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ORIGINAL RESEARCH

Effect of Accessory Renal Arteries on Essential Hypertension and Related Mechanisms

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BACKGROUND: This case-control study aimed to determine whether there were differences between patients with essential hypertension with accessory renal arteries (ARAs) and those without ARAs.

METHODS AND RESULTS: The enrolled patients with essential hypertension were divided into the ARA group (n=200) and control group without ARAs (n=238). After propensity matching, 394 patients (197 in each of the 2 groups), were included. The 24-hour BP (4.33/2.43 mm Hg) and daytime BP (4.48/2.61 mm Hg) of patients in the ARA group were significantly higher than those of the control group (P<0.05). The flow-mediated dilation was lower in the ARA group (5.98±2.70 versus 5.18±2.66; P<0.05). In correlation analysis, the horizontal plasma aldosterone concentration had the highest correlation with 24-hour, daytime, and nighttime systolic BP (r=0.263, 0.247, and 0.243, respectively; P<0.05) and diastolic BP (r=0.325, 0.298, and 0.317, respectively; P<0.05). As for multivariate regression analysis, plasma aldosterone concentration was a significant risk factor for elevated 24-hour, daytime, and nighttime systolic BP (β=0.249 [95% CI, 0.150–0.349], 0.228 [95% CI, 0.128–0.329], and 0.282 [95% CI, 0.187–0.377], respectively; P<0.05) and elevated diastolic BP (β=0.289 [95% CI, 0.192–0.385], 0.256 [95% CI, 0.158–0.353], and 0.335 [95% CI, 0.243–0.427], respectively; P<0.05). Direct renin concentration was also a risk factor for 24-hour and daytime BPs, whereas heart rate was a risk factor correlated with 24-hour, daytime, and nighttime diastolic BP (all P<0.05). For the mixed-effects model for repeated measures, the results were similar to results of the multivariate regression analysis (all P<0.05).

CONCLUSIONS: ARAs could contribute a higher BP of patients with essential hypertension and might promote the development of essential hypertension. The mechanism might be related to overactivation of the renin-angiotensin-aldosterone system and sympathetic nervous system.

Key Words: accessory renal artery ■ aldosterone ■ essential hypertension ■ renin ■ sympathetic nervous activity

The accessory renal arteries (ARAs), also known as multiple or additional renal arteries, are a common anatomic variation of renal vessels. There are different definitions of ARAs. They were defined as directly derived from the abdominal aortic or its branches (except main renal arteries) and terminated in the kidney, including the hilum and the superior or inferior renal poles in most studies.[1–3] The prevalence of ARAs is various in different studies, which may be associated with the definitions of ARAs. Besides, racial differences may also result in the disparity of the incidence of ARAs.[4–7] As a variation of the renal vessels, the ARAs play an important role in the success rate of operation. They can also bring several postoperative complications and other renal diseases if not taking note.[3]

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CLINICAL PERSPECTIVE

What Is New?

- From this research, we found that patients with primary hypertension with accessory renal arteries have higher blood pressure and more severe target organ damage.
- The mechanisms might be associated with overactivation of the renin-angiotensin-aldosterone system and sympathetic nerve fibers.

What Are the Clinical Implications?

- The results of our study could provide evidence of the need for ablation of accessory renal arteries in renal denervation.

Nonstandard Abbreviations and Acronyms

ARA	accessory renal artery
CTA	computed tomography angiography
DBP	diastolic blood pressure
DRC	direct renin concentration
FMD	flow-mediated dilation
HR	heart rate
IMT	intima-media thickness
LVMI	left ventricular mass index
PAC	plasma aldosterone concentration
PWV	pulse-wave velocity
RAAS	renin-angiotensin-aldosterone system
RDN	renal denervation
RWT	relative wall thickness
SBP	systolic blood pressure
TOD	target organ damage

Hypertension refers to the increase of arterial pressure in systemic circulation with the genetic and environmental factors, whereas the cause and pathogenesis have still been unclear in nearly 95% patients with hypertension called essential hypertension.[8] In 1951, Marshall et al[9] showed that the incidence of multiple renal arteries in patients with hypertension was significantly higher than that in nonhypertensive ones; they were the first to propose a close relationship between hypertension and multiple renal arteries. However, the diagnosis of hypertension was based on postmortem results in their study, which limited the accuracy of the conclusion. Later, Robertson et al[10,11] drew the same conclusion via radiography, and they claimed that abnormalities in juxtaglomerular vessels may be associated with abnormal blood pressure (BP) regulation. There was no direct evidence to support the idea. With the development of technology, renal denervation (RDN) is regarded as an effective method to control resistant BP, and the anatomy of distribution of periarterial nerve in ARAs has been explored in a recent study.[12] Id et al[13] found that the presence of ARAs could abolish the BP reduction after RDN, which showed that ARAs might be involved in the mechanism of hypertension. However, some studies presented an opposing view. Lauder et al[14] revealed that there was no incidence difference in ARAs between patients with controlled hypertension and uncontrolled hypertension. Therefore, further studies are needed to clarify whether ARAs are associated with hypertension.

The objective of this study was to determine whether there were discrepancies of BP in patients with essential hypertension with and without ARAs. It was also explored if there was any hypertension-related target organ damage (TOD) between the 2 groups and the related mechanisms, which might provide new evidence on the need for ARA ablation in RDN.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. The Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guideline was used to be understood better.[15]

Definition of ARAs

In this study, ARAs were defined as extrarenal arteries directly derived from the abdominal aortic or its branches (like arteries A and C in Figure S1) instead of renal arteries (like artery B in Figure S1) to serve a portion of renal parenchyma.

Study Population

This was a case-control study. There were 3280 patients diagnosed with hypertension who were admitted to the First Affiliated Hospital of Dalian Medical University in 2018 to 2020, and they underwent physical examinations, including biochemistry and imaging measurements, as described below, for screening secondary hypertension and evaluating the TOD. Besides, we also performed computed tomography of the adrenal gland to help exclude adrenal-related hypertension, rhythm of cortisol secretion to exclude Cushing syndrome, and thyroid hormone to exclude thyroid disease, according to the current guideline.[16] A total of 438 patients finally diagnosed with essential hypertension were consecutively enrolled. Eligible patients, aged 18 to 65 years, were allocated to the control group and the ARA group, according to the computed tomography angiography (CTA) of renal arteries. Patients in the control group had bilateral single renal arteries, whereas others in the ARA group had ≥1 ARAs. All

enrolled patients withdrew angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, β-adrenergic blockers, and central α-agonists for at least 2 weeks, diuretics for at least 4 weeks, and aldosterone receptor antagonists for at least 6 weeks for secondary hypertension screening. Nondihydropyridine calcium channel blockers or α-adrenergic blockers were used to control BP. A medication index was calculated to compare the specific dosage of antihypertensive medications.[17] Exclusion criteria were set, including secondary hypertension proposed by the latest guideline,[16] such as primary aldosteronism, Cushing syndrome, severe renal artery stenosis (≥75%), pheochromocytoma, white-coat hypertension, pseudohypertension, pregnancy, malignant tumor, infection, history of major surgery within 1 year, severe liver or kidney dysfunction (3-fold aspartate aminotransferase or alanine aminotransferase level, estimated glomerular filtration rate <60 mL/[min×1.73 m^2]), history of acute myocardial infarction or stroke within 3 months, or heart failure with left ventricular ejection fraction of <50%.

Biochemistry Measurements

The clinical characteristics, including sex, age, hypertension duration, smoking index, body mass index, history of family hypertension, antihypertensive medications, and diabetes, were reviewed and recorded. The laboratory examinations, including fasting plasma glucose, hepatic and renal function, lipid profile, electrolyte, serum uric acid, homocysteine, hs-CRP (high-sensitivity C-reactive protein), B-type natriuretic peptide, and glycated hemoglobin A1c, were measured by the serum taken through peripheral veins after fasting for at least 8 hours. Urinary albumin/creatinine ratio was determined by analyzing the first urine voided in the morning. Urinary 24-hour sodium, potassium, and protein were measured from the collection of 24-hour urine. All laboratory examinations mentioned before were measured by automated biochemical instrument. Estimated glomerular filtration rate was calculated by Chronic Kidney Disease Epidemiology Collaboration formula.[18,19] Direct renin concentration (DRC) and plasma aldosterone concentration (PAC) in vertical and horizontal positions were measured by chemiluminescence (DiaSorin S.P.A, Saluggia, Italy). Angiotensin II was measured by radioimmunoassay (Bnibt, Beijing, China). The concentration of plasma norepinephrine was collected after fasting for at least 8 hours in the morning at the same time in a horizontal position and measured by ELISA (Abnova, Taipei, Taiwan).

BP and Heart Rate Measurements

Ambulatory BP monitoring was performed using Spacelabs 90207 devices. BP readings were recorded per 30 minutes at daytime and per 60 minutes at nighttime (daytime: 6:00 AM–10:00 PM; nighttime: 10:00 PM–6:00 AM). Holter ECG monitoring was performed using BI 9800 devices, and the 24-hour mean heart rate (HR) was recorded. The specific criterion of measurement was dated by the latest guideline.[20]

CTA of Renal Arteries

The report for CTA of renal arteries was analyzed by a radiologist with 10 years of experience in CTA diagnosis and a radiology graduate student with 2 years of experience in CTA diagnosis. The anatomic characteristics of ARAs among patients were recorded.

Echocardiogram

The echocardiographic measurement and calculation were referred to the guideline.[21,22] There were 4 left ventricular geometries: normal geometry (normal left ventricular mass index [LVMI] and relative wall thickness [RWT]), concentric remodeling (normal LVMI and increased RWT), concentric hypertrophy (increased LVMI and RWT), and eccentric hypertrophy (increased LVMI and normal RWT).[23]

Vascular Functional Index

The function of the vessels was evaluated by these indices, including the carotid intima-media thickness (IMT; normal range: ≤0.9 mm), pulse-wave velocity (PWV; normal range: ≤1000 cm/s), ankle-brachial index (normal range: ≥0.9), and flow-mediated dilation (FMD; normal range: ≥6%).[24,25]

Ethical Statement

This study was designed and performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University. All patients enrolled provided written informed consent.

Statistical Analysis

Data analysis was performed using SPSS Statistics, version 26.0, and R software, version 4.2.2. A propensity score matching analysis was used to minimize the impact of confounding factors between the 2 groups. The propensity score was calculated according to the logical equation, where the variable of sex was entered for each patient. To compare with the difference of clinical characteristics and examination parameters between the 2 groups, continuous variables with normal distribution were reported as the mean±SD and compared by independent-sample *t*-test, whereas continuous variables with nonnormal distribution were reported as median and 25th and 75th percentiles and compared by Mann-Whitney *U*-test. Categorical

variables were presented as percentages and compared by Pearson χ^2 test or Fisher exact test, depending on the sample size and theoretical frequency. The correlation coefficient of continuous variables was introduced to observe the correlation of BP with the partial parameters. When the variables were of normal distribution, Pearson test would be chosen, whereas those with nonnormal distribution were evaluated by Spearman test. The multivariate stepwise regression was used to explore the independent risk factors for BP, and variables with $P<0.1$ in univariate analyses were entered into the model. Considering the correlation of daytime and nighttime BP because they were from the same patient, a mixed-effects model for repeated measures was performed. $P<0.05$ was considered statistically significant.

RESULTS

Characteristics of Participants

There were 394 patients, with 197 each in the 2 groups, after propensity matching (Figure 1). There was no difference in these clinical characteristics, including age, sex, hypertension duration, body mass index, and smoking index, medication history before and after withdrawal, medication index after withdraw, and laboratory examinations between the 2 groups (all $P>0.05$) (Table 1). The anatomic characteristics of ARAs were recorded and analyzed, which showed that left ARAs were more common than right and bilateral ARAs (43.7% versus 34.0% versus 22.3%, respectively; $P<0.05$; Figure S2A), and single ARAs were more common than multiple ARAs (73.6% versus 26.4%; $P<0.05$; Figure S2B). There was no difference in the distribution of ARAs between men and women (Figure S2C versus S2E, Figure S2D versus S2F; $P>0.05$).

Comparison of Ambulatory BP Monitoring Between the 2 Groups

The 24-hour mean systolic blood pressure (SBP) was 147.21±16.37 mm Hg in the control group and 151.54±15.01 mm Hg in the ARA group. The daytime mean SBP was 150.43±16.91 mm Hg in the control group and 154.91±15.23 mm Hg in the ARA group,

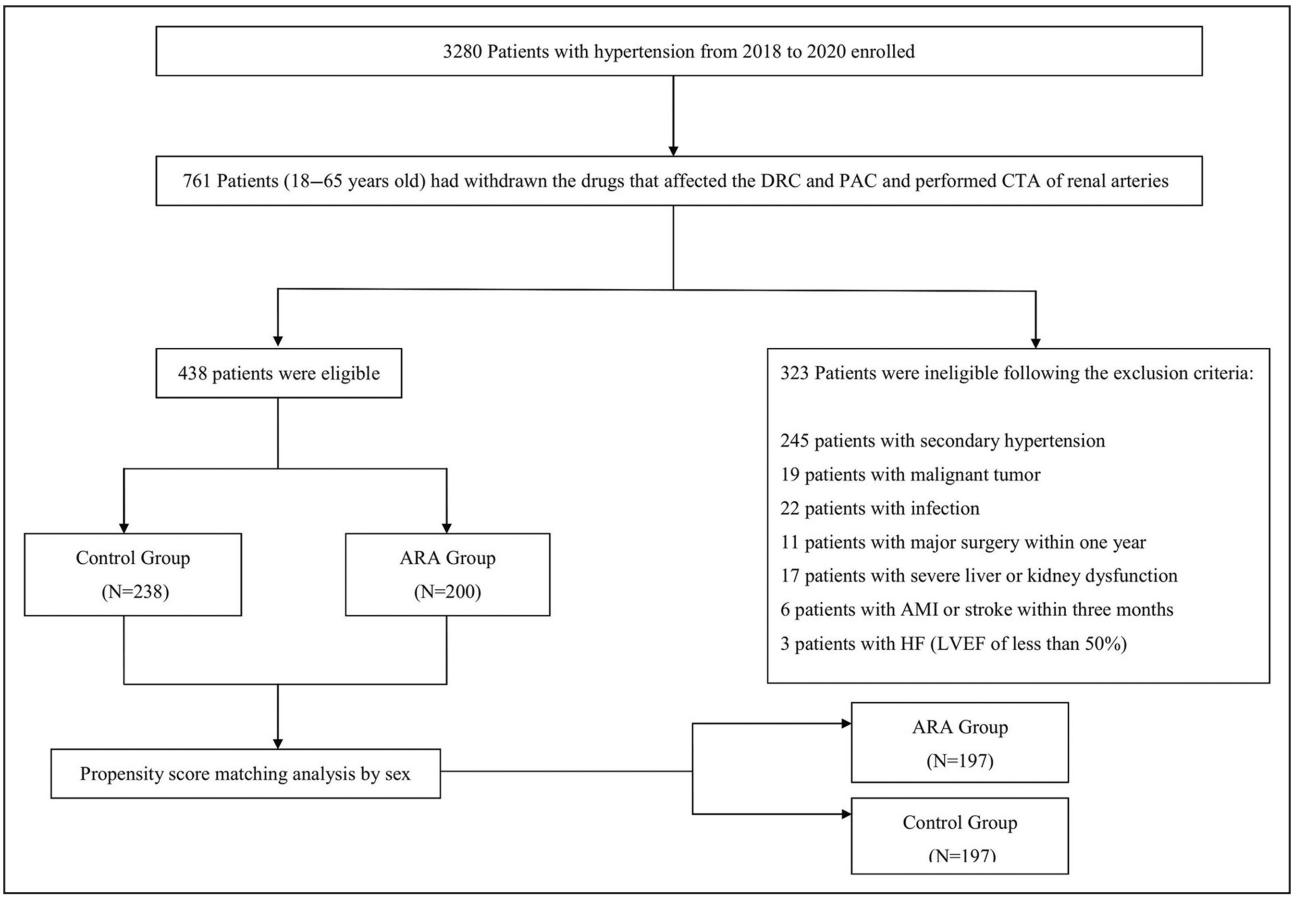

Figure 1. Flowchart of the study.
AMI indicates acute myocardial infarction; ARA, accessory renal artery; CTA, computed tomography angiography; DRC, direct renin concentration; HF, heart failure; LVEF, left ventricular ejection fraction; and PAC, plasma aldosterone concentration.

Table 1. Population Characteristics

Characteristic	Control group (N=197)	ARA group (N=197)	*P* value
Male sex, n (%)	147 (74.6)	147 (74.6)	1.000
Age, y	41.23±10.84	40.52±10.30	0.502
Hypertension duration, y	1.00 (0.15–5.00)	2.00 (0.10–5.00)	0.484
Smoking index	0.00 (0.00–190.00)	0.00 (0.00–175.00)	0.804
BMI, kg/m^2	27.41±4.04	27.71±3.97	0.466
Family history of hypertension, n (%)	110 (55.8)	126 (64.0)	0.100
Diabetes, n (%)	16 (8.1)	19 (9.6)	0.694
Medication history before withdrawal, n (%)			
ACEI/ARB	35 (17.8)	31 (15.7)	0.589
Dihydropyridine CCB	38 (19.3)	48 (24.4)	0.223
β-Adrenergic blocker	18 (9.1)	20 (10.2)	0.733
Diuretic	4 (2.0)	2 (1.0)	0.406
Spironolactone	1 (0.5)	0 (0.0)	1.000
Medication history after withdrawal,			
Nondihydropyridine CCB, n (%)	124 (62.9)	136 (69.0)	0.202
α-Adrenergic blocker, n (%)	58 (29.4)	56 (28.4)	0.824
Medication index	0.66±0.75	0.77±0.74	0.174
Laboratory tests			
FPG, mmol/L	4.59 (4.23–5.16)	4.63 (4.35–5.07)	0.436
HbA1c, %	5.60 (5.40–5.80)	5.60 (5.30–5.90)	0.798
ALT, U/L	27.00 (17.50–43.50)	28.00 (17.00–45.50)	0.878
AST, U/L	20.00 (16.00–26.50)	19.00 (16.00–24.00)	0.401
TC, mmol/L	4.72±0.84	4.72±0.96	0.992
Triglycerides, mmol/L	1.48 (1.01–2.05)	1.54 (1.15–2.31)	0.094
HDL-C, mmol/L	1.02 (0.90–1.19)	1.03 (0.87–1.22)	0.996
LDL-C, mmol/L	2.62±0.59	2.61±0.69	0.910
Na^+, mmol/L	141.31±1.87	141.30±2.07	0.957
K^+, mmol/L	3.81±0.32	3.81±0.40	0.933
Urinary sodium, mmol/24 h	161.30±67.74	160.85±71.66	0.949
Urinary potassium, mmol/24 h	40.28±14.79	40.62±16.42	0.828
UA, μmol/L	383.37±89.89	373.93±98.27	0.321
Homocysteine, μmol/L	12.97 (11.08–16.11)	12.62 (10.60–15.46)	0.282
hs-CRP, mg/L	1.30 (0.52–3.54)	1.03 (0.47–2.32)	0.047*
BNP, pg/mL	10.91 (5.87–21.20)	12.31 (4.88–25.56)	0.624

Data are given as mean±SD or median (25th–75th percentile) unless otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARA, accessory renal artery; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; and UA, uric acid.

*P<0.05.

which were both significantly higher compared with that in the control group (P<0.05). However, there was no significant difference of the nighttime mean SBP between 2 groups (136.62±17.26 versus 139.64±16.23 mm Hg; P>0.05; Figure 2A).

The 24-hour mean diastolic blood pressure (DBP) was 95.72±12.58 mm Hg in the control group and 98.15±11.26 mm Hg in the ARA group. The daytime mean DBP was 97.88±12.88 mm Hg in the control group and 100.49±11.38 mm Hg in the ARA group, which were both significantly higher compared with that in the control group (P<0.05). However, there was no significant difference of the nighttime mean DBP between 2 groups (88.11±14.10 versus 90.13±12.84 mm Hg; P>0.05; Figure 2B).

Comparison of TOD Between the 2 Groups

Echocardiography showed that there were no differences in interventricular septal thickness, left ventricular posterior wall thickness, left atrial diameter,

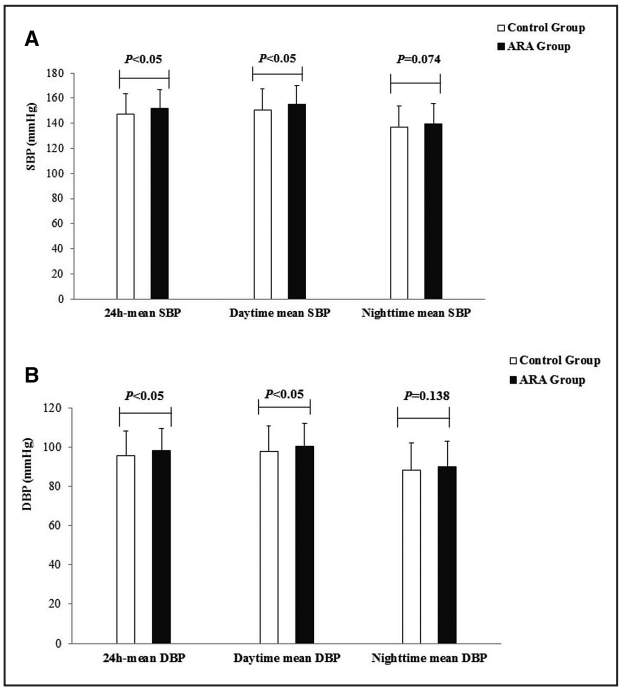

Figure 2. Comparison of ambulatory blood pressure (BP) monitoring.
A, Systolic BP (SBP) in the control group and accessory renal artery (ARA) group. **B**, Diastolic BP (DBP) in the control group and ARA group.

left ventricular end-diastolic diameter, left ventricular systolic function, or left ventricular diastolic function between the 2 groups (*P*>0.05). Although the e deceleration time in the ARA group was significantly shorter, both of them were in a normal range. A comparison of left ventricular geometries revealed that the proportion of abnormal geometries in the ARA group was higher than that in the control group (68.0% versus 58.9%), whereas there was no statistical difference between the 2 group (*P*=0.060). There was no significant difference in the classification of specific geometries between the 2 groups either (*P*>0.05; Table 2). Parameters related to renal damage showed that the 24-hour urinary protein was significantly higher in the ARA group than that in control group, but both of them in these 2 groups were in the normal range though (102.00 [range, 61.00–143.00] versus 80.00 [range, 54.00–116.00]; *P*<0.05), whereas there was no difference in cystatin C, serum creatinine, estimated glomerular filtration rate, and urinary albumin/creatinine ratio (*P*>0.05; Table 2). The parameters assessing vascular function, including IMT, PWV, and ankle-brachial index, showed no significant differences between the 2 groups (*P*>0.05), whereas FMD in the ARA group was significantly lower than that in the control group (5.98±2.70 versus 5.18±2.66; *P*<0.05; Table 2).

Differences in the Activity of Renin-Angiotensin-Aldosterone System and Sympathetic Nervous System

The horizontal and vertical position DRCs in the ARA group were 14.60 (range, 6.79–30.28) and 31.80 (range, 15.38–54.79) μIU/mL, respectively, both of which were significantly higher than those in the control group (9.23 [range, 3.57–20.63] and 19.25 [range, 10.44–36.44] μIU/mL; both *P*<0.05; Figure 3A). The levels of horizontal and vertical PACs in the ARA group were also increased compared with those in the control group (103.88±51.88 versus 91.64±41.82 pg/mL and 151.20±79.84 versus 134.54±64.71 pg/mL, respectively; both *P*<0.05; Figure 3B). The horizontal and vertical position angiotensin II levels were 61.89±15.37 and 68.49±18.98 pg/mL, respectively, in the ARA group, and 60.03±12.57 and 68.37±12.25 pg/mL, respectively, in the control group, which indicated no difference between the 2 groups (*P*>0.05; Figure 3C).

The concentration of norepinephrine was 239.18 (range, 180.09–312.28) pg/mL in the ARA group and 202.79 (range, 146.20–279.63) pg/mL in the control group, which was dramatically increased in the ARA group compared with the control group (*P*<0.05; Figure 3D). The HR was 74.80±8.55 beats per minute in the ARA group and 73.09±8.43 beats per minute in the control group, indicating a significantly faster HR in the ARA group compared with the control group (*P*<0.05; Figure 3E).

Correlation Analysis, Multivariate Regression Analysis, and Mixed-Effects Model for Repeated Measures of Ambulatory BP Monitoring Risk Factors

In correlation analysis, the horizontal PAC had the highest correlation with 24-hour, daytime, and nighttime SBP (*r*=0.263, 0.247, and 0.243, respectively; *P*<0.05) and DBP (*r*=0.325, 0.298, and 0.317, respectively; *P*<0.05). The BP was also positively correlated with the DRC, angiotensin II, plasma norepinephrine, and HR (all *P*<0.05; Table 3). As for multivariate regression analysis, horizontal PAC was the significant risk factor of 24-hour, daytime, and nighttime SBP (β=0.249 [95% CI, 0.150–0.349], 0.228 [95% CI, 0.128–0.329], and 0.282 [95% CI, 0.187–0.377], respectively; *P*<0.05) and DBP (β=0.289 [95% CI, 0.192–0.385], 0.256 [95% CI, 0.158–0.353], and 0.335 [95% CI, 0.243–0.427], respectively; *P*<0.05). Horizontal DRC was also the risk factor of these BPs, except for nighttime DBP, whereas HR was the risk factor of DBP, including 24-hour, daytime, and nighttime values (all *P*<0.05; Table 4). For the mixed-effects model for repeated measures, the results were similar to those of the multivariate regression analysis.

Table 2. Comparison of TOD

Variable	Control group (N=197)	ARA group (N=197)	*P* value
Heart			
IVST, mm	10.54±1.32	10.71±1.45	0.245
LVPWT, mm	10.11±1.17	10.27±1.14	0.176
LAD, mm	36.01±3.58	36.06±3.44	0.886
LVEDD, mm	47.55±3.59	47.30±3.81	0.505
EDT, ms	189.89±36.69	182.76±33.24	0.044*
E/A	1.09±0.32	1.10±0.37	0.897
LVEF, %	59.00 (59.00–60.00)	59.00 (59.00–60.00)	0.800
LVMI, g/m^2	90.02±17.26	91.25±18.32	0.493
RWT, cm	0.43±0.04	0.44±0.05	0.046*
Abnormal LV geometry, n (%)	116 (58.9)	134 (68.0)	0.060
Concentric remodeling, n (%)	91 (46.2)	107 (54.3)	0.107
Concentric hypertrophy, n (%)	20 (10.2)	23 (11.7)	0.628
Eccentric hypertrophy, n (%)	5 (2.5)	4 (2.0)	1.000
Kidney			
Cystatin C, mg/L	0.94±0.16	0.92±0.16	0.239
Scr, μmol/L	68.59±14.63	68.75±13.91	0.916
eGFR, mL/(min×1.73 m^2)	123.54±26.46	123.30±24.74	0.926
UACR, μg/mg	13.21 (8.89–30.98)	16.18 (9.09–34.78)	0.116
Urinary protein, mg/24 h	80.00 (54.00–116.00)	102.00 (61.00–143.00)	0.003†
Blood vessel			
Carotid IMT, mm	0.94±0.16	0.94±0.16	0.974
PWV, cm/s	1494.89±263.60	1530.57±281.94	0.195
ABI	1.15±0.07	1.16±0.13	0.302
FMD, %	5.98±2.70	5.18±2.66	0.003†

Data are given as mean±SD or median (25th–75th percentile) unless otherwise indicated. ABI indicates ankle-brachial index; ARA, accessory renal artery; E/A, early peak/atrial peak; EDT, e deceleration time; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; IMT, intima-media thickness; IVST, interventricular septal thickness; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWT, left ventricular posterior wall thickness; PWV, pulse-wave velocity; RWT, relative wall thickness; Scr, serum creatinine; TOD, target organ damage; and UACR, urinary albumin/creatinine ratio.

*P<0.05.

†P<0.01.

Besides, the factor of time and ARA could also have an effect on BP (all P<0.05; Table 5).

DISCUSSION

As a common anatomic variation of renal arteries, ARAs have been found to be related to renal diseases, like nontraumatic renal bleeding and hydronephrosis, and are an important anatomic variation in kidney transplantation.[3] With the development of radiology, ARAs could be detected through imaging technology. CTA has become the first consideration for its faster scanning and fewer invasions. It could also show the morphology and structure of ARAs more clearly and comprehensively.[26] In this study, CTA was chosen to detect the location and number of ARAs, and it was found that left ARAs and single ARAs were more common, which differed from the results of previous studies.[4–7] In fact, the patients enrolled to this study were aged 18 to 65 years in consideration of relatively low levels of renin in elderly patients, which might be a possible reason for various distribution of ARAs. Besides, there is no definite prevalent data because of the various races and definitions of ARAs, and more studies need to be performed to explore the characteristic of ARAs. There was a higher incidence of ARA in men from the previous studies,[27,28] which was also found in this study. There was no significant difference in the location and number of ARAs with sex. As the difference rate of sex might bring an impact on the reliability of the results, a propensity score matching was applied to balance the sex ratio, which showed a higher BP, DRC, PAC, norepinephrine, and HR and more severe vessel function damage in the ARA group. It also showed that BPs were positively correlated with DRC, angiotensin II, PAC, norepinephrine, and HR, and DRC, PAC, and HR were risk factors of BP. Besides, time and ARA could also have an effect on BP.

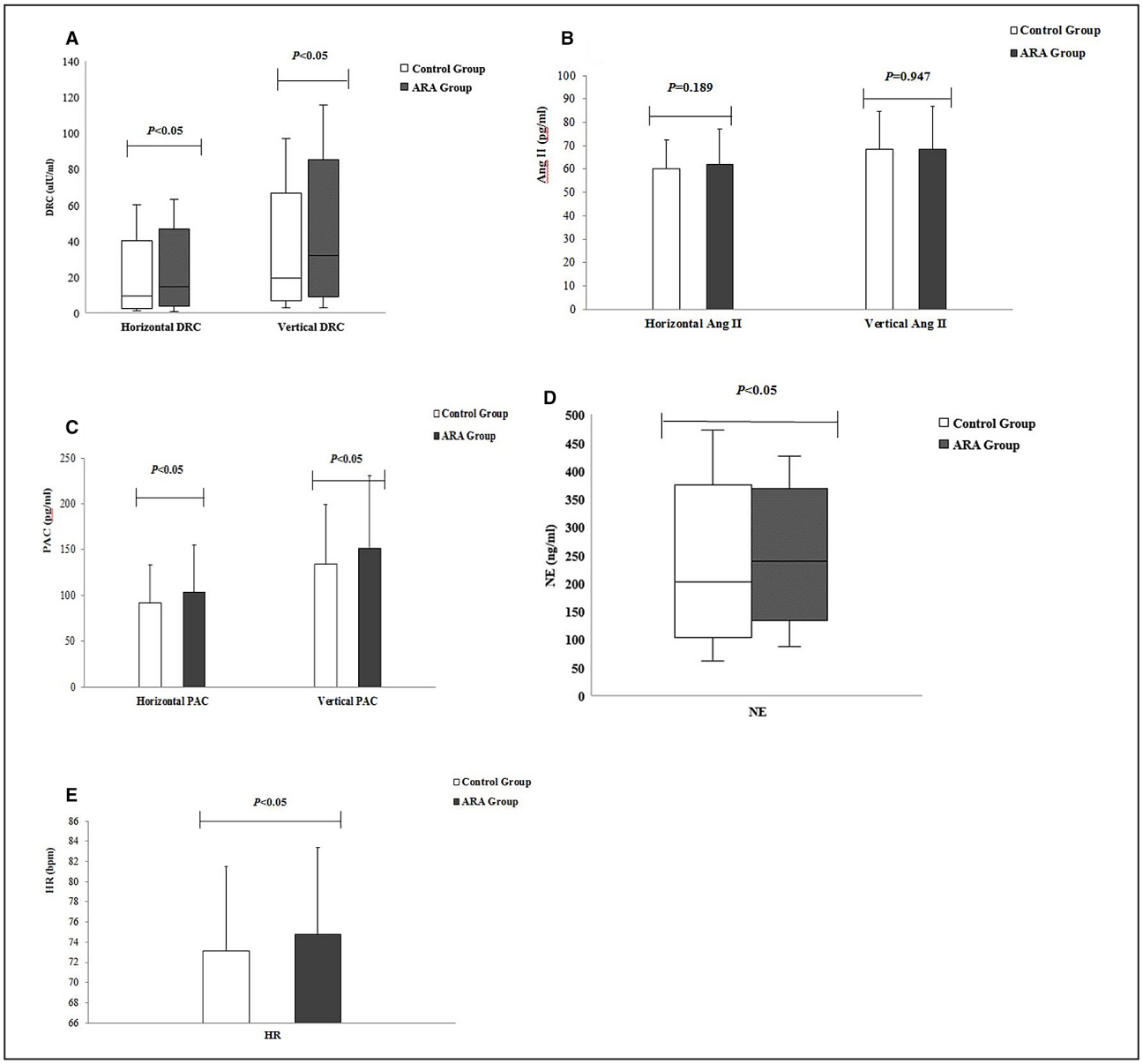

Figure 3. Comparison of the renin-angiotensin-aldosterone system and sympathetic nervous system.
A, Direct renin concentration (DRC) in the control group and accessory renal artery (ARA) group. **B**, Angiotensin II (Ang II) in the control group and ARA group. **C**, Plasma aldosterone concentration (PAC) in the control group and ARA group. **D**, Norepinephrine (NE) in the control group and ARA group. **E**, Heart rate (HR) in the control group and ARA group.

Despite some controversies about the relationship between ARAs and hypertension, the studies have confirmed that patients with hypertension have a higher incidence of ARAs.[9–11] Similarly, patients with ARAs have a higher incidence of hypertension.[29] Our study revealed that the 24-hour BP in the ARA group was 4.33/2.43 mm Hg higher than that of the control group, and the daytime BP in the ARA group was 4.48/2.61 mm Hg higher than that of the control group. ARA was also a factor influencing the SBP. There were no significant differences for other confounding factors, such as sex, hypertension duration, diabetes, smoking, body mass index, antihypertensive medication history, and laboratory examinations, between the 2 groups. These findings suggest that ARAs could contribute a higher BP of essential hypertension.

Hypertension could bring TOD if not controlled timely and effectively, and whether ARAs played a role was unknown. Echocardiogram was used to evaluate the structure and function of myocardium. For evaluating the left ventricular function, only e deceleration time was shorter in the ARA group in our study; both were in a normal range and could not be sufficient to explain

Table 3. Correlation Analysis

Variable		Horizontal DRC	Vertical DRC	Horizontal angiotensin II	Vertical angiotensin II	Horizontal PAC	Vertical PAC	HR	Norepinephrine
24-h SBP	*r*	0.252	0.191	0.148	0.105	0.263	0.191	0.148	0.127
	P value	†	†	†	*	†	†	†	*
24-h DBP	*r*	0.257	0.200	0.165	0.082	0.325	0.196	0.258	0.181
	P value	†	†	†	0.102	†	†	†	†
Daytime SBP	*r*	0.261	0.203	0.146	0.109	0.247	0.177	0.145	0.140
	P value	†	†	†	*	†	†	†	†
Daytime DBP	*r*	0.268	0.210	0.159	0.079	0.298	0.176	0.270	0.202
	P value	†	†	†	0.116	†	†	†	†
Nighttime SBP	*r*	0.161	0.099	0.127	0.081	0.243	0.185	0.138	0.064
	P value	†	0.050	*	0.107	†	†	†	0.208
Nighttime DBP	*r*	0.170	0.126	0.163	0.088	0.317	0.183	0.212	0.102
	P value	†	*	†	0.083	†	†	†	*

DBP indicates diastolic blood pressure; DRC, direct renin concentration; HR, heart rate; PAC, plasma aldosterone concentration; and SBP, systolic blood pressure.

*$P<0.05$.

†$P<0.01$.

that ARAs lead to a more severe cardiac dysfunction. Left ventricular hypertrophy is a manifestation of cardiac remodeling that is usually evaluated with LVMI. On the basis of LVMI and RWT, left ventricular geometry can be categorized into normal geometry, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy. A study showed that the risk of cardiovascular adverse events in patients with concentric remodeling was higher than in patients with normal left ventricular geometry.[30] In our study, patients with ARAs had a higher proportion of concentric remodeling than patients without ARAs; however, there was no statistically significant difference. Arteriosclerosis could be observed among patients with hypertension. There are noninvasive detection methods to evaluate the degree of arteriosclerosis, including carotid IMT, PWV, ankle-brachial index, and FMD. In our study, the carotid IMT, PWV, and FMD were abnormal in the 2 groups, whereas only the difference of FMD between the 2 groups was significant. FMD was a crucial factor for the risk of cardiovascular adverse events. It could help to evaluate the vascular endothelial function earlier.[31] The FMD was lower in the ARA group, which suggests more severe arteriosclerosis. The renal function was evaluated by serum creatinine, estimated glomerular filtration rate, urinary albumin/creatinine ratio, and urinary protein. It showed that there was significant difference of urinary protein between the 2 groups, although these parameters were in the normal range. These findings indicated that more attention was needed to

Table 4. Multivariate Regression Analysis

Variable		Horizontal DRC	Horizontal PAC	HR
24-h SBP	β (95% CI)	0.154 (0.054–0.254)	0.249 (0.150–0.349)	…
	P value	†	†	…
Daytime SBP	β (95% CI)	0.167 (0.067–0.267)	0.228 (0.128–0.329)	…
	P value	†	†	…
Nighttime SBP	β (95% CI)	0.105 (0.010–0.200)	0.282 (0.187–0.377)	…
	P value	*	†	…
24-h DBP	β (95% CI)	0.108 (0.008–0.029)	0.289 (0.192–0.385)	0.191 (0.097–0.286)
	P value	*	†	†
Daytime DBP	β (95% CI)	0.123 (0.022–0.225)	0.256 (0.158–0.353)	0.197 (0.102–0.292)
	P value	*	†	†
Nighttime DBP	β (95% CI)	…	0.335 (0.243–0.427)	0.175 (0.083–0.267)
	P value	…	†	†

DBP indicates diastolic blood pressure; DRC, direct renin concentration; HR, heart rate; PAC, plasma aldosterone concentration; and SBP, systolic blood pressure.

*$P<0.05$.

†$P<0.01$.

Table 5. Mixed-Effect Models for Repeated Measures

Variable		Horizontal DRC	Horizontal PAC	HR	Time	ARA
SBP	β (95% CI)	2.731 (2.663–2.799)	0.019 (0.018–0.020)	…	12.764 (12.445–13.083)	3.038 (2.962–3.114)
	P value	*	*	…	†	*
DBP	β (95% CI)	…	0.022 (0.021–0.023)	0.281 (0.274–0.288)	8.842 (8.621–9.063)	…
	P value	…	†	†	†	…

ARA indicates accessory renal artery; DBP, diastolic blood pressure; DRC, direct renin concentration; HR, heart rate; PAC, plasma aldosterone concentration; and SBP, systolic blood pressure.

*$P<0.05$.

†$P<0.01$.

concentrate on patients with hypertension with ARAs to prevent the development of TOD.

In our study, all enrolled patients experienced enough drug elution, avoiding a recognized confounding effect on the renin-angiotensin-aldosterone system (RAAS). Nevertheless, we found that the DRC, angiotensin II, and PAC levels of the ARA group were higher than those of the control group, and there was a positive correlation between ambulatory BP monitoring and the activity of RAAS. DRC and PAC were risk factors for both SBP and DBP. Therefore, we supposed that ARAs might maintain a higher BP through overactivation of RAAS. RAAS plays an important role in the regulation of BP. High activity of RAAS, resulting from renal parenchymal ischemia and renal artery stenosis, is a common cause of secondary hypertension. Some researchers hold the opinion that hypertension associated with ARAs is renin dependent.[29,32,33] ARAs were often narrow and winding, and renal segments supplied by ARAs have lower blood flow because of this character of ARAs, according to the Poiseuille law of fluid flow.[34] Kem et al[35] revealed the presence of a lower perfusion in the segment of ARA supplied. They also showed an increase of renal vein renin on the same side of the ARA after oral captopril that was 4.3 times higher than the contralateral side, which was consistent with the observation in patients with renin-dependent renovascular stenosis.[35] In this study, the DRC and PAC of patients with ARA were higher, which is compatible with the previous study. However, the level of angiotensin II was also increased in the ARA group without significant difference. It was inferred to be associated with the sample size.

Hyperactivity of the sympathetic nervous system is an important cause of resistant hypertension. On the basis of the role of the renal sympathetic nerve in hypertension, RDN can achieve effective BP reduction in patients with resistant hypertension, as well as in those with mild and moderate hypertension.[36–39] However, there has been controversy about whether ARAs need to be ablated. Our study showed that patients with ARAs had higher sympathetic nervous system activity and HR, which reflected sympathetic nervous system activity was a risk factor for nighttime BP. Therefore, we speculated that the increase in sympathetic activity might be 1 of the mechanisms by which ARAs contributed to the development of hypertension. Anatomic studies have revealed that sympathetic nerve fibers related to ARAs arise from the same ganglia as those related to the main renal arteries.[40] Many studies have demonstrated that ARAs could reduce the BP response to RDN, and ARAs were thought to be 1 of the important factors leading to the success rate of RDN.[13,38,41–43] Mark et al[44] found that, after successful RDN of the main renal arteries, renal nerve stimulation in the ARAs still resulted in a significant BP increase to the same level as the BP before RDN, which further confirmed that ARAs might be the residual source of sympathetic activity, and that the sympathetic fibers in ARAs could play an important role in hypertension.

There are also some limitations in this study. First, it was a single-center study without estimation for sample size. A multicenter study with an adequate sample size needs to be performed to confirm the results. Second, the diameters of ARAs failed to be discussed because they were too small and varied in length and thickness. Besides, it was hard to standardize the position when measuring, and errors by various staff remained, which affected the accuracy. Third, data regarding the BP variability could not be obtained because of the limitation of the machine. It could reflect the fluctuation degree of BP in a certain period of time and help to explore the effect of sympathetic nerve fibers. Finally, there was lack of the grading of hypertension, which could analyze the effect of ARAs better.

Our findings suggest that ARAs could contribute to a higher BP of patients with essential hypertension and might promote the development of essential hypertension. The mechanisms might be associated with the overactivation of RAAS and sympathetic nerve fibers.

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None.

Supplemental Material

Figures S1–S2

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