Application of Metanephrine and Normetanephrine in Evaluating the Selectivity of Adrenal Vein Sampling

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ABSTRACT

The aim of the study was to investigate the usefulness of metanephrine (MN) and normetanephrine (NMN) in bilateral simultaneous adrenal vein sampling (AVS) with and without ACTH stimulation. The study was conducted in a single referral center. Prospective recruited patients with PA were treated with AVS. The effects of cortisol, MN and NMN on selectivity catheterization were assessed and determined by lateralization. We enrolled 54 patients with PA who were treated with simultaneous bilateral AVS with ACTH. The Selectivity Index (SI) calculated by MN was higher than that calculated by other indicators ($p < 0.001$), the catheterization success rate of MN at baseline was the same as that of cortisol after ACTH stimulation, and in lateralization diagnosis, MN was not inferior to cortisol. In conclusion, among the studied indicators, MN is the best index for determining the catheterization selectivity in AVS, especially in the absence of ACTH stimulation.

Introduction

Primary aldosteronism (PA) is a common cause of secondary hypertension. The main etiological diagnoses include bilateral PA (idiopathic aldosteronism) and unilateral PA (adrenal adenoma or hyperplasia). Surgery is the first choice for lateralized PA, which may cure the disease. Adrenal vein sampling (AVS) is recommended as the gold standard for differentiating unilateral and bilateral PA. The procedure is technically demanding, the location of catheter placement depends on the Selectivity Index (SI). At present, cortisol is the only indicator used to determine the placement of catheters. However, cortisol has a relative long half-life, is released via pulsatile secretion, and is easily affected by stress. In clinical practice,

SI_{cor} (SI calculated by cortisol) sometimes cannot reach the cutoff value when catheterization is successful. To solve this problem, some studies have proposed steroid markers for AVS data interpretation, including androstenedione, dehydroepiandrosterone, 17α-hydroxyprogesterone, and 11-deoxycortisol [1–3]. NMN and MN are the metabolites of norepinephrine and epinephrine. They are stable and will not change as a response to stress [4]. Dekkers et al. tried to compare MN with cortisol in the sequential catheterization AVS without ACTH stimulation [5], and Goupil et al. tried to use plasma metanephrine to aid AVS in a patient with aldosterone and cortisol co-secretion [6]. As one of the few clinical centers in China using simultaneous bilateral AVS with ACTH stimulation, we intend to compare MN and NMN with cortisol in determining the selectivity of AVS before and after ACTH stimulation

Patients and Methods

Patients

From March 2018 to December 2019, we prospectively recruited 54 PA patients from the Department of Metabolism and Endocrinology, Xiangya Second Hospital, Central South University who were diagnosed with PA and seeking cure with adrenalectomy. The protocol was approved by the clinical research ethics committee of Xiangya Second Hospital of Central South University. Written consent has been obtained from each patient after full explanation of the purpose and nature of all procedures used.

Clinical assessment

The diagnosis of PA was made according to the diagnostic criteria of the Endocrine Society guidelines [7]. Before screening, all patients were evaluated after discontinuing all antihypertensive drugs, except for non-dihydropyridine calcium channel blockers and alpha-adrenergic blockers, such as spironolactone, eplerenone (mineralocorticoid receptor antagonist) and potassium (K) diuretics for at least 4 weeks, and beta blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists for at least 2 weeks. Renin-angiotensin-aldosterone system (RAAS) screening included measurement of the plasma aldosterone concentration (PAC) and plasma renin activity (PRA) and calculation of the aldosterone-renin ratio (ARR). Patients with a PAC ≥ 15 ng/dl and an ARR ≥ 30 ng/dl/ng/ml/h underwent a further captopril challenge test (CCT) and/or saline infusion test (SIT). Diagnostic criteria were as follows: After CCT, patients who met all of the following criteria were diagnosed with PA: (1) PAC decreased < 30 %, (2) ARR maintained ≥ 30 ng/dl/ng/ml/h, and (3) PAC was ≥ 11 ng/dl [8]. After SIT, patients who met post-infusion plasma aldosterone levels > 10 ng/dl were diagnosed with PA.

A low-dose dexamethasone suppression test was performed to exclude Cushing's syndrome. The serum cortisol concentration of less than 50 nmol/l at 8:00 AM in the morning after 1 mg dexamethasone given at midnight is considered to be normal response.

Hypokalemia was corrected before AVS. All AVS procedures were performed by the same experienced interventional radiologist at Xiangya Second Hospital of Central South University. Samples were obtained simultaneously from the inferior vena cava (IVC) and both adrenal veins (AVs) before (t0) and 10 minutes after ACTH stimulation (t10). ACTH (produced by Shanghai No. 1 Biochemical and Pharmaceutical Corp) was injected as a 0.125 mg (25 U) bolus followed by continuous infusion (0.125 mg/h). Heparin was injected intravenously during the operation to avoid the risk of thrombosis.

All assays were performed in the biochemistry laboratory at the Second Xiangya Hospital of Central South University. The plasma aldosterone concentration (PAC) was measured using a chemiluminescence assay (Maglumi 2000 Plus, China); the intra- and inter-assay CV for the PAC was ≤ 5 and ≤ 10 %, respectively. The concentration of Angiotensin I (AI) was also measured by a chemiluminescence assay (Maglumi 2000 Plus, China); the intra- and inter-assay CV for the PRA was ≤ 15 and ≤ 10 %, respectively. The centrifuged plasma samples were divided into two parts. One of the plasma samples was placed in an ice bath and the other was incubated at 37 °C for 1 hour (the exact time was recorded). Plasma renin activity (PRA) = AI concentration in incubated samples at 37 °C–AI concentration in ice bath samples. The serum cortisol level was measured by a competitive chemiluminescent immunoassay (Maglumi 2000 Plus, China), with a CV of 5.1–7.1 %. Plasma free MN and NMN were measured by a radioimmunoassay (LDN, Germany, code, BA R-8300). the intra- and inter-assay CV for the NMN was ≤ 8.4 and ≤ 12 %. the intra- and inter-assay CV for the MN was ≤ 13.6 and ≤ 15.1 %. Computed tomography (CT) scans of the adrenal glands with contiguous 2.5 mm slices were performed for all PA patients before undergoing AVS.

For the analysis, PRA values < 0.1 ng/ml per h were set to 0.1 ng/ml per h. The standard of interpretation of the results was as follows: Successful catheterization was defined by a SI (derived from AV/IVC cortisol concentrations) ≥ 2 before and ≥ 3 after ACTH administration. The source of aldosterone excess was assessed by the lateralization index (LI), which was calculated by dividing the dominant adrenal cortisol-corrected aldosterone level (A/C_{DOM}) by that of the opposite side (A/C_{OPP}). Unilateral PA was diagnosed if the LI was ≥ 2 before and ≥ 4 after ACTH administration [9].

Statistical analysis

Statistical Package for the Social Sciences version 23.0 for Windows (SPSS) and GraphPad Prism 5.0 (GraphPad Prism Software, Inc.) were used for plotting the results. Descriptive statistics are reported as the mean ± SD or median [interquartile range [IQR)], as appropriate. Classification variables are expressed as numbers and percentages. A normality test was used to determine the distribution of the variables. ANOVA was used to compare normally distributed variables among groups. The nonparametric Friedman test was used to compare variables with a nonnormal distribution among groups. p-Values < 0.05 were considered statistically significant.

Results

Clinical characteristics of participants

A total of 54 patients were included. There was no significant difference between sex. The average blood pressure reached grade 2 hypertension. A total of 89 % of the patients had hypokalemia. The clinical characteristics of all patients are shown in ▶ **Table 1**.

Comparison of the SI of different indexes and the influence of ACTH

After ACTH stimulation, concentration of cortisol was significantly elevated in both sides of adrenal veins, and there was no significant change for NMN or MN (▶ **Table 2**).

The SI calculated by cortisol, NMN, and MN were pairwise compared. At baseline, the bilateral SI_{MN} (SI calculated by MN) was significantly higher than the SI of other indicators ($p < 0.001$, ▶ **Fig. 1a**). After ACTH stimulation, the absolute value of the bilateral SI_{NMN} (SI calculated by NMN) was lower than that of the other indicators ($p < 0.001$, ▶ **Fig. 1b**).

▶ **Table 1** Clinical characteristics of the participants.

Variable	
Age, median (range), years	47 (42, 55)
Male sex, n (%)	25 (46 %)
Duration of hypertension median, (IQR), years	7.0 (4.0–10.0)
Systolic BP, mmHg	154 ± 21
Diastolic BP, mmHg	92 ± 15
Serum K^+, mmol/l	3.10 ± 0.39
Serum K^+<3.50 mmol/l, n (%)	48 (89 %)
PRA, median (IQR), ng/ml per hour	0.10 (0.05, 0.16)
PAC, median (IQR), ng/dl	38.2 (262.8, 617.5)
ARR, median (IQR), (ng/dl)/(ng/ml per hour)	281.9 (200.5, 465.5)
CT results, no. (%)	
Unilateral lesion	40 (74.1 %)
Bilateral lesion	13 (24.1 %)
Negative	1 (1.8 %)
lesion diameter on CT, median (IQR), mm	15 (10, 20)

For ARR calculation, PRA the minimum value was set at 0.10; BP: Blood pressure; PAC: Plasma aldosterone concentration; PRA: Plasma renin activity; ARR: Aldosterone-renin ratio; CT: Computed tomography.

Success rate of catheterization according to different indicators before and after ACTH

Among the 54 patients, after ACTH stimulation, 51 patients reached the success criteria of selective bilateral catheterization ($SI_{Cor} \geq 3$). For the other 3 patients (right 2, left 1), either before or after ACTH, neither the SI_{Cor} nor the SIs calculated from any other indicator met the criteria for selective. These patients were considered to have failed unilateral catheterization and were not included in further analysis (Supplementary **Table 1S**).

Comparison of the proportion of selective catheterization with different hormone indicators: at baseline, the proportion of bilateral selective catheterization using MN was significantly higher than that using cortisol. After ACTH stimulation, on the right side, the proportion of selective catheterization was not significantly different among the indicators. On the left side, the proportion of selective catheterization using NMN was lower than that using cortisol and MN. ACTH significantly increased the proportion of selective catheterization using cortisol (bilateral, $p < 0.01$) (▶ **Table 3**).

The patients who were assessed as unsuccessful catheterization at baseline and successful catheterization after ACTH stimulation by SI_{Cor} (right 12, left 13) were evaluated by other indicators at baseline. SI_{MN} on both sides was significantly higher than SI_{Cor} (both side $p < 0.001$). Compared with cortisol, MN can protect most cases (right 11/12, left 12/13) from being classified as unsuccessful catheterization (▶ **Fig. 2**).

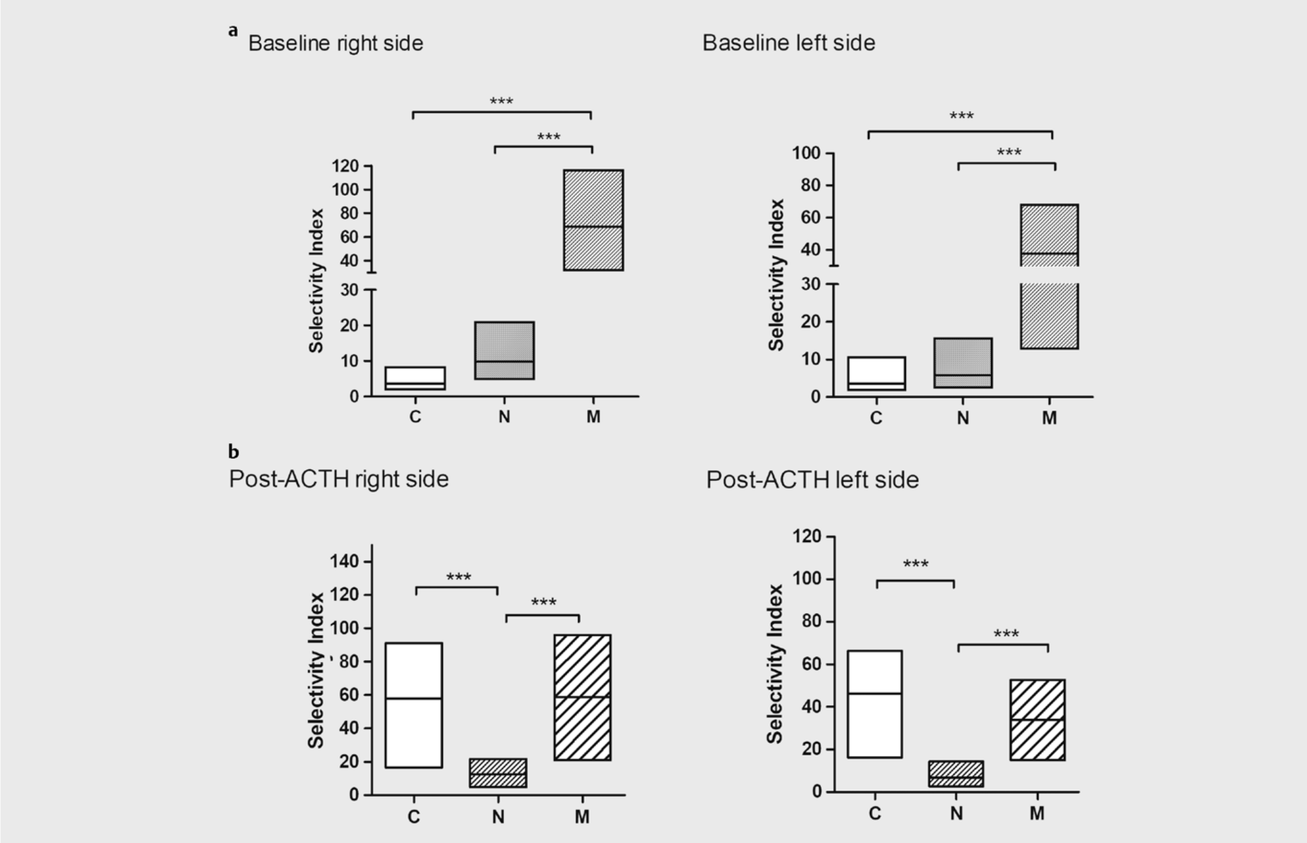
Determination of the dominant lesion side by different indicators

For the 51 patients with successful bilateral catheterization, LI_{Cor} was used to evaluate laterality. Before and after ACTH stimulation, 31 (60.8 %) patients consistently showed unilateral dominance, 14 (27.5 %) patients consistently showed bilateral lesions, and 6 (11.7 %) patients showed laterality changes (all from unilateral before ACTH to bilateral after ACTH stimulation). The CT coincidence rate was 47.1 % (24/51) (Supplementary **Table 2S**). Adrenalectomy was performed in 28 patients with unilateral lesions. Patients in laterality changes group did not choose surgery and treated with oral medication. In all patients, blood pressure significantly improved (before operation 161 ± 21/97 ± 16 mmHg, post operation 131 ± 13/82 ± 9 mmHg, $p < 0.001$), and serum potassium returned to normal (before operation 2.97 ± 0.34 mmol/l, post operation 3.94 ± 0.32 mmol/l, $p < 0.001$) (Supplementary **Table 3S**). All the

▶ **Table 2** The increase multiple of indicators after ACTH stimulation compared to the baseline level.

Variable	RAV(IQR), (times)	p-Value RAV vs. IVC	IVC(IQR), (times)	p-Value LAV vs. IVC	LAV(IQR) (times)	p- Value RAV vs. LAV
COR	19.94 (4.02, 47.30)	0.000[a]	1.66 (1.36, 2.23)	0.000[a]	15.61 (4.38, 37.23)	0.371
NMN	0.98 (0.64, 1.46)	0.555	1.00 (0.78, 1.36)	0.729	0.91 (0.60, 1.28)	0.910
MN	0.96 (0.65, 1.18)	0.247	1.01 (0.76, 1.43)	0.935	0.95 (0.54, 1.57)	0.261

The value after ACTH stimulation was divided by the value at baseline and obtain the multiple of increase of each indicator. In both adrenal veins, after ACTH stimulation cortisol increased significantly, but MN and NMN did not change. There were no significant changes of all the indicators in inferior vena cava after ACTH stimulation; RAV: Right adrenal vein; IVC: Inferior vena cava; LAV: Left adrenal vein; COR: Cortisol; NMN: normetanephrine; MN: metanephrine; [a] $p < 0.05$.



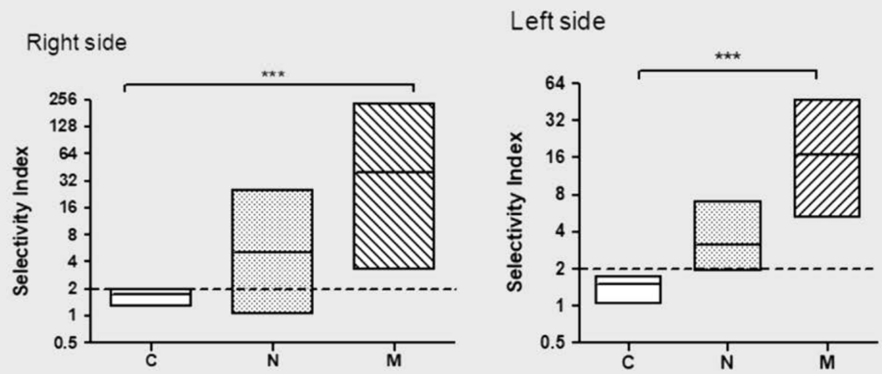
▶ **Fig. 1** Absolute value of bilateral SI calculated by cortisol, NMN and MN at baseline and after ACTH stimulation respectively. *** $p<0.001$, C: Cortisol, N: Normetanephrine, M: Metanephrine.

patients had biochemical and clinical improvements, indicating that AVS was successful in determining lateralization. There was no significant difference between any of the indicators in the accuracy of the dominant side (Supplementary **Table 4S**), indicating that NMN and MN were not inferior to cortisol in terms of determining lateralization.

Discussion

PA is the most common cause of secondary hypertension. Given the increasing understanding of the disease, the incidence rate of PA is quite high, accounting for 5–13 % of patients with hypertension [10, 11]. Adrenal CT cannot be used to make functional diagnoses. Therefore, all guidelines recommend AVS as the gold standard test to distinguish unilateral from bilateral disease in patients with PA. The anatomic characteristics of the bilateral adrenal veins are quite different. The right side is straight, and the angle between the right side and the inferior vena cava is large, so it is difficult to place the catheter during the operation. The left adrenal vein is thick and short and easy to collect hormone diluted by the inferior phrenic vein. Therefore, the interpretation of AVS results can be divided into two steps: first, determine whether the catheterization is successful, and then determine whether there is lateralized-dominant secretion. At present, SI_{Cor} is used to determine the position for catheterization. Cortisol has good specificity, but its half-life in plasma is relative long (100 min), it is released via pulsatile secretion, and it is easily affected by stress. For these reasons, sometimes successful catheterization is unable to yield a sufficient gradient SI. The current solution is to stimulate the secretion of adrenal cortisol with ACTH; however, there are some potential problems in the use of this compound. The aldosterone secretion of some aldosterone tumors or adrenal hyperplasia [12] associated with particular mutations (such as KCNJ5) can be stimulated by ACTH. In addition, many studies have shown that aldosterone and cortisol co-secretion in adrenal adenomas is not uncommon [13–15]. For these patients, the use of cortisol may affect the determination of the dominant side. Although there are still controversies regarding its influence on final surgical decision [16–19], the adverse effect of ACTH on LI is possible. Therefore, it is of great clinical important to find a more specific detection indicator. Some studies evaluated adrenocortical steroids and adrenal androgens in AVS [1–3, 20, 21], and ACTH significantly increased the adrenal output of hormones including adrenal medullary hormones norepinephrine and epinephrine [22, 23].

NMN and MN are the metabolites of norepinephrine and epinephrine. They are stable and will not change as a response to stress [4]. Under physiological conditions, more than 90 % of circulating MN comes from the adrenal glands [24]. Therefore, MN is assumed to be used as the localization index of AVS catheterization. Dekkers et al. tried to compare MN with cortisol in the sequential catheter-



▶ **Fig. 2** The box plots in ▶ **Fig. 2** show the SI values for patients with baseline SI < 2.00 on at least one side using cortisol assessment. The dotted horizontal line represents the cutoff value for the SI definition of selectivity. Compared with cortisol, MN can protect more patients from being classified as nonselective (* * * p < 0.001). The median and IQR are used to create the boxes in the figure.

▶ **Table 3** Comparison of the proportion of successful catheterization using different indicators [number of patients (%)].

		Catheterization n (%)	COR	NMN	MN	p-Value
Right side	Baseline	Successful	39 (76.5)	43 (84.3)	49 (96.1)[a]	0.018*
		Unsuccessful	12 (23.5)	8 (15.7)	2 (3.9)	
	Post-ACTH	Successful	48 (94.1)	44 (86.3)	46 (90.2)	0.412
		Unsuccessful	3 (5.9)	7 (13.7)	5 (9.8)	
	p-Value		0.012*	0.780	0.433	
Left side						
	Baseline	Successful	38 (74.5)	42 (82.4)	49 (96.1)[a]	0.010*
		Unsuccessful	13 (25.5)	9 (17.6)	2 (3.9)	
	Post-ACTH	Successful	49 (96.1)	37 (72.5)[b,c]	49 (96.1)	0.000*
		Unsuccessful	2 (3.9)	14 (27.5)	2 (3.9)	
	p-Value		0.002*	0.236	1.000	

[a] Compared with the baseline cortisol group; *Significant. [a] Compared with the baseline cortisol group; [b] Compared with the post-ACTH COR group; [c] Compared with the post-ACTH MN group; *Significant; COR: Cortisol; NMN: Normetanephrine; MN: Metanephrine.

ization AVS, found that MN provides a superior analyte compared with cortisol in assessing the selectivity of adrenal vein sampling during procedures without ACTH stimulation [5]. But this study was done at two different centers with different AVS process. In our study, bilateral simultaneous AVS with ACTH stimulation was performed by one experienced radiologist, and laboratory tests were performed by the same methods. The same standard sampling procedure was applied in every patient. And results confirm the view that MN is better than cortisol in assessing AVS selectivity without ACTH stimulation. Only 23 % of plasma NMN is produced in the adrenal gland, but adrenal gland is the largest single tissue source of NMN. Therefore, we also selected NMN as detection indicator to evaluate it use of determining AVS catheterization success and lateralization. It was found that SI_{MN} was significantly higher than the SI values calculated for the other indicators in the absence of ACTH, and the percentage of successful catheterization according to the level of MN was similar to that for cortisol after ACTH stimulation. Therefore, it is better to determine catheterization by using MN if without ACTH. After ACTH stimulation, MN had no significant advantage over the other indicators, and SI_{NMN} was significantly lower than that of the other indexes. This conforms to the physiological mechanism underlying the different regulation of the adrenal medulla and cortical hormones. MN and NMN are not stimulated by ACTH. Furthermore, NMN can be produced in extra-adrenal organs such as the digestive tract and the paraganglia, so the concentration gradient of NMN between the AV and iliac vein is small. Especially after ACTH stimulation, the SI of the other cortical hormone indexes is significantly increased, while the NMN concentration gradient is relatively lower, showing a significant difference.

Summary

Highlights

We compared the roles of cortisol NMN and MN in bilateral simultaneous AVS with and without ACTH stimulation. It was found that the SI calculated by MN was higher than that calculated by cortisol and NMN. At baseline, the success rate of catheterization using MN was the same as that using cortisol after ACTH stimulation. Based on this finding, we believe that MN is a better indicator in AVS, especially in the absence of ACTH stimulation.

Limitation

This was a single-center study with a small sample size. Larger, multicenter prospective studies using standardized procedures are needed to further elucidate the clinical effects. The LC-MS/MS detection method is used in many studies and may yield more accurate results. Further pathological and genetic evidence is required, as well as long-term follow-up analysis.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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