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Original Article

Effect of Sacubitril/Valsartan on Hemodynamic Parameters, Biomarkers of Inflammation and Cardiac Remodeling in Rats with DOCA-Salt-Induced Hypertension

Goloshvili Davit[1]*, Okujava Maia[1], Liluashvili Konstantine[2], Mirziashvili Makrine[1], Ghonghadze Manana[1], Pachkoria Ketevan[1], Gongadze Nikoloz[1]

[1]*Tbilisi State Medical University, Department of Medical Pharmacology, Tbilisi, Georgia*
[2]*Tbilisi State Medical University, Department of General Internal Medicine, Tbilisi, Georgia*

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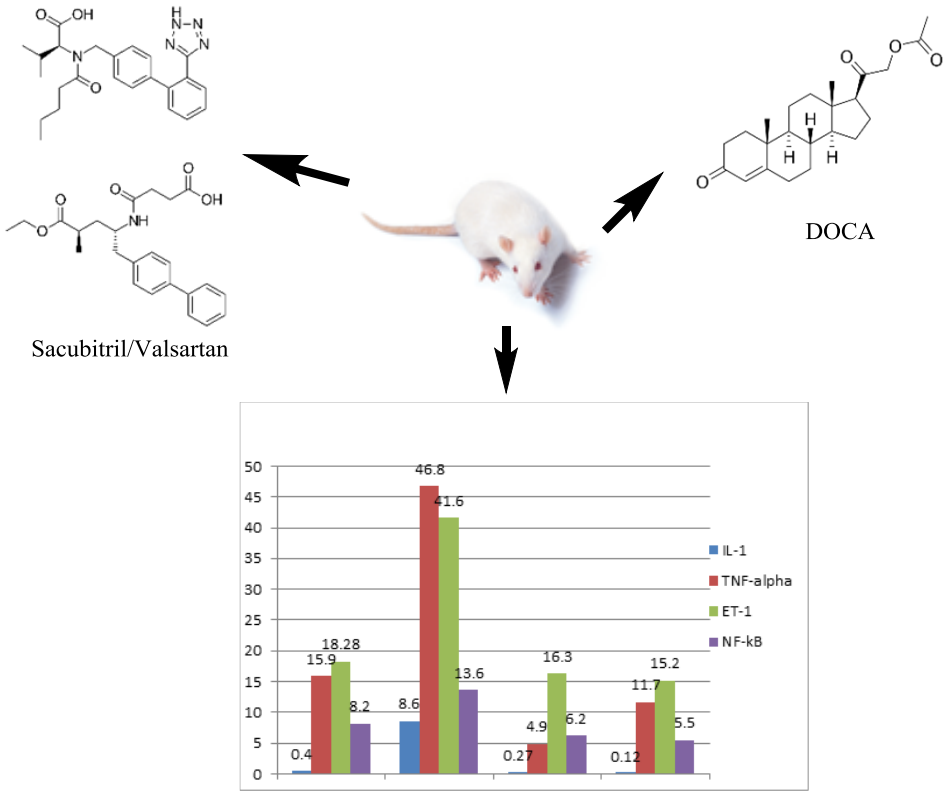
ABSTRACT

The aim of the study was to assess the influence of Sacubitril/Valsartan (S/V) on hemodynamic indices and heart remodeling events in rats with DOCA-salt arterial hypertension (AH). Experiments were performed on Wistar rats. Animals were randomly divided into the four groups: (I) Control (C) group, (II) DOCA-salt group, (III) S/V + DOCA -salt as drinking water, and (IV) S/V after development of DOCA-salt hypertension. Heart beat (HB)/min and systolic and diastolic blood pressure (SBP, DBP, mmHg) were obtained by tail-cuff method in the morning hours. The level of ET-1, IL-1, TNF-alpha, and NF-kB transcription factor were measured in the blood plasma of rats by ELISA kits method. Morphometric and histomorphological changes in heart and aorta were analyzed in the tissue sections using electronical microscope. In the second group of animals, the mean values of SBP – 153,6 ± 5,4 mmHg, DBP – 67,9 ± 2,8 mmHg, and HB – 394 ± 12/min were significantly increased in comparison with C group of animals (123,0 ± 5,2 mmHg ($p<0,001$), 55,6 ± 3,0 mmHg ($p<0,05$), and 361 ± 24/min ($p<0,001$), respectively). Such alterations in cardiovascular parameters correlated with marked increase in DOCA-salt group blood plasma levels of ET-1, IL-1, TNF-alpha, and NF-kB vs. C animals. S/V treatment significantly reduced SBP, DBP, and HB (-30,2 ± 4 mmHg, ($p<0,001$), -11,4 ± 2,2 mmHg ($p<0,05$), and -33 ± 12/min, $p<0,002$, respectively) in hypertensive rats (HR) associated with marked decrease in blood levels of ET-1 (56,9%, $p<0,01$), IL-1 (67,3%, $p<0,001$), TNF-alpha (75,1%, $p<0,001$), and NF-kB (59,2%, $p<0,001$), with significant improvement of morphological changes of the heart in this group of animals. It is suggested that S/V in hypertensive state exerts a positive effect on hemodynamic parameters, providing reverse action on heart remodeling and can be considered as a valuable drug for the AH treatment and prevention of structural changes in target organs.

* Corresponding author: Goloshvili Davit
✉ E-mail: d.goloshvili@tsmu.edu

GRAPHICAL ABSTRACT



Introduction

Arterial hypertension (AH) is the most widespread cardiovascular disease, resistant forms of which lead to various complications including stroke, myocardial infarction, and kidney damage sometimes leading to fatal outcome [1, 2]. Despite certain achievements in the AH treatment with already accepted and well-studied drugs including angiotensin converting enzyme inhibitors, angiotensin-II receptor blockers, calcium channels blocking agents, etc. an adequate control of arterial blood pressure, especially in resistant forms of AH, remains a great problem [3, 4]. The analysis of fatal outcomes from cardiovascular causes associated with AH revealed the death prevalence in patients with non-proper control of resistant hypertension [5].

The attention of many investigators is directed to relatively newer drugs that along with main indications, according to a number of evidence, may provide an effective control of arterial pressure. Sacubitril/Valsartan (S/V) is one of such drugs that has been introduced into the medical practice for the treatment of heart failure and has a dual effect due to the content of angiotensin II receptor blocker- valsartan and neprilysin inhibitor - sacubitril [6, 7]. According to some findings, S/V revealed more efficacy than angiotensin- II receptor blockers to control hypertension in patients with heart failure [8, 9]. However, S/V effectiveness and safety as an antihypertensive drug has not yet been fully evaluated [10-12]. Several mechanisms explain the positive combination of S/V in AH including its resistant forms [13, 14].

Neprilysin (neutral endopeptidase) inhibition increases in plasma antidiuretic peptides level with their consequent binding with particulate guanylate cyclase/cyclic guanylate monophosphate linked receptors resulting in vasodilation, diuresis, decreases in oxidative stress [15], reduction in the sympathetic nervous system activity, and diminution in release of vasoconstrictive agents endothelin and vasopressin [16, 17].

It has been confirmed that in addition to effective blood pressure control in hypertension, S/V can provide cardioprotective efficacy by improving heart structure [18]. The lack of data on the signaling mechanisms involved in the antihypertensive and cardiovascular effects of

S/V is still the main disturbing factor to the repeated and reproducible demonstration of the S/V effectiveness against hypertension due to possible anti-inflammatory and antioxidant effects, as well as the effect on heart remodeling by improving histomorphological changes accompanying the hypertension development. In addition, the preventive effect of S/V on the formation and progression of various forms of hypertension and its modulating effect on the relationship between changes in hemodynamic parameters and the production of various cytokines and transcription factors contributing to the inflammation were not fully evaluated. Hence, novelty of this investigation is associated with findings possible additional pathways involving in the beneficial effect of S/V which may change the heart remodeling and helps to suspend decrease of arterial pressure during the AH monotherapy with this drug.

Materials and Methods

Experiments were carried out on male Wistar rats weighing 200, 0-250, and 0 g. In compliance with the rules that coincide to recognized standards developed by the Bioethical Commission of Tbilisi State Medical University (N51 meeting of the ethics committee, TSMU). The animals were placed in a vivarium at a temperature of 23 ± 1° C, 50 ± 5% humidity, and 12 hours of light -12 hours of darkness, in terms of free access to food and water. Animals were randomly divided into the following groups: (I) control group (C) with 1% NaCl and 0.2% KCl as drinking water during 4 weeks (n=10), (II) DOCA-salt hypertensive group (25 mg/kg DOCA + 1% NaCl and 0.2% KCl as drinking water) (n = 10), (III) sacubitril/valsartan oral dose 30 mg/day + DOCA + 1% NaCl + 0.2% KCl as drinking water for 4 weeks (n = 10), and (IV) sacubitril/valsartan oral dose of 30 mg/day after 28 days administration of DOCA and salt solutions (n = 10) [19, 20].

To monitor the dynamics of the development of DOCA-salt hypertension, systolic, diastolic and mean blood pressure have been measured per week in non-anesthetized rats by tail-cuff sphygmomanometric method in a special chamber. For this purpose, the animals were placed in the chamber for adaptation for 2 h, after which the pressure indicators were determined 5 times, at intervals of 5-10 min, and average values were calculated (Figure 1) [21].

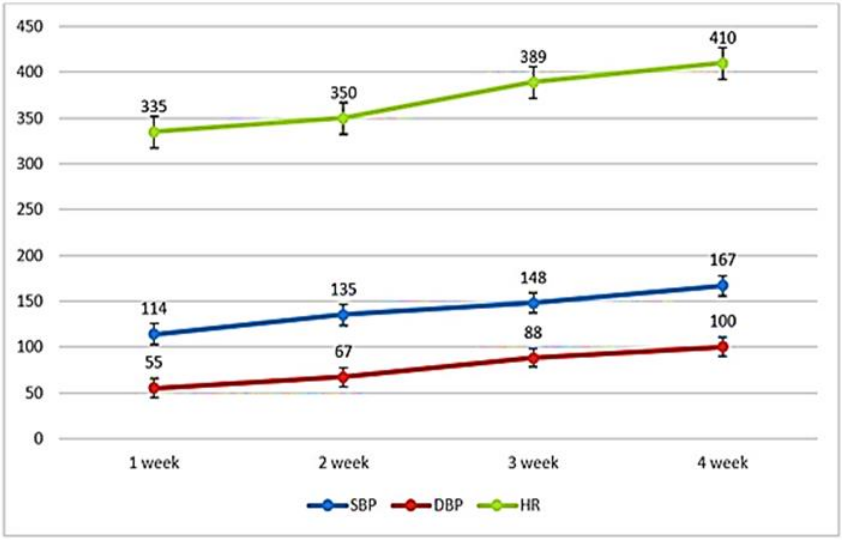


Figure 1: Change of hemodynamic parametrs in hypertensive rats (II experimental group) SBP: Systilic blodd pressure, DBP: Diastolic blood pressure, and HR: Heart rate

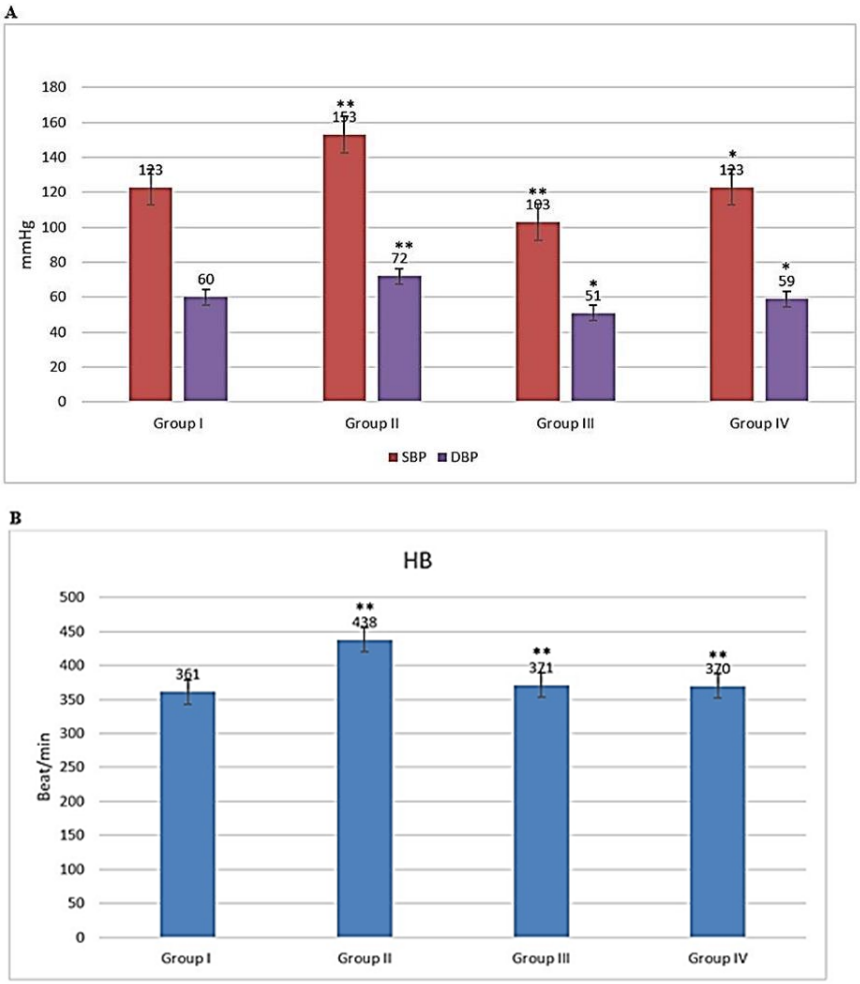


Figure 2: Hemodynamic parameters in different groups of rats. A- arterial blood pressure, and B- Heart beats. In the second group of rats with DOCA-salt arterial hypertension, the mean values of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart beats (HB) were significantly higher compared with I-C group of animals, respectively. In the third experimental group, S/V revealed preventive action regarding hemodynamic changes during the AH development by decreasing values of SBP and HB. The combination of sacubitril/valsartan also demonstrated a consistent hypotensive effect. Compared to the second experiment group, the hemodynamic parameters changed significantly in the animals of the fourth group-SBP, DBP, I-control (C) group; II-DOCA-salt group (Doca+1% NaCl+0.2% KCl as drinking water); III-S/V+DOCA+1%NaCl+0.2%KCL in drinking water, IV-S/V after development of DOCA-salt hypertension. SBP: Systolic blood pressure, mmHg, DBP: Diastolic blood pressure, mmHg; HR: Heart rate, beat/min. *p<0.05, and **p<0.001

At the end of the experiment, rats were anesthetized (with pentobarbital 65 mg/kg intraperitoneally) to take samples of organs and blood from a catheter in the carotid artery.

After centrifugation for 15 minutes the samples were frozen at -60 ^{o}C, and then the concentrations of Interleukin-1 (IL-1), Tumor Necrosis Factor-alpha (TNF-alpha), Endothelin-1 (ET-1), Nuclear Factor Kappa B (NFkB) were determined using the ELISA kit (CUSABIO, WUHAN HUAMEI BIOTECH Co., LTD) according manufacturer instructions [22, 23].

A study of morphometric and histomorphological changes in organ tissue (heart, aorta) has been performed in DOCA- salt hypertensive rats, DOCA + sacubitril/valsartan treated groups (III and IV) and control group of rats. Tissue sections stained with hematoxylin/eosin and masson trichrome were examined using an electronical microscope. To compare the data of two groups, Students-test was used and multiple indicators from several study groups were by the ANOVA method.

Results and Discussion

In the second group of rats with DOCA-salt arterial hypertension, the mean values of systolic blood pressure (SBP) – 153,6 ± 5,4 mmHg, diastolic blood pressure (DBP) – 67,9 ± 2,8 mmHg, and heart beats (HB) – 394 ± 12/min were significantly higher in comparison with I-C group of animals (123,0 ± 5,2 mmHg, P<0.001), (55,6 ± 3,0 mmHg, p<0.05), and (361 ± 24/min, p<0.001), respectively.

In the third experimental group, S/V revealed preventive action regarding hemodynamic changes during the AH development by decreasing values of SBP (-50 ± 11,8 mmHg, p<0,001), DBP (-16 ± 6,0 mmHg, p<0,001), and HB (- 67 ± 15,6 beat/min, p<0,001). Likewise, the combination of sacubitril/valsartan demonstrated a consistent hypotensive effect. Compared to the second experimental group, the hemodynamic parameters changed significantly in the animals of the fourth group-SBP (-20 ± 9 mmHg, p<0,001), DBP (-8 ± 3 mmHg, p<0.05), and HB (-68 ± 25 beat/min, p<0,001) (Figure 2).

Changes in hemodynamic values in hypertensive rats were correlated with significant increase in blood plasma levels and achieved the maximum value of ET-1 (41,6 ± 17,4 pg/mL, p<0,001), IL-1 (8,6 ± 1,7 pg/mL, p<0,001), TNF-alpha (46,8 ± 17,9 pg/mL, p<0,001), and NFkB (13,6 ± 3,8 pg/mL, p<0,05) vs. C animals. In the third experimental group, S/V markedly reduced plasma levels of inflammatory markers compared with the second group of animals: ET-1 (-16,3 ± 2,7 pg/mL, p<0,001), IL-1 (-8,2 ± 0,17 pg/mL, p<0,001), TNF-alpha (-42 ± 4,6 pg/mL, p<0,001), and NFkB (-7,4 ± 1,9 pg/mL, p<0,05). Levels of inflammatory biomarkers and vasoconstrictor agents were also significantly reduced in the fourth experimental group compared to control group of animals-ET-1-(-26,5 ± 6,5 pg/mL, p<0.001), IL-1- (-8,7 ± 1,4 pg/mL, p<0,001), TNF-alpha- (-35,1 ± 11,4 pg/mL, p<0,001), and NFkB-(-8 ± 3,3 pg/mL, p<0,001) (Figure 3), accompanied with significant reduction of morphometric and morphological alterations in the heart of rats. Comparative analysis of the cardiomyocytes of the anterior wall of the left ventricle of the heart muscle revealed the following points.

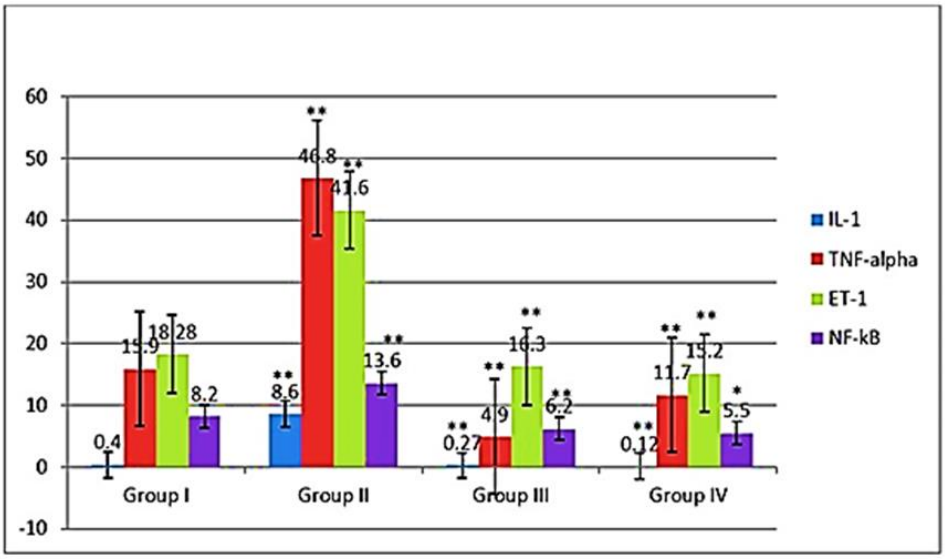


Figure 3: Inflamatori biomarkers. Changes in hemodynamic values in hypertensive rats were correlated with significant increase in blood plasma levels of ET-1, IL-1, TNF-α, and NFkB vs. C animals. In the third experimental grou, S/V markedly reduced plasma levels of inflammatory markers compared with the second group of animals: ET-1, IL-1, TNF-α, and NFkB. levels of inflammatory biomarkers and vasoconstricor agents were also significantly reduced in the fourth experimental group compared to control group of animals, accompanied with a significant reduction of morphometric and morphological alterations in the heart of rats (in group II and III). (I) Control (C) group, (II) Doca-salt group (DOCA+ 1% NaCl+ 0.2% KCl as drinking water), (III) S/V+Doca+1% NaCl+ 0.2% KCl in drinking water, (IV) S/V after development of DOCA-salt hypertension IL-1: Interleukin-1, TNF-α: Tumor necrosis factor alpha, ET-1: Endothelin-1, NF-kB: Nuclear factor pappa B, pg/ml. *p<0.05, and **p<0.001

The samples of the anterior ventricular wall from rats with arterial hypertension and the control group were compared. The microscopy of the samples revealed cardiomyocyte hypertrophy and fibrosis of the perivascular space; acute dyscirculation with filling of the venous and capillary network, dilation of large parts of arteries, and emptying of the lumen, endothelial damage, stasis of shaped elements, and impregnation of the intima of the subendothelial layer with lipid inclusions.

Comparison of the third experimental group of concomitant administration of sacubitril/valsartan and DOCA + saline in drinking water with control group and the second experimental group (hypertensive rats) revealed preservation of predominantly transverse striations against the focal loss of the architectonics of the fibrous structure of cardiomyocytes; myocardial hypertrophy; in some cases, fullness of the venous and capillary network, stasis and hemorrhages, and moderate fibrosis of the arterial wall.

The microscopy of cardiomyocytes from the rats after treatment with sacubitril/valsartan revealed preservation of transverse striations with focal loss of the architectonics, acute dyscirculation in some loci, with fullness of the venous, capillary network, and haemorrhages, as well as stasis of blood cells. Microscopy of samples of the anterior wall of the left ventricle revealed a balanced histostructural state of the myocardium in the prevention group compared with hypertensive and treated rats (Figure 4).

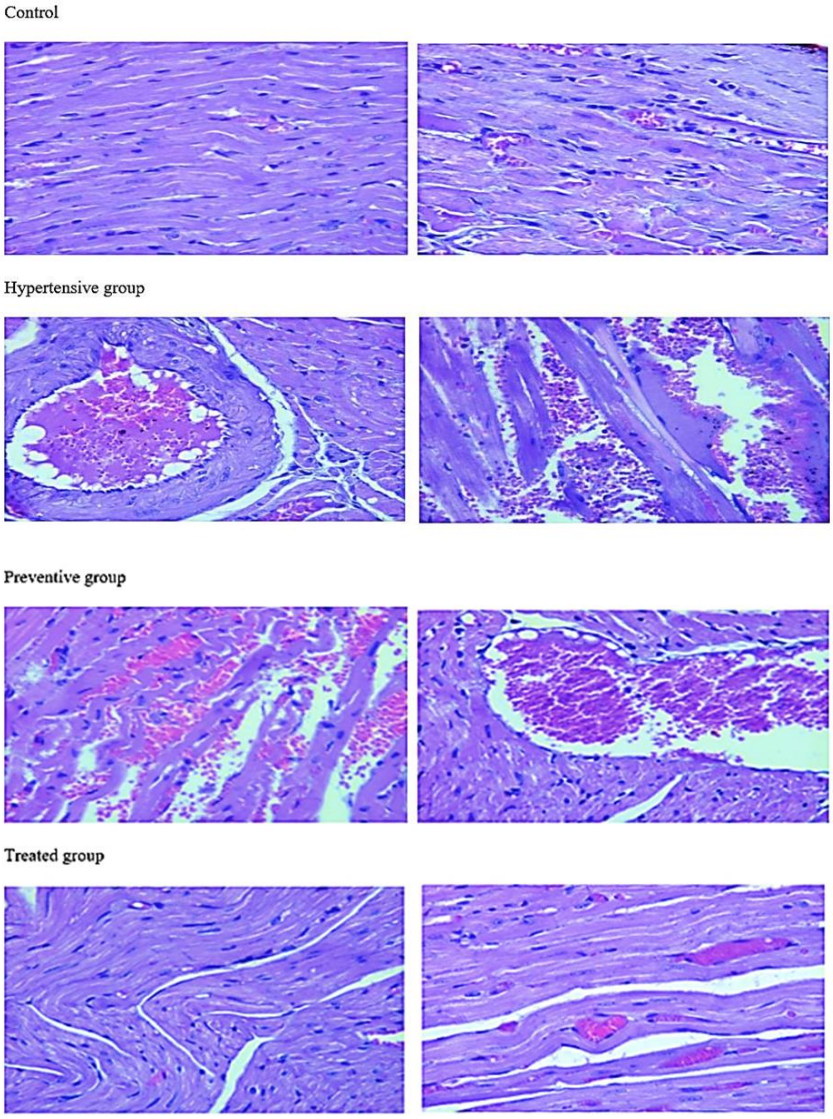


Figure 4: Histomorphological changes in different group of animals. Microscopy of samples of the anterior wal of the left ventricle revealed a balanced histostructural state of the myocardium in the prevention group compared with hypertensive and treated rats

Arterial hypertension is a multifactorial disease, the resistant forms of which are particularly difficult to treat effectively [24, 25].

In our experiments, we used Sacubitril/Valsartan (S/V) combination in DOCA-salt induced hypertension which resulted in significant reduction of elevated systolic and diastolic blood pressure and the frequency of cardiac rhythm. Our data regarding hemodynamic alterations during treatment of arterial hypertension (AH) with S/V are comparable with results of other studies showing the same influence of S/V [26]. A number of evidence suggests that the AH progression is accompanied by remodeling of organs being targets of damage during formation of AH, involving in this process endothelium dysfunction, inflammatory changes, developing of free radicals, and morphometric-histomorphological alterations [27, 28]. Our results showed marked increase in blood plasma levels of vasoconstrictor- ET-1, inflammatory cytokines IL-1, TNF-alpha, and transcription factor NF-kB contributing to remodeling process that significantly reduced by S/V treatment. These findings are in agreement with results obtained by other authors that confirmed S/V efficacy in events facilitating to remodeling process in AH [29, 30]. Our experiments on DOCA-salt hypertensive rats revealed changes in cardiomyocytes structure with myocardial hypertrophy associated in some cases with stasis and hemorrhages as well as the moderate fibrosis of the arterial wall. Such type of histopathomorphological changes associated with cardiac remodeling has been further described by other researchers [31]. The medication under the study showed a better preventive result in group of rats with concomitant administration of S/V and DOCA-saline solution. In these animals, the preventive treatment with S/V in a high degree precluded the AH development and associated changes in hemodynamic parameters, endothelium dysfunction, inflammatory markers plasma levels, and cardiac remodeling. Our findings are consistent with results obtained by other authors demonstrating the same positive hemodynamic changes regarding cardiac remodeling influenced by S/V [32-38], which further supports the assumption a beneficial effect of S/V in AH [39, 40]. Besides, S/V combination has not been approved for using in AH the obtained experimental data allow us to propose this drug for further study of effectiveness and possibility of its use in resistant forms of arterial hypertension

Conclusion

Based on the results, we can suggest that dual acting drug Sacubitril/Valsartan (S/V) reveals antihypertensive and cardioprotective properties in DOCA-salt induced experimental arterial hypertension, providing significant reduction in systolic and diastolic arterial pressure and cardiac rhythm potentially resulted from diminution of sympathetic nervous system activity. Antihypertensive action of S/V was accompanied with beneficial effect on remodeling of the heart by reducing its hypertrophic and fibrotic changes during development of arterial hypertension, preservation of mitochondrial and cardiomyocyte function and improving of endothelial dysfunction at the expense of reduction in vasoconstrictive agent- endothelin-1, proinflammatory cytokines IL-1and TNF-alpha, as well as transcription nuclear factor NF-kB production that facilitate to oxidative stress condition. Such findings may contribute to the additional experimental and clinical investigation to clarify other signaling mechanisms involved in the antihypertensive and cardioprotective action of S/V for the successful expansion of its therapeutic indication regarding effective control of arterial hypertension including its resistance.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the article and agreed to be responsible for all the aspects of this work.

ORCID

Goloshvili Davit
https://orcid.org/0000-0002-9305-060X
Okujava Maia
https://orcid.org/0009-0005-4083-0812
Liuluashvili Konstantine
https://orcid.org/0009-0000-2067-3729
Mirziashvili Makrine
https://orcid.org/0009-0003-8783-8382
Ghonghadze Manana
https://orcid.org/0000-0002-6224-6458
Pachkoria Ketevan
https://orcid.org/0009-0000-3240-4972
Gongadze Nikoloz
https://orcid.org/0000-0002-4869-5599

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