

## Endothelial dysfunction in patients with salt-sensitive essential hypertension

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### ABSTRACT

The aim of the present study was to evaluate the role of endothelium-derived factors (NO and ET) in the development of the salt-sensitive hypertension and to assess possible interaction between these substances. A total of 52 patients with mild arterial hypertension were studied. Patients were divided in two groups (salt-sensitive and salt-resistant groups) in accordance with the type of their response to the changes in dietary sodium content. Data obtained show that all hypertensive patients irrespective from their type of salt-sensitivity exhibited significantly decreased NO and ET plasma levels. The salt sensitive hypertensive patients showed significant decreases in plasma NO concentrations compared to salt-resistant patients. The highest levels of ET were found in salt-sensitive hypertensives. In conclusion, salt-sensitive hypertension is accompanied by endothelial dysfunction expressed by decreased NO and elevated ET plasma levels with significant negative correlation between these endothelium-derived agents. It might be suggested that salt-sensitivity additionally contributes to the further deterioration of the endothelial function, presumably via impairing NO production and enhancing ET release.

**KEYWORDS:** *endothelial function, NO, endothelin, salt-sensitive hypertension*

Numerous studies demonstrate that endothelium releases specific substances that influence blood flow and vascular tone resulting in regulation of blood pressure [1,2]. Nitric oxide (NO) and endothelin (ET) are the main endothelial factors involved in above-mentioned process. It is considered that hypertension is manifested by imbalance of vasodilator and vasoconstrictor factors with the predominance of the latter ones. As a result vasoconstriction persists that leads to the persistence of high blood pressure. At the same time little is known regarding the role of endothelial factors in the pathogenesis of the salt-sensitive hypertension. The latter is usually have been revealed in 40-55% of patients with essential hypertension.

There are a number of rather controversial studies regarding the influence of salt intake on endothelial factors [3]. Shultz and Tolins [4] demonstrated increased NO urinary excretion in rats being on high-salt diet). Experimentally in Dahl salt-sensitive rats the elevation of blood pressure induced by a high-salt intake can be prevented by the concomitant administration of L-arginine [5]. Decreased NO<sub>x</sub> production has been reported in patients with essential hypertension compared with normotensive controls [6,7]. Also, a high salt intake has been shown to decrease plasma levels of NO<sub>x</sub> in Afro-American and Japanese patients with hypertension [8,9]. Both Afro-Americans and Japanese are well known as predisposed to the salt-sensitivity and severe hypertension.

Based on the aforementioned, the aim of the present study was to evaluate the role of endothelium-derived factors (NO and ET) in the development of the salt-sensitive hypertension and to assess possible interaction between these substances.

### MATERIALS AND METHODS

A total of 52 patients (21 females and 31 males, mean age 49±1,7 yrs) with mild (I stage) arterial hypertension (with diastolic pressure 90-99 mmHg and/or systolic pressure 140-159 mmHg) were studied. Patients were divided in two groups in accordance with the type of their response to the changes in dietary sodium content: group I was composed of salt-sensitive 18 patients, while 34 salt-resistant patients represented group II. Similarly, age-matched control group (composed of 22 healthy subjects,

7 females, 15 males) was divided into two groups (8 salt-sensitive and 14 salt-resistant subjects).

All patients underwent treatment in cardiology unit at the Tbilisi State Medical University hospital (2001-2003). Secondary forms of hypertension were excluded by routine diagnostic procedures. The exclusion criteria were the following: heart failure, valvular heart disease, unstable angina, renal, liver pathology, secondary hypertension, diabetes mellitus, patients taking steroids or nonsteroid anti-inflammatory drugs (NSAIDs), tranquilizers, contraceptive drugs); incapacity or refusal to give informed consent. Patients smoking more than five cigarettes per day and/or consuming more than 40 g of pure ethanol per day, as well as women taking oral contraceptives or oestrogen replacement therapy, were also excluded.

Blood pressure was measured twice with 2 min intervals taking into account postural changes. If changes in systolic and/or diastolic pressure exceeded 5 mm, blood pressure was taken again. One week prior to examination patients stopped taking hypotensive medicines, as well as diuretics, hormonal preparations. Salt sensitivity was detected by M.Weir method [10] that implies detection of changes in mean arterial pressure (MAP) after transferring from low salt diet (40-50 mmol sodium daily equal to 3 g sodium chloride) to high salt diet (200 mmol sodium daily equal to 12 g sodium chloride). Compliance with the diet was assessed twice weekly by measuring 24-h urinary Na<sup>+</sup> excretion throughout the study.

Nitric oxide (NO) level in the blood was determined by electron-paramagnetic resonance (EPR) method. EPR spectrum was determined on radio spectrometer RE-1307 at the temperature of liquid nitrogen. Endothelin 1 (ET-1) was detected using radioimmunoassay (IBL, Hamburg, Germany).

Data obtained were analyzed with SPSS (version 11.0). Variables were analyzed according to the Student t test. A value of p<0,05 was considered statistically significant.

### RESULTS AND DISCUSSION

Significant changes in NO and ET plasma levels were revealed in hypertensive patients compared to the controls (Tab.1). All hypertensive patients irrespective from

their type of salt-sensitivity exhibited significantly decreased NO and ET plasma levels.

Groups	NO (mm/mg)	ET (pg/ml)
Controls (n = 22)	13,72 ± 2,43	6,15 ± 0, 78
Hypertensives (n = 52)	8,72 ± 1,97*	36,5 ± 8,58**

Note: \* -  $p < 0,05$ ; \*\* -  $< 0,01$  compared to the control group.

**Tab.1** Plasma levels of NO and ET in healthy subjects and in patients with essential hypertension.

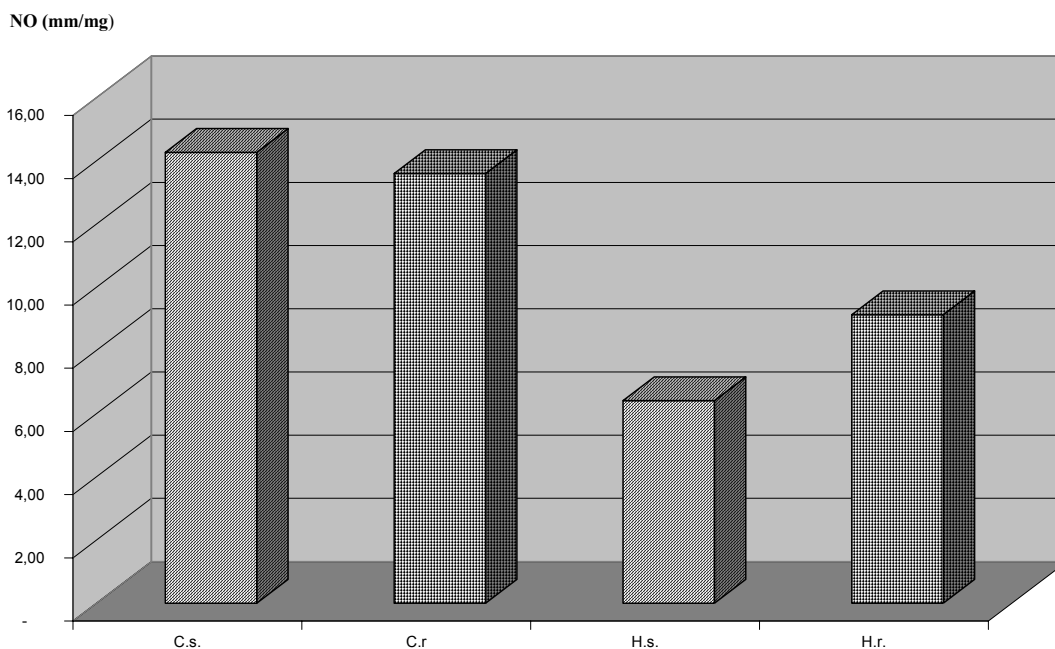
As it is shown in Fig.1, there were not significant differences in NO plasma levels in healthy subjects in accordance with their salt-sensitivity, though salt sensitive subjects exhibited slightly decreased NO levels. On contrary, The hypertensive patients showed significant decreases in plasma NO concentrations with minimal levels in salt-sensitive patients ( $6,41 \pm 0,57$  mm/mg in salt-sensitives and  $9,13 \pm 0,98$  mm/mg in salt-resistant patients;  $p < 0,01$  compared to control group).

Opposite changes were observed regarding ET plasma levels (Fig.2). While there was not any difference in control group depending on salt-sensitivity, the highest levels of ET were found in salt-sensitive hypertensives ( $46,43 \pm 7,24$  pg/ml in salt-sensitives and  $23,4 \pm 5,12$  pg/ml in salt-resistant patients;  $p < 0,01$  compared to control group).

Thus, data obtained confirm results of those experimental and clinical studies that showed marked decrease in NO production in salt-sensitive hypertension. Shultz and Tolinz [4] first demonstrated that a high dietary salt intake was associated with an increases in the plasma levels and urinary excretion of NO, as well as an increase in cGMP excretion, in normotensive Sprague–Dawley rats. Additionally, they found a significant correlation between urinary sodium and NOx excretion rate. Based on these results, the authors concluded that exposure to high dietary salt resulted in increased endogenous NO production, and that this could contribute to the regulation of blood pressure by facilitating sodium excretion after sodium load. Endothelium-derived factors have also been measured in relation to salt intake in normotensive subjects and in patients with essential hypertension [9].

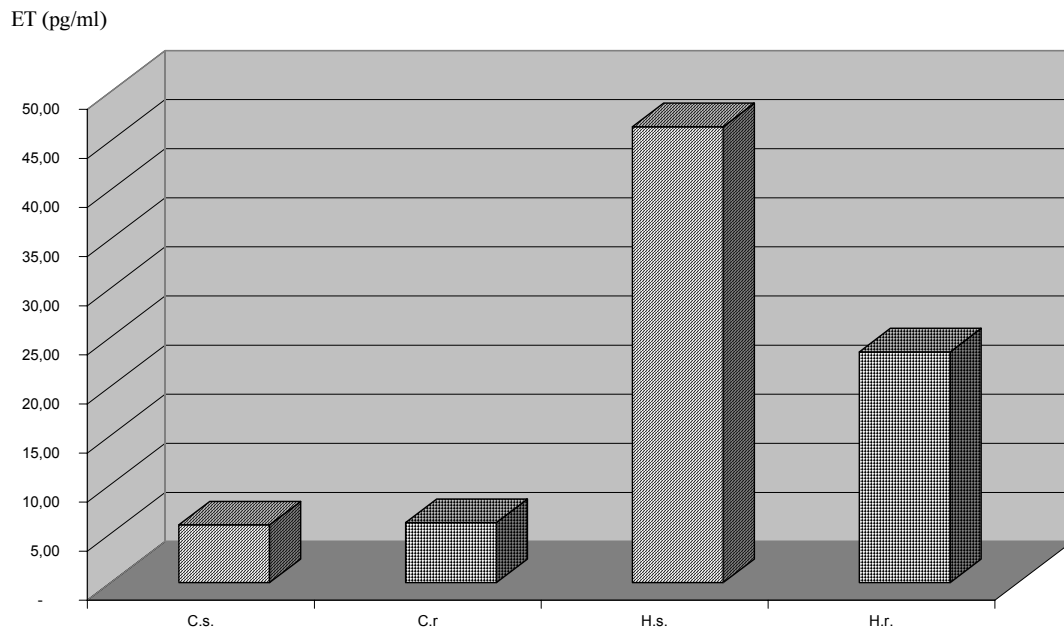
Our results show significant elevation ET plasma levels in hypertensives with the highest concentrations in salt-sensitive ones. Although slight, however elevation of ET plasma levels was detected in salt-sensitive healthy subjects compared to the salt-resistant ones. Some authors have reported normal or minimally increased concentrations in hypertensive patients, in comparison with normal subjects [11,12].

In conclusion, salt-sensitive hypertension is accompanied by endothelial dysfunction expressed by decreased NO and elevated ET plasma levels with significant negative correlation between these endothelium-derived agents. It might be suggested that salt-sensitivity additionally contributes to the further deterioration of the endothelial function, presumably via impairing NO production and enhancing ET release.



Cs – salt-sensitive controls; Cr – salt-resistant controls, Hs – Salt-sensitive hypertensives, Hr – salt-resistant hypertensives.

**Fig.1** NO plasma levels in healthy subjects and hypertensive patients according to their salt-sensitivity.



Cs –salt-sensitive controls; Cr – salt-resistant controls, Hs – Salt-sensitive hypertensives, Hr – salt-resistant hypertensives.

**Fig.2** ET plasma levels in healthy subjects and hypertensive patients according to their salt-sensitivity.

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## Эндотелиальная дисфункция у больных соль-чувствительной эссенциальной гипертензией

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### РЕЗЮМЕ

Целью исследования являлось изучение роли эндотелиальных факторов (NO и ЭТ) в развитии соль-чувствительной гипертензии и оценка взаимодействия между этими факторами. Обследовано 52 больных с начальной стадией эссенциальной гипертензии. Больные были разделены на две группы в зависимости от соль-чувствительности (соль-чувствительные и соль-резистентные). Полученные результаты показали, что у всех больных, независимо от типа соль-чувствительности, отмечалось значительное снижение уровня NO и концентрации ЭТ в плазме крови. В то же время у соль-чувствительных больных уровень NO оказался значительно ниже, чем у соль-резистентных больных. Максимальный уровень ЭТ в крови был отмечен также у соль-чувствительных больных. На основании вышеизложенного можно заключить, что соль-чувствительная эссенциальная гипертензия характеризуется выраженной эндотелиальной дисфункцией, проявляющейся в значительном снижении NO и повышении уровня ЭТ в крови, и существовании обратной корреляции между этими факторами. Предполагается, что соль-чувствительность углубляет эндотелиальную дисфункцию при эссенциальной гипертензии, возможно посредством нарушения продукции NO и усиления секреции ЭТ.

**Ключевые слова:** эндотелиальная функция, NO, эндотелин, соль-чувствительная гипертензия

□ **International committee of medical journal editors. Uniform requirements for manuscripts submitted to biomedical journals.** Ann Intern Med 1997;126:36–47.

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