ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 616.073

Renal sympathetic denervation in patients with resistant hypertension. Results of long-term prospective follow-up

M. V. Ionov[1], I. V. Emelyanov[1], Yu. S. Yudina[1], S. A. Panarina[1], D. A. Zverev[1], N. G. Avdonina[1], N. E. Zvartau[1, 2], A. O. Konradi[1, 2]
[1] Almazov National Medical Research Centre, St Petersburg, Russia
[2] ITMO University, St Petersburg, Russia

Corresponding author:
Mikhail V. Ionov,
Almazov National Medical Research Centre,
2 Akkuratova street, St Petersburg, 197341 Russia.
Phone: 8(812)702–37–56.
E-mail: ionov_mv@almazovcentre.ru

Received 29 December 2020; accepted 3 February 2021.

Abstract

Objective. Renal sympathetic denervation (RDN) is one of the invasive treatment options for the patients with hypertension (HTN) who are resistant to antihypertensive therapy (AHT). The short-term efficacy of RDN has been proven in a number of randomized clinical trials, but remains controversial, the data on its long-term efficacy are limited. **The aim** of our **study** was to evaluate the natural course of HTN, to assess long-term major adverse cardiovascular events (MACE) and other outcomes, as well as AHT efficacy and its features in patients with resistant HTN after bilateral RDN during extended prospective follow-up. **Design and methods.** We included 22 patients with truly resistant HTN (median 57 y.o., 9 males), in whom RDN was performed during 2012–2015 in the clinical center of excellence. We assessed initial and further (after 1 year and after ≥ 5 years) clinical, laboratory and anthropometric parameters, as well as detailed AHT history. Long-term MACE and other clinically significant outcomes were recorded. At baseline and follow-up, the quality of life (QoL) was determined with the use of EQ-5D questionnaire at all time points. Multiple linear regression was used to find possible predictors of the efficacy of RDN. **Results.** A significant and sustained drop in office and ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP) was observed at 12 months after RDN compared to baseline values (Δ –24 and –12 mm Hg, $p < 0,005$; Δ –10 and –7 mm Hg, $p < 0,05$, respectively). There were 7 patients with office SBP on-target, and 12 patients were considered responders (Δ SBP > 10 mm Hg). These numbers increased to 10 and 14 patients after ≥ 5 years after RDN. A causal relationship between changes in office SBP was found only for the baseline SBP (β -0,6, $p = 0,02$). No differences in the number of medications were noted during follow-up (4,4; 4,1 and 4,1 drugs, $p = 0,41$). During the follow-up 10 MACE occurred and 5 patients were diagnosed with various types of cancer; there were no fatal outcomes. The QoL significantly improved a year after RDN (+9,7 points, $p = 0,01$), however, a negative trend was observed in the next 5 years with return to reference level. No association was observed between BP and QoL changes at two timepoints. **Conclusions.** The RDN

shows a pronounced clinical effect in patients with resistant HTN up to 5 years, and is not accompanied by an AHT intensification, but is not associated with QoL changes. The initial positive trend for QoL completely harked back after 5 years which may be associated with the development of MACE. The only predictor of RDN positive effect is baseline SBP level.

Key words: hypertension, resistant hypertension, renal denervation, antihypertensive therapy, quality of life, long-term follow-up, major adverse cardiovascular events, outcomes

For citation: Ionov MV, Emelyanov IV, Yudina YuS, Panarina SA, Zverev DA, Avdonina NG, Zvartau NE, Konradi AO. Renal sympathetic denervation in patients with resistant hypertension. Results of long-term prospective follow-up. Arterial'naya Gipertenziya = Arterial Hypertension. 2021;27(3)10.18705/1607-419X-2021-27-3-318-332

Результаты длительного проспективного наблюдения пациентов с резистентной артериальной гипертензией, прошедших процедуру радиочастотной аблации симпатических почечных нервов

М. В. Ионов[1], И. В. Емельянов[1], Ю. С. Юдина[1], С. А. Панарина[1], Д. А. Зверев[1], Н. Г. Авдонина[1], Н. Э. Звартау[1, 2], А. О. Конради[1, 2]

[1] Федеральное государственное бюджетное учреждение «Национальный медицинский исследовательский центр имени В. А. Алмазова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Россия

[2] Федеральное государственное автономное образовательное учреждение высшего образования «Санкт-Петербургский национальный исследовательский университет информационных технологий, механики и оптики» (Университет ИТМО), Санкт-Петербург, Россия

Контактная информация:
Ионов Михаил Васильевич,
ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России,
ул. Аккуратова, д. 2, Санкт-Петербург, Россия, 197341.
Тел.: 8(812)703–37–56.
E-mail: ionov_mv@almazovcentre.ru

Статья поступила в редакцию 29.12.20 и принята к печати 03.02.21.

Резюме

Радиочастотная аблация симпатических почечных нервов (ренальная денервация (РД)) — один из наиболее известных подходов инвазивного лечения трудно контролируемой артериальной гипертензии (АГ). Краткосрочная эффективность РД была показана в ряде рандомизированных исследований, но до сих пор остается предметом дискуссий, тогда как отдаленные эффекты изучены недостаточно. **Цель** настоящего **исследования** состояла в оценке течения заболевания, регистрации отдаленных сердечно-сосудистых осложнений (ССО) и иных исходов, а также эффективности и объема антигипертензивной терапии (АГТ) при длительном наблюдении пациентов с резистентной АГ, прошедших процедуру двухсторонней РД. **Материалы и методы.** В исследование были включены 22 пациента с истинно резистентной АГ (медиана возраста 57 лет, 9 мужчин), которым в период с 2012–2015 годов была выполнена РД в экспертном центре. Проводилась базовая и динамическая (через 1 год и через ≥ 5 лет) оценка клинико-лабораторных и антропометрических характеристик, регистрировались объем и детальный характер принимаемой АГТ, а также отдаленные ССО и иные клинические исходы. Во всех точках было проведено анкетирование пациентов с опросником EQ-5D для определения базового качества жизни (КЖ) и его динамики. Был выполнен

подгрупповой анализ в зависимости от достижения целевого артериального давления (АД) и случившихся ССО. Множественная линейная регрессия была использована для поиска возможных предикторов эффективности РД. **Результаты.** Через 12 месяцев после РД наблюдалось значимое и устойчивое снижение офисного АД (ОАД) и 24-часового систолического АД (САД) и диастолического АД (ДАД) по сравнению с исходными показателями (Δ –24 и –2 мм рт. ст., $p < 0,005$; Δ –10 и –7 мм рт. ст., $p < 0,05$ соответственно). У 7 пациентов было зафиксировано целевое офисное САД, а 12 пациентов считались «респондерами» (снижение САД более чем на 10 мм рт. ст.). В точке отдаленного наблюдения ОАД оставалось значительно ниже исходного, но не отличалось от 12-месячных результатов (Δ–1 и –5 мм рт. ст., $p > 0,05$). Через 5 лет и более 10 пациентов находились в целевом диапазоне САД и 14 могли быть признаны респондерами на вмешательство. Из всех включенных в регрессионную модель ковариат причинно-следственная связь изменения офисного САД была найдена только для его исходного показателя (β –0,6, $p = 0,02$). На всех этапах наблюдения не было отмечено отличий в объеме и отдельных паттернах назначенной АГТ (4,4; 4,1 и 4,1 препарата, $p = 0,41$). В течение срока наблюдения произошло 10 сердечно-сосудистых событий, и у 5 пациентов документирован тот или иной онкологический процесс; летальных исходов не было. Уровень КЖ стал значительно выше спустя 1 год после РД (+9,7 балла, $p = 0,01$), однако с течением времени наблюдались отрицательная динамика и возвращение балльной оценки КЖ к исходной, при этом ассоциации динамики АД с изменениями КЖ как через 1, так и через 5 и более лет найдено не было. **Заключение.** Процедура РД вызывает выраженный и продленный клинический эффект у пациентов с резистентной АГ в течение 5 и более лет, который не сопровождается интенсификацией АГТ. При этом КЖ, имея первоначально позитивную динамику, при длительном наблюдении не улучшается, что может быть связано с развивающимися ССО. Единственным предиктором непосредственного и отдаленного эффекта является исходный уровень офисного САД.

Ключевые слова: артериальная гипертензия, резистентная артериальная гипертензия, ренальная денервация, антигипертензивная терапия, качество жизни, длительное наблюдение, сердечно-сосудистые осложнения, исходы

Для цитирования: Ионов М.В., Емельянов И.В., Юдина Ю.С., Панарина С.А., Зверев Д.А., Авдонина Н.Г., Звартау Н.Э., Конради А.О. Результаты длительного проспективного наблюдения пациентов с резистентной артериальной гипертензией, прошедших процедуру радиочастотной аблации симпатических почечных нервов. Артериальная гипертензия. 2021;27(3):318–332. ***doi:10.18705/1607-419X-2021-27-3-318-332***

Introduction

Current epidemiological data indicate a continuing increase in the number of adults with persistently high blood pressure (BP) across the globe. This allows one to speak of hypertension (HTN) as the largest epidemic ever known to mankind [1]. According to expert opinion, the total number of hypertensive patients will reach 1.5 billion by 2025 but already exceeds 1 billion. Up to 30 % of them do not reach the target blood pressure (BP) despite the ongoing therapeutic interventions thus denoting the category of resistant to antihypertensive therapy (AHT) [2, 3].

The natural course of resistant HTN significantly worse in prognosis when compared with sustained uncontrolled HTN because the risk of cardiovascular mortality and morbidity multiplies. Great hopes for overcoming AHT resistance were associated with the introduction of renal sympathetic denervation (using radiofrequency or ultrasound energy, as well as application of an alcohol) [4].

To date, the most common and well-studied technology is radiofrequency ablation of sympathetic renal nerves (so-called renal denervation, RD), although the results of the studies are quite ambiguous [5]. The initial optimism of experts on this procedure [6] was replaced by the deep disappointment the results of a randomized trial (RCT) Symplicity HTN-3 (Renal Denervation in Patients with Uncontrolled Hypertension) were published, which did not demonstrate the advantages of RD over sham procedure after 6 months in terms of reducing average 24-hour systolic blood pressure (SBP) [7]. A careful analysis of the reasons for such serious disagreements in the results of the first

two generations of Symplicity HTN RCTs with the third one, posed a number of questions for the researchers regarding the design (need for liable adherence assessment, obligatory sham control), periprocedural aspects (e.g. incompetence of operators in some medical centers), technical flaws of RD systems [8, 9].

Today we are witnessing a new era of RCTs with an emphasis on stricter inclusion and selection criteria, on the use of multipolar electrodes with distal exposures (SPYRAL HTN OFF-MED Pivotal, SPYRAL HTN ON-MED). To date there are mostly the immediate and short-term (from 6 to 12 months of follow-up) RD results presented in the scientific literature [10–12]. Anecdotal data available on 24–36 months of follow-up [13–15]. Furthermore, the majority of research cases report only clinical efficacy, while other indicators (i.e. health-related quality of life, HRQoL), and on long-term hard outcomes remain underreported, albeit they are of special interest in the conceptual framework of value-based medicine [16].

The results of a meta-analysis of 6 RCTs [17] recommend the use of RD as a crucial intervention, but only for scientific purposes in clinical trials (albeit large ones) [18].

The aim of this study is to assess the course of the disease, to record long-term major adverse cardiovascular events (MACEs) and other hard outcomes, to evaluate efficacy of AHT in long-term follow-up of patients with resistant HTN who underwent bilateral RD.

Methods and design

This was an open-label prospective observational single-center single-arm study.

Patients with apparent resistant HTN were screened in at the Almazov National Medical Research Centre in 2012–2015. Inclusion/exclusion criteria were the following: age from 20 to 65 years; confirmed true resistant HTN (SBP ≥ 140 and / or diastolic blood pressure (DBP) ≥ 90 mm Hg despite taking ≥ 3 antihypertensive drugs in adequate doses, including a diuretic; secondary HTN had to be excluded); absence of CKD ≥G3b; satisfactory renal artery anatomy; absence of significant concomitant pathology (e.g., clinically-significant cardiovascular diseases, active oncological process of any localization in the previous 5 years, any systemic connective tissue disease).

First stage (before the RD procedure): anamneses morbi and vitae were collected, concomitant diseases were recorded, a clinical and laboratory study was carried out: measurement of office BP and heart rate (HR) in accordance with the current 2018 ESC/ESH Guidelines [19] with a validated device Omron M3 Expert (Omron HealthCare, Kyoto, Japan); ambulatory BP monitoring (ABPM) using the SpaceLabs Medical device (SpaceLabs HealthCare, Snoqualmie, WA, USA) according to the standard methodology [20]; laboratory tests including fasting glucose, total cholesterol, serum creatinine with eGFR (CKD-EPI) calculation. Patients were offered to fill out the generic HRQoL questionnaire — EuroQoL- 5D-5L (EQ-5D) available fully in Russian [21].

The procedural aspects of the implementation of the RD have been provided in detail elsewhere [22]. Briefly, after performing direct renal angiography through the femoral artery, a unipolar RD catheter (Symplicity, Medtronic Inc., Mountain View, Canada) was inserted alternately into the renal arteries with an introducer sheath to deliver 8W energy from the distal end (renal artery bifurcation) to the proximal (renal artery ostium) in a spiral, with a spatial step of 5 mm under temperature control (target temperature range at the end of the electrode 40–75 °C). A maximum of 8 applications were performed in each renal artery to ensure complete destruction of the nerve plexuses in the vascular adventitia. The average duration of the RD procedure and the time of fluoroscopy was 40 (35;45) minutes. After the RD procedure, the patients were observed in the cardiological ward for an average of 3 days (2; 5), then they were discharged with general recommendations and specifically on antihypertensive therapy (AHT).

Second stage: after 12 months patients were invited to visit Centre, which consisted of clinical and laboratory examination (same as baseline). The AHT was assessed and corrected by the researcher if necessary.

The third stage was performed in 2020 after the onset of 5 years from the date of the RD for the last of the patients enrolled (2015). It was carried out in the form of telehealth interaction between the researcher and the patient using a telephone survey; the receipt of medical documentation in electronic form for the past period was carried out using a previously developed telehealth platform

[16]. The following information was recorded: office BP values which were recorded at the last in-person medical appointment; cardiovascular events (myocardial infarction, unstable angina pectoris, acute cerebrovascular accident, atrial fibrillation, clinical manifestations of peripheral atherosclerosis except carotid sites). Moreover, the de novo cancer-related diseases with their sites were recorded.

Adherence to AHT at each visit was assessed based on standard interviews conducted with patients.

Statistical analysis

Continuous variables were presented as means and standard deviation (SD) or median (Me) with interquartile ranges (IQR) or minimum/maximum ratios where applicable. The distribution of the variables was tested via Kolmogorov-Smirnov Z-test. Between-group and within-group differences in continuous variables were tested using Student's t-test or Wilcoxon-Mann-Whitney test, according to the type of a distribution. The Friedman F-test and the Kendall W-test were used to assess differences for related samples at more than two time points. Categorial variables were presented as counts and percentages and compared between groups using $\chi 2$-test. Changes in medications between baseline and follow-up were compared with McNemar's test. Missing values were excluded from the analysis.

Multivariable linear regression analysis performed to assess independent correlates of the change in office SBP at 12 months and ≥ 5 years of follow-up. The following baseline characteristics were considered for regression model: age, sex, BMI, baseline office SBP, presence/absence of diabetes mellitus and/or dyslipidemia, baseline number of antihypertensive medications. Only covariates with a univariate $p < 0.2$ were considered in the multivariate model. Multivariable predictors were then determined from these covariates using a stepwise selection method with entry/stay significance levels of 0.1/0.1.

A two-tailed p-value <0.05 was considered statistically significant. Analyses were performed using SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA).

The study was conducted in according to ICH-GCP and Declaration of Helsinki principles (2013 revision). The study protocol was approved by the local Ethics Committee. Written informed consent was obtained from all participants prior to enrollment.

Results

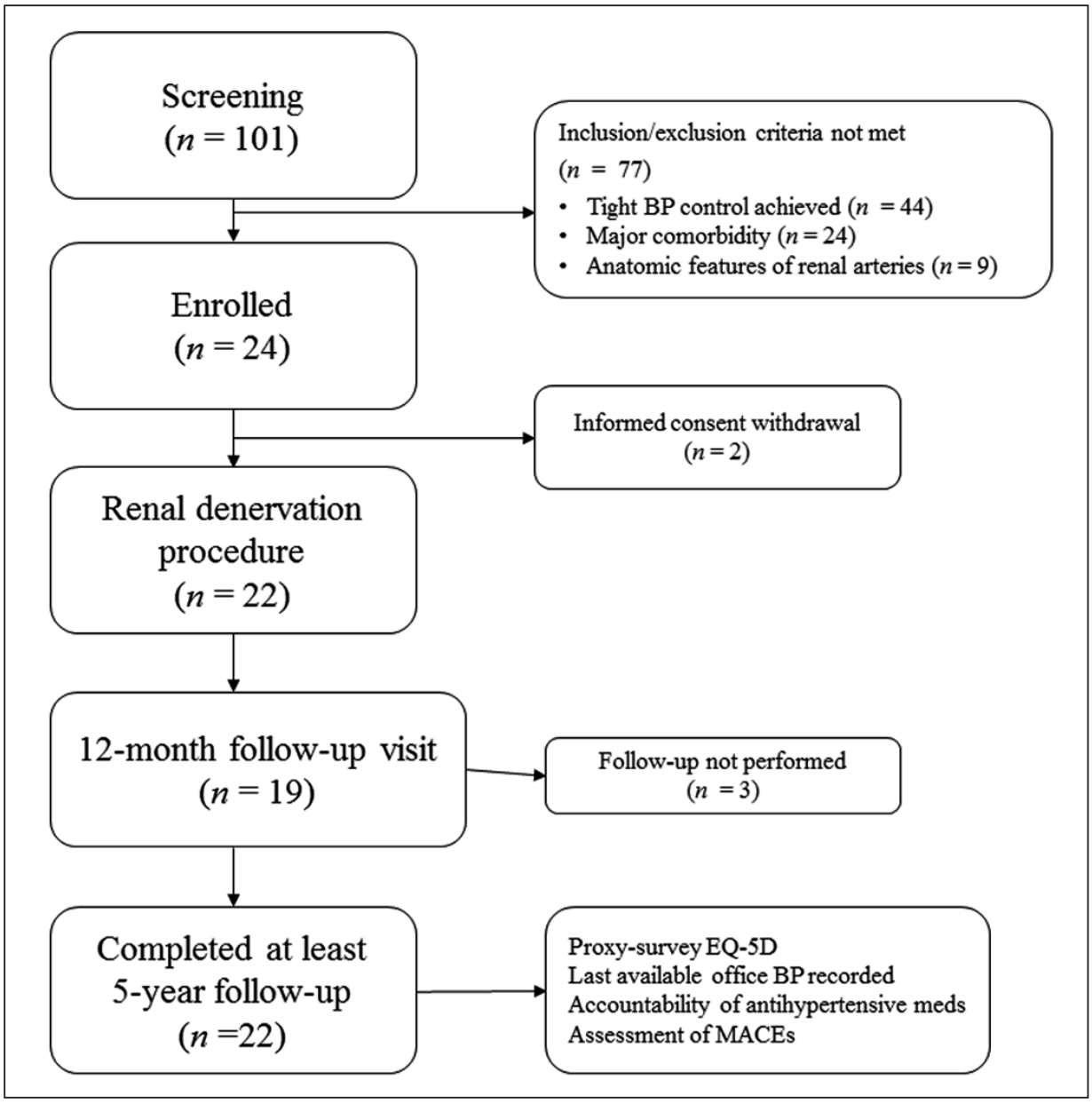
Overall, 101 patients were screened of which 77 patients were excluded for various reasons (Figure 1): BP on-target after AHT adjustment, comorbidity, unsatisfactory renal anatomy.

The average duration of the screening period was 8 ± 2 weeks. We included 24 patients, two of whom withdrew their informed consent before the RD was performed. The remaining 22 patients (median age 57 y.o., 9 males) underwent RD procedure. The perioperative period was silent for all patients and without serious complications. Specifically, there were no renal artery dissection wall and/or contrast-induced acute kidney injury. Rare adverse events related to the formation of a subcutaneous hematoma in the puncture site of the femoral artery which resolved without sequelae.

All patients received the baseline-like AHT at discharge after RD. On average, patients were recommended to take 4.4 medications on average (from 3 to 7).Three patients did not receive diuretic therapy due to its unsatisfactory subjective tolerance and concomitant uncontolled diabetes mellitus. In these patients, diuretic therapy was replaced by maximally tolerated doses of other drugs (centrally acting drugs/α-adrenergic blockers/peripheral vasodilators).

During the first 12 months, we noted a significant decrease in office SBP and DBP (–24 mmHg 95% CI [–37; –12], $p = 0.001$ and –12 mmHg 95% CI [–19; –4], $p = 0.004$, respectively). This was also true and for the mean daytime SBP and DBP (–10 mmHg 95% CI [–19; –1], $p = 0.033$- and –7-mmHg 95% CI [–14; –0, 5], $p = 0.038$, respectively). At 1 year after RD, 7 patients had reached the target office SBP (<140 mmHg) and 4 of them had office SBP below 130 mmHg. Nevertheless, there were 12 responders (significant clinical response to the RD procedure, indicated as a decrease in office SBP by > 10 mmHg) by the end of the first 12 months. We noticed a significant improvement in HRQoL at 12 months compared to the baseline (+9.7 points, 95% CI [1.7; 17.7], $p = 0.01$). The latter did not correlate with the dynamics of office SBP ($p = 0.46$).

Figure 1. Study design



The first patient underwent RD in 2012, the last procedure is dated October 2015. Thus, the median duration of long-term follow-up of patients was 6 years (from 5 to 8 years).

At the extended follow-up compared with the baseline values (n = 22), the average levels of office SBP and DBP remained noticeably lower. However, compared with the indicators achieved after 12 months (n = 19), in the 5-year office SBP and DBP values did not change (–1 mm Hg, 95 % CI [–12; 11], p = 0.862 and — 5 mm Hg, 95 % CI [–11; 1], p = 0.127, respectively), Figure 2.

Based on the data from the repeated office BP measurement, it was noted that 10 patients reached the target SBP (<140 mm Hg). Fourteen patients were recognized as "responders", since the decrease in office SBP exceeded 10 mm Hg.

After 12 months and after 5 years, there was no significant change in the number of prescribed antihypertensives (4.1 at both time points, p> 0.05).

The HRQoL level (according to proxy interview) did not significantly differ from the baseline (–3.8 points, 95 % CI [–14.0; 6.5], p = 0.37) values at the 5-year follow-up, although there was an obvious decrease in comparison with 12 months data (–13.8 points 95 % CI [–25.0; –2.7], p = 0.02).

During the long-term follow-up period, 10 patients had MACEs (the average time to first MACE 4±2.5 years) and 5 patients had cancer (time

Table 1

BASELINE CHARACTERISTICS

Parameter	Value
Age (years old), (Me, Q1;Q3)	57 (51; 65)
Males (n)	9
Anamnesis of HTN at the time of RD (years) (Me, Q1;Q3)	21 (13; 30)
Diabetes mellitus (n)	7
Dyslipidemia (n)	20
Obesity(n)	11
BMI (kg/m2)	30.7 ± 4.8
Office SBP (mmHg)	165 ± 23
Office SBP (mmHg)	95 ± 19
HR (bpm)	74 ± 11
24-h SBP (mmHg)	157 ± 20
24-h DBP (mmHg)	91 ± 17
Daytime SBP (mmHg)	161 ± 19
Daytime DBP (mmHg)	95 ± 17
Nighttime SBP (mmHg)	148 ± 24
Nighttime DBP (mmHg)	77 ± 24
EQ-5D (points of 100)	66 ± 19
Serum creatinine (μmol/L)	79.3 ± 24.5
eGFR (CKD-EPI), ml/min/1,73m^2	85.1 ± 17.8
Fasting glucose (mmol/L)	6.2 ± 1.0
Total cholesterol (mmol/L)	5.4 ± 1.1
Antihypertensive therapy	
Number of AHT (n), (Me, min-max)	4.4 (3–7)
ACE inhibitors	9
Angiotensin receptor blockers (n)	11
Diuretics (n)	20
β-blockers (n)	16
Calcium channel blockers (n)	19
Centrally acting agents (n)	13
Aldosterone antagonists (n)	3
α- adrenergic blockers (n)	5
Vasodilating agents (n)	1
Concomitant therapy	
Statins (n)	11
Aspirin (n)	16

Note: the variable "age" is presented as Me with an IQR, and AHT as Me and extreme (min-max) values. Other variables are presented as M ± SD.

Table 2

ANTIHYPERTENSIVE MEDICATION CHANGES IN PATIENTS THROUGHOUT FOLLOW-UP

Parameter	Baseline (n = 22)	12 months (n = 19)	≥ 5 years (n = 22)	*p*-value
Number of AHT (Me, Min-Max)	4.4 (3–7)	4.1 (2–7)	4.1 (1–6)	0.409
Guideline directed AHT (n)	13	14	14	0.774
ACE inhibitors (n)	9	10	5	0.289
Angiotensin receptor blockers (n)	11	6	15	0.125
Receiving maximally tolerated doses of iRAAS (n)	13	9	10	0.453
Thiazide diuretics (n)	14	11	13	0.739
Loop diuretics (n)	5	7	4	0.705
β-blockers (n)	16	13	14	0.625
Calcium channel blockers (n)	19	17	18	0.987
Aldosterone antagonists (n)	3	1	5	0.625
Centrally-acting agents (n)	13	10	11	0.934
α- adrenergic blockers (n)	5	1	2	0.453
Vasodilating agents (n)	1	2	1	1.00
Concomitant therapy				
Statins (n)	11	13	11	1.00
Aspirin (n)	16	17	11	0.344

Note: Extended follow-up versus baseline using the McNemar's test for categorical variables and the paired t-test for number of anti-hypertensive medications.

to diagnose 3.2±1.8 years) (Table 3). It should be noted that both MACEs and/or oncological processes did not lead to permanent disability.

In a subgroup analysis, there was a significant decrease in office SBP values in patients with controlled HTN (vs. peers with office SBP > 140/90 mmHg) (Table 4). In the other subgroup analysis of patients according to MACEs, there were no differences between the clinical and demographic baseline and their dynamic variables at all. Nevertheless, patients without MACEs were characterized by mild HTN, smaller AHT burden, and a positive HRQoL changes when compared with those who have suffered any CV events (Table 5). Differences in the decrease in office SBP among patients with baseline isolated systolic HTN and persistent systolic-diastolic HTN (Δ SBP –3 mm Hg versus –30 mm Hg after 5 years or more) were also not statistically significant (p = 0.051). Again, no association was found between the dynamics in office SBP and EQ-5D points (p = 0.624).

Baseline SBP was the only initial variable that was considered as a possible predictor for the SBP drop after 5 years of RD based on the results of multiple regression analysis (Table 6).

Discussion

In this study we have shown that RD is a clinically effective intervention in 12 months, and this effect persists for a longer period (from 5 years and beyond) while the volume and individual patterns of AHT do not significantly change over time.

The results of the very first study called SYMPLICITY HTN-1 [14] testified to the indisputable effect of the RD on office SBP and DBP. With increase in follow-up, the proportion of responders with also went up (from 69% after 1 month to 93% after 36 months after the RD). At the same time, the number of medications did not change signif-

Figure 2. The changes in office blood pressure after renal denervation

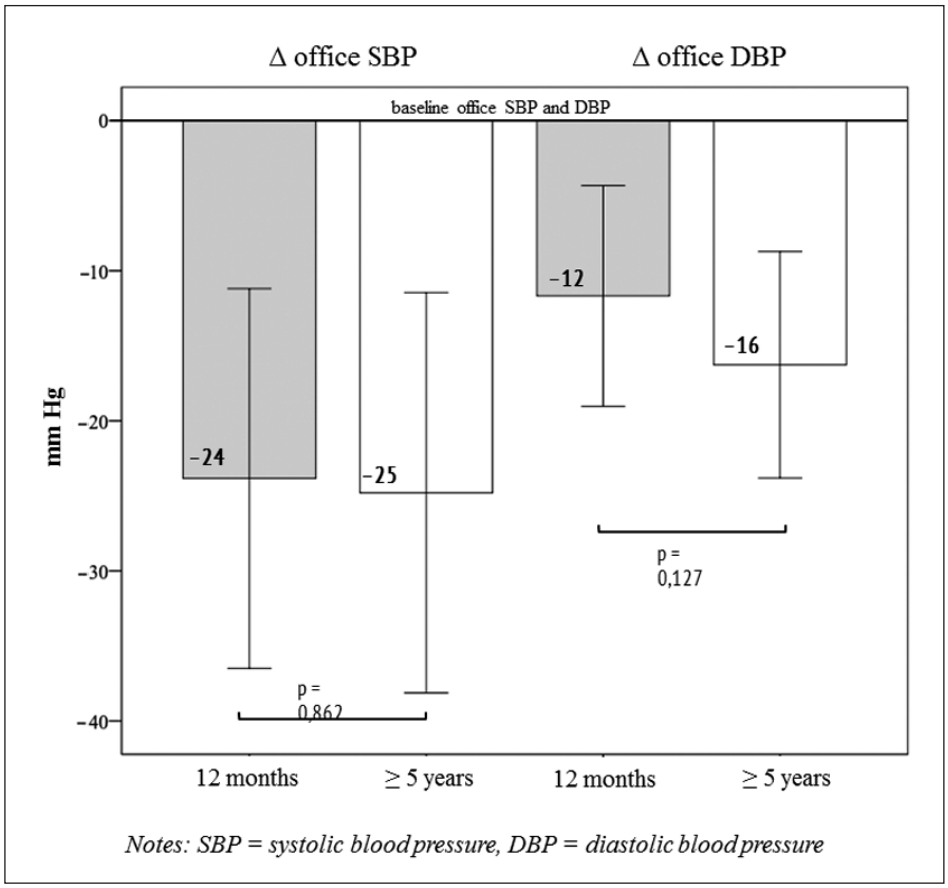


Table 3

LONG-TERM HARD CLINICAL ENDPOINTS

Type of outcome	
MACEs	
Any of MACE	10
Unstable angina	1
Myocardial infarction	1
Stroke	5
Atrial fibrillation	2
Low extremity arterial disease	1
Cancer	
Any of cancer-related diseases	5
Site: breast	1
Site: gaster	1
Site: large bowel	2
Site: uterus	1

Table 4

COMPARISON OF CLINICAL AND DEMOGRAPHIC CHARACTERISTICS AND EFFICACY PARAMETERS ACCORDING TO THE FACT OF BP CONTROL IN 5 OR MORE YEARS AFTER RD PROCEDURE

Parameter	Office SBP on target (n=10)	Office SBP not on target (n=12)	*p* value
Age (years old) (Me)	55	57	0,603
BMI (kg/m^2)	29,6 ± 3,0	31,7 ± 5,8	0,127
Baseline office SBP (mmHg)	167 ± 22	164 ± 24	0,891
Δ office SBP ≥ 5 years (mmHg)	–40 ± 23	–0,6 ± 24	0,001*
Baseline 24-h SBP (mmHg)	151 ± 18	163 ± 21	0,811
Baseline HRQoL (points EQ-5D)	63,7 ± 17,7	67,9 ± 21,2	0,424
HRQoL ≥ 5 years (points EQ-5D)	61,0 ± 16,1	64,6 ± 11,7	0,568
Δ HRQoL (Δ points EQ-5D) ≥ 5 years	–4,2 ± 19,1	–3,4 ± 24,9	0,61
Diabetes mellitus (n)	7	5	0,278
Dyslipidemia (n)	9	11	0,893
Number of AHT at baseline (Me)	4,2	4,6	0,623
Number of AHT ≥ 5 years (Me)	3,7	4,6	0,173

Note: variables "age", "the number of AHT taken at baseline and after ≥ 5 years" are indicated as Me, the values of the remaining continuous variables are indicated as M ± SD.

The indicated levels of differences in age and the number of AHT taken were assessed using the Mann-Whitney U-test, the rest of the variables were compared with each other using the Student's t-test

icantly, making up an average of 5 drugs (from 1 to 7) at baseline and after 3 years. In our study the dynamics of AHT remained unchanged. In the SYMPLICITY HTN-1, the proportion of patients taking diuretics in the cohort also did not reach 100%. The number of patients who received guideline-directed medical therapy (a diuretic, a RAAS inhibitor, and a calcium channel antagonist) — also remained unclear.

By the way the SYMPLICITY HTN-1 researchers have demonstrated the safety of RD in terms of adverse renal events. Among the undesirable events, 3 complications associated with arterial access were found. The SYMPLICITY HTN-2 study [23] reported one case of hematoma at the vascular access site, one case of renal artery dissection, 2 cases of delayed acute renal injury, and 15 cases of HTN-related hospitalizations over a three-year follow-up. All these cases were successfully resolved, but hemodynamically significant renal artery stenosis was subsequently detected in 4 patients. In our study, there were no clinically significant complications perioperatively and within 12-month of intensive observation.

Krum H. et al. (2014) reported 3 deaths not related to the RD procedure among the patients included in the study: one case of myocardial infarction 6 days after the intervention, 1 sudden cardiac death at 18 months, and 1 respiratory and circulatory arrest 24 months after surgery [14]. In our study we did not record fatal outcomes.

Only a small number of original studies in Russian are devoted to the use of RD in the treatment of resistant HTN. Anyway, all of them consistently demonstrate effectiveness of this intervention in reducing office and 24-hour BP values for 6–12 months and up to 5 years. Pilot study of Danilov NM et al. (2012) on the monthly effectiveness of RD in 5 patients opened the way for Russian research in the area [24].

According to Agaeva R.A. et al. (2018), 14% of patients who underwent RD with unipolar elec-

Table 5

CLINICAL AND DEMOGRAPHIC PARAMETERS AND EFFICACY OF THE INTERVENTION DEPENDING ON THE 5-YEAR OUTCOME STATUS AFTER RENAL DENERVATION

Parameter	MACE (n = 10)	No MACE (n = 12)	*p* value
Age (years old) (Me)	58	55	0.722
BMI (kg/m^2)	29.6 ± 3.0	31.7 ± 5.8	0.628
Baseline office SBP (mmHg)	167 ± 21.9	164 ± 24.0	0.821
Δ office SBP ≥5 years (mmHg)	–7 ± 30	–28 ± 29	0.180
Baseline 24-h SBP (mmHg)	164 ± 22	151 ± 17	0.180
Baseline HRQoL (points EQ-5D)	69.1 ± 19.1	63.5 ± 20.1	0.370
HRQoL ≥5 years (points EQ-5D)	60.5 ± 15.9	65 ± 11.8	0.468
Δ HRQoL (Δ points EQ-5D) ≥5 years	–10.2 ± 27.3	+1.5 ± 15.7	0.095
Diabetes mellitus (n)	3	4	0.868
Dyslipidemia (n)	9	11	0.893
Number of AHT at baseline (Me)	4.2	4.6	0.345
Number of AHT ≥5 years (Me)	4.7	3.6	0.099

Note: variables "age", "the number of AHT taken at baseline and after ≥5 years" are indicated as Me, the values of the remaining continuous variables are indicated as M ± SD.

The indicated levels of differences in age and the number of AHT taken were assessed using the Mann-Whitney U-test, the rest of the variables were compared with each other using the Student's t-test.

Table 6

MULTIVARIABLE PREDICTORS OF BASELINE CHARACTERISTICS CORRELATED WITH CHANGES IN OFFICE SBP AFTER ≥ 5 YEARS AFTER RD PROCEDURE

Covariates	β estimate (95% CI)	p-value
Sex	–0,9 (–36; 25)	0,7
Age	–0,1 (–2,1; 1,7)	0,8
BMI	–0,01 (–4; 4)	0,97
Baseline office SBP	–0,6 (–1,5; –0,2)	0,02*
Diabetes mellitus	–0,3 (–42; 38)	0,9
Dyslipidemia	–0,1 (–75; 57)	0,8
Baseline number of AHT medications	0,3 (–6,5; 21)	0,3

trode achieved the target BP values after 3 years comparing to 33 % on-target with a multipolar electrode after 1 year [25]. In our single-arm group, no differences were noted in the effectiveness of RD between males and females. On the contrary, the results of study conducted by Gapon L. I. et al. (2017) demonstrated intersex differences: both SBP and DBP decreased more noticeably in females [26].

Results of long-term observation made by Glybochko P. V. et al. (2018) [27] show that the number of medications dramatically decreases over time (from baseline of 4.6 drugs to 3.1 after 5 years after RD) and the level of office SBP and DBP progressively decreased more pronounced than even in the first year after the completion of the RD ($p < 0.05$). The researchers demonstrated that the indicators of the filtration function of the kidneys did not significantly change in the long-term follow-up and after 5 years the dynamics was –9.5 ml/min/1.73 m^2, which was associated with age-related changes. In our study, the eGFR indicator was assessed only after 1 year (that is, after the end of the active

observation period) and was not quantified further, but the qualitative analysis (patient survey) showed that none of the 22 operated patients had any significant adverse renal events.

The Global SYMPLICITY Registry (Global proSpective registrY for sympathetic renaL denervatIon in seleCted Indicators Through 3 Years Registry) [15] included 2237 patients who underwent RD with a flexible unipolar catheter electrode. The results of a 3-year follow-up were analyzed in 1742 patients. The volume and natural course of AHT are close to those described for patients in our study. The patients received 4 medications, as well as the participants in the Registry.

It is not entirely clear from the Registry data in how many patients the RD procedure was effective. The intragroup variance of BP indicators after the intervention suggests that not all patients have adequate BP decrease after the intervention. Subgroup analysis suggests that the magnitude of BP reduction was stronger in patients with severe HTN than in patients with "apparent" resistance and lower baseline office SBP. In our study, we also tried to subdivide patients according to some specific characteristics (target BP or MACEs) but this separation was futile. There are also Registry data available on the responders for the performed procedure: in 85% of patients, office SBP decreased by more than 10 mm Hg and in 68% it decreased by more than 20 mm Hg. When studying possible predictors of RD success, a set of found parameters is reported, but the initial SBP level is present at all time points, being the most stable of all the others (sex, age, antihypertensive medication classes). In our study we also have detected that baseline SBP only the baseline variable to predict further SBP drop at 5 years. Early data from the Global Registry [28] suggested that isolated systolic HTN may be one of the predictors of RD failure (the hypothesis of high vascular stiffness and low arterial compliance), and patients with this form of the disease were even excluded from the second wave of RCTs but this hypothesis was not confirmed in the following [29]. In our study, there was only a tendency for a less pronounced response in patients with isolated systolic HTN compared to the rest of the patients, without statistical significance ($p = 0.051$).

We specifically aimed to assess the dynamics of HRQoL after RD. It is of special interest because barely a small number of studies brushes against this problem in hypertensive patients. Lambert G.W. et al. [30] noted that 6 months after the procedure HRQoL (assessed by MOS SF-36 and Beck Depression Inventory) improved significantly, both in terms of overall vitality and in the emotional, social, and mental domains. Long-term HRQoL results were described in one of the Russian studies [27]: in 14 patients the EQ-5D score 12 months after RD increased by an average of 20 points but then it decreased by 6 points in the next 5 years. Neither study found an association between the magnitude of BP reduction after RD and changes in HRQoL (irrespectively of the questionnaire being used).

In our study we have observed an obvious positive trend in the EQ-5D score 12 months after the RD. However, there was a significant drop in the HRQoL to the baseline between the second and the third stage of the trial. Within the framework of this small study, one can only assume the association of such a recession 1) gradual increase in the number MACEs and cancer-related illnesses; 2) lack of close medical supervision in the center of excellence from after 12 months. These assumptions require confirmation in larger longitudinal studies; also it is worth mentioning that a more accurate assessment of a HRQoL can be obtained using disease-specific questionnaires [31].

Limitations

It must be acknowledged that our research has certain limitations which should be considered.

Firstly, based on design, our study is single-arm with no control group. Since only unipolar catheter was used in all the RD procedures, a comparative analysis with other cohorts (from the second generation of RCTs with multipolar or ultrasound catheters [32]) sems to be irrelevant. Secondly, the sample size of patients included in the study was rather small, limiting the possibilities for adequate statistical processing. One should also make a point of the fact that out-of-office BP (24-hour and home) was not evaluated albeit in most modern RD trials, the main efficacy endpoint is the average ambulatory BP [33]. Finally, there was no AHT standardization and no direct adherence assessment.

Conclusions

Our study demonstrated that in most patients with resistant HTN office SBP and DBP decreased significantly after RD procedure. This clinical effect was not accompanied by an increase in the number and dosages of AHT or by changes in HRQoL. The only baseline variable associated with a greater reduction in office SBP was higher baseline SBP.

No differences were found in subgroup analyses according to presence of MACEs and target BP. At 12 months after RD there was an obvious improvement in HRQoL, followed by restoring the initial levels which is probably linked to MACEs accumulation, as well as a decrease in the intensity of medical follow-up over time.

Larger studies are needed focusing on long-term follow-up of patients undergoing RD, with control groups, standardization of therapy and control of adherence.

Funding

This work was supported by the Russian Science Foundation, project № 17–15–01177.

Conflict of interest

The authors declare no conflict of interest.

References

1. Yusuf S, Wood D, Ralston J, Reddy KS. The World Heart Federation's vision for worldwide cardiovascular disease prevention. Lancet. 2015;386(9991):399–402. doi:10.1016/S0140-6736(15)60265-3

2. Egan BM, Kjeldsen SE, Grassi G, Esler M, Mancia G. The global burden of hypertension exceeds 1.4 billion people: should a systolic blood pressure target below 130 become the universal standard? J Hypertens. 2019;37(6):1148–1153. doi:10.1097/HJH.0000000000002021

3. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension. 2018;72(5):e53–e90. doi:10.1161/HYP.0000000000000084

4. Shaw JA, Warren JL. Resistant hypertension and renal denervation where to now? Cardiovasc Ther. 2015;33(1):9–14. doi:10.1111/1755-5922.12103

5. Gulati R, Raphael CE, Negoita M, Pocock SJ, Gersh BJ. The rise, fall, and possible resurrection of renal denervation. Nat Rev Cardiol. 2016;13(4):238–44. doi:10.1038/nrcardio.2016.1

6. Schlaich MP, Schmieder RE, Bakris G, Blankestijn PJ, Böhm M, Campese VM et al. International expert consensus statement: Percutaneous transluminal renal denervation for the treatment of resistant hypertension. J Am Coll Cardiol. 2013;62(22):2031–2045. doi:10.1016/j.jacc.2013.08.1616

7. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393–1401. doi:10.1056/NEJMoa1402670

8. Ott C, Schmieder RE. Renal denervation for resistant hypertension: past, present, and future. Curr Hypertens Rep. 2015;17(8):65. doi:10.1007/s11906-015-0577-6

9. Ukena C, Cremers B, Ewen S, Böhm M, Mahfoud F. Response and non-response to renal denervation: who is the ideal candidate? EuroIntervention. 2013;9 Suppl R: R54–R57. doi:10.4244/EIJV9SRA10

10. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018;391(10137):2346–2355. doi:10.1016/S0140-6736(18)30951-6

11. Böhm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet. 2020;395(10234):1444–1451. doi:10.1016/S0140-6736(20)30554-7

12. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet. 2015;385(9981):1957–1965. doi:10.1016/S0140-6736(14)61942-5

13. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension. 2011;57(5):911–917. doi:10.1161/HYPERTENSIONAHA.110.163014

14. Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet. 2014;383(9917):622–629. https://doi.org/10.1016/S0140-6736(13)62192-3

15. Mahfoud F, Böhm M, Schmieder R, Narkiewicz K, Ewen S, Ruilope L et al. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. Eur Heart J. 2019;40(42):3474–3482. doi:10.1093/eurheartj/ehz118

16. Ionov MV, Zhukova OV, Yudina YS, Avdonina NG, Emelyanov IV, Kurapeev DI et al. Value-based approach to blood pressure telemonitoring and remote counseling in hypertensive patients. Blood Press. 2020:1–11. doi:10.1080/08037051.2020.1813015

17. Sardar P, Bhatt DL, Kirtane AJ, Kennedy KF, Chatterjee S, Giri J et al. Sham-controlled randomized trials of catheter-based renal denervation in patients with hypertension. J Am Coll Cardiol. 2019;73(13):1633–1642. doi:10.1016/j.jacc.2018.12.082

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. Eur Heart J. 2018;39(33):3021–3104. doi:10.1093/eurheartj/ehy339

19. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–2219. doi:10.1093/eurheartj/eht151

20. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G et al. European society of hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014;32(7):1359–1366. doi:10.1097/HJH.0000000000000221

21. The questionnaire about health (EQ-5D-5L). Russian vesion. URL: https://scardio.ru/content/activities/2016/Russia_(Russian)_EQ-5D-5L.pdf. Access date: 14.12.2020. In Russian.

22. Panarina SA, Yudina YuS, Ionov MV, Avdonina NG, Emelyanov IV, Vasileva EU et al. Impact of aggressive blood pressure reduction on kidney function after renal denervation: long-term outcome. Arterial'naya Gipertenziya = Arterial Hypertension. 2020;26(1):94–106. doi:10.18705/1607-419X-2020-26-1-94-106. In Russian.

23. Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. Eur Heart J. 2014;35(26):1752–1759. doi:10.1093/eurheartj/ehu209

24. Danilov NM, Matchin YuG, Chazova IE. Endovascular radiofrequency denervation of renal arteries as an innovation method of treatment of refractory arterial hypertension: first experience in Russia. Angiology and Vascular Surgery. 2012;18(1):51–54. In Russian.

25. Agaeva RA, Danilov NM, Shelko-va GV, Sagaydak OV, Grigin VA, Matchin UG et al. Radiofrequency renal denervation with different device for treatment in patient with uncontrolled hypertension. Syst Hypertens. 2018;15(4):34–38. doi:10.26442/2075082X.2018.4.000043. In Russian.

26. Gapon LI, Mikova EV, Savelyeva NYu, Kolumin GV, Zherzhova AYu. Clinical efficacy of sympathetic denervation of renal arteries in patients with resistant arterial hypertension as part of annual prospective follow-up. Syst Hypertens. 2017;14(2):41–44. doi:10.26442/2075-082X_14.2.41-44. In Russian.

27. Glybochko PV, Svetankova AA, Rodionov AV, Maltseva AS, Sulimov VA, Fomin VV. Renal denervation with a resistant arterial hypertension: the results of a five-year follow-up. Ter Arkh. 2018;90(9):88–91. doi:10.26442/terarkh201890988-91. In Russian.

28. Mahfoud F, Bakris G, Bhatt DL, Esler M, Ewen S, Fahy M et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. Eur Heart J. 2017;38(2):93–100. doi:10.1093/eurheartj/ehw325

29. Kandzari DE, Mahfoud F, Bhatt DL, Böhm M, Weber MA, Townsend RR et al. Confounding factors in renal denervation trials. Hypertension. 2020;76(5):1410–1417. doi:10.1161/HYPERTENSIONAHA.120.15745

30. Lambert GW, Hering D, Esler MD, Marusic P, Lambert EA, Tanamas SK et al. Health-related quality of life after renal denervation in patients with treatment-resistant hypertension. Hypertension. 2012;60(6):1479–1484. doi:10.1161/HYPERTENSIONAHA.112.200865

31. Ionov MV, Zvartau NE, Dubinina EA, Khromov-Borisov NN, Tregubenko IA, Konradi A. O. Hypertension specific patient-reported outcome measure. Part III: validation, responsiveness and reliability assessment. Russ J Card. 2020;25(3):109–120. doi:10.15829/1560-4071-2020-3-3438. In Russian.

32. Papademetriou V, Stavropoulos K, Doumas M, Tsioufis K. Now that renal denervation works, how do we proceed? Circ Res. 2019;124(5):693–695. doi:10.1161/CIRCRESAHA.119.314695

33. Gupta A, Prince M, Bob-Manuel T, Jenkins JS. Renal denervation: alternative treatment options for hypertension? Prog Cardiovasc Dis. 2020;63(1):51–57. doi:10.1016/j.pcad.2019.12.007

Author information

Mikhail V. Ionov, MD, PhD, Junior Researcher, Research Laboratory of Pathogenesis and Treatment of Hypertension, Department of Hypertension, Almazov National Medical Research Centre, ORCID: 0000–0002–3664–5383, e-mail: ionov_mv@almazovcentre.ru;

Igor V. Emelyanov, MD, PhD, Senior Researcher, Research Laboratory of Pathogenesis and Treatment of Hypertension, Department of Hypertension, Almazov National Medical Research Centre, ORCID: 0000–0002–3176–0606, e-mail: emelyanov_iv@almazovcentre.ru;

Yulia S. Yudina, MD, Junior Researcher, Research Laboratory of Pathogenesis and Treatment of Hypertension, Research Department of Hypertension, Almazov National Medical Research Centre, e-mail: yudina_ys@almazovcentre.ru;

Svetlana A. Panarina, MD, PhD, Junior Researcher, Research Laboratory of Pathogenesis and Treatment of Hypertension, Research Department of Hypertension, Almazov National Medical Research Centre, e-mail: panarina_sa@almazovcentre.ru;

Dmitryi A. Zverev, MD, PhD, Senior Researcher, Department for Inverventional Surgery, Almazov National Medical Research Centre;

Natalia G. Avdonina, MD, Researcher, Research Laboratory of Pathogenesis and Treatment of Hypertension, Research Department of Hypertension, Almazov National Medical Research Centre, e-mail: avdonina_ng@almazovcentre.ru;

Nadezhda E. Zvartau, MD, PhD, Deputy General Director for Work with Regions; Senior Researcher, Research Laboratory of Pathogenesis and Treatment of Hypertension, Research Department of Hypertension, Almazov National Medical Research Centre, Senior Researcher, Translational Medicine Institute, ITMO University, ORCID: 0000–0001–6533–5950, e-mail: zvartau_ne@almazovcentre.ru;

Aleksandra O. Konradi, MD, PhD, DSc, Professor, Corresponding Member of RAS, Head, Research Laboratory of Pathogenesis and Treatment of Hypertension, Research Department of Hypertension, Deputy General Director on Research, Almazov National Medical Research Centre, Director, Translational Medicine Institute, ITMO University, ORCID: 0000–0001–8169–7812, e-mail: konradi_ao@almazovcentre.ru.

Информация об авторах

Ионов Михаил Васильевич — младший научный сотрудник научно-исследовательской лаборатории патогенеза и терапии артериальной гипертензии научно-исследовательского отдела артериальной гипертензии ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, ORCID: 0000–0002–3664–5383, e-mail: ionov_mv@almazovcentre.ru;

Емельянов Игорь Витальевич — кандидат медицинских наук, старший научный сотрудник научно-исследовательской лаборатории патогенеза и терапии артериальной гипертензии научно-исследовательского отдела артериальной гипертензии ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, ORCID: 0000–0002–3176–0606, e-mail: emelyanov_iv@almazovcentre.ru;

Юдина Юлия Сергеевна — младший научный сотрудник научно-исследовательской лаборатории патогенеза и терапии артериальной гипертензии научно-исследовательского отдела артериальной гипертензии ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: yudina_ys@almazovcentre.ru;

Панарина Светлана Алексеевна — младший научный сотрудник научно-исследовательской лаборатории патогенеза и терапии артериальной гипертензии научно-исследовательского отдела артериальной гипертензии ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: panarina_sa@almazovcentre.ru;

Зверев Дмитрий Анатольевич — кандидат медицинских наук, ведущий научный сотрудник, заведующий научно-исследовательской лабораторией интервенционной хирургии ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России;

Авдонина Наталья Георгиевна — научный сотрудник научно-исследовательской лаборатории патогенеза и терапии артериальной гипертензии научно-исследовательского отдела артериальной гипертензии ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: avdonina_ng@almazovcentre.ru;

Звартау Надежда Эдвиновна — кандидат медицинских наук, заместитель генерального директора по работе с регионами, старший научный сотрудник научно-исследовательской лаборатории патогенеза и терапии артериальной гипертензии, научно-исследовательского отдела артериальной гипертензии ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, старший научный сотрудник Института трансляционной медицины Университета ИТМО, ORCID: 0000–0001–6533–5950, e-mail: zvartau_ne@almazovcentre.ru;

Конради Александра Олеговна — доктор медицинских наук, профессор, член-корреспондент Российской академии наук, заместитель генерального директора по научной работе, заведующая научно-исследовательской лабораторией патогенеза и терапии артериальной гипертензии научно-исследовательского отдела артериальной гипертензии ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, директор Института трансляционной медицины Университета ИТМО, ORCID: 0000–0001–8169–7812, e-mail: konradi_ao@almazovcentre.ru.