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Safety and efficacy of bilateral superselective adrenal arterial embolization for treatment of idiopathic hyperaldosteronism: a prospective single-center study

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Abstract

Objective This study aimed to assess the efficacy and safety of bilateral superselective adrenal arterial embolization (SAAE) in patients with bilateral idiopathic hyperaldosteronism (IHA), a subtype of PA.

Methods Ninety-eight patients with bilateral IHA underwent bilateral SAAE between August 2022 and August 2023. Sixty-eight patients were followed up for up to 12 months. The study outcomes were evaluated using the criteria provided by the Primary Aldosteronism Surgical Outcome (PASO) guidelines.

Results The mean reductions in systolic and diastolic blood pressure were 27.4 ± 21.3 mmHg and 23.1 ± 17.4 mmHg, respectively ($p < 0.001$). The rates of clinical success and biochemical success after adrenal artery ablation were 63.2% (43/68) and 39.7% (27/68), respectively. Overall, there were significant reductions in daily defined doses (DDD), aldosterone/renin ratio (ARR), and plasma aldosterone levels ($p < 0.001$). Plasma renin levels increased by a mean value of 10.4 ± 39.0 pg/mL ($p = 0.049$), and potassium levels increased by 0.40 ± 0.63 mmol/L ($p < 0.001$). No significant adverse events were reported during SAAE or the follow-up period of up to one year. Additionally, no abnormalities were detected by adrenal 68Ga-Pentixafor PET/CT scans before or after SAAE.

Conclusion Bilateral SAAE appears to lead to sustained improvements in blood pressure and biochemical parameters in patients with bilateral PA, with minimal adverse effects. This suggests that bilateral SAAE could serve as an effective alternative approach for treating bilateral IHA, potentially curing this condition.

Keywords Primary aldosteronism, Adrenal arterial ablation, Hypertension, Idiopathic hyperaldosteronism, Superselective adrenal arterial embolization

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Introduction

Primary aldosteronism (PA) is the potential and leading cause of secondary endocrine hypertension, and it is reported that globally 5%~15% of hypertension patients and 15%~20% of resistant hypertension due to autonomous secretion of aldosterone along with suppression of plasma renin level [1]. According to the epidemiological and clinical evidence, there has been a higher rate of cerebrovascular, cardiovascular, metabolic, and renal manifestations in PA patients, as compared to the patients with essential hypertension with matched sex, age, blood pressure, and other metabolic levels [2]. Hence, early diagnosis and proper management of PA is crucial. PA patients are classified mainly into unilateral PA and bilateral PA, and the bilateral idiopathic hyperaldosteronism (IHA) is the most reported PA subtype, which is responsible for 60%~70% of PA cases [3]. It was reported that unilateral adrenalectomy is an effective treatment for unilateral PA and mostly recommended by guideline. The incidence of heart failure, atrial fibrillation, and chronic renal failure is lower with unilateral adrenalectomy in comparison to mineralocorticoid receptor antagonists (MRA) long-term therapy [4].

For bilateral PA patients, MRAs are the most commonly used medication for treating IHA patients. However, PA patients treated with MRAs (spironolactone or eplerenone) have more cardiovascular events (stroke, coronary artery disease, atrial fibrillation, heart failure, etc.) than patients with essential hypertension independent of blood pressure [5, 6], and higher plasma aldosterone signifies an increased cardiovascular risk for PA patients. In addition, undesirable adverse effects, including gynecomastia and menstrual disturbances, limit the life-long application of spironolactone. As a selective MRA without antiandrogen and progesterone agonist effects, eplerenone reduces the rate of adverse endocrine side effects. Nevertheless, eplerenone in vivo has only 50% of the MRA potency of spironolactone. It was reported that renin targets are achieved only in less than half of IHA cases, and unsatisfactory outcomes are related to MRA treatment [7]. Therefore, a significant number of IHA patients are treated inadequately, which calls for an emergent need for a more appropriate and effective treatment for IHA.

The feasibility of superselective adrenal arterial embolization (SAAE) for treating APA was first reported in 1994, and it was reported that 33 cases of APA treated by SAAE, with a mean follow-up duration of 45 months, had a high technically successful rate (82%) and an excellent safety profile [5, 8]. In the following clinical studies, SAAE has shown promising efficacy in treating unilateral PA patients, including APA and unilateral adrenal hyperplasia [9, 10]. It is an interventional procedure with minimal invasion, which ablates the abnormal functioning part of adrenal tissue via the hormonal debulking procedure, and the embolization is usually caused by injecting the anhydrous ethanol through the feeding adrenal artery. Recent years it was reported that SAEE was an effective procedure for treating bilateral IHA [5, 11, 12], which indicated clinical success (38.7%) and biochemical success (58.6%), implying the potential to cure bilateral IHA. These studies about the treatment of bilateral IHA employed the unilateral ablation of the adrenal arteries. Based on the experience of adrenalectomy for unilateral PA which has indicated long-term effectiveness and safety, also based on the anatomic structure of three branches of adrenal arteries in each side, exploration is needed to highlight the safety and efficacy of bilateral SAAE for bilateral IHA management. Compared to previous studies, this cross-sectional and prospective study aimed to determine the efficacy and safety of SAAE in treating bilateral IHA characterized by bilateral embolization of adrenal arteries, higher degree of BP reductions, larger sample size and at least six-month follow-up period. In addition, understanding the major complications that arise during treatment is crucial for improving patient outcomes. In our study, we also observed numbers of patients developed major complications, including stroke. Our objective was to identify the risk factors and underlying mechanisms contributing to the development of these complications.

Materials and methods

Selection of bilateral IHA patients

Two hundred and sixteen patients with suspected primary aldosteronism (PA) were screened and confirmed based on current guidelines [13] out of 970 outpatients presenting with resistant hypertension or adolescent hypertension at the Cardiac Center of the First Affiliated Hospital of Chongqing Medical University from 20/08/2022 to 31/08/2023 under registration number of ChiCTR2200062738. The inclusion and exclusion criteria used in this study are in accordance with the protocol registered on the China Clinical Trials Registry ((https://www.chictr.org.cn/hvshowprojectEN.html&id=217705&v=1.2).

Inclusion criteria:

1. Patients who have been diagnosed with primary aldosteronism;
2. Refuse drug treatment or drug treatment failure due to adverse reaction intolerance, or refuse adrenalectomy due to surgical risks, or have persistent aldosteronism after adrenalectomy, but not Adrenal insufficiency;
3. Patients with primary aldosteronism who voluntarily underwent adrenal artery embolization.

Exclusion criteria:

1. History of serious contrast agent allergy;
2. Complication with severe liver diseases;
3. History of myocardial infarction and stent implantation within the past 3 months;
4. Renal insufficiency, serum creatinine > 176 mmol/L;
5. Pregnancy or lactation;
6. Participation in another clinical trial in the past 3 months;
7. Any serious complications.

However, the selection procedure was described in more detail in supplementary material as well (see Supplementary Material for details). After receiving full information regarding the three treatment options for IHA, including MRAs, adrenalectomy (in selected cases where medical therapy is insufficient or contraindicated), and SAAE, ninety-eight eligible bilateral IHA patients voluntarily enrolled in this study after providing informed consent approved by the ethical and clinical committee prior to embolization with the ethics reference number of 2022−146. This study was conducted as part of a trial registered with the Chinese Clinical Trial Registry on 17/08/2022 under registration number ChiCTR2200062738 (https://www.chictr.org.cn/hvshowprojectEN.html&id=217705&v=1.2). Following SAAE, thirty patients discontinued follow-up for various reasons (Fig. 1).

Non-enhanced magnetic resonance angiography (MRA)

All patients underwent 3.0-T non-enhanced magnetic resonance angiography (NE-MRA) using a balanced steady-state free precession (bSSFP) sequence combined with respiratory gating on the Philips Ingenia DNA 3.0T MRI system (Netherlands) to visualize the suprarenal arteries (see supplementary material for detail procedure).

^{68}Ga-Pentixafor PET/CT scans

Among the 68 patients diagnosed with PA, 20 of them underwent ^{68}Ga-Pentixafor PET/CT scans both before and after SAAE (see supplementary material for detail procedure). In addition, we assessed the remaining blood flow to the adrenals using post-procedural imaging and PET scans. The completeness of the SAAE procedure was evaluated by comparing the proportion of embolized arteries to all visualized adrenal arteries. Clinical

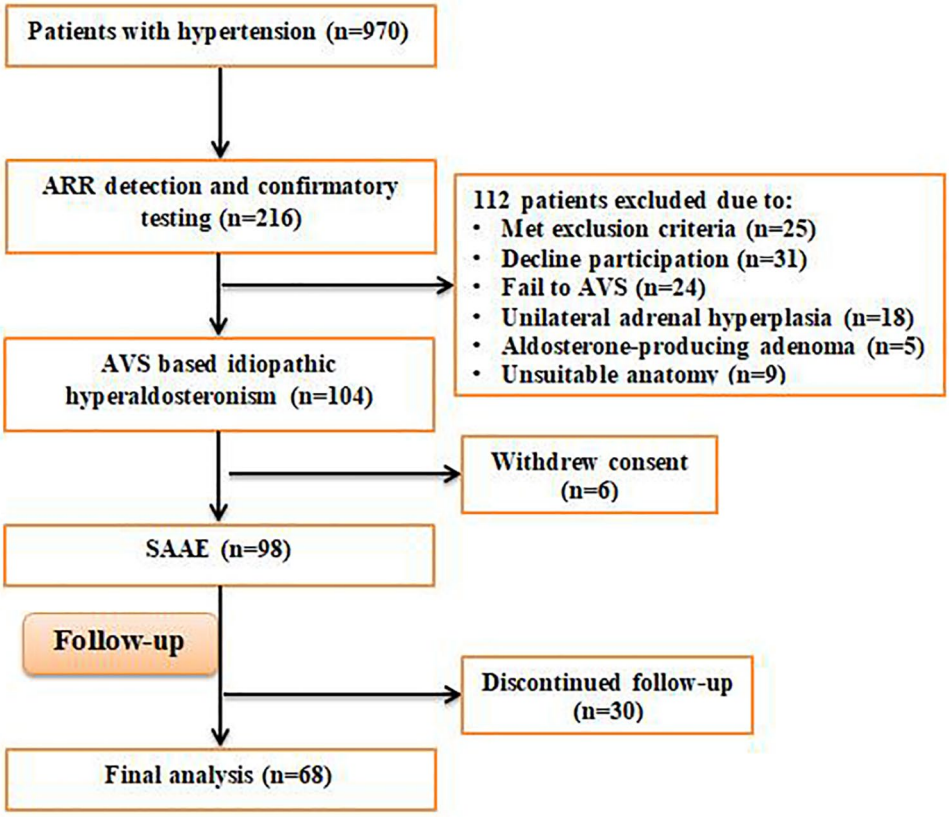

Fig. 1 Patient selection and distribution of PA. Adrenal vein catheterization was considered successful when selectivity index (SI) was ≥ 2 without cosyntropin administration. Unilateral PA was diagnosed if lateralized index (LI) was ≥ 2. Abbreviation: PA, primary aldosteronism; AVS: Adrenal vein sampling; ARR: aldosterone to renin ratio; SAAE: superselective adrenal arterial embolization

outcomes and biochemical markers were analyzed in relation to the completeness of the procedure.

Procedure of AVS

Adrenal venous sampling (AVS) was performed via the right femoral vein, with the right median cubital vein used as an alternative approach, utilizing the DAS system of GE IGS 520 or 630 (American) (see supplementary material for detail procedure).

Procedure of SAAE

The enrolled bilateral IHA patients were provided counseling on all available treatment options, including medications, surgery, and SAAE. Patients who expressed willingness to undergo SAAE were selected for the procedure. Following the guidelines outlined by the Endocrine Society Clinical Practice Guideline, terazosin or verapamil was prescribed for patients with mild hypertension, while continuous administration of antihypertensive medications such as calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) was recommended for patients with high-grade hypertension due to safety concerns.

In contrast to previous studies utilizing unilateral SAAE, patients in this study underwent bilateral SAAE. Patients with unsuitable anatomy for embolism of the adrenal artery on one side were excluded, typically due to one of the following reasons: (i) the diameter of the adrenal artery being smaller than the diameter of the microcatheter; (ii) the adrenal artery being too curved to allow the guidewire to enter; (iii) failure to identify the origin and distribution of the adrenal artery; (iv) deemed too risky to embolize the adrenal artery due to anatomical variation.

The SAAE procedure was conducted according to the previously described method via the right femoral artery under local anesthesia using the DAS system of GE IGS 520 or 630 (GE Co, USA) [14]. A 7-French artery sheath (Medtronic Co. 061102 A, Ireland) was introduced into the right femoral artery, and 25 mg of heparin was administered via the sheath for anticoagulation. To accurately identify the feeding arteries of the adrenal gland, adrenal magnetic resonance angiography (MRA) was performed by a collaborative radiology team in advance. Nonselective abdominal angiography was also performed before SAAE to confirm the position of the adrenal artery and obtain input from the collaborative radiology team. After confirming the route, origin, and distribution of the selected adrenal arteries, a 1.9 F tantpass microcatheter (Epot Co., Ref 60192405, Lot SP6023082308, China) was introduced into the distal segment of the targeted adrenal artery along with a 0.035-inch guiding wire (Cordis Co., EMERALD Guidewire, Ref 502–521, 0.89 mm/150 cm, USA). One of the three adrenal arteries (superior, middle, or inferior) was carefully selected based on the patient's specific anatomical and clinical characteristics. Selective adrenal angiography was performed using the microcatheter filled with an ethanol-lidocaine solution. To prevent backflow, a balloon inflation device for balloon dilation catheters (Emax Co., Ref DMKID30S, Lot TJ230572, Israel) was employed before injecting anhydrous ethanol. Anhydrous ethanol was then injected over the wire balloon at a flow rate of 1 ml/min, typically totaling 2–4 mL for each adrenal artery. After a few minutes, superselective adrenal angiography was repeated via the microcatheter to confirm the success of embolization. If the contrast medium remained in the arterial cavity without forward flow, it indicated successful adrenal artery embolization. If bold flowing contrast medium persisted, additional anhydrous ethanol injections were administered until contrast retention was achieved. This process was repeated on the other side. However, a successful SAAE was considered as the complete embolization of the targeted adrenal arteries, confirmed by post-procedural imaging that showed no abnormal adrenal venous drainage.

Measurement of clinical outcomes

In-hospital patient data were obtained from our hospital's electronic medical record system (EMRS). The primary outcome of this study was clinical success in the reduction of systolic blood pressure, while the primary endpoint was the change in ambulatory systolic blood pressure at six months compared to baseline. Home blood pressure was used to assess clinical success in the present study. Following six months, data were obtained by follow-up records in the EMRS system, the interview in outpatient-department or by telephone, including their related complaints, 24-hour mean systolic blood pressure, and antihypertensive regimens. Biochemical data (including plasma aldosterone level, plasma renin level and plasms serum potassium level) was assessed quantitatively at follow-up visits.

Criteria for categorization of patients

All the study outcomes were assessed according to the PASO criteria, and the obtained outcomes of this study were classified into the three clinical success categories such as complete, partial, or absent of success [15]. Complete clinical success is considered as normal blood pressure without given any antihypertensive medication; partial clinical success is the same blood pressure as recorded at baseline with less antihypertensive medication; absent clinical success is considered as no changed were observed in blood pressure along with the administration of same or an increase amount of antihypertensive medication [16]. Complete biochemical success is defined

as correcting hypokalemia (if present pre-treatment) and normalization of the ARR; partial biochemical success is defined as the correction of hypokalemia (if present pre-treatment), a decreased ARR and ≥50% decrease plasma aldosterone concentration compared with pre-treatment; absent biochemical success is defined as persistent hypokalemia (if present pre-treatment) or persistent raised ARR and plasma aldosterone concentration compared with the baseline of pre-treatment. We also calculated the daily defined dose (DDD) of antihypertensive drugs to calculate the intensity of antihypertensive medications before and after SAAE.

Statistical analysis

The Shapiro-Wilk statistical inferential analysis test was used to evaluate the distribution pattern of continuous outcomes. Normally distributed outcomes were expressed as mean ± SD, while the categorical outcomes were given as their percentages. The changes in clinical and biochemical analysis from baseline to follow-up periods were statistically evaluated using the Student's paired T-test. However, to compare the differences among the three groups, one-way analysis of variance (ANOVA) was conducted for continuous variables. Post-hoc comparisons were performed using the Tukey-Kramer test to identify specific group differences following a significant ANOVA result. The Fisher Exact test was used to evaluate the categorical data. A P-value of <0.05 was used as statistically significant. In addition, we conducted Multivariate logistic regression to control for confounding variables and determine the independent predictors of major complications. Kaplan-Meier survival curves were used to compare the incidence of complications over time between different patient groups. All descriptive and inferential analysis was performed using SPSS version 23.

Table 1 Baseline characteristics of study patients with PA

Characteristics	(*n* = 68)
Age in years (Mean ± SD) (Range)	53.2 ± 13.1 (28–74)
Male/Female (n, %)	31/37 (45.5/54.5)
Body mass index (BMI)	25.0 ± 11.3
Duration of hypertension (y)	9.09 ± 6.8
Hypertension grade (1/2/3) (%)	2.9/14.7/82.4
Smoking (n, %)	14 (20.5)
Diabetes (n, %)	15 (22.0)
Obstructive sleep apnea syndrome (OSAS) (n, %)	37 (54.4)
Blood pressure (mm/Hg)	
Systolic	160.6 ± 18.4
Diastolic	95.9 ± 14.5
Serum potassium (mmol/L)	3.83 ± 0.58
Hypokalemia (n, %)	33 (48.5)
Plasma aldosterone (pg/mL)	190.8 ± 130.2
Aldosterone-to-renin ratio (ARR)	135.4 ± 100.3
Plasma renin (pg/mL)	2.41 ± 2.11
Defined daily dose (DDD)	1.72 ± 1.36

Data are presented as mean ± SD or *n* (%). BMI = Body mass index

Results

Baseline characteristics of study participants

Two hundred and sixteen patients were initially screened from 970 hypertensive patients with suspicion of primary aldosteronism. Among them, 112 patients were excluded due to different reasons, including met exclusion criteria ($n=34$), declined participation ($n=31$), failed AVS ($n=24$), unilateral adrenal hyperplasia ($n=18$) and aldosterone-producing adenoma ($n=5$). At the same time, six participants withdrew their study consent after a confirmed diagnosis of AVS-based idiopathic hyperaldosteronism. Among these patients, 31 declined participation citing personal reasons, such as preference for alternative treatments or concerns about procedural risks. The remaining 23 patients were excluded due to failed adrenal vein sampling (AVS), primarily because of anatomical challenges or technical difficulties during the procedure. The remaining 98 patients opted for SAEE, and 30 dropped out during the study's follow-up period. Finally, the study was completed on 68 patients with complete analysis and follow-up (Fig. 1).

All 68 patients underwent successful SAEE procedures, and the baseline characteristics of PA patients are given in Table 1. For SAAE, success was defined as the complete embolization of the targeted adrenal arteries. The age of patients ranged from 28 to 74 (mean 53.2) years, while the percentage ratio of male versus female participants was 45.5% vs. 54.5%, with an average BMI of 25 ± 11.3 kg/m^2. The mean duration of hypertension diagnosis among study participants was 9.0 ± 6.8 years, with 82.4% of participants suffering from Grade III hypertension. Among them, 14 (20.5%) were found to be current smokers, while 15 (22%) and 37 (54.4%) patients were found with diabetes and OSAS, respectively. The mean 24-hour systolic and diastolic blood pressures were 160.6 ± 18.4 mm/Hg and 95.9 ± 14.5 mm/Hg, respectively. Hypokalemia was observed in 48.5% of patients with a mean serum potassium level of 3.83 ± 0.58 mmol/L. In addition, different other parameters were also recorded as baseline, including plasma aldosterone (190.8 ± 130.2 pg/mL), ARR (135.4 ± 100.3), plasma renin (2.41 ± 2.11 uIU/mL) and DDD (1.72 ± 1.36).

Procedural characteristics of AVS and SAAE

Successful AVS and SAAE had been performed in all the 68 bilateral IHA patients. The successful rate of AVS in this study was 100%, due to the employment of adrenal MRV and the portable immunofluorescence analyzer which could instantly determine whether the blood sample was collected from adrenal vein by the criterion

of selective index (SI) (SI: ratio of cortisol of adrenal vein to cortisol of inferior vena cava) which is more than 2. Patients who failed in SAAE had been ruled out from this study due to the difficult to locate or pass into the adrenal artery. Details of the procedural characteristics are shown in Table S1. Among all the 68 bilateral IHA patients, 8 and 60 patients underwent successful AVS via the median cubital vein and femoral vein respectively, and all the 68 patients underwent SAAE via femoral artery. The mean duration of the procedure (from puncture to withdrawal of the sheath) for AVS and SAAE were 46±23 min and 86±31 min, respectively, and the mean radiation exposure time for AVS and SAAW were 17±6 min and 29±7 min, respectively. The mean volume of contrast medium for AVS and SAAW were 42±22 mL and 69±49 respectively, and the mean volume of absolute ethanol was 2.6±1.4 mL, 72.0% of the embolized adrenal arteries were inferior adrenal artery (98/136), 19.8% of the embolized adrenal arteries were middle adrenal artery (27/136), and 10.2% of the embolized arteries were superior adrenal artery (14/136).

Patient follow-up and data reporting

We have provided detailed data on patient follow-up and outcomes for our study on SAAE.

Intention-to-treat analysis

Out of the initial 104 patients who consented to undergo SAAE, comprehensive data including those who withdrew (6 patients) and discontinued follow-up (30 patients) have been reported (See Table S2).

Per protocol analysis

For the 98 patients who underwent SAAE as per protocol (excluding withdrawals and discontinued follow-up), detailed data on initial procedural success rates and subsequent clinical outcomes are given in Table S3.

Comparison of adrenal MRV/angiographic images of AVS and adrenal MRA/angiographic images of SAAE

For all 68 patients in our study, adrenal magnetic resonance venography (MRV) was performed to ensure the successful procedure of AVS. The images obtained from adrenal MRV depicted the right and left adrenal veins in all patients, showing high consistency with the AVS images (Fig. 2). This 100% success rate of AVS indicates the guiding effect of adrenal MRV, particularly for the sampling of the right adrenal vein, which is prone to significant anatomical variations.

Similarly, adrenal MRA was conducted for all 68 patients to ensure the successful procedure of SAAE. The MRA images revealed the right and left adrenal arteries in all patients, with most of them being consistent with the images obtained during SAAE (Fig. 3). This highlights the guidance effect of adrenal MRA for the SAAE procedure. However, upon detailed analysis of each branch of the adrenal artery, it was observed that no superior adrenal artery (SAAE) was visualized by non-enhanced MRA (NE-MRA). This suggests that SAAE embolism may be more challenging due to increased anatomical variants, complex vascular distribution, and smaller vessel diameters. Regarding the middle adrenal artery (MSA), including both right and left sides, NE-MRA and digital subtraction angiography (DSA) revealed a total of 40 (29.5%) and 27 (19.8%) MSAs, respectively. Among the MSAs observed by NE-MRA, 30% of right MSAs and 70% of left MSAs originated from the abdominal aorta, while 7% originated from the celiac trunk, 3% from the accessory renal artery, and 1% from the superior mesenteric artery. As for the inferior adrenal artery (IAA), NE-MRA and DSA revealed that 117 (86%) and 98 (73%) of them, respectively, originated from the renal arteries. This indicates that IAA could be the main targeted adrenal artery for SAAE due to their stable anatomical origin from the renal arteries and their larger diameters compared to the other branches of the adrenal arteries.

Changes of ^{68}Ga-Pentixafor PET/CT scans before and after SAAE

Of all patients enrolled, 20 of them underwent adrenal ^{68}Ga-Pentixafor PET/CT scans before SAAE and one month postoperatively. No significant abnormality was indicated by the adrenal ^{68}Ga-Pentixafor PET/CT scans both before and after SAAE.

Clinical and biochemical success after adrenal artery ablation

After consent, patients underwent bilateral ablation based on confirmed AVS. The overall reduction in blood pressure after ablation was highly significant ($p<0.001$), and the mean reduction values for systolic and diastolic blood pressures were 27.4±21.3 mm/Hg and 23.1±17.4 mm/Hg, respectively, which was shown in Table 2; Fig. 4. The overall mean reduction values of DDD, ARR and plasma aldosterone were 0.706±1.22, 75.9±189.0 and 40.8±118.3 pg/mL, respectively, which were high-significantly reduced after ablation with the p-values of <0.001, 0.004, and 0.013 respectively. Furthermore, overall mean increased values of plasma renin and serum potassium were 10.4±39.0 pg/mL ($P=0.049$) and 0.40±0.63 mmol/L ($p<0.001$), respectively, which were high-significantly increased.

Clinical success after ablation in PA patients was shown in Tables 3 and Fig. 5. Complete clinical success after ablation was achieved in 17/68 (25% of patients), partial clinical success after ablation was achieved in 26/68 (38.2%) patients, and absent success after ablation happened in 26/68 (38.2%). For complete clinical success PA patient

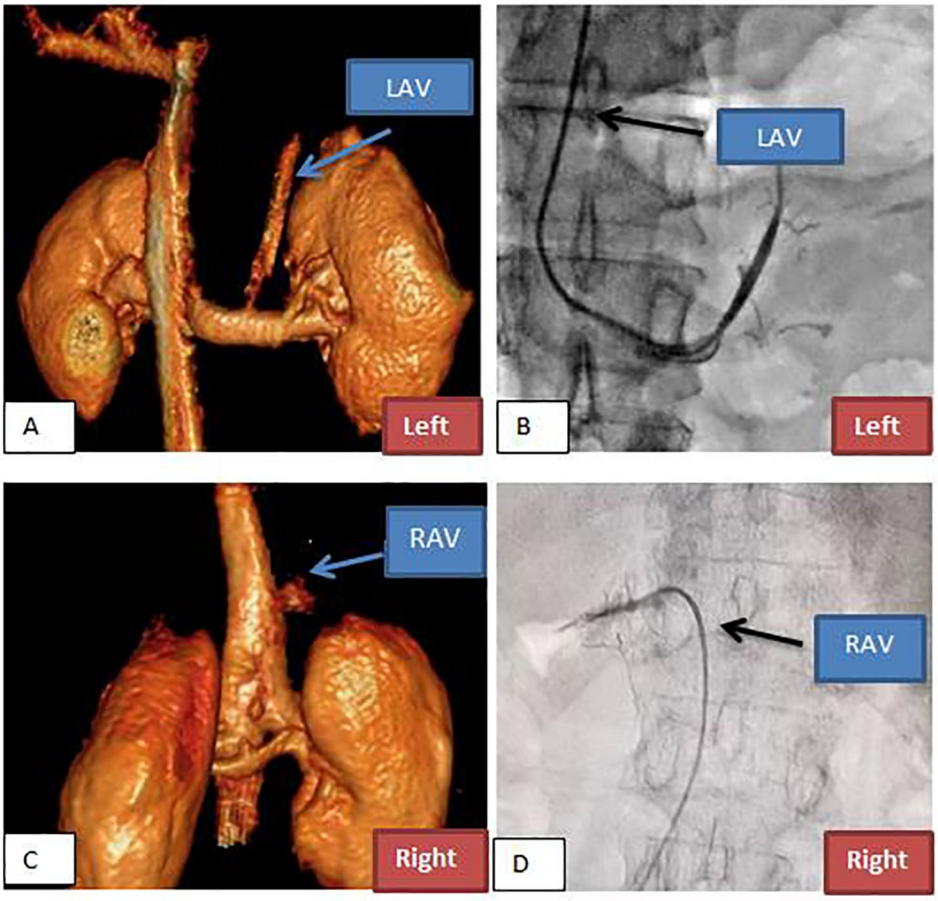

Fig. 2 Left and right adrenal veins observed by NE-MRA and AVS with highly consistence, which indicated the guidance effect of MRV by NE-MRA for the procedure of AVS of PA patients (**A**) LAV observed by NE-MRA; (**B**) LAV observe d by AVS; (**C**) RAV observed by NE-MRA; (**D**) RVA observed by AVS
LAV: Left adrenal vein RAV: Right adrenal vein AVS: Adrenal venous sampling

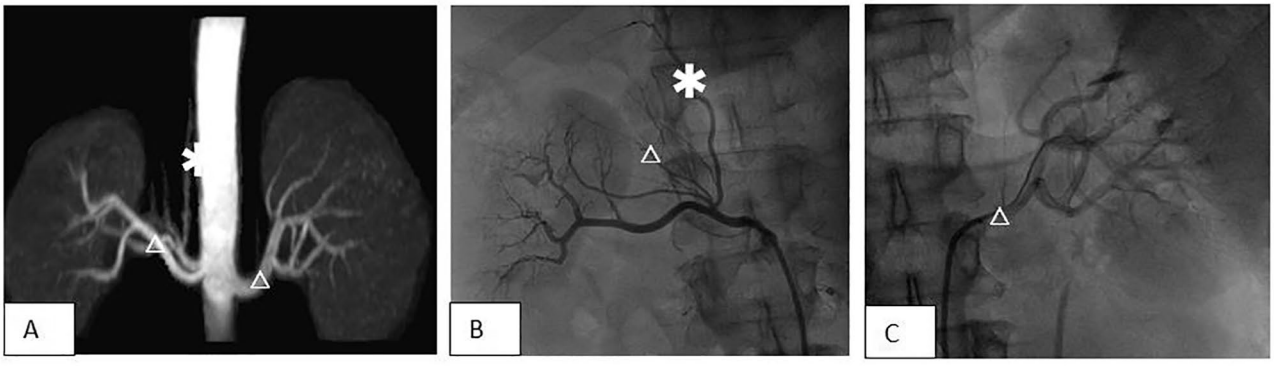

Fig. 3 Left and right adrenal arteries observed by NE-MRA and adrenal angiograph during SAAE of bilateral IHA patients (**A**) NE-MRA showed the left IAA originated from left renal artery, the right IAA originated from right accessory renal artery; (**B**) During SAAE, the adrenal angiograph showed left IAA originated from left renal artery, which was highly consistent with NE-MRA and implied the important role of NE-MRA for the procedure of SAAE; (**C**) During SAAE, the adrenal angiograph showed right IAA originated from right accessory renal artery, which was highly consistent with NE-MRA and implied the important role of NE-MRA for the procedure of SAAE. Triangle represents IAA, star represent inferior phrenic artery
IAA: inferior adrenal artery; SAAE: superselective adrenal artery embolism

Table 2 Descriptive and inferential statistical analysis using paired T-test on overall pre and post ablation outcomes

Pairs	Pre-treated	Post-treated	Paired Reduction			*P*-value
			(Post – Pre) Mean ± SD	95% Confidence Interval of the Difference		
				Lower	Upper	
Pre-B.P vs. Post-B.P (Systolic)	156.2 ± 18.4	128.7 ± 12.3	27.4 ± 21.3	22.3	32.6	$p < 0.001$
Pre-DDD vs. Post-DDD	1.82 ± 1.3	1.12 ± 1.2	0.70 ± 1.2	0.40	1.00	$p < 0.001$
Pre-ARR vs. Post-ARR	148.50 ± 200.3	84.18 ± 116.5	75.94 ± 189.0	25.77	126.1	0.004
Pre-Renin vs. Post-Renin	2.53 ± 2.5	12.61 ± 38.4	-10.40 ± 39.0	-20.76	-0.05	0.049
Pre-Aldosterone vs. Post-Aldosterone	196.78 ± 130.2	155.76 ± 80.3	40.82 ± 118.3	9.14	72.5	0.013
Pre-Potassium vs. Post-Potassium	3.77 ± 0.5	4.11 ± 0.4	-0.40 ± 0.6	-0.57	-0.2	$p < 0.001$

DDD = Defined daily dose; ARR = Aldosterone-to-renin ratio

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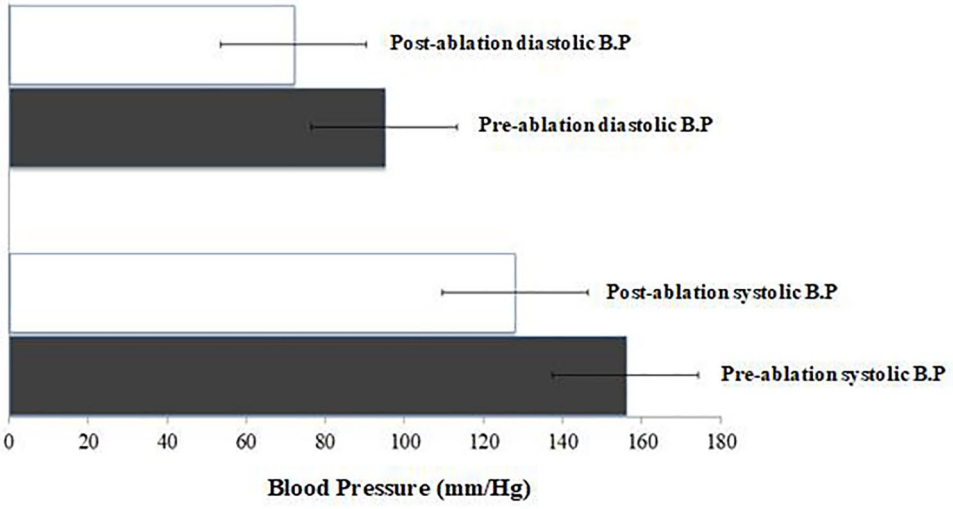

Fig. 4 The difference of blood pressure in IHA patient's pre- and post- ablation of bilateral adrenal arteries The overall reduction in blood pressure after ablation was highly significant ($P = 0.000$), and the mean reduction values for systolic and diastolic blood pressures were 27.4 ± 21.3 mm/Hg and 23.1 ± 17.4 mm/Hg, respectively

Table 3 Clinical success achievement after ablation on patients with PA

Variable	Clinical success			*P*-value
	Complete (*n* = 17, 25%)	Partial (*n* = 26, 38.2%)	Absent (*n* = 25, 36.7%)	
Pre-ablation				
Blood pressure (mm/Hg)				
Systolic	147 ± 16	163 ± 15	149 ± 11	0.156
Diastolic	97 ± 12	102 ± 12	94 ± 15	0.144
DDD	1.2	1.8	1.5	0.035
Post-ablation				
Blood pressure (mm/Hg)				
Systolic	124 ± 11	134 ± 15	147 ± 16	0.016
Diastolic	78 ± 13	89 ± 16	93 ± 18	0.058
DDD	NA	1.2	1.6	NA
Pre-Post ablation change				
Blood pressure (mm/Hg)				
Systolic	23 ± 14	29 ± 22	2 ± 14	$p < 0.001$
Diastolic	19 ± 12	13 ± 7	1 ± 21	$p < 0.001$

DDD = Defined daily dose, Values are presented as mean ± SD or *n* (%)

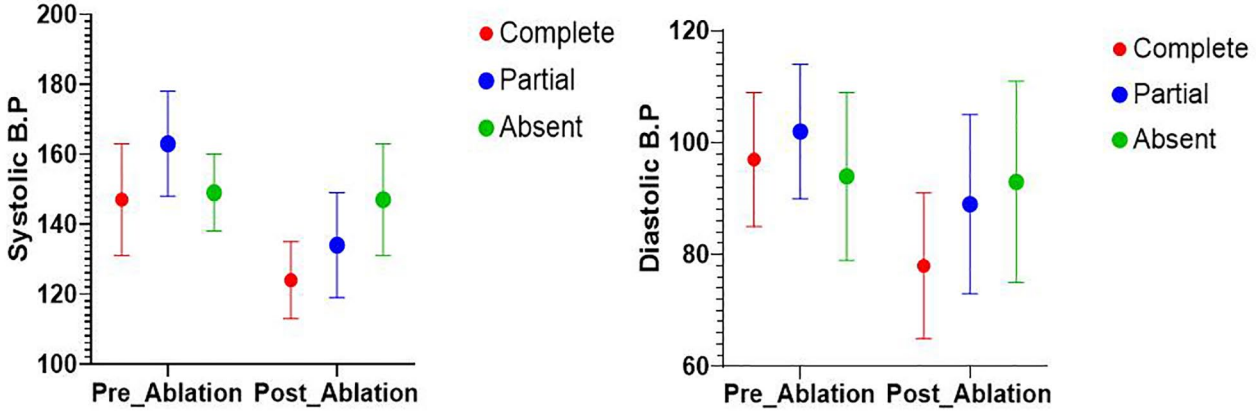

Fig. 5 The changes of blood pressure pre- and post- ablation of bilateral adrenal arteries in different groups (complete clinical success, partial clinical success and absent clinical success) For complete clinical success PA patient group, the mean reduction of systolic BP and diastolic BP were 23 ± 14 mm/Hg and 19 ± 12 mm/Hg, respectively; for partial clinical success PA patient group, the reduction of systolic BP and diastolic BP were 29 ± 22 mm/Hg and 13 ± 7 mm/Hg, respectively

Table 4 Biochemical success achievement after ablation on patients with PA

Variable	Biochemical success			*P*-value
	Complete (*n* = 23, 33.8%)	Partial (*n* = 4, 5.8%)	Absent (*n* = 41, 60.2%)	
Pre-ablation				
Serum potassium (mmol/L)	4.31 ± 0.16	3.75 ± 0.43	3.24 ± 0.64	0.007
Plasma aldosterone (pg/mL)	201 ± 26	178 ± 21	195 ± 15	0.646
ARR	101 ± 32	125 ± 27	138 ± 22	0.674
Plasma renin (pg/mL)	2.65 ± 0.67	2.26 ± 0.56	2.43 ± 0.22	0.625
Post-ablation				
Serum potassium (mmol/L)	4.49 ± 0.23	3.94 ± 0.38	3.31 ± 0.52	0.632
Plasma aldosterone (pg/mL)	178 ± 25	167 ± 21	189 ± 32	0.474
ARR	13 ± 8	85 ± 27	160 ± 37	0.037
Plasma renin (pg/mL)	3.87 ± 0.67	3.44 ± 0.86	2.11 ± 0.66	0.074
Pre-Post ablation change				
Serum potassium (mmol/L)	-0.18 ± 0.17	-0.19 ± 0.78	-0.07 ± 1.67	0.526
Plasma aldosterone (pg/mL)	23 ± 15	11 ± 21	6 ± 10	0.414
ARR	88 ± 22	40 ± 22	-22 ± 26	0.063
Plasma renin (pg/mL)	-1.22 ± 1.45	-1.18 ± 1.89	0.32 ± 0.35	0.081

ARR = Aldosterone-to-renin ratio, Values are presented as mean ± SD or *n* (%)

group, the mean reduction of systolic BP and diastolic BP were 23±14 mm/Hg and 19±12 mm/Hg, respectively; for partial clinical success PA patient group, the reduction of systolic BP and diastolic BP were 29±22 mm/Hg and 13±7 mm/Hg, respectively. Biochemical success after ablation in PA patients was presented in Tables 4 and Fig. 6. Complete biochemical success after adrenal artery ablation was achieved in 23/68 (33.8%) patients, partial biochemical success after adrenal artery ablation was observed in 4/68 (5.8%) patients and absent success after artery ablation happened in 41/68 (60.2%). In complete biochemical success patient group after ablation, the reduction of plasma aldosterone and ARR were 230±150 pg/mL and 88±22, respectively, and the serum potassium level and plasma renin increased 0.18±0.17 mmol/L and 1.22±1.45 uIU/mL, respectively. In partial clinical success patient group, the reduction of plasma aldosterone and ARR were 110±210 pg/mL and 40±22, respectively, and the serum potassium level and plasma renin increased 0.19±0.78 mmol/L and 1.18±1.89 uIU/ml, respectively.

PET Pre/Post results

The PET scans performed before and after the procedure indicated the level of residual adrenal activity (Table S4). A reduction in PET activity post-procedure correlated with a higher proportion of embolized arteries and better clinical outcomes. These findings suggest that the completeness of the SAAE procedure, as indicated by the

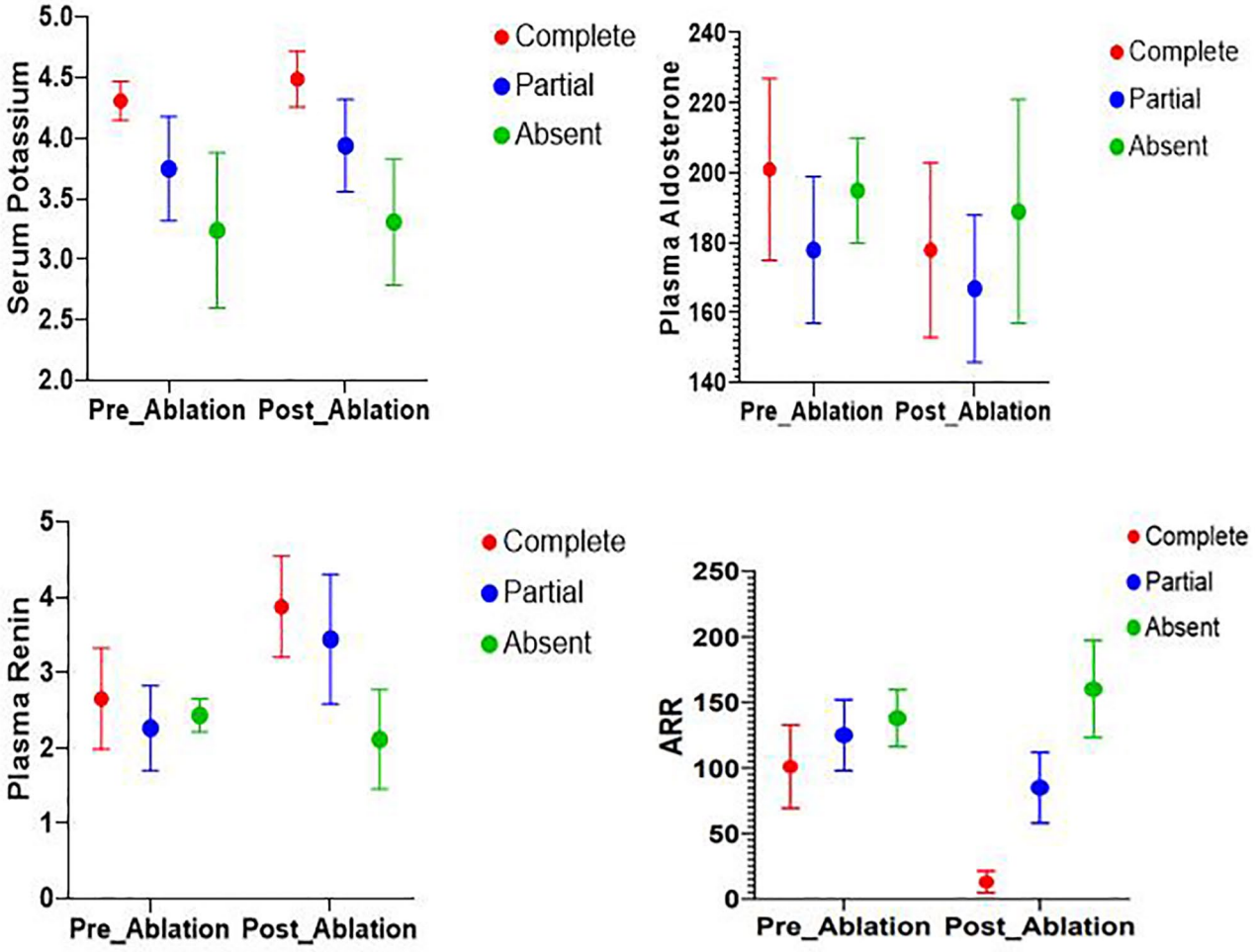

Fig. 6 Changes in bilateral IHA patient categorized by PASO biochemical success after bilateral ablation of adrenal arteries In complete biochemical success patient group after ablation, the reduction of plasma aldosterone and ARR were 230 ± 150 pg/mL and 88 ± 22, respectively, and the serum potassium level and plasma renin increased 0.18 ± 0.17 mmol/L and 1.22 ± 1.45 uIU/ml, respectively. In partial clinical success patient group, the reduction of plasma aldosterone and ARR were 110 ± 210 pg/mL and 40 ± 22, respectively, and the serum potassium level and plasma renin increased 0.19 ± 0.78 mmol/L and 1.18 ± 1.89 uIU/ml, respectively

Table 5 Adverse events during and after SAAE

Adverse events	Occurrence	Length of time
Abdominal pain/back pain	40/68 (58.8%)	1–5 days
Elevated BP during embolism	39/68 (57.4%)	2–15 min
Nausea and vomiting	13/68 (19%)	0.5-1 days
Dizziness	9/68 (13.1%)	0.5-1 days
Fever	8/68 (11.8%)	1–2 days
Ventricular premature beats	26/68 (38.3%)	2–5 min
Atrial premature beats	18/68 (26.5%)	2–5 min
Ventricular tachycardia	9/68 (13.3%)	2–5 min
Atrial tachycardia	17/68 (25%)	1 min
Atrial flutter	3/68 (4%)	1 min
Atrial fibrillation	8/68 (11.7%)	2–3 min
Sinus arrest	2/68 (2.9%)	0.5–2 min
Stroke	2/68 (2.9%)	5–7 days

Values are presented as *n/N* (%)

proportion of arteries embolized, is crucial for achieving optimal outcomes.

Adverse events during SAAE and follow-up period

All 68 patients underwent successful SAAE procedures without major adverse effects related to SAAE, while some minor adverse effects were observed, which was shown in detail in Table 5. During follow-up, less than 5% developed major complications. Specifically, 2% experienced a stroke, which we defined as a sudden loss of neurological function due to an interruption in blood supply to the brain (ischemic stroke). The multivariate analyses identified several significant predictors of major complications, including age, and pre-existing conditions, as indicated in Table S5. The Kaplan-Meier survival curves (Fig. 7) further illustrate these findings.

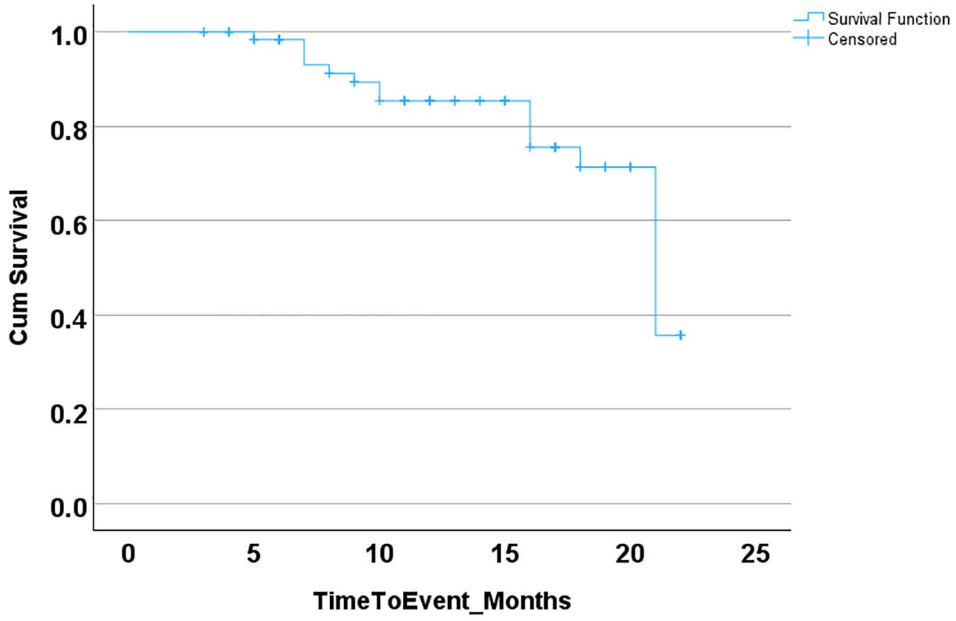

Fig. 7 Kaplan-Meier Survival Curve for Major Complications with respect to time period in months

However, forty six (40/68, 58.8%) of the patients complained tolerable intraoperative abdominal pain and back pain associated with ethanol embolization, some of which radiated to the shoulder on the side of the embolization, usually relieved very soon, while some lasted for 3–5 days. Slight fever occurred in 16 (16/68, 23.5%) patients, which was relieved with nonsteroidal anti-inflammatory drugs. Thirteen (13/68, 19%) patients also complained postoperative nausea and vomiting, and nine patients (9/68, 13.1%) had postoperative dizziness due to the elevated BP (7/68) or reduced BP (2/68). The pain, anxiety and catecholamine release during the embolism of adrenal artery induced dramatic intraoperative blood pressure fluctuations for 39 (39/68, 57.3%) of them, usually higher than 180/90 mmHg, even too high to test, therefore nitroglycer was routinely prepared to help control blood pressure fluctuations during the procedure. Nitroglycer was injected into adrenal artery via microcatheter intraoperatively at doses ranging from 0.5 μg/kg to 3 μg/kg according to the patient's intraoperative blood pressure fluctuations. No intraoperative hypertensive crisis and no cerebral hemorrhage happened even when the blood pressure significantly elevated. There were two cases of pain-induced vagal reflex, which resulted in hypotension and bradycardia with the symptoms of palpitation, dizziness, nausea and vomiting, which were relieved effectively by the intravenous injection of atropine and the intravenous infusion of physiological saline rapidly. Different kinds of arrhythmias were recorded during embolism of adrenal artery which lasted usually a few seconds and disappeared without medication, including ventricular premature beats (26/68, 38.3%), ventricular tachycardia (9/68, 9.18%), atrial premature beats (18/68, 26.5%), atrial tachycardia (17/68, 25%), atrial flutter (3/68, 4%), atrial fibrillation (8/68, 11.7%) and sinus arrest (2/68, 2.9%). All the above postoperative symptoms disappeared before discharge from the hospital. No procedure-related complications were reported at a median follow-up of 1 year. We measured the patients' cortisol levels at 8 am at three-time points: preoperatively, 24 h postoperatively, and at a median follow-up of 6 month or 1 year, and there was no significant difference in plasma cortisol levels between the above three time points and no clinical manifestations of adrenal cortical dysfunction were observed during the follow-up. Reoccurrence of stroke happened in two patients, one was bleeding stroke and the other was ischemia stroke, both of them had the history of stroke 1–10 years before ablation of adrenal arteries. No elevation of serum creatinine was observed after SAAE and during the follow-up period. Minor adverse effects detailed in Table S6 were noted in discontinued patients, with no significant difference compared to patients who completed their follow-up period.

Discussion

To the best of our knowledge, the present study is the first cohort study of bilateral adrenal artery ablation for bilateral IHA. In this study, among 68 PA patients without lateralized secretion (bilateral IHA), the clinical success (complete+partial) and biochemical success (complete+partial) achieved by bilateral SAAE were 63.2% and 39.6%, respectively, and the cases with complete clinical success and complete biochemical success

were 17 (25%) and 23 (33.8%), respectively. The mean reduction of systolic and diastolic blood pressures were 27.4±21.3 mmHg and 23.1±17.4 mmHg, respectively. The mean reduction of DDD, ARR and plasma aldosterone was 0.706±1.22, 75.9±189.0 and 40.8±118.3 pg/mL, respectively. The mean increases of plasma renin and serum potassium were 10.4±39.0 uIU/mL and 0.40±0.63, respectively. No major adverse safety events and no adrenocortical hypofunction related to bilateral SAAE were reported during the intraoperative, postoperative, and follow-up periods. The outcomes revealed that bilateral SAAE might be an effective and safe therapeutic strategy for treating hypertension due to bilateral IHA, without serious complications, and bilateral SAAE provides a new promising strategy for the management of bilateral IHA, with the potential to cure bilateral IHA. However, clinical success rates were higher than biochemical success rates, which is atypical according to PASO criteria. This discrepancy may be due to unique patient characteristics, differences in success definitions, partial adrenal function post-procedure, and variability in measurement sensitivity. The occurrence of few major complications, such as stroke, significantly impacts patient outcomes. In our study, stroke was defined as an ischemic event leading to a sudden loss of neurological function. Our statistical analysis revealed that age, and pre-existing conditions, were significant predictors of major complications. These findings underscore the need for careful monitoring and tailored treatment strategies for high-risk patients.

For unilateral PA patients, unilateral adrenalectomy, recommended by the Endocrine Society Clinical Practice Guidelines, achieves a complete clinical success rate of 34% and a complete biochemical success rate of 94% [17]. Surgical adrenalectomy effectively reverses biochemical abnormalities and mitigates long-term risks associated with PA, offering potential cure [18]. However, in bilateral adrenal disease, including bilateral idiopathic hyperaldosteronism (IHA) and bilateral aldosterone-producing adenomas (APA), adrenalectomy yields lower rates of cure (15–19%) and hypertension improvement (20%) [19, 20]. In these cases, the guidelines recommend MRAs like spironolactone or eplerenone, which achieve a 60–75% success rate in normalizing blood pressure and aldosterone levels [17, 21, 22]. Despite their efficacy, MRAs are associated with increased cardiovascular events due to persistently elevated aldosterone levels in PA patients compared to essential hypertension. Additionally, adverse effects such as gynecomastia and menstrual disturbances limit long-term use, though newer MRAs like eplerenone offer reduced endocrine side effects [23–25].

The feasibility of SAAE for treating APA was first reported in 1993, Hokotate et al. [26] reported 33 cases of APA treated by SAAE, with a mean follow-up duration of 45 months, the technical successful rate was 82% with excellent safety profile. During follow-up period, for the 27 patients who underwent successful SAAE, blood pressure normalized in 9 of them and decreased in 10 of them, and other research centers subsequently reported encouraging long-term results [27]. However, the effect of SAAE for patients with IHA is seldom evaluated. Previously, Hexuan Z in 2020 [28] and Hui Dong et al. in 2021 [14] have reported about the effect of SAAE for IHA patient, in which 36 and 39 patients respectively with IHA underwent SAAE successfully at and at the follow-up time of 12-months. From the report of Hexuan Zhang, the mean reduction of Office-based and ambulatory blood pressures were reduced by 17/7 and 11/2 mmHg at 6 months after ablation, respectively. Similarly, from the report of Hui Dong, et al., the reduction of 24-hour blood pressure were 13/7 and 11/7 mmHg, respectively, and the standing plasma aldosterone was reduced from 524.0 pmol/L at baseline to 293.4 pmol/L without severe complications. The blood pressure changes and biochemical responses of SAAE were improved compared with the results of unilateral adrenalectomy for patients with IHA, which indicated that SAAE might be a safety and effective therapeutic strategy for patients with IHA. In our study, successful bilateral SAAE have been undergone in 68 bilateral IHA patients and followed up for at least six month, and the longest follow-up period was 12 months. The mean reduction of blood pressure after ablation of bilateral adrenal arteries were 27.4±21.3 mmHg for systolic blood pressure and 23.1±17.4 mmHg for diastolic blood pressure, respectively, which was more predominant compared with effect of unilateral ablation of adrenal artery in IHA patients. At the same time, the level of plasma aldosterone, ARR and DDD decreased 40.8±118.3 pg/mL, 75.9±189.0 and 0.706±1.22, respectively. Our results indicated that bilateral ablation of adrenal could be a more effective as well as safe therapeutic strategy compared with unilateral ablation of adrenal artery for bilateral IHA patients. The reason why we choose bilateral ablation of adrenal arteries for the bilateral IHA was based on the experience of surgical adrenalectomy which offers the potential for cure of the adrenal disease without the occurrence of adrenal cortical insufficiency in the long-term follow-up periods, and also based on the anatomy of adrenal arteries which compose three adrenal arteries in each side. In order to avoid the influence of plasma aldosterone and renin activity by the medication after ablation, diuretics (including hydrochlorothiazide, furosemide and spirolactone) and beta blocks were not administered during the follow-up period, and doxazosin along with diltiazem were the most frequently prescribed medicine after the ablation during the follow-up period. The complete clinical (25%) and biochemical (33.8%) success in this study was achieved after bilateral adrenal ablation, which is equivalent to the previously

reported clinical success (27%) after unilateral adrenalectomy and unilateral SAAE [14, 29]. The study indicates that bilateral SAAE appears safe and effective for treating idiopathic hyperaldosteronism (IHA), without serious complications like adrenocortical hypofunction observed. Variations in treatment outcomes among different groups (complete, partial, absent success) may stem from factors such as individualized anhydrous ethanol volumes based on adrenal artery size and varying adrenal histopathology influencing post-procedure clinical and biochemical responses. Further research is needed to better understand these mechanisms in bilateral IHA patients. In addition, the stable findings from 68Ga-Pentixafor PET/CT scans post-SAAE support the safety and efficacy of this procedure in managing bilateral IHA without compromising adrenal CXCR4 receptor expression. Integrating CXCR4 imaging into clinical practice may enhance our ability to monitor treatment outcomes and tailor therapeutic strategies in adrenal disorders effectively. Future studies on IHA should focus on refining procedural aspects such as precise evaluation of adrenal artery anatomy using NE-MRA, optimizing microcatheter placement, controlling embolic agent injection speed, and implementing real-time imaging for confirmation of successful embolization. Additionally, investigating anesthesia strategies for pain management and monitoring cardiovascular changes during procedures will be crucial for enhancing outcomes and patient safety.

Limitations

This study has several limitations. Firstly, the sample size and the follow-up time were limited, and it was single-center study. Therefore, further multi-center trials with larger patient populations and longer-term follow-up periods are expected. Secondly, it was not a randomized controlled study and classified as feasibility study. The decision to proceed without a control group was based on difficulties in patient recruitment, changes in study design, and logistical constraints. The study thus primarily provides feasibility data rather than a comparative efficacy assessment. The absence of a control group (e.g., medication-only group), the results can only be compared with the data from the literature. Thirdly, this procedure cannot evaluate the destruction area and other pathological changes in the adrenal tissue, which is not helpful for our deep understanding for the mechanism of this disease and for the precise prediction of the effect of embolism. Also, the results of the current procedure may also vary if performed in different group, which depends on the capability of intervention team. In our study, the intervention team is a highly skilled and technical multidisciplinary team, which comprise of hypertension specialists, cardiologists, cardiovascular intervention specialists, endocrinologists, urologists, nuclear medicine experts and radiology experts.

Conclusion

These clinical and biochemical data indicated that bilateral SAAE might be a more effective therapeutic management for reducing blood pressure as well as the levels of plasma aldosterone compared with unilateral SAAE for bilateral IHA patients., and offers the potential for disease cure with minimal side effects and persistent blood pressure control. It is also reasonable to expect the reduction of cardiovascular events during the long-term follow-up periods.

Abbreviations

ARR	ARR Aldosterone/renin ratio
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
AVS	Adrenal venous sampling
bSSFP	Balanced steady-state free precession
CLIA	Chemiluminescent immunoassay
CT	Computerized tomography
CCT	Captopril challenge test
CCBs	Calcium channel blockers
DDD	Daily defined doses
EMRS	Electronic medical record system
IHA	Idiopathic hyperaldosteronism
LI	Lateralization index
PA	Primary aldosteronism
PASO	Primary Aldosteronism Surgical Outcome
SAAE	Superselective adrenal arterial embolization
SIT	Saline infusion test
SUVmax	Maximal standardized uptake value
SI	Selective index

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

(1) Design: Chang Jing, Xiang Rui. (2) AVS and SAAE: Chang Jing, Xiang Rui, Mao min, Feng Rui, Zhao Yong Peng. (3) MRA: Tao Li. (4) Management of Pain: Tang Ping, Lv Feng Jie. (5) Data collection: Chen Jie, Li Xin, Zhao Hong, Shi Qiuyue, Wang Ling, He Yutian. (6) Data analysis: Nouman Ali Khan, Muhammad Arif Asghar. (7) Manuscript writing: Nouman Ali Khan, Chang Jing. All authors reviewed the manuscript.

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Data availability

There are ethical restrictions on sharing of de-identified data for this study. The ethics committee has not agreed to the public sharing of data as we do not have the participants' permission to share their anonymous data. Further, the dataset includes sensitive injury cases and descriptions of the mechanism of injury. It is likely given the nature of the dataset that patients may still be identifiable despite efforts to anonymize the data. Qualified and interested researchers may request access to the data by contacting corresponding author Professor Chang Jing (Phone: +0086 023 89011513, Email: 1584105002@qq.com). Ethics reference number is 2022-146, which is approved by Ethics Committee of the First Affiliated Hospital of Chongqing Medical University(Phone +0086 023 89011876).

Declarations

Ethical approval and consent to participate

Ethics reference number is 2022 – 146, which is approved by Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Phone + 0086 023 89011876). This study was part of a trial registered with the Chinese Clinical Trial Registry number ChiCTR2200062738 (http://wwwchictr.org.cn). All participants gave their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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