



Adrenal ablation therapy for unilateral primary aldosteronism: pros and cons

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Primary aldosteronism (PA) is one of the most prevalent causes of endocrine hypertension [1–3]. A recent meta-analysis on the prevalence of PA showed that 4.3% of hypertensive patients in a primary care setting and 9.0% of referred patients had confirmed PA. Patients with PA present with high plasma aldosterone concentration, suppressed plasma renin activity or concentration, and salt-sensitive hypertension. Compared to age- and sex-matched essential hypertensive patients with similar extents of hypertension, PA patients show significantly higher cerebro- and cardiovascular comorbidities [1–4]. The two most common subtypes of PA are aldosterone-producing adenoma (mostly unilateral) and bilateral adrenal hyperplasia. The former subtype shows markedly high plasma aldosterone concentration, suppressed plasma renin activity, spontaneous hypokalemia, and frequently resistant hypertension, whereas the latter subtype shows a milder clinical phenotype, including mild hypertension, normal to high plasma aldosterone concentration and normokalemia. Based on clinical practice guidelines, laparoscopic unilateral adrenalectomy is recommended for unilateral PA, whereas medical treatment with MR antagonists is recommended for bilateral PA as well as patients who do not desire surgery or are not eligible for surgery.

Recently, increasing numbers of papers have been published with regard to alternative therapies for unilateral PA other than conventional unilateral laparoscopic adrenalectomy. These include CT-guided radiofrequency ablation (RFA), transvenous RFA, catheter-based adrenal ablation (transarterial embolization) and medical therapy with a

mineralocorticoid receptor (MR) antagonist (Fig. 1). Since treatment with MR antagonists is a lifelong treatment and not fundamental, alternative therapies are needed, particularly for unilateral PA patients who refuse surgery and cannot tolerate MR antagonist therapy.

There have been several previous reports comparing CT-guided RFA with unilateral adrenalectomy for unilateral PA [5–8]. All these studies were small, retrospective non-randomized studies. No studies adjusted the cure rate with the pretreatment features of the patients in both groups. Liu and coworkers [5] compared 27 and 36 patients who underwent adrenalectomy and RFA, respectively, and patients chose the therapy they preferred. A higher cure rate was observed in the adrenalectomy group (70.4% vs. 36.1%, $p = 0.007$). Laparoscopic adrenalectomy was more effective in most series, but the difference was only statistically significant in one study [5]. Treatment selection is

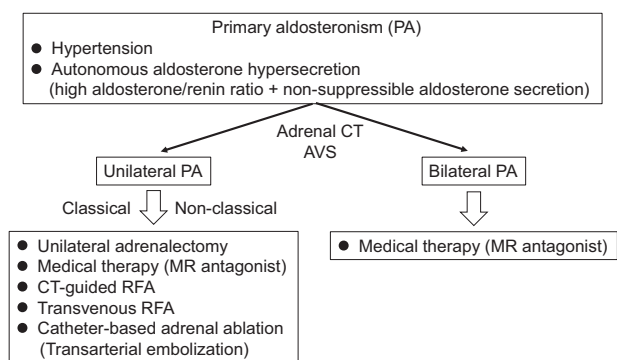


Fig. 1 Algorithm of lateralizing diagnosis and management of primary aldosteronism. Lateralizing diagnosis should be performed based on the findings of adrenal CT and adrenal vein sampling (AVS). For unilateral primary aldosteronism, laparoscopic unilateral adrenalectomy is the treatment of choice in principle; however, there are alternative therapies, such as CT-guided or transvenous radiofrequency ablation and catheter-based transarterial embolization. Medical therapy, including MR antagonists, can be administered to either subtype of patients

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another important problem in published studies. All previously published articles provide unadjusted data without considering possible confounding variables.

Sakakibara et al. [9] reported an experimental study using transvenous RFA of the adrenal gland in animal models. Catheter-based RFA may be another option for unilateral PA, but its effectiveness and safety in humans remain to be established.

Recently, 'unilateral PA' has been considered not that simple because there are several histopathological subtypes in 'unilateral PA' based on the International Histopathology Consensus for unilateral PA [10]. Unilateral PA is classified into two types: classical and nonclassical. The former refers to solitary macro- or micronodules that stain for both hematoxylin-eosin and CYP11B2, with no additional extranodular staining. The latter refers to any other variant, including multiple micronodules, nodules or hyperplasia negative for HE but positive for CYP11B2. Functional aldosterone-producing cells can be distributed all around the gland (hyperplasia) or in small areas (micronodules/clusters), even in patients with macroscopic nodules.

From a histopathologic point of view, laparoscopic adrenalectomy appears to be more effective than CT-guided RFA for the treatment of unilateral PA. As RFA is performed to treat only macroscopic nodules, the clinical success rate is dependent on how aldosterone-producing cells are distributed in the adrenal gland, which is not possible to determine before adrenalectomy. It is therefore likely that RFA of a macroscopic nodule in a patient with adrenal micronodule/clusters or hyperplasia would not be enough to cure PA.

Second, another possible advantage of adrenalectomy is the fact that it is followed by a histological study of the adrenal gland. 'Nonclassical' forms would be more likely than 'classical' forms to have a bilateral feature, which may result in a lower cure rate than the 'classical' form.

Interestingly, a recent article published by Sun et al. [11] in Hypertension Research compared the clinical and biochemical outcomes of adrenalectomy ($n=52$) with catheter-based adrenal ablation (transarterial embolization) ($n=60$) for unilateral aldosterone-producing adenoma patients at 6 months of treatment. According to the primary aldosteronism surgical outcome criteria, complete and partial clinical success (remission of hypertension) was achieved in 21 (40.4%) and 23 (44.2%) patients in the ablation group vs. 33 (55.0%) and 23 (38.3%) patients in the adrenalectomy group, respectively. Complete and partial biochemical success (improvement of serum potassium and plasma renin) was achieved in 30 (57.7%) and 17 (32.7%) patients in the ablation group vs. 51 (85.0%) and 5 (8.3%) patients in the adrenalectomy group, respectively. The complete biochemical success rate but not the complete clinical success rate was significantly higher in the

adrenalectomy group. Hypertension duration and baseline serum potassium level were associated with clinical success by adrenal ablation. Compared with surgery, adrenal ablation requires a shorter operating time and time to resume physical activity. Based on these findings, the authors conclude that catheter-based adrenal ablation may be a feasible alternative for unilateral PA patients unwilling to undergo surgery.

There are several concerns in this study. First, patients selected the treatment option they preferred after counseling; this was not a randomized controlled study. This would add selection bias. Second, the gold standard of lateralizing diagnosis would be adrenal vein sampling; while this was done in all 52 cases with adrenal ablation, it was done in only 15 (25%) of 60 cases with unilateral adrenalectomy. Therefore, the evaluation of clinical success in the adrenalectomy group was heavily affected by the accuracy of lateralizing diagnosis. Third, excessive unilateral lesion was diagnosed when the lateralization index was >2 . This cutoff value was slightly lower than that of other clinical practice guidelines [2, 3], for which the most prevalent cutoff value of the lateralization index was more than 4. Despite these concerns, the results of this study suggest that catheter-based adrenal ablation may be an alternative for patients with adrenal vein sampling-confirmed unilateral PA. While this study recruited unilateral PA patients with macroscopic nodules upon CT, the approach used here may be applied to cases even in the absence of macroscopic nodules upon CT because, unlike RFA, the transarterial approach does not require macroscopic nodules.

The Chongqing Endocrine Hypertension Collaborative Team conducted several other studies. Zhang et al. [12] reported a prospective cohort study of catheter-based adrenal ablation in 36 PA patients without apparent aldosteronoma. Complete and partial clinical success was achieved in 9 (25.0%) and 13 (36.1%) patients, respectively. Complete biochemical success was achieved in 16 cases (44.4%). Zhao et al. [13] compared adrenal ablation therapy ($n=26$) with medical therapy with spironolactone 20–60 mg daily ($n=25$). Both adrenal ablation and medication could reduce blood pressure levels in PA patients, but adrenal ablation could also significantly reduce the defined daily dose of antihypertensive drugs and plasma aldosterone concentrations. Adrenal ablation achieved 81% complete or partial hypertension remission plus biochemical improvement and did not cause serious complications, such as adrenal insufficiency. Taken together with these data, catheter-based adrenal ablation may be an option for unilateral PA. A randomized controlled trial of catheter-based adrenal ablation is definitely required in the future. As this procedure is now performed in very select centers worldwide and was developed not so long ago, it should be used cautiously as an alternative for unilateral PA after sufficient

counseling. For now, laparoscopic adrenalectomy remains the treatment of choice for unilateral PA.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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