a population of elderly men. J Hypertens 2004; 22: 899-905.

[18] Poredos P, Golob M, Jensterle M. Interrelationship between peripheral arterial occlusive disease, carotid atherosclerosis and flow mediated dilation of the brachial artery. Int Angiol 2003; 22(1): 83-7.

[19] Yataco AR, Corretti MC, Gardner AW, Womack CJ, Katzel LI. Endothelial reactivity and cardiac risk factors in older patients with peripheral arterial disease. Am J Cardiol 1999; 83: 754-8.

[20] Silvestro A, Scopacasa F, Ruocco A, *et al*. Inflammatory status and endothelial function in asymptomatic and symptomatic peripheral arterial disease. Vasc Med 2003; 8: 225-32.

[21] Taniwaki H, Shoji T, Emoto M, *et al*. Femoral artery wall thickness and stiffness in evaluation of peripheral vascular disease in type 2 diabetes mellitus. Atherosclerosis 2001; 158: 207-14.

[22] Cheng KS, Tiwari A, Baker CR, Morris R, Hamilton G. Seifalian AM. Impaired carotid and femoral viscoelastic properties and elevated intima-media thickness in peripheral vascular disease. Atherosclerosis 2002; 164: 113-20.

[23] Lind L, Fors N, Hall J, Marttala K, Stenborg A. A comparison of three different methods to evaluate endothelium-dependent vasodilation in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Arterioscler Thromb Vasc Biol 2005; 25: 2368-75.

[24] Lind L, Fors N, Hall J, Marttala K, Stenborg A. A Comparison of Three Different Methods to Evaluate arterial compliance in the Elderly. The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study. J Hypertens 2006; 24: 1075-82.

[25] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998; 97: 1837-47.

[26] Duprez DA, De Buyzere MM, De Bruyne L, Clement DL, Cohn JN. Small and large artery elasticity indices in peripheral arterial occlusive disease (PAOD). Vasc Med 2001; 6: 211-4.

[27] Resnick HE, Lindsay RS, McDermott MM, *et al*. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation 2004; 109: 733-9.

[28] Witte DR, van der Graaf Y, Grobbee DE, Bots ML. SMART Study Group. Measurement of flow-mediated dilatation of the brachial artery is affected by local elastic vessel wall properties in high-risk patients. Atherosclerosis 2005; 182: 323-30.

[29] Lind L. Arterial compliance influences the measurement of flow-mediated vasodilation, but not acetylcholine-mediated forearm blood flow The prospective investigation of the vasculature in uppsala seniors (PIVUS) study. Atherosclerosis 2007; 190: 212-5.

[30] Gokce N, Keaney JF Jr, Hunter LM, *et al.* Predictive value of non-invasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. J Am Coll Cardiol 2003; 41: 1769-75.

[31] Brevetti G, Silvestro A, Schiano V, Chiariello M. Endothelial dysfunction and cardiovascular risk prediction in peripheral arterial disease: additive value of flow-mediated dilation to ankle-brachial pressure index. Circulation 2003; 108: 2093-8.

[32] Weiss T, Fischer D, Hausmann D, Weiss C. Endothelial function in patients with peripheral vascular disease: influence of prostaglandin E1. Prostaglandins Leukot Essent Fatty Acids 2002; 67: 277-81.

[33] Lind L, Hall J, Larsson A, Annuk M, Fellström B. Lithell H. Evaluation of endothelium-dependent vasodilation in the human peripheral circulation. Clin Physiol 2000; 20: 440-8.

Received: September 19, 2008 Revised: October 10, 2008 Accepted: October 29, 2008