

Characteristics of calcium homeostasis in patients with different degrees of arterial hypertension

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Abstract

Background: Calcium is the most common cation in the human body. An abnormal distribution of intracellular and extracellular ionized Ca plays a significant role in the formation of arterial hypertension. The purpose of the study is to analyze the fractional composition of calcium in blood serum and urinary calcium excretion in patients with hypertension, as well as to identify the features of the distribution of these.

Material and methods: The study included 80 patients. The population of the study consisted of 60 patients with various degrees of hypertension (38 women and 22 men) aged from 65 to 74 years old and the control group composed of 20 patients (12 men and 8 women) in the same age group without signs of hypertension. The patients with clinically expressed coronary heart disease requiring specific therapy, heart defects, impaired liver function and impaired kidney function were excluded from this study. Patients were divided into three groups, according to the World Health Organization (WHO) classification of arterial hypertension. Indicators of calcium concentration in blood and urine were determined using test kits for determining calcium with glyoxal bis-2 hydroxyanil from LACHEMA. To determine the ionized calcium, a standard technique of ion-selective electrode was used.

Results and conclusion:

1. In patients with arterial hypertension, a redistribution of the calcium pool in the blood is noted due to a decrease in the concentration of ionized calcium and an increase in the bound calcium, depending on the severity of the disease.
2. An increase in urinary calcium excretion in patients with arterial hypertension is characteristic of moderate and severe forms of arterial hypertension, which given the age of patients, may be one of the causes of osteoporosis.
3. The increase in the level of intracellular calcium with the progression of arterial hypertension is an example of pathophysiological reactions that occur at the body level, the result of which can be not only banal muscle constriction but also a violation of the synthesis and production of biologically active substances that regulate blood pressure.

Key words: calcium; arterial hypertension; calcium concentration; severity of arterial hypertension; intracellular calcium; ionized calcium

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Introduction

Calcium is the most common cation in the human body. Currently, many fields of medicine (epidemiology, biochemistry, cell biology) have accumulated data which prove the relationship between calcium homeostasis disorders and the development of hypertension [1, 2]. Given the fact that the integral value of the concentration of calcium in the blood, as a rule, does not go beyond the functional range, it is of particular interest to know about the question of changing the ratio of calcium fractions in blood plasma and the effect of these changes on blood pressure. Thus, in a number of studies on the role of ionized calcium in the development of hypertension as the functionally most active fraction, it was found that plasma Ca^{2+} levels in patients with hypertension are lower than in individuals in the control group [3, 4]. Moreover, an abnormal distribution of intracellular and extracellular ionized Ca plays a significant role in the formation of arterial hypertension [5–7]. In particular, an increase in the intracellular concentration of Ca^{2+} in patients with hypertension stimulates a reduction in the smooth muscle of arterioles, the secretion of catecholamines by the adrenal glands, and an increase in the sensitivity of peripheral tissue cells to hormonal and mediator effects. An important pathophysiological role is played by serum calcium in renal and cardiovascular functions [8–10].

The purpose of the study was to analyze the fractional composition of calcium in blood serum and urinary calcium excretion in patients with hypertension, as well as to identify the features of the distribution of these indicators depending on the severity of the course of hypertension.

Material and methods

The study included 80 patients. The population of the study consisted of 60 patients with various degrees of hypertension (38 women and 22 men) aged from 65 to 74 years old and the control group composed of 20 patients (12 men and 8 women) in the same age group without signs of hypertension. The diagnosis of hypertension was made on the basis of complaints, collection of an anamnesis of the disease and anamnesis vitae, family history, clinical picture of the disease, objective examination data, laboratory and instrumental methods of investigation (CBC, clinical urine test, glycemic profile, biochemical blood tests, ophthalmoscopy, chest X-ray, ECG). The patients with clinically expressed coronary heart disease requiring specific therapy, heart defects, im-

paired liver and kidney function were excluded from this study.

For the distribution of patients into groups, the World Health Organization (WHO) arterial hypertension (AH) classification was used (1993): group I consisted of patients with mild AH, group II — patients with moderate AH and group III — patients with severe AH.

Blood was taken from a cubital vein in the morning on an empty stomach with minimal venostasis. Indicators of calcium concentration in blood and urine were determined using test kits for determining calcium with glyoxal bis-2 hydroxyanil from LACHEMA. To determine the ionized calcium, a standard technique of ion-selective electrode was used.

Statistical processing of the results was carried out using non-parametric statistical methods — Wilcoxon-Mann-Whitney test, Spearman's rank correlation coefficient. All materials were analyzed by using variation statistics with program of Microsoft Excel 2013 and Statistica 12.

Our study involving all human participants was performed in accordance with ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later amendments. Our study is also in accordance with rules and regulations of the Ethical Committee of our Institution named Ethics Committee of V.I. Vernadsky Crimean Federal University (Ethics Committee Protocol No. 4. 13/03/2018).

Results

Table 1 shows the results of measurements of total plasma calcium (Cao) in patients participating in the study. In patients with mild hypertension the calcium concentration in plasma was 2.53 ± 0.04 mmol/L, which is 0.04 mmol/L higher than in the control group, but this difference is not statistically significant ($p > 0.5$). In patients with moderate and severe arterial hypertension, the Cao levels in the blood were almost identical (2.49 ± 0.02 mmol/L and 2.52 ± 0.04 mmol/L, respectively) and also did not go beyond physiological fluctuations ($p > 0.5$). Thus, there was no difference in Cao concentration in patients with different degree of arterial hypertension, which confirms the validity on the stability of the concentration of total calcium in the blood.

Table 1 shows that the concentration of ionized Ca in the control group was 1.25 ± 0.02 mmol/L, which corresponds to a normal value. A study of the

Table 1. The concentration of total calcium, ionized calcium, calcium bound to plasma proteins in patients with arterial hypertension of the elderly and senile age ($M \pm m$)

	Control group (n = 20)	Degree of AH		
		Mild (n = 18)	Moderate (n = 26)	Severe (n = 16)
Total calcium concentration [mmol/L]	2.51 ± 0.03	2.53 ± 0.04*	2.49 ± 0.02*	2.52 ± 0.04*
Concentration of ionized Ca (Ca ²⁺) [mmol/L]	1.25 ± 0.02	1.05 ± 0.06*	0.83 ± 0.04*	0.56 ± 0.07*
Ca bound [mol/L]	1.26 ± 0.02	1.48 ± 0.05*	1.66 ± 0.05*	1.96 ± 0.06*

Significance differences in indicators with those in the control group; *reliable; $p < 0.05$; AH — arterial hypertension

Table 2. The concentration of calcium (Ca) in red blood cells (RBC), as well as the daily excretion of calcium in the urine in patients with hypertension of the elderly and senile age ($M \pm m$)

	Control group (n = 20)	Degree of AH		
		Mild (n = 18)	Moderate (n = 26)	Severe (n = 16)
Concentration of Ca in RBC [mmol/L]	1.26 ± 0.05	1.74 ± 0.09**	1.95 ± 0.13***	2.09 ± 0.14**b
Daily diuresis [mL]	1394 ± 83	1338 ± 116	1272 ± 149	1247 ± 136
Daily urinary excretion of Ca [mmol/L]	3.10 ± 0.11	3.82 ± 0.15	4.22 ± 0.13***	4.36 ± 0.14**b

Differences in indicators compared with the control group; **significant $p < 0.001$; *a significant difference with mild hypertension ($p < 0.05$), ^aa significant difference with moderate hypertension ($p < 0.05$); AH — arterial hypertension

concentration of ionized calcium in blood plasma indicates that the value of this indicator depends on the severity of hypertension. In particular, in patients with mild hypertension, the concentration of ionized Ca was 1.05 ± 0.06 mmol/L, which is 0.2 mmol/L lower than normal; however, the detected difference is not statistically significant ($p > 0.05$). More convincing differences were obtained by analyzing the concentration of ionized calcium in patients with moderate to severe hypertension. In the second group of patients, the studied parameter was reduced to 0.83 ± 0.04 mmol/L and in the third group it was reduced to 0.56 ± 0.07 mmol/L. Both of the above indicators are outside the limits of physiological fluctuations, since comparison with the norm shows the statistically significant reliability ($p < 0.05$).

Correlation analysis showed that the degree of decrease in the concentration of ionized calcium is strongly dependent on the degree of arterial hypertension ($r_1 = 1.2$; $r_2 = 1.4$; $r_3 = 0.8$).

An analysis of the calcium bound to the plasma proteins in the blood revealed a significant increase in patients with moderate and severe arterial hypertension. In patients with moderate hypertension, this indicator was 1.66 ± 0.05 mmol/L, and in patients with severe hypertension — 1.96 ± 0.06 mmol/L,

which is 0.4 mmol/L and 0.76 mmol/L higher than in the control group respectively ($p < 0.05$).

The concentration of calcium in erythrocytes (Tab. 2) in patients with mild AH was 1.74 ± 0.22 mmol/L, which is 0.48 mmol/L more than in the control group, but still there is no statistical significance ($p > 0.05$). In patients with moderate and severe AH, the concentration of calcium in erythrocytes was 1.95 ± 0.13 mmol/L and 2.09 ± 0.14 mmol/L respectively, which is significantly higher than in the control group. Analysis of the concentration of Ca in red blood cells in the body of patients with arterial hypertension shows an increase in this indicator. These changes are detected even with the mild arterial hypertension; however, statistical significance was found only in patients with moderate and severe arterial hypertension.

Correlation analysis showed a direct correlation of weak strength ($r_1 = 0.1$; $r_2 = 0.05$; $r_3 = 0.001$).

Daily diuresis was similar in all examined groups. In patients with mild AH, daily calcium excretion was 3.82 ± 0.15 mmol/L, which is 0.72 mmol/L more than in the control group. In the group of patients with moderate and severe hypertension, this indicator was 4.22 ± 0.13 mmol/L and 4.36 ± 0.18 mmol/L, respectively, which is significantly higher than the control group; a high degree of reliability of

the differences is noteworthy. A correlation analysis revealed a direct correlation of weak strength ($r_1 = 0.05$; $r_2 = 0.06$; $r_3 = 0.07$).

Discussion

As a result of the study, it was found that the concentration of total calcium in the blood plasma in patients with arterial hypertension was within normal values, regardless of the severity of the disease. Data obtained by other researchers also indicates that in arterial hypertension the concentration of total calcium in the blood plasma remains constant [11–15]. A correlation between hypertension and serum calcium has been studied in different ethnicities and races [9, 16–19].

At the same time, a study of calcium metabolism in the body of patients with arterial hypertension revealed changes already in the early stages of the disease. The ionized fraction of calcium in plasma is a physiologically active fraction responsible for maintaining calcium homeostasis in the body. According to our data, in the body of patients with arterial hypertension, changes observed in the concentration of ionized calcium in blood plasma depend upon the severity of the course of arterial hypertension. The statistical significance of a decrease in the concentration of ionized calcium was noted in groups of patients with moderate and severe arterial hypertension. The concentration of ionized calcium in patients with moderate arterial hypertension was 1.5 times lower when compared with the control group, and in patients with severe arterial hypertension this parameter was 2.2 times lower compared with the control group.

For a correct assessment of changes in calcium metabolism in hypertension, it is necessary to study the concentration of intracellular Ca. According to A.N. Kravchenko, there is an increase in the content of basal Ca — concentration of the Ca in the cytoplasm of platelets, lymphocytes, adipocytes in patients with hypertension [20].

In 1975, Yu. V. Postnov proposed a concept, according to which the development of hypertension is primarily associated with a deficiency in the Ca-regulatory function of cell membranes and a decrease in the activity of the calcium pump. It was shown that in the cytoplasm of erythrocytes, adipocytes, cardiomyocytes and other cells of rats with spontaneous hypertension (an experimental model closest to human hypertension) an increase in Ca level is noted. The latter is explained by a decrease in the Ca-binding ability of the membrane,

an increase in the Ca²⁺ entry rate, and a decrease in its elimination from the cell. This concept has been confirmed by a number of clinical and biophysical data. In addition to the reasons associated with systemic alteration of cell membranes, it is possible to distinguish the disturbances in the relationship of the enzyme protein with the calmodulin pool in the cell [21] and cyclic nucleotides [22]. It is known that the activity of cyclic nucleotides, which mediate hormonal effects in the blood plasma and inside the cell, is inversely related to the level of Ca²⁺ in it [23, 24]. Under these conditions, the functional activity of both pressor and depressor systems can change, which ultimately leads to dysregulation of blood pressure.

Also, to assess changes in Ca metabolism in hypertensive patients, we studied the daily excretion of calcium by the kidneys. A significant increase in daily urinary Ca excretion was found in patients with hypertension. An increase of this indicator was noted in comparison with the control group: in patients with mild arterial hypertension by 1.2 times, in patients with moderate arterial hypertension by 1.3 times, and severe arterial hypertension by 1.5 times. The highest daily Ca excretion rates were found in patients with severe arterial hypertension. Correlation analysis showed a weak positive correlation.

Considering that proteins with the ability to bind blood calcium, like all protein compounds, do not penetrate the membrane barrier of the renal glomeruli, the excreted calcium fraction in the urine is represented by ionized and easily filtered calcium. In the experimental data of some authors [25], a direct dependence of calcium excretion on processes associated with sodium transport has been shown. Thus, one of the reasons for increased urinary calcium excretion in elderly patients with AH may be an increase in sodium excretion, which can probably be explained by age-related thinning of the renal cortex, a decrease in their mass, and a decrease in sensitivity to catecholamines. An increase in urinary Ca excretion may also be associated with a decrease in Ca reabsorption. Considering that in our patients we did not notice an increase in the concentration of total Ca in plasma, we can assume that an increase in the activity of the parathyroid glands to some extent compensates for the loss of Ca in the proximal tubules, with increased reabsorption of Ca in the distal part of the nephron.

Thus, the results obtained indicate a generalized violation of Ca metabolism in patients with arterial hypertension. The concentration of total Ca is constant in this group of patients, which indicates the

activation of compensatory mechanisms for maintaining calcium homeostasis.

Conclusions

1. In patients with arterial hypertension, a redistribution of the calcium pool in the blood is noted due to a decrease in the concentration of ionized calcium and an increase in the bound calcium, depending on the severity of the disease.
2. An increase in urinary calcium excretion in patients with arterial hypertension is characteristic of moderate and severe forms of arterial hypertension, which given the age of patients, may be one of the causes of osteoporosis.
3. The increase in the level of intracellular calcium with the progression of arterial hypertension is a kind of example of pathophysiological reactions that occur at the body level, the result of which can be not only banal muscle constriction, but also a violation of the synthesis and production of biologically active substances that regulate blood pressure.

Conflict of interest

The authors declare that they have no conflict of interest.

Source of funding

Self-funding by authors.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Our study is also in accordance with rules and regulations of the Ethical Committee of our Institution named Ethics Committee of V.I. Vernadsky Crimean Federal University (Ethics Committee Protocol No. 4. 13/03/2018).

Implications and Contribution

Our study reveals the characteristics of calcium dynamics and homeostasis in patients with different degrees of arterial hypertension. This study has a significant clinical impact, which have been never discussed or published before in any article or journal. This has an enormous human and socio-economic impact and this is going to be an interesting article for Researchers, Cardiologists, Public Health management all over the world and

for readers too. This article may help improve public health in the future.

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