

Application of the Captopril Suppression Test in the Diagnosis, Subtyping, and Clinical Outcomes of Primary Aldosteronism: Postprint

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Abstract

Background Primary aldosteronism (PA), as the disease with the highest incidence among secondary hypertension, is associated with significant cardiovascular and cerebrovascular hazards but offers high cure rates following surgery, and has been recommended by major hypertension guidelines for expanded screening, early diagnosis, and treatment. However, the methods for confirming diagnosis, subtyping, and evaluating post-treatment clinical outcomes in these patients are numerous and controversial. The captopril challenge test (CCT), due to its convenience and safety, can be directly performed in community and outpatient settings, with the expectation that CCT may be utilized for the entire management process of PA patients to improve prognosis.

Objective To investigate the diagnostic efficacy of CCT for PA, its ability to determine subtypes, and its capacity to assess clinical outcomes.

Methods A total of 824 patients who underwent screening for endocrine hypertension causes and were registered in the Department of Endocrinology and Metabolism, West China Hospital of Sichuan University from October 1, 2020, to December 30, 2022, were selected as study subjects. After screening, 370 patients were finally included in the study, comprising 123 patients with essential hypertension (EH) in the EH group, and 247 PA patients who were assigned to the unilateral aldosterone-producing adenoma (APA) group (n=81), idiopathic hyperaldosteronism (IHA) group (n=55), and unclassified PA (u-PA) group (n=111). Differences among the four groups were compared, and receiver operating characteristic (ROC) curves for each post-CCT indicator and combined diagnosis of PA were plotted to determine optimal cutoff values. Secondly, ROC curves for each post-CCT indicator in diagnosing APA and IHA subtypes were plotted, and the area under the ROC curve (AUC) was calculated to evaluate the ability of CCT to determine subtypes of APA and IHA.

Finally, based on postoperative clinical outcomes, patients undergoing unilateral adrenalectomy were divided into three groups: non-remission group (n=11), clinical improvement group (n=27), and clinical remission group (n=54). Differences among the three groups were compared to assess the ability of CCT to evaluate postoperative clinical outcomes in APA patients.

Results Post-CCT plasma aldosterone concentration (PAC) demonstrated the highest diagnostic efficacy for PA (AUC=0.921, 95%CI=0.893~0.950), with an optimal cutoff value of 11.7 ng/dL, and sensitivity and specificity of 84.6% and 86.0%, respectively. Post-CCT aldosterone-to-renin ratio (ARR) also showed good diagnostic efficacy for PA (AUC=0.868, 95%CI=0.823~0.923), with an optimal cutoff value of 2.8 (ng/dL)/(mU/L), and sensitivity and specificity of 82.2% and 81.0%, respectively. Post-CCT PAC>17.0 ng/dL could assist in diagnosing the APA subtype, while patients with post-CCT PAC<11.7 ng/dL and simultaneously ARR<2.8 (ng/dL)/(mU/L) could be excluded from the APA subtype. The post-CCT PAC suppression rate and the postoperative PAC reduction rate from baseline showed low efficacy in determining biochemical remission, whereas post-CCT PAC or post-CCT ARR better reflected postoperative biochemical remission.

Conclusion CCT can be utilized throughout the entire process for diagnosis, subtyping, and clinical outcome evaluation in PA patients. The optimal cutoff values for post-CCT PAC and post-CCT ARR in diagnosing PA are 11.7 ng/dL and 2.8 (ng/dL)/(mU/L), respectively, which can also be applied to APA subtyping determination and postoperative biochemical remission assessment. Pre-CCT blood sampling has minimal clinical significance, and the procedure can be appropriately simplified.

Full Text

Preamble

Application of Captopril Challenge Test in the Diagnosis, Classification, and Clinical Outcomes of Primary Aldosteronism

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Abstract

Background: Primary aldosteronism (PA), as the most common cause of secondary hypertension with significant cardiovascular and cerebrovascular risks

but high cure rates after surgery, has been recommended by major hypertension guidelines for expanded screening, early diagnosis, and treatment. However, the methods for confirming diagnosis, classification, and evaluation of post-treatment clinical outcomes in these patients remain varied and controversial. The captopril challenge test (CCT) is expected to enable whole-course management of PA patients due to its convenience and safety for direct application in community and outpatient settings, potentially improving prognosis.

Objective: To investigate the diagnostic efficacy, classification capability, and clinical outcome assessment of CCT in PA patients.

Methods: A total of 824 patients who underwent screening for endocrine hypertension and were registered in the Department of Endocrinology and Metabolism at West China Hospital of Sichuan University between October 1, 2020, and December 30, 2022, were selected as study subjects. After screening, 370 patients were ultimately included in the study, comprising 123 patients with essential hypertension (EH) in the EH group and 247 patients with PA, who were further divided into the unilateral aldosterone-producing adenoma (APA) group (n=81), idiopathic hyperaldosteronism (IHA) group (n=55), and unclassified PA (u-PA) group (n=111). Inter-group differences were compared, and receiver operating characteristic (ROC) curves were plotted for post-CCT indicators alone and in combination for diagnosing PA to determine optimal cut-off values. Additionally, ROC curves for post-CCT indicators in diagnosing APA and IHA subtypes were constructed, and the area under the ROC curve (AUC) was calculated to evaluate CCT's ability to distinguish APA and IHA. Finally, based on postoperative clinical outcomes, patients who underwent unilateral adrenalectomy were divided into three groups: non-remission group (n=11), clinical improvement group (n=27), and clinical remission group (n=54). Inter-group differences were compared to assess CCT's ability to evaluate postoperative clinical outcomes in APA patients.

Results: Post-CCT plasma aldosterone concentration (PAC) demonstrated the highest diagnostic efficacy for PA (AUC=0.921, 95%CI=0.893-0.950), with an optimal cut-off value of 11.7 ng/dL, achieving sensitivity and specificity of 84.6% and 86.0%, respectively. Post-CCT aldosterone-to-renin ratio (ARR) also showed good diagnostic performance for PA (AUC=0.868, 95%CI=0.823-0.923), with an optimal cut-off value of 2.8 (ng/dL)/(mU/L), yielding sensitivity and specificity of 82.2% and 81.0%, respectively. Post-CCT PAC >17.0 ng/dL could assist in diagnosing the APA subtype, while patients with post-CCT PAC <11.7 ng/dL combined with ARR <2.8 (ng/dL)/(mU/L) could be excluded from the APA subtype. Post-CCT PAC suppression rate and the percentage decrease in postoperative PAC from baseline showed low efficacy in assessing biochemical remission, whereas post-CCT PAC or post-CCT ARR better reflected postoperative biochemical remission status.

Conclusion: CCT can be applied throughout the entire course of PA management, including diagnosis, classification, and clinical outcome evaluation. The optimal cut-off values for diagnosing PA are 11.7 ng/dL for post-CCT PAC

and 2.8 (ng/dL)/(mU/L) for post-CCT ARR, which can also be used for APA subtype classification and postoperative biochemical remission assessment. Pre-CCT blood sampling has minimal clinical significance and the procedure can be appropriately simplified.

Keywords: Primary aldosteronism; Captopril; Captopril challenge test; Aldosterone-producing adenoma; Aldosterone-to-renin ratio; Receiver operating characteristic curve

Primary aldosteronism (PA) is the most common cause of curable hypertension [1] and poses greater risks of cardiac, cerebral, and renal organ damage compared to patients with essential hypertension (EH) [2]. Following surgical treatment, 80% of PA patients experience improvement in blood pressure and electrolyte disturbances [3]. Consequently, current domestic and international PA guidelines continue to expand screening of high-risk populations [4] to improve prognosis among hypertensive patients. The main confirmatory tests for PA currently include the captopril challenge test (CCT), saline infusion test (SIT), and fludrocortisone test. The fludrocortisone test is rarely performed in China due to lack of drug availability, while SIT, particularly the seated saline test, has high diagnostic value [5]. CCT is widely used in clinical practice due to its simple methodology, low cost, and high safety profile, especially as it can be safely performed in most patients with cardiac or renal insufficiency [4,6]. However, studies from various centers show controversy regarding the diagnostic threshold of CCT for PA, and while some research suggests CCT may assist in PA subtype classification and analysis of postoperative clinical outcomes in patients with unilateral aldosterone-producing adenoma (APA), relevant domestic studies are limited. Therefore, this study explored the application value and accuracy of CCT in the diagnosis, classification, and prognostic evaluation of PA patients to provide evidence for whole-course management of PA patients.

1.1 Study Subjects

A total of 824 patients who underwent screening for endocrine hypertension and were registered in the Department of Endocrinology and Metabolism at West China Hospital of Sichuan University between October 1, 2020, and December 30, 2022, were retrospectively selected as study subjects. All participants provided informed consent. This study was approved by the Ethics Committee of West China Hospital of Sichuan University (approval number: 2022 Review No. 1197).

Exclusion criteria: (1) Combined moderate or severe hepatic or renal insufficiency; (2) History of malignant tumors within 3 years prior to enrollment; (3) Occurrence of severe acute cardiovascular disease (acute myocardial infarction, stroke, coronary intervention) within 3 months prior to enrollment; (4) Pregnant or lactating women; (5) Current use of oral steroid hormones, contraceptives, licorice, or other interfering medications.

1.2 PA Diagnostic Criteria

According to the “Expert Consensus on the Diagnosis and Treatment of Primary Aldosteronism (2020 Edition)” (hereinafter referred to as the CSE Consensus) issued by the Chinese Society of Endocrinology (CSE) [7], all medications affecting screening were discontinued prior to screening as per guidelines [4,7]. Based on our center’s previous research, an initial screening aldosterone-to-renin ratio (ARR) >2.4 (ng/dL)/(mU/L) was considered positive [8]. All included patients were required to complete both SIT and CCT. PA was confirmed based on SIT results: post-SIT plasma aldosterone concentration (PAC) >10 ng/dL confirmed PA, PAC <5 ng/dL with exclusion of other secondary hypertension diseases was diagnosed as EH, and patients with post-SIT PAC between 5–10 ng/dL were defined as a gray zone and excluded from the study.

CCT Procedure: After maintaining a non-supine position for 2 hours, patients orally administered 50 mg captopril at approximately 8:00 AM. Blood samples were collected at 0 and 2 hours after administration to measure PAC, direct renin concentration (DRC), ARR, and serum potassium. Patients remained in a non-supine position and fasted during this period.

SIT Procedure: After sitting for 2 hours, patients received an intravenous infusion of normal saline at 500 mL/h starting at approximately 8:00 AM for 4 consecutive hours. Blood samples were collected before infusion and after 4 hours of infusion to measure PAC, DRC, ARR, and serum potassium. Patients remained seated and fasted during this period.

1.3 Bilateral Adrenal Venous Sampling (AVS)

All patients with surgical intent and feasibility, who showed unilateral or bilateral adrenal morphological abnormalities on adrenal CT, underwent asynchronous AVS with continuous intravenous adrenocorticotropic hormone (ACTH) infusion. Patients under 35 years of age with spontaneous hypokalemia, massive aldosterone secretion, and CT findings consistent with unilateral adenoma could proceed directly to unilateral adrenalectomy without AVS [4,7]. Criteria for successful sampling: adrenal vein to inferior vena cava cortisol ratio >3 , and dominant side aldosterone...

1.4 APA Diagnosis and Grouping

According to the Primary Aldosteronism Surgery Outcomes (PASO) study, CCT-related indicators can be used to evaluate surgical outcomes: a post-CCT PAC suppression rate $>30\%$ indicates biochemical remission; if the post-CCT PAC suppression rate $\leq 30\%$ but PAC decreased by $\geq 50\%$ from preoperative baseline, it is considered biochemical improvement [3]. Patients underwent unilateral adrenalectomy and were followed up for 6 months postoperatively. Follow-up results were grouped according to PASO clinical criteria: (1) Clinical remission group: normal blood pressure without need for antihypertensive medication; (2) Clinical improvement group: lower blood pressure with fewer

antihypertensive medications than preoperatively, or blood pressure reduction while using the same or fewer medications; (3) Non-remission group: unchanged or elevated blood pressure while taking the same or increased doses of antihypertensive medications. Patients with clinical remission or improvement were included in the APA group, while non-remission patients were included in the u-PA group.

1.5 Observation Indicators

General patient data were collected, including sex, age, height, weight, maximum blood pressure, hypertension duration, renal function, electrolytes, and pre- and postoperative PAC, DRC, ARR, and serum potassium. PAC and DRC were analyzed using the LIAISON fully automated chemiluminescence immunoassay analyzer with test kits purchased from Diasorin, Italy. The intra-assay coefficient of variation was 2.1%-4.2% for PAC and 2.1%-4.9% for DRC; the inter-assay coefficient of variation was 5.8%-10.8% for PAC and 6.8%-13.0% for DRC. Reference ranges were: PAC (supine: 3-23.6 ng/dL, upright: 3.0-35.3 ng/dL); DRC (supine: 2.8-39.9 mU/L, upright: 4.4-46.1 mU/L).

1.6 Statistical Methods

Statistical analysis was performed using SPSS 27.0 software. Normally distributed continuous variables were expressed as mean \pm standard deviation ($\bar{x}\pm s$) and compared between groups using one-way ANOVA with Bonferroni correction. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared using independent samples nonparametric tests. Categorical data were expressed as relative numbers and compared using χ^2 test or Fisher's exact test. The post-CCT PAC suppression rate was calculated as $[(\text{pre-CCT PAC} - \text{post-CCT PAC}) / \text{pre-CCT PAC}] \times 100\%$. ROC curves were plotted for PAC suppression rate and post-CCT indicators for PA diagnosis. Delong's test was used to analyze differences in AUC among various models, with $P < 0.05$ considered statistically significant.

2.1 Screening Process

Among the 824 subjects, 776 hypertensive patients met the PA screening criteria of the CSE Consensus. After examination, 134 patients with other secondary hypertension causes were excluded. One hundred ninety patients withdrew from the study after negative ARR screening and refused to complete CCT or SIT; 54 patients (12.4%) could be directly diagnosed with PA based on initial screening (diagnostic criteria: PAC > 20 ng/dL and DRC below the lower limit of normal), of whom 18 refused to complete SIT and CCT. Ultimately, 434 patients with positive screening underwent SIT and CCT. Based on SIT results, 370 patients were included in the final comparative study, comprising 123 in the EH group, 81 in the APA group, 55 in the IHA group, and 111 in the u-PA group. The screening process is shown in Figure 1 [Figure 1: see original paper].

Comparison of sex, age, maximum systolic blood pressure, maximum diastolic blood pressure, creatinine, and eGFR among the four groups showed no statistically significant differences ($P>0.05$), as presented in Table 1 .

2.3 Comparison of Renin-Angiotensin-Aldosterone System (RAAS) Parameters

One-way ANOVA of supine and upright RAAS parameters before and after captopril challenge test among the four groups showed statistically significant differences ($P<0.05$), as presented in Table 2 . The DRC, PAC, and ARR parameter levels in the u-PA group were intermediate between those of the APA and IHA groups.

2.4.1 Diagnostic Efficacy of Post-CCT Indicators for PA

Since the ROC curve for DRC in PA diagnosis uses a lower test result to indicate a more positive finding, while ROC curves for PAC, ARR, and PAC suppression rate use higher results to indicate more positive findings, the reciprocal of DRC was used along with PAC, ARR, and PAC suppression rate to plot ROC curves (Figure 2A [Figure 2: see original paper]). The AUCs for post-CCT PAC, DRC, ARR, and PAC suppression rate were 0.921 (95%CI=0.893-0.950), 0.785 (95%CI=0.730-0.840), 0.868 (95%CI=0.823-0.923), and 0.737 (95%CI=0.681-0.793), respectively, indicating that all these indicators have certain diagnostic efficacy. Post-CCT PAC was the best diagnostic indicator for PA, with an optimal cut-off value of 11.7 ng/dL, sensitivity of 84.6%, specificity of 86.0%, positive predictive value of 92.8%, and negative predictive value of 73.1%.

Post-CCT ARR also demonstrated good diagnostic efficacy for PA, with an optimal cut-off value of 2.8 (ng/dL)/(mU/L), sensitivity of 82.2%, and specificity of 81.0%. Using the 30% suppression rate recommended by the CSE guidelines as a cut-off yielded a sensitivity of 87.4% but specificity of only 48.0%. A post-CCT PAC suppression rate of 18.7% provided the maximum Youden index (sensitivity 75.6%, specificity 64.5%), but both sensitivity and specificity were lower than those of post-CCT PAC and post-CCT ARR.

2.4.2 Diagnostic Efficacy of Pre-CCT Indicators for PA

The AUCs for pre-CCT PAC and ARR were 0.826 (95%CI=0.785-0.867) and 0.858 (95%CI=0.814-0.903), respectively.

2.4.3 Combined Diagnostic Efficacy of Post-CCT Indicators for PA

ROC curves for PA were plotted for the combination of post-CCT PAC plus ARR, and for the combination of post-CCT PAC, ARR, and PAC suppression rate (Figure 2B [Figure 2: see original paper]), with AUCs of 0.925 (95%CI=0.898-0.952) and 0.928 (95%CI=0.900-0.955), respectively.

Delong's test comparing the AUCs of the two combined indicators with post-CCT PAC alone showed no statistically significant difference between post-CCT PAC combined with ARR versus post-CCT PAC alone ($Z=-1.610$, $P=0.107$). Similarly, no significant difference was found between the combination of PAC, ARR, and PAC suppression rate versus post-CCT PAC alone ($Z=-0.980$, $P=0.327$).

2.5.1 Classification Efficacy of Post-CCT Indicators for PA Subtypes

ROC curves for post-CCT PAC, PAC suppression rate, and ARR in diagnosing APA and IHA were plotted separately (Figures 3 [Figure 3: see original paper] and 4 [Figure 4: see original paper]). The AUC for post-CCT PAC in diagnosing APA was 0.817 (95%CI=0.768-0.865), with an optimal cut-off value of 17 ng/dL, sensitivity of 81.4%, specificity of 68.1%, positive predictive value of 41.7%, and negative predictive value of 92.9% (Figure 3 [Figure 3: see original paper]). The AUCs of ROC curves for post-CCT indicators in diagnosing IHA ranged between 0.5-0.6 (Figure 4 [Figure 4: see original paper]).

2.5.2 Combined CCT Indicators for PA Classification

Although post-CCT PAC had low positive predictive value for APA, the simultaneous application of the two optimal diagnostic cut-off values for PA could serve as exclusion criteria for APA patients. The combination of post-CCT PAC <11.7 ng/dL and post-CCT ARR <2.8 (ng/dL)/(mU/L) achieved a negative predictive value of 100% for APA.

2.6 CCT for Evaluating Postoperative Clinical Outcomes in APA

Among the 247 PA patients, 124 underwent surgery and 92 completed postoperative follow-up, including 11 in the non-remission group and 81 in the APA group (comprising 27 in the clinical improvement group and 54 in the clinical remission group). Comparison among the three groups showed statistically significant differences in age, hypertension duration, upright PAC, upright ARR, preoperative serum potassium, post-CCT PAC, and post-CCT ARR ($P<0.05$), but no significant differences in sex or upright DRC ($P>0.05$), as presented in Table 3.

According to PASO clinical outcome criteria, the effective rate after surgical treatment reached 88.04% (81/92). Among the 92 patients who completed postoperative follow-up, 78 underwent captopril challenge testing. Analysis using PASO biochemical outcome criteria revealed: (1) Only 18% (14/78) of patients had post-CCT PAC suppression rate $>30\%$; (2) 80.76% (63/78) of patients showed $\geq 50\%$ reduction in postoperative PAC compared to preoperative baseline; (3) 87.18% (68/78) of patients had post-CCT PAC <11.7 ng/dL; (4) 89.74% (70/78) of patients had post-CCT ARR <2.8 (ng/dL)/(mU/L).

Figure 2. ROC curves of independent and combined post-CCT index for PA diagnosis

Note: CCT = captopril challenge test, PAC = plasma aldosterone concentration, DRC = direct renin concentration, ARR = aldosterone-to-renin ratio.

Figure 3. ROC curves of post-CCT index in APA patients

Note: CCT = captopril challenge test, PAC = plasma aldosterone concentration, DRC = direct renin concentration, ARR = aldosterone-to-renin ratio.

Figure 4. ROC curves of post-CCT index in IHA patients

Note: CCT = captopril challenge test, PAC = plasma aldosterone concentration, DRC = direct renin concentration, ARR = aldosterone-to-renin ratio.

Table 2. Comparison of RAAS among the four groups [M(P25, P75)]

Note: DRC = direct renin concentration, PAC = plasma aldosterone concentration, ARR = aldosterone-to-renin ratio, K = serum potassium, CCT = captopril challenge test.

Table 3. Clinical parameters after unilateral adrenalectomy [M(P25, P75)]

Discussion

CCT is widely used in PA patients due to its simplicity, low cost, and high safety profile, particularly as it can be safely performed in most patients with cardiac or renal insufficiency. The currently accepted CCT protocol involves the seated position with blood drawn 2 hours after oral administration of 50 mg captopril [9]. However, controversies persist regarding its diagnostic efficacy, classification capability, and clinical outcome assessment. Current consensus recommendations propose three diagnostic indicators for PA using CCT: post-CCT PAC suppression rate, post-CCT PAC, and post-CCT ARR, with varying diagnostic thresholds for each indicator. Additionally, CCT has received insufficient attention for PA subtype classification and postoperative biochemical remission assessment. This study confirms through analysis that CCT plays a valuable role throughout the entire management course of PA patients, including diagnosis, subtype classification, and clinical outcome evaluation.

This study recommends an optimal cut-off value of 11.7 ng/dL for post-CCT PAC as the primary diagnostic criterion for PA, with post-CCT ARR as a secondary diagnostic criterion at a cut-off of 2.8 (ng/dL)/(mU/L). The CSE Consensus recommends a post-CCT PAC suppression rate <30% as the diagnostic standard for PA [6,9]; however, multiple studies have shown that post-CCT ARR or PAC are more suitable than post-CCT PAC suppression rate for diagnosing Chinese PA patients [11]. Chen et al. [12] compared 674 patients and concluded that post-CCT ARR is superior to PAC suppression rate as a

diagnostic criterion for PA, with an optimal cut-off value of 46.2 (ng/dL)/(g · L⁻¹ · h⁻¹), although their study used 25 mg captopril. A Japanese study of 71 patients recommended post-CCT ARR >200 (pg/mL)/(ng · L⁻¹ · h⁻¹) as the most valuable diagnostic criterion for PA [13].

An increasing number of studies recommend post-CCT PAC as the diagnostic standard for PA. A Korean study comparing 64 PA patients confirmed that post-CCT PAC had superior diagnostic performance to post-CCT ARR, with an optimal cut-off value of 13 ng/dL [14]. The Chongqing Primary Aldosteronism Study (CONPASS) team plotted ROC curves for post-CCT PAC, ARR, and PAC suppression rate for PA diagnosis, with corresponding AUCs of 0.86 (95%CI=0.83-0.89), 0.78 (95%CI=0.74-0.82), and 0.62 (95%CI=0.56-0.67), respectively, confirming that post-CCT PAC had the highest diagnostic efficacy and recommending a post-CCT PAC level of 110 ng/L as the optimal cut-off [15], which is similar to the 11.7 ng/dL cut-off identified in this study.

Our center previously used radioimmunoassay to demonstrate that both post-CCT ARR (AUC=0.860, 95%CI=0.800-0.907) and PAC (AUC=0.881, 95%CI=0.825-0.924) had higher diagnostic value than post-CCT PAC suppression rate (AUC=0.632, 95%CI=0.558-0.701), with post-CCT PAC being more suitable as a confirmatory standard for PA [16]. The current study using chemiluminescence immunoassay again confirms that post-CCT PAC has the highest diagnostic efficacy.

In PA subtype analysis, post-CCT PAC and ARR can assist in distinguishing APA from non-APA patients. A Japanese study of 238 patients strongly recommended using post-CCT ARR >897 (pg/mL)/(ng · L⁻¹ · h⁻¹) combined with PAC >203 pg/mL for APA identification [17]. A Beijing study of 91 patients also recommended that both pre-CCT ARR and post-CCT ARR could assist in APA subtype classification [18], with corresponding optimal cut-off values of 7.12 (ng/dL)/(mU/L) (sensitivity 35.85%, specificity 77.78%) and 4.23 (ng/dL)/(mU/L) (sensitivity 71.43%, specificity 62.22%). When pre-CCT ARR was combined with a history of hypokalemia, the diagnostic efficacy for APA classification could be improved to 80% [18]; however, that study used CCT as the diagnostic standard for confirming PA. Our study, with a larger sample size and using SIT as the diagnostic standard for PA, recommends an optimal post-CCT PAC cut-off of 17 ng/dL (sensitivity 81.4%, specificity 68.1%) to assist in APA diagnosis. When ARR <2.8 (ng/dL)/(mU/L) and PAC <11.7 ng/dL are both present, APA can be essentially excluded, and patients in this category should not be recommended for aggressive surgical treatment.

CCT shows poor efficacy in classifying IHA subtypes, which may be related to angiotensin-II type-1 receptor autoantibody (AT1AA) titers. AT1AA directly participates in the pathogenesis of PA, with antibody titers in APA patients being twice those in IHA patients. Particularly after CCT, AT1AA titers increase significantly in APA, helping to differentiate APA patients from those with EH or IHA [19].

CCT can also be used to evaluate outcomes after unilateral adrenalectomy in APA patients. Studies have shown that biochemical remission after APA surgery is significantly higher than clinical remission, as PA often coexists with EH, and aldosterone-induced hypertension before surgery causes persistent vascular and renal damage that does not resolve immediately after surgery. A Czech study of 87 patients confirmed this view, reporting that 77% of patients achieved complete biochemical success postoperatively, 22% achieved partial biochemical success, but only 22% normalized blood pressure and discontinued all antihypertensive medications, while 65% achieved partial clinical success [20]. Our study showed that only 18% (14/78) of patients had post-CCT PAC suppression rate $>30\%$, because pre-CCT PAC was already significantly reduced, and 80.76% (63 patients) had $\geq 50\%$ reduction in postoperative PAC compared to preoperative levels. Therefore, post-CCT PAC suppression rate is not suitable as a postoperative remission indicator for Chinese patients. Using post-CCT ARR <2.8 (ng/dL)/(mU/L) and post-CCT PAC <11.7 ng/dL as indicators of biochemical remission more closely approximates clinical remission status.

Comparative analysis in this study revealed that pre-CCT factors have weak roles in PA diagnosis, classification, and clinical outcome assessment. In PA diagnosis, the AUCs of ROC curves for pre-CCT PAC and ARR were lower than those of post-CCT indicators. Furthermore, the diagnostic efficacy of post-CCT PAC suppression rate calculated from pre-CCT PAC was also inferior to post-CCT indicators. Pre-CCT indicators have minimal clinical significance, and post-CCT PAC is more suitable for PA diagnosis confirmation regardless of whether chemiluminescence or radioimmunoassay is used. We recommend omitting pre-captopril blood sampling for hormone testing.

The main limitation of this study is that u-PA patients accounted for 45% (111/247) of all PA patients. These patients had clinical characteristics, serum potassium levels, and adrenal imaging features more consistent with IHA. After fully understanding the condition, costs, risks of AVS failure, and potential clinical benefits, they declined AVS examination. No meaningful diagnostic indicators or cut-off points were identified to distinguish u-PA from IHA during subtype classification, suggesting that u-PA and IHA may represent a single subtype.

This study applies the captopril challenge test to the whole-course management of primary aldosteronism patients, including not only diagnosis but also subtype classification and postoperative outcome assessment, using the same parameters and cut-off values as much as possible to facilitate clinical memorization and application. Post-CCT PAC at 11.7 ng/dL and post-CCT ARR at 2.8 (ng/dL)/(mU/L) can assist in PA diagnosis, serve as exclusion criteria for APA classification, and function as indicators of postoperative biochemical remission. Additionally, pre-CCT blood sampling and testing have weak clinical significance and can be omitted to simplify the procedure and reduce costs.

Author Contributions: Tan Lu, Chen Tao, and Ren Yan designed the study; Tan Lu, Gao Hongjiao implemented the study, organized data, and performed

statistical analysis; Chen Yanxi assisted with data entry and organization; Tan Lu drafted the manuscript; Chen Tao and Ren Yan revised the manuscript; Ren Yan takes responsibility for the final version.

Conflict of Interest: None declared.

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References

- [1] XU Z X, YANG J, HU J B, et al. Primary aldosteronism in patients in China with recently detected hypertension[J]. *J Am Coll Cardiol*, 2020, 75(16): 1913-1922. DOI: 10.1016/j.jacc.2020.02.052.
- [2] TURCU A F, YANG J, VAIDYA A. Primary aldosteronism—a multi-dimensional syndrome[J]. *Nat Rev Endocrinol*, 2022, 18: 665-682. DOI: 10.1038/s41574-022-00730-2.
- [3] WILLIAMS T A, LENDERS J W M, MULATERO P, et al. Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort[J]. *Lancet Diabetes Endocrinol*, 2017, 5(9): 689-699. DOI: 10.1016/S2213-8587(17)30135-3.
- [4] MULATERO P, MONTICONE S, DEINUM J, et al. Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension[J]. *J Hypertens*, 2020, 38(10): 1919-1928. DOI: 10.1097/HJH.0000000000002510.
- [5] KANEKO H, UMAKOSHI H, ISHIHARA Y, et al. Seated saline infusion test in predicting subtype diagnosis of primary aldosteronism[J]. *Clin Endocrinol*, 2019, 91(6): 737-742. DOI: 10.1111/cen.14111.
- [6] JAHAN S, YANG J, HU J B, et al. Captopril challenge test: an underutilized test in the diagnosis of primary aldosteronism[J]. *Endocr Connect*, 2024, 13(3): e230445. DOI: 10.1530/EC-10.12182/20201260301.
- [7] 王卫庆. 原发性醛固酮增多症诊断治疗的专家共识 (2020 版) [J]. *中华内分泌代谢杂志*, 2020, 36(9): 727-736. DOI: 10.3760/cma.j.cn311282-20200615-00444.
- [8] 唐佳, 陈涛, 谭璐, 等. 采用化学发光法测定的立位醛固酮与肾素比值筛查四川省高血压人群中原发性醛固酮增多症的切点 [J]. *中华高血压杂志*, 2023, 31(3): 241-246. DOI: 10.16439/j.issn.1673-7245.2023.03.009.
- [9] XIANG Q, WANG W, CHEN T, et al. The value of the post-captopril aldosterone/renin ratio for the diagnosis of primary aldosteronism and the influential factors: a meta-analysis[J]. *J Renin Angiotensin Aldosterone Syst*, 2020, 21(4): 1470320320972032. DOI: 10.1177/1470320320972032.
- [10] FUNDER J W, CAREY R M, MANTERO F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine

society clinical practice guideline[J]. J Clin Endocrinol Metab, 2016, 101(5): 1889-1916. DOI: 10.1210/jc.2015-4061.

[11] ZHU K Y, ZHANG Y, ZHANG W J, et al. The captopril challenge test for diagnosing primary Aldosteronism in a Chinese population[J]. BMC Endocr Disord, 2019, 19(1): 65. DOI: 10.1186/s12902-019-0390-3.

[12] CHEN S, ZENG Z P, SONG A L, et al. The application of captopril challenge test in the diagnosis of primary aldosteronism[J]. Zhonghua Nei Ke Za Zhi, 2017, 56(6): 402-408. DOI: 10.3760/cma.j.issn.0578-1426.2017.06.004.

[13] KIDOGUCHI S, SUGANO N, HAYASHI-ISHIKAWA N, et al. The characteristics of captopril challenge test-positive patients using various criteria[J]. J Renin Angiotensin Aldosterone Syst, 2019, 20(3): 1470320319870891. DOI: 10.1177/1470320319870891.

[14] KIM J H, PARK K S, HONG A R, et al. Diagnostic role of captopril challenge test in Korean subjects with high aldosterone-to-renin ratios[J]. Endocrinol Metab, 2016, 31(2): 277-283. DOI: 10.3803/EnM.2016.31.2.277.

[15] LUO Y, HE W W, CHENG Q F, et al. Re-evaluation of the diagnostic value and optimal cutoff point of captopril challenge test in diagnosis of primary aldosteronism[J]. Zhonghua Nei Ke Za Zhi, 2022, 61(1): 60-65. DOI: 10.3760/cma.j.cn112138-20201215-00444.

[16] CHEN S H, LUO P Y, YU Y R. The diagnostic value of captopril challenge test for primary aldosteronism[J]. Sichuan Da Xue Xue Bao Yi Xue Ban, 2021, 52(1): 134-141. DOI: 10.12182/20201260301.

[17] WADA N, MIYOSHI A, USUBUCHI H, et al. Prediction of unilateral hyperaldosteronism on adrenal vein sampling using captopril challenge test in patients with primary aldosteronism[J]. Endocr J, 2021, 68(1): 45-51. DOI: 10.1507/endocrj.EJ20-0432.

[18] DONG B, MA X W, GUO X H, et al. Clinical value of captopril test in noninvasive diagnosis of aldosterone-producing adenoma[J]. Beijing Da Xue Xue Bao Yi Xue Ban, 2021, 53(6): 1128-1132. DOI: 10.19723/j.issn.1671-167X.2021.06.020.

[19] ROSSITTO G, REGOLISTI G, ROSSI E, et al. Elevation of angiotensin-II type-1-receptor autoantibodies titer in primary aldosteronism as a result of aldosterone-producing adenoma[J]. Hypertension, 2013, 61(2): 526-533. DOI: 10.1161/HYPERTENSIONAHA.112.202945.

[20] HARTMANN I, HRUSKA F, VACLAVIK J, et al. Hypertension outcomes of adrenalectomy for unilateral primary aldosteronism[J]. Endocrine, 2022, 76(1): 142-150. DOI: 10.1007/s12020-022-02988-y.

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