DAVID GOLOSHVILI [1], ZURAB ZAALISHVILI [2], DIANA KERATISHVILI [2],
MAIA OKUJAVA [1], NIKOLOZ GONGADZE [1], MANANA GHONGHADZE [1]

PATHOPHYSIOLOGICAL PRINCIPLES UNDERLYING THE EFFECT OF SACUBITRIL-VALSARTAN ON HYPERTENSION-INDUCED CARDIOVASCULAR REMODELING

[1]Tbilisi State Medical University, Department of Medical Pharmacology; [2]American MD Program

დავით გოლოშვილი [1], ზურაბ ზაალიშვილი [2], დიანა კერატიშვილი [2], მაია ოკუჯავა [1],
ნიკოლოზ გონგაძე [1], მანანა ღონღაძე [1]

საქუბიტრილ-ვალსარტანის მოქმედების პათოფიზიოლოგიური პრინციპები ჰიპერტენზიით გამოწვეული გულ-სისხლძარღვთა რემოდელირების დროს

[1]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, სამედიცინო ფარმაკოლოგიის დეპარტამენტი; [2] დიპლომირებული მედიკოსის ამერიკული პროგრამა

რეზიუმე

მიოკარდიუმის რემოდელირება არის პროცესი, რომელსაც კარდიომიოციტები, მიოკარდიუმის სხვა უჯრედები (ენდოთელური უჯრედები, ფიბრობლასტები, პერიციტები და იმუნური უჯრედები), მექანიკური და არა მექანიკური სტიმულის საპასუხოდ ცირკულაციიდან გადმოსროლილი უჯრედები (მაგ., იმუნური და ანთებითი უჯრედები) ახორციელებენ. შედეგად, კარდიომიოციტების, ინტერსტიციული მატრიქსისა და კორონარული სისხლძარღვების შემადგენლობა, მოცულობა და ფიზიოლოგია ურთიერთდაკავშირებულ ცვლილებებს განიცდის. ეს ცვლილებები საზიანო გავლენას ახდენს ჰიპერტენზიული პაციენტების კლინიკურ შედეგებზე - გაზრდილი პარკუჭის რიგიდულობა იწვევს სისტოლურ ან დიასტოლურ დისფუნქციას და ზრდის ფიბრილაციის რისკს. ამიტომ, გულ-სისხლძარღვთა რემოდელირების შემცირება არის ამ პაციენტების კლინიკური მართვის მთავარი მიზანი. რამდენიმე წამალი, როგორიცაა ანგიოტენზინ-გარდამქმნელი ფერმენტის ინჰიბიტორები, ბეტა ბლოკატორები და ალდოსტერონის ანტაგონისტები, მუდმივად ამცირებენ მიოკარდიუმის რემოდელირებას ცხოველურ მოდელებსა და კლინიკურ კვლევებში, ამიტომ, ამ მიზნით, ისინი ფართოდ გამოიყენება პრაქტიკაში.

ნეპრილიზინის ინჰიბიტორ - საკუბიტრილისა, და ანგიოტენზინის რეცეპტორების ანტაგონისტ - ვალსარტანის კომბინაციამ, რომელსაც დადებითი კლინიკური შედეგები აქვს შემცირებული განდევნის ფრაქციის მქონე გულის უკმარისობიან პაციენტებში, ბოლო დროს მეცნიერების დიდი ყურადღება მიიპყრო შენარჩუნებული განდევნის ფრაქციის მქონე გულის უკმარისობიანი პაციენტების სამკურნალოდაც. ამ ორი პრეპარატის კომბინაცია იწვევს ნატრიურეზული პეპტიდების დაგროვების (რომლებსაც ნატრიურეზული და სისხლძარღვების გლუვი კუნთების მოსადუნებელი ფუნქციები აქვს) და რენინ-ანგიოტენზინ-ალდოსტერონის სისტემის ეფექტების შემცირებას, რაც კარდიოპროტექტორული და ანტიჰიპერტენზიული ეფექტებით გამოირჩევა და ამცირებს გულ-სისხლძარღვთა ფიბროზს.

აღსანიშნავია, რომ საკუბიტრილ/ვალსარტანს ანგიოტენზინ-გარდამქმნელი ფერმენტის ინჰიბიტორ, პერინდოპრილთან შედარებით, ვირთაგვებში უკეთესი ეფექტი ჰქონდა გულის რემოდელირებისა და განდევნის ფრაქციაზე. თუმცა, ეს მხოლოდ წინასწარი მონაცემებია და უფრო ფართო კვლევები უნდა ჩატარდეს როგორც ექსპერიმენტულ, ასევე კლინიკურ გარემოში, რათა სრულად გამოვლინდეს პრეპარატის მოქმედების მექანიზმები სხვადასხვა ტიპის არტერიული ჰიპერტენზიის მართვაში.

Introduction. One of the major effects of hypertension on the heart is diffuse myocardial fibrosis. Fibrosis is caused by increased deposition of extracellular matrix (ECM), particularly collagen type I and type III fibers within the interstitium and coronary arteries [3]. Excessive collagen within the myocardium in HHD results from several steps: [12,15] resident fibroblasts and other cells differentiate into myofibroblasts; synthesis and secretion of procollagen increase; procollagen is converted into microfibril-forming collagen by proteinases; collagen microfibrils assemble to form fibrils; and a lysyl oxidase cross-links the fibrils to form collagen fibers. The key points are the following: myocardial stretch releases growth factors such as TGF-β and angiotensin II [24], both of which induce fibrosis

[16,19]; and TGF-β1 upregulates lysyl oxidase, which creates collagen crosslinks [21]. Therefore, there are known mechanisms both for the stretch-up-regulated production of collagen and its cross linking. While myocardial hypertrophy can potentially compensate for fibrosis [8,9], ECM deposition is almost always pathological due to the risk of fibrillation and increased ventricular stiffness leading to systolic or diastolic dysfunction [5].

The hypertrophy of cardiomyocytes is another consequence of cardiovascular remodeling secondary to hypertension. It is the main mechanism by which the wall stress imposed on the LV wall by pressure overload decreases. Myocardial hypertrophy involves stimulation of intracellular signaling cascades, Janus kinase 2 (JAK2) way, activates gene expression, and promotes protein synthesis [11,28].

The hypertrophy of cardiomyocytes may be linked to their death as well. The dysregulated protein synthesis and processing cause the accumulation of unfolded proteins. This can lead to the activation of the unfolded protein response, which, in turn, may induce cardiomyocyte apoptosis [7]. In cardiomyocytes isolated from spontaneously hypertensive rats with left ventricular hypertrophy (LVH), an association was found between the activation of unfolded protein response and cardiomyocyte apoptosis [26,27]. Additionally, clinical evidence suggests that in the hypertrophied myocardium, there is a deficiency of the factors that prevent apoptosis (eg, gp130/leukemia inhibitory factor receptor survival pathway) [2,4]. Therefore, cardiomyocyte apoptosis is abnormally stimulated in patients with hypertensive heart disease (HHD) [23,13].

In elderly patients, the myocardial contractility is often preserved even when the myocardial relaxation is significantly impaired [25] either due to myocardial fibrosis, hypertrophy, or both. This suggests the existence of a compensatory mechanism that increases contractility and maintains cardiac output despite impaired relaxation.

The arterial baroreflex is one of the factors that regulate blood pressure and cardiovascular variability in the short term. Several humoral, environmental, and behavioral factors can affect the function of the baroreflex, as well as cardiovascular variability. Many central neural structures also regulate blood pressure and contribute to the integrity of the baroreflex. Therefore, brain injuries or ischemia can impair baroreflex and derange blood pressure regulation. Baroreflex dysfunction is also commonly seen in cardiovascular disease. A blunted baroreflex and impaired heart rate variability predict poor outcomes in patients with hypertension, heart failure, and myocardial infarction. The mechanisms underlying these relationships are not well understood and may partly be due to cardiac structural changes secondary to hypertension and/or altered central neural processing of baroreflex signals [54,55].

One such compensatory mechanism is the high activity of the cardiac sympathetic nervous system (CSNS) that increases myocardial contractility [10]. Catecholamines (eg, norepinephrine, epinephrine) stimulate β-receptors in the heart that raises both heart rate and contractility. Similar to fibrosis, increased sympathetic activity is often considered pathological because it is found in dilatation-induced heart failure [18].

Recent studies also indicate the pivotal role of inflammation and immune activation in the pathophysiology of hypertension-induced end-organ damage [17,1]. Experimental evidence shows extensive inflammation in hypertensive animal model-dependent cardiac damage, especially in response to administration of exogenous aldosterone [29], angiotensin II, [2,22] stimulation of the sympathetic nervous system [20] and pressure overload [6]. Injured cardiomyocytes release damage-associated molecular pattern (DAMP) molecules that cause the healthy cardiomyocytes to produce inflammatory mediators such as IL [interleukin]-1β, IL-6, and TNF-α [tumor necrosis factor α]. Activation of these mediators, in turn, leads to leukocyte stimulation and recruitment [14].

Several factors contribute to cardiovascular remodelings, such as increased production of vasoconstrictor agents and inflammatory cytokines, endothelial dysfunction, myocardial hypertrophy, and oxidative stress [30,31]. This is why a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor antagonist, has recently gained public and scientific attention. Neprilysin (neutral endopeptidase, also known as NEP) breaks down natriuretic peptide, one of the major targets for treating hypertension. Neprilysin Inhibition increases natriuretic peptide levels. Natriuretic peptides, in turn, induce natriuresis and vasodilation and inhibit the renin-angiotensin-aldosterone system.

Neprilysin also breaks down vasoconstrictive peptides such as angiotensin II and endothelin. Therefore, the hypotensive effect of the neprilysin inhibitor is mitigated by increased vasoconstrictive peptides [32]. Although the combined inhibitor of neprilysin and ACE, omapatrilat, has a stronger hypotensive effect than enalapril [33], concomitant use of neprilysin and ACE inhibitors increases the risk of angioedema. This is because inhibition of neprilysin leads to accumulation of substance P while inhibition of angiotensin-converting enzyme leads to accumulation of bradykinin. Substance P and bradykinin both cause angioedema. In contrast, AT1 receptor antagonists do not inhibit bradykinin metabolism. This is why valsartan was selected for combination sacubitril. The positive clinical outcome of sacubitril/valsartan has been well documented in patients with heart failure with reduced ejection fraction. Additionally, this combination is promising for patients with heart failure with preserved ejection fraction and hypertension, especially for those with isolated systolic hypertension [34,35,36,37].

Literature Review. While blood pressure is regulated by various interconnected mechanisms, the vasoactive peptides, hormones, and the enzymes involved in their synthesis and degradation play a key role. Peptidases and peptide receptors are important targets for the development of new antihypertensive medications [39]. The combination of a dual-acting, neprilysin (NEP) inhibitor and an angiotensin receptor antagonist (ARB) (LCZ696 or sacubitril/valsartan, called), is a new drug containing the equivalent amount of valsartan and sacubitril. It is the first and, so far, the only representative of this group of drugs [40]. On one hand, these drugs inhibit neprilysin and promote the accumulation of natriuretic peptides. On the other hand, they reduce the effects of the renin-angiotensin-aldosterone system without accumulation of bradykinin [41]. Natriuretic peptides are structurally similar molecules that activate guanylyl cyclase. They have natriuretic and vascular smooth muscle relaxant properties and, therefore, regulate cardiovascular and renal systems. In general, natriuretic peptides have cardioprotective and antihypertensive effects; they maintain homeostasis and reduce cardiovascular fibrosis [42]. Three forms of the natriuretic peptide are known: atrial natriuretic peptide (ANP), type B natriuretic peptide first isolated from the brain (BNP), and type C natriuretic peptide (CNP). Expression and accumulation of ANP in granules occur mostly in the atrium. However, it is also found in other tissue, such as ventricles and kidneys. It is released in response to the atrial wall stretching as well as the hormones and peptides such as endothelin, angiotensin 1-9, angiotensin 1-7 [43]. BNP is identified in greater numbers in the ventricles, where its gene transcription is regulated by myocardial strain. The amount of both natriuretic peptides increases more than 100-fold in patients with heart failure [38,44]. There is a minimal amount of CNP in the heart so its concentration in plasma does not change in heart failure. CNP is present in large numbers in chondrocytes, and it regulates bone growth. CNP is also found in the endothelium and it causes hyperpolarization and relaxation of the blood vessel wall [45]. Intravenous use of ANP and BNP recombinant peptides has shown positive effects in patients with heart failure. Although pronounced hypotension and a short half-life have limited their use in patients with heart failure [46], more stable analogs are currently being studied. A different approach to increasing the amount of circulating natriuretic peptides is to use a neprilysin (NEP) inhibitor. The use of a NEP inhibitor to lower blood pressure is effective only in combination with renin-angiotensin-aldosterone system inhibitors [47]. Neprilysin (also known as Neutral Endopeptidase 24.11, Encephalinase or CD10; EC 3.4.24.11) binds to the cell surface. It has a large extracellular catalytic domain C-terminal that degrades physiologically active peptides, namely natriuretic II S, endothelin-1, etc. However, clinical trials have not shown the high efficacy of these drugs [48]. Inhibition of NEP has been shown to increase plasma levels of vasodilatory natriuretic peptides, adrenomedullin, and bradykinin. However, studies have also shown that inhibition of NEP increases the levels of angiotensin II and endothelin-1, which have the vasoconstrictive effect [49]. Angiotensin I is more of a substrate for NEP, so an increase in angiotensin II during inhibition of NEP is more driven by an increase in its production from angiotensin I than a decrease in angiotensin II degradation. Given this fact, the NEP inhibitor was initially proposed in combination with the angiotensin-converting enzyme (ACE) inhibitor. However, the ACE / NEP inhibitor, omapatrilat, turned out not promising drug due to the increased risk of angioedema. Angiotensin 1 (AT1) and 2 (AT2) receptors are G protein-coupled receptors. The binding of angiotensin II to the AT1 receptor activates various signaling systems, leading to hypertension, endothelial dysfunction, vascular remodeling, and organ damage. Valsartan is an orally active

nonspecific triazoline product that reduces angiotensin II-induced vasoconstriction and water and salt retention by inhibiting AT1 receptors.

The combination of the NEP inhibitor sacubitril and the angiotensin receptor antagonist valsartan increases NEP activity and inhibits the renin-angiotensin system without interfering with bradykinin accumulation and NEP-associated vasoprotective effects [14]. A large-scale clinical trial of PARADIGM-HF evaluated the use of sacubitril/valsartan in patients with heart failure with impaired ejection fraction (HFrEF) and sustained ejection fraction (HFpEF) and confirmed its superior efficacy over enalapril [50,51]. The use of sacubitril/valsartan was in patients with HfrEF. Despite the clinical benefits of this drug, it has since been used only for heart failure in European and American guidelines. However, the other possible indications for this medication are less explored. This, relatively, could be explained by the so-called " Clinical inertia&quot [52], which is associated with lower awareness of the drug, refraining from changing treatment in stable patients, and reimbursement problems by insurance companies. Although studies have shown that widespread use of sacubitril/valsartan can reduce mortality and stabilize patient status.

Possible future indications for sacubitril/valsartan include arterial hypertension, heart failure with sustained ejection fraction, myocardial infarction, diabetic nephropathy, stroke. Importantly, sacubitril/valsartan showed a better effect on cardiac remodeling and ejection fraction compared with ACE inhibitor perindopril in rats [53]. It is noteworthy, that based on several small-scale pilot studies, the antihypertensive effect of sacubitril/valsartan was particularly pronounced in systolic blood pressure and isolated systolic hypertension in the elderly. However, these are only preliminary data and it is necessary to conduct additional experimental studies and more extensive randomized clinical trials. It will aid in fully revealing the mechanisms of action of the drug in the management of various types of arterial hypertension, especially in its resistant forms.

Conclusion. Putting together the links between hypertension-induced cardiovascular remodeling and the detrimental clinical outcomes of patients with hypertensive heart disease, aiming to reduce cardiovascular remodeling is key for the overall clinical care of these patients. A combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor antagonist, which has positive clinical outcomes in patients with heart failure with reduced ejection fraction, has recently gained public and scientific attention for patients with heart failure with preserved ejection fraction and hypertension (especially for those with isolated systolic hypertension). Importantly, sacubitril/valsartan showed a better effect on cardiac remodeling and reversal fraction compared with ACE inhibitor perindopril in rats. However, these are only preliminary data and further research should be conducted in both experimental and clinical settings.

References:

1. Altara R, Mallat Z, Booz GW, Zouein FA. The CXCL10/CXCR3 axis and cardiac inflammation: implications for immunotherapy to treat infectious and noninfectious diseases of the heart. J Immunol Res. 2016; 2016:4396368. doi: 10.1155/2016/4396368.
2. Behr TM, Willette RN, Coatney RW, Berova M, Angermann CE, Anderson K, Sackner-Bernstein JD, Barone FC. Eprosartan improves cardiac performance, reduces cardiac hypertrophy and mortality and downregulates myocardial monocyte chemoattractant protein-1 and inflammation in hypertensive heart disease. J Hypertens. 2004; 22:583–592.
3. Berk BC, Fujiwara K, Lehoux S. ECM remodeling in hypertensive heart disease. J Clin Invest. 2007; 117:568–575. doi: 10.1172/JCI31044.
4. Chen MA (2009). Heart failure with preserved ejection fraction in older adults. Am J Med122, 713–723.
5. Creemers EE & Pinto YM (2011). Molecular mechanisms that control interstitial fibrosis in the pressure-overloaded heart. Cardiovasc Res 89, 265–272.
6. Deckx S, Heggermont W, Carai P, Rienks M, Dresselaers T, Himmelreich U, van Leeuwen R, Lommen W, van der Velden J, Gonzalez A, Diez J, Papageorgiou AP, Heymans S. Osteoglycin prevents the development of age-related diastolic dysfunction during pressure overload by reducing cardiac fibrosis and inflammation. Matrix Biol. 2018; 66:110–124. doi: 10.1016/j.matbio.2017.09.002.

7. Dickhout JG, Carlisle RE, Austin RC. Interrelationship between cardiac hypertrophy, heart failure, and chronic kidney disease: endoplasmic reticulum stress as a mediator of pathogenesis. Circ Res. 2011; 108:629–642. doi: 10.1161/CIRCRESAHA.110.226803.
8. Drazner MH (2011). The progression of hypertensive heart disease. Circulation123, 327–334.
9. Egan Benova T, Szeiffova Bacova B, Viczenczova C, Diez E, Barancik M & Tribulova N (2016). Protection of cardiac cell-to-cell coupling attenuates myocardial remodeling and proarrhythmia induced by hypertension. Physiol Res 65 Suppl 1, S29–S42.
10. Goldberg LI, Bloodwell RD, Braunwald E & Morrow AG (1960). The direct effects of norepinephrine, epinephrine, and methoxamine on myocardial contractile force in man. Circulation 22, 1125–1132.
11. González A, Arantxa González From the Program of Cardiovascular Diseases, Ravassa S, et al. Myocardial remodeling in hypertension. Hypertension. https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.118.11125. Published July 23, 2018. Accessed April 13, 2022.
12. González A, López B, Querejeta R & Díez J (2002). Regulation of myocardial fibrillar collagen by angiotensin II. A role in hypertensive heart disease? J Mol Cell Cardiol 34, 1585–1593.
13. González A, Ravassa S, Loperena I, López B, Beaumont J, Querejeta R, Larman M, Díez J. Association of depressed cardiac gp130-mediated antiapoptotic pathways with stimulated cardiomyocyte apoptosis in hypertensive patients with heart failure. J Hypertens. 2007; 25:2148–2157. doi: 10.1097/HJH.0b013e32828626e2.
14. González GE, Rhaleb N-E, D'Ambrosio MA, Nakagawa P, Liao T-D, Peterson EL, Leung P, Dai X, Janic B, Liu Y-H, Yang X-P & Carretero OA (2016). Cardiac-deleterious role of galectin-3 in chronic angiotensin II-induced hypertension. Am J Physiol Hear Circ Physiol 311, H1287–H1296.
15. González A, Schelbert EB, Díez J, Butler J. Myocardial interstitial fibrosis in heart failure: biological and translational perspectives. J Am Coll Cardiol. 2018; 71:1696–1706. doi: 10.1016/j.jacc.2018.02.021.
16. Knöll R, Iaccarino G, Tarone G, Hilfiker-Kleiner D, Bauersachs J, Leite-Moreira AF, Sugden PH, Balligand JL; European Society of Cardiology. Towards a re-definition of 'cardiac hypertrophy' through a rational characterization of left ventricular phenotypes: a position paper of the Working Group 'Myocardial Function' of the ESC. Eur J Heart Fail. 2011; 13:811–819. doi: 10.1093/eurjhf/hfr071.
17. Kvakan H, Luft FC, Muller DN. Role of the immune system in hypertensive target organ damage. Trends Cardiovasc Med. 2009; 19:242–246. doi: 10.1016/j.tcm.2010.02.004.
18. Kyuma M, Nakata T, Hashimoto A & Nagao K (2004). Incremental prognostic implications of brain natriuretic peptide, cardiac sympathetic nerve innervation, and noncardiac disorders in patients with heart failure. J Nucl Med 45, 155–164.
19. Leask A & Abraham DJ (2004). TGF-β signaling and the fibrotic response. FASEB J 18, 816–827.
20. Levick SP, Murray DB, Janicki JS, Brower GL. Sympathetic nervous system modulation of inflammation and remodeling in the hypertensive heart. Hypertension. 2010; 55:270–276. doi: 10.1161/HYPERTENSIONAHA.109.142042.
21. McCormick RJ & Thomas DP (1998). Collagen crosslinking in the heart: relationship to development and function. Basic Appl Myol8, 143–150.
22. Ogata T, Miyauchi T, Sakai S, Takanashi M, Irukayama-Tomobe Y, Yamaguchi I. Myocardial fibrosis and diastolic dysfunction in deoxycorticosterone acetate-salt hypertensive rats is ameliorated by the peroxisome proliferator-activated receptor-alpha activator fenofibrate, partly by suppressing inflammatory responses associated with the nuclear factor-kappa-B pathway. J Am Coll Cardiol. 2004; 43:1481–1488. doi: 10.1016/j.jacc.2003.11.043.
23. Ravassa S, González A, López B, Beaumont J, Querejeta R, Larman M, Díez J. Upregulation of myocardial Annexin A5 in hypertensive heart disease: association with systolic dysfunction. Eur Heart J. 2007; 28:2785–2791. doi: 10.1093/eurheartj/ehm370.
24. Ruwhof C & Laarse A Van Der (2000). Mechanical stress-induced cardiac hypertrophy: mechanisms and signal transduction pathways. Cardiovasc Res47, 23–37.

25. Santulli G & Iaccarino G (2016). Adrenergic signaling in heart failure and cardiovascular aging. Maturitas93, 65–72.
26. Sun Y, Liu G, Song T, Liu F, Kang W, Zhang Y, Ge Z. Upregulation of GRP78 and caspase-12 in diastolic failing heart. Acta Biochim Pol. 2008; 55:511–516.
27. Swynghedauw B. Molecular mechanisms of myocardial remodeling. Physiol Rev. 1999; 79:215–262. DOI: 10.1152/physrev.1999.79.1.215.
28. Tomek J, Bub G. Hypertension-induced remodeling: on the interactions of cardiac risk factors. J Physiol. 2017;595(12):4027-4036. doi:10.1113/JP273043
29. Yoshida K, Kim-Mitsuyama S, Wake R, Izumiya Y, Izumi Y, Yukimura T, Ueda M, Yoshiyama M, Iwao H. Excess aldosterone under normal salt diet induces cardiac hypertrophy and infiltration via oxidative stress. Hypertens Res. 2005; 28:447–455. doi: 10.1291/hypres.28.447.
30. González A, Ravassa S, López B, Moreno MU, Beaumont J, San José G, Querejeta R, Bayés-Genís A, Díez J. Myocardial Remodeling in Hypertension. Hypertension. 2018 Sep;72(3):549-558.
31. Renna NF, de Las Heras N, Miatello RM. Pathophysiology of vascular remodeling in hypertension. Int J Hypertens. 2013;2013:808353. doi: 10.1155/2013/808353. Epub 2013 Jul 22. PMID: 23970958; PMCID: PMC3736482.
32. James PA, Oparil S, Carter BL, *et al.*: 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8).JAMA. 2014; 311(5): 507–20.
33. Kostis JB, Packer M, Black HR, *et al.*: Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs.Enalapril (OCTAVE) trial. Am J Hypertens. 2004; 17(2):103–11.
34. Oparil S, Schmieder RE: New approaches in the treatment of hypertension. Circ Res. 2015; 116(6): 1074–95.
35. Macdonald PS: Combined angiotensin receptor/neprilysin inhibitors: a review of the new paradigm in the management of chronic heart failure. Clin Ther. 2015; 37(10): 2199–205.
36. Hubers SA, Brown NJ: Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition.Circulation. 2016; 133(11): 1115–24
37. Riddell E, Vader JM. Potential expanded indications for neprilysin inhibitors. Curr Heart Fail Rep. 2017; 14(2):134-145.
38. Renato De Vecchis, Silvia Soreca, Carmelina Ariano, Anti-Hypertensive Effect of Sacubitril/Valsartan: A MetaAnalysis of Randomized Controlled Trials, Cardiol Res. 2019; 10 (1), 24-33.
39. Andersen MB, Simonsen U, Wehland M, Pietsch J, Grimm D. LCZ696 (Valsartan/Sacubitril) - A possible new treatment for hypertension and heart failure. Basic Clin Pharmacol Toxicol. 2016; 118(1):14-22.
40. Guet al., 2010; Ruilope et al., 2010; McMurray et al., 2013;Vardeny et al., 2014.
41. Lauren B. Arendse, A. H. Jan Danser, Marko Poglitsch, Rhian M. Touyz, John C. Burnett, Jr., Catherine Llorens-Cortes, Mario R. Ehlers, and Edward D. Sturrock, Novel Therapeutic Approaches Targeting the Renin-Angiotensin System and Associated Peptides in Hypertension and Heart Failure, Pharmacol Rev, 2019; 71:539–570
42. Pandey KN (2005) Biology of natriuretic peptides and their receptors. Peptides 26:901–932.
43. Soualmia H, Barthelemy C, Masson F, Maistre G, Eurin J, and Carayon A (1997) Angiotensin II-induced phosphoinositide production and atrial natriuretic peptide release in rat atrial tissue. J Cardiovasc Pharmacol 29:605–611.
44. Abassi Z, Karram T, Ellaham S, Winaver J, and Hoffman A (2004) Implications of the natriuretic peptide system in the pathogenesis of heart failure: diagnostic and therapeutic importance. Pharmacol Ther 102:223–241.
45. Villar IC, Panayiotou CM, Sheraz A, Madhani M, Scotland RS, Nobles M, KempHarper B, Ahluwalia A, and Hobbs AJ (2007) Definitive role for natriuretic peptide receptor-C in mediating the vasorelaxant activity of C-type natriuretic peptide and endothelium-derived hyperpolarising factor. Cardiovasc Res 74:515–525.

46. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, et al. (2011) Effect ofnesiritide in patients with acute decompensated heart failure [published correctionappears in N Engl J Med (2011) 365:773]. N Engl J Med 365:32–43.
47. Campbell DJ and Habener JF (1986) Angiotensinogen gene is expressed and differentially regulated in multiple tissues of the rat. J Clin Invest 78:31–39.
48. Cleland JG and Swedberg K; The International Ecadotril Multi-centre Dose-ranging Study Investigators (1998) Lack of efficacy of neutral endopeptidase inhibitor ecadotril in heart failure. Lancet 351:1657–58.
49. Roksnoer LC, van Veghel R, de Vries R, Garrelds IM, Bhaggoe UM, Friesema EC, Leijten FP, Poglitsch M, Domenig O, Clahsen-van Groningen MC, et al. (2015) OptimumAT1 receptor-neprilysin inhibition has superior cardioprotective effects comparedwith AT1 receptor blockade alone in hypertensive rats. Kidney Int 88:109–120.
50. HFrEF (McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al.; PARADIGM-HF Investigators and Committees (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371:993–1004.
51. Mogensen UM, Gong J, Jhund PS, Shen L, Kober L, Desai AS, Lefkowitz MP, Packer M, Rouleau JL, Solomon SD, et al. (2018) Effect of sacubitril/valsartan on recurrentevents in the Prospective.
52. Jarcho J (2019) PIONEERing the in-hospital initiation of sacubitril-valsartan. N Engl J Med 380:590–91.
53. Kompa AR, Lu J, Weller TJ, Kelly DJ, Krum H, von Lueder TG, and Wang BH (2018) Angiotensin receptor neprilysin inhibition provides superior cardioprotection compared to angiotensin converting enzyme inhibition after experimental myocardial infarction. Int J Cardiol 258:192–198.
54. Kougias P, Weakley SM, Yao Q, Lin PH, Chen C. Arterial baroreceptors in the management of systemic hypertension. Med Sci Monit. 2010; 16(1): RA1-RA8.
55. Head GA. Baroreflexes and cardiovascular regulation in hypertension. J Cardiovasc Pharmacol. 1995; 26 Suppl 2: S7-16. PMID: 8642810.

ДАВИД ГОЛОШВИЛИ [1], ЗУРАБ ЗААЛИШВИЛИ [2], ДИАНА КЕРАТИШВИЛИ [2], МАЙЯ ОКУДЖАВА [1], НИКОЛОЗ ГОНГАДЗЕ [1], МАНАНА ГОНГАДЗЕ [1]

ПАТОФИЗИОЛОГИЧЕСКИЕ ПРИНЦИПЫ, ЛЕЖАЩИЕ В ОСНОВЕ ВЛИЯНИЯ САКУБИТРИЛ-ВАЛСАРТАНА НА РЕМОДЕЛИРОВАНИЕ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ, ВЫЗВАННОЕ ГИПЕРТОНИЕЙ

[1]Тбилисский Государственный Медицинский Университет, факультет медицинской фармакологии;
[2] Американская программа дипломированного врача

РЕЗЮМЕ

Ремоделирование миокарда - это процесс, выполняемый кардиомиоцитами, другими клетками в миокарде (эндотелиальные клетки, фибробласты, перициты и иммунные клетки). В результате композиция, объем и физиология кардиомиоцитов, интерстициальной матрицы и коронарных сосудов подвергаются взаимосвязанным изменениям. Эти изменения вредно влияют на клинические результаты пациентов с гипертонической болезнью сердца (HHD) из-за риска фибрилляции и повышенной жесткости желудочков, приводящих к систолической или диастолической дисфункции. Следовательно, уменьшить сердечно-сосудистые ремоделирование является основной целью для общей клинической помощи этим пациентам.

Несколько препаратов, таких как ангиотензиновые ингибиторы фермента, бета-блокаторы и антагонисты альдостерона широко используется для уменьшения ремоделирования миокарда. Комбинация сакубитрила, ингибитора неприлизина и вальсартана, антагониста рецептора ангиотензина, который имеет положительные клинические результаты у пациентов с сердечной

недостаточностью с уменьшенной фракцией выброса, недавно привлекло общественное и научное внимание для пациентов с сердечной недостаточностью с сохраненной фракцией выброса. Способствуя накоплению натрийуретических пептидов, которые обладают натрийуретическими и сосудистыми релаксантными свойствами и снижением влияния системы ренин-ангиотензин-альдостерона, комбинация этих двух препаратов имеет кардиопротективные и антигипертензивные эффекты и уменьшает кардиоподобный фиброз. Следует отметить, что Sacubitril/Valsartan показал лучшее влияние на ремоделирование сердца и фракцию обращения по сравнению с периндоприлом ингибитора ACE у крыс. Тем не менее, это только предварительные данные, и более широкие исследования должны проводиться как в экспериментальных, так и в клинических условиях, чтобы полностью выявить механизмы действия препарата при лечении различных типов артериальной гипертонии.

DAVID GOLOSHVILI [1], ZURAB ZAALISHVILI [2], DIANA KERATISHVILI [2],
MAIA OKUJAVA [1], NIKOLOZ GONGADZE [1], MANANA GHONGHADZE [1]

PATHOPHYSIOLOGICAL PRINCIPLES UNDERLYING THE EFFECT OF SACUBITRIL-VALSARTAN ON HYPERTENSION-INDUCED CARDIOVASCULAR REMODELING

[1]Tbilisi State Medical University, Department of Medical Pharmacology; [2]American MD Program.

SUMMARY

Myocardial remodeling is a process executed by cardiomyocytes, other cells within the myocardium (i.e, endothelial cells, fibroblasts, pericytes, and immune cells), and cells recruited from the circulation (e.g, immune and inflammatory cells) in response to mechanical and non-mechanical stimuli. As a result, the composition, volume, and physiology of cardiomyocytes, the interstitial matrix, and the coronary vessels undergo interrelated changes. These changes detrimentally affect the clinical outcomes of patients with hypertensive heart disease (HHD), due to the risk of fibrillation and increased ventricular stiffness leading to systolic or diastolic dysfunction. Therefore, to reduce cardiovascular remodeling is the main aim for the overall clinical care of these patients.

Several drugs, such as angiotensin-converting enzyme inhibitors, beta blockers, and aldosterone antagonists, have been consistently shown to decrease remodeling in animal models and in clinical trials, and are currently widely used to decrease myocardial remodeling. A combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor antagonist, which has positive clinical outcomes in patients with heart failure with reduced ejection fraction, has recently gained public and scientific attention for patients with heart failure with preserved ejection fraction. By promoting the accumulation of natriuretic peptides, which have natriuretic and vascular smooth muscle relaxant properties and by reducing the effects of the renin-angiotensin-aldosterone system, the combination of these two drugs has cardioprotective and antihypertensive effects and reduces cardiovascular fibrosis. It is noteworthy, that sacubitril/valsartan showed a better effect on cardiac remodeling and reversal fraction compared with ACE inhibitor perindopril in rats. However, these are only preliminary data and more extensive studies should be conducted in both experimental and clinical settings in order to fully reveal the mechanisms of action of the drug in the management of various types of arterial hypertension.

Keywords: sacubitril/valsartan, arterial hypertension, cardiac remodeling