Arablinskiy *et al. Vessel Plus.* 2025;9:6
DOI: 10.20517/2574-1209.2025.38

Vessel Plus

Original Article

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Two-year follow-up outcomes of renal denervation in polymorbid patients with true resistant hypertension, type 2 diabetes mellitus and coronary artery disease

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How to cite this article: Arablinskiy NA, Feshchenko DA, Vasiliev DK, Shanoyan AS, Shukurov FB, Taliuridze MT, Kiselev AR, Drapkina OM. Two-year follow-up outcomes of renal denervation in polymorbid patients with true resistant hypertension, type 2 diabetes mellitus and coronary artery disease. *Vessel Plus.* 2025;9:6. https://dx.doi.org/10.20517/2574-1209.2025.38

Received: 8 Apr 2025 **First Decision:** 26 May 2025 **Revised:** 9 Jun 2025 **Accepted:** 25 Jun 2025 **Published:** 1 Jul 2025

Academic Editor: Aijun Sun **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Aim: To study the clinical effects and long-term outcomes of radiofrequency renal denervation (RDN) in patients with true resistant arterial hypertension, type 2 diabetes mellitus, and coronary artery disease after completed myocardial revascularization.

Methods: 75 patients were randomized into RDN and control groups (1:1.5). RDN was performed via femoral access using a Spyral catheter (Medtronic, USA). The primary endpoint was the change in blood pressure (BP). Secondary endpoints were: the development of cardiovascular and cerebral complications, changes in laboratory and instrumental parameters, changes in antihypertensive medication, late lumen loss (LLL) in the stented segments [measured by computer-assisted quantitative coronary angiography analysis (QCA)], and the frequency of *de novo* stenosis.

Results: In the RDN group, there was a significant decrease in both office (o) and average daily (ad) systolic (S) and diastolic (D) BP (oSBP: -8 mmHg; oDBP: -6 mmHg; adSBP: -11 mmHg; adDBP: -8 mmHg - $P < 0.05$); decreased activity of plasma renin Δ-2.44 ng/mL/h; concentrations of angiotensin I Δ -1.27 ng/mL and aldosterone Δ -13 pg/mL - $P < 0.05$); decrease in fasting glycemia (Δ -2.73 mmol/l - $P < 0.05$), HbA1c (Δ -1% - $P < 0.05$) and the level of insulin resistance according to HOMA-IR index (Δ -1.78 - $P < 0.05$), as well as a decrease in the

concentration of C-reactive peptide in the blood (Δ -1.84 mg/L - $P < 0.05$). No significant dynamics of these indicators were recorded in the control group. The effectiveness of RDN was highest in the cohorts of obese patients - OR 1.31 (95%CI: 1.17-1.44), patients with obstructive sleep apnea syndrome - OR 1.73 (95%CI: 1.23-2.26) and tachycardia - OR 2.02 (95%CI: 1.69-3.10); $P < 0.001$ in all cases. The incidence of major adverse cardiovascular events (26.7% in the RDN group; 24.4% in the control group), the average LLL (24.7% in the RDN group; 28.1% in the control group), and the incidence of de novo stenosis (23.3% in the RDN group; 22.2% in the control group) did not differ between the groups.

Conclusion: The use of RDN in the cohort of comorbid patients is safe and enables better control of modifiable risk factors of progression of resistant arterial hypertension and type 2 diabetes mellitus due to an improvement of BP, carbohydrate metabolism parameters, regulatory factors of the renin-angiotensin-aldosterone system (RAAS), and factors of the systemic inflammatory response.

Keywords: Comorbidity, diabetes, insulin resistance, hypertension, coronary artery disease, renal denervation, radiofrequency ablation

INTRODUCTION

Despite significant progress in the quality of medical care, cardiovascular diseases remain the leading cause of death worldwide. Arterial hypertension (AH) and diabetes mellitus (DM) have a number of common mechanisms of development and progression and their complications within micro- and macroangiopathies largely overlap, which makes these two diseases the main risk factors for vascular disasters[1].

Unfortunately, despite significant progress in the quality of medical care, resistant AH, in which the target blood pressure (BP) level is not reached by prescribing ≥ 3 antihypertensive drugs (AHD) in optimal doses with proven patient compliance and exclusion of secondary causes of hypertension, is quite common in clinical practice[2]. Poorer BP control is associated with an increased risk of adverse cardiovascular events, disability and a worse long-term life prognosis. The presence of comorbid conditions in the form of a combination of AH with obesity, metabolic syndrome, DM, obstructive sleep apnea syndrome (OSAS), and chronic kidney disease (CKD) supports the vicious cycle of AH progression and increases the risk of resistance to various antihypertensive therapy regimens[3,4].

The global increase in the number of patients with DM is clearly noticeable[5,6]. Hyperglycemia, insulin resistance, and high levels of glycation products are associated with an increased risk of atherosclerosis in the coronary and peripheral arteries[7,8]. Therefore, DM plays a key role in the development of chronic coronary artery disease (CAD). Due to the accelerated loss of lumen in the stented arterial segment and the development of restenosis after revascularization in patients with type 2 DM, it is important to control hyperglycemia and reduce insulin resistance.

The pathophysiological processes that underlie the development and progression of DM and AH have several similarities, although the combined presence of these conditions accelerates the damage of target organs and increases the risk of severe complications. Treatment strategies for patients with comorbid DM and AH require a comprehensive approach that addresses multiple systems and targets. This includes controlling blood glucose levels, reducing insulin resistance, and managing BP. Insulin resistance and hyperactivity of the sympathetic nervous system are key factors in the progression of both conditions, forming a vicious cycle that must be interrupted. Due to the growing prevalence of comorbidities and the increasing number of patients with resistant AH, ongoing research is focused on effective and safe

interventions to target these underlying mechanisms.

The technique of renal denervation (RDN) involves the destruction (ultrasound or radiofrequency) of high-density sympathetic nerve fibers located in the perivascular tissue of the renal arteries. The selective destruction of these nerve endings results in a reduction in sympathetic innervation to the kidneys, leading to a decrease in systemic hyperactivity of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS)[9].

Results of multicenter randomized controlled trials have demonstrated the antihypertensive effectiveness and safety of this procedure in patients with preserved kidney function (glomerular filtration rate (GFR) greater than 40 mL/min/m^2)[10]. This has led to the inclusion of RDN in the arsenal of cardiologists and interventional radiologists, as well as its approval as a complementary treatment option for optimal medical therapy in managing resistant AH[8]. In addition, during the study of the technique in clinical practice, several pleiotropic effects of RDN were identified, the exact mechanism of which has not been fully understood. The procedure has been shown to have a positive impact on the course of CKD and chronic heart failure and to reduce the frequency of paroxysmal atrial fibrillation and ventricular arrhythmias[11]. Contradictory findings regarding the effect of RDN on glycemic control and insulin resistance prevent us from fully answering the question of its efficacy in correcting metabolic disorders in patients with DM[12,13].

The benefits of renal denervation for patients with resistant hypertension have been studied, and the impact of this procedure on metabolic syndrome and type 2 DM is currently under investigation. However, there has been no published data on the effects of RDN among patients with comorbid conditions such as AH, DM, and CAD. This is where the novelty of this study lies. It is hypothesized that by better controlling BP and blood sugar levels in these patients, it may be possible to improve their long-term prognosis and reduce the risk of cardiovascular events.

The aim of this study is to investigate the clinical effectiveness of RDN performed by a radiofrequency catheter (Spyral, Medtronic, USA) in patients suffering from resistant AH, type 2 DM and CAD after full endovascular revascularization.

MATERIALS AND METHODS

A prospective, randomized, controlled single-center study was conducted on 75 patients with true resistant AH, combined with type 2 DM and CAD after complete myocardial revascularization by percutaneous coronary intervention. The study took place between 2021 and 2024 at the Department of Interventional Cardiology of the "National Medical Research Center for Therapy and Preventive Medicine", Moscow, Russia.

The inclusion criteria for the study were the presence of essential AH, with a BP level of ≥ 140/90 mmHg, on at least three AHD at their maximum doses for more than four weeks before screening [compliance to therapy was evaluated based on results from the Morisky adherence questionnaire and the Brief Medicine Questionnaire (BMQ)]; type 2 DM and completed endovascular myocardial revascularization. The study excluded patients with secondary AH, incomplete myocardial revascularization, CKD stages 4 and 5, abnormalities and/or atherosclerotic lesions of the renal arteries (stenosis > 70%), stented renal arteries, type 1 DM, or anaphylaxis to contrast agents. Participants were informed about the importance of following a regimen of antihypertensive, lipid-lowering, and hypoglycemic medications throughout the study. During follow-up visits, compliance with treatment was monitored and changes in medication were made if needed.

Seventy-five patients were randomized in a 1:1.5 ratio into RDN and control groups. Randomization was performed using a computer-generated sequence. All patients underwent a series of tests and examinations. These included a survey (collecting complaints and medical history), physical examination, laboratory tests, and instrumental examinations. The laboratory tests included a general blood test and biochemical blood tests to determine lipid levels and parameters of carbohydrate metabolism, such as fasting glucose and glycated hemoglobin. Additionally, renal function was assessed using the estimated glomerular filtration rate and indicators of the RAAS and cortisol were measured. Other tests included determining the levels of adiponectin, leptin, and C-reactive protein (CRP). Instrumental examinations included echocardiography to assess heart function, 24H BP monitoring, and coronary angiography to evaluate the severity of coronary artery stenosis.

RDN was performed under intravenous sedation with a puncture of the right common femoral artery performed under ultrasound guidance. Using a Symplicity Spyral catheter, Medtronic (USA), both the main trunk and distal branches of the renal arteries were subjected to ablation, with the number of ablations determined by the anatomical features of the vessels. All patients underwent pre- and post-procedure angiography of their renal arteries.

Follow-up visits were conducted after 12 and 24 months, and patients were followed with structured clinical evaluations, ABPM, lab testing, and coronary angiography (QCA-based) performed at both time points. The main endpoint of the study was the change in the average daily BP level. Secondary endpoints included the development of cardiovascular and cerebral complications (death, non-fatal myocardial infarction, acute cerebrovascular event, death from cardiovascular causes, repeated revascularization in the coronary artery), as well as changes in laboratory and instrumental parameters, medication adjustments, stent patency as assessed by average late lumen loss (LLL) in stented segments using computer-assisted quantitative coronary angiography analysis (QCA), and the incidence of de novo stenosis. All adverse cardiovascular events (MACE) were adjudicated by an independent cardiologist blinded to treatment allocation, based on predefined criteria consistent with the ESC definitions for clinical trials.

The statistical analysis was done using the IBM SPSS version 23 software (developed by IBM). Quantitative indicators were reported using the median (Me) and interquartile range. Categorical variables were represented quantitatively and as percentages. Standard methods of descriptive statistics were used to identify differences between continuous variables in independent samples (Mann-Whitney U test) and paired samples (Wilcoxon W test). To analyze qualitative data, Fisher's exact test (two-way significance level) and χ^2 test were used. To identify indicators that determine the success of the proposed method, one-factor Cox regression analysis was performed. A critical significance level of 0.05 was considered for all tests. Missing data were < 5% for all primary variables. No imputation was used.

RESULTS

In the RDN group, the average age of participants was 65 years, and in the control group, 66 years. The groups were comparable in gender, body mass index, smoking status, and other diseases. Most of the participants had obesity, the majority of participants had multifocal atherosclerosis, and 10% of the subjects in each group had a history of cardiovascular events. Despite this, the left ventricular ejection fraction and renal function (according to the calculated GFR) were preserved and comparable [Table 1]. All patients in both groups received multicomponent antihypertensive therapy, maximum-dose statin therapy, and sugar-lowering therapy [Table 2]. It was observed that the achievement of the target HbA1c value was noted. Unfortunately, despite high-dose statin therapy and combinations with ezetimibe, the target LDL cholesterol level was not reached in both groups.

Table 1. Basic characteristics of the patients

Parameters	Group		*P*
	RDN	Control	
	n = 30	*n* = 45	
Age, years	65 (52, 70)	66 (55, 71)	0.184
Gender, male (%)/female (%)	14 (47)/16 (53)	27 (60)/18 (40)	0.901
Body mass index, kg/m^2	33.9 (28.4, 38.1)	32.0 (28.1, 38.0)	0.552
Smoking, yes/no, n (%)	9 (30)/21 (70)	15 (33.3)/30 (66.7)	0.797
OSAS, yes/no, n (%)	5 (16.7)/25 (83.3)	7 (15.5)/38 (86.7)	0.321
Stroke, yes/no, n (%)	3 (10)/27 (90)	5 (11)/40 (89)	0.866
Multifocal atherosclerosis, yes/no, n (%)	26 (86.7)/4 (13.3)	39 (86.6)/6 (13.4)	0.616
LV EF, (%)	58 (52, 64)	61 (50, 65)	0.911
Lp(a), mg/dL	19.85 (7.37, 28.82)	13.60 (8.50, 27.60)	0.688
Stented coronary segments			
Segments: n (%)			
Left main	2 (6.67)	3 (6.67)	
LAD	18 (60)	27 (60)	
Circumflex	4 (13.33)	6 (13.33)	
RCA	6 (20)	9 (20)	
Number of stents for each patient, n	1.27	1.31	0.695
Length of stented segments, mm	29 (23, 38)	31 (26, 43)	0.390

Values are median with low and upper quartiles - Me (LQ, UQ); LAD: left arteria descending; Lp(a): lipoprotein (a); LV EF: left ventricle ejection fraction; OSAS: obstructive sleep apnea syndrome; RCA: right coronary artery; RDN: renal denervation.

During renal denervation, an average of 91.3 ± 25.2 mL of X-ray contrast agent was used, and the procedure lasted an average of 78.5 ± 14.8 min. A total of 41.9 ± 6.8 complete ablations were performed, including 18.3 ± 6.3 in the main branches and 23.0 (range: 17.2-28.8) in the daughter branches. No systemic or access site complications occurred in any case.

After 12 and 24 months, the intervention group showed a significant antihypertensive effect of the procedure, demonstrated by a decrease in both systolic and diastolic BP ($P < 0.05$). In the RDN group, there was a significant decrease in plasma renin activity by two times compared with baseline values. There was also a decrease in the level of other indicators of the RAAS: angiotensin I and aldosterone ($P < 0.05$ for both indicators); the level of CRP significantly decreased, with a 2-fold decrease in its concentration compared to the baseline. These indicators showed no significant variation in the control group. The intervention did not affect the concentration of cortisol and fibrinogen. In addition, the procedure led to a significant reduction in fasting glycemia levels, HbA1c, and the estimated insulin resistance index (HOMA-IR) ($P < 0.05$), without a corresponding significant decrease in participants' body mass index. During the 2-year follow-up period, GFR in the intervention group participants remained stable. The procedure had no effect on the parameters of lipid metabolism. There were no significant dynamics of these indicators in the control group [Table 3].

Based on a detailed analysis of the laboratory and instrumental parameters assessing procedural efficacy, and supported by literature data, two main criteria for maximal effectiveness of RDN were identified: a decrease in average daily systolic BP > 10 mmHg and a decrease in HbA1c levels by 1%. In the intervention group, 73% and 53% of patients achieved these respective criteria, compared to 23% and 10% in the control group (intergroup $P < 0.05$ for both). When determining the indicators that determine the success of RDN, it was found that the effectiveness of this procedure is highest in the cohorts of obese patients - OR 1.31

Table 2. Initial drug therapy

Parameter	RDN (*n* = 30)	Control (*n* = 45)	*P*
Antihypertensive therapy			
Number of medicaments	4,00	4,00	
ACE inhibitors/ARBs, abs. (%)	22/8 (100)	36/9 (100)	0.579
Diuretics, abs. (%)	30 (100)	45 (100)	
β-blockers, abs. (%)	30 (100)	45 (100)	
Ca-antagonists, abs. (%)	30 (100)	45 (100)	
Sugar-lowering therapy			
Insulin + Metformin	-	1 (2)	
Insulin + Dapagliflozin	2 (6.7)	3 (6.7)	
Insulin + Metformin + Dapagliflozin	2 (6.7)	3 (6.7)	
Metformin	23 (76.7)	36 (80.0)	0.758
Metformin + Dapagliflozin	3 (10)	5 (11)	0.495
Lipid-lowering therapy			
Atorva/rosuvastatin	24/6	37/8	0.373
Statin + ezetimibe	7 (23.3)	8 (17.8)	0.232
Antiplatelet therapy			
ASA + Clopidogrel, n (%)	25 (83.3)	39 (86.7)	
ASA + Ticagrelor, n (%)	1 (3.4)	1 (2.2)	
NOAC + Clopidogrel, n (%)	4 (13.3)	5 (11.1)	
DAPT duration			
6 months, n (%)	12 (40)	17 (38)	
12 months, n (%)	18 (60)	28 (62)	

Values are n (%); ACE: Angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers; ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; NOAC: novel oral anticoagulant; RDN: renal denervation.

(95%CI: 1.17-1.44), patients with OSAS - OR 1.73 (95%CI: 1.23-2.26) and tachycardia - OR 2.02 (95%CI: 1.69-3.10); $P < 0.001$ in all cases. This can be explained by hyperactivation of the sympathetic nervous system in this group of patients.

Analyzing the drug therapy received after 24 months, a decrease in the number of medications taken in the intervention group was noted [Table 4]. Correction of antihypertensive therapy occurred due to the exclusion of diuretics from prescribed medications. There were no significant changes in sugar-lowering therapy in the participants of both groups: 4 patients in the RDN group underwent dose adjustment of insulin therapy and metformin due to the development of episodes of symptomatic hypoglycemia.

When determining clinical outcomes after 24 months of follow-up, the frequency of repeated revascularization in the pool of previously stented coronary arteries was extremely high in both groups; in the control group, there were two deaths due to cardiac arrest (ventricular arrhythmias). However, there were no significant differences in the incidence of adverse cardiovascular events and the degree of LLL in the stented segment [Table 5].

DISCUSSION

We present the results of a first prospective, randomized, controlled single-center study on the use of RDN in a cohort of comorbid patients with a combination of resistant AH, type 2 DM, and CAD after myocardial revascularization. Due to the extremely limited number of studies on the use of RDN in this patient cohort, it was not possible to determine the expected level of clinically significant effect, nor to perform a sample size calculation. Therefore, the study design was based on the hypothesis of a probable pleiotropic effect

Table 3. Initial, 12- and 24-month clinical and laboratory parameters

Parameter	RDN			Control		
	Initial	12 months	24 months	Initial	12 months	24 months
Office systolic BP, mmHg	160 (140, 180)	146 (130, 156)** Δ-14 (-16,-10)	152 (130, 160)** Δ-8 (-14,-6)	156 (140, 170)	150 (136, 164)	156 (140,174)
Office diastolic BP, mmHg	94 (90, 100)	84 (80, 94)** Δ-10 (-12,-6)	88 (80, 94)** Δ-6 (-10,-4)	94 (80, 100)	94 (80, 96)	96 (90, 100)
24H systolic BP, mmHg	158 (144, 167)	143 (135, 154)** Δ-15 (-18,-13)	147 (137, 156)** Δ-11 (-15,-8)	157 (145, 172)	152 (141, 170)	153 (136, 169)
24H diastolic BP, mmHg	97 (82, 112)	86 (70, 98)** Δ-11 (-13,-8)	89 (75, 101)** Δ-8 (-11,-7)	94 (81, 108)	94 (84, 107)	93 (84, 110)
Renin, ng/mL/h	4.65 (1.88, 7.79)	-	2.21 (0.87, 5.49)*	4.32 (1.66, 8.4)	-	3.89 (1.54, 7.38)
Angiotensin I, ng/mL	1.73 (0.34, 3.22)	-	0.46 (0.31, 1.95)*	1.17 (0.35, 3.65)	-	1.58 (0.77, 3.69)
Aldosterone, pg/mL	131 (78, 173)	-	118 (68, 153)*	120 (61. 158)	-	153 (81. 174)
Cortisol, nmol/L	334 (264, 367)	-	302 (249, 340)	314 (261, 366)	-	282 (264, 363)
CRP, mg/L	3.51 (1.38, 6.39)	-	1.73 (1.04, 5.62)*	3.33 (2.13, 5.45)	-	3.55 (2.01, 5.4)
Fibrinogen, g/L	4.1 (3.8, 4.8)	-	3.8 (3.6, 4.2)	3.9 (3.7, 4.6)	-	4.1 (3.8, 4.6)
Glucose, mmol/L	9.30 (7.67, 10.12)	6.05 (5.20, 8.30)* Δ-3.25 (-5.0, -2.4)	6.57 (5.8, 8.1)* Δ-2.73 (-4.6, -2.3)	10.45 (7.60, 12.40)	9.30 (7.90, 11.75)	9.57 (7.52, 11.10)
HbA1c, %	7.6 (6.9, 8.4)	6.5 (6.0, 7.2)* Δ-1.1 (-1.2, -0.9)	6.6 (6.2, 7.2)* Δ-1.0 (-1.2, -0.7)	7.8 (6.9, 8.5)	7.4 (6.7, 8.5)	7.7 (6.2, 8.4)
HOMA-IR	6.60 (3.73, 11.20)	4.76 (2.73, 7.10)* Δ-1.84 (-3.9, -1)	4.82 (2.92, 7.50)* Δ-1.78 (-3.7, -0.8)	6.88 (3.90, 21.84)	7.68 (4.80, 14.84)	7.20 (4.4, 17.69)
GFR, mL/min/1.73 m^2	77.8 (60, 87)	74 (60.25, 85.5)	78 (60, 89)	79.9 (59, 87)	84.5 (66, 87.7)	80 (66, 86)
Cholesterol, mmol/l	3.95 (3.20, 4.72)	3.7 (3.3, 4.7)	3.85 (3.35, 4.5)	3.80 (3.40, 4.40)	3.6 (3.3, 4.4)	3.9 (3.3, 4.6)
LDL, mmol/l	1.965 (1.51, 2.86)	1.90 (1.18, 2.58)	1.87 (1.7, 2.28)	1.91 (1.62, 2.42)	1.80 (1.53, 2.29)	1.95 (1.65, 2.16)
HDL, mmol/l	1.04 (0.89, 1.17)	1.15 (0.94, 1.32)	1.08 (0.92,1.22)	1.02 (0.82, 1.25)	1.13 (0.99, 1.45)	1.08 (0.93, 1.31)
Triglycerides, mmol/l	1.70 (1.17, 2.29)	1.47 (0.90, 1.77)	1.61 (1.10, 1.96)	1.66 (1.33, 2.17)	1.57 (0.91, 2.33)	1.62 (1.21, 2.15)
Leptin, ng/mL	32.36 (13.33, 67.57)	39.75 (14.53, 100)	-	28.2 (14.42, 68.3)	25.83 (12.17, 100)	-
Adiponectin, mkg/mL	8.38 (4.78, 10.63)	8.29 (4.9, 9.9)	-	8.7 (4.44, 15.62)	8.9 (7.15, 12.7)	-

Values are median with low and upper quartiles - Me (LQ, UQ); *$P < 0.05$; **$P < 0.01$ by the Wilcoxon test for intragroup comparison and by the Mann-Whitney test for intergroup comparison; Δ (95% CI); 24H: 24 hours blood pressure monitoring; BP: blood pressure; CRP: C-reactive protein; HDL: high density lipoprotein; HOMA-IR: Homeostasis model assessment of insulin resistance; GFR: glomerular filtration rate; LDL: low density lipoprotein; RDN: renal denervation.

Table 4. Antihypertensive therapy

Parameter	RDN			Control		
	Initial (*n* = 30)	12 months (*n* = 30)	24 months (*n* = 30)	Initial (*n* = 45)	12 months (*n* = 45)	24 months (*n* = 45)
Number of medicaments, Me (LQ, UQ)	4.00	4.00 (2.00, 4.00)	3.0 (3.0, 4.0)	4.00	4.00 (3.00, 4.00)	4.0 (3.0, 4.0)
ACE inhibitors/ARBs, abs. (%)	22/8 (100)	21/9 (100)	21/9 (100)	36/9 (100)	35/10 (100)	33/12 (100)
Diuretics, abs. (%)	30 (100)	18 (60)*	16 (53)*	45 (100)	41 (91.1)	36 (80)
β-blockers, abs. (%)	30 (100)	26 (86)	27 (90)	45 (100)	45 (100)	45 (100)
Ca-antagonists, abs. (%)	30 (100)	20 (66.7)	25 (83)	45 (100)	39 (86.7)	41 (91.1)

*$P < 0.05$, ACE: angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers; RDN: renal denervation.

Table 5. Clinical outcomes

Parameter	Group		*P*
	RDN	Control	
	n = 30	*n* = 45	
MACE, yes n (%)	8 (26.7)	11 (24.4)	0.836
Death	0	2	
Myocardial Infarction	2	1	
Stroke	0	0	
Coronary revascularization	6	8	
QCA			
12 months			
LLL, %	21.8 (17.3, 28.8)	26.5 (19.4, 42.2)	0.090
Restenosis > 50%, n (%)	-	1 (2.22)	
De novo stenosis > 50%, n (%)	1 (3.33)	-	
24 months			
LLL, %	24.7 (18.1, 32.0)	28,1 (19.0, 35.4)	0.672
Restenosis > 50%, n (%)	-	-	
De novo stenosis > 50%, n (%)	7 (23.3)	10 (22.2)	

QCA: Quantitative coronary angiography analysis of coronary arteries, LLL: late lumen loss, RDN: renal denervation.

of the intervention. The results of a 2-year follow-up period confirmed the persistent antihypertensive effect of RDN in a cohort of these comorbid patients and also showed a long-term positive effect of the procedure on carbohydrate metabolism, the mechanism of which is currently unclear. Despite better control of the risk factors for the progression of AH and DM in the intervention group (BP, glycemia, and HbA1c), there were no differences in clinical outcomes over 2 years of follow-up. We attribute this to the high baseline cardiovascular risk of the cohort, the limited sample size, and the relatively short follow-up for cardiovascular events.

It is not surprising that indicators of the RAAS decrease after RDN, as the sympathetic influence on the kidneys is reduced. This leads to decreased renal resin secretion and, consequently, reduced activity of angiotensin I. In our study, the effect of RDN on changes in RAAS parameters generally aligns with the results of other studies[14]. For instance, Mahfoud *et al.* also reported reductions in plasma renin and aldosterone levels three months after the procedure- findings that were corroborated by our results over a 24-month follow-up period. However, the procedure did not appear to affect cortisol concentrations, an outcome that warrants further investigation[14]. It is likely that more complex regulatory pathways are involved in the synthesis and action of cortisol, and that isolated RDN may not sufficiently influence cortisol activity.

The design of our study did not include a detailed assessment of the immunological status after the intervention, which is a limitation of our work. CRP and fibrinogen are non-specific markers of inflammation. Our results revealed a positive effect of RDN on CRP levels. Sympathetic overactivity contributes to systemic inflammation via catecholamine-mediated pathways and immune cell modulation. RDN may attenuate this response through neural inhibition. While RDN appears to reduce the intensity of inflammatory processes, the limited amount of available data necessitates further investigation and additional evidence to clarify its effects on inflammation in patients.

There is experimental evidence of sympathetic nerve regeneration after RDN in sheep, along with isolated observations of similar phenomena in humans. This may contribute to reduced long-term efficacy of the intervention and the resumption of resistant AH[15,16]. However, studies with extended follow-up periods have demonstrated a sustained antihypertensive effect of RDN without the need to increase the dosage or number of antihypertensive medications - findings that are consistent with the results of the present study[17,18].

The potential impact of RDN on carbohydrate metabolism is currently being actively studied. This study demonstrates a beneficial effect of the procedure on parameters of carbohydrate metabolism, consistent with other observational studies reporting improvements in HbA1c and insulin sensitivity in obese patients undergoing RDN[19]. However, data from large multicenter randomized controlled trials have not confirmed similar effects of RDN on glycemia, HbA1c, or calculated insulin resistance indices. Therefore, the potential benefits of RDN in patients with metabolic syndrome and type 2 DM remain uncertain and require further accumulation and synthesis of scientific evidence.

Given the significant individual variability in BP response after RDN, efforts to identify predictors of treatment response and define responder profiles began shortly after the introduction of this therapeutic approach. As early as 2017, initial attempts were made to systematize the existing findings and identify factors predictive of optimal outcomes. Fink *et al.* found that among patients with resistant AH on at least three antihypertensive drugs, the only significant predictor of response was pre-procedural BP level[20]. As clinical experience with RDN expanded, further attempts were made to identify likely respondents. Several studies have reported that the greatest benefits are seen in younger male patients with heart failure symptoms, individuals intolerant to conventional medications due to adverse events, or those with low compliance to pharmacologic therapy - for whom RDN may represent the only viable treatment option[21,22]. Other studies have identified particularly strong responses in patients with chronic obstructive pulmonary disease[23], CKD[24], and especially OSAS[25]. OSAS is closely correlated with hypersympathicotonia in the context of hypoxia/hypercapnia. While CPAP therapy can partially correct this imbalance, it has limited efficacy in controlling BP and reducing cardiovascular risk. As a result, patients with both AH and OSAS are considered prime candidates for RDN.

Due to the limited sample size in the present study, only univariate analyses were performed; multivariable adjustments and collinearity diagnostics were not possible. Univariate analysis identified that RDN was most effective in patients with obesity, OSAS, and sinus tachycardia - conditions associated with hypersympathicotonia, thereby supporting the mechanism of RDN and aligning with previously published data. In contrast, factors such as male sex, age, average daily systolic BP before RDN, and baseline glycemic level did not sufficiently influence the procedure's effectiveness.

This study has several limitations. True resistant hypertension was assessed using validated adherence questionnaires (Morisky and BMQ), but not confirmed biochemically (e.g., via urinary drug screening). The

small sample size, determined pragmatically by the number of eligible patients during the inclusion period, further limits generalizability. Additionally, the trial was open-label and did not include a sham control group due to ethical and logistic constraints.

It is important to emphasize that this was a pilot study. The results should serve as a foundation for larger, randomized, controlled trials with extended follow-up and greater statistical power. Moreover, the study cohort - patients with multifocal atherosclerosis and type 2 DM - are already at elevated risk for cardiovascular complications. Despite the pleiotropic effects of RDN observed here, strict control of other cardiovascular risk factors remains essential to improve long-term outcomes and survival. It is also possible that differences in the incidence of cardiovascular events may occur later, necessitating prolonged observation.

Despite these limitations, several important conclusions can be drawn. First, RDN appears safe for patients with type 2 DM, resistant AH, and CAD, as no perioperative complications were recorded. The antihypertensive effects observed are consistent with those reported in large RCTs. A statistically significant decrease in HbA1c levels was also observed in the RDN group, suggesting improved glycemic control. Possible explanations include heightened baseline sympathetic activity (as reflected by the high prevalence of OSAS, obesity, and tachycardia in the cohort), the relatively long 24-month follow-up, and ethnic, clinical, or pharmacologic differences among study populations. Finally, this study identified clinical indicators associated with successful RDN outcomes in patients with resistant AH, type 2 DM, and CAD.

CONCLUSION

Through its influence on neurohumoral regulatory pathways, RDN exerts systemic effects in polymorbid patients, including improvements in BP control, carbohydrate metabolism, inflammatory activity, and markers of renin-angiotensin-aldosterone system activation. Despite its favorable clinical outcomes - namely antihypertensive and hypoglycemic effects - comprehensive management of all cardiovascular risk factors remains crucial to minimize the incidence of adverse events.

The present work confirms that RDN has clinically beneficial effects in polymorbid patients with high cardiovascular risk, supporting further research and broader implementation of this interventional strategy.

DECLARATIONS

Authors' contributions

Collected the data, performed the analysis, and wrote the paper: Arablinskiy NA
Conceived and designed the analysis, collected the data, and wrote the paper: Feshchenko DA
Contributed data or analysis tools, reviewed & edited the paper: Vasiliev DK
Conceived and designed the analysis: Shanoyan AS
Reviewed & edited the paper: Shukurov FB, Taliuridze MT, Drapkina OM
Performed the analysis, wrote the paper: Kiselev AR

Availability of data and materials

The data set is available from the correspondent author upon reasonable request.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of the National Medical Research Center for Therapy and Preventive Medicine, Russia (Protocol No. 06-04/21 dated September 09, 2021), and all experimental procedures were performed in accordance with the ethical standards laid down in the Declaration of Helsinki. All subjects were informed about the experimental procedures in detail and have signed standard consent forms.

Consent for publication

Not applicable.

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