

Editorial

Primary Hyperaldosteronism.....it's not about which side to take!

Primary hyperaldosteronism (PA) is one of most common causes of surgically remediable hypertension. The incidence of PA is much higher (5-10%) compared to what was previously (<1%) reported.¹ Patients with PA are at a greater risk for development of cardiovascular morbidity and mortality, renal and metabolic complications when compared to other hypertensive patients.² The most common causes of PA are aldosterone producing adenomas (APA), unilateral and bilateral diffuse hyperplasia (DH). Sixty percent of patients with aldosterone over production have bilateral disease, and mineralocorticoid antagonists are the treatment of choice whereas, 40% have unilateral disease and may be cured by unilateral laparoscopic adrenalectomy (LA). Unilateral adrenal hyperplasia (UAH) is a rare entity. Recently a Swedish study showed that 50 patients were detected to have UAH postoperatively.³ The long term follow-up data on postoperative adrenalectomy for cases of UAH is limited. A retrospective study from China reported unilateral LA in 164 patients. Following surgery, blood pressure normalised in 54%, improved in 44% and hypokalemia resolved in all patients.⁴

Preoperative work-up is critical for distinguishing unilateral from bilateral disease. Aldosterone-renin ratio (ARR) is the most sensitive screening test for PA but the levels may be altered depending on the testing conditions, medications, variable assay methods and different cut-off levels for diagnosis. An elevated ARR >30 along with PAC >20 ng/dL is now universally accepted as a further confirmatory test in patients with PA. Hypokalemia as a screening test has low sensitivity and even the presence of hypokalemia has low negative predictive value. The commonly used confirmatory tests are saline infusion test (SIT), oral sodium loading test, fludrocortisone suppression test, and Captopril challenge test. There is no single gold standard confirmatory test for PA, thus patients usually required more than one test to establish the diagnosis. Confirmatory tests that are also helpful in ruling out false ARR positive cases and thereby one can avoid invasive procedures like adrenal venous sampling (AVS). There is no single gold standard confirmatory test for PA as reliability, sensitivity and specificity varies, as shown by different studies. A prospective study from Italy showed that on the saline infusion test aldosterone with a cut-off of >6.8ng/dL has moderate sensitivity and specificity in discriminating between APA and idiopathic bilateral hyperplasia (IHA).⁵

An adrenal computed tomography (CT) is the initial test of choice for localizing and sub-typing of aldosterone producing tumors. The CT scan finding in PA can be classified into cross-sectional image positive lesions which include APA and aldosterone producing carcinoma. The image negative PA includes unilateral micro-APA (<1 cm), UAH, IHA, multiple adrenocortical micronodule (MN) and bilateral macro- or microadenomas (or a combination of the two). The APA is typically characterized by a <2 cm size unilateral hypodense lesion (Hounsfield units <10) on CT scan. However, in the elderly (>35 years) a non-functioning adenoma is not uncommon, and can mimic APA on a CT scan. The AVS is essential in such cases to rule out APA. The CT scan findings may be normal or show nodular changes in patients with IHA. It also had several limitations and micro-APA is often incorrectly reported as normal or IHA. On the other hand the CT scan is often normal in subjects with UAH and MN and given the limitations of CT scans, further lateralization of aldosterone excess production by AVS is critical. A study from the Mayo clinic studied the accuracy of CT and AVS in 203 patients with PA. Both CT scan and AVS correctly identified unilateral disease in 53% of patients. A CT scan alone could have resulted in unnecessary adrenalectomy in one-fourth and one-fifth of patients who have been cured by unilateral adrenalectomy (UA) might have been incorrectly excluded.⁶ Magnetic resonance imaging (MRI) has no added advantage over CT scan in characterising the lesion. A systematic review has shown that CT scan and MRI misdiagnose PA in 40% of cases while AVS shows definite lateralization.⁷



Dukhabandhu Naik



Nihal Thomas

Adrenal venous sampling remains the gold standard test for lateralization. Many groups recommend sequential sampling with continuous cosyntropin (ACTH) infusion during AVS due to minimal stress induced fluctuation in aldosterone secretion. With the continuous cosyntropin infusion selectivity index (cortisol adrenal/ cortisol IVC) of >5 and lateralization index (cortisol corrected aldosterone ratio of >4 is used for unilateral aldosterone excess , without the ACTH stimulation selectivity ratio (Ca/ C ivc) of >2 and lateralization ration of (A/C dominant /A/C nondominant) >2 used for unilateral aldosterone excess.⁸ The AVS has several limitations, it is costly, more invasive, technically challenging due to anatomical variations, needs an expert interventional radiologist and the availability of cosyntropin. The success rate of AVS was documented to be only 31-61% from the German Coons Registry group.⁹ The intra-procedural cortisol assay (IPCA) can improve the AVS success rate and in a recent study the new quick gold nano-particle cortisol assay was used to improve the outcome.¹⁰ On the other hand, the AVS is not mandatory in young hypertensive patients (<35 years) with a typical clinical presentation and CT scan showing typical features of cortical adenoma. Medical treatment should be considered in patients not willing for surgery or no candidates for surgery and AVS should be avoided in these patients.

Recently published data on surgery for primary aldosteronism surgery outcomes (PASO) looks at complete, partial and absent successes on six outcome variables (Blood pressure, use of anti-hypertensive drugs, plasma potassium level and aldosterone concentration, and plasma renin concentrations and activities among 705 patients with unilateral LA. Complete clinical success was achieved in 37% and partial clinical success in 47% and 94% had complete biochemical success. Younger and female patients had better outcomes overall.¹¹ Similarly, a study from Italy prospectively compared the effect of unilateral adrenalectomy (n-110) versus medical treatment (n-70) on blood pressure and left ventricular hypertrophy for a median period of 36 months. Patients with adrenalectomy had a lower anti-hypertensive requirement and markedly decreased left ventricular mass.¹² In the Swedish study, patients with UAH showed a reduction in the number of anti-hypertensive agents and a resolution of hypokalemia.³

Iodocholesterol scintigraphy (NP-59) is another mode of lateralization, however, this test is no longer being used in many countries because of its poor sensitivity. The data on ¹¹C-Metomidate PET-CT based lateralization has also limited value and is not routinely recommended for localization.

Even after proper lateralization, some patients do not get cured following adrenalectomy probably due to bilateral disease. Therefore, postoperatively a proper distinction between APA and DH is essential to predict the outcome. With routine histopathology it is sometimes difficult to distinguish between APA and DH. Thus, Immuno histochemistry (IHC) and *in situ* hybridization can clearly distinguish between cases with an unequivocal diagnosis. Yamazaki et al¹³ showed that CYP-11 B-2 IHC may clearly differentiate between MN and DH.¹³ Recently the gain of somatic mutation of KCNJ5, ATP1A1, ATP2B3, CACNA1D, and CTNNA1 have been detected 50-80% of patients with APA. Identification of these mutations in sporadic APA has no clinical implications in the management as the role of these genetic mutations in tumor pathogenesis is not yet clear.⁸

In the current issue of this journal hypertensive patients with PAC/PRA ratio of >50 had undergone case detection testing. The SIT with an aldosterone levels $>5\text{ng/ml}$ along with 24 hours urinary sodium excretion greater than 200 mmol/day was used for case confirmation. On AVS, 14 patients had unilateral aldosterone excess and all patients undergone transperitoneal laparoscopic adrenalectomy. A large proportion of patients 12/14 (86%) had histopathological findings demonstrating nodular hyperplasia and only 2(14%) had adenoma. All patients with nodular hyperplasia were detected to have unilateral lesions on CT scan. In this study, investigators have highlighted that AVS remains the gold standard for lateralization of aldosterone over production. Investigators have also shown that there is an overall decrease in the mean blood pressure, decrease in the number of anti-hypertensive agents and improvement in potassium level on those with dominant adrenalectomy.

Though the study had some limitations that include a small study population and no continuous cosyntropin infusion was used during AVS procedure. Adrenal venous sampling with continuous cosyntropin infusion with current criteria for lateralization could better distinguish an adenoma from diffuse hyperplasia. The decision of adrenalectomy should be considered after integrating the clinical, biochemical, radiological and AVS findings. Unilateral AH is no more a rare entity. Currently, retroperitoneal adrenalectomy is the preferred procedure over the transperitoneal approach. Moreover, UAH may not totally rule out bilateral disease in patients with

unilateral dominant aldosterone production. Immunohistochemistry with (CYP- 11B2) is helpful in the diagnosis of aldosterone over production and subtype classifications. Unilateral Laparoscopic adrenalectomy is safer and cost beneficial over long term medical treatment in patients with PA.¹⁴

REFERENCES

1. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol* 2006;48(11):2293–300.
2. Varano M, Iacono P, Tedeschi MM, Letizia C, Curione M, Savoriti C, et al. Comparisons of microvascular and macrovascular changes in aldosteronism –related hypertension and essential hypertension. *Sci Rep* 2017 Jun ;7(1):2666. doi: 10.1038/s41598-017-02622-2.
3. Sigurjonsdottir HA, Gronowitz M, Andersson O, Eggertsen R, Herlitz H, Sakinis A, et al. Unilateral adrenal hyperplasia is a usual cause of primary hyperaldosteronism .results from a Swedish screening study. *BMC Endocr Disord* 2012 Sep ;12:17. doi: 10.1186/1472-6823-12-17.
4. Jiang SB, Guo XD, Wang HB, Gong RZ, Xiong H, Wang Z, et al. outcomes analysis of surgical and medical treatment for patients with primary aldosteronism. *Int Urol Nephrol* 2014 Jul;46(7):1283-8.
5. Rossi GP, Belfiore A, Bernini G, Desideri G, Fabris B, Ferri C, et al. Prospective evaluation of the saline infusion test for excluding primary aldosteronism due to aldosterone producing adenoma . *J Hypertens* 2007 Jul;25(7):1433-42.
6. Young WF, Stanson AW, Thompson GB, Grant CS, Farley DR, van Heerden JA. Role for adrenal venous sampling in primary aldosteronism. *Surgery* 2004 Dec;136(6):1227-35.
7. Kempers MJ, Lenders JW, van Outheusden L, van der Wilt GJ, Schultze Kool LJ, Hermus AR, et al . Systematic review : diagnostics procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. *Ann Intern Med* 2009 Sep 1;151(5):329-37.
8. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The Management of Primary Aldosteronism: case detection, Diagnosis, and treatment : an Endocrine Society Clinical Practical Guideline : *J Clin Endocrinol Metab* 2016 May;101(5):1889-916.
9. Vonend O, Ockenfels N, Gao X, Allolio B, Lang K, Mai K, et al. Adrenal venous sampling : evaluation of the German Coon’s registry. *Hypertension* 2011 May;57(5): 990-5.
10. Yoneda T, Karashima S, Kometani M, Usukura M, Demura M, Sanada J ,et al. Impact of new quick gold nanoparticle- based cortisol assay during adrenal vein sampling for primary aldosteronism. *J Clin Endocrinol Metab* 2016 june ;101(6):2554-61.
11. Williams TA, Lenders JWM, Mulatero P, Burrello J, Rottenkolber M, Adolf C, et al. Outcomes after adrenalectomy for unilateral primary aldosteronism : an international consensus on outcome measures and analysis of remission rates in international cohort. *Lancet Diabetes Endocrinol* 2017 May 30. pii: S2213-8587(17)30135-3.
12. Rossi GP, Cesari M, Cuspidi C, Maiolino G, Cicala MV, Bisogni V, et al. Long term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. *Hypertension* 2013 july;62(1):62-9.
13. Yamazaki Y, Nakamura Y, Omata K, Ise K, Tezuka Y, Ono Y, Morimoto R, Nozawa Y, Gomez-Sanchez CE, Tomlins SA, Rainey WE, Ito S, Satoh F, Sasano H. Histopathological classification of cross –sectional image negative hyperaldosteronism. *J Clin Endocrinol Metab* 2017 Apr 1;102(4):1182-119.
14. Christakis I, Livesey JA, Sadler GP, Mihai R. Laparoscopic Adrenalectomy for Conn’s syndrome is beneficial to patients and is cost effective in Enlgand. *J Invest Surg* 2017 May 12:1-7.

Dukhabandhu Naik MD, DM

Assistant Professor

Department of Endocrinology, Diabetes and Metabolism
Christian Medical College, Vellore, Tamil Nadu, India

Nihal Thomas MD, MNAMS, DNB

FRACP, FRCP, FRCP, FRCP, PhD

Department of Endocrinology, Diabetes and Metabolism
Christian Medical College, Vellore, Tamil Nadu, India