



在线全文

不同剂量促肾上腺皮质激素兴奋试验在原发性醛固酮增多症分型诊断中的比较*

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【摘要】目的 比较午夜地塞米松联合不同剂量的促肾上腺皮质激素(adrenocorticotrophic hormone, ACTH)兴奋试验对原发性醛固酮增多症(primary hyperaldosteronism, PA)分型的诊断价值。**方法** 本试验为前瞻性试验。对2020年1月1日-2022年9月30日解放军总医院第一医学中心内分泌科确诊为PA的患者进行不同剂量ACTH兴奋试验(所有患者午夜1 mg地塞米松抑制后,按照1:2随机分为25单位ACTH组和50单位ACTH组);根据肾上腺静脉取血和/或手术后病理、临床随访分型判断为肾上腺醛固酮瘤(aldosterone-producing adenoma, APA)和特发性醛固酮增多症(idiopathic hyperaldosteronism, IHA)。通过绘制受试者工作特征(receiver operating characteristics, ROC)曲线,研究不同剂量ACTH兴奋试验对鉴别APA和IHA的诊断效能及其差异。**结果** 本研究纳入82例PA患者,包括APA 49例(59.8%)和IHA 33例(40.2%);25单位ACTH组29例(35.4%)和50单位ACTH组53例(64.6%)。两组基线资料在年龄、性别构成比、血压、血钾及生化指标方面差异无统计学意义;两组ACTH刺激后各时间点血浆醛固酮(plasma aldosterone concentration, PAC)、血皮质醇(cortisol, F)、血醛固酮/同步血皮质醇(PAC/F)无明显差异($P>0.05$)。25单位ACTH组PAC值ROC曲线下面积(area under the curve, AUC)较PAC/F更大;其中90 min时AUC最大[0.948, 95%置信区间(confidence interval, CI): 0.870 ~ 1.000],最佳切点为38.0 ng/dL,敏感性和特异性分别为92.9%和86.7%。50单位ACTH组PAC值AUC同样较PAC/F更大,AUC最大值仍然为90 min时(0.930, 95%CI: 0.840 ~ 0.994),最佳切点为39.6 ng/dL,敏感性和特异性分别为91.2%和83.3%。25单位ACTH组各点PAC值AUC(0.862 ~ 0.948)较50单位ACTH组(0.823 ~ 0.930)更大,但差异无统计学意义。**结论** 小剂量地塞米松联合25单位ACTH或50单位ACTH兴奋试验用于PA分型(APA和IHA)鉴别中的最佳PAC切点值接近,分别为38.0 ng/dL和39.6 ng/dL,均在90 min时具有较高的敏感性和特异性。25单位ACTH剂量小、安全性更好,可推荐用于PA分型诊断。

【关键词】 原发性醛固酮增多症 分型诊断 促肾上腺皮质激素兴奋试验 前瞻性研究

Comparison of Different Doses of ACTH Used in ACTH Stimulation Test to Determine the Subtypes of Primary Aldosteronism QIU Ping^{1,2}, ZANG Li¹, ZHANG Li^{1,3}, LYU Zhaohui¹, MU Yiming¹, GUO Qinghua^{1△}. 1. Department of Endocrinology, The First Medical Center of Chinese PLA General Hospital, Beijing 100853, China; 2. Department of Endocrinology, The First Affiliated Hospital of Chengdu Medical College, Chengdu 610500, China; 3. Department of Endocrinology, The Fifth Affiliated Hospital of Xinjiang Medical University, Wulumuqi 830011, China

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【Abstract】 Objective To compare the diagnostic value of adrenocorticotrophic hormone (ACTH) stimulation test (AST) with different doses of ACTH combined with midnight administration of 1 mg dexamethasone for the determination of the subtypes of primary hyperaldosteronism (PA). **Methods** This is a prospective observational study. Patients diagnosed with PA in the Department of Endocrinology, the First Medical Center of of Chinese PLA General Hospital from January 1, 2020 to September 30, 2022 underwent AST with different doses of ACTH. All patients received 1 mg dexamethasone at midnight for inhibition. Then, the patients were randomly assigned to 25-unit and 50-unit ACTH treatment groups by a ratio of 1:2. Subtype classification and diagnosis of aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA) was made on the basis of adrenal venous blood samples and/or postoperative pathology and clinical follow-up findings. Receiver operating characteristics (ROC) curves were plotted to examine the diagnostic efficacy and the difference of AST by varying doses of ACTH in distinguishing APA and IHA. **Results** A total of 82 patients, including 49 patients with APA (59.8%) and 33 patients with IHA (40.2%), were enrolled. There were 29 patients in the 25-unit ACTH group (35.4%) and 53 patients in the 50-unit ACTH group (64.6%). There were no significant differences in age, sex, blood pressure, minimum serum potassium, and biochemical parameters between the 25-unit and 50-unit groups. After ACTH stimulation, plasma aldosterone concentration (PAC), cortisol (F), and PAC/F at

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different points of time showed no statistical difference between the two groups ($P>0.05$). The area under the curve (AUC) of PAC in the 25-unit group was higher than that of PAC/F. The AUC of PAC reached the maximum at 90 minutes (0.948, 95% confidence interval [CI]: 0.870-1.000) and the optimal cutoff was 38.0 ng/dL, which had a sensitivity of 92.9% and a specificity of 86.7% for differentiating APA and IHA. Similar to the 25-unit group, the maximum AUC of PAC in the 50-unit group was greater than that of PAC/F. The AUC of PAC reached the maximum 90 minutes (0.930, 95% CI: 0.840-0.994) and the optimal cutoff was 39.6 ng/dL, which had a sensitivity of 91.2% and a specificity of 83.3%. The AUC of PAC at different points of time in the 25-unit ACTH group (0.862-0.948) was greater than that of 50-unit ACTH group (0.823-0.930), but the difference was not statistical significance. **Conclusion** AST with 25-unit or 50-unit ACTH combined with small-dose dexamethasone can be used in PA subtype determination, ie, differentiation between APA and IHA. The optimal PAC cut-off values for 25-unit or 50-unit ACTH are similar, being 38.0 ng/dL and 39.6 ng/dL, respectively, and both cutoff values show higher sensitivity and specificity at 90 min. The AST with 25-unit ACTH has the smaller dose and the better safety. Therefore, it is recommended for the diagnosis of PA subtypes.

【Key words】 Primary hyperaldosteronism Subtype ACTH stimulation test Prospective study

原发性醛固酮增多症(primary aldosteronism, PA)是一组醛固酮自主分泌异常增多导致的疾病,其典型临床特点为高血压伴或不伴低血钾。PA在高血压患者中占5%~10%,在难治性高血压中占比则高达20%^[1]。PA有独立于血压之外的心血管疾病、肾脏病和代谢综合征风险,导致早发房颤、脑卒中及脑出血,造成严重靶器官损伤^[2]。

PA的分型是临床治疗策略选择的前提,然而目前分型诊断仍是临床的难点。最常见PA类型为肾上腺醛固酮瘤(aldosterone-producing adenoma, APA)和特发性醛固酮增多症(idiopathic hyperaldosteronism, IHA)。APA(占比35%)主要为单侧腺瘤, IHA(占比60%)则以双侧增生为主^[3]。肾上腺CT作为形态学检查对分型诊断存在一定的错误率;肾上腺静脉取血(adrenal venous sampling, AVS)被共识推荐为区分单侧优势或者双侧分泌的金标准,但该项检查为有创性,且费用高、技术难度较大、结果难以标准化,诊断切点值不统一^[4]。因此,临床亟需一种无创、可普及性高的替代方法。

意大利学者研究发现APA组织过表达ACTH受体mRNA(MC2R)^[5],证实了ACTH可调控APA分泌过多醛固酮的分子机制。此后国内外学者在临床尝试采用ACTH兴奋试验来鉴别经典的APA和IHA,有望绕过AVS成为一种无创、经济、有效的PA分型方法^[6-7]。但有限的文献报道中^[8],不同中心使用的ACTH剂量存在差异,最佳切点值、敏感性和特异性也存在差异,而且多为单中心小样本回顾性资料,值得进一步探索。

本研究为前瞻性单中心诊断性试验,通过对解放军总医院第一医学中心内分泌科确诊为PA的患者进行不同剂量ACTH兴奋试验;根据AVS和/或手术后病理、临床随访分型判断为AHA和IHA;比较25单位和50单位两种剂量ACTH兴奋试验联合地塞米松对鉴别APA和IHA的差异及其诊断效能。

1 对象和方法

1.1 研究对象

纳入2020年1月1日–2022年9月30日本中心确诊PA的患者。PA的诊断标准^[9-10]:①初筛试验阳性:立位醛固酮(ng/dL)/肾素浓度(μ IU/mL)比值(ARR)>3.7,且血浆肾素浓度<5 μ IU/mL或血浆醛固酮浓度(plasma aldosterone concentration, PAC)>10 ng/dL。②确诊试验:卡托普利抑制试验(captopril challenge test, CCT)服药后2 h PAC>11 ng/dL;卧位盐水输注试验(saline infusion test, SIT)输注后PAC>10 ng/dL。排除标准:难治性高血压;严重心衰及心律失常;年龄大于80岁不宜行ACTH兴奋试验;皮质共分泌瘤。本研究通过解放军总医院第一医学中心伦理委员会批准(批准号2022年30号),所有受试者均知情同意并签署知情同意书。

分型诊断:所有PA患者住院期间完善肾上腺薄层CT增强扫描或者肾上腺MRI检查;肾上腺CT表现不典型或临床特征分型困难者行AVS检查。APA诊断标准:确诊PA且肾上腺影像学显示一侧存在典型肾上腺腺瘤且满足以下任意一条:①AVS提示腺瘤侧优势分泌;②手术后病理明确提示腺瘤,并且单侧肾上腺切除术后患者临床、生化结果完全缓解符合原发性醛固酮增多症术后评估(primary aldosteronism surgical outcome, PASO)标准^[11]。IHA诊断标准:确诊PA且影像学双侧肾上腺正常或者双侧/单侧肾上腺结节样增生且满足以下任意一条:①AVS无优势分泌;②口服醛固酮受体拮抗剂(spironolactone receptor antagonists, MRA)后较前血压控制良好、血钾恢复正常,同时肾素水平超过8.2 μ IU/L^[12]。

1.2 检测指标

收集患者临床资料,包括性别、年龄、出院诊断、身高、体质量、体质量指数、平均血压、最低血钾水平、肾

素-血管紧张素-醛固酮系统、糖皮质激素自主分泌评估、肾上腺CT和/或MRI。对于诊断为APA的患者术后1个月、3个月、6个月、1年门诊随访,包括血钾、血压、口服降压药及手术后ARR;IHA患者服药后同样时间随访了解相同内容。

1.3 AVS方法

采用ACTH持续静滴刺激下非同步双侧肾上腺静脉采血。插管前30 min内注入ACTH,速度为50 $\mu\text{g/h}$ 持续整个操作过程。选择指数(selectivity index, SI) ≥ 3 判断插管成功;侧向指数(lateral index, LI) ≥ 4 判断为单侧优势分泌^[13]。

1.4 ACTH兴奋试验方法

本研究按2:1随机对确诊PA患者行50单位或者25单位ACTH兴奋试验。试验开始当天午夜24点使用1 mg地塞米松抑制内源性ACTH分泌;在尽量避免应激因素的前提下,于次晨8点检测立位基础PAC和皮质醇(cortisol, F)(27.7 nmol/L=1 $\mu\text{g/dL}$)后,静推25单位或者50单位ACTH,注射后每30 min抽血检测PAC及同步F直至120 min,共5点标本^[6-7]。

1.5 统计学方法

呈正态分布的计量资料采用 $\bar{x} \pm s$ 表示,组间比较采

用独立样本 t 检验;计数资料以百分率表示,组间比较采用 χ^2 检验;重复测量计量资料采用方差分析。采用受试者工作特性(receiver operating characteristic, ROC)曲线评价诊断效能,以约登指数最大确定诊断指标的最佳切点值;曲线下面积(area under the curve, AUC)之间的比较采用非参数检验。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般资料

90例患者完成ACTH兴奋试验,排除数据不完整、失访、分型诊断不确定的病例。本研究共纳入82例PA患者,男性43例(52.4%),女性39例(47.6%);APA 49例(59.8%),IHA 33例(40.2%);20例患者行AVS,其中APA组12例,IHA组8例;所有患者平均随访时间(12.4 $\pm$ 5.2)个月。两组之间的性别构成比、体质量指数、收缩压和舒张压差异均无统计学意义。APA组年龄、血钾水平、立位肾素值和肾上腺CT双侧病变比例均低于IHA组,差异有统计学意义($P < 0.01$);APA组立位醛固酮值、CCT后醛固酮值、SIT后醛固酮值、肾上腺CT单侧病变比例和1 mg地塞米松过夜抑制后醛固酮水平均高于IHA组,差异有统计学意义($P < 0.01$)。临床资料结果见表1。

表 1 APA和IHA两组之间临床生化指标的差异性比较

Table 1 The differences in clinical biochemical indices between patients with APA and IHA

Index	APA group (n=49)	IHA group (n=33)	P
Male/case (%)	21 (42.9)	22 (66.7)	0.059
Age/yr.	47.71 $\pm$ 10.09	55.33 $\pm$ 11.71	0.003
BMI/(kg/m ²)	25.48 $\pm$ 3.29	26.01 $\pm$ 4.28	0.526
SBP/mmHg	164.3 $\pm$ 17.3	158.5 $\pm$ 16.0	0.130
DBP/mmHg	103.1 $\pm$ 14.4	99.8 $\pm$ 13.5	0.299
Potassium/(mmol/L)	2.71 $\pm$ 0.51	3.29 $\pm$ 0.47	<0.001
Upright renin ^a /($\mu\text{IU/mL}$)	1.84 $\pm$ 2.69	4.75 $\pm$ 5.66	<0.001
Upright aldosterone ^b /(ng/dL)	40.48 $\pm$ 21.39	26.07 $\pm$ 10.92	<0.001
Aldosterone after CCT/(ng/dL)	34.96 $\pm$ 17.63	18.64 $\pm$ 7.22	<0.001
Aldosterone after SIT/(ng/dL)	27.30 $\pm$ 18.00	14.23 $\pm$ 5.35	<0.001
CT Unilateral/case (%)	36 (73.4)	11 (33.3)	<0.001
CT Bilateral/case (%)	13 (26.6)	22 (66.7)	<0.001
Aldosterone after 1 mg dexamethasone/(ng/dL)	17.13 $\pm$ 8.60	13.01 $\pm$ 6.56	0.016

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ARR: aldosterone/renin ratio; SIT: saline infusion test; CCT: captopril challenge test. ^a Reference range: 4.4-46.1 $\mu\text{IU/mL}$; ^b reference range: 3.0-35.3 ng/dL. 1 mmHg=0.133 kPa.

2.2 25单位ACTH组与50单位ACTH组患者一般资料比较

25单位ACTH剂量组患者29例(35.4%),50单位ACTH剂量组患者53例(64.6%),患者一般资料见表2。两组年龄、BMI、性别构成比、收缩压、舒张压、血钾水

平、立位肾素值、立位醛固酮值、CCT后醛固酮值、SIT后醛固酮值和肾上腺CT单侧病变比例均无明显差异($P > 0.05$);使用地塞米松抑制后两组醛固酮水平较基础醛固酮均降低($P < 0.05$),但两组相比无明显差异($P > 0.05$)。

表 2 25单位ACTH组和50单位ACTH组临床生化指标的差异性比较

Table 2 The differences in clinical biochemical indices between groups receiving 25 units ACTH and 50 units ACTH

Index	ACTH 25 units group (n=29)	ACTH 50 units group (n=53)	P
Age/yr.	51.3±11.2	50.5±11.6	0.771
BMI/(kg/m ²)	25.62±3.81	25.84±3.63	0.843
Male/case (%)	13 (44.8)	30 (56.6)	0.307
SBP/mmHg	162.8±19.1	161.8±16.1	0.812
DBP/mmHg	104.9±15.9	100.3±12.9	0.159
Ptassium/(mmol/L)	3.05±0.71	3.01±0.56	0.726
Upright renin ^a /(μIU/mL)	3.34±4.02	2.86±4.53	0.627
Upright aldosterone ^b /(ng/dL)	32.72±17.64	35.82±20.16	0.488
Aldosterone after CCT/(ng/dL)	27.34±18.81	28.5±14.92	0.751
Aldosterone after SIT/(ng/dL)	21.16±18.52	21.24±12.53	0.985
CT Unilateral/case (%)	15 (51.7)	32 (60.4)	0.455
CT Bilateral/case (%)	14 (48.3)	21 (39.6)	0.449
Aldosterone after 1 mg dexamethasone/(ng/dL)	15.10±9.41	15.71±7.32	0.678

The abbreviations are explained in the note to Table 1.

2.3 25单位及50单位ACTH刺激后各时点PAC及PAC/F结果

不同剂量ACTH刺激后显示,随着时间延长两组皮质醇水平较基线迅速升高,120 min达到高峰($P<0.01$),两组皮质醇在各时间点相比均无明显差异($P>0.05$)。醛固酮分泌水平30 min时即明显升高,两组不同剂量ACTH刺激后各时间点醛固酮较基线均升高($P<0.01$);

50单位ACTH组刺激后醛固酮值略高于25单位组,但无明显差异($P>0.05$)。随着ACTH刺激,由于皮质醇对ACTH的直接刺激反应高于醛固酮刺激,故经同步血皮质醇校正的醛固酮比值(PAC/F)较基线逐渐降低,120 min达到最低点($P<0.05$);50单位组各时间点略高于25单位组,但差异无统计学意义($P>0.05$)(见图1)。说明25单位ACTH可表现出足够的醛固酮刺激作用。

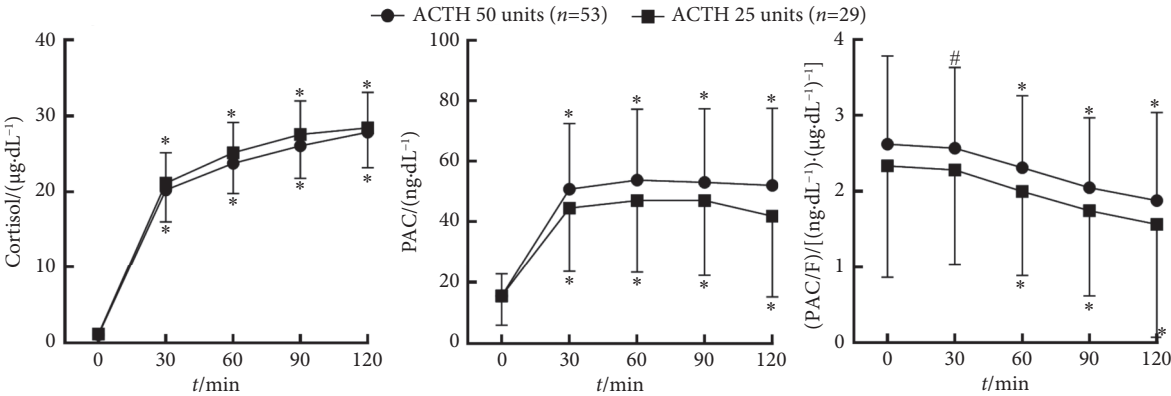


图 1 25/50单位ACTH刺激后皮质醇(F)、醛固酮(PAC)及PAC/F值的比较

Fig 1 Comparison of cortisol (F), plasma aldosterone concentration (PAC), and PAC/F between groups receiving 25 or 50 units of ACTH

* $P<0.05$, * $P<0.01$, vs. baseline of the same group.

2.4 25单位及50单位ACTH兴奋试验对PA的分型诊断效能

分别绘制50单位及25单位两种剂量ACTH兴奋试验后醛固酮30 min、60 min、90 min、120 min、最大值及峰值醛固酮/同步血皮质醇(PACmax/F)区别APA和IHA的ROC曲线,计算AUC及最佳切点。研究显示,无论25单位还是50单位ACTH刺激后,各点PAC/F的AUC均低于PAC值的AUC,但差异均无统计学意义;而25单位

ACTH组各时点醛固酮的AUC(0.862~0.948)与50单位组(0.823~0.930)相比更大,但两者无明显差异($P>0.05$),说明25单位ACTH足以有效鉴别PA分型。25单位剂量组90 min醛固酮值AUC最大,最佳切点为38 ng/dL时敏感性92.9%,特异性86.7%;50单位剂量组醛固酮值AUC最大也为90 min,最佳切点为39.6 ng/dL,敏感性91.2%,特异性83.3%。ROC曲线见图2,诊断效能见表3。

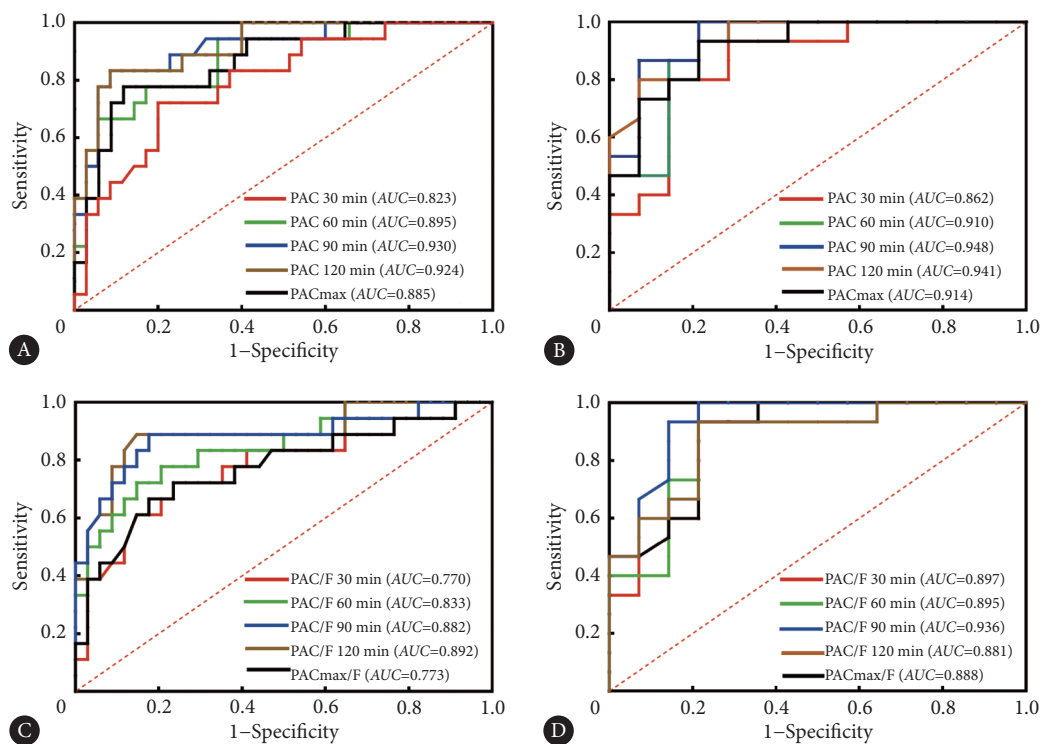


图 2 25/50单位ACTH刺激醛固酮 (PAC) 及醛固酮/同步血皮质醇 (PAC/F) 的ROC曲线

Fig 2 ROC curves of plasma aldosterone concentration (PAC) and PAC/cortisol (PAC/F) after stimulation by 25 or 50 units of ACTH

A: ROC curves of PAC for 50 units; B: ROC curves of PAC for 25 units; C: ROC curves of PAC/F for 50 units; D: ROC curves of PAC/F for 25 units.

表 3 25/50单位ACTH刺激各时点醛固酮值的AUC及诊断效能比较

Table 3 Comparison of the AUC and diagnostic performance of PAC at different points of time after stimulation with 25 or 50 units of ACTH

Index	Dose	AUC (95% CI)	Cutoff/(ng/dL)	Sensitivity/%	Specificity/%	YD index	P
PACmax	25 units	0.914 (0.813, 1.000)	51	78.6	93.3	0.719	0.501
	50 units	0.885 (0.760, 0.968)	45.25	88.2	77.8	0.66	
PAC at 30 min	25 units	0.862 (0.724, 1.000)	40.05	85.7	80.0	0.657	0.444
	50 units	0.823 (0.660, 0.916)	40.95	79.4	72.2	0.516	
PAC at 60 min	25 units	0.910 (0.799, 1.000)	40.6	85.7	86.7	0.724	0.587
	50 units	0.895 (0.765, 0.970)	37.95	94.1	66.7	0.608	
PAC at 90 min	25 units	0.948 (0.870, 1.000)	38	92.9	86.7	0.796	0.517
	50 units	0.930 (0.824, 0.995)	39.05	91.2	83.3	0.833	
PAC at 120 min	25 units	0.941 (0.862, 1.000)	28.95	92.9	80.0	0.657	0.672
	50 units	0.924 (0.840, 0.994)	36.55	91.2	83.3	0.745	

AUC: area under the curve; CI: confidence interval; YD index: Youden index; PAC: plasma aldosterone concentration.

3 讨论

PA的分型诊断一直是临床上的难点, 目前研究均以AVS作为分型诊断“金标准”, AVS有创、费用高、操作难度大、患者不易接受, 因此临床应用受到限制。AVS结果显示的是优势侧, 而不能完全提示单侧; AVS不能排除不对称的双侧PA^[14], 这也是本文探讨ACTH兴奋试验为PA分型诊断的意义所在。本研究通过前瞻性试验对我中心确诊的PA患者进行地塞米松抑制联合ACTH兴奋试验, 对比两种不同剂量(25单位/50单位)ACTH的分型诊断(APA和IHA)效能。结果首次证实, 25单位ACTH或

50单位ACTH兴奋试验用于APA和IHA鉴别中的最佳PAC切点值接近, 在PA分型诊断中价值相当, 两组均在90 min时具有较高的敏感性和特异性, 最佳切点分别为38.0 ng/dL和39.6 ng/dL。25单位ACTH可作为更小、更安全刺激剂量在APA疑似患者中开展, 当肾上腺CT表现典型, 可望略过AVS直接推荐手术。

本研究纳入APA 49例, IHA 33例, 以腺瘤为主, 结果显示APA组患者较IHA血钾水平、立位肾素水平明显降低; 立位醛固酮、CCT后醛固酮及SIT后醛固酮水平均明显高于IHA组。这与大部分研究结果类似, 说明APA醛固酮自主分泌能力更强; 但生化异常并不能很好鉴别APA

和IHA,这和以往研究结果保持一致^[15-16]。

本研究显示使用1 mg地塞米松抑制后无论APA组醛固酮值还是IHA组醛固酮值均较基础醛固酮明显降低,证实ACTH能够抑制醛固酮分泌,醛固酮的合成和分泌受到ACTH调节,因此ACTH兴奋试验在PA分型鉴别中具有良好的验证基础。国内资料显示^[17]APA肿瘤中发现体细胞KCNJ5的突变率高达91%,远超过IHA;KCNJ5突变APA在1 mg地塞米松抑制期间醛固酮水平比KCNJ5野生型APA下降更多,这表明在KCNJ5突变APA中ACTH通路可能更加敏感和激活^[18]。醛固酮对ACTH的反应可能因基因突变而异,APA患者醛固酮分泌对内源性ACTH的依赖性更强。

既往研究对ACTH兴奋试验采取的剂量存在差异,最佳切点及敏感性和特异性不一致,因此本研究首次比较了25单位和50单位两种不同剂量对鉴别APA和IHA是否不同。首先两组基线一般资料和生化结果无明显差异;其次25单位和50单位ACTH在刺激皮质醇分泌方面亦无明显差异;25单位ACTH刺激的醛固酮值虽然略低于50单位,但刺激后醛固酮水平变化趋势、峰值醛固酮水平及醛固酮/同步皮质醇比值两组均保持一致,无明显差异。以上结果表明,25单位足以刺激PA患者内源性醛固酮分泌,因此近期的相关研究均采用25单位作为兴奋剂量^[15-16, 19-20],较小剂量ACTH减少皮质醇及醛固酮过度刺激,减少血压升高、心律失常、心衰等风险。

关于25单位和50单位ACTH剂量的诊断效能目前研究结果并不一致。日本学者SONOYAMA等^[6]采用25单位ACTH,证实刺激后APA患者的PAC显著高于IHA及非PA患者。其中ACTH注射后90 min的PAC作为PA分型诊断的准确度最高,切点值为37.90 ng/dL,诊断APA敏感性为91.3%,特异性为80.6%。这与本研究结果相似,本研究证实25单位组90 min醛固酮AUC最大,最佳切点为38 ng/dL时敏感性为92.9%,特异性为86.7%。国内王卫庆团队^[7]使用50单位ACTH兴奋试验结果显示,120 min的PAC作为诊断单侧PA的准确度最高,最佳切点值为77.90 ng/dL,远高于本研究50单位组90 min最佳切点39.05 ng/dL,也高于后续25单位ACTH的队列研究^[15-16]。由于该切点值较高,其敏感性降低为76.8%(本研究敏感性91.2%),特异性为87.2%(本研究特异性83.3%)。通过比较两种剂量ACTH兴奋后不同时间点醛固酮诊断性能,结果显示两组均在90 min显示出较好的诊断效能,醛固酮切点值相似,并且敏感性高于特异性。作为更安全剂量,25单位更适合在APA疑似患者中开展筛查。疑似PA且使用25单位ACTH刺激后90 min PAC值低于38.0 ng/dL可被排除在

AVS之外,因为他们最有可能为双侧PA。当PAC 90 min大于38.0 ng/dL更可能是APA,当CT表现不典型时,可选择AVS;CT表现典型,略过不必要AVS获得直接手术治愈APA的机会。

本研究同时比较研究25单位和50单位ACTH刺激后PAC/F的诊断价值。结果表明,与PAC(90 min醛固酮最佳切点39.05 ng/dL,敏感性91.8%,特异性84.8%)相比,PAC/F对鉴别APA和IHA特异性升高、敏感性降低。但无论25单位还是50单位,各点PAC/F的AUC均低于PAC值的AUC,PAC仍是较好的指标。同时无论25单位还是50单位刺激后PACmax及PACmax/F并未显示最大的AUC,结果与既往研究一致^[15-16]。25单位组90 min PAC/F AUC为0.936,最佳切点为1.635,敏感性81.6%,特异性90.9%。KITA等^[15]不使用1 mg地塞米松显示120 min时间点PAC/F切点值 ≥ 1.2 时,对确定PA为单侧病变的敏感性为95.5%,特异型为88.9%,其敏感性高于本研究,特异性相似。MORIYA等^[16]结果显示PACmax/F以18.3(醛固酮单位pg/mL)作为分型诊断切点时,对确定PA分型的敏感性为83%,特异型为88%,其敏感性与本研究相似,特异性略低。上述PAC/F切点差异主要来自不同中心选择性偏倚(样本量及APA/IHA入组比例)以及AVS判断侧向指数不同所致。是否可将PAC/F和PAC进行联合诊断,需要更多的数据研究证明。

本研究由于样本量较小,并且为单中心研究,随访时间较短,目前的切点是否进一步推广需要临床更大样本量、多中心临床研究、更长时间随访来验证。由于本研究并非所有患者行AVS,故IHA诊断标准存在缺陷:采用口服MRA后血压控制良好、血钾恢复正常,并且肾素水平超过8.2 μ U/L来判断IHA目前依据尚不充分。目前日本学者KOBAYASHI双侧预测模型的JPAS评分值可在今后研究中借鉴^[21]。

综上,本研究探索了午夜地塞米松联合不同剂量ACTH兴奋试验对PA分型的诊断价值。研究结果显示1 mg地塞米松联合25单位的ACTH兴奋试验可作为最佳剂量用于PA分型,其中90 min醛固酮以38 ng/dL作为分型诊断切点具有较高的敏感性,结合肾上腺CT及患者临床特征可更好筛查出APA,从而避免部分患者行AVS。

* * *

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