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Treatment of Essential Arterial Hypertension with Enalapril Does Not Result in Normalization of Endothelial Dysfunction of the Conduit Arteries

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It is assumed that endothelial dysfunction due to arterial hypertension could be improved or even normalized by antihypertensive treatment. The present study was designed to explore that assumption in patients with essential hypertension treated with an angiotensin-converting enzyme (ACE) inhibitor-enalapril. Twenty-eight patients (mean age: 55.1 years) who fulfilled the following criteria were included: essential arterial hypertension present for more than 2 years, monotherapy with enalapril for at least 1 year, adequate treatment (blood pressure in the last year < 140/90 mm Hg) and absence of other factors (smoking, hypercholesterolemia, diabetes, obesity), which could importantly influence endothelial function. The flow-mediated (endothelium-dependent) dilation (FMD) of the brachial artery was assessed by high-resolution ultrasound and compared with that of 22 age-matched healthy normotensive controls. The patients and controls did not differ in regard to body mass index, lipids, and plasma glucose and insulin; there were no smokers. FMD of the brachial artery was significantly decreased in patients in comparison to controls (7.9% vs 13.5%, $p < 0.01$). FMD in patients was inversely correlated with the duration of hypertension ($r = -0.52$, $p < 0.01$) and with both systolic ($r = -0.72$, $p < 0.01$) and diastolic ($r = -0.43$, $p < 0.05$) blood pressure (measured after temporary withdrawal of treatment). This study showed that the adequate control of blood pressure achieved with enalapril is not followed by normalization of endothelial function, measured by FMD of the brachial artery.

Introduction

Endothelial dysfunction of conduit arteries is an important early event in the atherosclerotic process, known to precede morphologic changes of the arterial wall.¹ Endothelial dysfunction has been demonstrated in patients with risk factors for atherosclerosis such as arterial hypertension, hypercholesterolemia, diabetes, smoking, and obesity.^{2,3} A relatively close relationship exists between the intensity of an individual risk factor and degree of endothelial dysfunction.^{4,5} En-

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dothelial function can be assessed noninvasively by ultrasound. The flow-mediated dilation method (FMD) described by Celermajer et al,² appears to be the most appropriate method of studying the endothelial function of the conduit arteries and is becoming widely used.

Interventional studies have shown that treatment of risk factors, for example, hypercholesterolemia with statins, could result in regression of endothelial dysfunction.⁶ Considerably less interventional data are available concerning treatment of arterial hypertension and endothelial dysfunction. Several studies on animal models of arterial hypertension have shown that by normalization of blood pressure the impaired endothelium-dependent vascular responses could be completely restored.⁷ However, only limited and inconclusive data are available about the possible reversibility of endothelium dysfunction of the large conduit arteries in humans with arterial hypertension.⁸ Studies focusing on improvement of endothelial dysfunction by antihypertensive drugs are complicated by the common presence of other risk factors that influence endothelial dysfunction and by the common failure to achieve recommended levels of blood pressure by drugs. Several questions still remain unanswered. Thus, it is not clear whether endothelial dysfunction in hypertensive patients can be completely normalized, whether normalization of endothelial function is related to adequacy of antihypertensive treatment, and whether antihypertensive drugs importantly differ in their ability to improve endothelial dysfunction. In this regard, angiotensin-converting enzyme (ACE) inhibitors seem to be the most appropriate class of antihypertensive agents, and enalapril, which is the most widely used ACE inhibitor, seems to be the most suitable representative of ACE inhibitors.^{9,10} Thus, the present study was designed to explore whether in patients with isolated essential hypertension (and without other risk factors, that might influence endothelium function) the endothelium-dependent dilatation of the brachial artery (BA) is decreased despite achievement of recommended blood pressure levels with an ACE inhibitor, enalapril.

Materials and Methods

Study Population

The study group consisted of 28 patients (12 men and 16 women with a mean age of 55.1 years)

with essential hypertension. Inclusion criteria were the following: the presence of essential hypertension, defined as blood pressure above recommended levels (140/90 mm Hg); the presence of hypertension for more than 2 years; monotherapy with ACE inhibitor enalapril, 20–40 mg/day, for at least 1 year; and absence of risk factors that could importantly influence endothelial dysfunction: smoking, hypercholesterolemia, diabetes, and obesity (in order to exclude additional effects on endothelial dysfunction). The last and very important criterion was adequate treatment in the last year. All patients were followed up in the University Clinic and had blood pressures below recommended levels (140/90 mm Hg) at regularly monthly check-ups. No patient had a history of or any clinical signs of atherosclerosis (carotid, coronary, or peripheral), or end-organ damage. The patients who fitted our criteria were selected from a large group of 200 patients. Twenty-two healthy, normotensive volunteers (5 men and 17 women), matched with the patients for gender and age, served as a control group. They had no classic risk factors for atherosclerosis. All subjects were screened for the presence of classic risk factors or manifest atherosclerotic disease by history, clinical examination, and routine biochemical tests.

The patients had taken their last antihypertensive medication 24 hours before the investigation. Blood pressures were measured 3 times in a sitting position. Blood samples were taken in the morning, after overnight fasting. Biochemical examinations included determination of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), fasting plasma glucose, and insulin. The body mass index was calculated. All participants gave written informed consent for all procedures. The State ethical committee of Slovenia approved the study.

Hemodynamic Measurement

Endothelial function was studied by flow-mediated dilatation of the brachial artery by the well-known, noninvasive method described by Celermajer et al.² With use of a 10-MHz linear-array transducer, the right brachial artery was scanned in longitudinal section 2 to 10 cm above the elbow. From B-mode ultrasound images the mean vessel diameter was calculated. Measurements were taken from the anterior to posterior “m” line at the end of the diastole incident with the R wave on the simultaneously recorded electrocardiogram. At least 3 cardiac cycles were an-

alyzed for each scan and measurements were averaged. The flow velocity was measured by the pulsed-wave Doppler signal at a fixed incident angle of 68° to the vessel with the range gate of 1.5 mm in the center of the artery. The baseline blood flow was estimated by multiplying the velocity time integral of the Doppler flow signal (corrected for incident angle) and the vessel cross-sectional area. Hyperemic flow increase was induced by inflation of a blood pressure tourniquet, placed around the forearm, to the suprasystolic pressure (the pressure level that was 20 mm Hg higher than the patient's systolic blood pressure) for 4 minutes, causing ischemia and consequent vasodilation in the distal forearm. Hyperemic flow was recorded in the first 15 seconds and flow-mediated dilation of the BA diameter was measured 45 seconds after cuff release. The percentage increase in the vessel diameter was calculated. The interoperator coefficient of variation of measurements was 2.8%, which is in accordance with Celermajer et al.²

Statistical Analysis

Normally distributed variables of patients and controls were expressed as means \pm standard

error and were compared by the 2-tailed Student's *t* test. Variables not distributed normally were expressed as medians with ranges between the first and the third quartile, and differences between groups were assessed by the Mann-Whitney *U* test. Depending on the distribution, Pearson's or Spearman's correlation coefficients were calculated to test the associations between different variables. Statistical significance was defined as a 2-sided *p* value < 0.05 .

Results

Clinical Characteristics and Biochemical Parameters

There were no significant differences in the age, gender, and body mass index between the patients and the controls. There were no smokers in either group. Systolic and diastolic blood pressures were similar in both groups when patients had used enalapril regularly (Table I) and were significantly higher in the patients than in the control group after temporary (24 hours) withdrawal of treatment (152.7 ± 14.5 vs 123.0

Table I. Clinical characteristics and biochemical parameters of the patients and controls.

	Patients	Controls	<i>p</i>
Number	28	22	NS
Age, years	55.1 (40–65)	54.2 (42–65)	NS
Male/female	12/16	5/17	NS
Systolic blood pressure, mm Hg	125 \pm 10	123 \pm 10	NS
Diastolic blood pressure, mm Hg	80 \pm 5	82 \pm 8	NS
Body mass index, kg/m ²	26.0 \pm 4.7	25.0 \pm 4.0	NS
Total cholesterol, mmol/L	5.63 \pm 0.89	5.48 \pm 0.63	NS
LDL cholesterol, mmol/L	3.60 \pm 0.84	3.48 \pm 0.89	NS
HDL cholesterol, mmol/L	1.41 \pm 0.35	1.66 \pm 0.66	NS
Triglycerides, mmol/L	1.6 \pm 0.2	1.7 \pm 0.4	NS
Fasting glucose, mmol/L	5.2 \pm 0.5	4.9 \pm 0.4	NS
Insulin, mE/L	13.5 (7.4–48.9)	11.6 (5.0–26.3)	NS

NS = not significant.

± 10.8 mm Hg and 96.1 ± 8.1 vs 82.0 ± 8.1 ; both $p < 0.01$). There were no significant differences in the levels of total, LDL, and HDL cholesterol, triglycerides, lipoprotein (a), fasting glucose, and insulin between the patients and the controls (Table I).

Hemodynamic Measurements

There were no significant differences in the rest vessel diameter and the rest blood flow between the patients and the control group; the blood flow appropriately increased after cuff release in both groups (data not shown). Patients had a lower increase of FMD. Thus, the percentage increase in the FMD of the brachial artery was significantly lower in the group of patients in comparison to the control group ($7.9 \pm 3.5\%$ vs $13.5 \pm 4.5\%$, $p = < 0.01$) (Figure 1).

In patients a significant negative correlation was observed between FMD and the duration of hypertension ($r = -0.52$, $p < 0.01$) (Figure 2) and between FMD and the blood pressure levels (when treatment was temporarily withheld). FMD was significantly inversely related to both systolic ($r = -0.72$, $p < 0.01$) (Figure 3) and diastolic ($r = -0.43$, $p < 0.05$) blood pressure. In the control group the FMD was significantly inversely related only to the age ($r = -0.49$, $p < 0.05$).

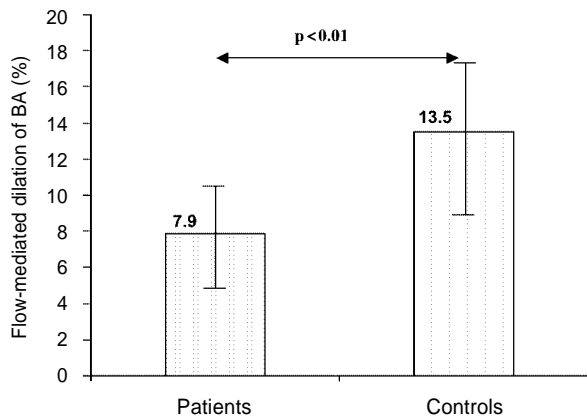


Figure 1. Flow-mediated dilation of the brachial artery (BA) in patients and controls.

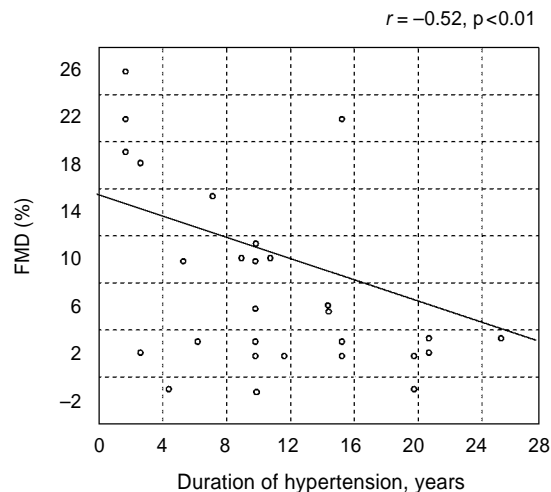


Figure 2. Relationship between flow-mediated dilation (FMD) of the brachial artery and duration of essential hypertension in patients.

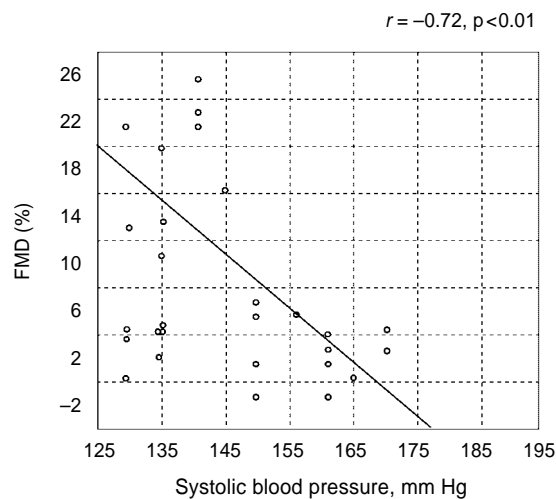


Figure 3. Relationship between flow-mediated dilation (FMD) of the brachial artery and systolic arterial pressure in patients.

Discussion

The endothelium plays an important role in the regulation of vascular tone by releasing relaxing and contracting factors that act on underlying vascular smooth muscle. Studies exploring endothelial dysfunction in patients with arterial hypertension showed impaired dilation of the con-

duit arteries,^{11,12} which plays a role in the process of atherosclerosis. Of particular clinical interest is the possibility that endothelial dysfunction of the large conduit arteries might be normalized by antihypertensive therapy.

We explored the endothelium-dependent dilation of the brachial artery in patients with isolated essential hypertension (and without other risk factors, which could importantly influence endothelium function), who were adequately (in terms of standard clinical practice) treated with an ACE inhibitor, enalapril. We found that patients with essential arterial hypertension have an impaired vasodilator response despite clinically considered adequate treatment with enalapril (lasting at least 1 year). The results of our study demonstrate that normalization of blood pressure by means of conventional antihypertensive therapy with enalapril does not normalize impaired endothelium dilation. The failure to normalize endothelial dysfunction could potentially be the consequence of the insufficient effect of enalapril on endothelial dysfunction (at the dosage used to treat arterial hypertension: 20–40 mg/day) and/or partial irreversibility of endothelial dysfunction in some subgroups of patients with essential hypertension.

Results obtained with enalapril could not be simply extrapolated to a whole group of ACE inhibitors and to other antihypertensives. Namely, the data show that important disparity among different antihypertensive agents^{8,13,14} and between different ACE inhibitors^{8,14} might exist regarding their potential to improve endothelial dysfunction. Further studies are needed to clarify that. Nevertheless, the failure to normalize endothelial dysfunction in our patients might be, despite the strict criteria used, the consequence of inefficient antihypertensive therapy.

The measurements of blood pressure that had been taken repeatedly during routine outpatient evaluation had proven that treatment was effective, as it is estimated in an ordinary clinical practice. The finding of a discrepancy between normalization of blood pressure and a continuing impairment of (hypertension-associated) endothelial dysfunction might be clinically relevant for the development of atherosclerosis in hypertensive patients.

The selection of patients (who did not have other factors, which could importantly influence endothelial dysfunction) enabled us to directly study correlations of endothelial dysfunction to duration of hypertension and severity of hypertension. We observed a significant negative corre-

lation between FMD and the duration of hypertension. This indicates that long-lasting elevated blood pressure has a duration-related harmful effect on vascular endothelium. A significant negative correlation was observed between blood pressure levels (when treatment was temporarily withheld) and FMD. This observation suggests that not only essential hypertension per se but also the severity of hypertension (despite effective treatment) affects the endothelial function. This could be the result of oxidative stress, which increases with increase of blood pressure, even though the latter is within recommended levels.¹⁵

Our results also revealed an age-related decrease of FMD of the brachial artery in the healthy normotensive subjects. This finding confirms the previous observations that aging is associated with impairment of endothelial function and with progression of endothelial dysfunction.^{16–18} On the other hand, in the present study, we did not find a significant negative correlation between age and FMD in patients with essential hypertension. This observation could be explained by a presumption that in the presence of essential hypertension, aging has much less effect on endothelium function than elevated blood pressure does. Therefore, the effect of aging in these patients is masked by hypertension-induced changes of endothelium.

Conclusion

In conclusion, our study revealed that middle-aged patients with essential hypertension who are adequately treated with enalapril have decreased FMD of the brachial artery. This result could be explained by the following assumptions: endothelial dysfunction due to essential hypertension might be at least partially irreversible; certain ACE inhibitors, like enalapril, might be ineffective in restoring endothelial dysfunction; and higher doses of enalapril might be needed to efficiently affect endothelial dysfunction. These hypotheses, which may be clinically important, require further studies to be clearly answered.

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