

**ASSESSMENT OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH ADRENAL TUMORS DURING SKIN THERMOMETRY WITH LOCAL HEATING**

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Цель. Изучить функциональное состояние эндотелия у пациентов с феохромоцитомами и гормононеактивными опухолями надпочечников с помощью кожной термометрии до и после оперативного лечения.

Материал и методы. Для выявления эндотелиальной дисфункции и оценки реакции микрососудистого тонуса у 19 пациентов с опухолями надпочечников использовали кожную термометрию с помощью прибора «Микротест» до и после оперативного вмешательства. Определяли индекс тепловой вазодилатации K в эндотелиальном, нейрогенном и миогенном диапазонах. Пациенты были разделены на две группы. В первую вошли пациенты с феохромоцитомой (8), во вторую – с гормононеактивными аденомами и гипертонической болезнью (11). В качестве группы сравнения обследовано 27 практически здоровых людей.

Результаты. У пациентов с феохромоцитомами индексы тепловой вазодилатации до операции во всех диапазонах были ниже, чем у практически здоровых лиц, однако разница была значима лишь в миогенном и нейрогенном диапазонах. У пациентов с гормононеактивными опухолями надпочечников в сочетании с артериальной гипертензией имелось достоверное снижение индексов тепловой вазодилатации во всех диапазонах. В раннем послеоперационном периоде у пациентов с феохромоцитомами отмечено значимое повышение показателей индексов тепловой вазодилатации в эндотелиальном и миогенном диапазонах, тенденция к росту – в нейрогенном диапазоне. Установлена сильная положительная взаимосвязь между проведением предоперационной подготовки альфа-2 адреноблокаторами ($r=0,74$; $p=0,04$), нормализацией артериального давления в послеоперационном периоде и величиной индекса тепловой вазодилатации в эндотелиальном диапазоне после операции ($r=0,75$; $p=0,03$).

Заключение. У пациентов с феохромоцитомами, гормононеактивными опухолями надпочечников и артериальной гипертензией имеются признаки нарушения функции эндотелия микрососудистого русла. Предоперационная подготовка и адреналэктомия при феохромоцитоме достоверно улучшают реакцию эндотелия микрососудистого русла в ответ на внешние тепловые раздражители.

Ключевые слова: дисфункция эндотелия, кожная термометрия с локальным нагревом, опухоли надпочечников, феохромоцитомы, предоперационная подготовка

Objective. To investigate the endothelial dysfunction in patients with adrenal tumors during skin thermometry before and after surgery.

Methods. "Microtest", a device for skin thermometry, was used to detect endothelial dysfunction in 19 patients with the adrenal tumors. The index of thermal vasodilation K was calculated for the endothelial, neurogenic and myogenic ranges. The patients were divided into two groups: patients with pheochromocytoma ($n=8$) and with hormonal inactive adrenal tumors and arterial hypertension ($n=11$). The comparison group consisted of 27 healthy adults.

Results. The patients with pheochromocytoma had lower thermal vasodilatation indices in all ranges in comparison to healthy adults; this difference was significant only in the myogenic and neurogenic ranges. A significant decrease of all indices of thermal vasodilation for patients of the second group was observed. A significant increase in indices of thermal vasodilatation in the endothelial and myogenic ranges was registered in patients with pheochromocytoma as well as the trend to rise in the neurogenic range during the early postoperative period. There was a strong positive association between the normalization of blood pressure in the postoperative period, the preoperative treatment with doxazosin, and the value of the index of thermal vasodilation in the endothelial range after the surgery.

Conclusions. All patients with pheochromocytomas, hormone-inactive adrenal tumors and arterial hypertension had the signs of impaired microvascular bed endothelial function. Preoperative treatment and adrenalectomy significantly improve the reaction of the microvascular endothelium in response to external heat stimuli in patients with pheochromocytoma.

Keywords: endothelial dysfunction, skin thermometry with local heating, adrenal tumors, pheochromocytoma, preoperative treatment

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Endothelial Dysfunction in Patients with Adrenal Tumors during
Skin Thermometry with Local Heating
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Научная новизна статьи

Впервые при помощи кожной термометрии с локальным нагревом у пациентов с феохромоцитомами, гормононеактивными опухолями надпочечников и артериальной гипертензией обнаружены признаки нарушения функции эндотелия микрососудистого русла. Установлено, что предоперационная подготовка и адrenaлэктомия при феохромоцитоме достоверно улучшают реакцию эндотелия микрососудистого русла в ответ на внешние тепловые раздражители.

What this paper adds

For the first time, skin thermometry with local heating in patients with pheochromocytomas, hormone-inactive adrenal tumors and arterial hypertension showed the signs of impaired microvascular bed endothelial function. The preoperative preparation and adrenalectomy in pheochromocytomas has been established to improve significantly the reaction of the microvascular bed endothelium in response to external heat stimuli.

Introduction

The vascular endothelium of the microvasculature plays an important role in the regulation of vascular tone, hemostasis, the development of remodeling and local inflammation, and its dysfunction leads to tissue hypoxia and related complications [1, 2]. To assess the dysregulation of the microcirculation system, laboratory methods, plethysmography, laser Doppler flowmetry (LDF) are used. The measurement of low-amplitude temperature fluctuations on the skin surface has been used recently when conducting a cold test or local heating [1, 2, 3, 4]. Studying the state of the mechanisms of regulation of the microcirculatory bed makes it possible to identify adaptation reserves in normal conditions and in various diseases, to evaluate the results of treatment, the possibility of restoring the functioning of the mechanisms regulating vasodilation [2, 4]. Endothelial dysfunction is characteristic of patients with essential arterial hypertension and is accompanied by a decrease in the bioactivity of nitric oxide [5]. Information about the functional assessment of the vascular bed in hypertension associated with surgical diseases of the adrenal gland is scarce [5, 6, 7], and the method of skin thermometry with local heating has not been used for this purpose.

Objective. To investigate the endothelial functional state in patients with pheochromocytomas, hormone-inactive adrenal tumors during skin thermometry before and after surgery.

Methods

To identify endothelial dysfunction and assess the reaction of microvascular tone, "Microtest" device was used (Perm, Russia, Roszdrav RU No. FSR 2012/14175). The study was approved by the ethics committee of E.A. Wagner Perm State Medical University and complies with Helsinki Declaration of 1975. Registration sensor of the device measures the skin temperature with an accuracy class of 10^{-3} degrees Celsius. Local heating of the palmar surface of the distal phalanx of the second finger of the left hand was used. Temperature fluctuations were measured continuously for 10 minutes initially, then for another 10 minutes after reaching a temperature of 40 degrees Celsius. To calculate the amplitude-frequency spectrum of blood flow oscillations, a special computer program of the inverse wavelet transform was used, which in the best way reveals the periodicity of short and long-term processes presented in one implementation. The software implementation of the wavelet transform is based on the term by term multiplication of the data set of the LDF-gram data by array containing wavelets for different frequencies [2]. At the same time, wavelet filtering made it possible to follow the changes in the signals allocated in a certain frequency range: in endothelial (0.0095-0.02 Hz), neurogenic (0.02-0.05 Hz) and myogenic (0.05-0.14) [3]. To assess various mechanisms of the vascular tone regulation, the root-mean-square value of the amplitude of skin temperature fluctuations in the corresponding frequency range was chosen. The thermal vasodilation index K was determined as the ratio of the amplitude difference after and before local heating to the amplitude value of the initial fluctuations.

18 patients with adrenal tumors aged 34-62 years were examined (54.4 ± 11.9 years ($M \pm \sigma$)) to study the nature of the vascular tone changes and assessment of its prognostic value of the adrenalectomy effectiveness for arterial pressure normalization by heating and precision thermometry. The patients were divided into two groups. The first group included 8 people, in whom pheochromocytoma was diagnosed during the morphological study of the removed tumor, the second – 11 patients with hormone-inactive adenomas and essential hypertension. The study was performed before surgery and on the 5th day of the postoperative period. Thermal vasodilation indices were determined in the endothelial (K_e), neurogenic (K_n) and myogenic (K_m) ranges. Practically healthy people were examined as a comparison group: 11 men and 16 women, aged 20-30 years with a body mass index of 21.71 ± 3.86 ($M \pm \sigma$).

Among the patients with pheochromocytoma, there were six women and two men aged 34 to 62 years. The mean age was 53.3 ± 9.5 years ($M \pm \sigma$).

Four patients had arterial hypertension with crisis course, in one hypertension had a malignant persistent character. Mixed form was detected in two cases, and in one patient there was no rise in blood pressure. The duration of arterial hypertension in the crisis course ranged from four months to three years, in the persistent course – for at least five years, in the mixed forms – from three to seven years. Two patients were diagnosed with type 2 diabetes mellitus of moderate severity. Three patients showed obesity grade 1, one – an excess of weight. The body mass index averaged 27.2 ± 5.1 ($M \pm \sigma$). During the laboratory examination in seven patients before surgery, 1.4-5.1 times increase in the metanephrine content of daily urine was found. In one case, there were no clinical and laboratory manifestations, typical for pheochromocytoma before the operation, and the diagnosis of pheochromocytoma were established after a histological examination of the removed adrenal tumor.

According to computed tomography (CT), the diameter of the tumor ranged from 30 to 100 mm, averaged 53.1 ± 23.4 mm ($M \pm \sigma$). Tumor density ranged from 17 to 43 units of the Hounsfield unit (HU) scale. On the right, the tumor was found in six cases, on the left – in two. Seven patients with arterial hypertension underwent preoperative preparation with alpha-2 adrenergic blockers.

Laparoscopic adrenalectomy was performed in six patients. In one case, the tumor was removed through the right thoracophrenolombotomy, in the other – through the median laparotomy. Intraoperative reduction in the blood pressure after clamping of the adrenal vein, which required drug correction, was noted in seven cases. There were no intra- and postoperative complications.

Pheochromocytoma was diagnosed in the morphological study of the removed adrenal tumor, and in four of them with high potential for malignancy: five or more points on the scale of assessment of the histological features of adrenal pheochromocytoma – PASS (Pheochromocytoma of the Adrenal gland Scaled Score) [8].

Among the patients of the second group with hormone-inactive adrenal tumors and essential arterial hypertension, there were eight women and three men aged from 35 to 60 years. The mean age was 48.2 ± 7.2 years ($M \pm \sigma$). In all patients, hypertension was persistent, requiring constant medical correction. The duration of arterial hypertension ranged from 4 to 15 years. Two patients of this group were diagnosed with moderate type 2 diabetes mellitus. Two of them showed obesity of the 1st degree, one – the 3rd degree; in five cases there was an excess of weight. The body mass index averaged 28.7 ± 5.6 ($M \pm \sigma$). In all patients of this group, in the preoperative period, the levels of

cortisol, aldosterone and renin in the blood serum, metanephrine and normetanephrine of daily urine were examined. Deviations from normal indicators were not revealed. According to CT, the diameter of the tumor ranged from 39 to 69 mm, averaged 47.5 ± 10.2 mm ($M \pm \sigma$). Tumor density according to CT data was from 20 to 44 HU, with an average of 32.2 ± 8.2 HU ($M \pm \sigma$). On the right, the tumor was found in four cases, on the left – in seven cases. All 11 patients underwent laparoscopic adrenalectomy. There were no intraoperative arterial blood pressure fluctuations that required drug correction. Intraoperative and postoperative complications were not observed.

Clear cell adrenocortical adenoma was diagnosed in the morphological study of the removed adrenal tumor in 8 cases was diagnosed with; in 3 cases adrenocortical carcinoma was diagnosed.

Statistics

The studied quantitative features of an approximately normal distribution are represented as $M \pm \sigma$, where M is the arithmetic average value, σ is the standard deviation. To identify significant differences in the groups under consideration, standard nonparametric statistics methods were used – the Wilcoxon test for comparing the quantitative features of one group at different periods of time and the Mann-Whitney test for comparing two independent groups. The relationship between individual pairs of features and the degree of its manifestation was established using a single-factor correlation analysis, the Spearman's correlation coefficient (r) was calculated, as well as the level of its significance. Differences were considered significant at a significance level of $p \leq 0.05$.

Results

In all patients with pheochromocytomas, before the operation, the violations of the vascular tone regulation mechanisms of the microvasculature were established. Thermal vasodilation indices in all ranges were lower than in practically healthy individuals, but the difference was significant only in the myogenic and neurogenic ranges (Table 1).

In patients with hormone-inactive adrenal tumors in combination with the essential arterial hypertension, there was a significant decrease in thermal vasodilation indices in all ranges compared with healthy individuals. Their thermal vasodilation indices were slightly lower in the endothelial and muscular ranges and slightly higher in the neurogenic than in patients with pheochromocytomas, but the difference was not significant.

Table 1

Group type	Indices of thermal vasodilation in all ranges		
	Ke	Km	Kn
Healthy, n=27	4.02±2.15	4.16±2.47	4.39±2.47
1 group, n=8 (with pheochromocytoma)	2.87±1.7 median 2.64	1.74±1.13 median 1.61	1.76±1.24 median 1.88
2 group, n=11 with pheochromocytoma)	2.56±1.72 median 2.26	1.38±1.17 median 0.96	1.99±1.44 median 2.00
The accuracy by the Mann-Whitney criterion	p ₁ =0.24 p ₂ =0.05* p ₃ =0.76	p ₁ =0.006* p ₂ =0.0002* p ₃ =0.44	p ₁ =0.006* p ₂ =0.003* p ₃ =0.81

Notes: Ke – thermal vasodilation index in the endothelial range, Kn – in the neurogenic, Km – in the myogenic. p₁ – accuracy between the 1st group and the healthy individuals, p₂ – accuracy between the 2nd group and the healthy individuals, p₃ – accuracy between the 1st and 2nd groups, * -differences are reliable.

Among all patients with adrenal tumors, no significant effect of overweight on the magnitude of amplitude changes of the skin temperature fluctuations during local heating was found (p=0.10). A statistically significant decrease in the thermal vasodilation index was found in the epithelial range (p=0.007, r=0.37) in patients with concomitant diabetes.

A correlation analysis showed that in patients with pheochromocytomas, changes in thermal vasodilation indices in the endothelial frequency range prior to surgical treatment did not depend on the patients' age (p=0.52), their gender (p=0.16), tumor size (p=0.26) and were not associated with increased levels of metanephrine and normetanephrine (p=0.36) or the presence of initial hypovolemia (p=0.19). One paid attention to a strong negative relationship between the value of the thermal vasodilation index in the endothelial range and the density of the pheochromocytoma. The higher its density was according to the CT data, the lower the index was (r=0.9, p=0.04).

In the early postoperative period, patients with pheochromocytomas showed an improvement in the endothelial function, which was manifested by a significant increase in the indices of thermal vasodilation in the endothelial and myogenic ranges and a tendency to increase in the neurogenic range (Table 2).

Seven of eight patients showed an increase in these parameters, in five cases more than doubled increase compared with the preoperative level. The

average figures of the thermal vasodilation index in the endothelial range exceeded those in the healthy men, and in the muscular and neurogenic ranges became the same.

A strong positive relationship was established between normalization of blood pressure in the postoperative period and the value of the thermal vasodilation index in the endothelial range before the surgery (r=0.75; p=0.03). A significant increase in the amplitude of fluctuation in response to a heat stimulus after adrenalectomy was found in these patients (p=0.03). A strong correlation was registered between the increase in the thermal vasodilation index in the postoperative period and the preoperative preparation with alpha-2 adrenergic blockers (r=0.74; p=0.04).

Discussion

Considering that local heating decreases the vascular tone, leading to their dilatation and to the increase in the amplitude of skin temperature fluctuations the obtained data testify to insufficient growth of the fluctuations amplitude in all patients with adrenal tumors compared with healthy individuals [1]. Deviations of thermal vasodilation indices in patients with hormone-active incidents in combination with essential arterial hypertension compared with patients with pheochromocytomas did not differ significantly. In the work of V. Vasilev et al. [5] in determining the endogenous inhibitor

Table 2

Group type	Indices of thermal vasodilation in all ranges		
	Ke	Km	Kn
Healthy, n=27	4.02±2.15	4.16±2.47	4.39±2.47
1 group, n=8 (with pheochromocytoma before surgery)	2.87±1.70	1.74±1.13	1.76±1.24
1 group, n=8 (with pheochromocytoma on the 5 th day after surgery)	5.03±3.48	4.47±3.69	3.79±2.82
The accuracy by the Mann-Whitney and Wilcoxon criteria	p ₁ =0.45 p ₂ =0.05*	p ₁ =0.96 p ₂ =0.02*	p ₁ =0.41 p ₃ =0.16

Notes: Ke – thermal vasodilation index in the endothelial range, Kn – in the neurogenic, Km – in the myogenic. p₁ – accuracy between the 2nd group and the healthy individuals, p₂ – accuracy between the 1st and 2nd groups, * – differences are reliable.

of nitric oxide synthesis in the blood - asymmetric dimethylarginine and the soluble form of the vascular adhesion molecule of the first type, the signs of endothelial dysfunction were also found in patients with pheochromocytomas. Patients with adrenal hormonal adenomas during flowmetry of the common carotid arteries were found to have impaired endothelium-dependent vasodilation [6].

The significance of endothelial dysfunction in the development of arterial hypertension was confirmed by determining the laboratory markers of microcirculation regulation in many studies [4, 5, 6, 7]. Its discovery was regarded as the preclinical stage of atherosclerosis. When studying biochemical markers of endothelial dysfunction (Willebrand factor, E-selectin, tissue plasminogen activator), patients with pheochromocytoma and essential hypertension showed signs of the endothelial dysfunction, but it turned out that its degree does not depend on the etiology of hypertension [7]. It has been established that in diabetes mellitus endothelial dysfunction develops even at the preclinical stage of the disease [4]. Using thermometry with local heating, a significant decrease in the thermal vasodilation index was also found in patients with adrenal tumors and concomitant diabetes mellitus, while the amplitude of fluctuations in response to heat stimulus in pheochromocytomas and hormone-inactive adenomas on the background of hypertensive disease differed insignificantly. The increased body weight did not have a significant effect on the development of endothelial dysfunction in patients with adrenal tumors. Probably, such results are associated with a small number of examined patients and a moderate increase in body mass index (BMI) up to 27.2 ± 5.1 in the 1st group and up to 28.7 ± 5.6 in the 2nd.

Using thermometry with local heating after adrenalectomy for pheochromocytoma, a significant improvement in the vascular endothelium of the microvasculature was established. The findings suggest that it is possible to restore the functioning of the mechanisms that regulate vasodilation, especially its endothelial component.

Conclusions

Patients with adrenal tumors and arterial hypertension have signs of the impaired endothelial function of the microvascular bed, more pronounced in the presence of hormone-inactive adrenal tumors in combination with arterial hypertension. Diabetes mellitus reliably reduces the increase in the amplitude of skin temperature fluctuations with localized heating. Preoperative preparation, adrenalectomy in pheochromocytomas significantly improve the reaction of the microvascular bed endothelium in response to external thermal stimuli.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical aspects

Ethics Committee approval

The work was approved by the Committee on the Ethics of Perm State Medical University named after E.A. Wagner.

Consent

Before starting the study, all patients gave their written consent to conduct thermometry with local heating.

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