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# NATRIURETIC RESPONSE TO HYPERVOLEMIA AND INJECTION OF DIURETICS IN PATIENTS WITH CHRONIC HEART FAILURE

*D.S. Frolov, S.B. Shustov, T.S. Sveklina, R.T. Sardinov, V.V. Saluhov*

S.M. Kirov Military Medical Academy, Saint Petersburg, Russia

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***Relevance.*** The article analyze the results of changes in the diuretic and natriuretic response to standard hypervolemic load and the injection of a diuretic in patients with chronic heart failure with preserved and reduced left ventricular ejection fraction.

***Purpose.*** Evaluation of changes in the natriuretic response to hypervolemia and diuretic injection in patients with chronic heart failure.

***Materials and methods.*** 25 men with chronic heart failure were examined; the average age was 68 y. o. (67; 73). Of these, 13 patients with chronic heart failure and a left ventricular ejection fraction (LVEF) of less than 50 % entered the first studied group and 12 patients with chronic heart failure with preserved LVEF (more than 50%), who entered the second studied group. In all the patients, hypervolemia was induced by Ringer's solution, followed by the injection of furosemide and the registration of diuresis and natriuresis.

***Results.*** When analyzing natriuresis in the studied patients, it was found that at the same concentration of serum sodium, there is a multidirectional reaction to the excretion of sodium in the urine in both groups. At the same time, the rates of diuresis in both groups did not differ significantly.

***Conclusion.*** Thus, with chronic heart failure and reduced LVF less than 50% patients had a lower natriuresis compared to those studied with preserved LVF. In the patients with chronic heart failure fluid overload on the mixed response it is noted that if the urine sodium level is at the lower limit of normal in patients with reduced LVF less than 50%, then, against the background of stimulation of diuresis, sodium begins to be excreted more intensively. In the patients with chronic heart failure with preserved LVF, the urine sodium level is at the upper limit of the norm and when furosemide is stimulated, there is a decrease in its excretion.

**Keywords:** natriuresis; hypervolemia; chronic heart failure.

# НАТРИЙУРЕТИЧЕСКИЙ ОТВЕТ НА ГИПЕРВОЛЕМИЮ И ВВЕДЕНИЕ ДИУРЕТИКОВ У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

*Д.С. Фролов, С.Б. Шустов, Т.С. Свеклина, Р.Т. Сардинов, В.В. Салухов*

Федеральное государственное бюджетное военное образовательное учреждение высшего образования «Военно-медицинская академия имени С.М. Кирова» Министерства обороны Российской Федерации, Санкт-Петербург

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***Актуальность.*** Проанализированы результаты изменений диуретического и натрийуретического ответа на стандартную гиперволемическую нагрузку и введение диуретика у пациентов с хронической сердечной недостаточностью с сохраненной и сниженной фракцией выброса левого желудочка.

***Цель*** — оценить изменения в натрийуретическом ответе на гиперволемию и введение диуретика у пациентов с хронической сердечной недостаточностью.

***Материалы и методы.*** Обследовано 25 мужчин с хронической сердечной недостаточностью, средний возраст которых составил 68 (67; 73) лет. Из них 13 пациентов с хронической сердечной недостаточностью и фракцией выброса левого желудочка менее 50 % вошли в первую группу, а 12 пациентов с хронической сердечной недостаточностью с сохраненной фракцией выброса левого желудочка (более 50 %) — во вторую группу. У всех больных индуцировали гиперволемию раствором Рингера с последующим введением фуросемида и регистрацией диуреза и натрийуреза.

***Результаты.*** Анализ натрийуреза у исследуемых больных показал, что при одинаковой концентрации сывороточного натрия наблюдается разнонаправленная реакция на выведение натрия с мочой у пациентов обеих групп. При этом темпы диуреза у пациентов обеих групп значимо не различались.

***Заключение.*** У пациентов с хронической сердечной недостаточностью и снижением фракции выброса левого желудочка менее 50 % отмечен более низкий натрийурез по сравнению с пациентами с сохраненной фракцией выброса левого желудочка. У больных хронической сердечной недостаточностью наблюдается разнонаправленная реакция на гиперволемию. Если у пациентов со снижением фракции выброса левого желудочка менее 50 % уровень натрия в моче находится на нижней границе нормы, то на фоне стимуляции диуреза натрий начинает интенсивнее выводиться. У больных хронической сердечной недостаточностью с сохраненной фракцией выброса левого желудочка уровень натрия в моче находится на верхней границы нормы и при стимуляции фуросемидом его выведение уменьшается.

◆ **Ключевые слова:** натрийурез; гиперволемия; хроническая сердечная недостаточность.

## Background

Severe congestion in the systemic and pulmonary blood circulation is the main cause of unexpected hospitalization of patients with heart failure.

With age, renal function decreases in a substantial proportion of patients with chronic heart failure (CHF), despite therapy with β-blockers and angiotensin-converting enzyme inhibitors. In addition, these patients may develop resistance to diuretics following their long-term use, which is associated with increased mortality [1].

Sodium is the main regulator of water and acid–base balance. It is a component of all body fluids and has the highest concentration in the blood and extracellular fluid. The level of extracellular sodium is mainly influenced by kidney function. Healthy people have stable concentration of blood electrolytes, since their food intake is balanced by defecation and excretion with urine and sweat.

The sodium concentration in the extracellular fluid is regulated by hormones that increase or decrease the loss of sodium in the urine (natriuretic peptide and aldosterone), prevent fluid loss in the urine (antidiuretic hormone), and control thirst (antidiuretic hormone). The human body takes a portion of sodium intake for its own needs, and the remaining amount is excreted by the kidneys in the urine. As a result, the concentration of electrolytes in the blood is maintained within a very narrow range [2].

**This study aimed** to evaluate changes in the natriuretic response to hypervolemia and diuretic administration in patients with CHF.

## Materials and methods

We examined 25 male patients with CHF, including 13 patients with left ventricular ejection fraction (LVEF) <50% (group 1) and 12 patients with LVEF >50% (group 2). The average patient age was 68 (67; 73; range, 61–78) years (Table 1). The study groups were comparable in terms of age, body mass index, and CHF duration. All patients were treated according to the clinical guidelines for the prevention, diagnosis, and treatment of CHF in the absence of contraindications to the drugs taken [3] (Table 1). In group 1, most patients received spironolactone, a mineralocorticoid receptor antagonist, at a dose of 25 mg/day, but it did not significantly affect natriuresis. The rest of the therapy was comparable. The level of the N-terminal fragment of the brain natriuretic peptide (NT-proBNP) was assessed. After evaluating the initial clinical and instrumental parameters for 9 h, the urine output volume and urine sodium level were determined every 3 h. After the 3-h period, hypervolemia was

*Table 1 / Таблица 1*

**Clinical characteristics of patients, Me (25; 75%)**
**Клиническая характеристика пациентов, Me (25; 75 %)**

| Parameters | Group 1 ($n$ = 13) | Group 2 ($n$ = 12) |
|---|---|---|
| Age, years | 70.5 (67.5; 75.5) | 68 (61; 69) |
| Body mass index, kg/m$^2$ | 34.3 (29.2; 39.4) | 30.8 (29.2; 37.8) |
| Left ventricular ejection fraction, % | 40.5 (38; 45)* | 54 (50; 57) |
| Duration of chronic heart failure, years | 14 (12.5; 17.5) | 10 (9; 18) |
| Drugs used to treat chronic heart failure | | |
| ACE inhibitors/ARBs | 13 (100%) | 12 (100%) |
| β-blockers | 12 (92%) | 10 (83%) |
| MCRA | 12 (92%) | 3 (25%) |
| Thiazide diuretics | 6 (46%) | 5 (42%) |
| Loop diuretics | 3 (23%) | 2 (17%) |

N o t e. ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; MCRA, mineralocorticoid receptor antagonist. * $p < 0.05$.

induced (10-min infusion of Ringer's solution in a volume of 0.5 L [8.6 g/L sodium chloride, 0.33 g/L calcium chloride, and 0.3 g/L potassium chloride], followed by parenteral administration of 0.5 Ringer's solution in a volume of 1 L for 1 h 50 min). Then, after 6 h of monitoring, 40 mg of furosemide was administered intravenously to the patients.

Statistical analysis of the results was performed using Statistica 10.0 Software Package (StatSoft, USA). Quantitative data were presented as Me (25%; 75%), where Me is the median and 25% and 75% are interquartile ranges in the form of the 25$^{th}$ and 75$^{th}$ percentiles. Quantitative indicators were compared using the Wilcoxon rank method (for dependent variables) and the Mann–Whitney *U*-test (for independent groups). To analyze the relations between the studied characteristics (correlations), the nonparametric Spearman method (*r*) was used.

## Results and discussion

The examination revealed that the NT-proBNP level was 2000 (1200; 2250) pg/ml in group 1 and 181.7 (140.6; 222.6) pg/ml in group 2 ($p < 0.05$), which corresponds to a more pronounced CHF with LVEF <50%.

The renal function assessment revealed that the glomerular filtration rate was significantly lower in patients with LVEF <50% at 60 (51; 66) ml/min per 1.73 m$^2$ than in patients with preserved LVEF at 73 (73; 74) ml/min per 1.73 m$^2$ ($p < 0.05$), which is consistent with the findings of other studies [4–6].

At the same concentration of serum sodium, natriuretic analysis showed a multidirectional response to sodium excretion in the urine. There was a tendency ($p = 0.051$) to lower values of the initial baseline natriuresis (3 h) as well as natriuresis with intravenous administration of Ringer's solution (6 h) in group 1 than in group 2. The absence of statistically significant differences is apparently due to the small sample size (Table 2).

Lower values of urine sodium in group 1 were possibly due to secondary hyperaldosteronism in the presence of CHF with LVEF <50%. A higher concentration of aldosterone leads to increased sodium reabsorption and a decrease in its excretion in the urine [6]. If the urine sodium level was at the lower limit of the normal in patients with CHF with LVEF <50%, sodium was excreted more intensively when diuresis was induced. In patients with CHF with preserved LVEF, the urine sodium level was at the upper limit of the normal, and when stimulated with furosemide, its excretion decreased (Fig. 1). The decrease in sodium excretion was probably due to the activation of the

*Table 2 / Таблица 2*

**The level of sodium in serum and urine, Me (25; 75%)**
**Уровень натрия в сыворотке крови и моче, Me (25; 75 %)**

| Parameters | Group 1 (*n* = 13) | Group 2 (*n* = 12) |
|---|---|---|
| Serum sodium, mmol/l | 142.5 (139.5; 143.5) | 144 (143; 145) |
| Urine sodium after 3 h, mmol/l (normal 40–220 mmol/l) | 62 (49.5; 71.5) | 203 (196; 204) |
| Urine sodium after 6 h, mmol/l | 63 (57.5; 70) | 126 (90; 204) |
| Urine sodium after 9 h, mmol/l | 112.5 (104.5; 120.5) | 105 (76; 145) |

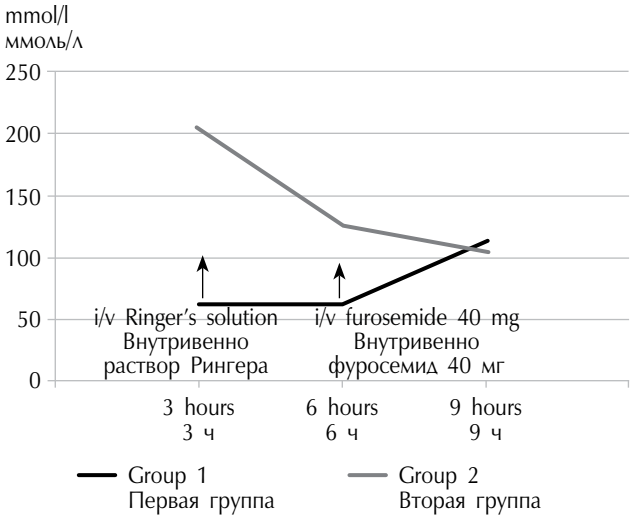


**Fig. 1.** Dynamics of urinary sodium levels

**Рис. 1.** Динамика уровня натрия в моче

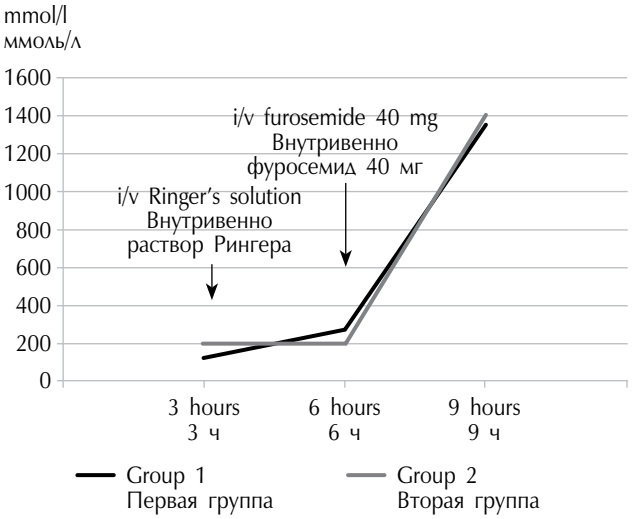


**Fig. 2.** Dynamics of diuresis

**Рис. 2.** Динамика диуреза

renin–angiotensin–aldosterone system and resulted in a decrease in sodium excretion in the urine. The syndrome of paradoxical sodium retention is also possible, which is accompanied by a decrease in sodium excretion in the urine, water retention, and an increase in body weight due to latent edema. The syndrome is associated with a paradoxical reaction to vasopressin; in response to hyperhydration with Ringer's solution, the release of vasopressin increases. Sodium remains in the body and retains water, but the diuresis volume does not decrease since sodium is exchanged for water in the collecting tubules [7].

The characteristics of diuresis in patients are presented in Table 3 and Fig. 2.

The rate of diuresis in both groups was quite comparable and increased significantly with the introduction of loop diuretics.

*Table 3 / Таблица 3*

**Characterization of diuresis, Me (25; 75%)**
**Характеристика диуреза, Me (25; 75 %)**

| Parameters | Group 1 (*n* = 13) | Group 2 (*n* = 12) |
|---|---|---|
| Diuresis volume after 3 h, ml | 125 (90; 375) | 200 (150; 400) |
| Diuresis volume after 6 h, ml | 275 (125; 575) | 200 (150; 300) |
| Diuresis volume after 9 h, ml | 1350 (1250; 1450) | 1400 (1100; 2200) |

Diuresis and sodium excretion correlated positively ($r = 0.99$; $p < 0.05$) in group 1 and negatively ($r = –0.76$; $p < 0.05$) in group 2, which confirms the theory of the activation of the renin–angiotensin–aldosterone system and the paradoxical reaction of vasopressin to sodium administration. Under physiological conditions, excess sodium blocks the release of vasopressin and is excreted in the urine. In a paradoxical response, an increase in the urine excretion of sodium with its excess in the blood still stimulates the release of vasopressin. As a result, sodium is exchanged for water in the collecting tubules and released into the blood, and the water is removed, but not completely. A portion of the water is retained due to the presence of excess sodium levels in the blood; the sodium particle enters the cells and pulls water with it, causing latent intracellular edemas [7, 8] which can be detected using modern bioimpedance body composition analyzers.

## Conclusion

Patients with CHF and LVEF <50% are characterized by a lower natriuresis than patients with preserved LVEF. Patients with CHF have a multidirectional response to hypervolemia. In patients with LVEF <50%, sodium is excreted more intensively when diuresis is stimulated, provided that the urine sodium level is at the lower limit of the normal. In patients with CHF and preserved LVEF, the urine sodium level is at the upper limit of the normal, and when stimulated with furosemide, its excretion decreases. Further research is required to clarify the causes of these changes.

## References


1. Фролов Д.С., Шустов С.Б., Барсуков А.В., и др. Вторичная нефропатия при артериальной гипертензии // Лечение и профилактика. – 2015. – № 3. – С. 39–45. [Frolov DS, Shustov SB, Barsukov AV, et al. The secondary nephropathy under arterial hypertension. *Lechenie i profilaktika*. 2015;(3):39-45. (In Russ.)]
2. Шейман Д.А. Патофизиология почки / под ред. Ю.В. Наточина. – М.: Бином, 2019. – 192 с. [Sheyman DA. Patofiziologiya pochki. Ed. by Y.V. Natochina. Moscow: Binom; 2019. 192 p. (In Russ.)]
3. Мареев В.Ю., Фомин И.В., Агеев Ф.Т., и др. Хроническая сердечная недостаточность (ХСН) // Журнал сердечная недостаточность. – 2017. – Т. 18. – № 1. – С. 3–40. [Mareyev VY, Fomin IV, Ageev FT, et al. Chronic heart failure (CHF). *Zhurnal serdechnaia nedostatochnost'*. 2017;18(1):3-40. (In Russ.)]. https://doi.org/10.18087/rhfj.2017.1.2346.
4. Фролов Д.С., Салухов В.В., Шустов С.Б., и др. Особенности структурно-функционального состояния миокарда у пациентов с хронической болезнью почек и хронической сердечной недостаточностью // Вестник Северо-Западного государственного медицинского университета им. И.И. Мечникова. – 2019. – Т. 11. – № 3. – С. 79–84. [Frolov DS, Salukhov VV, Shustov SB, et al. Features of the structural and functional condition of the myocardium in patients with chronic kidney disease and chronic heart failure. *Vestnik Severo-Zapadnogo gosudarstvennogo meditsinskogo universiteta im. I.I. Mechnikova*. 2019;11(3):79-84. (In Russ.)]. https://doi.org/10.17816/mechnikov201911379-84.
5. Knepper MA, Kwon TH, Nielsen S. Molecular physiology of water balance. *N Engl J Med*. 2015;372(14):1349-1358. https://doi.org/10.1056/nejmra1404726.
6. Felker GM, Ellison DH, Mullens W, et al. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75(10):1178-1195. https://doi.org/10.1016/j.jacc.2019.12.059.
7. Физиология почки / под ред. Ю.В. Наточина. – Л.: Наука, 1972. – 398 с. [Fiziologiya pochki. Ed. by Y.V. Natochin. Leningrad: Nauka; 1972. (In Russ.)]
8. Тюзиков И.А., Калинченко С.Ю., Ворслов Л.О., Тишова Ю.А. Вазопрессин: неклассические эффекты вазопрессина и их роль в патогенезе ассоциированных с возрастом заболеваний // Эффективная фармакотерапия. – 2015. – № 26. – С. 38–50. [Tyuzikov IA, Kalinchenko SY, Vorslov LO, Tishova YA. Vasopressin: Non-Classic Effects and Role in Pathogenesis of Age-Associated Diseases. *Effektivnaya farmakoterapiya*. 2015;(26):38-50. (In Russ.)]



◆ **Information about the author** *(Адрес автора для переписки)*

*Dmitriy S. Frolov / Дмитрий Сергеевич Фролов*
Tel. / Тел.: +79117891396
SPIN-code / SPIN-код: 4089-0078
E-mail: froloff_82@mail.ru