


Thirty-six-month results of laparoscopic-based renal denervation plus unilateral laparoscopic adrenalectomy for the treatment of patients with resistant hypertension caused by unilateral aldosterone-producing adenoma

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Abstract

The aim of this study was to explore the long-term clinical results of Renal denervation (RDN) from the adventitia of the renal artery plus unilateral laparoscopic adrenalectomy to treat patients with resistant hypertension caused by unilateral aldosterone-producing adenoma (APA). Sixty patients with resistant hypertension caused by APA who were treated at Henan Provincial People's Hospital from December 2016 to March 2018 were selected and randomly assigned to undergo RDN from the adventitia of the renal artery plus adrenalectomy (RDN group, $n = 30$) or adrenalectomy alone (control group, $n = 30$). Office blood pressure (BP), antihypertensive medication usage and other laboratory characteristics were followed every 6 months through 36 months. Follow-up data were available at 36 months for 23 of 30 subjects in the RDN group and for 21 of 30 subjects who were in the control group. At 36 months postprocedure, the reduction in the RDN group was 42.2 ± 21.6 mmHg and that in the control group was 29.8 ± 13.5 mmHg ($p = .029$ between the groups). During the follow-up to 36 months postprocedure, no patients in either the RDN group or the control group died due to surgical complications, and the RDN group had no procedural complications, including renal artery dissection, perforation, and renal artery stenosis. There was no change in the mean eGFR of the two groups, and no serious adverse events were reported. In conclusion, RDN from the adventitia of the renal artery plus unilateral laparoscopic adrenalectomy resulted in sustained lowering of BP at 3 years in a selected population of subjects with resistant hypertension caused by unilateral APA without serious safety concerns.

Yahui Liu and Binbin Zhu contributed equally to this work.

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1 | INTRODUCTION

In 2008, the American Heart Association (AHA) defined resistant hypertension as BP that does not remain within the normal range despite the administration of three antihypertensive medications at maximally tolerated doses, including a diuretic, or BP that can be effectively controlled by taking 4 or more antihypertensive drugs.¹ According to reports, resistant hypertension accounts for approximately 15%-18% of patients with hypertension.¹ Primary aldosteronism (PA) is the excessive secretion of aldosterone from the adrenal cortex, resulting in increased sodium retention, potassium excretion, blood volume, and inhibition of the activity of the renin-angiotensin-aldosterone system (RAAS). The main clinical manifestations of PA are mainly hypertension and hypokalemia, accounting for approximately 17 ~ 23% of patients with resistant hypertension.² Aldosterone-producing adenoma (APA) is the most common type of PA and is treated by surgery and medication therapy. Laparoscopic adrenalectomy is currently recommended as the standard treatment for APA. However, it has been reported that the control rate of BP in patients with APA is only 33%-85%³ by resecting the affected adrenal gland alone, which indicates that most patients still have poor long-term blood pressure control.

Renal denervation (RDN) refers to the purpose of lowering BP by blocking the activity of renal sympathetic nerves and inhibiting the activity of RAAS. Previous methods of performing RDN through the intima of the renal artery may damage the structure, increasing the risk of renal atherosclerosis.⁴⁻⁶ Therefore, our team tried to implement RDN from the adventitia of the renal artery with the help of current mature laparoscopic technology. On the premise that RDN is safe and effective after several animal experiments,⁷ we carried out a clinical trial of adventitia-RDN in the treatment of resistant hypertension. Our clinical study selected 60 patients with resistant hypertension caused by unilateral APA who were randomly divided into two groups to undergo RDN from the adventitia of the renal artery plus adrenalectomy (RDN group, $n = 30$) or adrenalectomy alone (control group, $n = 30$). At the 1-year postoperative follow-up, the decreases in the 24-hour average BP and office BP in the RDN group were more significant than those in the control group, and they were equally safe.⁸ After that, we conducted a 3-year long-term follow-up, and the relevant follow-up results are reported as follows.

2 | METHODS

2.1 | Study population and protocol

Sixty patients with resistant hypertension caused by APA who were treated at Henan Provincial People's Hospital from December 2016 to March 2018 were selected and randomly assigned to undergo RDN from the adventitia of the renal artery plus adrenalectomy (RDN group, $n = 30$) or adrenalectomy alone (control group, $n = 30$). The office BP, antihypertensive medication usage, and other

laboratory characteristics were followed every 6 months through 3 years. This study was approved by the Ethics Committee of Henan Provincial People's Hospital (Zhengzhou, China), and all selected patients were willing and able to comply with the protocol and provided written informed consent.

Inclusion criteria were as follows: (a) renal artery diameter ≥ 4 mm and length ≥ 20 mm; (b) 18 years \leq age ≤ 70 years; (c) PA was diagnosed before enrollment, and APA was diagnosed clearly; (d) patients had a clear diagnosis of hypertension; (e) estimated glomerular filtration rate (eGFR) ≥ 45 ml/min/1.73 m²; and (f) patients were willing and able to comply with the protocol, provided written informed consent and were willing to proceed with later follow-up. The exclusion criteria were as follows: (a) renal artery abnormalities: hemodynamic or anatomical stenosis of either side of the renal artery ($\geq 50\%$); renal artery balloon angioplasty or stent placement; multiple renal arteries in the side kidney and a main renal artery supplying less than 75% of the kidney; and obvious abnormalities in renal artery anatomy, making catheter insertion difficult; (b) cardiovascular instability, including myocardial infarction within 6 months, unstable angina or cerebrovascular disease events; extensive atherosclerosis with intravascular thrombosis or unstable plaque; and heart valve disease with markedly altered hemodynamics; (c) other serious organic diseases; and (d) participation in other clinical research.

2.2 | Surgical procedures and criteria

The specific surgical procedures and related diagnostic criteria and definitions have been reported in the previous literature.⁸

2.3 | Follow-up

The follow-up time was from the day of discharge to the last follow-up day. All patients were followed up every 6 months. The follow-up period was from postoperative to 3 years postprocedure. The common content included in each follow-up was demographic characteristics, disease characteristics, office BP, heart rate, and laboratory characteristics (kidney function, electrolytes). After each follow-up, according to the patient's BP level, an experienced hypertension physician adjusted the patient's antihypertensive medication.

2.4 | Statistical analysis

To evaluate differences in clinical success, patient demographic and clinical characteristics are reported. All data processing was performed using SPSS 22.0 software for statistical analysis. Continuous data are described as the means and standard deviations or medians and interquartile ranges, and categorical data are reported as counts and percentages. For continuous variables, the distributions of clinical success were compared using analysis of variance. For categorical data, differences in percentages across subgroups were assessed

using Pearson's chi-square test or Fisher's exact probability test as appropriate.

3 | RESULTS

3.1 | Population characteristics

A total of 43 subjects underwent the 3-year follow-up. A total of 23 of 30 subjects were followed up for 3 years in the RDN group, and 21 of 30 subjects were followed up for 3 years in the control group (Figure 1). The baseline characteristics of the patients are shown in Table 1.

3.2 | Changes in BP

At 36 months postprocedure, the reduction level of SBP was stratified and divided into 6 levels of 0-9, 10-19, 20-29, 30-39, 40-49, and ≥ 50 mmHg. The response rates were similar in both the RDN and control subjects: 95.7% of RDN subjects and 95.2% of control subjects had a ≥ 10 mmHg reduction in SBP. There was no significant

difference between the two groups in the proportion of each degree of patients ($p > .05$, Table 2).

Through 36 months postprocedure, the average office SBP change trends of the two groups of subjects are shown in Figure 2. Both the SBP and DBP of the two groups of subjects showed overall downward trends during the period. The average reductions in SBP and DBP are shown in Figure 3A,B. SBP and DBP measurements were significantly lower than the pre-procedure measurements at all time points (6, 12, 24, 30, and 36 months, Figure 3A,B). The SBP reductions at 36 months in the RDN and control groups were 42.2 ± 21.6 and 29.8 ± 13.5 mmHg, respectively ($p = .029$). The RDN and control group subjects also had significant reductions in DBP at 36 months (-18.1 ± 11.8 vs -11.5 ± 6.5 mmHg, $p = .032$).

3.3 | Changes in antihypertensive medications

Changes in medication class and/or prescribed dose were permitted beyond 12 months (Table 3). Comparison of the mean numbers of antihypertensive medications at the 3-year follow-up of the RDN and control groups showed a significant reduction (0.52 ± 0.51 vs 0.76 ± 0.83 , $p = .250$) vs the baseline (3.57 ± 0.69 vs 3.39 ± 0.50 , $p = .272$).

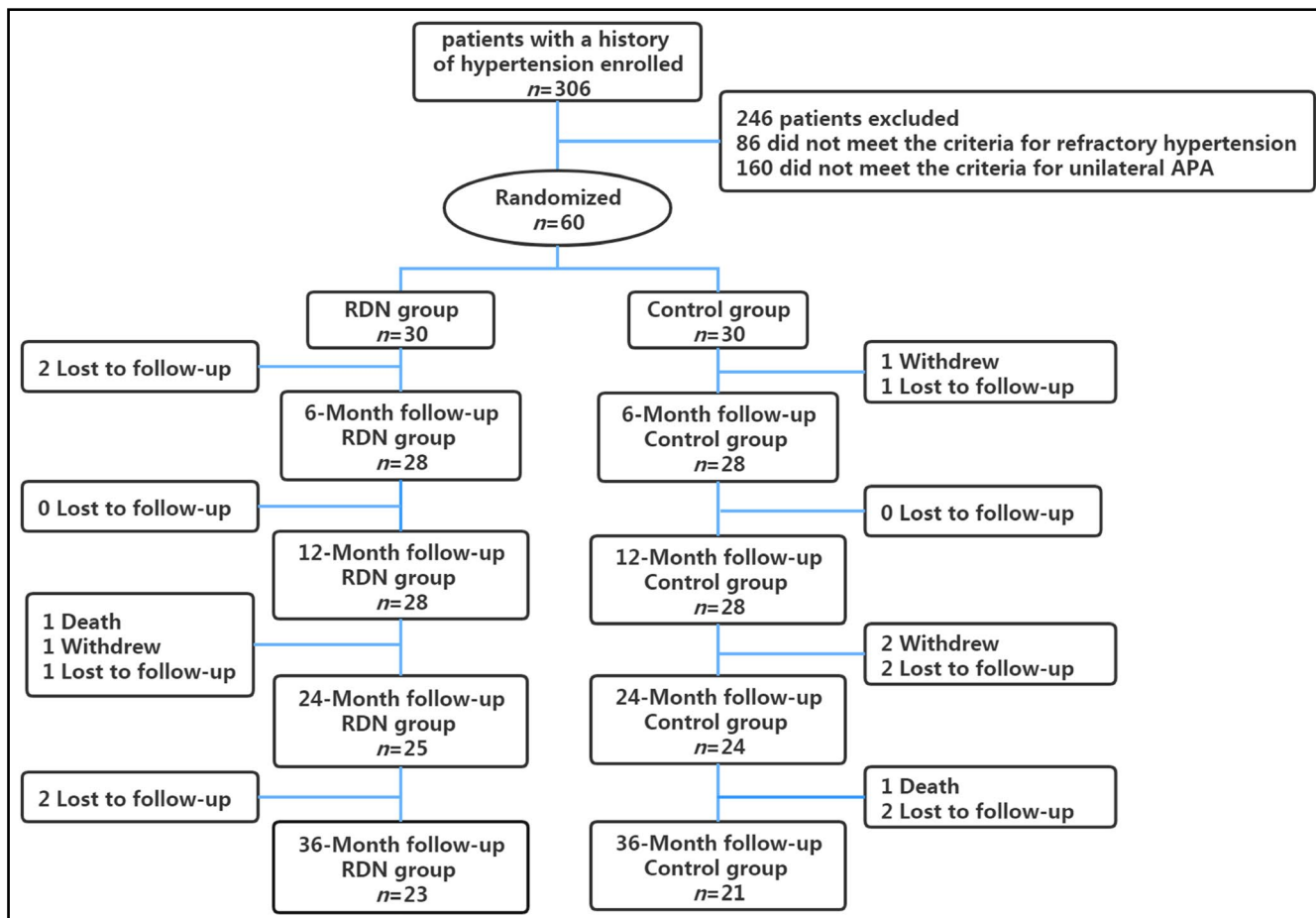


FIGURE 1 Study flowchart [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Basic characteristics of the two groups before and after 3 years postprocedure

Characteristics	All treated subjects pre-procedure			All treated subjects at 3 years		
	RDN group n = 30	Control group n = 30	p-Value	RDN group n = 23	Control group n = 21	p-Value
SBP, mmHg	170.0 ± 25.4	168.0 ± 13.0	.717	127.1 ± 7.9	137.1 ± 9.7	.001
DBP, mmHg	99.6 ± 14.2	98.4 ± 5.7	.676	79.6 ± 6.1	86.2 ± 7.5	.002
Age, years	50.0 ± 10.9	50.3 ± 9.7	.928	50.6 ± 9.1	51.3 ± 7.7	.778
Men, n (%)	11 (36.7)	13 (43.3)	.792	11 (47.8)	9 (42.9)	.741
eGFR, ml/min/1.73 m ²	88.2 ± 11.4	84.3 ± 14.9	.939	86.5 ± 7.9	85.8 ± 10.5	.647
Heart rate, b.p.m.	74.2 ± 11.0	78.0 ± 12.6	.235	68.8 ± 5.5	71.0 ± 7.2	.268
BMI, kg/m ²	26.0 ± 3.3	26.3 ± 3.3	.710	25.4 ± 2.7	25.9 ± 2.6	.548

Note: Data are expressed as N (%) or mean ± SD. Statistically significant differences between the RDN and control group are defined as those with p-value < .05.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate, calculated using the Cockcroft-Gault formula; SBP, systolic blood pressure.

TABLE 2 Reduction degree of SBP at 36 months postprocedure

Variable	No. (%)		p-Value
	RDN group n = 23	Control group n = 21	
Decrease in SBP, mmHg			
0-9	1 (4.3)	1 (4.8)	>.99
10-19	2 (8.7)	5 (23.8)	.23
20-29	5 (21.7)	6 (28.6)	.73
30-39	4 (17.4)	2 (9.5)	.67
40-49	6 (26.1)	6 (28.6)	>.99
≥50	5 (21.7)	1 (4.8)	.19

Note: Data are expressed as N (%).

Abbreviations: SBP, systolic blood pressure.

3.4 | Clinical results

The curative effect of hypertension in the two groups of subjects 3 years after the operation is shown in Table 4. There were no significant differences between the two groups of subjects in the cure, improvement, and failure rates of postoperative BP ($p > .05$).

3.5 | Safety

At 3 years postprocedure, the two groups of patients underwent CT or magnetic resonance imaging (MRI) examinations of the adrenal glands, ultrasound examinations of the kidneys and renal arteries, and biochemical examinations of renal function and electrolytes. During the follow-up to 3 years postprocedure, there were no deaths related to surgery or complications in the adventitia-RDN group or the control group. During and after the procedure, there were no complications related to the procedure, such as renal artery dissection, perforation, and renal artery stenosis. There was no change in

the mean eGFR of the two groups, and no serious adverse events were reported (Table 1).

4 | DISCUSSION

Studies have shown that the average BP of patients with PA is 184/112 ± 28/16 mmHg⁸; for the same degree of hypertension, the damage to target organs caused by PA is much greater than that of primary hypertension. The excessive activation of adrenal cortex hormone receptors caused by excessive aldosterone greatly increases the risk of cardiovascular disease, kidney disease, metabolic syndrome, diabetes, and death. For patients with APA, the purpose of laparoscopic adrenalectomy is to reduce the excessive secretion of aldosterone, thereby correcting hypokalemia and improving hypertension. However, for the surgical treatment of APA, many clinical studies have confirmed that almost all patients can achieve biochemical success after surgery, and the BP levels of most patients can also be improved to varying degrees. Approximately 40%-60% of patients do not need to take antihypertensive medications after surgery, which shows that there are still some patients with persistent hypertension after surgery.⁹

In this clinical study, 47.8% and 42.9% of the patients in the RDN and control groups, respectively, did not need to take any antihypertensive medications after 3 years, and their BP could be controlled within the normal range. These ratios were both higher than those of the two groups at 1 year postprocedure and higher than the 40% in the meta-analysis but lower than the 50% and 52% cure rates.¹⁰⁻¹² Since the definition of cure and remission in our study is different from that in the PASO study, it cannot be further compared with the cure rate in the PASO study.¹³ According to previous reports, first-degree relatives suffer from hypertension, preoperative hypokalemia, and the course of preoperative hypertension, which are all factors influencing persistent postoperative hypertension.¹⁴ The different factors of postoperative biochemical and hypertension

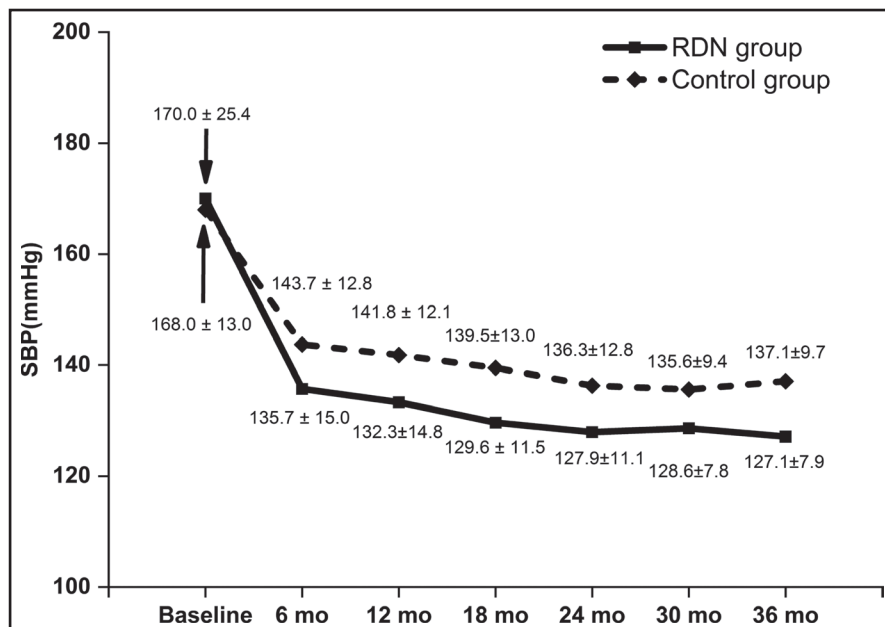


FIGURE 2 Changes in SBP within 36 months after surgery. SBP, systolic blood pressure

prognosis may be the duration of preoperative hypertension and its influence on heart and kidney function.¹⁵

This clinical trial is the first clinical trial in the world to implement RDN through the adventitia of the renal artery for the treatment of resistant hypertension. From the results of previous studies, the ambulatory BP and office BP of the RDN group decreased more significantly than those of the control group, and combined laparoscopic adrenalectomy with adventitia-RDN was equally safe at one year postprocedure.¹⁶ This report also carried out a 3-year long-term follow-up of the clinical study. From the results of our study, it can be seen that both laparoscopic adrenalectomy on the affected side alone and laparoscopic adrenalectomy combined with adventitia-RDN can safely and effectively reduce BP in patients with resistant hypertension caused by APA. Moreover, compared with the control group, the RDN group had more significant decreases in office SBP and DBP and used fewer antihypertensive medications at 3 years postprocedure.

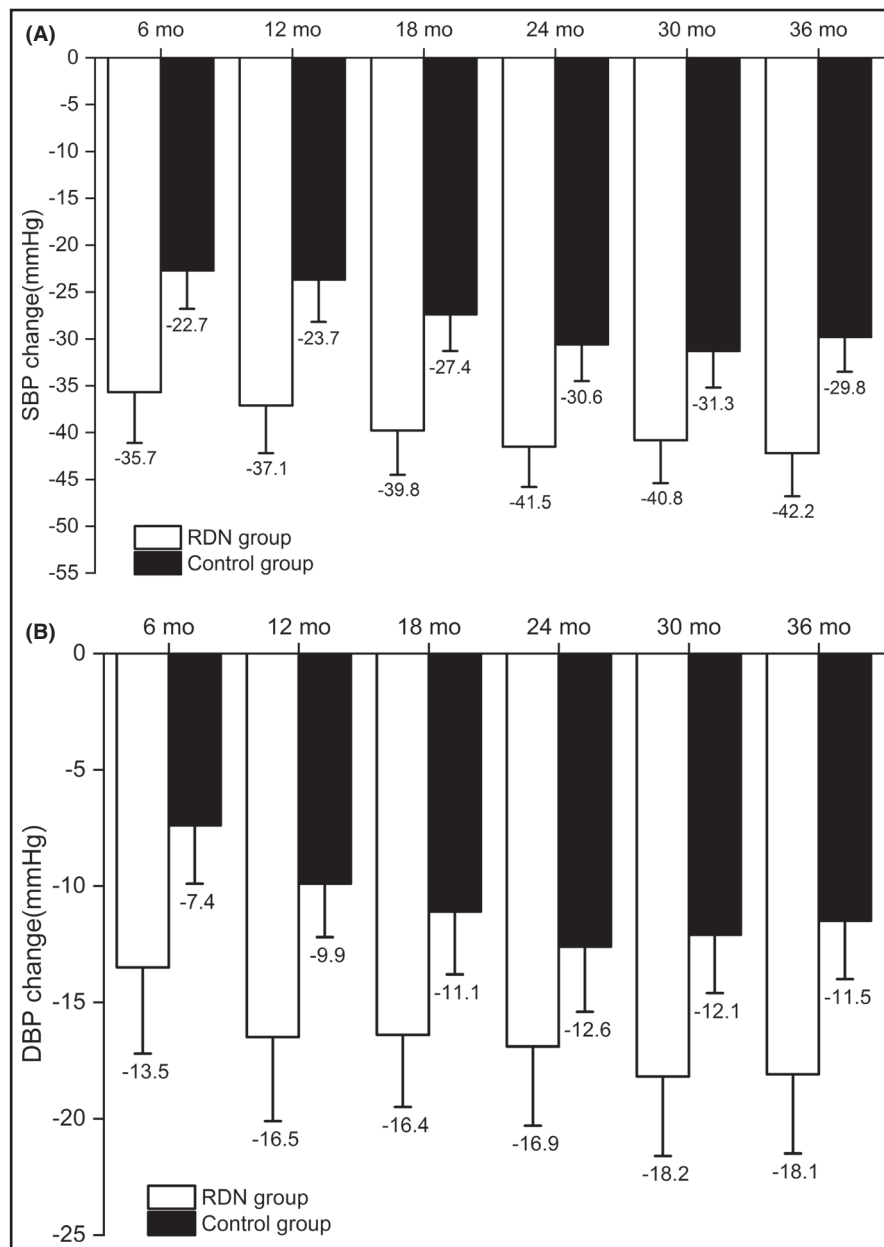
Aldosterone can cause BP to rise in the following ways: first, excessive aldosterone causes water and sodium retention, which is directly related to the development of hypertension; second, aldosterone can cause endothelial dysfunction, tissue inflammation and increased sympathetic nerve excitability, which can further increase BP.¹⁷ Laparoscopic adrenalectomy removes the tumor and reduces the excessive secretion of aldosterone, thereby improving hypertension. At the same time, RDN from the adventitia of the renal artery can reduce sympathetic nerve excitability, which can reduce the BP of these patients to a certain extent. Our clinical trial results show that in the RDN group, RDN from the adventitia of the renal artery has a certain effect on lowering BP. For patients who are completely cured, RDN from the adventitia of the renal artery is not obvious in reducing BP, but for patients whose BP improves postprocedure, RDN from the adventitia of the renal artery may show a certain

BP-lowering effect mainly by reducing sympathetic nerve excitability, which can reduce the BP of these patients to a certain extent.

There have been a few studies on RDN treatment of hypertension, but the current long-term follow-up studies on RDN treatment of hypertension are still limited. The SYMPPLICITY HTN-Japan study by Kazuomi Kario et al¹⁸ conducted a follow-up of up to 36 months after RDN treatment. In the RDN group, the office SBP decreased by 32.8 ± 20.1 mmHg, and the office DBP decreased by -15.8 ± 12.6 mmHg at 36 months postoperatively (both $p < .001$). These results are similar to the decreases in SBP and DBP at 3 years after RDN of SYMPPLICITY HTN-1 (-32 mmHg and -14 mmHg)¹⁹ and HTN-2 (-33 mmHg and -14 mmHg).²⁰ Another clinical study²¹ conducted a 7-year follow-up for the treatment of resistant hypertension with RDN and found that there were no abnormal renal function or renal artery complications related to the operation, which suggests that RDN is safe and reliable for the treatment of hypertension. At present, the mechanism by which RDN continues to lower BP is unclear, but it may be related to vascular remodeling or changes in RAAS system activity.^{18,22}

The innovation of this clinical trial lies in the application of the new technology of laparoscopic-based RDN from the adventitia of the renal artery to the clinic for the first time. Previous studies have proposed a technical model²³ for performing RDN from the adventitia of the renal artery with the help of laparoscopy, but this model has not been applied in clinical trials. The technical model is a circular electro-surgical instrument that can wrap the renal artery in a circular shape from the adventitia of the renal artery and release energy, thereby achieving the effect of ablating the renal nerve. The theoretical basis is that the team found that approximately 31% of the renal sympathetic nerves are located more than 2 mm from the arterial lumen. Compared with ablation catheters used in conventional RDN from the intima of the renal artery, this surgical instrument

FIGURE 3 (A) Postprocedure change in office SBP; (B) Postprocedure change in office DBP. DBP, diastolic blood pressure; SBP, systolic blood pressure. $p < .01$ at all time periods for BP difference from baseline



model can place the electrode directly on the adventitia of the renal artery, which can damage more renal nerves. Moreover, in the process of releasing energy from surgical instruments, the blood in the lumen of the renal artery can play a cooling role, which can reduce the harmful damage of heat to the renal artery. This technical concept is similar to our research, but in our current research, we used the same ablation catheter as the intima-RDN. This is also where our research is insufficient; however, this innovative idea will open up a new path for follow-up research on RDN treatment of resistant hypertension. Moreover, the surgical instrument designed by our team to perform RDN through the adventitia of the renal artery has been designed and is currently being tested and improved in animal experiments.

The results of our trial also have certain limitations. First, our patient enrollment and data collection were from a single center, which may cause certain biases to the research results. Second,

the number of subjects enrolled was relatively small, and during the 3-year follow-up process, some data are still missing, which may have a certain impact on the postoperative results. Third, although our team has conducted research on RDN technology from the adventitia of the renal artery for several years, the research data on this technology are still relatively scarce, both at home and abroad, and this dataset is too small to compare with other studies. Finally, our innovative technology requires the use of current mature laparoscopic technology, and we chose a group of patients with APA who required laparoscopy for adrenalectomy. Although the patients' symptoms satisfied the categorization of resistant hypertension, it is difficult to rule out whether the cause of the resistant hypertension is from tumors that continue to secrete aldosterone or whether the condition is combined with essential hypertension on this basis. Our follow-up research will consider these questions.

TABLE 3 Antihypertensive medication usage at baseline and at 3 years

Antihypertensive medications	All treated subjects pre-procedure			All treated subjects at 3 years		
	RDN group n = 30	Control group n = 30	p-Value	RDN group n = 23	Control group n = 21	p-Value
No. of antihypertensives/d	3.57 ± 0.69	3.39 ± 0.50	0.272	0.52 ± 0.51	0.76 ± 0.83	.250
ACE inhibitor	10 (33.3)	11 (36.7)	0.783	5 (21.7)	5 (23.8)	>.99
Angiotensin receptor blocker	12 (40.0)	11 (36.7)	0.786	4 (17.4)	5 (23.8)	.716
β Blockers	10 (33.3)	11 (36.7)	0.783	NA	1 (4.8)	.477
Calcium channel blocker	27 (90.0)	23 (76.7)	0.195	4 (17.4)	4 (19.0)	>.99
Other diuretics	6 (20.0)	9 (30.0)	0.371	NA	1 (4.8)	.477
Aldosterone antagonists	24 (80.0)	21 (70.0)	0.313	NA	NA	NA
α-adrenergic blocker	11 (36.7)	11 (36.7)	1.000	NA	NA	NA
Direct-acting vasodilators	1 (3.3)	NA	1.000	NA	NA	NA
Other antihypertensive agents	1 (3.3)	2 (6.7)	1.000	NA	NA	NA

Note: Data are expressed as N (%).

Abbreviation: ACE, angiotensin-converting enzyme.

	Clinical outcomes					
	Cured (n,%)	p-Value	Improved (n,%)	p-Value	Failed (n,%)	p-Value
RDN group n = 23	11 (47.8)	.741	12 (52.2)	.989	0	.477
Control group n = 21	9 (42.9)		11 (52.4)		1 (4.7)	

TABLE 4 Clinical results of two groups of patients at 3 years postprocedure

5 | CONCLUSION

In conclusion, RDN from the adventitia of the renal artery plus unilateral laparoscopic adrenalectomy resulted in sustained lowering of blood pressure (BP) at 3 years in a selected population of subjects with resistant hypertension caused by unilateral APA without serious safety concerns.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

LYH was mainly responsible for experimental design and data analysis, data interpretation and drafting of manuscripts. ZLJ and ZLW interpreted the data. DDG, LZH and FZQ performed surgery and revised of the manuscript. QDT and ZQP revised of the manuscript. Z. Y analyzed data. WJG revised the manuscript critically for important intellectual content. GCY designed and directed the clinical trials final.

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