Physiol. Res. 55 (Suppl. 1): S73-S80, 2006

Comparison of Vascular Function and Structure of Iliac Artery in Spontaneously Hypertensive and Hereditary Hypertriglyceridemic Rats

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Received October 27, 2006
Accepted November 17, 2006
On-line available December 22, 2006

Summary

The aim of this study was to compare the vascular reactivity and morphology of iliac artery (IA) in adult spontaneously hypertensive rats (SHR) and hereditary hypertriglyceridemic (hHTG) rats. The isolated rings of iliac artery (IA) from Wistar rats (controls), SHR and hHTG rats were used for measurement of relaxant responses to acetylcholine (ACh) and contractile responses to noradrenaline (NA). Morphological changes of IA were measured using light microscopy. Systolic blood pressure (BP) measured by plethysmographic method was increased in SHR approximately by 88 % and in hHTG rats by 44 % compared to controls. BP increase was accompanied by cardiac hypertrophy. In both SHR and hHTG groups (experimental groups) reduced relaxation to ACh and enhanced maximal contraction and sensitivity to adrenergic stimuli were observed. The sensitivity to NA in SHR was higher also in comparison with hHTG. Geometry of IA in both experimental groups revealed increased wall thickness and wall cross-sectional area, in SHR even in comparison with hHTG. Inner diameter was decreased in both experimental groups. Thus, independently of etiology, hypertension in both models was connected with impaired endothelial function accompanied by structural alterations of IA. A degree of BP elevation was associated with arterial wall hypertrophy and increased contractile sensitivity.

Key words
Spontaneously hypertensive rat • Hypertriglyceridemia • Vascular reactivity • Structure • Artery

Introduction

Essential hypertension is the most common form of high blood pressure but its pathogenesis still remains unclear. However, it is a "multifactorial" disease influenced by environmental factors in interaction with important genetic predisposition. Chronic hypertension is characterized by an increase of heart weight and by vascular hypertrophy, which could be connected with hemodynamic changes such as enhanced vasoconstriction and impaired vasodilation. It is well known that wall hypertrophy and remodeling of resistance arterioles together with enhanced activity of vasoconstrictor systems and attenuated efficiency of vasodilator systems belong to the principal factors augmenting systemic resistance in hypertensive subjects (Kuneš *et al.* 2004).

However incomplete data have been reported concerning altered vascular function and structure of conduit vessels.

There are several factors, which can increase the risk of developing of primary hypertension. The metabolic abnormalities, such as hypertriglyceridemia, were found to correlate with elevation of blood pressure (Klimeš *et al.* 1997). In addition, hereditary hypertriglyceridemia in rat was demonstrated to be accompanied by impaired endothelial function, as demonstrated by decreased endothelium-derived relaxation (Török *et al.* 2002). Causality of the possible relationship between hypertriglyceridemia, hypertension and vascular function is still the object of discussion.

Several experimental models have been developed to clarify pathophysiological background of hypertension. Spontaneously hypertensive rat (SHR) is the most frequently used genetic model of human essential hypertension. This model is used to study predominantly cardiovascular disease processes. Hereditary hypertriglyceridemic rat (hHTG), introduced by Vrána and Kazdová (1990) has become a suitable experimental model of human metabolic syndrome, characterized by metabolic abnormalities, apart from others by hypertriglyceridemia, which are connected with elevated blood pressure. This model enables to study separately the consequences of metabolic and hemodynamic abnormalities of organism. SHR and hHTG are two experimental models characterized by occurrence of hypertension and this elevation of blood pressure originates in various pathophysiological mechanisms. The question has appeared how the different etiopathogenic background of hypertension could affect vascular function and structure in two experimental models. The aim of the present study was to characterize and compare the vascular reactivity and morphological changes of isolated iliac artery in SHR and hHTG.

Methods

Animals

The procedures were approved by State veterinary and food administration of the Slovak Republic. The experiments were performed on the adult male 17-week-old Wistar rats (used as controls), SHR and hHTG rats. In all groups systolic blood pressure was measured noninvasively in pre-warmed rats by the tail-cuff plethysmographic method.

Functional studies

Animals were anesthetized with pentobarbital sodium, 50 mg/kg body weight, administered intraperitonealy. After opening the abdomen, the left iliac artery was isolated, cleaned of connective tissue and cut into rings (3-4 mm in length) for recording of isometric tension. The rings were vertically fixed between two stainless steel wires - triangles in 20 ml incubation organ bath with Krebs solutions (in mM): NaCl 118; KCl 5; $NaHCO_3$ 25; $MgSO_4$ 1.2; KH_2PO_4 1.2; $CaCl_2$ 2.5; glucose 11; ascorbic acid 1.1; $CaNa_2EDTA$ 0.032. The solution was oxygenated with 95 % oxygen and 5 % carbon dioxide and kept at 37 °C. The upper wire triangles were connected to electromechanical transducer Sanborn FT 10 and recorders (Labora) for recording of changes in tension. The resting tension, which ensured maximal responses to the contractile agonists used, was adjusted to 10 mN and applied to each ring. Subsequently, the preparations were allowed to equilibrate for 60-90 minutes until stress relaxation no longer occurred. Contractile responses were induced by increasing doses of noradrenaline (10^{-9}-3.10^{-5} mol/l) and concentration-response curves for noradrenaline were determined and expressed as the developed tension/cross-sectional area of tisue (mN/mm^2). Endothelium-dependent relaxations were measured in phenylephrine (10^{-5} mol/l) precontracted rings and expressed as a percentage of precontraction. Acetylcholine was added to the organ bath in a cumulative manner (10^{-8}-3.10^{-5} mol/l).

Morphometrical studies

The animals were sacrificed by an overdose (100mg/kg) of anesthesia (pentobarbital sodium), the chest was opened and the cardiovascular system perfused at a constant pressure of 120 mm Hg for 10 min *via* a cannula placed in the left ventricle. As fixative 300 mM/l glutaraldehyde in 100 mM/l phosphate buffer was used. The iliac artery was excised, cleaned, divided into four about 1 mm long segments, fixed with the same fixative, postfixed with 40 mM/l OsO_4 in 100 mM/l phosphate buffer, stained en block with uranylacetate, dehydrated through ascending concentration of alcohol and embedded in Durcupan ACM (Sigma). Three randomly selected blocks of each artery were cut perpendicularly to the longitudinal axis. The inner circumference and arterial wall thickness (tunica intima and tunica media) were measured in light microscopy. The arterial wall thickness (tunica intima and tunica media) was measured at about 45^o intervals around the circumference of the

Table 1. Basic cardiovascular characteristics and parameters of the concentration-dependent responses to noradrenaline.

A.	**Control n = 9**	**SHR n = 9**	**hHTG n = 9**
Systolic blood pressure (mm Hg)	114 ± 1.4	214 ± 7.3 *	164 ± 5.2 *$^{+}$
Body weight (g)	423.0 ± 3.8	324.0 ± 5.7 *	305.5 ± 5.6 *
Heart weight (g)	1.35 ± 0.03	1.59 ± 0.04 *	1.06 ± 0.03 * $^{+}$
Heart weight / Body weight (mg/g)	3.13 ± 0.03	4.91 ± 0.18 *	3.48 ± 0.07 * $^{+}$
B.			
Noradrenaline–logEC_{50}	6.64 ± 0.06	7.84 ± 0.23 *	7.08 ± 0.11 * $^{+}$
Noradrenaline MAX (mN.mm^{-2})	1.50 ± 0.33	3.23 ± 0.54*	5.10 ± 1.05*

Results are expressed as mean ± S.E.M.; n is the number of rats; * significantly different from control rats at P<0.01; $^{+}$ significantly different from SHR at P<0.01; –logEC_{50} is the negative logarithm of the molar concentration of noradrenaline causing 50 % of the maximal contraction; MAX is the maximal contraction to noradrenaline (absolute units).

artery. The inner diameter and cross sectional area (tunica intima and tunica media) were calculated.

Drugs

The following drugs were used: phenylephrine, acetylcholine (both from Sigma), noradrenaline (Zentiva). All drugs were dissolved in distilled water.

Data analysis

The data were expressed as means ± S.E.M of n experiments. The dose of the drug (expressed as the negative logarithm of molar concentration) required to produce 50 % of the maximum contraction -logEC_{50} was determined from individual dose-response curves determined for each ring. For the statistical evaluation of differences between groups, one-way analysis of variance (ANOVA) was used and followed by Bonferroni post-hoc test. The differences of means were considered to be significant at $p<0.01$.

Results

Basic cardiovascular characteristics of the control and experimental groups (SHR, hHTG) are in Table 1a. The mean systolic blood pressure was significantly higher in both experimental groups than in control group, in SHR group the pressure was augmented by 88 % and in hHTG group by 44 %, approximately. Elevation of blood pressure was significantly larger in SHR group compared to hHTG group. The augmentation of blood pressure was accompanied by increased heart weight-to-body weight ratio in both experimental groups, suggesting the occurrence of cardiac hypertrophy. Moreover, heart weight to body weight ratio was significantly increased in SHR group compared to hHTG group (Table 1a).

Acetylcholine induced a concentration-dependent relaxation of iliac artery, the maximum of which reached 74.9±8.4 % (n = 9) in the control group (Fig. 1). In both experimental groups, a relaxant response to acetylcholine was markedly decreased compared to the control group in the whole range of concentrations ($P<0.01$). There was no significant difference in maximal relaxant response between SHR (22.2±5.5 %, n = 9) and hHTG (29.7±6.4 %, n = 9) groups.

Figure 2 illustrates a contraction of the iliac artery to noradrenaline expressed as a change in active tension in response to cumulative addition of noradrenaline. As implies from graph, noradrenaline-induced contractions were increased in both experimental groups in the whole range of concentrations, but there was no significant difference in absolute contractile force between SHR and hHTG groups.

The values of the negative logarithm of noradrenaline molar concentration producing half-maximal contraction (–logEC_{50}) calculated from the individual dose-response curves expressed as a percent of the maximal noradrenaline contraction of iliac artery and the values of maximal contraction to noradrenaline expressed in absolute units (MAX) are registered in Table 1b. Half-maximal contraction was occurred at significantly lower noradrenaline concentration in both experimental groups than in control group. At the same time, a concentration of noradrenaline causing 50 % of the maximal contraction was significantly lower in SHR group than in hHTG group**.** It suggests that the iliac artery

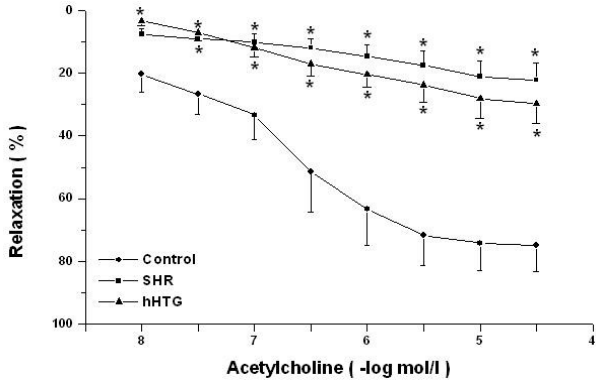

Fig. 1. Concentration-response curves for acetylcholine-induced relaxation of rat iliac artery precontracted by phenylephrine (10^{-5} mol/l) in Wistar rats (Control, n=9), spontaneously hypertensive rats (SHR, n=9) and hereditary hypertriglyceridemic rats (hHTG, n=9). Results are shown as means ± S.E.M. * P<0.01 vs Control

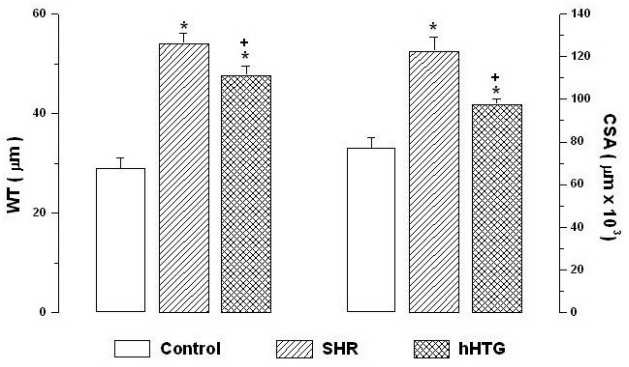

Fig. 2. Concentration-response curves for noradrenaline-induced contraction of rat iliac artery in Wistar rats (Control, n=9), spontaneously hypertensive rats (SHR, n=9) and hereditary hypertriglyceridemic rats (hHTG, n=9). Results are shown as means ± S.E.M. * P<0.01 vs Control

from SHR rats is more sensitive to the effect of noradrenaline compared to hHTG group. On the other hand, there was no significant difference in absolute maximal contraction to noradrenaline between SHR and hHTG rats.

The wall thickness of the iliac artery (n = 9, in control rats) was increased in SHR group by 87 % (n = 9, P<0.01) and in hHTG group by 65 % (n = 9, P<0.01). Significant difference was also found between SHR and hHTG groups, the wall thickness of the iliac artery in SHR group was significantly increased compared to hHTG group (P<0.01, Fig. 3, left). The calculated cross-sectional area was significantly increased in both SHR group by 59 %, (n = 9, P<0.01) and in hHTG group by 27 %, (n = 9, P<0.01, Fig. 3 right). The cross-sectional area of the iliac artery in SHR group was also significantly increased compared to hHTG group (P<0.01).

The inner diameter of the iliac artery was significantly decreased in SHR group by 18 % (n = 9, P<0.01) and in hHTG group by 26 % (n = 9, P<0.01, Fig. 4, left). No significant differences were observed between SHR and hHTG groups. The ratio of wall thickness to inner diameter was increased by 142 % in SHR group (n = 9, P<0.01) and by 122 % in hHTG group (n = 9, P<0.01) (Fig. 4, right). The difference in this respect was not found between SHR and hHTG groups.

Discussion

Our results showed that in two experimental models – SHR and hHTG – hypertension was associated with impaired endothelial relaxation, increased adrenergic vasoconstriction, which were accompanied by structural alterations of the iliac artery.

In the present study systolic blood pressure was accompanied by an increase in relative heart weight in both, SHR and hHTG rats indicating cardiac hypertrophy. The degree of blood pressure elevation, that was significantly higher in SHR than in hHTG rats, was closely associated with cardiac hypertrophy. In some variants of primary hypertension, as in SHR, structural adaptation even seems to be genetically reinforced and thus could also be considered one of the primary elements preceding the hemodynamic abnormalities (Folkow 1993). Cardiac hypertrophy is considered to be a universal mechanism for adapting the heart to long-lasting increased blood pressure and our results support this idea.

Functional studies showed that acetylcholine-induced endothelium-dependent relaxation was significantly impaired in both experimental groups. The effect of blood pressure elevation itself on the relaxation in hypertensive animals is not satisfactorily classified. Similar magnitude of depression of the endothelium-dependent relaxation observed in the iliac arteries from both, SHR and hHTG rats suggested that the influence of blood pressure level is of minor importance in this respect. This is supported by our morphological measurements, which revealed no differences in the decrease of iliac artery inner diameter between both strains. Metabolic changes such as hypertriglyceridemia can be associated with altered vascular function and structure. Our results are in agreement with observation that hereditary hypertriglyceridemia in rats was associated with impaired endothelium-dependent

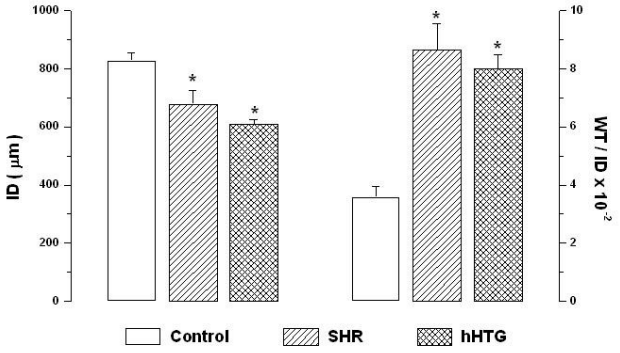

Fig. 3. Wall thickness (WT, tunica intima plus tunica media) and cross-sectional area (CSA) of rat iliac artery in Wistar rats (Control, n=9), spontaneously hypertensive rats (SHR, n=9) and hereditary hypertriglyceridemic rats (hHTG, n=9). Results are shown as means ± S.E.M. * P<0.01 vs Control; + P < 0.01 SHR vs hHTG

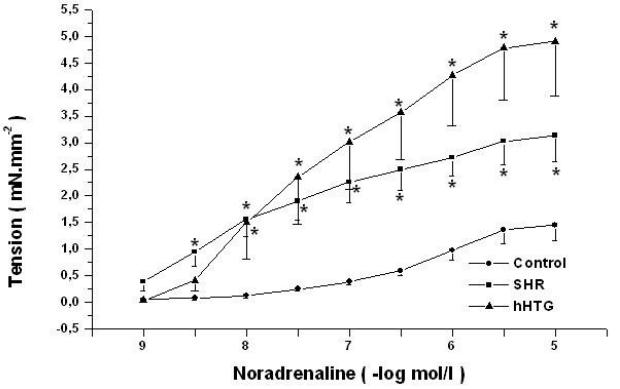

Fig. 4. Inner diameter (ID) and wall thickness to inner diameter ratio (WT/ID) of rat iliac artery in Wistar rats (Control, n=9), spontaneously hypertensive rats (SHR, n=9) and hereditary hypertriglyceridemic rats (hHTG, n=9). Results are shown as means ± S.E.M. * P<0.01 vs Control.

relaxation in the thoracic aorta, which was accompanied by marked changes in vascular architecture (Kristek *et al.* 1997, Šimko *et al.* 2005). Similar impairment of endothelium-dependent relaxation was also observed in mesenteric, carotid arteries, in the aorta as well as in the mesenteric resistance arteries in Wistar rats given the diet leading to a selective elevation of triglycerides (Banos *et al.* 1997, Kusterer *et al.* 1999, Bartus *et al.* 2005). It seems that hypertriglyceridemia leads to an endothelial dysfunction and several mechanisms could be attributed to this process. The decreased relaxation of the thoracic aorta to acetylcholine in hHTG rats was mediated mainly via the nitric oxide (NO) pathway and systemic inhibition of NO synthase enhanced the depression of relaxation (Török *et al.* 2002). On the other hand, Kusterer *et al.* (1999) showed that selective hypertriglyceridemia induced a progressive depression of endothelial vasodilator responsiveness, which was associated with no change in the expression of endothelial NO synthase, but with a marked increase in vascular superoxide anion production. Hypertriglyceridemia alters the normal pattern in the population of subclasses of the main lipoprotein (Lewis *et al.* 1999). Besides, as the level of plasma lipids increases, this may provide increased quantity of substrate for lipid peroxidation. Small dense particles, which are the main carriers of triglycerides (Chait *et al.* 1993) may themselves be prone to oxidation and could be responsible for impaired relaxation. Moreover, ultrastructural changes in hHTG aortic wall described by Kristek *et al.* (1997) were predominantly expressed as an accumulation of products of lipolysis in endothelial cells and in the subendothelial space. All mentioned abnormalities might be important contributors to impaired relaxation in hHTG we have observed and from the point of this view these effects are dissociable from those induced by elevation in pressure itself.

Alterations concerning arterial endothelium-dependent relaxation in mature SHR are known to be not uniform. The decreased endothelium-dependent relaxation in SHR was observed in coronary and mesenteric resistance arteries, mesenteric conduit arteries and in the aorta (Pourageaud and Freslon 1995, Kűng and Lűscher 1995, Chamiot-Clerc *et al.* 2001, Wuorela *et al.* 1994**).** Contrary to these findings Papapetropulos *et al.* (1990) observed increased endothelium-dependent relaxation in the aorta and the increased relaxation of the femoral artery was also observed by Bernátová *et al.* (2006). Török and Kristek (2001) found no difference between the carotid arteries and thoracic aorta from normotensive rats and SHR in the magnitude of the relaxation to acetylcholine. Our finding revealed significant depression of acetylcholine-induced endothelium-dependent relaxation in the iliac artery of SHR. It was similar to results observed by Sekiguchi *et al.* (2001), who registered the depression of acetylcholine-induced relaxation of the iliac arteries from stroke-prone SHR. In spontaneous hypertension no generalization can be made as to the role of NO in arterial relaxations. The observations showed that NO system may be overactive in SHR and probably counteracts the contradictory pressor effect of hypertrophied arterial wall in SHR (Arnal *et al.* 1993, Csizmadiová *et al.* 2006). On the other hand, Balbatun *et al.* (2003) elucidated the dynamic of NO release from endothelial cells isolated from iliac arteries of SHR. They documented that the rate of NO release and the maximal concentration of NO were

significantly lower in SHR than in normotensive controls, so the final concentration of NO on the smooth muscle cells was decreased and the efficiency of NO signaling was impaired. This observation supports our finding of depressed iliac artery relaxation. The different observations related to endothelial function in SHR might depend on the technique used and vascular bed studied. Winquist (1998) reviewed evidences for regional vascular differences, since the different level of relaxations (from unchanged to diminish) were observed in different parts of arterial tree. Our previous results (Gerová *et al.* 2005) showed the discrepancy between acetylcholine-induced enhanced hypotensive response of resistant arteries and attenuated relaxation of the iliac artery (conduit artery) in SHR. However, it seems that in both experimental models, hHTG and SHR, the decreased endothelium-dependent relaxation is not caused by decreased sensitivity of vascular smooth muscle cells to NO because relaxation elicited by nitropruside was not significantly different between either SHR or hHTG rats and normotensive controls (Kusterer *et al.* 1999, Pourageaud and Freslon 1995).

Our results showed that noradrenaline-induced contraction was augmented in both experimental groups compared to normotensive controls. The similar enhancement in absolute force of contraction was found in both strains, but the increased sensitivity to adrenergic stimuli was significantly larger in SHR than in hHTG rats. In SHR, central conduit as well as resistant arteries are hyperresponsive to α-adrenergic receptor stimulation (Chamiot-Clerc et al. 2001, Yamamoto *et al.* 1987). Besides the sympathetic overactivity and enhanced vasoconstrictor reactivity, the increased α-adrenergic mediated sensitivity of smooth muscle cells has also been found in SHR (Nyborg and Bevan 1988). These observations taken together with our results suggest that the smooth muscle vasoconstriction can be enhanced in SHR and it is probably associated with differences in the affinity and amount of the α-adrenergic receptors. The augmented contraction of the iliac artery in hHTG rats correspond with observations performed on the thoracic aorta and mesenteric artery isolated from hypertriglyceridemic rats, where noradrenaline-induced contractions were found to be increased (Banos *et al.* 1997). Similarly, the enhancement of vasoconstriction to noradrenaline released from sympathetic nerve system was found in resistance arteries of hHTG (Kuneš et al. 2002).

Our morphometrical studies indicated that the iliac arteries undergo structural changes in both experimental groups. The structural alterations in the arterial wall of the iliac arteries in SHR and hHTG revealed the increase in the media (wall thickness, cross-sectional area), which correlated with elevations in blood pressure. The arterial thickening has also been shown in the thoracic aorta in hHTG (Török *et al.* 2002) and in coronary, basilar and carotid arteries in SHR (Cebová and Kristek 2005, Kristek, 1998). These changes in vascular architecture are probably due to hypertrophy of the smooth muscle cells and may have the increasing effect on activation of vasoconstriction. Moreover, high level of triglycerides in hHTG rats can modulate cytosolic free Ca^{2+} concentration $[Ca^{2+}]i$ by affecting various aspects of Ca^{2+} handling, besides others an enhanced Ca^{2+} influx and mobilization of Ca^{2+} stores (Zicha *et al.* 1999). The increase in $[Ca^{2+}]i$ could be responsible for enhanced vasoconstriction. On the other hand, observations from SHR revealed that in prehypertensive period, the values of blood pressure levels and wall thickness did not distinguish from normotensive controls (Cebová *et al.* 2006). It suggests that the blood pressure itself probably play a key role in the thickening of arterial wall in SHR.

While the arterial thickening occurred in SHR was significantly larger than in hHTG rats, the augmentation of absolute contractile responses was similar in both experimental groups. The reason for this discrepancy remains to be determined. Loukotová *et al.* (2003) showed that the increased $[Ca^{2+}]i$ level after angiotensin stimulation in the aortic smooth muscle cells isolated from SHR was dependent on the level of superoxide anions. The exaggerated productions of superoxide anions described in SHR enhanced inactivation of NO (Nava *et al.* 1998) and the toxic products originating from this interaction may participate in the damage of smooth muscle cells and could lead to the weaken contractile efficiency in SHR.

In conclusion, our results showed that independently of etiology of hypertension, both strains revealed impaired endothelial function and increased vasoconstrictor reactivity, which were accompanied by morphological alterations of iliac artery. The degree of blood pressure elevation positively correlated with cardiac hypertrophy, arterial wall thickening and increased contractile sensitivity parameters, which could participate in chronic increase of vascular tone.

Acknowledgement

This study was supported by grants VEGA 2/6139/26 and

1M0510 (Cardiovascular Research Centre, Prague). Preliminary results were presented at COST 844 meeting "The role of nitric oxide in cardiovascular system", April 8-10, 2005, Bratislava, Slovakia (Čačányiová *et al.* 2005). We thank L. Kosnáčová for technical help and Y. Hanáčková for help with housing the animals.

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