DOI: 10.20514/2226-6704-2021-12-2-143-155 УДК 616.12-008.331.4-6:616.12-008.46

М.С. Бычкова*[1], Е.В. Резник[1,2]

[1] — Федеральное государственное автономное образовательное учреждение высшего образования «Российский Национальный Исследовательский Медицинский Университет имени Н.И. Пирогова» Министерства здравоохранения Российской Федерации, кафедра госпитальной терапии № 2, Москва, Россия
[2] — ГКБ № 31 ДЗМ, Москва, Россия

ВЕДЕНИЕ ПАЦИЕНТА С ТЯЖЕЛОЙ АРТЕРИАЛЬНОЙ ГИПОТОНИЕЙ НА ФОНЕ ТЕРМИНАЛЬНОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ СО СНИЖЕННОЙ ФРАКЦИЕЙ ВЫБРОСА ЛЕВОГО ЖЕЛУДОЧКА

M.S. Bychkova*[1], E.V. Reznik[1,2]

[1] — N.I. Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation, department of Hospital Therapy № 2, Moscow, Russia
[2] — City Clinical Hospital № 31, Moscow, Russia

Management of a Patient with Severe Hypotension and Advanced Heart Failure with Reduced Left Ventricular Ejection Fraction

Резюме

Артериальная гипотония часто встречается при хронической сердечной недостаточности. Снижение артериального давления может быть обусловлено различными причинами, в том числе снижением насосной функции сердца, лекарственными препаратами, измененной вазореактивностью, связанной с сопутствующими заболеваниями (например, сахарным диабетом) и др. Единых критериев оценки тяжести артериальной гипотонии нет. Степень влияния ее на прогноз и течение заболевания окончательно не изучены. Сложность ведения пациентов с сердечной недостаточностью и артериальной гипотонией заключается в подборе и титровании рекомендованных лекарственных препаратов для компенсации заболевания без развития дополнительных побочных эффектов. На сегодняшний день разработаны поэтапные алгоритмы назначения и коррекции лекарственной терапии пациентам с артериальной гипотонией. В данной статье представлен клинический случай ведения пациента с тяжелой артериальной гипотонией на фоне хронической сердечной недостаточности со сниженной фракцией выброса левого желудочка.

Пациенту с врожденным пороком сердца (двустворчатым аортальным клапаном) в 25 лет было выполнено протезирование аортального клапана. Спустя 13 лет, после перенесенной вирусной инфекции, развилась декомпенсация хронической сердечной недостаточности со снижением фракции выброса левого желудочка до 19% с последующим сохранением клинической симптоматики на уровне III — IV функционального класса, несмотря на оптимальную медикаментозную терапию в течение года. При наличии у пациента показаний к сердечной ресинхронизирующей терапии была имплантирована система модуляции сердечной сократимости, после чего улучшения клинической симптоматики не отмечалось, наблюдались частые (до 4 в течение год) декомпенсации, требовавшие госпитализаций. С целью предотвращения прогрессирования заболевания и улучшения прогноза, несмотря на гипотензию, был назначен сакубитрил/валсартан в минимальных дозах, на фоне чего удалось компенсировать пациента и добиться стабильного течения хронической сердечной недостаточности без потребности в госпитализации в течение 9 месяцев. Данный клинический случай позволяет рассматривать необходимость

*Контакты: Мария Сергеевна Бычкова, e-mail: mashabichkova@gmail.com
*Contacts: Maria S. Bychkova, e-mail: mashabichkova@gmail.com
ORCID ID: https://orcid.org/0000-0002-3453-5914

проведения дополнительных клинических исследований для изучения возможности назначения малых доз сакубитрил/валсартана у пациентов с артериальной гипотонией на фоне сердечной недостаточности с целью уменьшения выраженности клинической симптоматики и улучшения прогноза.

Ключевые слова: *терминальная сердечная недостаточность, двустворчатый аортальный клапан, сердечная ресинхронизирующая терапия, трансплантация сердца, система модуляции сердечной сократимости, гипотония, сакубитрил/валсартан*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 16.03.2021 г.

Принята к публикации 21.01.2022 г.

Для цитирования: Бычкова М.С., Резник Е.В. ВЕДЕНИЕ БОЛЬНОГО С ТЯЖЕЛОЙ АРТЕРИАЛЬНОЙ ГИПОТОНИЕЙ НА ФОНЕ ТЕРМИНАЛЬНОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ СО СНИЖЕННОЙ ФРАКЦИЕЙ ВЫБРОСА ЛЕВОГО ЖЕЛУДОЧКА. Архивъ внутренней медицины. 2022; 12(2): 143-155. DOI: 10.20514/2226-6704-2021-12-2-143-155

Abstract

Hypotension is often in chronic heart failure patients. It has various reasons, including a decrease in the pumping function of the heart, medications, altered vasoreactivity associated with concomitant diseases (for example, diabetes mellitus). There are no universal criteria for assessing the severity of hypotension. Its prognosis significance has not been studied well. It is difficult to select and titrate the drugs recommended for treatment of heart failure, so that the prescribed therapy compensates the patient and does not cause the development of side effects. Step–by–step algorithms for prescribing and correcting drug therapy for heart failure patients with hypotension have been developed. This article presents a clinical case of management of a patient with severe hypotension and chronic heart failure with a reduced left ventricular ejection fraction.

Aortic valve replacement was performed the patient with congenital heart disease (bicuspid aortic valve) in 25 years. In 13 years, after a viral infection, there was a decompensation of chronic heart failure with reduced ejection fraction to 19%. Against the optimal drug therapy, heart failure persisted III– IV functional class with 4 hospitalization during a year. Despite the indications for cardiac resynchronization therapy, a system for modulating cardiac contractility was implanted, after which there was no improvement in clinical symptoms, there were frequent decompensations up to. In order to prevent the progression of the disease and improve the prognosis, despite hypotension, sacubitril/valsartan was prescribed, against which it was possible to compensate the patient and achieve a stable course of chronic heart failure without the need for hospitalization for 9 months. This case report suggest that additional clinical researches are necessary to study the possibility of prescribing of small doses of sacubitril/valsartan in patients with hypotension and heart failure to reduce the severity of clinical symptoms and to improve the prognosis.

Key words: *terminal heart failure, bicuspid aortic valve, cardiac resynchronization therapy, heart transplantation, cardiac contractility modulation, hypotension, sacubitril/valsartan*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 16.03.2021

Accepted for publication on 21.01.2022

For citation: Bychkova M.S., Reznik E.V. Management of a Patient with Severe Hypotension and Advanced Heart Failure with Reduced Left Ventricular Ejection Fraction. The Russian Archives of Internal Medicine. 2022; 12(2): 143-155. DOI: 10.20514/2226-6704-2021-12-2-143-155

24h ECG — 24-Hour Holter monitoring, ACE inhibitors — angiotensin-converting enzyme inhibitors, ALT — alanine aminotransferase, ARB — angiotensin II receptor blocker, ARNI — angiotensin receptor-neprilysin inhibitor, ARVI — acute respiratory viral infection, AST — aspartate aminotransferase, AUS — ultrasound examination of abdominal organs, BMI — body mass index, BP — blood pressure, CHF — chronic heart failure, CKD — chronic kidney disease, CRTd — cardiac resynchronization therapy with a defibrillator, ECHO-CG — echocardiography, ECG — electrocardiography, EDV — end-diastolic volume, EGD — esophagogastroduodenoscopy, ESC — European Society of Cardiology, ESD — end-systolic dimension, FC — functional class, FDA — Food and Drug Administration, FS — fractional shortening, GFR — glomerular filtration rate, GGTP — gamma-glutamyl transpetidase, HF — heart failure, HFmrEF — heart failure with midrange LV ejection fraction, HFpEF — heart failure with preserved LV ejection fraction, HR — heart rate, IABP — intra-aortic balloon counterpulsation, INR — international normalized ratio, LA — left atrium, LBBB — left bundle branch block, LDH — lactate dehydrogenase, LVEF — left ventricular ejection fraction, MCS — mechanical circulatory support, MRA — mineralocorticoid receptor antagonist, NYHA — New York Heart Association, OM — omecamtiv mecarbil, RCT — randomized clinical trial, RV — right ventricle, sPAP — systolic pulmonary artery pressure, SV — stroke volume, T2DM — type 2 diabetes mellitus, QRS axis — electrical heart axis

Introduction

The management of chronic heart failure (HF) remains an extremely pressing issue today. In the Russian Federation, HF of functional class (FC) I-IV, according to the New York Heart Association (NYHA) classification, affects 7.9 million individuals [1]. Present-day advances in drug therapy can help improve the quality of life and increase life expectancy. However, they inevitably increase the number of patients with end-stage HF. End-stage HF is characterized by persisting severe clinical

Table 1. *Updated HFA–ESC criteria for defining advanced heart failure*

All the following criteria must be present despite optimal guideline–directed treatment:
1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by a reduced LVEF ≤30%, isolated RV failure (e.g., ARVC) or non–operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT–proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.
3. Episodes of pulmonary or systemic congestion requiring high–dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise

Note: BNP — B-type natriuretic peptid, NT–proBNP — N-terminal pro-BNP, HFpEF — heart failure with preserved ejection fraction, HFmrEF — heart failure with mid-range ejection fraction, ARVC — arrhythmogenic right ventricular cardiomyopathy, LV — left ventricular LVEF — left ventricular ejection fraction, NYHA — New York Heart Association, ESC — European Society of Cardiology, RV — right ventricular

symptoms despite optimal treatment (Table 1) [2]. There are reasons to establish the diagnosis of end-stage HF in 1–10% of all patients with HF [3].

Drug treatment currently plays a central role in preventing the progression of HF. According to modern approaches, patients with chronic heart failure (CHF) with decreased LV systolic function should receive the following if they have no contraindications [1, 4]:

1) Angiotensin receptor-neprilysin inhibitor (ARNI) OR, if it cannot be prescribed/is contraindicated/leads to intolerance, an angiotensin-converting enzyme (ACE) inhibitor OR, if an ACE inhibitor leads to intolerance and ARNI cannot be prescribed, an angiotensin II prescription blocker (ARB) [5–7].
2) Beta blocker (BB) [1, 6].
3) Diuretic (in the case of congestion) [6, 8].
4) If there is no effect from a three-component ongoing therapy and LV EF < 35%, a mineralocorticoid receptor antagonist (MRA) should be added [5, 6].
5) To improve the prognosis, all patients with CHFrEF are indicated to have sodium-glucose cotransporter-2 inhibitors (SGLT-2, "metabolic diuretics") added to their treatment.

If a patient takes ACE inhibitors/ARBs, BBs, MRAs and a diuretic and clinical symptoms persist, then, if there is sinus rhythm with HR > 70 bpm with the intake of a target dose of BBs or intolerance to them, the addition of If-channel blockers (ivabradine) is indicated. For patients with atrial fibrillation, oral anticoagulants should be prescribed, and for patients with HR > 70 bpm with the intake of a target dose of BB, digoxin should be added. If a patient takes ACE inhibitors/ARBs, BBs, MRAs and a diuretic and has systolic blood pressure (BP) > 100 mm Hg and clinical symptoms persist, an ACE inhibitor/ARB should be replaced with ARNI [5, 6].

In patients with end-stage CHF, the administration of these groups of medicinal agents is limited by the frequent development of severe arterial hypotension (synonym: hypotension).

Arterial hypotension is blood pressure more than 20% below normal values; in absolute terms, it is a decrease in systolic blood pressure < 90 mm Hg or mean BP < 60 mm Hg. [9]. According to randomized clinical trials (RCTs), arterial hypotension develops in 10–15% of patients with HF [2].

Arterial hypotension in cases of HF can be caused by decreased cardiac pumping function, medication-induced hypovolemia, vasodilation, impaired vasoreactivity (for example, in patients with diabetes mellitus) [3]. Arterial hypotension can be caused by high doses of loop diuretics, which remain the basis for managing congestion in patients with HF. Progression of heart failure is often accompanied by impaired renal function (development of chronic cardiorenal syndrome), which, in turn, is accompanied by resistance to diuretics [10, 11]. Chronic cardiorenal syndrome may have several mechanisms, including hemodynamic disturbances, neurohormonal activation, increased tubular sodium reabsorption, inflammation, oxidative stress and drug nephrotoxicity. Resistance to diuretics, in this case, usually develops due to a number of renal adaptations after the administration of diuretics ("braking phenomenon"), including hypertrophy and hyperfunction of nephron sites, as well as increased renin secretion. To manage the braking phenomenon, thiazide diuretics are used simultaneously with loop diuretics. However, there are no reliable RCT data regarding the effectiveness of this combination, and the combination may lead to the development/aggravation of arterial hypotension [3].

In patients with an inadequate response to treatment with oral diuretics, intravenous administration of diuretics is recommended, starting with a dose higher than for oral medications. However, this can also contribute to the development of arterial hypotension. If diuretic therapy has no effect, peritoneal dialysis can be prescribed [2]. Indications for dialysis include end-stage HF, fluid overload, progression of chronic kidney disease (CKD), and end-stage CKD [2].

Parenterally administered inotropic agents may improve hemodynamics in patients and delay deterioration in target organ function [2]. Inotropic agents can be conditionally divided into catecholamine derivatives (dopamine, dobutamine), positive inotropic agents with vasodilatory effect (levosimendan) and cardiac glycosides. These medications are indicated for CHF patients with persistent congestion, hypoperfusion, regardless of the administration of vasodilators or diuretics. Despite

the favorable effect on hemodynamics and severity of symptoms, long-term use of medications with positive inotropic effect (except digoxin) has a negative effect on the prognosis for CHF patients [12]: These agents increase myocardial oxygen demand and intracellular calcium concentration thereby increasing the risk of cardiac arrhythmia and death [12]. Therefore, such medications should be administered only during the acute period of hypoperfusion and hypotension that cannot be corrected with agents of other classes.

Levosimendan is a medication with three main properties: inotropic, vasodilatory and cardioprotective. Its half-life is 1–1.5 hours, and clinical effects are due to the formation of active metabolites OR-1855 and OR-1896, with the effect persisting for 7–9 days after the end of a 24-hour infusion. Its inotropic effect is due to the increased sensitivity of cardiomyocyte myofibrils to calcium, which leads to the binding of troponin C to calcium ions and the formation of a troponin C and calcium complex. This, in turn, leads to increased myocardial contractility without developing diastolic relaxation abnormalities. The vasodilatory effect is due to the opening of ATP-sensitive potassium channels on the membrane of smooth myocytes of the vascular wall, which reduces total peripheral and pulmonary vascular resistance and, therefore, pre- and afterload. The cardioprotective effect of levosimendan is also based on its effect on the opening of mitochondrial ATP-sensitive potassium channels [12].

The REVIVE and SURVIVE studies, the two largest studies to this date, showed that hypotension developed more frequently during treatment with levosimendan than with a placebo, but not with dobutamine. The incidence of atrial fibrillation in the levosimendan group was higher than in both comparator groups. Ninety percent of patients received levosimendan at a rate of 0.2 mg/kg/min during the first 2 hours; among them, 70–85% continued to receive the agent at the same rate over the next 24 hours. The main side effect of levosimendan was the development of hypotension (in 50% of subjects) and arrhythmias. Results of clinical trials indicate that levosimendan should be used with caution in patients with arterial hypotension, especially in cases of hypovolemia.

Inotropes may also be used in patients with end-stage HF prior to temporary mechanical circulatory support (MCS), long-term MCS or heart transplantation. Long-term treatment with inotropes is not recommended for patients awaiting transplantation. Long-term MCS is advisable in such cases. Long-term therapy with inotropes may be a palliative option for patients with no alternative treatment options [2].

Omecamtiv mecarbil (OM), a new selective oral inotrope, is a cardiac myosin activator that improves myocardial contractility in patients with CHF. The GALACTIC-HF study established the safety of OM, including the absence of adverse effects of OM on renal function, serum potassium levels, blood pressure or heart rate (HR) [13, 14]. The Food and Drug Administration (FDA) recently approved another new medication for the management of HF with reduced ejection fraction (HFrEF) — vericiguat, an oral soluble guanylate cyclase stimulator that increases the bioavailability of nitric oxide. The VICTORIA study, which included patients with LVEF < 45% after a recent hospitalization for decompensated HF or after receiving intravenous diuretics, revealed that this drug reduces mortality from cardiovascular events and the number of hospitalizations for HF [15].

The EMPEROR-Reduced trial demonstrated a lower risk of death due to cardiovascular causes or hospitalization for HF for 16 months due to the effect of empagliflozin at a dose of 10 mg per day compared with the placebo (1:1 ratio) in a group of 3,730 patients with HF with reduced LV ejection fraction ≤40% and increased NT-proBNP [16]. Empagliflozin reduced the risk of hospitalization for heart failure by 30% (HR 0.70; 95% CI 0.58–0.85; p < 0.001). In addition, the incidence of adverse renal events (required chronic hemodialysis or kidney transplantation or persistent reduction in estimated glomerular filtration rate) dropped by 50% in the empagliflozin group (HR 0.50; 95% CI 0.32–0.77; p < 0.01). BP in the empagliflozin and placebo group was 122.6 ± 15.9 and in the placebo group 121.4 ± 15.4 mm Hg, respectively; the proportion of patients with arterial hypertension was 1,349 (72.4%) and 1,349 (72.3%), respectively. No information was provided on the use of this medication in patients with arterial hypotension.

In the DAPA-HF study, the treatment of patients with HFrEF with and without T2DM with dapagliflozin led to a decrease in body weight (-0.7 kg after 4 months and –0.8 kg after 8 months, respectively, p = 0.14) and systolic BP (–1.6 mm Hg and –1.8 mm Hg after 4 months, respectively, p = 0.43) [17]. One of the key inclusion criteria in the DAPA-HF study was SBP ≥95 mm Hg. Baseline SBP in 1,205 patients was < 110 mm Hg, in 981 patients ≥110 < 120; in 1,149 patients ≥120 < 130; and in 1,409 patients ≥130 mm Hg. Placebo-adjusted SBP reduction from the baseline with up to 2 weeks of dapagliflozin administration was –2.54 (–3.33 to –1.76) mm Hg. Patients with the lowest SBP levels demonstrated more optimistic results in reducing the number of HF decompensations (per 100 person-years) [RR 20.6; 95% confidence interval (95% CI) 17.6–24.2] than patients with the highest SBP values (RR 13.8; 95% CI 11.7–16.4). The benefit and safety of dapagliflozin were similar throughout the SBP range (p = 0.78). The discontinuation of the study drug demonstrated no differences between dapagliflozin and placebo groups in the analyzed SBP categories. Dapagliflozin had little effect on SBP in patients with HFrEF, was superior to the placebo in HF stabilization and was well tolerated throughout the SBP range in patients enrolled in the DAPA-HF study [17].

Table 2. *Indications and contraindications to heart transplantation Patients to consider*

Indications	Contraindications
1. End–stage HF with severe symptoms, a poor prognosis, and no remaining alternative treatment options 2. Motivated, well informed, and emotionally stable 3. Capable of complying with the intensive treatment required postoperatively Contraindications	1. Active infection 2. Severe peripheral arterial or cerebrovascular disease 3. Pharmacologic irreversible pulmonary hypertension (LVAD should be considered with subsequent re–evaluation to establish candidacy) 4. Cancer (a collaboration with oncology specialists should occur to stratify each patient as to their risk of tumour recurrence) 5. Irreversible renal dysfunction (e.g. creatinine clearance 35 kg/m^2 (weight loss is recommended to achieve a BMI) 6. Systemic disease with multiorgan involvement 7. Other serious co– morbidity with poor prognosis 8. Pre– transplant BMI >35 kg/m^2 (weight loss is recommended to achieve a BMI 9. Current alcohol or drug abuse 10. Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting

Note: LVAD — left ventricular assistant device, BMI — body mass index, HF — heart failure

In general, SGLPT2 inhibitors do not increase the risk of arterial hypotension in patients with T2DM. Therefore, possible hypotension should be considered on a case-by-case basis, especially in patients with a history of low BP, long-term T2DM or comorbidities [18].

Intra-aortic balloon counterpulsation (IABP) can also be performed in patients with end-stage HF. A single-center study (n = 56) revealed that IABP provided clinical stabilization in 57% of patients before the implantation of the MCS system [2].

Despite the advances in medication management of end-stage HF, many of these patients require heart transplantation (Table 2). It significantly improves survival, quality of life and prognosis compared with drug treatment. If a patient's condition worsens, a short-term MCS may be required as a "bridge" to heart transplantation [2]. The main limitation of heart transplantation is the relatively small pool of donor hearts that varies from country to country.

According to the IRODAT registry for 2018, in Russia, the number of heart transplantations was 1.72 per 1 million of the population. Among patients with HF in Russia (2019), 900 individuals needed heart transplantation, and 337 transplantations were performed [18]. In 2020, the COVID-19 pandemic could not but have a negative impact on heart transplantation statistics. Since the prognosis for patients with end-stage HF is extremely poor, they often do not live to receive a heart transplant. In this regard, the issue of drug treatment for patients with end-stage HF while on the waiting list for heart transplantation is extremely urgent.

This article describes the case of managing a patient with end-stage HFrEF with severe arterial hypotension while on the waiting list for heart transplantation.

Description of Clinical Case

In 2003, the patient, 25, was diagnosed with congenital heart disease: bicuspid aortic valve disease with severe aortic regurgitation. The patient in severe state was hospitalized at the V. I. Burakovsky Institute of Cardiac Surgery of the A. N. Bakulev National Medical Research Center for Cardiovascular Surgery. On admission, BP was 105/50 mm Hg and HR — 90 bpm. Electrocardiography (ECG) results revealed sinus rhythm with HR 64 bpm, left QRS axis deviation, signs of LV hypertrophy, incomplete left bundle branch block (LBBB), diffuse changes in the myocardium. Echocardiography (ECHO-CG): LVEF 30%, left atrium (LA) 4.6 cm, LV end-systolic dimension (ESD) 8.4 cm, LV end-diastolic dimension (EDD) 9.9 cm, LV end-systolic volume (ESV) 384 mL, LV end-diastolic volume (EDV) 552 mL, LV stroke volume (SV) 168 mL. Leaflets of mitral valve were thin, mobile; anterior mitral leaflet was elongated. Aortic valve: 2 leaflets, with no coaptation, ascending aorta 35 mm, at the level of the sinus of Valsalva 51–52 mm, arch 30 mm, descending aorta 19 mm, fibrous ring (FR) 43–44 mm, aortic regurgitation III–IV. Ultrasound examination of abdominal organs (US of the abdominal cavity) revealed ascites, hepatomegaly (right lobe 143 mm, left lobe 55 mm). Aortic valve prosthetics with MIKS-27 was performed, as well as left atrial appendage ligation. Recommendations on discharge included warfarin 6.25 mg per day under the control of international normalized ratio (INR); perindopril 2 mg per day; spironolactone 50 mg per day; hydrochlorothiazide + triamterene 25 mg + 50 mg per week; as a result, a stable course of the disease was maintained for 12 years. LVEF increased to 47%, LV EDD decreased to 9.2 cm.

At the age of 38, after an acute respiratory viral infection (ARVI) with catarrhal symptoms and fever up to 39 ^{0}C, the following symptoms developed: shortness of breath with minimal physical exertion, at rest, when talking, and asthma attacks at night. Echocardiography revealed LVEF decrease to 23%.

From the age of 39, clinical symptoms increased; examination revealed an enlarged liver, elevated levels of alanine aminotransferase (ALT) up to 81 U/L, total bilirubin up to 34 μmol/L, creatinine up to 134 μmol/L, as well as decreased estimated glomerular filtration rate (eGFR) (CKD–EPI) to 61 mL/min/1.73 m^2. According to ECHO-CG data, the function of the prosthesis is

satisfactory, aortic regurgitation grade I, mitral regurgitation grade III, LV EDD 9.1 cm; LV EDV 458 mL, LVEF 19%, diffusely decreased left ventricular contractility, increased pulmonary hypertension (systolic pulmonary artery pressure sPAP — 66 mm Hg).

Despite drug treatment in accordance with clinical recommendations, there were complaints of shortness of breath with minimal physical exertion and at rest, weakness, low-productive cough; increased cytolysis (ALT increased to 111 U/L) and decreased renal function were observed for a year. Despite indications for cardiac resynchronization therapy (left bundle branch block, QRS — 160 ms, CHF stage IIB, NYHA class IV, low LVEF (19%) along with optimal drug treatment), a cardiac contractility modulation system was implanted as part of clinical testing. There was no subsequent improvement in clinical symptoms; blood pressure decrease to 85/65 mm Hg was often observed; decompensations became frequent, up to four times a year, and required hospitalization.

Nine months after implantation of the cardiac contractility modulation system, there were complaints of dull pain in epigastric and mesogastric areas, which worsened when eating, nausea, weakness; chronic gastroduodenitis, exacerbation of pancreatitis were suspected. The patient was hospitalized in Gastroenterology Department. The patient's state at admission was severe. Self-care was impossible due to shortness of breath. Body weight 64 kg, height 174 cm, BMI = 21.14 kg/m^2. Swelling of lower legs, up to the middle third. By auscultation: vesicular breathing, decreased in the lower parts on both sides, no rales, RR 16 per minute. Heart sounds are clear, the sounds of the prosthesis are heard. Regular rhythm with HR of 60 bpm, blood pressure 110/70 mm Hg. Dry tongue with whitish coating. Abdomen of normal shape. Abdomen was soft and painless on palpation. Peristalsis was heard. Stool is regular, formed, with no pathological admixtures. Liver is not enlarged, its lower edge of normal elasticity on palpation, rounded edge.

Complete blood count revealed no abnormalities. In blood biochemistry: increased total lactate dehydrogenase (LDH) — 492 IU/L (225–450), gamma-glutamyl transpetidase (GGTP) — 192 IU/L (9–39), alpha amylase — 268 IU/L (0–220), total bilirubin — 42.0 mmol/L (1.7–20.5), direct bilirubin — 19.00 mmol/L (0.86~5.00), creatinine 156.8 μmol/L (eGFR (CKD-EPI) — 46.88 mL/min/1.73 m^2), aspartate aminotransferase (AST) — 89 IU/L (5–34), ALT — 58 IU/L (0–32); INR 2.5. Ultrasound examination of the abdominal organs (US of abdominal cavity) revealed diffuse changes in liver, pancreas; cranio-caudal size of the left lobe of liver 104 mm, thickness — 53 mm, oblique vertical size of the right lobe — 148 mm, thickness — 105 mm, as well as normal size, increased echogenicity and heterogeneous structure of pancreas. Esophagogastroduodenoscopy (EGD) revealed a presentation of superficial gastritis, cardia insufficiency, esophageal candidiasis. Recto-, sigmo- and colonoscopy revealed no organic pathology of the colon.

According to the examination results, the following diagnosis was established: chronic pancreatitis, exacerbation. Chronic superficial gastritis, exacerbation. Subsequent laboratory tests after 14 days of treatment demonstrated decreased level of transaminases: ALT 81 U/L, AST 25 U/L, creatinine 134 μmol/L (eGFR (CKD-EPI) — 57.08 mL/min/1.73 m^2), total bilirubin 34.0 mmol/L, potassium 3.9 μmol/L.

On ECG during hospitalization in the Gastroenterological Department, sinus rhythm was registered with HR of 64 bpm, as well as sharp left deviation of QRS axis, ventricular extrasystole, left bundle branch block, repolarization disturbances in V5–6, probably due to the overload of the left ventricle (Fig. 1 A). Periodically, changes associated with the heart contractility modulation device were observed (Fig. 1 B).

А Б

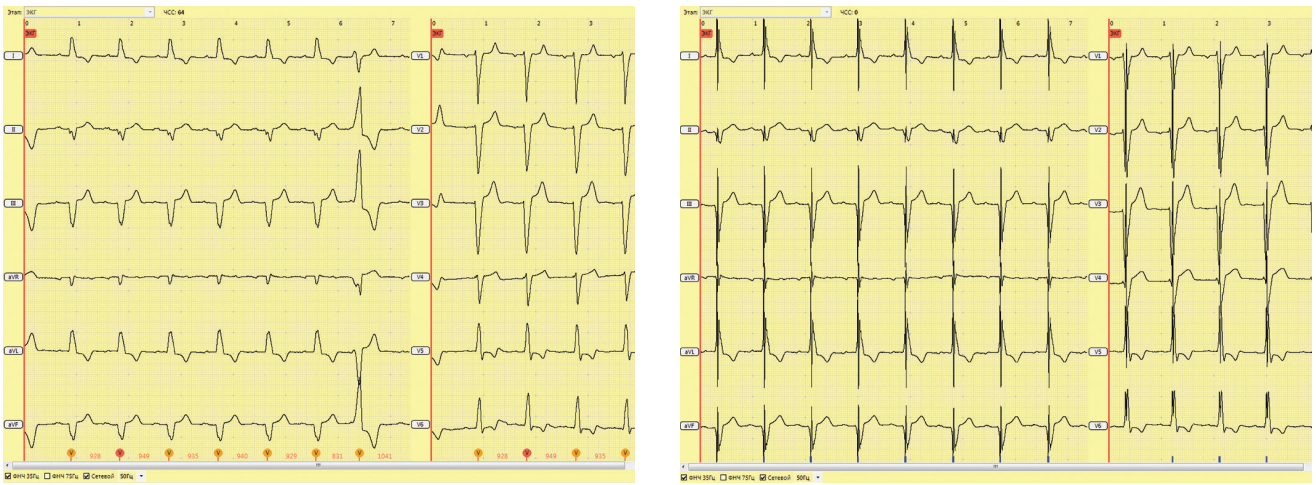
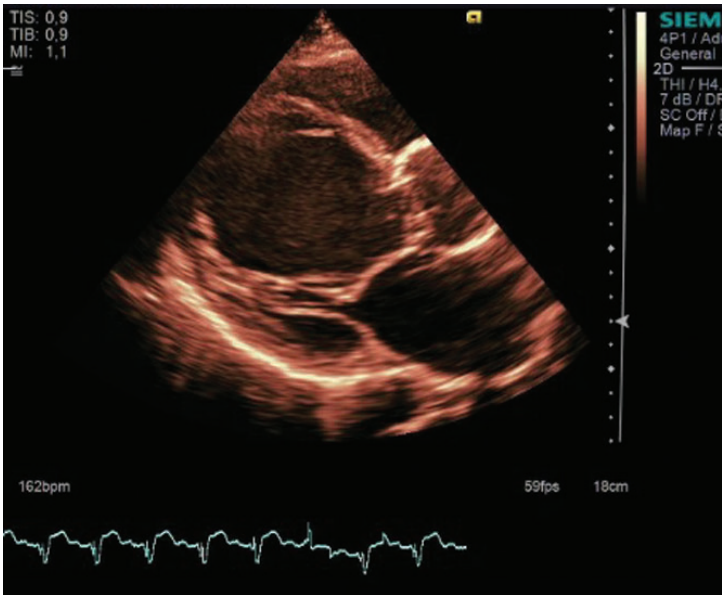
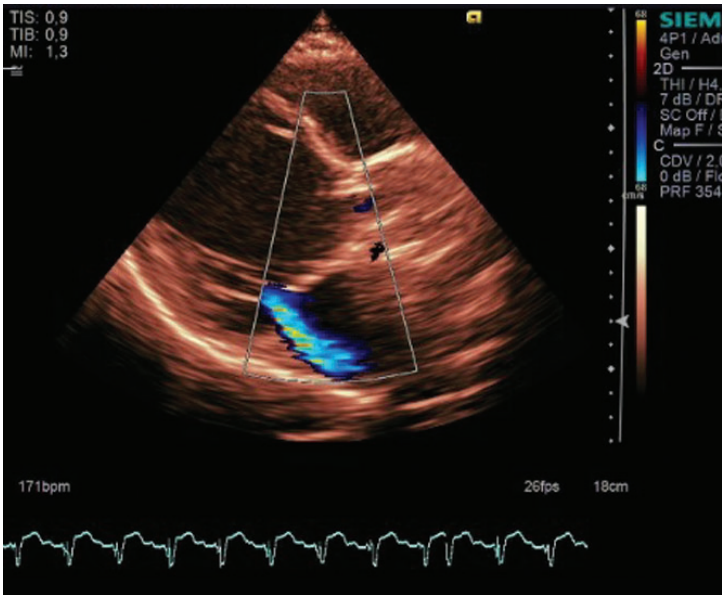


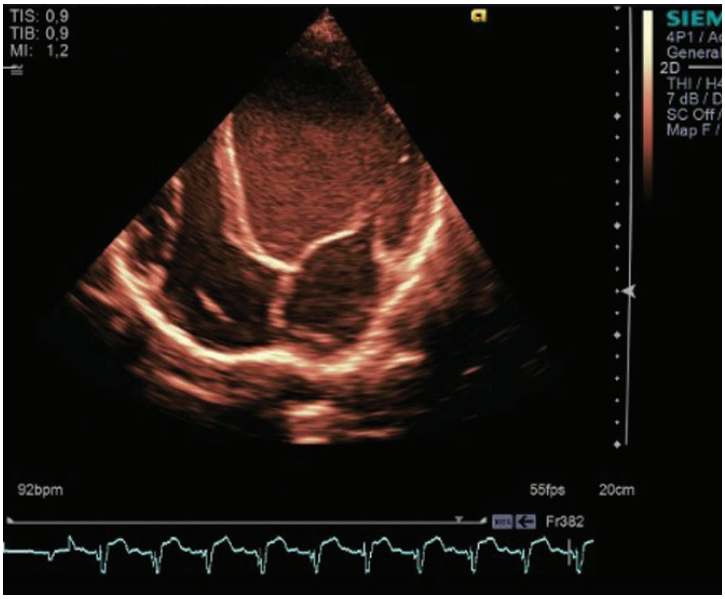
Figure 1. *Electrocardiogram*



A — parasternal position on the long axis

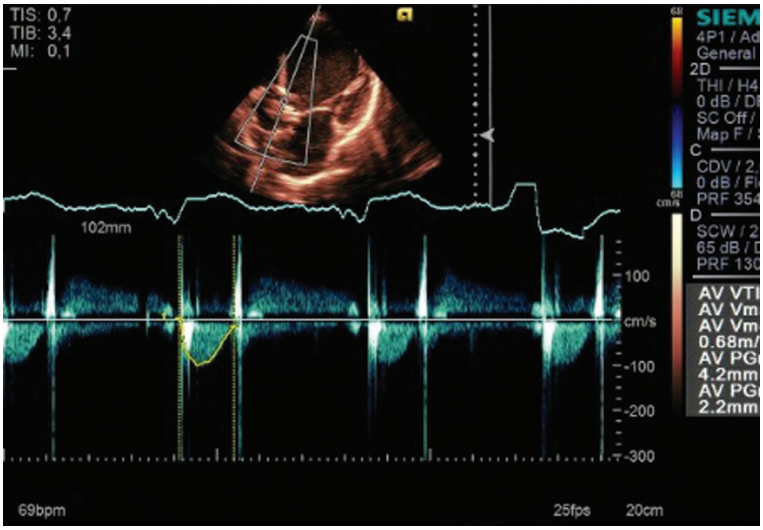


B — mitral regurgitation in the parasternal position along the long axis

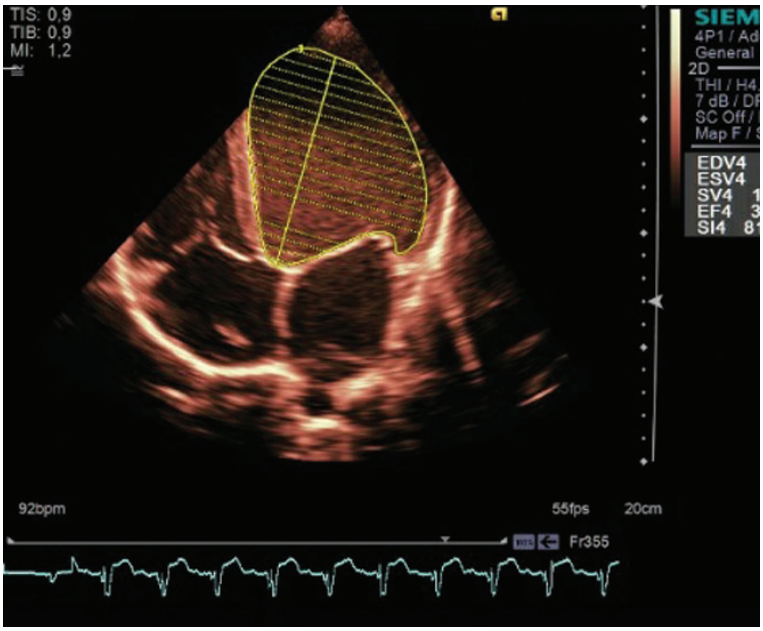


C — apical four-chamber position: dilatation of the left ventricle, the optimizer electrode in the right chambers

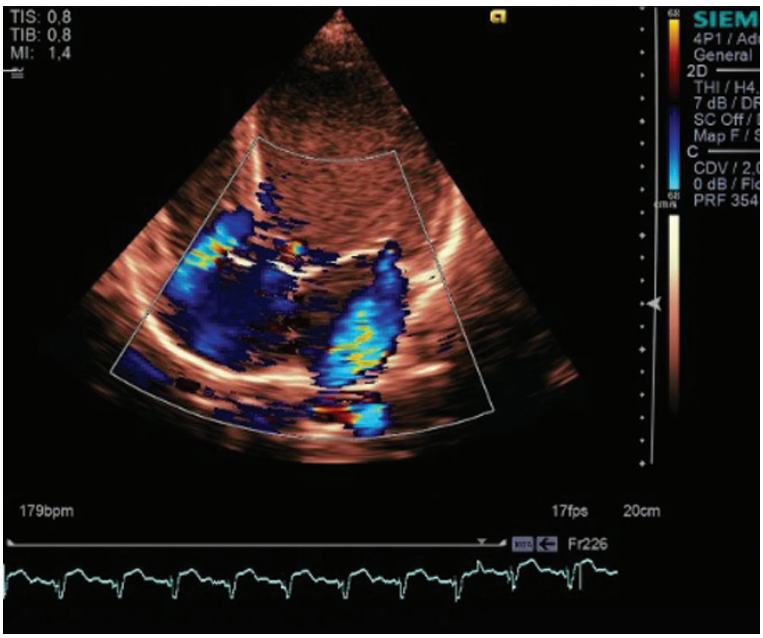
Figure 2 (A—C). *Echocardiograms from 2018*



D — gradient on the aortic prosthesis

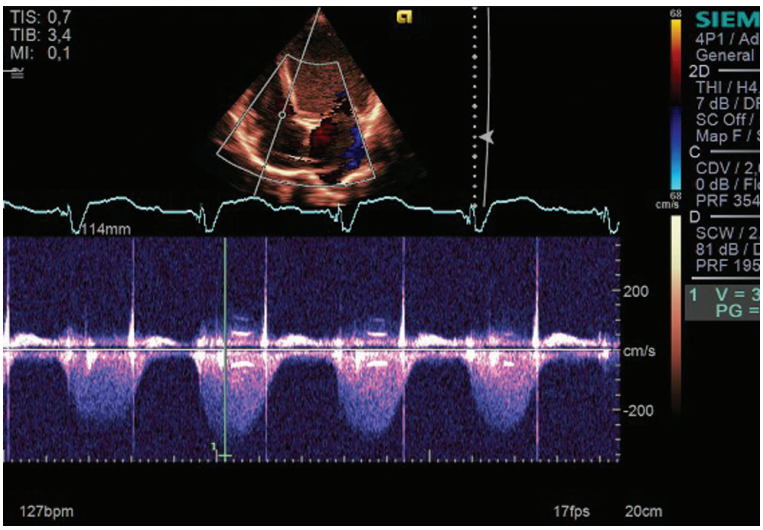


E — Left ventricular end diastolic volume

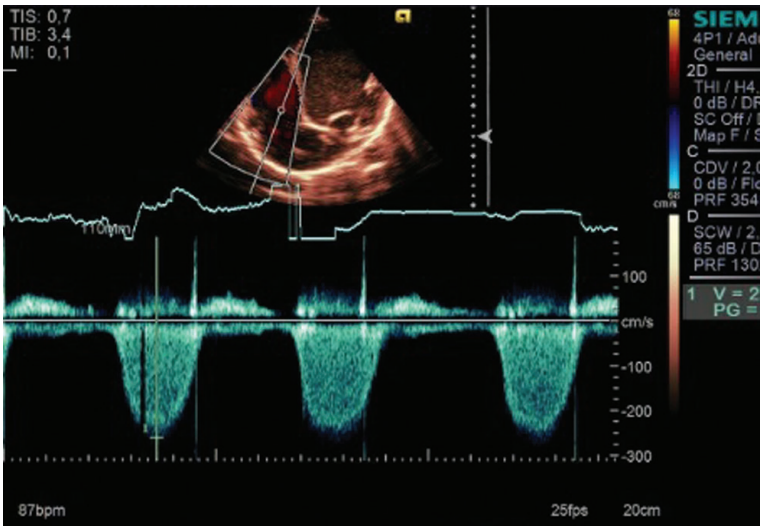


F — mitral and tricuspid regurgitation

Figure 2 (D—F). *Echocardiograms from 2018*



H — The maximal pressure gradient of tricuspid regurgitation is 50.71 mm Hg; systolic pressure in the pulmonary artery before taking sacubitril / valsartan is 70 mm Hg.



I — The maximal pressure gradient of tricuspid regurgitation is 27.47 mm Hg; systolic pressure in the pulmonary artery after 2 months sacubitril / valsartan treatment 32 mm Hg

Figure 2 (H—I). *Echocardiograms from 2018*

Holter ECG monitoring (24h ECG) revealed paroxysm of polymorphic ventricular tachycardia in the form of a 4-complex pirouette. Amiodarone, potassium asparaginate and magnesium asparaginate were added to the treatment, which aggravated weakness, yellowing of skin, nausea, vomiting. The medications were discontinued.

ECHO-CG revealed satisfactory function of the prosthesis, significant dilatation of heart chambers, decreased LV systolic function **(18%)**, relative insufficiency of atrioventricular valves.

Recommendations for outpatient treatment included warfarin 3.625 mg per day under the control of INR (target level 2.5–3.5), spironolactone 50 mg per day, carvedilol 6.25 mg per day, torasemide 20 mg per day, enalapril 2.5 mg per day. In the course of treatment, there was no significant improvement for two months.

Cardiac resynchronization therapy with a defibrillator (CRT-D) was considered. However, due to technical difficulties with the cardiac contractility modulation system, implantation of a resynchronization device was not performed.

Decompensation of HF with liver damage, development of hypoxic hepatitis, renal damage with the development of CKD stage C3aA1 were considered the symptoms that led to hospitalization in the Gastroenterology Department. There was a sharp deterioration two months after discharge, with dry cough, blood-streaked sputum. According to the results of ECHO-CG: sPAP 70 mm Hg, EF 19%, LV ESV 371 mL, LV EDV 458 mL (Fig. 2). The patient was examined by a transplantologist and was placed on the waiting list for heart transplantation. Considering the ineffectiveness of the treatment performed and four consecutive hospitalizations due to CHF decompensation during the previous year, enalapril was discontinued and, despite the tendency to arterial hypotension, sacubitril/valsartan 12.5 mg per day was prescribed [4, 5].

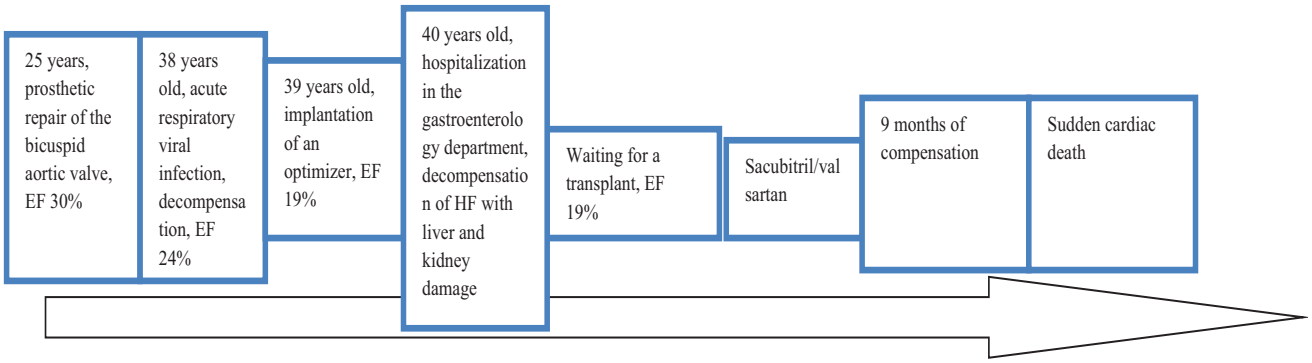


Figure 3. *Chronological sequence of the disease development*
Note: EF — ejection fraction

One month after this prescription, there was an improvement in general state, quality of life, increased exercise tolerance, regression of symptoms and signs of heart failure, and sPAP decreased to 53 mm Hg. Due to the decrease in blood pressure to 90/60 mm Hg, the dose of sacubitril/valsartan was reduced to 6.25 mg per day; the patient continued receiving carvedilol 6.25 mg per day, warfarin 4.375 mg per day under the control of INR, torasemide 20 mg per day, furosemide 120 mg per day; spironolactone was replaced with eplerenone 50 mg per day. A month later, hydrochlorothiazide 25 mg per day and acetazolamide 250 mg per day were added to therapy in order to achieve euvolemia. In the course of this treatment, HF was compensated, the patient started leading an active life, became in touch with friends and family and started tending to his garden.

Five months after starting sacubitril/valsartan, the transplantologist expressed doubts over the need for heart transplantation based on the clinical examination of the patient and the results of his clinical and biochemical tests. However, the patient remained on the waiting list for this intervention.

During nine months of treatment, the patient was stable, took care of himself, was in touch with his family, did chores and gardening. However, despite the ongoing therapy, the patient died suddenly (Fig. 3).

Discussion

Here is a case of HF progression in a patient after surgery for congenital heart disease (bicuspid aortic valve) during 16 years with a significant decrease in LV systolic function to 19% and increased FC.

The described clinical presentation was fully consistent with end-stage HF: the patient's state could not be stabilized, there were frequent episodes of HF decompensation that required four hospitalizations within 12 months despite treatment with ACE inhibitors, diuretics, MRAs.

Also, the patient tended to have arterial hypotension for a long time. Despite systolic blood pressure of less than 100 mm Hg, a drug from the ARNI group, sacubitril/valsartan, was prescribed as a "drug of last resort" at a minimum dose in order to improve the course of heart failure and the prognosis.

The effectiveness of sacubitril/valsartan in patients with HF was evaluated in the multicenter randomized phase III study PARADIGM-HF, which included 8,442 patients with HF II-IV FC and low LVEF that required no treatment with intravenous diuretics, with SBP above 100 mm Hg. Patients were randomized into groups taking enalapril 10 mg twice daily and sacubitril/valsartan 100 mg twice daily, with an increase to 200 mg twice daily. The study was terminated early due to a definite advantage of sacubitril/valsartan over the former drug of choice — enalapril — in the form of a 20% reduction in the relative risk of mortality and hospitalizations [1, 19].

The PIONEER-HF study demonstrated that the proportion of patients treated with ARNI and experiencing symptomatic hypotension was not significantly higher than in those treated with enalapril (15% vs 12.7%, $p = 0.95$). Switching from an ACE inhibitor to an ARNI had a significant beneficial effect on symptoms, morbidity and survival [1, 3].

Hypotension is an important factor limiting the titration of drugs for the treatment of HFrEF in routine practice [3]. There is evidence that sacubitril/valsartan has a modulating effect on blood pressure: it lowers BP in patients with initially high values and can increase it in patients with initially low BP [1]. Using sacubitril/valsartan for the treatment of patients with end-stage HF and severe hypotension was not studied in RCTs [19, 20]. In frail elderly patients, as well as in patients with systolic blood pressure of 100–110 mm Hg, an initial dose of ARNI 50 mg twice daily and slow titration (6–8 weeks) is recommended [3].

In this clinical case, despite indications for cardiac resynchronization therapy (CRT-D), the patient underwent implantation of a cardiac contractility modulation system. Five months later, instances of multiple organ failure increased, and LVEF did not increase.

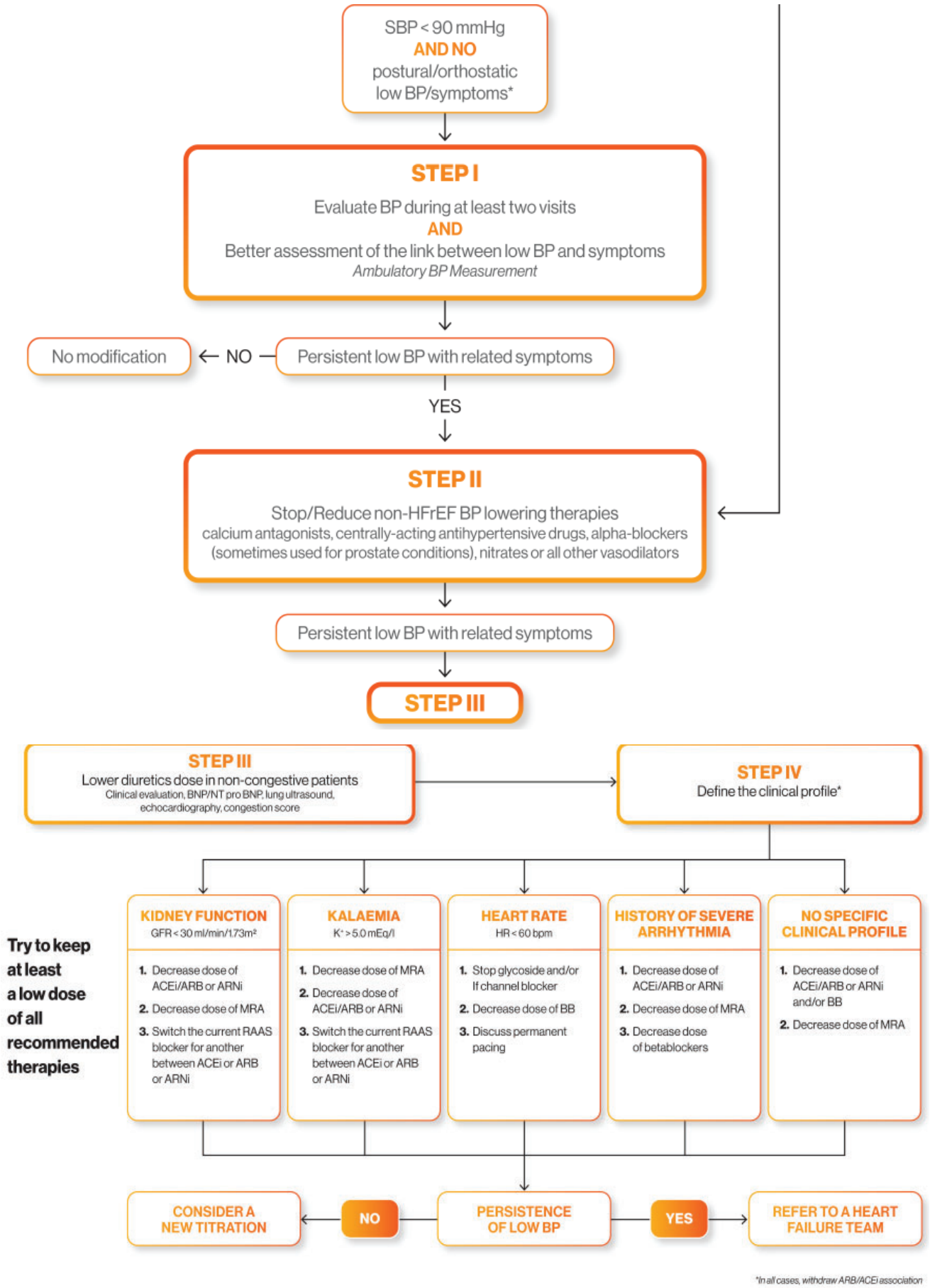


Figure 4. *Five–step algorithm for the management of patients with arterial hypotension [3]*

In this regard, the patient was on the waiting list for heart transplantation; the corresponding indication was end-stage HF (significant changes in hemodynamics and severe (irreversible) structural changes in target organs: heart, lungs, blood vessels, brain, kidneys).

The replacement of enalapril with sacubitril/valsartan in this case was a "treatment of last resort", which was prescribed despite the presence of arterial hypotension. Due to the "microdoses" (6.25 mg per day) of this agent, the patient's general state and quality of life improved; HF was compensated and hospitalizations for HF could be stopped. New oral inotropes, OM and vericiguat, were not recommended for this patient due to the unavailability of these agents in our country.

In 2020, the ESC working group developed a five-step algorithm for the drug treatment of patients with HFrEF in the presence of hypotension (Fig. 4). According to the algorithm, at the first stage, careful monitoring of BP and assessment of the relationship between low BP and clinical symptoms are recommended. At the second step, the discontinuation of several drugs in patients with HF and arterial hypotension, i.e. slow calcium channel blockers (SCCBs), alpha blockers, etc., taken for comorbid pathologies (glaucoma, benign prostatic hyperplasia, etc.) should be considered. At the third step, the dose of diuretics should be reduced. At the fourth step, dose reduction/withdrawal of the main groups of drugs for the treatment of CHF is considered depending on the clinical profile of the patient. For patients with GFR < 30 mL/min/1.73 m^2 and/or hyperkalemia, ACE inhibitors/ARA/ARNI/MRA should be discontinued. For patients with bradycardia, the BB, digoxin dose should be reduced/discontinued; the implantation of a pacemaker should be considered. At the fifth step, management of a patient should be discussed at a case conference [3].

There were no attempts to prescribe SGLPT2 inhibitors to the patient because, during the management of the patient, CHF was not indicated for them in our country.

Conclusion

Sacubitril/valsartan is the drug of choice for the treatment of patients with chronic HFrEF II-IV FC and should be used in combination with other agents (beta blockers, aldosterone antagonists) [1, 4, 21]. The discussed clinical case demonstrates the experience of prescribing sacubitril/valsartan for a patient with end-stage heart failure accompanied by severe arterial hypotension, which allowed to stabilize the patient's condition for nine months. In patients with failure of standard drug therapy for HF, careful dose titration of sacubitril/valsartan under close clinical and laboratory control may be performed; it may increase the chance of survival until surgery for patients on the waiting list for heart transplantation. RCTs should be conducted to investigate the possibility of prescribing low doses of sacubitril/valsartan for patients with hypotension associated with severe HF in order to reduce the severity of clinical symptoms and improve prognosis; this prescription can be performed simultaneously with new inotropes. Due to a large number of patients with arterial hypotension, the prescription of sacubitril/valsartan in low doses of 25, 12.5 and 6.25 mg is advisable.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Резник Е.В. (ORCID ID: https://orcid.org/0000-0001-7479-418X): ведение пациента, идея представления клинического случая, предоставление материалов для написания, редактирование, утверждение текста рукописи

Бычкова М.С. (ORCID ID: https://orcid.org/0000–0002–3453–5914): написание рукописи текста, обзора литературы по теме

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Reznik E.V. (ORCID ID: https://orcid.org/0000-0001-7479-418X): patient management, the idea of presenting a clinical case, providing materials for writing, editing, approving the text of the manuscript

Bychkova M.S. (ORCID ID: https://orcid.org/0000-0002-3453-5914): writing a manuscript of a text, a review of the literature on the topic

Список литературы/ References:

1. Мареев В.Ю., Фомин И.В., Агеев Ф.Т. и др. Клинические рекомендации ОССН — РКО — РНМОТ. Сердечная недостаточность: хроническая (ХСН) и острая декомпенсированная (ОДСН). Диагностика, профилактика и лечение. Кардиология. 2018;58(6S):8-158. https://doi.org/10.18087/cardio.2475
Mareev V.Yu., Fomin I.V., Ageev F.T. et al. Russian Heart Failure Society, Russian Society of Cardiology. Russian Scientific Medical Society of Internal Medicine Guidelines for Heart failure: chronic (CHF) and acute decompensated (ADHF). Diagnosis, prevention and treatment. Kardiologiia. 2018;58(6S):8-158. https://doi.org/10.18087/cardio.2475. [In Russian].
2. Crespo-Leiro M.G., Metra M., Lund L.H. et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018; 20(11):1505-35. doi: 10.1002/ejhf.1236.
3. Cautela J., Tartiere J.M., Cohen-Solal A. et al. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. Eur J Heart Fail. 2020; 22(8):1357-65. doi: 10.1002/ejhf.1835.
4. Geng Q., Yan R., Wang Z. et al. Effects of LCZ696 (Sacubitril/Valsartan) on Blood Pressure in Patients with Hypertension: A Meta-Analysis of Randomized Controlled Trials. Cardiology. 2020; 145(9): 589-98. doi: 10.1159/000507327.
5. Seferovic P.M, Ponikowski P., Anker S.D. et al.Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;21(10):1169-1186. doi: 10.1002/ejhf.1531.

6. Ponikowski P., Voors A.A., Anker S.D. et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129-200. doi: 10.1093/eurheartj/ehw128.
7. Резник Е.В., Лазарев В.А., Калова М.Р. и др. Ведение больных с хронической сердечной недостаточностью и сахарным диабетом с позиций современных рекомендаций и в реальной клинической практике. Consilium Medicum. 2020; 22 (5): 50–56. DOI: 10.26442/20751753.2020.5.200198.
Reznik E.V., Lazarev V.A., Kalova M.R. et al. Management of patients with chronic heart failure and diabetes mellitus from the standpoint of modern recommendations and in real clinical practice. Consilium Medicum. 2020; 22 (5): 50–56. DOI: 10.26442/20751753.2020.5.200198 [In Russian].
8. Seferovic P.M., Petrie M.C., Filippatos G.S. et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018; 20(5): 853-72. doi: 10.1002/ejhf.1170.
9. Михайлов А.А. Хроническая артериальная гипотензия: возможности медикаментозной коррекции. РМЖ. 2004; 12(7): 468-70.
Mikhailov A.A. Chronic arterial hypotension: possibilities of drug correction. RMJ. 2004; 12(7): 468– 470. [In Russian].
10. Резник Е.В., Никитин И.Г. Кардиоренальный синдром у больных с сердечной недостаточностью как этап кардиоренального континуума (часть II): прогностическое значение, профилактика и лечение. Архивъ внутренней медицины. 2019;9(2):93-106. https://doi.org/10.20514/2226-6704-2019-9-2-93-106.
Reznik E.V., Nikitin I.G. Cardiorenal syndrome in patients with heart failure as a stage of the cardiorenal continuum (part II): prognosis, prevention and treatment. The Russian Archives of Internal Medicine. 2019;9(2):93-106. https://doi.org/10.20514/2226-6704-2019-9-2-93-106 [In Russian].
11. Резник Е.В., Никитин И.Г. Кардиоренальный синдром у больных с сердечной недостаточностью как этап кардиоренального континуума (часть I): определение, классификация, патогенез, диагностика, эпидемиология (обзор литературы). Архивъ внутренней медицины. 2019; 9(1): 5-22. DOI: 10.20514/2226-6704-2019-9-1-5-22.
Reznik E.V., Nikitin I.G. Cardiorenal syndrome in patients with chronic heart failure as a stage of the cardiorenal continuum (part I): definition, classification, pathogenesis, diagnosis, epidemiology. The Russian Archives of Internal Medicine. 2019; 9(1): 5-22. [In Russian]. DOI: 10.20514/2226-6704-2019-9-1-5-22 [In Russian].
12. Nieminen M.S., Fruhwald S., Heunks L.M. et al. Levosimendan: current data, clinical use and future development. Heart, lung and vessels. 2013; 5(4): 227-45.
13. Кошелева Н.А., Пономарева Е.Ю., Седов Д.С. Ведение пациента с терминальной хронической сердечной недостаточностью. Клиническая медицина. 2018; 96(3): 273–6. doi: http://dx.doi.org/10.18821/0023–2149–2018–96–3–273–276 .
Kosheleva N.A., Ponomareva E.Yu., Sedov D.S. Management of a patient with terminal chronic heart failure. Klin. med. 2018; 96(3): 273–276. doi: http://dx.doi.org/10.18821/0023–2149–2018–96–3–273–276 [In Russian].
14. Teerlink J.R., Diaz R., Felker G.M. et al. Omecamtiv Mecarbil in Chronic Heart Failure with Reduced Ejection Fraction: Rationale and Design of GALACTIC-HF. JACC Heart Fail. 2020; 8(4): 329-40. doi: 10.1016/j.jchf.2019.12.001.
15. Armstrong P.W., Pieske B., Anstrom K.J. et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020; 382(20): 1883-93. doi: 10.1056/NEJMoa1915928.
16. Serenelli M., Bohm M., Inzucchi S.E. et al. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). Eur Heart J. 2020; 41(36): 3402-18. doi: 10.1093/eurheartj/ehaa496.
17. Кобалава Ж.Д., Медовщиков В.В., Ешниязов Н.Б. На пути к квадротерапии сердечной недостаточности с низкой фракцией выброса: данные вторичных анализов DAPA-HR. Российский кардиологический журнал. 2020; 25(5): 3870. doi: 10.15829/1560-4071-2020-3870.
Kobalava Zh.D., Medovshchikov V.V., Eshniyazov N.B. On the way to quadrotherapy of heart failure with a low ejection fraction: data from secondary analyses of DAPA-HR Russian Journal of Cardiology. 2020; 25(5): 3870. doi:10.15829/1560-4071-2020-3870. [In Russian].
18. International Registry in Organ Donation and Transplantation. [Electronic resource]. URL: https://www.irodat.org/. (Date of the application: 01.04.2021).
19. Solomon S.D., Claggett B., Desai A.S. et al. Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction: The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial. Circ Heart Fail. 2016; 9(3):e002744. doi: 10.1161/CIRCHEARTFAILURE.115.002744.
20. Khder Y, Shi V., McMurray J.J.V. et al. Sacubitril/Valsartan (LCZ696) in Heart Failure. Handb Exp Pharmacol. 2017; 243: 133-65. doi: 10.1007/164_2016_77.
21. McMurray J.J., Packer M., Desai A.S. et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371(11): 993-1004. doi: 10.1056/NEJMoa1409077.