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Cardioprotective effects of renal denervation in resistant hypertension: efficiency predictors

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Abstract

Objective. To assess the impact of renal sympathetic denervation (RSD) in patients with resistant hypertension (RH) on the structural and functional changes (SFC) of the heart, and to determine predictors of the effectiveness of the procedure. **Design and methods**. Sixty patients (54.6 ± 9.5 years) with RH were included in the analysis. They signed an informed consent for both research and RSD. All of them received full-dose antihypertensive therapy (AHT) (4.1 drugs), including at least one diuretic. BP and heart rate (HR) measurement and cardiac diastolic function (DF) assessment by echocardiography were performed at baseline and after 24 weeks in all subjects. RSD was completed by endovascular radiofrequency ablation of renal arteries. AHT remained unchanged. **Results.** There was a significant reduction of office BP, as well as a significant regression of myocardial mass in 36,7% patients at 24 weeks after the procedure. DF was initially impaired in 58.6%, and after the procedure it normalized in 31%, and the diastolic dysfunction decreased in 14% patients. Blood pressure, HR, ATH and left ventricular volume (LVV) were comparable in subgroups, and the dynamics of MM correlated only with the initial values of LV wall. **Conclusions.** Significant positive changes of DF and the decrease of LV MM were registered 24 weeks after RSD. The initial values of LV wall thickness were the only predictor of MM regression.

Key words: hypertension, renal denervation, heart, left ventricular hypertrophy, diastolic function, echocardiography

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Кардиопротективные возможности денервации почек при лечении резистентной гипертонии, поиск предикторов эффективности

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Резюме

Цель исследования — оценить влияние симпатической денервации почек (СДП) у пациентов с резистентной артериальной гипертензией (РАГ) на структурно-функциональные изменения (СФИ) сердца, определить предикторы эффективности процедуры. **Материалы и методы.** В анализ включено 60 пациентов (54,6 ± 9,5 года) с РАГ, подписавших информированное согласие для проведения исследований и лечения, получавших максимально переносимые дозы антигипертензивной терапии (4,1 препарата), включающей диуретик. Исследования, включая эхокардиографию с оценкой СФИ сердца, проведены исходно и через 24 недели. СДП проводилась путем эндоваскулярной радиочастотной аблации (РЧА) почечных артерий (ПА). Терапия в процессе наблюдения не менялась. **Результаты.** После проведения СДП отмечалось значимое снижение офисного артериального давления (АД), регрессия массы миокарда (ММ) левого желудочка (ЛЖ) ≥ 10 г наблюдалась у 36,7%. Диастолическая функция ЛЖ исходно была нарушена у 58,6%, после процедуры она нормализовалась у 31%, изменилась степень диастолической дисфункции (ДФ) у 14% пациентов. При соотносимых параметрах антропометрии, АД, частоты сердечных сокращений, терапии, конечного диастолического размера ЛЖ различия между группами и корреляции с динамикой ММ были определены для исходных размеров стенок ЛЖ. **Заключение.** Лечение с использованием СДП приводило к снижению ММ и положительным изменениям ДФ ЛЖ у части пациентов. Предикторами значимой регрессии ММ ЛЖ были исходные значения толщины стенок ЛЖ.

Ключевые слова: артериальная гипертензия, денервация почек, сердце, гипертрофия левого желудочка, диастолическая функция, эхокардиография

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Introduction

The scientific statement by the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research defines resistant hypertension (RAH) as "the sustained increase in BP above target levels in patients receiving 3 or more antihypertensive drugs (AHD) of different classes in optimal doses, including one diuretic" [1]. Despite the careful medical treatment strategy, target BP is achieved only in 25–40 % of patients [2–4]. RAH is distinguished in order to choose a rational diagnostic and treatment approach. The prognosis in patients with RAH was not assessed compared to patients with target BP achieved with a combination of at least three drugs, but sensibly, it should be worse due to the long-term deleterious effects of high BP and increased sympathetic activity, which plays a key role in RAH development [5–7]. These factors can lead to the early onset of target organ damage and, first of all, to the structural and functional changes (SFC) of the heart resulting in the development of left ventricular hypertrophy (LVH), myocardial fibrosis and chronic heart failure [8, 9]. LVH and diastolic dysfunction are directly related to the poorer prognosis: the development and progression of cardiovascular morbidity and mortality. Moreover, a number of studies showed that the regression of these changes can independently positively influence the outcomes [10–12].

The first clinical studies in humans have shown a decrease in sympathetic activity and an effective reduction in BP in patients with RAH after bilateral transcatheter radiofrequency ablation of the renal arteries by Symplicity system. The operations were named renal sympathetic denervation (RSD). As a result, antihypertensive effect was higher than the combination of pharmacological agents [13–15]. Single animal and human studies in a small number of participants showed positive effects on structural and functional myocardial changes, however, no definite answers about its connection to the dynamics of BP and heart rate (HR) were obtained [16, 17]. Undoubtedly, multicenter studies are required to confirm its organoprotective effects in target organs, and finding predictors of RSD is a relevant issue.

Therefore, the aim of our study was to evaluate the impact of RSD in patients with RAH on the structural and functional myocardial changes with referral to the regression of left ventricular hypertrophy depending on the dynamics of BP and heart rate, and search for possible predictors of cardioprotective efficacy of the procedure.

Design and methods

The study was approved by the Ethics Committee and approved at the meeting of the Academic Council of the Research Institute of Cardiology of the Siberian Branch of the Russian Academy of Sciences, Tomsk (Institute of Cardiology SB RAS, Tomsk). All included patients signed informed consent to participate in a prospective single-center study (number NCT01499810, www.ClinicalTrials.gov).

Inclusion criteria were: age from 18 to 80 years, a stable elevation of the office BP more than 160/100 mm Hg with long-term (3 months or more) therapy by a combination of at least three antihypertensive drugs in the maximal tolerated doses and mandatory use of a diuretic. Patients underwent a two-stage clinical examination: in the outpatient setting and at the specialized (department of arterial hypertension) clinics at the Institute of Cardiology SB RAS in Tomsk. The following patients were excluded: patients with low estimated glomerular filtration rate (MDRD < 30 ml/min/1.73 m^2); with symptomatic hypertension; with the mean daily BP (based on the results of daily BP monitoring) less than 135/85 mm Hg; with acute and chronic kidney diseases, the pathology of blood system, gastrointestinal tract, nervous and endocrine systems (except for type 2 diabetes mellitus), and other events associated with the development of the failure of any system; cancer relapses less than 5 years ago; pregnancy and women who were planning pregnancy during the follow-up period, as well as patients who did not sign informed consent. The interim analysis included 60 patients (33 men and 27 women) who were followed up for 24 weeks after RSD and who underwent the assessment of BP parameters, ultrasound evaluation of the myocardial structure and function. Responders were determined by the decrease of left ventricular myocardial mass by more than 10 g.

Transthoracic echocardiography was performed by a qualified technician with the use of the highest expert class systems — iE33 (Philips,

USA). Quantitative evaluation of the myocardial structure and function was performed according to the recommendations of the American and the European Society of Echocardiography [18]. LV ejection fraction and volumes were measured using a biplan disc method. LV myocardial mass was calculated according to the formula by R. B. Devereux [19], the relative thickness of the LV wall — by the formula: (the thickness of the interventricular septum (IVS) + thickness of the posterior wall (PW)) / end-diastolic dimension (EDD). LVH was diagnosed when LV MM index was more than 95 g/m^2 for women and more than 115 g/m^2 for men.

LV diastolic function was assessed based on the Doppler transmitral flow, blood flow in the pulmonary veins and tissue Doppler in accordance with the recommendations of the European Association and the American Society of Echocardiography [20]. The following parameters were measured: E, A and Ev, Av — peak rates of early and late LV filling at rest and during Valsalva maneuver; (A dur.) — A flow duration during atrial systole; DT — deceleration time of the flow in the phase of early diastolic filling, IRT — isovolumetric relaxation time; septal a, lateral a and septal e', lateral e' — peak diastolic velocity of the mitral fibrous ring at the site of the interventricular

Table 1

BLOOD PRESSURE AND ECHOCARDIOGRAPHY PARAMETERS AT BASELINE AND 24 WEEKS AFTER SYMPATHETIC DENERVATION OF THE KIDNEY ARTERIES (n = 60)

Options	Baseline		After 24 weeks		
	M	SD	M	SD	p
SBP, mm Hg	155.51	20.53	149.13	18.41	0.000
DBP, mm Hg	102.27	14.48	88.83	12.57	0.000
HR, beats/min	70.42	9.59	67.56	9.46	0.089
The left atrium, mm	40.64	4.83	40.80	6.50	0.80
EDD LV, mm	47.62	3.90	46.91	4.44	0.15
ESD LV, mm	29.67	3.71	29.49	3.48	0.70
EF LV, %	67.05	4.64	67.88	5.59	0.26
IVS, mm	14.27	2.96	14.06	2.40	0.37
PWLV, mm	13.14	2.27	12.85	1.96	0.18
LVMM, g	266.96	88.65	257.50	79.29	0.33
LVMI, g/m^2	100.59	45.95	98.60	43.93	0.51
RWT	0.59	0.11	0.58	0.10	0.80
LA, ml/m^2	41.18	9.75	38.13	10.45	0.44
E, cm/s	61.46	19.18	64.46	20.66	0.60
A, cm/s	73.62	12.00	77.31	14.52	0.25
E/A	0.85	0.29	0.85	0.28	0.95
IRT, sec	113.08	14.53	112.31	14.38	0.83
DT, msec	212.92	28.81	211.69	35.78	0.86
Duration A, msec	155.15	20.85	150.31	14.57	0.41
E v, cm/c	48.91	11.82	51.00	11.60	0.36
A v, cm/c	71.64	13.94	72.27	14.93	0.90
septal e', cm/c	6.88	3.70	7.70	3.94	0.57
septal a, cm/c	10.18	4.23	11.02	3.23	0.54
lateral e', cm/c	8.50	2.76	9.52	3.34	0.24
lateral a, cm/c	11.48	3.77	12.29	2.94	0.54
septal E/e'	11.05	5.41	9.96	4.55	0.54
lateral E/e'	7.85	3.02	7.45	3.14	0.71
Ar, msec	26.08	4.11	28.54	5.53	0.15

Note: p — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate; EDD LV — end-diastolic dimension left ventricular; ESD LV — end-systolic dimension left ventricular; EFLV — ejection fraction left ventricular; IVS — interventricular septum; PWLV — LVPW — posterior wall left ventricular; LVMM — left ventricular myocardial mass; RWT — relative wall thickness; LA — left atrium; IRT — isovolumetric relaxation time; DT — deceleration time; p — significance level.

septum and lateral wall of LV; Ar — duration of the retrograde wave in the pulmonary vein. The ratios E/septal e' and E/lateral e' were calculated showing the LV filling pressure.

RSD was carried out after an x-ray angiography via transfemoral access by radiofrequency ablation of renal artery trunk on both sides at 6–8 points under the control of the temperature with the target temperature at the electrode end of 50–60 °C, with the maximum power capacity of 8 watts, and up to 2 minutes in the X-ray surgery room. All patients were instructed to keep the former regimen of medication therapy.

Results are shown as M (mean value) ± SD (standard deviation) or Me (median) and 95 percent confidence interval (CI); to define the dynamics — the minimum-maximum values or Me and the 25–75 percentiles. The differences were assessed by the paired and unpaired Student's t-test for parametric variables; Mann-Whitney and Wilcoxon criteria were applied in case of non-normal distribution; χ^2-criteria was used to assess the differences in ratios. We also performed the pair correlation analysis with the assessment of Pearson's coefficient, and with Spearman coefficient in case of abnormal distribution, and multiple regression analysis was applied to determine the contribution of each single variable. We used STATISTICA 10 software, significant differences were considered when $p < 0.05$.

Results

The average age of the patients was 54.6 ± 9.5 years, body mass index (BMI) — 32.9 ± 6.2 kg/m^2, 71% patients were overweight. All patients had received combination therapy before RSD; and on average they got 4.1 antihypertensive drugs, including diuretics, for at least 24 weeks.

After RSD, there was a significant reduction in office systolic (SBP) and diastolic blood pressure (DBP) [the change was the following: –23.7 / –14.0, 95% CI (-34.5; –19.8 / –18.2; –8.0) mm Hg], and there was a trend towards regression of LVH, left ventricular geometry and diastolic function, but the changes were not statistically significant (Table 1).

The histograms demonstrated that all the patients were divided into 2 groups based on the LV parameters: in one group (n = 22; 36.7%) after RSD LVMM decreased, when the division was based in the criteria of LVMM change ≥ 10 g; in the second group (n = 38; 63.3%) LVMM decreased by less than 10 g or increased.

The patients of both groups (Table 2) were matched by gender [regression of the LVMM was found in the equal number of men (n = 11; 18%) and women (n = 11; 18%), in the 2nd group — 37% (n = 22) and 27% (n = 16), respectively ($\chi 2 = 0.35$, $p = 0.55$)], age, baseline BMI values, amount of drugs, the baseline heart rate and BP. The change in the studied parameters was also comparable: HR [–4.0 (–20, 4.0) and –5.0% (–18.0, 6.0)%, $p = 0.70$], and the average daily office SBP / DBP [–7.0 (–34.0, 3.0)% / –5.0 (–17.9, 3.0)% versus –8.3 (–40.1, 17.0)% / –4.24 (–15.8, 6.0)%, $p = 0.22$ / 0.08, and –4.05 (–15.0, 6.0)% / –1.3 (–8 0; 7.0)% versus –1.7 (14.1; 13.0)% / 0.8 (–10.0, 16.0)%, $p = 0.44$ / $p = 0.42$]. There were no significant differences between the groups in the parameters of LV diastolic function, heart chambers, and baseline LV wall thickness.

The unequal effect of various antihypertensive drugs on the regression of LVMM is well-known, so we performed a comparative analysis of the therapy in the studied groups. We found no significant differences in the structural approach to therapy, thereby no single class has certain benefits (Table 3).

Correlation analysis did not show any significant relations between the dynamics of LVMM and baselines SBP / DBP and heart rate, as well as their dynamics. At the same time it correlated with baseline heart rate and LV wall thickness, but not with the diastolic LV dimension in total and in the 1st group (Table 4).

Multiple regression analysis also demonstrated a significant relation between the dynamics of LVMM and baseline LV wall thickness: β (IVS) = –0.38, $p = 0.004$; β (AP LV) –0.4 = 0, $p = 0.003$; and mildly weaker with the heart rate when IVS was included in the model: β IVS (HR) = –0.23, $p = 0.14$ or β LV posterior wall (HR) = 0.15, $p = 0.334$ and total β LVMM (HR) = –0.22, $p = 0.118$.

At baseline, 58.6% of patients had signs of LV dysfunction: septal e' < 8 (5.4 ± 1.6 m/s), lateral e' < 10 (7.3 ± 2.0 m/s), left atrium ≥ 34 ml/m^2 (39.7 ± 6.2 m/s). Among them patients with minimal violation of LV diastolic function had higher response to the treatment: at 24 weeks after

Table 2

INITIAL CHARACTERISTICS OF THE PATIENTS OF THE 1ST AND 2ND GROUP

Parameters	1 group		2 group		
	M	SD	M	SD	p
Age, ears	54.18	6.36	54.63	11.02	0.862
BMI, kg/m^2	34.88	6.44	31.80	5.96	0.067
The number of medications, n	3.82	0.91	4.17	1.18	0.242
SBP, mm Hg	172.01	17.93	176.50	23.68	0.447
DBP, mm Hg	101.19	13.32	102.00	15.74	0.841
Mean daily SBP, mm Hg	155.55	15.12	15.23	162.13	0.125
Mean daily DBP, mm Hg	92.47	10.47	92.84	17.22	0.571
HR, beats/min	72.12	8.52	69.72	10.47	0.332
LA, mm	40.68	3.98	41.67	5.40	0.462
Aorta, mm	33.27	5.36	35.31	5.88	0.192
EDD, mm	48.32	3.06	47.08	4.52	0.263
ESD, mm	30.86	2.70	29.24	4.14	0.107
Ejection fraction, %	65.41	3.72	67.15	5.56	0.199
IVS, mm	15.57	3.38	13.71	2.27	0.015
LVPW, mm	14.52	2.69	12.68	2.69	0.005
LVMM, g	308.05	95.97	242.69	71.99	0.005
LA, ml/m^2	40.70	7.91	40.22	8.60	0.916
E, cm/c	63.33	14.61	58.47	20.37	0.603
A, cm/c	77.00	13.01	72.53	14.48	0.520
E/A	0.83	0.20	0.82	0.28	0.907
IRT, ms	109.83	14.72	118.00	16.99	0.316
DT, ms	210.00	27.59	206.33	38.35	0.835
Duration A, msec	151.33	12.39	155.13	19.37	0.663
E v, cm/c	47.50	5.09	50.29	15.04	0.667
A v, cm/c	68.67	13.82	69.07	20.09	0.965
septal e', m/c	6.85	2.78	6.61	3.37	0.881
septal a, m/c	10.47	3.48	9.75	3.52	0.679
lateral e', m/c	8.43	2.72	8.22	2.39	0.860
lateral a, m/c	10.95	2.64	11.97	3.50	0.531
septal E/e'	10.20	3.56	10.73	5.40	0.829
lateral E/e'	8.07	2.71	7.53	2.77	0.689
Ar, msec	27.52	3.86	28.84	5.62	0.22

Note: p — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate; LA — left atrium; EDD — end-diastolic dimension; ESD — end-systolic dimension; IVS — interventricular septum; LVPW — left ventricular posterior wall; LVMM — left ventricular myocardial mass; IRT — isovolumetric relaxation time; DT — deceleration time; p — significance level.

Table 3

MEDICATION THERAPY IN PATIENTS OF THE 1ST AND 2ND GROUP

Medications	1 group	2 group	χ^2	p
Beta-blockers, %	81.8%	71.1%	0.86	0.35
Calcium channel blockers, %	68.2%	78.9%	0.86	0.35
Angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists type 1, %	90.9%	94.7%	0.33	0.57
Other (alpha blockers, imidazoline receptor blockers, aldosterone antagonists)	40.9%	50.0%	0.46	0.49

Note: χ^2 — consent criterion; p — the level of significance.

Table 4

CORRELATIONS BETWEEN FOLLOW-UP PARAMETERS: DYNAMICS OF LEFT VENTRICULAR MYOCARDIAL MASS, BLOOD PRESSURE, HEART RATE, AND LEFT VENTRICULAR WALL THICKNESS

Parameters	All		Group 1		Group 2	
	r (x, y)	p	r (x, y)1	p1	r (x, y)2	p2
SBP, mm Hg	0.18	0.23	–0.26	0.30	0.25	0.15
DBP, mm Hg	–0.09	0.56	–0.16	0.48	0.21	0.24
Mean daily SBP, mm Hg	0.21	0.20	–0.20	0.32	0.28	0.23
Mean daily DBP, mm Hg	–0.05	0.42	–0.18	0.52	0.19	0.29
HR, beats/min	–0.34	0.02	–0.41	0.05	0.02	0.92
Dynamics of 24-week SBP, mm Hg	0.03	0.85	–0.14	0.57	–0.07	0.73
Dynamics of 24-week DBP, mm Hg	0.09	0.54	0.09	0.69	–0.27	0.18
Dynamics of 24-week mean daily SBP, mm Hg	–0.04	0.80	0,04	0.87	–0.08	0.67
Dynamics of 24-week mean daily DBP, mm Hg	0.04	0.79	0.07	0.77	–0.12	0.55
Dynamics of 24-week HR, beats/min	–0.03	0.87	0.25	0.30	–0.23	0.25
IVS, mm	–0.41	0.005	–0.56	0.02	0.11	0.57
LV posterior wall, mm	–0.37	0.01	–0.71	0.002	0.17	0.37
LVEDD, mm	–0.08	0.61	–0.10	0.65	0.34	0.06

Note: r (x, y) — the correlation coefficient; p — the level of significance; SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate; LV — left ventricle; IVS — interventricular septum; LVEDD — left ventricular end-diastolic dimension.

the procedure, it normalized in 31% of patients with 1st stage and in 14% of patients with 2nd stage of diastolic dysfunction, 74% of them were from group 1.

Discussion

Currently, most studies confirm the cardioprotective effect of RSD — LVMM reduction and normalization of LV cardiac function parameters, both in the experimental and clinical trials, 24 weeks after the RSD. The published studies showed a decrease in LVMM after RSD with no effect in the controls who continued therapy, which indicates an additional independent efficiency of the procedure [21, 22]. Despite the favorable data confirming the effects of RSD on the structural and functional myocardial parameters based on the long-term experience of prospective studies, the complete normalization of these disorders, especially in patients with severe hypertension never occurs in 100% of cases. This can be explained by the complex pathophysiological mechanisms of hypertension and target organ damage, so that none of the existing methods can be universal. In this regard, to assess the social and economic benefits of the new method and its implementation in practice, the actual issues is the search for predictors of the RSD efficiency with the subsequent development of the algorithm to select potential responders.

At the moment, we have followed up the largest number of patients who underwent RSD in Russia. We have found a decrease in LVMM and the change in LV diastolic function. However, only some patients demonstrated statistically significant changes. Importantly, the groups with and without the regression of increased LVMM were comparable by the type of medication therapy and anthropometry parameters, gender distribution, baseline and dynamics of BP and heart rate.

Considering the pathogenesis of hypertension and the target population for RSD, one could expect that patients with initially larger LV dimensions will have a more pronounced regression of increased LVMM due to the reduction of the circulating blood volume and, as a consequence, reduction in LV volume assessed by echocardiography. However, we found that only the baseline LV wall thickness predicted the regression of LVMM unlike other parameters including the values and the dynamics of heart rate and BP.

A mathematical model for calculating the LVMM includes the size of LV walls. Thus, the statistical significance could be determined by the role of these parameters, however, in this case end-diastolic dimension should have predict

the regression of LVMM, but it was not the case. In addition, to address the limitations of comparative statistics we performed correlation analysis, which confirmed the relations between the dynamics of LVMM and baseline IVS and LV posterior wall and showed no association with LV chamber dimensions. Multiple regression analysis confirmed an independent and greater significance of the baseline LV posterior wasll and IVS, but not the baseline end-diastolic dimension, heart rate or BP.

Hypertension-related diastolic dysfunction is associated with concentric LVH and may induce the onset of heart failure, playing a prognostic role. Therefore, the normalization of LV diastolic function should be regarded as a positive cardioprotective effect of the RSD on cardiovascular risk reduction. A more detailed analysis and the search for predicting indicators of the LV diastolic function seem to be still untimely, given the large range of total estimated parameters that objectively characterize the stage of diastolic dysfunction, and rather small number cases.

Conclusions

According to our study, RSD leads to the decrease in LVMM and positive changes in LV diastolic dysfunction, however, the changes were statistically significant only in a number of patients. Only baseline LV wall thickness was predictive for the regression of LVMM, although the groups were comparable by the type of medication and anthropometric data, gender distribution, baseline and follow-up changes in BP and heart rate: IVS — M/Me = 15.6 / 15.0 mm, posterior wall of LV — 13.9 / 13.5 mm defined the prognostic value of LV IVS and posterior wall thickness in potential responders.

Conflict of interest

The authors declare no conflict of interest.

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