

Application value of adrenal venous sampling in the surgical treatment of primary aldosteronism

LIN QIAO^{1*}, JING PENG^{1*}, XIAODONG HAO², CHENGHUI WANG¹, MINGLIANG XIE³ and HAO DING⁴

¹Department of Endocrinology, Liaocheng People's Hospital, Liaocheng, Shandong 252000; ²Department of Urology, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei 050000; ³Department of Andrology, Liaocheng People's Hospital, Liaocheng, Shandong 252000; ⁴Department of Urology, Liaocheng People's Hospital, Liaocheng, Shandong 252000, P.R. China

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Abstract. The diagnosis of primary aldosteronism (PA) is critical for determining treatment strategies. The aim of the present study was to investigate the clinical value of preoperative adrenal venous sampling (AVS) for determining the benefit of PA surgery. Patients diagnosed with PA at Liaocheng People's Hospital (Liaocheng, China) between January 2015 and December 2020 were selected and divided into two groups: Group A underwent adrenal computed tomography (CT) only, whereas Group B underwent adrenal CT and successful AVS. Subsequently, the improvement rate of adrenal CT and adrenal CT + AVS in the treatment of PA was compared. A total of 164 patients were included, with an average age of 46.69±13.64 years. There were 62 patients in Group A and 102 in Group B. Among the patients diagnosed with unilateral lesions on adrenal CT scan, 82.61% of patients in group A and 87.72% in group B showed improvement; however, the difference was not significant ($\chi^2=0.534$, $P=0.465$). Among the patients diagnosed with bilateral lesions on adrenal CT images, 62.50% of patients in Group A and 91.11% of patients in Group B showed improvement ($P=0.019$). In conclusion, unilateral adrenal lesions detected by CT did not benefit significantly from surgical decision-making after AVS. AVS should be advised for all patients with bilateral adrenal PA who are willing to undergo adrenal surgery, which is conducive to correct lateral segmentation and improve treatment choices.

Introduction

Diagnosis is important for helping patients choose the appropriate treatment strategy for primary aldosteronism (PA) (1). For patients with an aldosterone-producing adenoma, adrenal hyperplasia or unilateral tumor, partial glandectomy can correct hypokalemia and significantly reduce blood pressure (2). However, in some patients, neither hypertension nor hypokalemia can be corrected via surgery (3).

At present, adrenal computed tomography (CT) and adrenal venous sampling (AVS) are the most commonly used methods for diagnosing PA. Traditionally, CT of the adrenal gland is the main method used to distinguish unilateral and bilateral adrenal lesions, especially larger lesions, and it serves an important role in the bilateral diagnosis of PA. In recent years, several studies have assessed the value of adrenal CT in the bilateral diagnosis of PA. Williams *et al* (3) analyzed 235 and 526 patients with PA who were diagnosed with unilateral lesions based on adrenal CT or AVS, respectively, and who all underwent surgical resection, and revealed that the success rate of the former in achieving complete biochemical indices after surgery was significantly lower than that of the latter (80% vs. 93%, $P<0.001$). A systematic review by Kempers *et al* (4) showed that if AVS is used as the gold standard for the lateral diagnosis of PA and the treatment plan is based only on CT scan results, 37.8% of patients with PA will be misdiagnosed and undergo unnecessary treatment; specifically, 14.6% of patients will be selected for unnecessary adrenal surgery and 19.1% of patients will be recommended for non-surgical treatment when they should undergo surgery. The wrong adrenal gland side was selected for surgery in 4.6% of patients (4).

CT has some limitations in diagnosing PA, including that it can only provide structural information on adrenal lesions and cannot provide functional information on hyperaldosterone secretion in patients with PA (5). However, for lesions that are not clearly visible on CT, it remains unclear as to whether AVS affects recovery after surgical treatment when hypersecretion is detected on the surgical side. The present study explored the effect on recovery by comparing clinical symptom relief in patients after adrenal CT or CT + AVS, and discusses the

Correspondence to: Professor Hao Ding, Department of Urology, Liaocheng People's Hospital, 67 Dongchang West Road, Dongchangfu, Liaocheng, Shandong 252000, P.R. China
E-mail: dinghaourology@163.com

*Contributed equally

Abbreviations: AVS, adrenal venous sampling; PA, primary aldosteronism; CT, computed tomography

Key words: PA, adrenal CT, AVS

clinical application value of AVS and the patient population that may benefit from AVS.

Materials and methods

Patients. The present study retrospectively evaluated the data of 164 patients with adrenal gland disease who underwent resection and were monitored at Liaocheng People's Hospital (Liaocheng, China) between January 1, 2015, and December 31, 2020. All pertinent laboratory and pathology results (lesion size and number, postoperative therapy), and medical data were obtained from the hospital databases.

Diagnostic criteria for PA. The clinical guidelines of the American Endocrine Society (6) were followed. For patients with a suspected case of PA, the aldosterone/renin ratio screening test was performed first. If the screening test was positive (aldosterone/renin ratio ≥ 30), a diagnostic test (saline stress test or captopril test) was performed. If the concentration of aldosterone after saline infusion was >10 ng/dl or if the concentration of aldosterone after medication was $<30\%$ lower than that before medication according to the captopril test, PA was confirmed. The reference standard should be re-evaluation after surgery using the Primary Aldosteronism Surgical Outcome criteria (7).

Inclusion criteria. The inclusion criteria for the present study were: i) All patients included had symptoms of hypertension and hypokalemia simultaneously; ii) all patients had an adrenal multislice spiral 64-bar CT scan (Siemens AG) with millimetric acquisitions and multiplanar reconstructions; and iii) patients underwent AVS successfully without complications.

Exclusion criteria. The exclusion criteria for the present study were: i) The presence of diseases affecting blood pressure or potassium; ii) the long-term control of blood pressure with medicines and drugs or potassium; iii) pregnant women and lactating women; iv) a malignant tumor or patients with end-stage disease; v) severe peripheral vascular disease and abdominal aortic aneurysm; and vi) a 2-week history of acute coronary syndrome.

Research index. Patients were divided into two groups, Groups A and B, according to whether AVS was performed preoperatively. In addition, according to the CT findings in Groups A and B, the patients were divided into unilateral and bilateral adrenal lesion groups. The objective of the present study was to evaluate the clinical value of adrenal CT and adrenal CT + AVS in the surgical treatment of PA. The criteria for considering surgical treatment as beneficial were as follows: Any index of blood pressure (normal range, systolic 90-140 mmHg and diastolic 60-90 mmHg) or potassium (normal range, potassium 3.5-5.5 mmol/l) returning to the normal range (without drug control) at the postoperative follow-up of 6 months compared with the preoperative period.

CT examination of the adrenal gland. A plain scan and enhanced scan were used for CT examination of the adrenal glands in all patients. According to the CT image

of the adrenal glands, adrenal lesions can be divided into two categories: i) Adenoma, which was defined as unilateral or multiple small round or oval adrenal masses with clear boundaries and diameters usually >1 cm but <2 cm. The plain scan showed that the density of the mass was uniform and low. The CT value was <10 Hounsfield units. ii) Hyperplasia, which was defined as the presence of single or multiple adrenal circular nodules or circular nodules with unclear boundaries.

AVS. The AVS process was based on a previously published study (8). The AVS procedure is stimulated (using corticotropin) and sequential (the left and right adrenal veins were cannulated successively). The use of antihypertensive drugs that have a considerable influence on the determination of aldosterone concentration before surgery should be discontinued to correct hypokalemia. The success of AVS was defined as a ratio of adrenal blood cortisol to peripheral blood cortisol of ≥ 2 . The lateral index refers to the ratio of bilateral standardized adrenal venous aldosterone (adrenal venous aldosterone/corresponding lateral cortisol concentration), such as ≥ 2 , indicating high unilateral aldosterone secretion. A lateral index value of <2 suggests no dominant side of aldosterone secretion. In 2016, the American Endocrine Society recommended that patients who can choose unilateral adrenal surgery based on CT alone have the following characteristics (all of which must be met): <35 years of age; and PA is typically accompanied by spontaneous hypokalemia with aldosterone concentrations of >30 ng/dl and unilateral adrenal lesions with imaging features consistent with cortical adenoma on CT scan (6).

Surgical methods

Group A. For patients with unilateral lesions on CT images, the lateral adrenal tumor was surgically resected. For patients with bilateral lesions on CT images, adrenal tumors on the side with a larger tumor volume were resected when both sides had different sizes; when bilateral tumors were similar in size, bilateral lesions were resected simultaneously.

Group B. For unilateral lesions, when CT and AVS were consistent, the consistent lesion side was selected. When the CT findings were inconsistent with the AVS findings, the side identified by AVS was selected for surgical resection of the tumor. For bilateral lesions, surgical resection of the tumors was performed on either side or on both sides of the lesions identified by AVS.

Statistical analyses. Statistical analyses were performed using SPSS for Windows, version 26.0 (IBM Corp.). Continuous data are presented as the mean \pm standard deviation and were compared using unpaired Student's t-test. The χ^2 test or Fisher's exact test was used for comparisons of categorical data. Fisher's exact test was used when $n < 40$ or when $>20\%$ of expected cell counts were <5 . $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics of patients. Ultimately, 164 patients with a mean age of 46.69 ± 13.64 years were included in the

Table I. Baseline characteristics of patients with primary aldosteronism.

Parameter	Group A (n=62)	Group B (n=102)	P-value
Mean age, years	47.00±13.30	46.27±14.57	0.720 ^a
Mean BMI, kg/m ²	22.52±1.19	22.98±1.39	0.580 ^a
Mean operation time, min	55.22±11.02	49.80±9.76	0.810 ^a
CT-unilateral lesions	46	57	
Postoperative symptom improvement	38	50	0.465 ^b
CT-bilateral lesions	16	45	
Postoperative symptom improvement	10	41	0.019 ^c

^aStudent's t-test; ^b χ^2 test; ^cFisher's exact test.

present study (Table I). There were 87 men and 77 women. There were 62 patients in Group A and 102 patients in Group B. Of the patients, 15 had coronary heart disease, 12 had diabetes mellitus and 5 had peripheral vascular disease (their symptoms were not severe enough to exclude them as per the exclusion criteria).

Improvement rate of postoperative treatment effect. Among the patients diagnosed with unilateral adrenal disease with CT, 38 of the 46 patients in Group A showed that the treatment effectively improved postoperative hypertension and/or hypokalemia. A total of 50 of the 57 patients in Group B showed that the treatment effectively improved hypertension and hypokalemia. Among the patients diagnosed with unilateral adrenal disease with CT, 82.61% of patients in Group A and 87.72% of patients in Group B showed that the treatment was effective; however, the difference was not significant ($\chi^2=0.534$, $P=0.465$).

Among the patients diagnosed with bilateral adrenal lesions with CT, of the 16 patients in Group A, 10 patients experienced improvement in hypertension or hypokalemia after surgery. Of the 45 patients in Group B, 41 showed improvement in hypertension and hypokalemia after surgery. Among the patients diagnosed with bilateral adrenal disease with CT, 62.50% in Group A and 91.11% in Group B improved postoperatively ($P=0.019$).

Discussion

PA is a common clinical disease with a high prevalence rate, as well as clinical manifestations of hypertension, hypokalemia and other symptoms (9). Compared with that detected in response to essential hypertension, damage to the target organs of hypertension, such as the kidney and heart, is more serious in patients with PA (10). Notably, disease progression diminishes patient quality of life and safety; therefore, early diagnosis and treatment is important.

Traditionally, CT is the basic method used to distinguish unilateral or bilateral adrenal lesions, especially large space-occupying lesions, which serve an important role in the classification and diagnosis of PA. However, adrenal CT is limited in diagnosing PA. For example, CT reveals morphological abnormalities of the unilateral adrenal gland, whereas increased aldosterone can be caused by

the contralateral adrenal or bilateral adrenal glands. When CT exhibits bilateral morphological abnormalities, the increased aldosterone is often from a unilateral adrenal gland (11). Young *et al* (11) reported that 42 patients (21.7%) were wrongly excluded as candidates for adrenal resection based on CT findings alone, and 48 patients (24.7%) may have undergone unnecessary or inappropriate adrenal resection.

According to a systematic review by Kempers *et al* (4), if AVS is used as the gold standard for PA classification and treatment plans are based only on CT results, 37.8% of patients with PA will be misdiagnosed and treated unnecessarily. Therefore, AVS is recommended as the gold standard for PA classification in current clinical guidelines. However, due to the low success rate of intubation, difficult data interpretation, certain complications, the lack of a unified standard for AVS in clinical practice, case selection and other factors, the final result may be affected (12). To some extent, the application of AVS in the clinic is limited (13).

AVS is an invasive procedure with certain complications (AVS complication rates varying between 0.2 and 13.0%), including adrenal vein rupture, adrenal vein hematoma, embolism, infarction and hypertensive crisis, among which adrenal rupture is the most common (13). Rossi *et al* (14) collected a total of 2,604 AVS data points from 20 research centers, and the incidence of adrenal vein rupture was revealed to be 0.61%. Therefore, it is necessary to further analyze AVS to determine its use in diagnosing these lesions so as to formulate a scientific and accurate treatment plan. For patients aged <40 years with PA, AVS is not recommended if CT indicates obvious adrenal adenoma and direct surgery is acceptable (15); however, another study opposed this strategy (16). Zarnegar *et al* (17) reported that for adenomas with a unilateral diameter ≥ 1 cm, as indicated by CT, this side was the dominant secretory side, which could be used as an indication for adrenal resection and had a good correlation with clinical results. AVS should be used when CT findings are equivocal or both adrenal glands are abnormal (17). Therefore, the use of AVS and CT to improve the accuracy of localization has important clinical significance, especially when used to identify sites requiring surgical treatment.

In terms of morphological changes, CT is easy to use in combination with AVS for identifying endocrine changes.

In the present study, AVS was not significantly beneficial for patients with unilateral adrenal lesions identified on CT. However, the results indicated that AVS should be advised for all patients with bilateral adrenal PA willing to undergo adrenal surgery. These results are similar to those reported by Wolley *et al* (18). Therefore, CT may be used to visualize the structure of adrenal lesions and AVS can be used to visualize hypersecretion of aldosterone, and a combination of these techniques can be used to clearly identify bilateral diseases, and effectively determine surgical indications and sites to improve efficacy. Surgical treatment should be performed on the basis of consistent results to improve patient prognosis.

Notably, there are some limitations in the present study, such as the short observation period, insufficient number of selected cases and simple design. In addition, there are practical limitations of AVS, and it can be applied only in limited centers with experience. In view of this, it is necessary to optimize research design in the future, provide reference data for treatment through extensive data research, and conduct further research to ensure the authenticity and reliability of the diagnostic scheme.

In conclusion, patients with unilateral PA that did or did not undergo AVS after adrenal CT had similar rates of improvement in postoperative symptoms. For patients with bilateral adrenal disease that cannot be clearly defined by CT scan, AVS is recommended for diagnosis. Combination of these diagnostic techniques may provide a reference for follow-up treatment and significantly improve treatment outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LQ and HD conceptualized the present study. LQ, XH and HD acquired data. LQ, JP, XH and CW analyzed and interpreted the data. CW and MX used the software. LQ and JP drafted the manuscript. HD performed the review and editing. LQ, JP and HD confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the ethical standards of The 1964 Declaration of Helsinki and its later amendments; local ethical approval was obtained from the Ethics Committee of Liaocheng People's Hospital (approval no. 2022-06-132; Liaocheng, China). Written informed consent

was obtained from all individual participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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