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Diuretic resistance in patients with chronic heart failure: mechanisms, prevention, and treatment

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ABSTRACT

The authors analyzed the problem of diuretic resistance (DR) in patients with chronic heart failure (CHF). Most of the symptoms and signs of CHF are associated with hypervolemia and vascular congestion in the systemic and pulmonary circulation. The severity of the latter is the main factor which negatively affects the overall assessment of life satisfaction in patients with CHF. Since the patient, even at the incurable stage of CHF, primarily expects a rapid decrease in the severity of manifestations of decompensation from the prescribed therapy, achieving euvolemia is the essence of its short-term objective. Without diuretics, these immediate effects, according to which most CHF patients judge the qualifications of the doctor, are almost impossible to achieve. Unfortunately, apparently, not a single clinician was able to avoid disappointment in the effectiveness of CHF therapy associated with DR in their practice. As a rule, DR reflects the progressive course of CHF and is often associated with a poor prognosis. The review consistently covers the issues of terminology, diagnosis, pathogenesis, and prevention of DR, which aggravates CHF, and discusses measures aimed at restoring sensitivity to diuretics.

Keywords: chronic heart failure, diuretic resistance, terminology, mechanisms, water and salt restriction, sequential nephron blockade, gliflozines, vaptans, inotropes, vasoconstrictors, glucocorticoids, serelaxin, nesiritide, albumin, ultrafiltration

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Резистентность к диуретикам у пациентов с хронической сердечной недостаточностью: механизмы, профилактика и преодоление

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РЕЗЮМЕ

Проанализирована проблема резистентности к диуретикам (РД) у пациентов с хронической сердечной недостаточностью (ХСН). Большинство симптомов и признаков ХСН связаны с гиперволемией и застоем крови в большом и малом кругах кровообращения. Выраженность последних является основным фактором, негативно влияющим на общую оценку удовлетворенностью жизнью пациентов с ХСН. Так как пациент даже в инкурабельной стадии ХСН в первую очередь ожидает от назначенной врачом терапии быстрого снижения выраженности проявлений декомпенсации, достижение эуволемии представляет собой суть ее краткосрочной задачи. Без диуретиков этих немедленных эффектов, по которым большинство пациентов с ХСН судят о квалификации врача, добиться практически невозможно. К сожалению, по-видимому, ни одному клиницисту не удалось избежать в своей практике разочарования в эффективности терапии сердечной недостаточности, связанного с РД. Как правило, РД отражает прогрессирующее течение ХСН и часто ассоциируется с неблагоприятным прогнозом.

В лекции последовательно рассмотрены вопросы терминологии, диагностики, патогенеза и профилактики РД, отягощающей ХСН, а также обсуждается комплекс мероприятий, направленный на восстановление чувствительности к диуретикам.

Ключевые слова: хроническая сердечная недостаточность, резистентность к диуретикам, терминология, механизмы, водно-солевой режим, секвенциальная блокада нефрона, глифлозины, ваптаны, инотропы, вазоконстрикторы, глюкокортикостероиды, серелаксин, несиритид, альбумин, ультрафильтрация

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Many definitions of chronic heart failure (CHF) include a description of its main manifestations [1]. In particular, the experts of the European Society of Cardiology define clinically pronounced CHF as "a clinical syndrome characterized by typical symptoms (e.g. shortness of breath, swelling of the ankles, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, rales, and peripheral edema) caused by a structural and / or functional cardiac abnormality..." [2]. Most of the symptoms and signs presented in this definition are associated with hypervolemia and blood stasis in the systemic and pulmonary circulation. The severity of the latter is the main factor that negatively affects the overall assessment of life satisfaction in patients with CHF, including those with comorbidity [3–5].

Despite the fact that apologists for evidence-based medical practice consider an increase in life expectancy as the main aim of pharmacotherapy for CHF, it is equally important to ensure quality-adjusted life years during treatment [1, 6]. This determines the need for the most complete elimination of CHF symptoms, even at the incurable stage of the disease [7]. Since the patient primarily expects a rapid decrease in the severity of CHF manifestations from the therapy prescribed by the doctor, achieving euvolemia is the essence of its short-term objective [8]. Without diuretics, these immediate effects, according to which most CHF patients judge the qualifications of the doctor, are almost impossible to achieve [9]. It is no coincidence that diuretic therapy is sometimes called a cornerstone of treatment of patients with decompensated CHF [7, 10, 11].

Unfortunately, apparently, not a single clinician was able to avoid disappointment in the effectiveness of CHF therapy associated with diuretic resistance (DR) in their practice [7, 12, 13].

DR is a serious clinical issue which often portends a poor prognosis; hence this issue is actively discussed in peer-reviewed scientific journals [14]. Despite the fact that an expert consensus paper of the European, North American, and Russian task force on the use of diuretics in CHF has been published recently [9, 14, 15], there are still disputes about the most optimal strategy in a situation when it is impossible to achieve euvolemia and / or maintain it.

The titles of articles published in peer-reviewed scientific journals testify to the severity of this issue: "Diuretic resistance in acute decompensated heart failure: a challenging clinical conundrum", "The use of diuretics in heart failure with congestion: we can't judge a book by its cover", "The never-ending quest for the appropriate role of ultrafiltration" [16–18].

The aim of this review was to consider modern views on the issue of diuretic resistance that develops in up to 20–35% of patients with chronic heart failure (in acute decompensated heart failure – in 50% of patients) and on the possibility of overcoming it.

TERMINOLOGY AND DIAGNOSTIC CRITERIA

As the Persian poet As-Samarqandi said, if the disease is not defined, it is impossible to treat it. Since correct recognition of any pathology is not conceivable without a clear understanding of the aim its diagnosis, first of all, one should decide on the terminology. The problem consists in the fact that not all materials reflecting expert consensus statements on the use of diuretics in CHF attempt to define the concept of DR. In turn, the definitions of DR and the criteria for its verification may differ in various documents, which prevents establishing the boundaries of the application of this term (Table 1).

The experts of the American College of Cardiology suggest using the term DR to describe insufficient natriuresis, despite adequate diuretic therapy [14]. This non-quantifiable definition is scientifically grounded, but hardly acceptable for point of care testing, since in the vast majority of cases in clinical practice, the doctor evaluates not natriuresis (as well as not the volume of extracellular fluid during transpulmonary thermodilution, hematocrit, intrathoracic impedance, the number of hyperechoic artifacts on lung ultrasound or ventricular filling pressure according to invasive hemodynamic monitoring), but diuresis followed by a change in body weight [1, 19–21].

It is necessary to understand what adequate diuretic therapy implies, since we can talk about mono- or combination therapy with drugs of different groups, its different duration, as well as a wide range of drug dosages [22]. Since loop diuretics form the basis of diuretic therapy in CHF, the term DR in the vast majority of cases is used to denote resistance specifically to drugs that act along the thick ascending limb of the loop of Henle [9].

In addition to diverse ways of diuretic administration, the choice of which depends on the specific clinical situation, optimal therapy with saluretics involves the use of differentiated approaches to its escalation, taking into account the absence of a linear relationship between the change in the drug dose and the diuretic

effect. For example, increasing the dose of furosemide by 20 mg in a patient who previously received 20 mg of the drug per day will give a significantly greater increase in urine output than 20 mg added to therapy at a dose of 220 mg per day [14].

It is clear that the same dose of a loop diuretic can cause a variable diuretic effect in a population of patients with CHF. Conversely, the same volume of urine can be obtained in different patients with the use of saluretics in a wide range of doses. Therefore, when considering DR, the focus should be placed on evaluating the efficacy of a drug in promoting diuresis rather than on the absolute dose of the diuretic or urine levels [23].

Table 1

Examples of criteria for diagnosing diuretic resistance
I. Based on the assessment of natriuresis
Failure to increase sodium excretion by at least 90 mmol within 72 h with 160 g of furosemide given twice a day orally [24]
FES less than 0.2% [25]
Calculated by the formula: [25] 100 × (Scr × Una) / (Sna × Ucr), where Scr is serum creatinine; Una is urine sodium; Sna is serum sodium; Ucr is urine creatinine.
Cumulative 6-hour natriuresis of less than 50 mmol after intravenous administration of 2–4 mg of bumetanide (median – 3 mg) [26]
Daily sodium excretion of less than 100 mmol after intravenous administration of bumetanide at a dose of 2–4 mg (median – 3 mg) [26]
Sodium concentration of less than 50 mEq / l or Na+ / K+ ratio of less than 1.0 in a urine sample obtained 8 hours after diuretic administration [27]
The ratio of the sodium concentration / furosemide concentration in the urine is less than < 2 mmol / mg [28]
Expected cumulative natriuresis of less than 100 mmol 6 hours after intravenous administration of a loop diuretic [26]
Calculated by the formula: GFR×(BSA/1.73)×(Scr/Ucr)×150×(Una/1000); [26] where GFR is the glomerular filtration rate; Scr is serum creatinine; BSA is body surface area; Una is urine sodium; Ucr is urine creatinine
II. Based on the assessment of diuresis
Diuresis of less than 1,400 ml on the first day after the prescription of 40 mg of furosemide (or an equivalent dose of another diuretic) [28]
Diuresis of less than 2,000 ml / day after intravenous administration of 40 mg of furosemide [29]
III. Based on body weight dynamics
No weight loss within 48–96 hours after the initiation of therapy with furosemide 40 mg / day (or an equivalent dose of another diuretic) [28, 30]
IV. Based on the dose and route of administration of diuretics
The need for intravenous administration of furosemide at a dose of more than 80 mg / day [31]
Persistent stagnation despite the use of furosemide at a dose equal to or exceeding 80 mg / day [32]
The need for taking furosemide at a dose greater than 3 mg / kg / day (or an equivalent dose of another loop diuretic) [33]

Note: FES (fractional excretion of sodium) is a part of the electrolyte excreted with urine from the total amount passed through glomerular filtration.

Since impaired sensitivity to diuretics limits the possibility of achieving euvolemia, failure to achieve the so-called dry weight when using high doses of diuretics (primarily loop diuretics) (the ideal weight of the patient without excess body fluid) can be used as a DR criterion in clinical practice [9, 34–36]. Dry weight is the term most often used by renal replacement therapists to describe the patient's weight when they are euvolemic. This is the weight above which symptoms and signs of fluid retention are observed, and below which the patient develops hypotension (with normal dry weight, systemic blood pressure, as a rule, is not lower than 110 / 50 mm Hg) and often signs of kidney disease [37, 38].

The desire of physicians, starting to treat a patient with CHF, to achieve euvolemia, according to the figurative expression of K. Watson et al. [38], is as clear as that "the night is dark and the day is bright". However, the lack of a reliable and at the same time simple point of care method for determining euvolemia (dry weight) leads to the fact that on the way to the coveted euvolemia, internists have to give it a go and be ready to make mistakes, empirically trying to establish the optimal point for discontinuing / de-escalating anti-edematous therapy, determine the time for its intensification without a delay, and timely recognize the development of DR [9, 35].

The situation is deteriorated by the fact that clinicians are forced to act in a vacuum of generally accepted qualitative and quantitative criteria for DR verification. Unfortunately, we have to state that we should not expect quick changes for the better, since identification of a decisive diagnostic rule in this case can be compared with an attempt to solve an equation with many unknowns, which is known to have an infinite number of solutions.

Finally, we should not forget about the very common pseudo-resistance to diuretics, which the doctor

must exclude before speaking about DR. Pseudo-DR should be considered when a patient is not receiving optimal diuretic therapy for any reason. For example, when the doctor chooses an inadequate saluretic therapy strategy (prescribing a low dose of a loop diuretic or an intermittent use of it, as well as an unsuccessful combination with drugs that reduce the effectiveness of the diuretic) or in case of poor patient's adherence to treatment. Moreover, before discussing DR, the doctor should exclude edematous syndrome secondary to venous insufficiency, impaired lymph circulation (lymphedema), hypoalbuminemia, and endocrine gland disorders (for example, hypothyroidism or syndrome of inappropriate antidiuretic hormone secretion), as well as that associated with drug therapy (for example, with the use of dihydropyridine derivatives) [20].

MECHANISMS OF DEVELOPMENT OF DIURETIC RESISTANCE

The pathogenesis of fluid retention in CHF cannot be reduced to a single mechanism, since the expansion of extracellular fluid is a complex multistage process [39]. In turn, the pharmacokinetics and pharmacodynamics of saluretics include a number of discrete stages, and diverse disturbances at each stage provide the key to understanding the heterogeneity of the DR mechanisms [9, 14, 40].

Identification of the mechanism(s) of DR can contribute to the development of an effective individual strategy for improving the response to diuretics in a patient with CHF. It is important to consider that many mechanisms of DR have been described in studies performed in a population of healthy individuals and patients with arterial hypertension or chronic kidney disease. The intuitive conclusion that these results are fully applicable to patients with heart failure may be erroneous [20]. Thus, it is obvious that kidney dysfunction (a decrease in the glomerular filtration rate) as a cause of DR in patients with CHF is less significant than in chronic kidney diseases. We believe that, taking into account a large number of phenotypes of heart failure, which is not accidentally called multifaceted, caution is also necessary when extrapolating the results of studies in a cohort of patients with acute heart failure to the population of patients with CHF.

Z.I. Cox and J.M. Testani in their work "*Loop diuretic resistance in a patient with acute heart failure*" [36] identified the extrarenal and renal forms of DR and systematized the key mechanisms of development of the latter based on identifying predominantly involved segments of the nephron. The adapted results of this systematization, supplemented by other authors, are presented in Table 2.

Table 2

The main mechanisms of development of diuretic resistance [14, 36, 41]

Prerenal disorders	The level of real shifts		
	Before the loop of Henle	The loop of Henle	After the loop of Henle
Cardiorenal syndrome (types 1 and 2) Pathology of renal blood flow Hypoalbuminemia High sodium intake Impaired absorption of the diuretic Increased intra-abdominal pressure	Reduction of the number of nephrons Decreased glomerular filtration rate Competition for the penetration of diuretics into the nephron among organic anions Albuminuria	Low dose of the loop diuretic Non-optimal frequency of loop diuretic prescription Weak natriuretic response at the level of the loop of Henle Hypochloremic alkalosis	Distal tubular hypertrophy Hyperfunction of the distal tubules

Note: the list is not comprehensive.

The enumeration and detailing of the mechanisms of primary and secondary DR could be continued. For example, increased expression of the pendrin gene, polymorphism of other genes encoding ion transporters, cotransporters (symporters) or exchangers (antiporters), as well as vasopressin-induced activation of the incorporation of aquaporin-2 channels into the apical membrane of collecting duct epithelial cells [14, 41, 42]. Their prevalence and clinical and prognostic significance remain unclear and require future study. It is assumed that the most common forms of DR are associated with structural and functional changes that develop at the level of the distal tubules [36], and the most important causes of resistance to diuretics include compensatory sodium reabsorption in the distal tubules (regardless of the fact that only 10% of sodium is normally reabsorbed in this segment of the nephron) and a low dose of a loop diuretic [14]. However, the latter has nothing to do with DR, since true resistance, as noted above, implies the presence of adequate di-

uretic therapy that can provide a sufficient intrarenal diuretic concentration [20].

Despite the concurring opinion of the majority of experts on the association of DR with a poor prognosis in patients with heart failure (especially with acute decompensated heart failure) [41, 43], the mechanisms of resistance to saluretics cannot be considered as solely pathological [20]. The physiological meaning of the mechanisms of renal autoregulation and neurohormonal reactions is to eliminate excessive deviations in the fluid – electrolyte balance that develop after massive natriuresis already at the start of therapy with high doses of diuretics [44].

The first dose of a diuretic often causes encouraging diuresis. However, when the volume of extracellular fluid decreases after profuse diuresis, activation of the sympathetic and renin – angiotensin – aldosterone systems leads to the development of the so-called inhibition phenomenon [20, 44, 45]. The impossibility in all cases to effectively modulate the severity of the inhibition phenomenon with the help of neurohumoral blockers makes it possible to discuss alternative, volume-independent mechanisms of early DR. In particular, a hypothesis has been put forward about the memory effect of the epithelium of the renal tubules on the effect of diuretics [46]. Regardless of its mechanism, inhibition of the effect within certain limits is useful because it saves from diabetes, on the one hand, and, paradoxically, prevents the development of hypovolemia-related DR. If the initial diuretic effect associated with an increase in the excreted fraction of Na^+ by 20% persisted with continuous infusion of a loop diuretic, at a glomerular filtration rate of 120 ml/ m in, the patient would lose 280 grams of salt and 50 liters of osmotically bound water per day [20].

In contrast to early DR associated with the inhibition phenomenon, late refractoriness develops after weeks and months of continuous diuretic therapy. Diuretic-induced chronic intraluminal overload of the distal convoluted tubules and collecting ducts with Na^+ and Cl^- ions triggers structural and functional adaptation of the kidneys [40]. The leading mechanism of late DR is hypertrophy and hyperfunction of cells of the simple cuboidal epithelium of the distal convoluted tubules, as well as primary and intercalary cells of the collecting duct epithelium, which are sometimes erroneously called tubules [20].

Remodeling of the distal segment of the nephron and collecting ducts is associated with activation of the thiazide-sensitive Na^+-Cl^- cotransporter, aldosterone-sensitive epithelial sodium channel, chloride – bicarbonate exchanger (pendrin), which leads to an increase in tubular sodium reabsorption [47]. Thus, with chronic intravenous use of a high dose of the loop diuretic (median is 160 mg of furosemide per day), fractional sodium excretion in patients with acute heart failure increased by only 4.8% [48], indicating that about 70% of sodium ions leaving the loop of Henle undergo distal tubular reabsorption [20].

Along with remodeling and hyperfunction of the distal tubules, the development of hypochloremic metabolic alkalosis, usually caused by the simultaneous use of loop and thiazide diuretics, which promote the retention of bicarbonates, can also be noted as an important mechanism of DR. Even mild metabolic alkalosis, which is the most common acid – base disorder in CHF patients, leads to a decrease in the natriuretic effect of the loop diuretic by about 20% [46].

PREVENTION AND MANAGEMENT OF DIURETIC RESISTANCE

CHF is a syndrome and not a disease, and when developing individual treatment strategy, its etiological heterogeneity should be taken into account [49]. Properly selected treatment of the disease underlying CHF in many cases can significantly reduce the severity of manifestations of cardiac decompensation, and sometimes allows the patient to completely eliminate them (for example, after successful surgical correction of heart disease) [50]. Therefore, timely prescribed effective treatment of the underlying disease is the first step toward preventing the development of CHF requiring the use of diuretics, which reduces the likelihood that the doctor will face the problem of DR.

The key to the second step in the prevention of DR is understanding the multifaceted mechanisms of hypervolemia and congestion in patients with heart failure, which leads to the conclusion that diuretics should be considered only as one of the components in the complex of measures for secondary prevention of CHF, including non-drug interventions, optimal pathogen-specific combination pharmacotherapy, electrophysiological methods of treatment, surgical interventions, and the use of circulatory assist devices [1, 15, 51].

The use of diuretics should be preceded by non-drug interventions, which should be initiated already at the stage of latent CHF and continued after the appearance of signs of decompensation; the more pronounced the congestion, the more active the measures should be. Careful adherence to nutritional recommendations is perhaps the most effective and the least

costly non-pharmacological measure [1, 52]. Since observational studies suggest an association between sodium intake with fluid retention and the risk of hospitalization in patients with CHF [53–55], and sodium intake in the general population is usually high (> 4 g / day), limiting daily intake of Na^+ to the level recommended by WHO experts, equal to 2.5–3 grams (6–7 grams of table salt), is a reasonable goal for patients with moderate CHF [15, 46]. This approach prevents Na^+ retention in the postdiuretic period and is considered as a way to overcome the inhibition phenomenon [45]. For patients with DR, even more severe restriction of Na^+ intake to the level of 2 g per day is required (in this case, the help of a nutritionist is usually needed) [45]. Compliance with a diet with a more significant restriction of Na^+ in the outpatient setting is challenging, and its implementation may even significantly increase the risk of overall mortality and rehospitalizations due to exacerbation of CHF [56–58].

Limiting fluid intake to 1.5–2 liters per day is relevant only in severe CHF requiring intravenous administration of diuretics [15, 57]. It is worth noting that severe CHF is a term traditionally used in the Russian Federation to denote heart failure corresponding to stage II B [57] and functional class IV [59, 60]. With severe hypervolemic hyponatremia (Na^+ concentration in blood plasma below 125 mmol / l), more severe restriction (up to 800–1,000 ml / day) of fluid intake may be required [51]. In dilutional hyponatremia, the use of tolvaptan, i.e. a selective, competitive vasopressin V2 receptor antagonist, is indicated (the efficacy and safety of other vaptans, in particular, the non-selective V1a / V2 receptor antagonist pecavaptan [61]), without which in such a situation, effective and rapid DR management is practically impossible [62, 63].

To prevent the development of the inhibition phenomenon, diuretic therapy should be started with the lowest effective dose of the drug (preference should be given to a loop diuretic) [45]. For the same purpose, diuretics should be prescribed in combination with neurohumoral modulators (angiotensin-converting enzyme inhibitors or a combination of valsartan and sacubitril, beta-blockers, mineralocorticoid / aldosterone receptor antagonists) and sodium-glucose cotransporter-2 inhibitors (dapagliflozin or empagliflozin). Such combination therapy is also optimal in the development of late DR associated with adaptive changes in the distal nephron segments during long-term diuretic therapy [45, 51].

In the active phase of therapy, the dose of the diuretic should be gradually selected so that the excess of diuresis over the fluid taken is 1–2 l / day, with a daily body weight decrease by 0.75–1 kg. More rapid dehydration cannot be justified and only leads to hyperactivation of neurohormones and rebound fluid retention in the body [15, 45]. The strategy of using a diuretic in an intermittent mode with "shocking" diuresis once every few days is definitely flawed (every other day, once a week, etc.), as it inevitably leads to pseudo-resistance. Nevertheless, intermittent intravenous bolus administration of diuretics may be useful to maintain the euvolemic state in hemodynamically stable outpatients receiving continuous oral saluretic therapy [64]. This strategy leads to a decrease in the number of hospitalizations due to cardiac decompensation by preventing the development of resistance to oral forms of loop diuretics. In particular, in moderately decompensated patients, euvolemia may require as little as one or two doses of intravenous diuretics [64–67].

In the maintenance phase of therapy, which proceeds after reaching the euvolemic state, the dose of the diuretic can be reduced. But in any case, the latter should be above the natriuretic threshold (the steep part of the dose – response curve) providing balanced diuresis and maintaining lean body mass [45]. Like in the active phase, taking into account the pharmacokinetic features that reduce the likelihood of developing DR (high and predictable bioavailability, smooth and prolonged action with minimal postdiuretic sodium retention even with a single use during the day) and pleiotropic anti-aldosterone activity, torasemide is the drug of choice [68–70].

Patients should be taught to self-adjust diuretic doses based on monitoring of symptoms / signs of congestion and daily weight measurements [51]. In the event of a significant increase in dyspnea and edema, or an unexpected weight gain of more than 2 kg in 3 days, the patient should immediately inform their physician [51]. In such a situation, the first step in escalating therapy is to double the dose of a loop diuretic (if for some reason it has not been used before, then a dose should be equivalent to 40–80 mg of furosemide) until the effect or the maximum safe dose is reached [14, 45, 51]. At the same time, intravenous administration of a loop diuretic is preferable to its oral administration (Figure) [64].

It should be borne in mind that it is often not enough to simply increase the dose of an intravenously administered diuretic to overcome DR. With preserved kidney function, the maximum daily dose of furosemide, above which there is only a slight further increase in

natriuresis, is 80–160 mg; in patients with stage 3–4 chronic kidney disease or nephrotic syndrome, this dose is 160–240 mg [46]. Very high doses (500 mg of furosemide or more) may be required in patients with end-stage renal disease [45]. Most experts agree that shortening the intervals between diuretic administration (or their continuous infusion) allows to overcome postdiuretic sodium retention and is more effective than a single high-dose administration of the drug [9, 14]. Thus, a daily dose of a diuretic divided into two injections gives a greater effect than the same dose administered once a day, provided that both doses exceed the diuretic threshold [45].

Combination therapy with diuretics of different groups is the next step in overcoming DR after increasing the dose [14]. The effect is achieved both due to sequential blockade of the nephron and mutual potentiation of diuretic activity [21, 29]. For example, acetazolamide increases sensitivity to loop diuretics by correcting metabolic alkalosis [71, 72] and to thiazide diuretics by reducing the expression of pendrin [40].

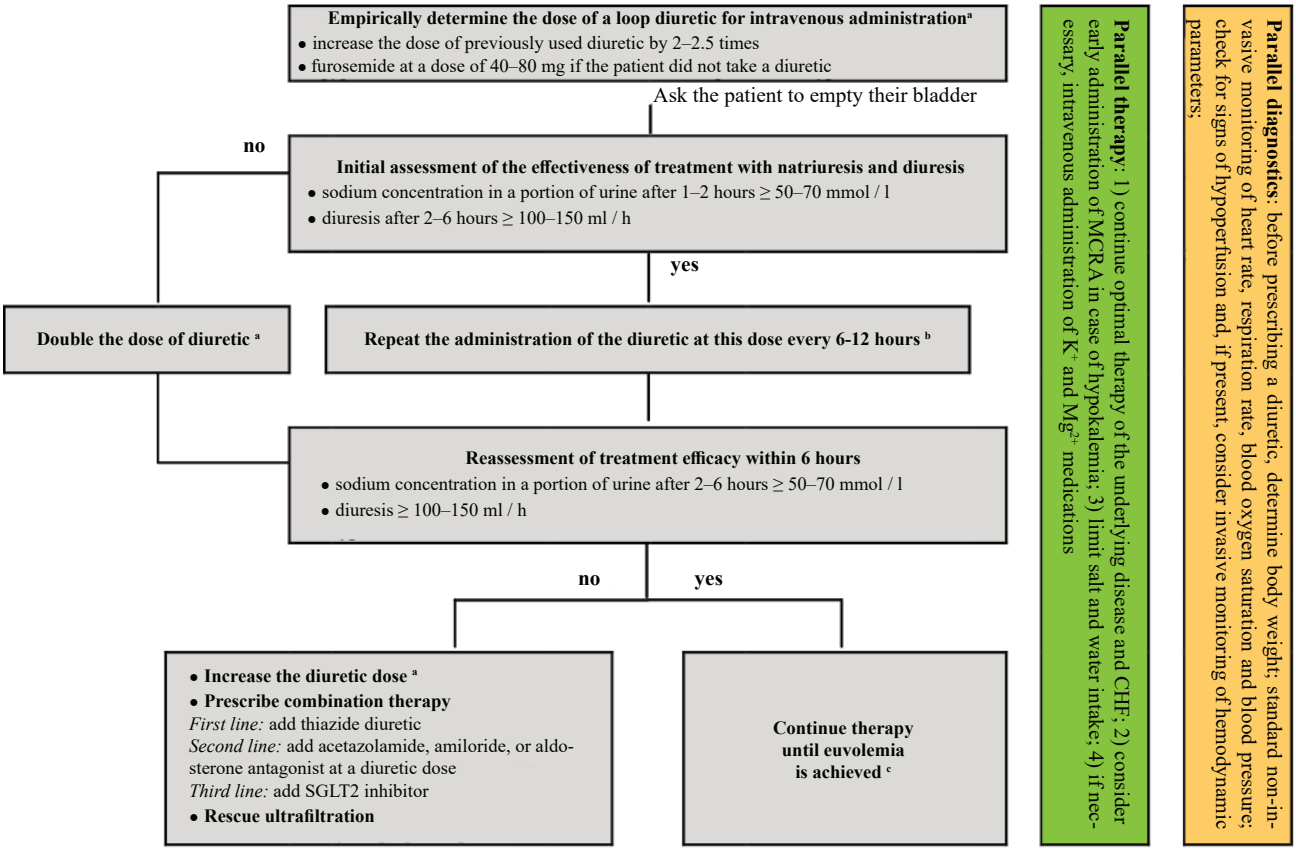

Figure. Block diagram of the use of diuretics in decompensated heart failure and resistance to diuretics [9, 14, 51].

[a] the maximum daily dose of an intravenous diuretic is a dose equivalent to 400–600 mg of furosemide (for example, bumetanide – 10–15 mg), however, in patients with severe renal dysfunction, an increase in the dose to 1,000 mg may be required; [b] in patients with good diuresis after a single administration of a diuretic, dosing once a day may be considered; [c] consider reducing the diuretic dose if daily urine output exceeds 5 liters; [d]> 50 mg / day; IV – intravenously (in the form of continuous infusion, or bolus); CHF – chronic heart failure; MCRA – mineralocorticoid receptor antagonists; BP – blood pressure; SGLT2, sodium-glucose cotransporter type 2

In addition to evaluating the effectiveness of combination therapy, careful clinical and laboratory monitoring of its safety is required. At the start of aggressive combination therapy with diuretics, which is combined with the use of modern neurohumoral modulators, some decrease in blood pressure, an increase in the level of urea and creatinine in the blood (a decrease in the estimated glomerular filtration rate), and a change in the concentration of potassium in the blood plasma are expected. Asymptomatic hypoten-

sion usually does not require any change in therapy. Faintness / slight dizziness is common and often stops over time – patients should be soothed by careful monitoring of blood pressure. An increase in creatinine by 20–30% above the baseline level is acceptable [51]. The key point of therapy in DR is that, although aggressive anti-edematous treatment is associated with deterioration in renal function, survival paradoxically improves [46, 73, 74].

The algorithm shown in the figure is fully applicable only to hemodynamically stable patients with hypervolemia demonstrating DR [14]. Clinicians are well aware that one of the main reasons preventing the use of high doses of diuretics (as well as titration of the dose of disease-modifying drugs to the target level) in patients with decompensated heart failure is systemic hypotension [75, 76]. Between 5 and 25% of patients with symptomatic CHF have low systolic blood pressure with or without signs and / or symptoms of hypoperfusion [75–78]. Symptomatic or severe asymptomatic hypotension (SBP < 90 mm Hg) may be aggravated by diuretic-induced vasodilation and hypovolemia [51].

Despite the fact that routine use of non-glycoside inotropic agents and vasoconstrictors as a tool to solve the problem of DR is not recommended [14], in a clinical situation with low cardiac output and hemodynamic instability, they cannot be avoided [51]. In this case, their use can have dramatic effectiveness and ensure DR management [36]. The arsenal of well-studied drugs and those currently under study includes vasoconstrictors (e.g., norepinephrine, midodrine, and vasopressin), inotropes with vasoconstrictive properties (e.g., dopamine, epinephrine, and droxidopa), cardiotonic agents (e.g., dobutamine, milrinone, and omecamtiv mecarbil), and inodilators, among which, according to some experts, the use of levosimendan is the most promising (the use is acceptable in the absence of a pronounced decrease in systolic blood pressure > 85 mm Hg) [51, 79–84].

If DR is associated with persistent clinically pronounced hypotension, which is figuratively called the Achilles heel of a patient with heart failure [85], short-term use of glucocorticoids may also be required, which not only contribute to an increase in blood pressure, but also have a positive effect on the functional state of the kidneys, demonstrating an increased renal response to diuretics in the experiment and in the clinical setting [85–88].

In patients with normal or elevated systemic blood pressure, a combination of diuretics with vasodilators, in particular, serelaxin (a recombinant analogue of human relaxin-2), low doses of nesiritide (a recombinant human brain natriuretic peptide), the vasopressin antagonist tolvaptan (especially in dilutional hyponatremia when an aquaretic has a significant advantage over a saluretic), and adenosine type 1 receptor antagonists (for example, aminophylline) may be effective [7, 14, 45, 89–96].

The use of drugs from the group of sodium – glucose cotransporter 2 inhibitors (for example, dapagliflozin or empagliflozin), which not only improve the prognosis in CHF, but also have diuretic and nephroprotective effects, can contribute to achieving euvolemia in refractory edema [14, 97–100].

In the presence of hypoalbuminemia (less than 35 g / l) in a patient with CHF (for example, in combination with nephrotic syndrome or liver cirrhosis), the effectiveness of diuretics is significantly reduced [15, 36]. In this case, to enhance the diuretic effect (especially at albumin levels below 25 g / l), intravenous administration of albumin immediately before diuretic therapy should be discussed [40, 101, 102], although the feasibility of this approach is not always supported by the results of clinical studies [45, 103]. Albumin should also be administered to compensate for its loss after laparocentesis (20-50 g with each procedure) with the evacuation of a large volume of ascites fluid (sometimes 4–6 liters per day are removed), which is performed in patients with CHF complicated by stable DR at the terminal stage of the disease [45].

Renal replacement therapy is the last resort for some patients with DR [9, 104]. So, one should not wonder why it is called life-saving [105]. Taking into account the fact that at the stage of deciding on renal replacement therapy, many patients have clinically pronounced hypotension (remember, the Achilles heel), it is preferable to choose sparing regimens using a minimum volume of extracorporeal blood and an ultrafiltration rate of no more than 250 ml / hour or peritoneal dialysis [79, 106–108].

It should be clearly understood that if it comes to ultrafiltration, its use does not always improve the fate of a patient with advanced heart failure. Mortality in patients with DR who need dialysis support is higher than among those patients for whom optimized pharmacotherapy was enough to achieve euvolemia (the probability of all-cause mortality is 3 times higher) [109]. Mechanical circulatory support (mono- and biventricular) can improve the prognosis in this cohort

of severe patients, often with unstable hemodynamics [79, 110–112].

Promising approaches aimed at overcoming DR, which are currently being discussed, include administration of hypertonic saline in combination with a high dose of a loop diuretic [113, 114], the subcutaneous route of furosemide infusion [115, 116], improvement of sequential nephron blockade due to the chronotherapeutic approach (for example, prescription of a thiazide drug 30 minutes before a loop diuretic) [43, 117], the use of non-neutralizing monoclonal anti-adrenomedullin antibodies, which increase its half-life and promote movement of this vasoactive peptide from the interstitium into the bloodstream (Adrecizumab) [117, 118], effects on the apelinergic system [119, 120], as well as thoracic sympathetic ganglia blockade (at the level from T6 to T11) with lidocaine [121, 122]. The results of prescribing anticoagulants in the nephrology clinic [19, 123] allow to hope that their use in DR will help restore sensitivity to loop diuretics in patients with CHF [19, 124]. Taking into account the well-known role of inflammatory mediators in the mechanisms of renal dysfunction in patients with type 1 and 2 cardiorenal syndrome, unloading of the heart and kidneys may also be useful [125-128].

CONCLUSION

The term “diuretic resistance” remains poorly defined, but it is usually considered that this is an inability to maintain natriuresis and diuresis at a level sufficient to ensure euvolemia, despite an adequate dose and regimen of loop diuretic administration. DR can develop both at the start of diuretic therapy and during their long-term use and is determined by various mechanisms. As a rule, DR reflects the progressive course of CHF and is often associated with a poor prognosis. Prevention, early detection of progression, and a set of measures aimed at overcoming DR contribute to improving the prognosis and significantly increasing the quality of patients’ life.

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