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Hypertension. 2012;60:431-436; originally published online June 25, 2012;

doi: 10.1161/HYPERTENSIONAHA.112.195891

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Hyperparathyroidism Can Be Useful in the Identification of Primary Aldosteronism Due To Aldosterone-Producing Adenoma

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Abstract—Hyperparathyroidism represents as a novel feature of primary aldosteronism (PA). Its occurrence in patients with the surgically correctable aldosterone-producing adenoma (APA) and not in those with bilateral adrenal hyperplasia suggested that the measurement of parathyroid hormone could help in differentiating between these subtypes of PA. To test this hypothesis we measured the plasma levels of intact parathyroid hormone, Ca^{2+} , and several markers of calcium/phosphorus metabolism in 132 hypertensive patients, including 74 with primary (essential) hypertension and 58 consecutive PA patients. Of the latter, 46 were conclusively diagnosed as APA (by finding of lateralized aldosterone excess, pathology, correction of the hyperaldosteronism, and evidence of a fall of blood pressure after adrenalectomy) and 12 as bilateral adrenal hyperplasia. Based on these diagnoses we used the area under the receiver operator characteristic curve analysis to assess the accuracy of serum parathyroid hormone for identifying the PA cases in the whole group and for distinguishing between APA and bilateral adrenal hyperplasia. In this selected population of hypertensive patients for identifying PA cases, the accuracy of serum parathyroid hormone tended to be lower than that of the aldosterone:renin ratio. However, for discriminating between APA and bilateral adrenal hyperplasia patients it was better than that under the identity line and also that for the aldosterone:renin ratio for pinpointing APA cases among patients with PA. Hence, these findings indicate that raised serum parathyroid hormone levels are a feature of APA that can be useful for selecting the PA patients to be submitted to adrenal vein sampling. (*Hypertension*. 2012;60:431-436.)

Key Words: aldosterone ■ mineralocorticoids ■ PTH ■ endocrine hypertension ■ secondary hypertension ■ aldosterone-producing adenoma ■ diagnosis ■ calcium

In patients with primary aldosteronism (PA), the discrimination between the surgically curable aldosterone-producing adenoma (APA) and the medically treatable bilateral adrenal hyperplasia (BAH) is a challenging task that usually requires adrenal vein sampling,¹ a minimally invasive, risky, expensive, and not widely available procedure. Accordingly, there is an unmet need of a better strategy for selecting patients more likely to have an APA to be submitted to adrenal vein sampling (AVS). After the pilot reports of secondary hyperparathyroidism in patients with PA^{2,3} and also with secondary aldosteronism attributed to congestive heart failure,⁴⁻⁶ we and others recently documented an elevation of serum parathyroid hormone (PTH) levels in large cohorts of patients with confirmed PA.^{7,8}

These observations are of great interest given the adverse cardiovascular consequences of excess PTH, which is now appreciated as a cardiovascular risk factor,^{9,10} and also because of the evidence that PTH can exert a secretagogue effect on aldosterone. In vitro studies consistently showed that PTH

concentration-dependently increases aldosterone in rat,¹¹ bovine, and human dispersed adrenocortical cells^{12,13} and enhanced the secretagogue effect of angiotensin II on aldosterone.¹⁴ The PTH-related peptide, a mediator of cancer hypercalcemia that also acts on the type 1 PTH receptor, was also reported to stimulate aldosterone^{13,15} and to induce proliferation of human adrenocortical carcinoma cells.¹⁶ Furthermore, infusion of aldosterone in rats caused an increase of PTH, thus suggesting a cause-effect relationship between hyperaldosteronism and hyperparathyroidism.¹⁷

The observations that in patients with primary hyperparathyroidism: (1) plasma aldosterone and PTH concentrations were positively correlated; (2) at multivariate analysis, preoperative PTH was an independent predictor of plasma aldosterone concentration; (3) PTH levels >100 ng/L were an independent predictor of abnormally elevated plasma aldosterone concentration,¹⁸ are also consistent with the concept that PTH plays a role in triggering or maintaining aldosterone secretion in vivo. Hence, accumulating evidence altogether

Received March 27, 2012; first decision April 9, 2012; revision accepted May 29, 2012.

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DOI: 10.1161/HYPERTENSIONAHA.112.195891

Table 1. Demographic, Clinical, and Biochemical Features of the Patients

Variable	APA (n=46)		P Value (Baseline vs Follow-Up)	P Value (APA Baseline vs BAH)	BAH (n=12)	P Value (BAH vs PH)	PH (n=74)	P Value (APA Baseline vs PH)
	Baseline	Follow-Up						
Age, y	51±13	52±12	NS	NS	45±10	NS	50±14	NS
Systolic BP, mm Hg	155±17	131±5	<0.001	NS	155±33	NS	149±16	NS
Diastolic BP, mm Hg	94±10	82±6	0.005	NS	92±19	NS	93±15	NS
Serum K ⁺ , mmol/L	3.5±0.7	4.4±0.7	<0.001	NS	3.6±0.4	NS	4.5±0.6	<0.001
Estimated GFR, mL/min	86±25	81±19	NS	NS	103±29	NS	92±21	NS
PRA, ng/mL/h	0.78 (0.31–1.31)	1.3 (0.72–1.50)	0.006	NS	0.20 (0.15–1.00)	NS	1.92 (0.98–6.2)	0.003
PAC (ng/dL)	19 (12.2–26.7)	9 (6.7–13.5)	<0.05	NS	17.4 (11.8–18.8)	NS	13.5 (9.4–10.4)	<0.001
ARR (ng/dL)/(ng/mL/h)	35 (16–76)	9 (7–12)	<0.05	NS	65 (12–113)	NS	10 (9–11)	<0.001
Urinary Na ⁺ excretion, mEq/24 h	154±66	160±85	NS	NS	148±44	NS	168±65	NS
Lateralization index	8.7 (3.2–19.4)	NA	NA	0.005	1.27 (1.08–1.60)	NA	NA	NA

Mean±SD or median and interquartile range, as appropriate. PRA indicates plasma:renin ratio; PAC, plasma aldosterone concentration; ARR, aldosterone:renin (PRA) ratio; APA, aldosterone-producing adenoma; ctrl, control; PH, primary (essential) hypertension; NA, not applicable; NS, not significant; GFR, glomerular filtration rate; BP, blood pressure; BAH, bilateral adrenal hyperplasia. Lateralization index at adrenal vein sampling was calculated as $(PAC_{APA}/PCC_{APA})/(PAC_{ctrl}/PCC_{ctrl})$. Normal values are as follows: serum K⁺, 3.4–4.5 mmol/L; PRA, 0.2–3.3 ng/mL/h; PAC, 0.8–15 ng/dL; ARR, <26; U-Na⁺, 40–220 mEq/24 h. LI cutoff to diagnose lateralization is 2.0.¹²

suggest that PTH could play a role in human PA by triggering and/or maintaining aldosterone secretion, by stimulating adrenocortical cell proliferation, and also by contributing to the excess cardiovascular damage documented in PA patients.^{19,20}

Of note, we found the increase of PTH to be peculiar to APA⁷ and to be corrected by adrenalectomy.⁷ These findings, which are in keeping with earlier observations,^{2,3} show altogether a causal relationship between the aldosterone-producing tumor and PTH elevation. Of clinical relevance, these observations raise the contention that the measurement of serum PTH could help in differentiating between APA and BAH.^{7,8} This study was, therefore, set up to test this hypothesis.

Patients and Methods

We prospectively recruited 132 hypertensive patients referred to the Center of Excellence of the European Society of Hypertension based in our unit. All of the patients underwent a systematic screening for APA, as reported. The latter included measurement of serum ions (Na⁺, K⁺, P, Ca²⁺, and Mg²⁺), 25OH vitamin D, and 1-25OH vitamin D, supine plasma renin activity, and plasma aldosterone concentration, both under baseline conditions and 45 minutes after 50 mg of captopril PO. Twenty-four-hour urinary excretion of deoxyypyridinoline was assessed as a marker of bone metabolism. In the same day, 24-hour urinary excretion rates of Na⁺, K⁺, P, Ca²⁺, norepinephrine, epinephrine, normetanephrine, and metanephrine were measured.

Hormonal measurements were performed with commercially available kits in an ISO 9001 certified laboratory as described.⁷ In particular, PTH was assayed with a kit (DiaSorin Liaison, Stillwater, MN; normal values, 26–73 ng/L) in the first 90 patients and thereafter with a novel kit (DiaSorin Liaison, chemiluminescence kit; normal values, 4.6–26.8 ng/L) in the rest. The data obtained in these last patients with the second kit were homogenized to those obtained with the first kit using regression lines of standards curves.

Diagnostic Criteria

The diagnosis of PA was made as described²¹; APAs were diagnosed by the “4-corners criteria,” which entail the following: (1) a biochemical diagnosis of PA; (2) lateralization of aldosterone secre-

tion at AVS; (3) adenoma at histopathology; and (4) outcome of adrenalectomy at follow-up.²² Of these patients, 116 were reported recently in a study that provided the first evidence for an increase of PTH in PA patients.⁷

Statistical Analysis

The diagnostic accuracy of the aldosterone:renin ratio (ARR) and serum PTH was analyzed by the receiver operator characteristic curves with MedCalc (version 12, MedCalc Software, Mariakerke, Belgium). Calculation of the power of the study for showing a statistically significant difference at the 5% significance level between the receiver operator characteristic area under the curve (AUC) of the 2 tests for detecting PA was conducted with the SAS macro ROCPOWER (SAS Institute Inc, Cary, NC) using the method reported elsewhere.^{23,24} The SPSS software (version 18.0 for Mac, SPSS Inc, Bologna, Italy) was used for all of the other analyses.

Results

After the diagnostic workup, the diagnosis of APA was conclusively established in 46 of the 58 patients.²² Twelve PA patients without lateralization at AVS were held to have BAH. In the rest, no evidence for any secondary form of hypertension was found; therefore, they were held to have primary (essential) hypertension (PH). The main anthropometric and clinical characteristics of all of the populations are shown in Table 1. In the APA patients the diagnosis was unequivocally proven by the high values of the lateralization index at AVS, which were far above the cutoff of 2.0 in all cases, as well as by the BP outcome and the normalization of the ARR postadrenalectomy.

Table 2 shows the values of the main indices of calcium and phosphorus metabolism in the APA, both at baseline and after adrenalectomy, and in BAH and PH patients. At baseline, serum-ionized Ca²⁺, Mg²⁺, and 1-25OH vitamin D, and 24-hour urinary excretion of Ca²⁺, phosphorus, cAMP, and deoxyypyridinoline showed no significant differences across groups of patients. Serum 25OH vitamin D levels were in the deficiency range in all of the groups without significant differences among them. Serum PTH was higher in the APA

Table 2. Biochemical Indices of Calcium and Phosphorus Metabolism of the Patients

Variable	APA (n=46)		P Value Baseline vs Follow-Up	P Value APA Baseline vs BAH	BAH (n=12)	P Value BAH vs PH	PH (n=74)	P Value APA Baseline vs PH
	Baseline	Follow-Up						
Serum PTH, ng/L	113.4±45.7	74.6±22.2	0.02	0.026	81.7±29.9	NS	79.0±30.8	<0.001
Urinary cyclic AMP, mmol/24 h	3.09±1.64	3.07±1.71	NS	NS	3.54±1.99	NS	4.43±1.78	NS
Serum total Ca ²⁺ , mmol/L	2.30±0.10	2.38±0.11	0.043	0.051	2.38±0.11	NS	2.34±0.09	NS
Serum ionized Ca ²⁺ , mmol/L	1.18±0.04	1.21±0.03	0.05	NS	1.19±0.04	NS	1.19±0.03	NS
Serum ionized Mg ²⁺ , mmol/L	0.83±0.05	0.84±0.06	0.027	NS	0.83±0.04	NS	0.81±0.04	NS
Serum phosphorus (IP), mmol/L	0.99±0.14	0.96±0.15	NS	NS	1.06±0.20	0.004	0.91±0.13	0.025
25 OH vitamin D, nmol/L	44.6±27.3	46.5±22.2	NS	NS	54.4±20.4	NS	47.2±22.0	NS
1–25 OH vitamin D, pmol/L	101.8±33.1	76.3±40.3	NS	NS	101.3±36.8	NS	95.9±32.9	NS
Urinary Ca ²⁺ excretion, mmol/24 h	5.66±3.4	4.11±2.3	0.038	NS	4.19±2.10	NS	8.53±28.84	NS
Urinary phosphorus excretion, mmol/24 h	24.70±12.1	28.80±10.30	0.004	NS	23.28±9.30	NS	31.38±32.61	NS
Urinary deoxyypyridinoline, nmol/mmol of creatinine	6.18±1.32	5.62±1.23	NS	NS	7.03±2.45	NS	6.11±3.67	NS

Data expressed in mean±SD. NS indicates not significant; PTH, parathyroid hormone; BAH, bilateral adrenal hyperplasia; APA, aldosterone-producing adenoma; PH, primary (essential) hypertension. Normal values are as follows: PTH intact, 10–65 ng/L; serum Ca²⁺, 1.19–1.29 mmol/L; serum Mg²⁺, 0.70–1.05 mmol/L; serum IP, 0.87–1.45 mmol/L; 25 OH vitamin D, 75–250 nmol/L; 1–25 OH vitamin D, 43–148 pmol/L; urinary Ca²⁺ excretion, 2.5–7.5 mmol/24 h; urinary phosphorus excretion, 12.9–42.0 mmol/24 h; urinary deoxyypyridinoline, 3.0–7.4 nmol/mmol creatinine.

than in the other 2 groups at baseline and fell significantly after adrenalectomy. This was accompanied by a decrease of urinary Ca²⁺ excretion and an increase of urinary phosphorus excretion and by a small but statistically significant increase of ionized Ca²⁺ and Mg²⁺, whereas serum 25OH vitamin D levels did not change after adrenalectomy.

Figure 1 shows the serum PTH levels in the cohorts of PA and PH patients (Figure 1A) and in the PA patients divided according to subtype into BAH and APA (Figure 1C). The corresponding receiver operator characteristic curves of serum PTH and, for reference, of the ARR for identifying PA from the patients with PH are shown in the box and whisker plots and in Figure 1B and 1D. These curves showed that, for identification of PA among hypertensive patients, the 2 tests performed equally well, with a slight nonsignificant advantage for the ARR (Figure 1D). At variance, for discriminating between patients with APA or BAH, the AUC of the receiver operator characteristic curve for PTH was significant higher than that for ARR (Figure 1D). This finding was not unexpected, because PTH was elevated only in patients with APA.

For all of the receiver operator characteristic curves, the dashed line and square dot, respectively, identifies the Youden Index, which corresponds with the value providing the best tradeoff of sensitivity and specificity. For the discrimination between BAH and APA, the Youden Index of PTH was 80 ng/mL, which corresponded with a sensitivity and a specificity of 74% and 82%, respectively. Hence, overall these findings indicate that, whereas both the ARR and serum PTH are useful for pinpointing the PA patients in our population of referred hypertensive patients, only PTH is useful for discriminating between APA and BAH patients.

Discussion

In this study we followed the recommendations of the Standards for Reporting of Diagnostic Accuracy committee²⁵

in that we used an unequivocally established diagnosis of APA as reference test (gold standard) to examine the diagnostic accuracy of novel, for example, serum PTH levels, as compared with an established test, for example, the ARR, for case detection of PA.¹ We found that, at variance with the ARR, which is known to be elevated in both APA and BAH patients albeit more so in the former than in the latter, PTH was found to be elevated only in the APA patients. A formal assessment of the accuracy of serum PTH, which was never used for distinguishing between PA and PH patients before, showed an AUC that was worse, but not significantly so, than that for the ARR (Figure 1B). However, when PTH was used only in patients who had received a biochemical diagnosis of PA for distinguishing between APA and BAH (Figure 1D), the AUC was not only higher than the AUC of the identity line but also than that of the ARR. These findings indicate that serum PTH is useful for discriminating between subtypes of PA. Hence, once PA has been demonstrated by use of the ARR,²¹ the measurement of PTH could be useful to decide whether to submit the patients to AVS, as indicated in the purposed algorithm (Figure 2). This gain of diagnostic information can be particularly important for those centers where AVS procedure is not readily available and systematically used.²⁶

Some plausible explanation can be offered as to why PTH is elevated in APA patients.^{7,17} Infusion of aldosterone in uninephrectomized rats submitted to a 1% NaCl intake showed that the hypercalciuria that accompanies the natriuresis occurring during the aldosterone escape phenomenon lowers ionized serum calcium and thereby triggers the release of PTH.¹⁷ This was suggested to occur also in human PA³ and was supported by the observation of a greater fall of serum ionized Ca²⁺ and a greater increase of PTH with a saline infusion in PA than in PH patients.²⁷ Our finding of a significant fall of urinary Ca²⁺ excretion and of an increase of

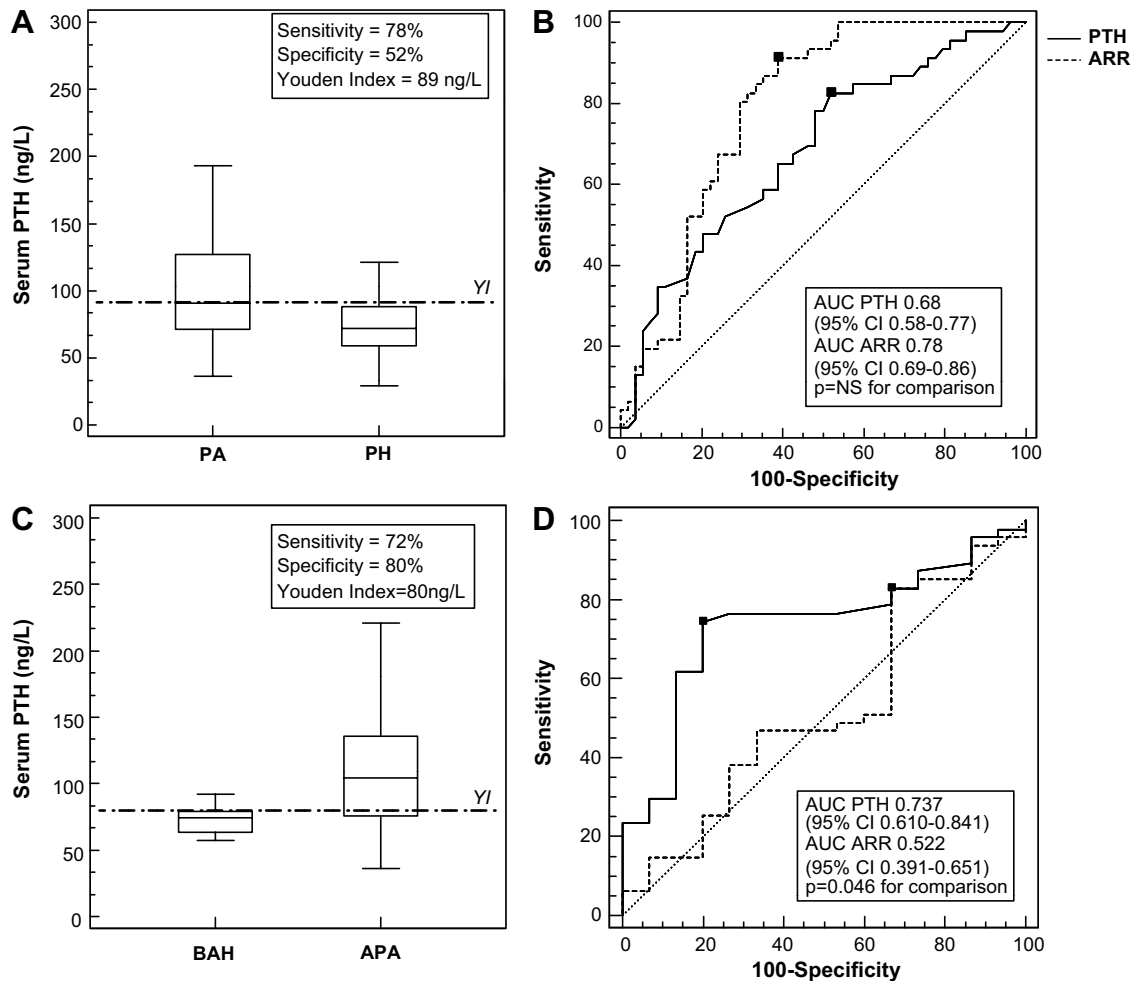


Figure 1. The box and whisker plots show the serum parathyroid hormone (PTH; **solid line**) values in the hypertensive patients with primary aldosteronism (PA), in those with primary hypertension (PH; **A**), and in those with an aldosterone-producing-adenoma (APA) because of bilateral adrenal hyperplasia (BAH; **C**). The corresponding receiver operator characteristic (ROC) curves are shown in **B** and **D**, respectively. In the box and whisker plot (**dashed line**) and on the ROC curves (**square dots**), the Youden Index (YI), for example, the serum PTH values corresponding with the highest accuracy (YI) are also shown. Please note that, whereas PTH and the ARR performed similarly for the identification of PA among patients with high blood pressure, only PTH provided a discrimination between APA and BAH (**B** and **D**).

serum ionized Ca^{2+} after adrenalectomy (Table 2)⁷ also reinforces this interpretation. At variance with this contention we could find neither overt ionized hypocalcemia nor hypercalciuria at a chronic stage of PA (Table 2). Hence, it is likely that additional mechanisms intervene as, for example, an increased sensitivity to ionized calcium lowering of the parathyroid cells, as reported recently.⁷ Relevant to the present study is, however, the fact that both in ours and in others' hands,² the elevation of PTH was corrected by adrenalectomy (Table 2), thus providing evidence for a direct causal relation between the tumorous form of PA and the increase of PTH.⁸

Some limitations must be appreciated in this study: because it included no cases of multinodular adrenocortical hyperplasia,^{1,7} whether PTH elevations could help in the identification of this condition, which is also surgically curable, remains to be demonstrated. It has to be acknowledged that, because ours is a referral center for the most severe and/or difficult-to-treat cases of high BP, the present series included a high proportion of patients with PA. Hence, it remains to be verified whether the same elevation of PTH is present also in less selected popula-

tions of hypertensive patients in whom the prevalence of PA could be lower than in this series. Based on the evidence herein furnished, further research on larger series of patients with surgically curable and not surgically curable subtypes of PA is, therefore, warranted.

Conclusions

In conclusion, this study with the strength of a design following the recommendations of the Standards for Reporting of Diagnostic Accuracy Committee²⁵ suggests that the measurement of serum PTH in patients with biochemically confirmed PA could be useful for the identification of those who are more likely to have the surgically curable APA to be submitted to AVS.

Perspectives

The increase serum levels of PTH in patients with the tumorous subtype of PA adds another piece of information to the puzzle of the relationships between 2 endocrine glands, the parathyroid and the adrenocortical zona glomerulosa,

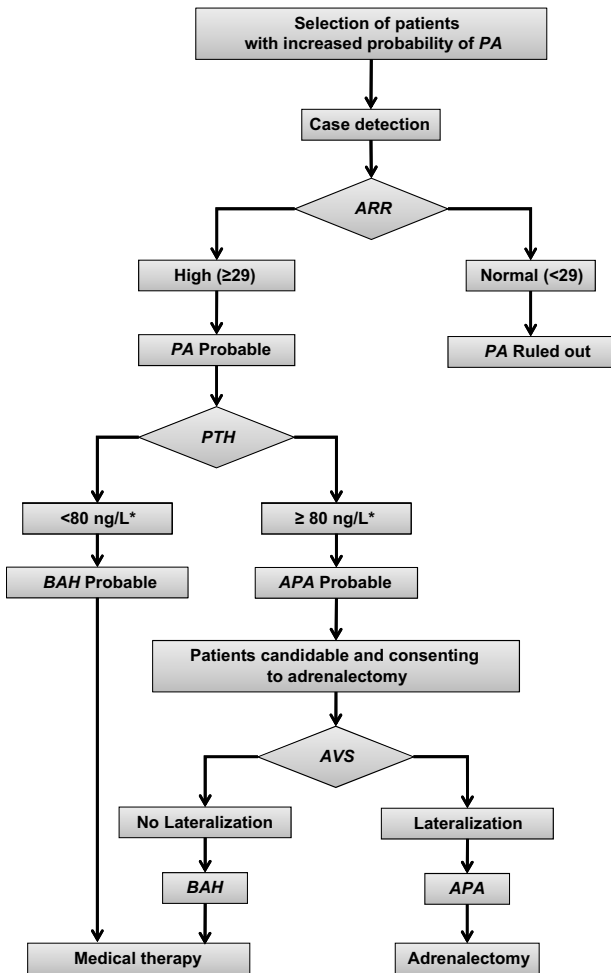


Figure 2. Suggested algorithm for selection of the primary aldosteronism (PA) patients to be submitted to adrenal vein sampling (AVS) according to parathormone level (*1–84 intact parathyroid hormone [PTH]) in patients with high aldosterone:renin ratio (ARR). BAH indicates bilateral adrenal hyperplasia; APA, aldosterone-producing adenoma.

which have been regarded as independent thus far.^{9,10} Moreover, given the emerging evidence implicating hyperparathyroidism as a cardiovascular risk factor,¹⁰ it could be that the high serum PTH found in this study contributes both to the excess cardiovascular damage and to the persistent hyperaldosteronism of PA patients. Therefore, the provoking findings of this study should prompt further research on a larger population of different ethnicities with the aim of conclusively proving whether raised PTH is a marker of APA.

Sources of Funding

This study was supported by research grants from the Foundation for Advanced Research in Hypertension and Cardiovascular Diseases, the Società Italiana dell’Ipertensione Arteriosa, the University of Padua Research Projects Program, and the International PhD Program in Arterial Hypertension and Vascular Biology of the University of Padua.

Disclosures

None.

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Novelty and Significance

What Is New?

- Serum PTH is elevated in primary aldosteronism caused by aldosterone-producing adenoma.
- It is not elevated in primary aldosteronism due to BAH.
- Hence, it is useful in the differential diagnosis between the surgically curable and incurable subtypes of primary aldosteronism.

What Is Relevant?

- Guidelines recommend that AVS be offered to all patients who are candidates for adrenalectomy.

- However, it is expensive and not available for all patients in most centers.
- Hence, PTH is useful for selecting the patients for AVS.

Summary

An elevated serum PTH could be useful for identifying the surgically curable subtypes of primary aldosteronism.