Falkovskaya A. Yu., Mordovin V. F., Pekarskiy S. E., Manukyan M. A.,
Ripp T. M., Zyubanova I. V., Lichikaki V. A., Sitkova E. S., Gusakova A. M., Baev A. E.
Research Institute of Cardiology, Tomsk National Research Medical Center, Russian Academy of Science, Tomsk, Russia

Refractory and Resistant Hypertension in Patients with Type 2 Diabetes Mellitus: Different Response to Renal Denervation

Aim	To compare the antihypertensive effectivity of renal denervation in patients with diabetes mellitus (DM) and associated refractory arterial hypertension (rfAH) (treated with 5 or more classes of antihypertensive drugs, including a thiazide diuretic and a mineralocorticoid receptor antagonist) and uncontrolled resistant AH (ucAH) (treated with 3–4 drugs).
Material and methods	This interventional study with renal denervation included 18 DM patients with rfAH and 40 DM patients with ucAH; 16 and 36 of them, respectively, completed the study in 6 months. At baseline, patients were sex- and age-matched. Study methods included measurement of office blood pressure (BP; systolic/diastolic BP, SBP/DBP); outpatient BP monitoring; evaluation of kidney function (estimated glomerular filtration rate by the CKD-EPI formula); diurnal diuresis volume; diurnal urinary excretion of albumin, potassium and sodium; diurnal excretion of metanephrines and normetanephrines; and plasma levels of glucose and glycated hemoglobin, aldosterone, and active renin. Patients were instructed about maintaining compliance with their antihypertensive and hypoglycemic therapy throughout the study.
Results	At baseline, patients of both groups were comparable by BP and major clinical indexes, except for higher values of nocturnal SBP variability ($p<0.05$) in patients with rfAH. At 6 months following renal denervation, both groups displayed significant decreases in office and average daily SBP and also in the «load» with increased mean diurnal SBP. However, the decrease in average daily SBP was almost 4 times greater in the rfAH group than in the ucAH group (– 19.9 and –5.1 mm Hg, respectively, $p=0.02$). Moreover, 81% of patients in the rfAH group responded to the intervention (average daily SBP decrease ≥10 mm Hg) while the number of responders in the ucAH group was considerably smaller (42%; $p=0.02$). In patients with rfAH, renal denervation was associated with a significant decrease in pulse BP and nocturnal SBP variability and with the increase in diurnal diuresis. No other alterations were noted in laboratory test results in either group.
Conclusion	DM patients with rfAH may be the best candidates for the procedure of renal denervation.

Keywords	Refractory arterial hypertension; resistant arterial hypertension; type 2 diabetes mellitus; renal denervation
For citation	Falkovskaya A. Yu., Mordovin V. F., Pekarskiy S. E., Manukyan M. A., Ripp T. M., Zyubanova I. V. et al. Refractory and Resistant Hypertension in Patients with Type 2 Diabetes Mellitus: Different Response to Renal Denervation. Kardiologiia. 2021;61 (2):54 – 61. [Russian: Фальковская А. Ю., Мордовин В. Ф., Пекарский С. Е., Манукян М. А., Рипп Т. М., Зюбанова И. В. и др. Рефрактерная и резистентная артериальная гипертония у больных сахарным диабетом 2-го типа: различия ответа на денервацию почек. Кардиология. 2021;61 (2):54 – 61]

Corresponding author Falkovskaya A. Yu. E-mail: alla@cardio-tomsk.ru

Arterial hypertension (AH) is the most common cardiovascular disease and significantly increases cardiovascular mortality [1]. The rate of AH continues to grow in the Russian population and now exceeds 40% [2]. The prognosis for resistant arterial hypertension (RAH) is particularly unfavorable [3]. In 2012, the term «hard-to-treat AH,» previously considered synonymous with RAH, was proposed to denote an extreme phenotype of uncontrolled AH [4]. According to the new nomenclature, hard-to-treat AH is characterized by the loss of antihypertensive efficacy and inability to control blood pressure (BP) despite taking antihypertensive drugs of five or more classes, including long-acting thiazide diuretics (TD) and mineralocorticoid receptor antagonists (MCRA) [4–6], which is associated with an even higher risk of cardiovascular complications [4–10]. Hard-to-treat AH and uncontrolled RAH are considered to differ in etiopathogenesis. For example, the mechanism of uncontrolled RAH depends on volume and is associated with fluid delay, and hard-to-treat AH is most likely of neurogenic etiology and is caused by excessive sympathetic hyperactivity [5, 6, 8, 9]. According to the previous research, carbohydrate disorders are associated with an increased tone of the sympathetic branch of the autonomic nervous system,

ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1102

and patients with concomitant diabetes mellitus (DM) and AH have the highest sympathetic activity [11], which explains the frequent combination of DM and RAH [3].

The ever-increasing incidence of DM [12] does not suggest a positive outlook for improving BP control in the coming decades. The discovery of the role of renal nerves in the mechanism of BP increase, however, has expanded the possibilities of antihypertensive treatment, with renal denervation a promising new therapeutic option. At the same time, it should be acknowledged that this procedure has been found ineffective in almost 30% of patients [13–16], and it is unclear which patients can get the most benefit from renal denervation.

This study is based on the hypothesis that, if hard-to-treat AH does have a predominantly neurogenic etiology, sympathetic renal denervation in such patients should be accompanied by a greater decrease in BP than in uncontrolled RAH. Moreover, in the context of the close association of hard-to-treat AH and DM with sympathetic hyperactivation, patients with such a combination may be the best candidates for the intervention.

Objective

To compare the antihypertensive efficacy of renal denervation in patients with DM with hard-to-treat AH and uncontrolled RAH.

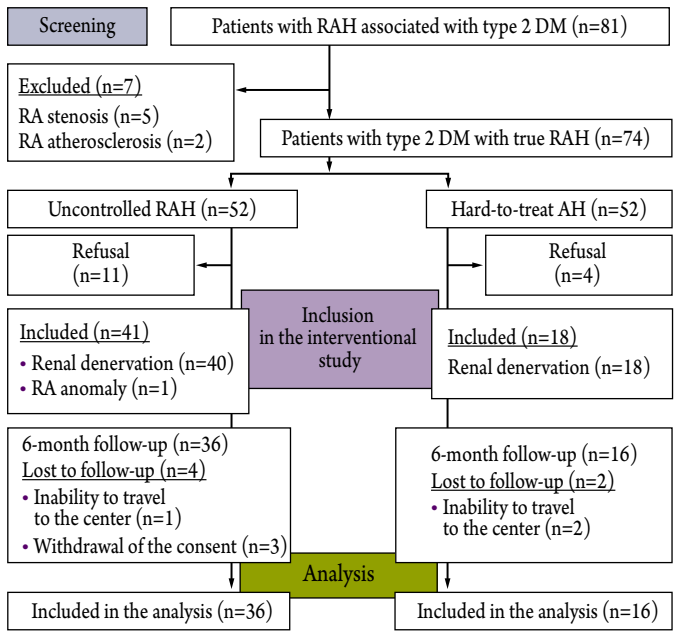
Material and methods

A prospective interventional study of renal denervation included 18 patients with hard-to-treat AH and 40 patients with uncontrolled RAH with concomitant type 2 DM hospitalized at the Research Institute for Cardiology at Tomsk National Research Medical Center from 2010 to 2018. The criterion for hard-to-treat AH was the documented 6-month absence of BP control despite the use of antihypertensive drugs of five or more classes, including long-acting TDs and MCRAs. Uncontrolled RAH included the absence of BP control despite the use of three to four classes of antihypertensive drugs, including long-acting TDs. Patients with pseudoresistance and secondary forms of AH were excluded from the study. Additional exclusion criteria were renal artery diameter >3 mm, HbA1c >10%, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, pregnancy, >12-month history of acute vascular complications, unstable angina, chronic heart failure higher than the New York Heart Association (NYHA) functional class II, severe peripheral atherosclerosis, type 1 DM, severe concomitant diseases, drug therapy affecting BP (nonsteroidal anti-inflammatory drugs, sympathomimetics, oral contraceptives, etc.). Treatment adherence was assessed according to patient survey.

The study design is shown in Figure 1. A total of 16 patients with hard-to-treat AH and 36 patients with uncontrolled RAH completed follow-up. Clinical investigations, office BP measurements, ambulatory BP monitoring (ABPM), and laboratory tests were carried out at baseline and after 6 months of follow-up. Patients were instructed to follow antihypertensive and sugar-lowering therapy throughout the study.

Systolic and diastolic blood pressure (SBP/DBP) was measured following the standard technique. ABPM was carried out using the ABPM-04 and BpLab computer systems. Blood samples were collected from the median cubital vein using the standard technique in the morning after 12-hour fasting. Blood glucose levels were determined by an enzyme (glucose oxidase) method using standard BIOCON kits, and HbA1c was measured using ionic exchange with the BIOCON kits. Plasma levels of active renin were measured using the IBL International kits by enzyme-linked immunoelectrodiffusion essay (ELIZA); aldosterone levels were determined using the DBC kits. Twenty-four-hour albumin excretion was quantified using immunoturbidimetry and an FP-900 semi-automatic biochemical analyzer with standard RANDOX and

Figure 1. Study flowchart



n, number of observations; RAH, resistant arterial hypertension; DM, diabetes mellitus; RA, renal arteries; AH, arterial hypertension.

ORGenTecDiagnostika kits. Potassium and sodium ions in 24-hour urine collection were quantified using a Konelab automatic biochemical analyzer. Methanefrin and normethanefrin in 24-hour urine collection were determined by ELIZA with the IBL International kits. The CKD-EPI formula was used to calculate eGFR.

Sympathetic renal denervation was performed using three types of catheters:

- 1) Symplicity Fleh4F with Symplicity TM G2 Generator – 9 patients with hard-to-treat AH and 18 patients with uncontrolled RAH, with a mean of 13±1.8 ablations per patient
- 2) Standard electrophysiologic system (MarinR 5F catheter with ATAKR-II generator) – 6 patients with hard-to-treat AH and 19 patients with uncontrolled RAH; 6–8 bilateral RF applications in the end-electrode temperature control mode (50–60 °C)
- 3) Symplicity Spyral catheters – 3 patients in each group

Given the absence of differences in fundamental design features and the similar physical impact, the analysis was expected to produce correct results. The study is registered at ClinicalTrials.gov (NCT02667912 and NCT01499810).

The main evaluation criterion (primary endpoint) of the renal denervation efficacy was reduction of the mean 24-hour SBP. Depending on a decrease in the mean 24-hour SBP, patients were retrospectively divided into two groups: responders (those with a decrease in BP of 10 mmHg or more) and non-responders (those with a lower decrease). Additional evaluation criteria (secondary endpoints) of efficacy were decreases in other ABPM parameters and office BP values, and changes in laboratory measurements.

The safety of the intervention was monitored by laboratory tests, renal Doppler sonography, and magnetic resonance imaging of the kidneys and renal arteries.

The study was approved by the Biomedical Ethics Committee of the Research Institute for Cardiology of the Tomsk National Research Medical Center. All patients signed informed consent before being included in the study.

The statistical analysis of findings was carried out using the Statistica 10.0 suite for Windows. The normality of variable distribution was evaluated using the Shapiro-Wilk test. Continuous variables are represented as the mean and the standard deviation (M±SD) or as the mean and 95% confidence interval to estimate the intervention effect, and in the absence of normal distribution, as the median and

Table 1. Clinical characteristics of patients

Parameter	Hard-to-treat AH (n=18)	Uncontrolled RAH (n=40)	p
Clinical data			
Age, years	59.1±7.9	60.3±8.2	0.61
Female	10 (55)	25 (63)	0.62
BMI, kg/m^2	35.6±6.8	34.7±6.4	0.61
Duration of AH, years	19.3±10	24.3±9.9	0.08
Duration of DM, years	8.1±5.1	8.9±6.4	0.62
CKD stage III	4 (22.2)	11 (27.5)	0.67
Albuminuria (30–300 mg/day)	7 (39)	18 (45)	0.66
HbA1c , %	7.2±1.1	7.1±1.4	0.92
Basal glucose level, mmol/L	8.4±2.2	8.5±2.6	0.96
LVH	18 (100)	36 (90)	0.32
CAD	13 (72)	23 (58)	0.32
BP parameters			
Office* SBP, mmHg	170.8±22.1	169.7±16.2	0.84
Office* DBP, mmHg	90±18.8	89.4±13.3	0.89
SBP 24-hour, mmHg	160±18.1	155.3±14.2	0.29
DBP 24-hour, mmHg	80.7±12.4	81.5±12.4	0.84
Office* HR, bpm	69.3±9.5	70.2±10.6	0.77
HR 24-hour, bpm	64.8±12.1	66.4±10.8	0.60
SBP load 24-hour, %	89.2±13.5	84.4±13.6	0.25
DBP load 24-hour, %	41±32.6	36.1±30.4	0.60
SBP daytime, mmHg	164.1±19.8	158.4±15.1	0.24
DBP daytime, mmHg	85.6±14.9	84.7±12.8	0.82
SBP load, daytime, %	83.3±21.3	79.5±18	0.48
DBP load, daytime, %	38.3±34.7	37±32.6	0.9
SBP nighttime, mmHg	152.3±17.6	149.6±16.2	0.57
DBP nighttime, mmHg	73.3±13.1	74.7±12.5	0.70
SBP load, nighttime, %	94.3±10.8	94.6±11.1	0.92
DBP load, nighttime, %	33.4±27.7	40±36.3	0.50
SD_{SBP} 24-hour, mmHg	18.4±5	17.4±4.9	0.45
SD_{DBP} 24-hour, mmHg	13.3±3.6	12±3.1	0.20
SD_{SBP} daytime, mmHg	17.7±4.6	17.4±4.7	0.79
SD_{DBP} daytime, mmHg	12.7±3.6	11.4±3.5	0.20
SD_{SBP} nighttime, mmHg	15.7±3.5	13.2±4.4	0.04
SD_{DBP} nighttime, mmHg	9.8±3.4	9.6±2.8	0.75
SD_{HR} 24-hour, bpm	7.2±3.2	7±2.8	0.84
SD_{HR} daytime, bpm	7.3±3.4	6.7±2.7	0.49
SD_{HR} nighttime, bpm	4.3±1.7	4.7±2.3	0.47
SBP 24-hour index, %	7.2±8.4	5.4±7.8	0.43

Data are presented as the mean and standard deviation (M±SD) or the absolute and relative values (n (%)). * —measured by a physician. AH, arterial hypertension; RAH, resistant arterial hypertension; BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; HbA1c, glycated hemoglobin; LVH, left ventricular hypertrophy; CAD, coronary artery disease; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; 24 hour, mean 24-hour values; SD, standard deviation (variability).

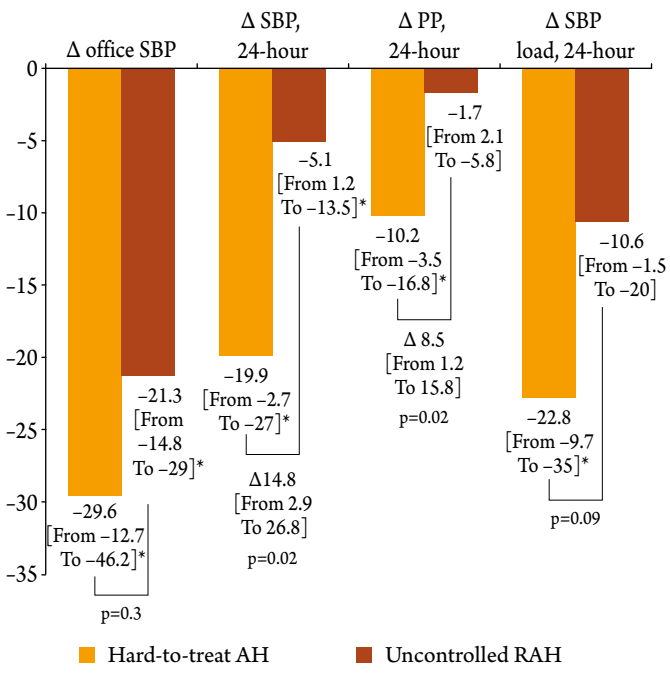
ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1102

Table 2. Characteristics of sugar-lowering and antihypertensive therapy

Parameter	Hard-to-treat AH (n=18)	Uncontrolled RAH (n=40)	p
Sugar-lowering therapy			
Insulin therapy + OHGD	8 (44)	11 (27.5)	0.39
Nutrition therapy	2 (11)	5 (12.5)	0.88
Metformin	5 (28)	12 (30)	0.86
Combination OHGD	3 (17)	12 (30)	0.48
Antihypertensive therapy			
Number of antihypertensive drugs	5.5±0.5	3.9±0.8	< 0.0001
Beta-blockers	18 (100)	29 (73)	0.01
ACE inhibitors/sartans	17 (94)	38 (95)	0.93
Diuretics	18 (100)	40 (100)	—
Calcium antagonists	17 (94)	29 (73)	0.08
Spironolactone	18 (100)	5 (13)	0.0000
Other	10 (56)	14 (35)	0,14
• Imidazoline receptor agonists	6 (33%)	10 (25%)	0,51
• Alpha-blockers	5 (27%)	4 (10%)	0,08

Data are expressed as the absolute and relative values, n (%).
AH, arterial hypertension; RAH, resistant arterial hypertension.;
OHGD, oral hypoglycemic drugs;
ACE, angiotensin-converting enzyme.

Figure 2. Changes in the office and 24-hour BP in 6 months after renal denervation



AH, arterial hypertension; RAH, resistant arterial hypertension; Δ, change; office SBP, systolic blood pressure measured by the physician, mmHg; SBP 24-hour, mean 24-hour systolic blood pressure, mmHg; PP 24-hour, mean 24-hour pulse pressure, mmHg; SBP load 24-hour, increased mean 24-hour systolic blood pressure load. * – $p < 0.05$.

the interquartile range (Me [25th percentile; 75th percentile]). Categorical variables are expressed as the absolute number and the percentage. The analysis was performed depending on the treatment (intention-to-treat). No additional analysis was performed to reconstruct data of patients who did not complete the study. The standard methods of descriptive statistics were used, and differences in continuous variables were determined in the independent samples (t-test, Mann – Whitney U-test) and paired samples (t-test, Wilcoxon W-test). The contingency tables (Pearson's chi-square or Fisher's exact test with a two-tailed level of significance) were used to analyze qualitative data. The critical level of significance was p=0.05.

Results

As shown in Table 1, patients with hard-to-treat AH and uncontrolled RAH were comparable in the main baseline findings of the laboratory tests, clinical investigations, and ABPM parameters except for higher values of nighttime SBP variability in the group of patients with hard-to-treat AH. Naturally, patients with hard-to-treat AH took more antihypertensive drugs, particularly attributable to more frequent use of spironolactone (χ^2=22.3) and beta-blockers (χ^2=6.1) (Table 2). The composition of sugar-lowering therapy was comparable in the two groups, and all patients used statins. Six months after renal denervation, a statistically significant decrease in office and mean 24-hour SBP, as well as the elevated mean 24-hour SBP «load,» was observed in both groups (Figure 2). Changes in office SBP and elevated mean 24-hour SBP «load» in the study groups were comparable, but the decrease in the mean 24-hour SBP was almost four times higher in patients with hard-to-treat AH than in those with uncontrolled RAH. There were intergroup differences in both the daytime and nighttime SBP (Table 3). Moreover, patients with hard-to-treat AH, unlike those with uncontrolled RAH, had a significant decrease in pulse BP and nighttime SBP variability, as well as a significant increase in 24-hour diuresis (Figure 3). There were no significant changes in the mean heart rate (HR) and 24-hour BP indices in both groups.

Figure 4 shows that most patients with hard-to-treat AH responded to the intervention, whereas the number of responses in the RAH group was significantly lower. The changes in catecholamines, albumin, and electrolytes in 24-hour urine collection, as well as eGFR and the blood levels of renin and aldosterone, were not statistically significant in either group (Table 4). The number of antihypertensive drug classes remained the

Table 3. Changes in ABPM parameters 6 months after renal denervation

Parameter	Hard-to-treat AH	Uncontrolled RAH	Difference	p
ABPM parameters				
ΔSBP office, mmHg	29.6±15.7*	19.9±14.4*	9.7 (-2.84–27.3)	0.30
ΔDBP office, mmHg	12.3±18.1*	5.1±13.8*	7.2 (-4.11–16)	0.24
ΔSBP daytime, mmHg	20.8±21.1*	7.1±19.8*	13.5 (0.38–27.8)	0.03
ΔDBP daytime, mmHg	9.1±13.3	5.2±12.8	6.3 (-4.1–16.6)	0.37
ΔPP daytime, mmHg	10.0±10.2*	2.2±12.2	7.9 (0.2–15.6)	0.04
ΔSBP nighttime, mmHg	19.4±17.3*	3.2±16	16.3 (5.17–27.4)	0.005
ΔDBP nighttime, mmHg	7.6±12.4	2.5±10.1	5.1 (-2.2–12.4)	0.16
ΔPP nighttime, mmHg	9.2±13.5*	1.5±10.7	7.8 (0.2–15.3)	0.04
ΔSDDBP 24-hour, mmHg	0.3±4.8	0.2±5.1	0.1 (-3.3–3.5)	0.95
ΔSDDBP daytime, mmHg	-3.4±3.7	0.3±5.3	-0.2 (-3.6–3.2)	0.91
ΔSDDBP nighttime, mmHg	2.6±4.0	-0.3±5.6	3.7 (0.4–7.0)	0.03
ΔHR 24-hour, bpm	2.7±8.3	0.8±9.4	1.9 (-4.3–8.2)	0.54
ΔHR daytime, bpm	2.8±8.9	0.4±10.7	2.4 (-4.6–9.5)	0.48
ΔHR nighttime, bpm	2.3±6.7	1.3±9	1 (-4.8–6.7)	0.73
ΔSBP 24-hour index	0.78±12.9	1.5±9.1	-0.7 (-7.2–5.9)	0.83

Data are presented as the mean and standard deviation (M±SD) or the mean and 95% confidence interval. ABPM, ambulatory blood pressure monitoring; AH, arterial hypertension; RAH, resistant arterial hypertension.; Δ, change; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HR, heart rate; 24 hour, mean 24-hour values; SD, standard deviation (variability). * – $p < 0.05$.

same (5.0±0.7 in patients with hard-to-treat AH and 3.9±0.9 in patients with uncontrolled RAH).

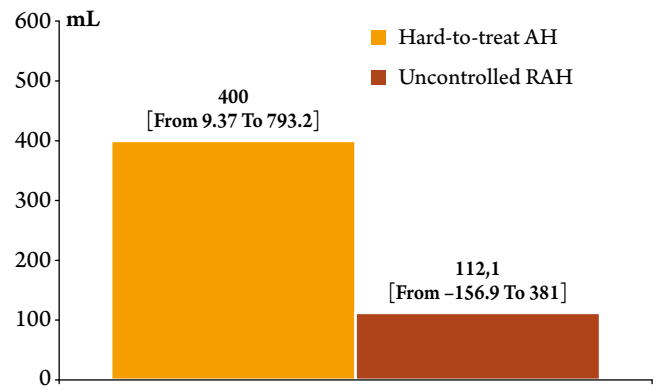
No one had intervention-related post-procedural complications in our study. Two patients had hematoma due to femoral artery puncture, which resolved soon after surgery without complications. There were no deteriorations of renal blood flow or visual changes of renal arteries after the renal arteries interventions.

Discussion

The major finding of the study was the identification of a more significant decrease in the mean 24-hour SBP after renal denervation in patients with DM and hard-to-treat AH compared to patients with uncontrolled RAH despite comparable changes in office SBP. Since the mean 24-hour SBP is a more sensitive predictor of the risk of cardiovascular complications than office SBP [17, 18], these differences are of apparent clinical significance.

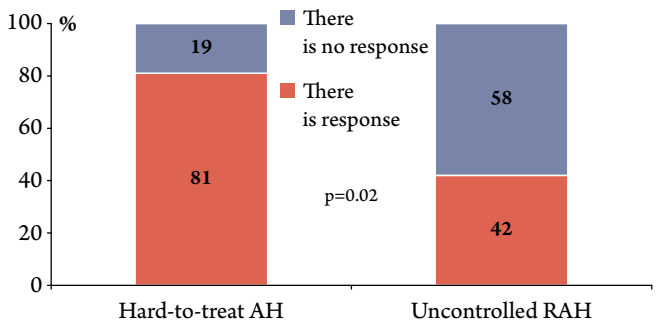
In accordance with Wilder's principle, it is known that the higher the baseline BP level is, the more apparent is the effect of the intervention [19]. However, in our study, patients had comparable BP in both

Figure 3. Changes in 24-hour diuresis 6 months after renal denervation



AH, arterial hypertension; RAH, resistant arterial hypertension.

Figure 4. Response rate (%) 6 months after renal denervation



AH, arterial hypertension; RAH, resistant arterial hypertension.

ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1102

Table 4. Laboratory measurements at baseline and 6 months after denervation

Parameter	Hard-to-treat AH		Uncontrolled RAH		p	
	To	After	To	After	p_1	p_2
24-hour albumin excretion in urine, mg/day	21.7 [16.9; 110.5]	18.9 [9.7; 45.9]	33.5 [9.8; 63.25]	15.8 [10.5; 39.2]	0.50	0.2
eGFR, mL/min/1.73m^2	78.1±22.7	78.4±19.6	71.9±20	67.8±17.9	0.97	0.43
Sodium excretion, mmol/day	159±100	150.1±76.4	127.2±53.9	137.9±59.0	0.79	0.53
Potassium excretion, mmol/day	35.7±18.4	32.6±12.8	41.2±22.4	34.8±9.6	0.61	0.22
Metanephrine excretion, mg/day	125.8±67.8	183.2±103.1	128.9±72.7	131.4±100.4	0.12	0.92
Normetanephrine excretion, mg/day	297.8±254.7	363.5±240.9	201.2±119.1	246.5±140.6	0.50	0.21
Serum aldosterone, pg/mL	202.9±51.6	214.2±98.3	220.8±92.4	228.3±99.8	0.75	0.79
Active plasma renin, pg/mL	16.3 [10.2; 69.6]	36.8 [14.1; 68]	44.8 [16.9; 82.8]	54.9 [18.9; 87.3]	1.0	0.17

Data are expressed as the mean and the standard deviations (M±DM) or the median and the interquartile range (Me [25th percentile; 75th percentile]). AH, arterial hypertension; RAH, resistant arterial hypertension; eGFR, estimated glomerular filtration rate; p_1, compared to baseline in a patient with hard-to-treat AH; p_2, compared to baseline in patients with uncontrolled RAH.

groups; therefore, the greater decrease in BP in patients with hard-to-treat AH could not be due to differences in baseline BP values. Higher sympathetic activity in hard-to-treat AH compared with uncontrolled RAH may serve a pathophysiological justification for a more significant antihypertensive effect of renal denervation. We did not have the opportunity to measure and compare sympathetic activity, but the higher variability of nighttime SBP in patients with hard-to-treat AH may be an indirect indicator of a higher tone of the sympathetic vegetative nervous system. For example, it has been previously found that sympathetic hyperactivity, as well as environmental factors, is associated with increased variability of BP [20, 21]. Since external factors and psychosocial stresses have less influence on the variability of nighttime BP, this indicator may reflect the actual level of sympathetic activity to a greater degree than daytime BP. In the DENERHTN study, the increased variability of nighttime SBP was the predictor of response to renal denervation [22].

The more pronounced decrease in variability of nighttime SBP and pulse BP in patients with hard-to-treat AH in our study can confirm the more pronounced sympatholytic and organoprotective effects of renal denervation in patients with hard-to-treat AH. The possible reason for the absence of changes in variability of daytime SBP may be relatively trivial, since the BP decrease after renal denervation is accompanied by a general increase in well-being [23], which increases a patient's daily performance and physical activity and can reduce the effect of the decreased sympathetic influence on daytime BP variability.

Moreover, the examined patients with hard-to-treat AH more often experienced a more severe sympatho-adrenal blockade due to more frequent use of beta-blockers. Nevertheless, the levels of BP and HR before the intervention were comparable in both groups. This may indirectly confirm higher baseline sympathetic activity in hard-to-treat AH and the insufficiency of drug therapy in suppressing it.

According to our findings, renal denervation was accompanied by a significant increase in 24-hour diuresis in patients with hard-to-treat AH over the effect of previous diuretic therapy. This is likely due to decreased sympathetic kidney activity and the restoration of pressure diuresis, a natural mechanism of lowering BP. There were no intergroup differences in the baseline levels of catecholamines and their change after renal denervation. The analysis of catecholamines in urine may not always allow assessing global sympathetic activity adequately. One of the reasons for the lack of changes in renin and aldosterone levels could be a short follow-up period in our study as, in other studies, the decrease in the activity of these hormones was observed not earlier than 1 year after the intervention [24].

Despite the discussed relevance of comparing the response to renal denervation in patients with hard-to-treat AH and uncontrolled RAH [5–7], we could not find similar studies, which did not allow for comparing our findings with those of others.

Our study was limited by a small number of subjects, assessment of treatment adherence from the survey, inability to measure the rate of metanephrine and normetanephrine coming into the blood from the kidneys, and sympathetic muscle activity as indicators

of renal and global sympathetic tone. However, these issues may be subjects of future studies.

Conclusion

According to our findings, patients with diabetes mellitus and hard-to-treat arterial hypertension may be the best candidates for renal denervation, which may hold the key to optimizing patient selection for this procedure, with the predictably higher benefit of the intervention.

Acknowledgements

The authors thank Researcher of the Department of X-Ray and Tomographic Diagnostic Methods, N. I. Ryumshina, MD, who performed magnetic resonance tomography of kidneys and renal arteries, and Senior Researcher of the Department of Functional and Laboratory Diagnostics, T. R. Ryabova, MD, who performed renal Doppler sonography.

Funding

State Assignment of the Research Institute of Cardiology and the Tomsk National Research Medical Center, State Registration AAAA-A17-117052310076-7 of 23.05.2017.

No conflict of interest is reported.

The article was received on 25/03/2020

REFERENCES

1. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. The Lancet. 2014;383 (9932):1899–911. DOI: 10.1016/S0140–6736 (14) 60685–1
2. Badin Yu. V., Fomin I. V., Belenkov Yu. N., Mareev V. Yu., Ageev F. T., Polyakov D. S. et al. EPOCHA-AH 1998–2017. Dynamics of prevalence, awareness of arterial hypertension, treatment coverage, and effective control of blood pressure in the European part of the Russian Federation. Kardiologiia. 2019;59 (1S): 34–42. [Russian: Бадин Ю. В., Фомин И. В., Беленков Ю. Н., Мареев В. Ю., Агеев Ф. Т., Поляков Д. С. и др. ЭПОХА – АГ 1998–2017 гг.: Динамика распространенности, информированности об артериальной гипертонии, охвате терапией и эффективного контроля артериального давления в европейской части РФ. Кардиология. 2019;59 (1S): 34–42]. DOI: 10.18087/cardio.2445
3. Kasiakogias A, Tsioufis C, Dimitriadis K, Konstantinidis D, Koumelli A, Leontsinis I et al. Cardiovascular morbidity of severe resistant hypertension among treated uncontrolled hypertensives: a 4-year follow-up study. Journal of Human Hypertension. 2018;32 (7):487–93. DOI: 10.1038/s41371-018-0065-y
4. Acelajado MC, Pisoni R, Dudenbostel T, Dell'Italia LJ, Cartmill F, Zhang B et al. Refractory Hypertension: Definition, Prevalence, and Patient Characteristics. The Journal of Clinical Hypertension. 2012;14 (1):7–12. DOI: 10.1111/j.1751–7176.2011.00556.x
5. Dudenbostel T, Siddiqui M, Oparil S, Calhoun DA. Refractory Hypertension: A Novel Phenotype of Antihypertensive Treatment Failure. Hypertension. 2016;67 (6):1085–92. DOI: 10.1161/HYPERTENSIONAHA.116.06587
6. Aksenova A. V., Esaulova T. E., Sivakova O. A., Chazova I. E. Resistant and refractory arterial hypertension: similarities and differences, new approaches to diagnosis and treatment. Systemic Hypertension. 2018;15 (3):11–3. [Russian: Аксенова А. В., Есаулова Т. Е., Сивакова О. А., Чазова И. Е. Резистентная и рефрактерная артериальные гипертензии: сходства и различия, новые подходы к диагностике и лечению. Системные гипертензии. 2018;15 (3):11–13]. DOI: 10.26442/2075-082X_2018.3.11–13
7. Kuzmin O. B., Buchneva N. V., Zhezha V. V., Serdyuk S. V. Uncontrolled Arterial Hypertension: Kidney, Neurohormonal Imbalance, and Approaches to Antihypertensive Drug Therapy. Kardiologiia. 2019;59 (12):64–71. [Russian: Кузьмин О. Б., Бучнева Н. В., Жежа В. В., Сердюк С. В. Неконтролируемая артериальная гипертензия: почка, нейрогормональный дисбаланс и подходы к антигипертензивной лекарственной терапии. Кардиология. 2019;59 (12):64–71]. DOI: 10.18087/cardio.2019.12.n547
8. Velasco A, Siddiqui M, Kreps E, Kolakalapudi P, Dudenbostel T, Arora G et al. Refractory Hypertension Is not Attributable to Intravascular Fluid Retention as Determined by Intracardiac Volumes. Hypertension. 2018;72 (2):343–9. DOI: 10.1161/HYPERTENSIONAHA.118.10965
9. Dudenbostel T, Acelajado MC, Pisoni R, Li P, Oparil S, Calhoun DA. Refractory Hypertension: Evidence of Heightened Sympathetic Activity as a Cause of Antihypertensive Treatment Failure. Hypertension. 2015;66 (1):126–33. DOI: 10.1161/HYPERTENSIONAHA.115.05449
10. Calhoun DA, Booth JN, Oparil S, Irvin MR, Shimbo D, Lackland DT et al. Refractory Hypertension: Determination of Prevalence, Risk Factors, and Comorbidities in a Large, Population-Based Cohort. Hypertension. 2014;63 (3):451–8. DOI: 10.1161/HYPERTENSIONAHA.113.02026
11. Huggett RJ, Scott EM, Gilbey SG, Stoker JB, Mackintosh AF, Mary DASG. Impact of Type 2 Diabetes Mellitus on Sympathetic Neural Mechanisms in Hypertension. Circulation. 2003;108 (25):3097–101. DOI: 10.1161/01.CIR.0000103123.66264.FE
12. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Research and Clinical Practice. 2019;157:107843. DOI: 10.1016/j.diabres.2019.107843
13. Symplicity HTN-2 Investigators, Estel MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. The Lancet. 2010;376 (9756):1903–9. DOI: 10.1016/S0140–6736 (10) 62039–9
14. Frolova E. V., Vachev A. N., Morkovskikh N. V., Korytsev V. K. Selection of Patients with Resistant Arterial Hypertension for the Catheter-Based Renal Sympathetic Denervation. Kardiologiia. 2019;59 (4):21–5. [Russian: Фролова Е. В., Вачев А. Н., Морковских Н. В., Корытцев В. К. Отбор больных с резистентной артериальной гипертензией на процедуру внутрисосудистой ренальной симпатической денервации. Кардиология. 2019;59 (4):21–5]. DOI: 10.18087/cardio.2019.4.10234
15. Agaeva R. A., Danilov N. M., Shelkova G. V., Sagaydak O. V., Grigin V. A., Matchin Yu. G. et al. Radiofrequency renal denervation with different device for treatment in patient with uncontrolled hypertension. Systemic Hypertension. 2018;15 (4):34–8. [Russian: Araeва Р. А., Данилов Н. М., Щелкова Г. В., Сагайдак О. В., Григин В. А., Матчин Ю. Г. и др. Радиочастотная денервация почечных артерий с применением различных устройств у пациентов с неконтролируемой артериальной гипертонией. Системные гипертензии. 2018;15 (4):34–8]. DOI: 10.26442/2075082X.2018.4.000043

ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1102

16. Savelyeva N. Yu., Zherzhova A. Yu., E. V Mikova, Gapon L. I., Kolunin G. V., Krinochkin D. V. Radiofrequency denervation of the renal arteries in patients with resistant arterial hypertension: 3 years of observation experience. Systemic Hypertension. 2019;16 (4):65–9. [Russian: Савельева Н. Ю., Жержова А. Ю., Микова Е. В., Гапон Л. И., Колунин Г. В., Криночкин Д. В. Радиочастотная денервация почечных артерий у больных резистентной артериальной гипертонией: трехлетний опыт наблюдения. Системные гипертензии. 2019;16 (4):65–9]. DOI: 10.26442/2075082X.2019.4.190596
17. Roush GC, Fagard RH, Salles GF, Pierdomenico SD, Reboldi G, Verdecchia P et al. Prognostic impact from clinic, daytime, and nighttime systolic blood pressure in nine cohorts of 13844 patients with hypertension. Journal of Hypertension. 2014;32 (12):2332–40. DOI: 10.1097/HJH.0000000000000355
18. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018;39 (33):3021–104. DOI: 10.1093/eurheartj/ehy339
19. Messerli FH, Bangalore S, Schmieder RE. Wilder's principle: pretreatment value determines post-treatment response. European Heart Journal. 2015;36 (9):576–9. DOI: 10.1093/eurheartj/ehu467
20. Ostroumova O. D., Borisova E. V., Ostroumova T. M., Kochetkov A. I. 24 Hour Arterial Pressure Variability: Prognostic Significance, Methods of Evaluation, Effect of Antihypertensive Therapy. Kardiologiia. 2017;57 (12):62–72. [Russian: Остроумова О. Д., Борисова Е. В., Остроумова Т. М., Кочетков А. И. Вариабельность артериального давления в течение суток: прогностическое значение, методы оценки и влияние антигипертензивной терапии. Кардиология. 2017;57 (12):62–72]. DOI: 10.18087/cardio.2017.12.10068
21. Mancia G, Grassi G. Mechanisms and Clinical Implications of Blood Pressure Variability. Journal of Cardiovascular Pharmacology. 2000;35 (7 Suppl 4):S15–9. DOI: 10.1097/00005344-200000004-00003
22. Gosse P, Cremer A, Pereira H, Bobrie G, Chatellier G, Chamontin B et al. Twenty-Four-Hour Blood Pressure Monitoring to Predict and Assess Impact of Renal Denervation: The DENERHTN Study (Renal Denervation for Hypertension). Hypertension. 2017;69 (3):494–500. DOI: 10.1161/HYPERTENSIONAHA.116.08448
23. Kindermann I, Wedegärtner SM, Mahfoud F, Weil J, Brilakis N, Ukena J et al. Improvement in health-related quality of life after renal sympathetic denervation in real-world hypertensive patients: 12-month outcomes in the Global SYMPLICITY Registry. The Journal of Clinical Hypertension. 2017;19 (9):833–9. DOI: 10.1111/jch.13007
24. Zyubanova I. V., Mordovin V. F., Pekarskiy S. E., Ripp T. M., Falkovskaya A. Yu., Lichikaki V. A. et al. Possible mechanisms of renal denervation long-term cardiac effects. Arterial Hypertension. 2019;25 (4):423–32. [Russian: Зюбанова И. В., Мордовин В. Ф., Пекарский С. Е., Рипп Т. М., Фальковская А. Ю., Личикаки В. А. и др. Возможные механизмы отдаленных кардиальных эффектов ренальной денервации. Артериальная гипертензия. 2019;25 (4):42332]. DOI: 10.18705/1607-419X-2019-25-4-423-432