Natriuretic peptides-alternative pathways for the activation of intracellular signaling axis-cyclic guanylyl-monophosphate-protein kinase G at the background of preserved ejection fraction during chronic heart failure

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Abstract

At the background of preserved ejection fraction clinical and hemodynamic impairment developed in the patients with heart failure (HFpEF) significantly is associated with progression of diastolic dysfunction of left ventricle (LV). A key role in the maintaining normal diastolic heart function is assigned to a high level of intracellular signaling axis – cyclic guanylyl-monophosphate-protein kinase G (cGMP-PK-G) activation, which significantly reduces during HFpEF.

Besides nitrogen oxide (NO), natriuretic peptides (NPs) also have the ability to activate the intracellular signaling axis. However, by neutral endopeptidase – neprilysin, NPs are rapidly degraded and fail to develop clinically significant effects. The neprilysin inhibitors appear to be one of the mechanisms for NPs level increasing. The opportunities for the usage of Sacubitril-Valsartan during HFpEF have been analyzed. (**TCM-GMJ December 2024; 9 (2): P60-P65)**

Keywords: natriuretic peptides (NPs), cyclic guanylyl-monophosphate (cGMP), heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction, Valsartan, Sacubitril

Introduction

At the background of preserved ejection fraction clinical and hemodynamic impairment developed in the patients with heart failure (HFpEF) significantly is associated with progression of diastolic dysfunction of left ventricle (LV). A key role in the maintaining normal diastolic heart function is assigned to a high level of intracellular signaling axis – cyclic guanylyl-monophosphate-protein kinase G (cGMP-PK-G) activation, which significantly reduces during HFpEF.

Besides nitrogen oxide (NO), natriuretic peptides (NPs) also have the ability to activate the intracellular signaling axis. However, by neutral endopeptidase – neprilysin, NPs are rapidly degraded and fail to develop clinically significant effects. The neprilysin inhibitors appear to be one of the mechanisms for NPs level increasing. The opportunities for the usage of Sacubitril-Valsartan during HFpEF have been analyzed.

The diagnostic algorithm of chronic heart failure provided by European Society of Cardiology (ESC-Guideline -2016) is based on clinical probability, estimation of circulating natriuretic peptides and the data of transthoracic echocardiography {1}. Based on new recommendation test, heart failure with ≤40% ejection fraction (EF) is called heart failure with reduced ejection fraction (HFrEF) within the ranges of 40-49% - heart failure with mid-range ejection fraction (HFmrEF), while at ≥50% - heart failure with preserve ejection fraction (HFpEF) (1). Above 50% HFpEF in chronic heart failure is observed. Their number is constantly increasing. 6 months after discharge from the hospital, every other patient because of the impairment of hemodynamics needs a repeated hospitalization, and annual mortality reaches 30% {1-5, 7, 8}. The patients with HFpEF are elderly women with concomitant diseases: atrial fibrillation (AF), cardiac coronary disease (CCD), arterial hypertension, obesity, type 2 diabetes mellitus, chronic kidney disease, anemia, chronic obstructive pulmonary disease {6-8}. All of the above-mentioned induces pro-inflammatory status in the organism, which appears to be a trigger mechanism for endothelium systemic dysfunction, including the coronary mi-

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crocirculation bed {9}. There is no ideal strategy for treatment of these patients. Drugs are prescribed empirically without clearly expressed pathophysiological conception. All the preparations, which improve HFrEF prognosis, are not enough effective for the patients with HFpEF (10, 11).

During HFpEF with diagnostic criteria: LV mass index should exceed ≥95 g/m² (women), ≥115 g/m² (men), left atria volume index - >34 ml/m² at sinus rhythm (SR), 40 ml/m² at atrial fibrillation (AF), E/e ratio should exceed >9 at rest, N-terminal pro B-type natriuretic peptide (NT-pro BNP) should exceed 125 pg/ml (SR) or >365 pg/ml (atrial fibrillation -AF), B-type natriuretic peptide (BNP) - >35 pg/ml (SR) or >105 pg/ml (AF), systolic pressure in pulmonary artery should exceed >35 mmHg {10, 11}.

Clinical and hemodynamic impairment in the patients with HFpEF is significantly related to the progression of left ventricle diastolic dysfunction, while a key role in the maintaining normal diastolic heart function is assigned to a high level of intracellular signaling axis – cyclic guanylyl-monophosphate-protein kinase G (cGMP-PK-G) activation, which is significantly reduced during HFpEF {12}. PK-G is expressed in endothelial and smooth muscular ells of the blood vessels, cardiomyocytes and fibroblasts. In the experimental researches the administration of PK-G inhibited an important cytokine of fibrosis – transforming growth factor β (TGF β) and prevented the transformation of fibroblasts into active myofibroblasts in the heart and other tissues {12}. In norm PK-G blocks intercellular growth signals and the removal of this inhibitory action determines the development of cardiomyocyte hypertrophy {13}, while cGMP injection by means of PK-G activation inhibits embryonic pro-hypertrophic genes {14, 15}.

PK-G participates in intracellular calcium ions circulation and determines a normal active relaxation. In norm a high tension of the myocardium is maintaining by means of phosphorylation of the spring elements of titin molecules, which is achieved at the expense of a high activity of PK-G and other proteins {16-18}.

Based on numerous experimental evidences an activation of PK-G promotes for the improvement of left ventricle (LV) relaxation, and reduction of myocardium fibrosis {19-23}.

One more alternative mechanism of the activation of cGMP and PK-G intercellular signal axis appears to be the activation of natriuretic peptides (NPs). The representatives of a large family of NPs appear to be: atrial (ANP), type B (BNP) and type C (CNP). ANP is predominantly produced in the atria, BNP – predominantly in the ventricles, CNP – in vascular endothelium {24}. The main biological effects of NPs are determined by their interaction with A and B type receptors. Having been related to the mentioned receptors, NPs activate receptory (corpuscular) guanylate cyclase (GC rec.), which appear to be an intracellular catalyzing domain of these receptors. Therefore, these receptors are designated as pGC (pGC-particulata guanylyl cyclase, corpuscular guanylate cyclase). ANP and BNP act by means of A type receptors (or pGC A receptors), while CNP – by means of B type receptors (or pGC B receptor). By action of receptory guanylate cyclase the secondary intracellular messenger cGMP is produced, which further activates PK-G {24, 25}.

As is known, a main stimulus of ANP and BNP synthesis appears to be a mechanical tension of cardiomyocytes {25}. In norm, NP transfers into the blood in small amounts, however, at hemodynamic overload of the heart the content of peptides increases in the blood {26}. *De novo* synthesized NP are not rapidly transferred into the blood, it is reserved in special intracellular granules as a precursor of atrial peptide (pro ANP), at atrial tension, for example, during supraventricular paroxysmal tachyarrhythmia, ANP sharply increases because of transfer of mentioned reserve molecules into the blood flow [27]. At the same time, pro-ANP released outside, splits with the participation of enzyme Corin, which appears to be a special myocardial transmembrane protease – C and at N-final fragments {28}.

In contrast to ANP, BNP is not deposited inside the cell, but it rapidly transfers into the blood flow. During transferring into the blood flow, pro BNP is broken down into biologically active terminal fragments, presented by the residues of 32 amino acids (BNP, itself), as well as biologically inactive N-terminal fragments (NT-pro-BNP) with the residues composed by 76 amino acids {29}.

NPs belong to vasodilatory neurohormonal systems. They are released in response to increased tension on heart wall and promotes the increased vasodilation, natriuresis and diuresis. This latter is reached at the expense of reduction of sodium reabsorption in kidneys collecting tubes and increasing glomerular filtration speed {30}. Along with the mentioned, NPs weaken renal effects of antidiuretic hormone and angiotensin-II, reduce renin and aldosterone release {31}. NPs can reduce sympathetic nervous activity {32}.

Along with the above-said, NPs have also additional effects: they accelerate the myocardium releasing processes, reduce proliferative response on heart and blood vessels damage, prevent the packing of connective tissues in the myocardium, maintain the integrity of endothelial barrier, participate in angiogenesis and, what is very important, have anti-inflammatory action {33, 34}. In the experiment ANP inhibited collagen synthesis in fibroblasts, as well as inhibited the production of some pro-inflammatory cytokines {12, 35}, while BNP – inhibited cell proliferation by the action of TGF-β {35}. In rats with ANP gene deficiency the development of arterial hypertension, myocardial hypertrophy and fibrosis, as well as the enlargement of left ventricular cavity were observed {36}. In rats with BNP gene deficiency, arterial hypertension and LV hypertrophy (LVH) were not observed, however, fibrosis of the myocardium, increased LV rigidity and the reduction of its constriction were seen {37}.

The advanced stages of chronic heart failure are characterized by retention of sodium and water in the organism, narrowing of systemic and renal blood vessels, impairment of heart structure and function. The above mentioned is contributed by chronic activation of sympatho-adrenal (SAS) and renin-angiotensin-aldosterone systems (RAAS).

The increase of NPs level during chronic heart failure can be considered as a compensatory reaction of the organism directed to reduce a negative influence of neurohormones narrowing blood vessels. In fact, NPs have the ability to induce a number of positive effects at the early stage of chronic heart failure. However, with time pass, these effects weaken, as despite a high level of NPs in the blood, the organism does not react to NPs any more. The retention of sodium and water is increasing more and more, while LV dysfunction constantly increases. In the available literature the decreased response reaction of the organism to NPs action is known as "natriuretic paradox". The higher is NP level, the more unfavorable is the prognosis. It is also known that during years BNP and NP-pro-BNP have been used for the diagnosis of development risk and stratification, while the effectiveness of therapy is estimated based on BNP reduction rate {38, 39}. Gradual reduction of NPs receptors density and decrease in the organism's reaction to NPs action appears to be a basis for "natriuretic paradox". The mentioned is associated with the excess of immature forms of NPs in the blood flow, which have lost the ability to activate the receptors at the appropriate level. As is seen, the occurrence of immature NPs forms in the blood is related to the disturbance of peptides processing – the impossibility of transformation of immature NP into mature biologically active forms {40, 41}. According to T, Ichiki et al., in dogs with heart failure a level of Corin expression (Corin – enzyme participating in NPs processing) was significantly low both at gene and protein levels {40]. In the experiment of Tripathi et al. [41}) it has been established that in rats with cardiomyopathy the expression of Corin gene was already reduced at the early stage of heart failure, while an increased expression of ANP and BNP was observed only at the final stage {42, 43}.

Thus, at the background of decreased Corin and other enzymes activity, the disturbed biochemical processes of NPs precursors make possible the decrease in biopenetration of the peptides into the organism and the progression of heart failure. X. Zhou et al. {44} have shown that a low level of Corin is associated with a high risk of complications of cardiovascular system, the progression of chronic heart failure and the impairment of the prognosis.

In reducing NPs biopenetration the most attention is paid to accelerated elimination. There are two mechanisms for the excretion of NPs from the blood flow. The first – by binding NP to C type (NPR-C) NP receptors with further endocytosis and intracellular proteolysis {45} and the second – by means of NPs cleavage performed by a special enzyme – neutral endopeptidase. During chronic heart failure the acceleration of the both processes is noted {46}.

NPs enzyme degradation takes place under the influence of transmembrane neutral endopeptidase type II in the micro blood vessels or by means of neprilysin. It breaks down all the biologically active NPs {47}, as well as bradykinin, P substance, adrenomedulin and vasoactive intestinal peptides, but does not break down N-terminal fragments of NPs precursors. Because of it, at clinical trial of neprilysin inhibitors for evaluation of the effectiveness of therapy, the orientation should be focused on NT-pro BNP and not on BNP, a level of which can be increased at the expense of reducing its elimination, despite the normalization of LV replenishment pressure and reduction of peptide production {48}.

For the amplification of NPs effects, at the beginning the injection of BNP recombinant drug Nesiritide into the organism was provided. The drug revealed an enhanced natriuretic effect, reduced LV replenishment pressure and increased heart ejection [49, 50}. Nesiritide positive hemodynamic effects were confirmed in NSG research during acute heart decompensation {51}. Based on the obtained results, Nesiritide was considered as a first-line drug at acute heart decompensation. However, J.D. Sackner-Bernstein et al. {52} using a meta-analysis had revealed the increase of mortality and the frequency of renal dysfunction in patients with acute heart decompensation while using this drug. Today Nesiritide usage is not recommended during decompensated heart failure.

The increase in NPs biopenetration during chronic heart failure appears to be one more method, particularly, by means of the reduction of endogenous NPs degradation F. Martin et al. {53} had shown that in dogs with chronic heart failure Neprilysin's inhibitor Candoxatril prolonged compensation phase of disease, enhanced NPs renal effects, reduced sodium retention and suppressed aldosterone activation. However, it should be noted that besides NPs, Neprilysin also breaks down angiotensins {54} and Neprilysin blockade is accompanied by angiotensin II accumulation, which causes the reduction of NP positive hemodynamic effects. Taking of Candoxatril (Neprilysin's inhibitor) by healthy volunteers increased not only NPs level, but also of angiotensin II and endothelins levels {55}, it had no significant clinical effects in the patients with chronic heart failure {56}. The above said occurred to be the basis for the creation of such a combined preparation that would simultaneously increase NPs biopenetration (at the expense of Neprilysin blockade) and inhibit RAAS activity. The first combined preparation that simultaneously decrease Neprilysin level (Sacubitril) and RAAS plasmic activity (inhibitor of angiotensin converting enzyme -ACEI) is drug Omapatrilat, which is perfectly studied in randomized research during heart failure taking place at the background of low ejection fraction {57}). The analysis of subgroups performed during the observation revealed a heterogeneous efficiency of combined therapy, a possible advantage of therapy in women and in the patients with low ejection.

IMPRESS research has shown Omapatrilat's advantage on the hemodynamics as compared to lysinopril {57}. Unlike it, in the research OVERTURE the differences between Omapatrilat and Enalapril regarding the frequency of mortality and hospitalization were not revealed. In this research in Omapatrilat groups angioneurotic edema was very often observed (0.8% unlike 0.5% in Enalapril group) {58}.

Valsartan/Sacubitril combination revealed especially high clinical and prognostic efficiency during HFpEF,

which was confirmed in large-scale research PARADIGM-HF. Total of 8442 patients with HFpEF were randomized in Enalapril and Valsartan+Sacubitril groups. The observations on the patients were stopped earlier than it was planned because of a significant preference of combined preparation as compared to Enalapril on the mortality and a frequency of hospitalization [59].

Valsartan/Sacubitril combination found to have anti-inflammatory properties, which is especially important during HFpEF, taking into account the role that has a chronic myocardial inflammation in the pathogenesis of mentioned condition [60-62]. For example, in mice with apolipoprotein E deficit and atherosclerosis of carotid artery, the injection of this combination slows down the growth of atherosclerotic plaques, reduces the expression of pro-inflammatory cytokines (interleukin-5, matrix metaloproteinaza-8), as compared to Valsartan isolated injection [61, 62].

According to PARAMOUNT study (multicenter, pilot) with the participation of 301 patients with HFpEF and increased NT-pro BNP level, the administration of combined preparation Valsartan/Sacubitril, as compared to Valsartan, during 36 months sharply decreased NT-pro BNP level in the blood and a volume of left ventricle [64]. Taking into account the positive results of the above-said research, multicenter, International III phase study PARACON-HF was carried out. The action of Valsartan/ Sacubitril on disease and mortality was assessed in this study during HFpEF. Total of 4822 patients with increased NPs level were randomized in Valsartan or Valsartan/Sacubitril groups. The combined therapy has not shown a reliable reduction of mortality evoked by cardiovascular disease and hospitalization frequency evoked by heart failure. However, the improvement of life quality was noted [64].

Thus, during HFpEF the activity of cGMP-PKG intracellular axis decreases not only by entering a small number of NO in cardiomyocytes, but also as a result of disturbance of natriuretic peptides production by the myocardium, and first of all, BNP. At the same time, the experts agree that the activity of cGMP-PKG axis by means of NO biopenetration restoration is extremely difficult, as for today there are no methods restoring the function of endothelial bed of coronary microcirculation except of statins (6, 60). It is much easier and faster to activate the axis of natriuretic peptides by increasing their biopenetration with the help of neprolysin inhibitors.

From the point of view of pathophysiology, the use of Valsartan/Sacubitrilis is more justified at NFpEF, than at HFrEF, as for many reasons at HFpEF the NPs biopenetration is especially low and many experts call this phenotype of heart failure "NP-deficit" syndrome. During the mentioned condition, the peptides are synthetized in a small amount, they break down rapidly and fail to develop clinically significant effects [6]. At HFpEF except of the ability to low absorption of the organism to NP action, there are some reasons, characteristic of this particular phenotype of heart failure. As mentioned earlier, a main triggering mechanism of BNP excretion appears to be an excess tension of the myocardium, expressed by the increase in diastolic tension on LP wall. However, the majority patients have a concentration hypertrophy of LP, when the action of LV pressure on diastolic tension is leveled by thickened myocardial walls and a small size of the cavity. Proceeding from this, diastolic tension (which means a level of brain peptide) may be normal in the patients of this category, despite increasing filling pressure, one can explain this by a low content of brain NP at HFpEF, unlike the patients with HFrEF. It is no coincidence that in the recent European recommendations on HFpEF diagnostics, a level of brain NP does not appear a necessary diagnostic criterion any more, and is considered as only one of the possible criterion [62].

Results

The reasons for clinical and hemodynamic impairment in the patients with HFpEF developed at the background of preserved ejection fraction are discussed in this review, which is associated with the progress of diastolic function of left ventricle. A key role in the maintaining normal heart diastolic function is assigned to a high level of intracellular signaling axis – cyclic guanylyl-monophosphate-protein kinase G (vGMP-PK-G) activity, which significantly reduces at HFpEF.

Besides nitrogen oxide (NO), natriuretic peptides (NPs) also have the ability to activate the intracellular signaling axis. However, by neutral endopeptidase - neprilysin they are rapidly degraded and fail to develop clinically significant effects. The neprilysin inhibitors appear to be one of the mechanisms for NPs level increasing. The opportunities for the usage of Valsartan/ Sacubitril during HFpEF have been analyzed. It can be assumed that the patients with HFpEF appear to be the ideal candidates for a combined therapy (Valsartan-Sacubitril).

Conclusion

At the background of preserved ejection fraction (HFpEF) at heart failure, the biopenetration of natriuretic peptides is particularly low that promotes the reduction in the activity of cyclic guanylyl-monophosphate-protein kinase G (cCMP-PKG) of intracellular signal axis, and this latter is important for myocardial normal functioning in diastole.

Despite the encouraging data of experimental and earlier clinical studies, the combined drug Valsartan/Sacubitrilis (PARACON-HF) at HFpEF appeared to be not enoughly effective combination regarding action of disease prognosis, but it was enough effective combination for the improvement of life quality. The mentioned contingent was composed by elderly and old patients and proceeding from their age, their expected life expectancy is limited. Therefore, the experts engaged in heart failure study consider that a main effort in the treatment of these patients, first of all, should be directed to the improvement of life quality, decrease in the exacerbation of disease risk - maximally expressed in the conditions of syndrome of "natriuretic peptides deficit" and a maximal concentration hypertrophy of left ventricle [66]. The idea of the increase of biopenetration of natriuretic peptides by the usage of synthetic peptides is still relevant today [67].

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