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Endothelial function in primary hyperaldosteronism vs essential arterial hypertension

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Abstract

Objective. To estimate and compare the endothelial function in patients with essential arterial hypertension (HTN) and primary hyperaldosteronism (PHA). **Design and methods.** Eighty-two patients were examined. Among them, PHA was verified in 19 patients, while 36 patients had essential HTN stage II (blood pressure (BP) elevation of 1st or 2nd degree), and 27 age-matching healthy people formed control group. The HTN duration in PHA patients was 1.95 ± 0.24 years, and in patients with essential HTN — 5.5 ± 0.5 years. Both patients and healthy peoples were examined within the hospital, in compliance with the hospital regime and diet. Endothelial function was assessed by several methods: the number of circulating desquamated endothelial cells (the method by Hladovec J.), reactive hyperemia test and evaluation of endothelium-dependent vasodilation (as a percentage of the brachial artery diameter increase), total blood nitrates and nitrites level (Griss-reaction method), nitric oxide excretion in urine. **Results.** Endothelial dysfunction (ED) was found in all patients with high BP. We found more profound ED in PHA patients compared to patients with essential HTN, which resulted in a significantly higher number of circulating endothelial desquamated cells, lower percentage of vasodilation response in reactive hyperemia test, decreased blood levels of total nitrites/nitrates and elevated nitric oxide urine excretion. Discriminant analysis was applied to range the severity of ED. Patients with essential HTN had moderate ED, while patients with PHA had severe ED. **Conclusions.** The proposed classification approach can be successfully applied for monitoring changes in ED and the effectiveness of treatment in patients with various diseases associated with BP elevation.

Key words: primary hyperaldosteronism, essential arterial hypertension, symptomatic arterial hypertension, endothelial dysfunction, circulating endothelial cells, endothelium-dependent vasodilatation, nitric oxide, total nitrites/nitrates

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Сравнительная оценка дисфункции эндотелия у больных первичным гиперальдостеронизмом и эссенциальной гипертензией

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Резюме

Цель исследования — оценить и сравнить функциональное состояние эндотелия у больных эссенциальной артериальной гипертензией (АГ) и первичным гиперальдостеронизмом (ПГА). **Материалы и методы.** Проанализированы результаты обследования 82 человек: 19 пациентов с ПГА, 36 пациентов с эссенциальной АГ II стадии с повышением уровня артериального давления (АД) 1–2-й степени и 27 практически здоровых лиц. Средний возраст пациентов в группах значимо не отличался. Длительность АГ у лиц с ПГА составила 1,95 ± 0,24 года, у лиц с гипертонической болезнью (ГБ) — 5,5 ± 0,5 года. Обследование больных и лиц контрольной группы проводилось в стационарных условиях в соответствии с общепринятыми стандартами на фоне соблюдения клинического режима и диеты. Оценка функции эндотелия проводилась с использованием следующих методик: оценки количества циркулирующих десквамированных эндотелиоцитов (ЦЭК) в крови по методике Hladovec J., пробы с реактивной гиперемией и последующим расчетом эндотелийзависимой вазодилатации в виде процента прироста диаметра плечевой артерии (ПА), исследования содержания в плазме крови суммы нитратов и нитритов по методике, основанной на реакции Грисса, оценки экскреции оксида азота с мочой. **Результаты.** Дисфункция эндотелия (ДЭ) была характерна для всех обследованных лиц с повышенным АД. Однако результаты свидетельствуют о более выраженной степени нарушений функционального состояния эндотелия при ПГА по сравнению с эссенциальной АГ, что выражалось в значимо более высоком содержании количества ЦЭК, значимо более низком приросте диаметра ПА в пробе с реактивной гиперемией, значимом снижении уровня суммарных нитритов/нитратов в крови, повышенном уровне экскреции оксида азота с мочой. С помощью метода дискриминантного анализа на основании этих показателей разработана классификация степени тяжести ДЭ, в результате чего было констатировано, что пациенты с эссенциальной АГ имели умеренную, а с ПГА — выраженную степень ДЭ. Предложенный классификационный подход может быть успешно использован для динамического контроля эффективности медикаментозной коррекции ДЭ у лиц с различными заболеваниями, сопровождающимися подъемом АД.

Ключевые слова: первичный гиперальдостеронизм, эссенциальная артериальная гипертензия, симптоматическая артериальная гипертензия, эндотелиальная дисфункция, циркулирующие эндотелиальные клетки, эндотелийзависимая вазодилатация, оксид азота, суммарные нитраты и нитриты плазмы крови

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Introduction

Cardiovascular mortality is gradually growing, resulting in a steady increase in research in this field worldwide [1]. Arterial hypertension (HTN) is one of key reasons of adverse cardiovascular events, including cardiovascular deaths [2, 3].

Essential HTN takes the leading position in HTN structure. The rate of symptomatic HTN varies from 5% [1, 4] to 25% [5]. Among secondary forms renal HTN is the most common [4, 6], and endocrine HTN rate is 3–6% [7, 8]. Endocrine HTN more often appear as adrenal hyperfunction or Cushing's disease [1]. Prevalence of primary aldosteronism in general population is low comprising 0.03–0.1% [9]. However, primary aldosteronism comprises at least 7% of uncontrolled HTN [10].

Endothelial dysfunction (ED) plays an important role in the development of cardiovascular diseases and, in particular, arterial hypertension. Endothelium dysfunction appears to be both a part of pathology and its primary inductor, which contribute to ED progression. ED development is accompanied by abnormal regulatory vascular response to the usual hemodynamic shifts. Patients with essential HTN demonstrate decreased endothelium-dependent vasodilatation resulted from excessive production of vasoconstrictors. In this regard, endothelial dysfunction is considered as one of the leading mechanisms underlying hypertension development. According to current concepts, nitric oxide (NO) is one of the most important bioactive endothelial products with strong vasodilatory effect. Moreover, it delays vascular remodeling. In HTN patients, endotheliocytes show lower capacity to release NO and other vasodilators. At the same time production of vasoconstrictors increases, leading to ED. Also HTN patients show impaired endothelium-dependent vasolidation caused by abnormal NO production and release.

However, while ED role in essential HTN is proved, the endothelium changes in the endocrine symptomatic hypertensions are unexplored. The comparative studies of endothelial function in essential HTN versus endocrine hypertension are lacking. Few studies show contradictory results and do not provide data on ED severity in symptomatic HTN, its triggers, and prognostic role. Therefore, such research is highly relevant.

Objective

To estimate and compare endothelium functional status in essential HTN versus primary hyperaldosteronism.

Design and methods

Altogether 82 subjects were examined: 19 patients with primary hyperaldosteronism (12 males and 7 females), 36 patients with essential HTN II degree with blood pressure (BP) elevation of I–II degree (25 males and 11 females), and 27 healthy subjects (18 males and 9 females) who formed the control group. Sex distribution was comparable in all groups (according to χ^2-test). At baseline, mean age of subjects with primary hyperaldosteronism was 49.05 ± 1.58 years, among patients with essential HTN — 52.89 ± 1.24 years, in the control group — 45.26 ± 1.83 years ($p > 0.05$ for all comparisons). The mean HTN duration was 1.95 ± 0.24 years among subjects with primary hyperaldosteronism, and 5.5 ± 0.5 years among subjects with essential HTN.

All subjects were examined in the hospital. All clinical, laboratory and instrumental examinations were performed according to the common standards and on conditions of in-hospital regimen and diet. Diagnostic of primary hyperaldosteronism was based on typical disease pattern, low potassium level at single evaluation or in series of examinations, detection of aldosterone level and plasma renin activity. Localization was established by computer tomography of adrenal glands. Aldosteronoma was diagnosed by histological verification after surgical intervention. Diagnosis of HTN and BP increase were established according to the Expert guidelines of the Russian Society of Cardiology. Essential HTN was diagnosed after final exclusion of symptomatic HTN. Patients with chronic heart failure II NYHA functional class and higher, essential HTN III degree, myocardial infarction in past, acute cerebrovascular accident, and clinically significant concomitant diseases of digestive, pulmonary systems were not excluded.

Endothelial function was estimated by J. Hladovec's method, and circulating desquamated endotheliocytes were calculated. According to this method, the circulating desquamated endotheliocytes count is 2–4 cells in 100 mcl in healthy individuals.

Endothelium vasomotor function was assessed by reactive hyperemia test and endothelium-dependent vasodilation of brachial artery. We estimated the increase in the brancial artery diameter after the mechanical stress exposure by the linear probe 7.5 MHz (Siemens Omnia). At the next step, we assessed the ratio of endothelium dependent vasodilation of brachial artery to the baseline data by the following formula: (D2-D1)/D1 × 100 % (D2 — brachial artery diameter after occlusion, D1 — baseline brachial artery diameter). Brachial artery diameter growth of 10 % and more was considered normal. Lower values or vasoconstriction were considered as a pathological response [1]. Total blood level of nitrates and nitrites (NOx) was determined in fasting blood samples (after 10-hour fast), after following diet with nitrate- and nitrite-free food and excluding nitrate-containing drugs. We used a method based on Griece reaction: optical density was defined by spectrophotometer KFK-3 (wavelength 543 nmol), then a calibration plot was drawn: NOx (nmol) was indicated on X axis and optical density — on Y axis. NOx content was evaluated in accordance with the calibration plot.

The study was approved by the Ethical Committee of Military Medical Academy. Prior to any procedures, all subjects signed informed consent to participate in the study.

Statistical analysis was performed with the use if program STATISTICA 6.0. Non-parametric tests were used. Discriminatory analysis method was used to distinguish critical features of ED.

Results and discussion

Baseline diameter of brachial artery did not differ in the groups ($p > 0.05$) (Table 1). Reactive hyperemia test demonstrated an increase in the brachial artery diameter in all groups. However, HTN patients showed lower increase than patients in the control group. Brachial artery diameter increase was much lower in the groups with essential HTN and primary hyperaldosteronism than in the control group ($p < 0.001$), and its value < 10 % proves impairment of endothelial vasomotor function in HTN patients. Importantly, the impairment of brachial artery diameter increase was more profound in patients with primary hyperaldosteronism in comparison with the group of essential HTN.

In patients with primary hyperaldosteronism, the number of desquamated endotheliocytes indicating endothelial dysfunction is much higher than in healthy subjects and hypertensive patients. So endothelial dysfunction is more profound intensity in patient with symptomatic HTN than in patients with essential HTn (Table 2).

The next parameter reflects endothelial function (total content of nitrates/nitrites in blood plasma) and it shows similar trends. NO content in the blood of patients with primary hyperaldosteronism was 4-time lower than in healthy subjects.

Moreover, NO blood level in patients with primary hyperaldosteronism was much lower compared to patients with essential HTN. On the contrary, urine nitrite excretion was much higher in patients with primary hyperaldosteronism than in control group and in patients with essential HTN. The role of ED in BP elevations in patients with primary hyperaldosteronism was confirmed by negative correlation between bra-

Table 1

THE CHANGES IN THE BRACHIAL ARTERY DIAMETER DURING REACTIVE HYPEREMIA TEST IN THE STUDY GROUPS (M ± m)

Indicator	Healthy, n = 27	HTN, n = 36	PHA, n = 19
Baseline brachial artery diameter, mm	4.27 ± 0.05	4.44 ± 0.07	4.32 ± 0.10
Post-test brachial artery diameter, mm	4.98 ± 0.06	4.76 ± 0.08*	4.54 ± 0.11**
Ratio of baseline and post-test values, %	16.53 ± 0.74	6.97 ± 0.47**	5.15 ± 0.87**#

Note: differences with control group: * — $p < 0.05$; ** — $p < 0.001$; differences between patients with essential hypertension and hyperaldosteronism: # — $p < 0.05$.

Table 2

CIRCULATING DESQUAMATED ENDOTHELIOCYTES, BLOOD NITRATES AND NITRITES IN THE STUDIED GROUPS (M ± m)

Indicator	Healthy, n = 27	HTN, n = 36	PHA, n = 19
Circulating desquamated endotheliocytes, cell/ml	3.0 ± 0.17	8.58 ± 0.20*	27.37 ± 0.48*#
Blood nitrates and nitrites, nmol/ml	37.49 ± 0.92	17.86 ± 0.53*	10.03 ± 0.29*#

Note: differences with control group: * — $p < 0.05$; ** — $p < 0.001$; differences between HTN and PHA patients: # — $p < 0.001$.

chial artery diameter and the mean BP. In primary hyperaldosteronism, NO content in blood inversely correlates with the thickness index indicating that aldosterone directly contributes to the development of myocardial hypertrophy and also has an indirect impact by impairing endothelial function. In primary hyperaldosteronism, aldosterone level directly correlates with flow-dependent vasodilatation, which proves participation of this hormone in the development of endothelial dysfunction.

Therefore, we conclude that endothelial dysfunction occurs in all subjects with high BP. However, the severity of endothelial dysfunction is different in the studied groups. Thus, we attempt to develop criteria for classifying endothelial dysfunction degree by applying the discriminatory analysis. Usually this analysis is used for recognition of images and objects with specific features to one of the known classes [15]. The key objects of our research was the classification of endothelial dysfunction into different degrees. For this purpose parameters characterizing endothelial function (excluding normal values) were ranged, and the median was determined. Values lower than median characterize moderate ED and values higher than median shows severe ED. Quantitative estimation of 4 parameters — brachial artery diameter increase, circulating desquamated endotheliocytes level, nitrate/nitrite content in blood and nitrite urine excretion — allows classification of ED in HTN patients as moderate and severe. The findings were proven by contingency table analysis (Table 3). Discriminative model appeared to be statistically significant ($p < 0.001$) and highly informative (for 96.1%).

Therefore, we found moderate endothelial dysfunction in HTN by applying classification method for estimating endothelial dysfunction severity in HTN of different origin and assessing brachial artery diameter increase, circulating desquamated endotheliocytes level, nitrate/nitrite content in blood and urine excretion of nitrites. ED in patients with primary hyperaldosteronism is more profound in comparison with patients with essential hypertension (Table 4).

Conclusions

Endothelial vasomotion dysfunction and increased number of circulating desquamated endotheliocytes are found in patients with different hypertensions. However, impairment of flow-dependent vasodilatation and circulating desquamated endotheliocytes number differ in patients with essential HTN and with primary hyperaldosteronism.

Low NO production is one of the most important pathogenesis mechanisms of high vascular tone in HTN, because NO is the natural endothelium-produced antagonist of different vasoconstriction factors. However, the degree of the impairment of NO-production is not similar in different HTN forms. Patients with primary hyperaldosteronism are characterized by more profound decline in NO production (bioavailability decline is also possible) followed by the more profound endothelial secretory dysfunction.

We believe that our classification can be also used the follow-up control of endothelial dysfunction reversibility in treated patients.

Conflict of interest

The authors declare no conflict of interest.

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Table 3

CLASSIFICATION OF ENDOTHELIAL DYSFUNCTION SEVERITY IN HYPERTENSIVE PATIENTS

The severity of endothelial dysfunction	Brachial artery diameter increase, %	Desquamated endotheliocytes level, cell/ml	Nitrate / nitrite content in blood, nmol/ml	Urine excretion of nitrates / nitrites, mcmol/l
Normal	> 10	0–4	> 28	до 0.1
Moderate	5.1–10	5–19	13–28	0.1–0.17
Severe	от –5 до +5	> 19	до 13	> 0.17

Table 4

ПОКАЗАТЕЛИ ДИСФУНКЦИИ ЭНДОТЕЛИЯ У БОЛЬНЫХ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ (M ± m)

Indicators	Essential AH n = 36	Primary hyperaldosteronism n = 19
Brachial artery diameter increase, %	6.97 ± 0.47***	5.15 ± 0.87***#
Circulating desquamated endotheliocytes, cell/ml	8.58 ± 0.2***	27.37 ± 0.48***###
Nitrate/nitrite content in blood, nmol/ml	17.9 ± 0.53***	10.03 ± 0.29***###
Urine excretion of nitrites, mcmol/l	0.13 ± 0.01***	0.19 ± 0.01***###

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$ — differences compared to the control group; # — $p < 0.05$; ## — $p < 0.01$; ### — $p < 0.001$ — differences between essential hypertension and primary hyperaldosteronism patients.

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