

Approach to the surgical management of primary aldosteronism

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Abstract: Primary aldosteronism (PA) is the most common cause of endocrine hypertension; it has been reported in more than 11% of referred hypertensive patients. PA may be caused by unilateral adrenal involvement [aldosterone producing adenoma (APA) or unilateral adrenal hyperplasia (UAH)], and bilateral disease (idiopathic adrenal hyperplasia). Only patients with unilateral adrenal hypersecretion may be cured by unilateral adrenalectomy, while patients with bilateral and non-surgically correctable PA are usually treated by mineralocorticoid receptor antagonists; thus the distinction between unilateral and bilateral aldosterone hypersecretion is crucial. Most experts agree that the referral diagnostic test for lateralization of aldosterone hypersecretion should be adrenal venous sampling (AVS) because the interpretation of other imaging techniques [computed tomography (CT), magnetic resonance imaging (MRI) and scintigraphy] may lead to inappropriate treatment. Adrenalectomy represents the elective treatment in unilateral PA variants. Laparoscopic surgery, using transperitoneal or retroperitoneal approaches, is the preferred strategy. Otherwise, the indications to laparoscopic unilateral total or partial adrenalectomy in patients with unilateral PA remain controversial. Adrenalectomy is highly successful in curing the PA, with correction of hypokalemia in virtually all patients, cure of hypertension in about 30-60% of cases, and a marked improvement of blood pressure values in the remaining patients. Interestingly, in several papers the outcomes of surgery focus only on blood pressure changes and the normalization of serum potassium levels is often used as a surrogate of PA recovery. However, the goal of surgery is the normalization of aldosterone, because chronically elevated levels of this hormone can lead to cardiovascular complications, independently from blood pressure levels. Thus, we strongly advocate the need of considering the postoperative normalization of aldosterone-renin ratio (ARR) as the main endpoint for determining outcomes of PA.

Keywords: Adrenalectomy; hypertension; hypokalemia; laparoscopy; primary aldosteronism (PA)

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Introduction

Primary aldosteronism (PA) is an adrenal disease which causes sodium and water retention and potassium excretion, with ensuing hypertension and hypokalemia.

This condition was first described by Litynski in Poland and Conn in the USA (1,2). Recent guidelines have defined PA as “a group of disorders in which aldosterone production is inappropriately high, relatively autonomous from the

renin-angiotensin system, and non-suppressible by sodium loading” (3).

The guidelines recommend case detection of PA by using the aldosterone-renin ratio (ARR) measured under standard conditions, followed by one of four commonly used confirmatory tests (oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge) (3), although the accuracy of these tests has been called into question (4).

Despite being regarded as a very rare (less than 1%) cause of arterial hypertension for several decades, PA has been now recognized to be the most common cause of endocrine hypertension, since it was found to involve more than 11% of referred hypertensive patients (5-8).

Because of its prevalence, and also because patients with PA have higher cardiovascular morbidity and mortality than age-, blood pressure (BP)- and sex-matched patients with essential hypertension (9,10), it is important to search for PA in a systematic way at least in some categories of patients. These include patients with Joint National Commission stage 2 (>160-179/100-109 mmHg), stage 3 (>180/110 mmHg), or drug-resistant hypertension; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension with adrenal incidentaloma; or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years). Case detection is also recommended for all hypertensive first-degree relatives of patients with PA (3) (*Table 1*).

PA may be caused by unilateral adrenal involvement [aldosterone producing adenoma (APA)] (*Figure 1A*), which is considered a surgically curable form, and bilateral adrenal involvement (idiopathic adrenal hyperplasia) that is considered non-surgically curable. APA and idiopathic adrenal hyperplasia were claimed to account for more than 95% of all cases (11), but several studies have recently reported novel variants of surgically treatable PA, including diffuse or nodular unilateral adrenal hyperplasia (UAH) (*Figure 1B*). This variant was previously considered to be a very rare disease (0.1%) (11), but was thereafter found to involve from 8% to 70% of cases of surgically treated PA (12-16).

The normalization of aldosterone is a fundamental goal of treatment, because chronic hyperaldosteronism concurs with high BP in causing cardiovascular complications, including, left ventricular hypertrophy, arterial wall stiffening, metabolic syndrome, renal damage, myocardial infarction and atrial fibrillation (17,18).

The role of lateralizing techniques

Only patients with lateralized adrenal hypersecretion can be cured by unilateral adrenalectomy; hence, the distinction between unilateral and bilateral aldosterone hypersecretion is the key.

To this end adrenal venous sampling (AVS), computerized tomography (CT), magnetic resonance imaging (MRI) and adrenocortical scintigraphy have been used.

AVS was introduced in the late 1960s and became the first test to distinguish unilateral from bilateral PA (19). Adrenocortical scintigraphy, CT and MRI were developed later and were adopted as primary procedures to differentiate unilateral from bilateral adrenal abnormalities, because they are less invasive than AVS.

Adrenal venous sampling

AVS involves the measurement of aldosterone and cortisol levels in the infra-adrenal inferior vena cava and in the adrenal veins of both sides (*Figure 2*). Considering the variability of aldosterone secretion, some experts advocate AVS during exogenous adrenocorticotrophic hormone (ACTH) infusion to maximize cortisol secretion, enhancing the assessment of selectivity of catheterization and to maximize differences of aldosterone between sides (13). Other experts suggest AVS in the early morning, when ACTH secretion peaks (3). Most experts agree that ACTH does facilitate the assessment of selectivity, but may confound the ascertainment of lateralization; to the contrary, a comparative study reported that exogenous ACTH infusion does not improve the detection of unilateral aldosterone hypersecretion if the two adrenal veins are catheterized simultaneously (20).

There is not general agreement regarding the definition of successful selectivity and lateralization in AVS (3). Catheter insertion is considered successful under unstimulated conditions, if cortisol concentrations are 1.1 to 3 times higher in the adrenal veins than in the inferior vena cava or in a peripheral vein. Aldosterone secretion is considered to be lateralized if the aldosterone to cortisol ratio is 2 to 5 times higher on the dominant side than contra-laterally.

AVS has a rate of failure between 3% and 22% (21,22). It is an invasive procedure, which carries a very tiny risk of complications, but requires skilled radiologist to minimize morbidity (23,24). The only clinically relevant complication is the rupture of the adrenal veins (0.6%) which is usually managed with conservative treatment (23).

The key message is that the objective of surgery is to resolve the aldosterone hypersecretion, and not just to remove a nodule. Since aldosterone hypersecretion can occur even with no adrenal enlargement (as detected by CT and MRI), AVS was found to be superior to image-based techniques for surgical decisions, as unilateral hypersecretion may be associated with UAH that can be undetectable on usual imaging techniques (13,22,25).

Recently, some authors tried to develop a score to avoid the use of AVS. Küpers *et al.* published data on a clinical

Table 1 Indications to screen hypertensive patients at risk of primary aldosteronism
Patients with hypertension >160/100 mmHg
Patients with drug-resistant hypertension
Patients with hypertension and spontaneous or diuretic-induced hypokalemia
Patients with hypertension and adrenal incidentaloma
Patients with hypertension and a family history of early-onset hypertension or cerebrovascular accident at age <40 years
Hypertensive first-degree relatives of patients with primary aldosteronism

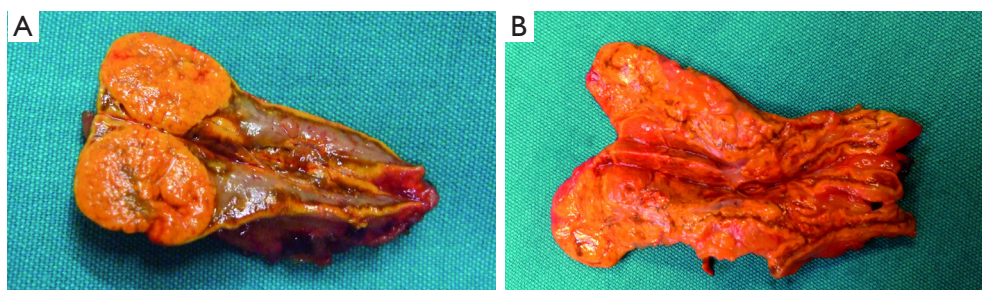


Figure 1 Surgical specimens. (A) Aldosterone producing adenoma; (B) micronodular diffuse hyperplasia.

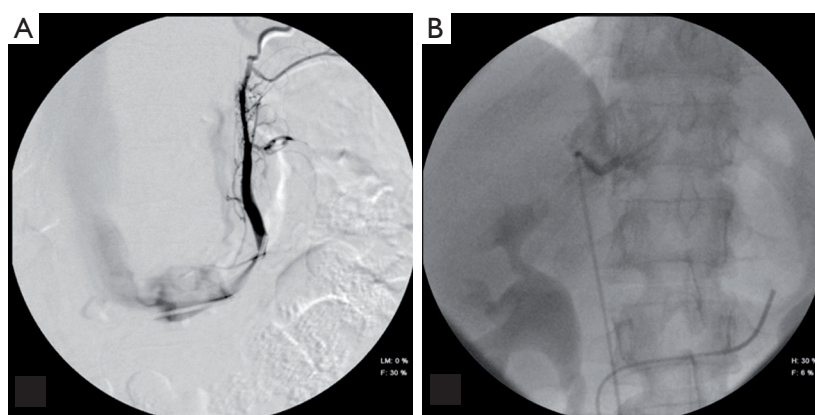


Figure 2 Adrenal venous sampling (angiographic images). (A) Identification of left adrenal vein; (B) simultaneous catheterization of both adrenal veins.

prediction score (CPS), developed to diagnose unilateral PA, using a combination of biochemical and radiological characteristics (26). By applying this score, they reported that 30% of the cohort of patients could potentially have avoided AVS and proceeded straight to surgery. Likewise Sze *et al.* used CPS for a prospectively gathered cohort of patients with PA (27). The results suggest that CPS has the potential to lead to occasional erroneous decision-making regarding patient selection for adrenalectomy and therefore CPS may be useful for clinical decisions only in cases of unsuccessful AVS or in centers where AVS is not available.

Iodo-cholesterol scintigraphy

[¹³¹I] 19-Iodocholesterol scintigraphy was first used in the early 1970s (28). The NP-59 scan [6-¹³¹I] iodomethyl-19-norcholesterol (NP-59), performed with dexamethasone suppression, was introduced in 1977 and had the advantage of correlating anatomical abnormalities with function (29). However, its sensitivity depends heavily on the size and the degree of hyperfunction of the adenoma (30,31). Improved imaging resolution achieved by the introduction of the multiple head gamma camera and Single Photon Emission

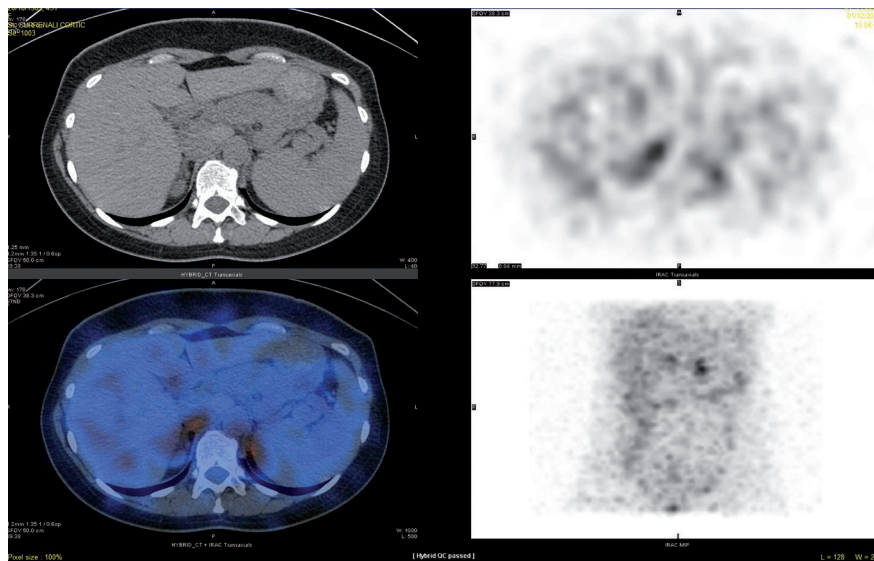


Figure 3 NP-59 scintigraphy SPECT/CT fusion image: bilateral adrenal uptake.

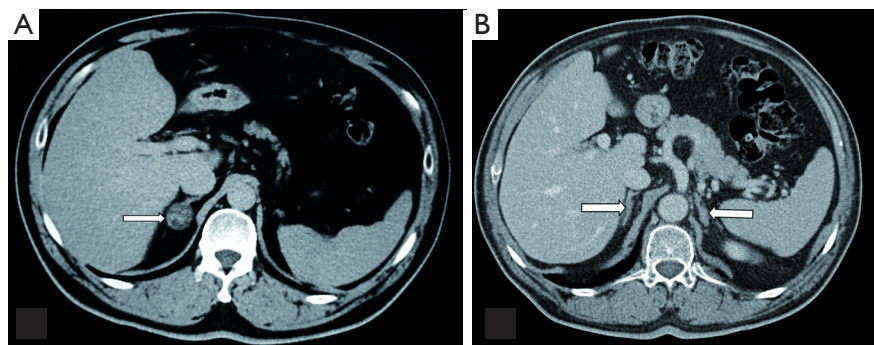


Figure 4 Computed tomography. (A) Right aldosterone producing adenoma (arrow); (B) bilateral adrenal hyperplasia (arrow).

Computed Tomography (SPECT) technique enhanced the ability of NP-59 scintigraphy to detect smaller adrenal lesions (32) (*Figure 3*).

However, because of a poor tracer uptake in adenomas smaller than 1.5 cm in diameter, this technique is often not helpful in interpreting micronodular findings obtained with high-resolution CT (33).

In 2009 a study by Yen *et al.* evaluated the ability of NP-59 scintigraphy to predict the outcome in PA after adrenalectomy (34). The postsurgical outcomes were consistent with the presurgical NP-59 SPECT/CT results: 16 out of 23 patients showed unilateral NP-59 uptake, and 10 of these 16 (62.5%) showed postsurgical improvement; of seven patients with negative NP-59 SPECT/CT results, none showed postsurgical clinical improvement.

In 2014 Lu *et al.* applied a similar approach in a study of

49 patients, of which 40 had an APA and 9 had hyperplasia. They concluded that semiquantification of NP-59 scintigraphy shows an ability similar to AVS in differentiating APA from bilateral idiopathic adrenal hyperplasia and has an excellent ability to predict postsurgical outcomes of adrenalectomy (35).

However, other series have found misleading results in establishing lateralization with NP-59 (36). Moreover, NP-59 is an expensive and time-consuming procedure and its use is limited by the poor availability of the radiotracer (37).

Image-based techniques

CT is the most widely used imaging test (*Figure 4*); although less diffuse, MRI performs similarly (38).

Most aldosterone-producing adenomas are less than

20 mm in diameter (25,39). The presence of a small adrenal nodule in patients with PA suggests the presence of an APA, but it does not exclude the combination of a non-secreting adenoma and idiopathic PA (3,40).

A meta-analysis including 38 studies (6) demonstrated that the proportion of patients with unilateral nodule on CT or MRI imaging, and a bilateral or contralateral secretion documented by AVS, was about 20%.

Since the prevalence of non-secreting adenomas increase with age, their presence is less likely in young patients with PA. Thus, the occurrence of an isolated characteristic adrenal nodule in PA patients aged less than 40 has been proposed as a surrogate for diagnosing unilateral aldosterone hypersecretion (8,13), although results from a recent series do not support this strategy (36).

The guidelines recommend CT in all patients with confirmed PA to detect an adrenal carcinoma, even when an adrenalectomy is not considered (3). However, adrenal carcinomas presenting as isolated PA are rare (2.5% of patients with adrenocortical carcinoma, which represents 0.05-0.2% of all malignancies) (41).

Moreover, CT and MRI results were found to disagree with AVS in a considerable proportion of patients. CT/MRI would show, for example, a unilateral abnormal adrenal gland when aldosterone hypersecretion was occurring in the contralateral gland or bilaterally, or would show bilateral normal or abnormal adrenal glands when aldosterone hypersecretion was occurring in only one gland (22,42-45).

A prospective study of 203 patients showed that operative planning based on anatomical imaging alone would have inappropriately excluded 21.7% of patients from adrenalectomy and would have led to unnecessary surgery in 24.7%, which led to a “renaissance” of AVS (13).

A recent systematic review concluded that when AVS is used as the standard criterion test for the lateralization of aldosterone hypersecretion in patients with PA, CT and MRI may misdiagnose the cause of PA in 37.8% of patients (6).

Thus, most experts now agree that the referral diagnostic test for lateralization of aldosterone hypersecretion is AVS, because the interpretation of other imaging techniques (CT, MRI, adrenocortical scintigraphy) may lead to inappropriate treatment of PA patients (3,6,12,13).

Medical treatment vs. surgery

In APA and other unilateral PA variants, adrenalectomy represents the elective treatment, while the administration of mineralocorticoid receptor antagonists (MRAs) is indicated

for patients with bilateral disease and non-surgically correctable PA. The two main MRAs currently available are spironolactone and eplerenone (46); the guidelines recommend spironolactone as the primary agent for the management of PA, with eplerenone as an alternative (3). Potassium canrenoate and/or canrenone may be also used.

MRAs or potassium chloride are commonly prescribed also to hypokalemic patients with APAs to correct hypokalemia before surgery, in order to avoid the risk of hypokalemia-related arrhythmia during anesthesia (47). The preoperative treatment does not increase the incidence of hypoaldosteronism or hyperkalemia after surgery (48).

Some studies that compared spironolactone to surgery also in patients with APA reported no differences between treatments for the control of either BP or serum potassium concentrations (49). Some studies with long-term follow up seem to suggest that spironolactone may induce a regression of left ventricular hypertrophy (50).

In the few studies on echocardiographic follow-up of PA patients treated by either adrenalectomy or MRAs, adrenalectomy was almost systematically found to rapidly decrease left ventricular mass (LVM), while the effects of MRAs were more controversial (51-54). According to the meta-analysis of five selected studies, there would be no significant difference in LVM change between patients with PA undergoing adrenalectomy or medical treatment with MRAs, despite a greater effect of surgery in reducing BP (55).

However, the impact on the quality of life and costs should be also considered.

In fact, spironolactone has adverse effects such as gynaecomastia, mastodynia, menstrual abnormalities and erectile dysfunction (56); otherwise the newest eplerenone is better tolerated, but more expensive and less effective (57).

A recent study reported that the quality of life would be lower in patients with unilateral PA than in the general population, while administration of spironolactone or amiloride would improve quality of life scores after 6 months. However, the improvement was slower and smaller in medically treated than in operated patients (58).

According to some authors, it remains uncertain whether adrenalectomy for lateralized disease should routinely be offered to PA patients (59). Ideally, a prospective randomized clinical trial could be performed, but it could be extremely challenging to manage, given the large number of patients and the length of the follow-up required to demonstrate a meaningful difference in cardiovascular outcomes.

Reimel *et al.* attempted to compare the cost-effectiveness



Figure 5 Right laparoscopic transperitoneal adrenalectomy: patient position.

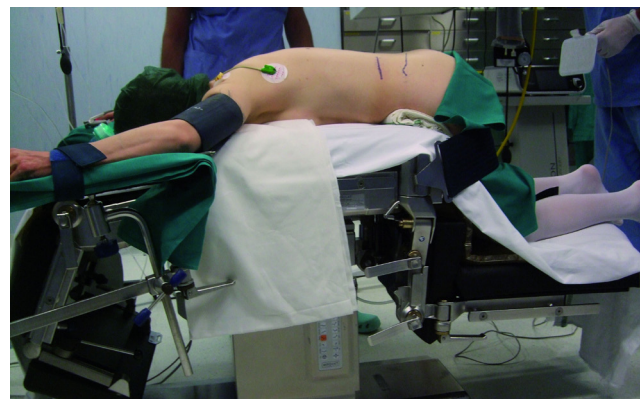


Figure 6 Left retroperitoneoscopic adrenalectomy: patient position.

of a guideline-based surgical strategy with universal pharmacologic management, using a Markov state transition model (60). They demonstrated that screening for PA and resecting an APA was the least costly strategy. Even though most APA patients can be managed medically, in order to make universal pharmacologic therapy the less costly strategy for patients with an approximate 40-year life expectancy, the probability of finding a unilateral APA should be less than 10%; the cost of adrenalectomy should be more than double; the cost of AVS should be more than 4-fold higher than current and the surgical failure rate should be more than sextuple.

Surgical procedures

Open vs. laparoscopic adrenalectomy

Open removal of the aldosterone secreting tumors, by either the transabdominal or the lumbar approach, was unchallenged until 1992, when Gagner, Suzuki and Higashihara published the first series of laparoscopic excision, performed via a transperitoneal approach (61-63). The supine anterior approach was described in 1995 (64), whilst other authors have described the retroperitoneoscopic approach (65,66).

Laparoscopic adrenalectomy (LA), has now been proven to be a safe and effective treatment for PA (67); laparoscopically treated patients have fewer postoperative complications and are equally likely to improve in BP and correct hypokalemia, if present preoperatively, when compared with patients treated with open adrenalectomy. Additional benefits of LA are smaller incisions, decreased

postoperative pain, and a shorter hospital stay (68,69).

In a review by Steichen *et al.*, LA showed a morbidity of 5-14%, a mortality below 1%, and a mean hospital stay around 3 days (70). The increasing confidence in this technique led to proposal for adrenalectomy also in an outpatient setting (71).

Complications of laparoscopic surgery may include conversion to open surgery, hematoma due to intraoperative vascular injury, thromboembolism, pneumothorax or hemothorax.

Adrenalectomy generally results in the normalization of aldosterone secretion and in close to 100% of the cases if patients are selected with AVS, and in a large decrease of BP and antihypertensive medication; however normotension without treatment is achieved only in 42% of cases (70).

Transperitoneal vs. retroperitoneal approach

Laparoscopic surgery using the transperitoneal or retroperitoneal approaches is currently the preferred strategy to treat patients with unilateral PA (72,73) (Figures 5,6).

In general, three recent meta-analyses compared the transperitoneal and retroperitoneal adrenalectomy: two concluded that both techniques have equivalent outcomes (74,75) whereas the other claimed the retroperitoneal approach to be superior in short-term outcomes (76).

In the transperitoneal approach, the procedure is performed with the patient in lateral decubitus flank position. Pneumoperitoneum (at 12-14 mmHg by CO₂) is usually made by Hasson cannula inserted by open technique. A subcostal port is placed for the laparoscope, and two/three other 5/10 mm ports sited.

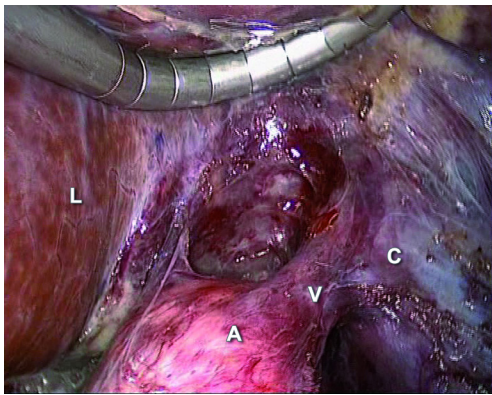


Figure 7 Intraoperative image of right transperitoneoscopic adrenalectomy. A, adrenal gland; C, inferior vena cava; L, liver; V, main adrenal vein.

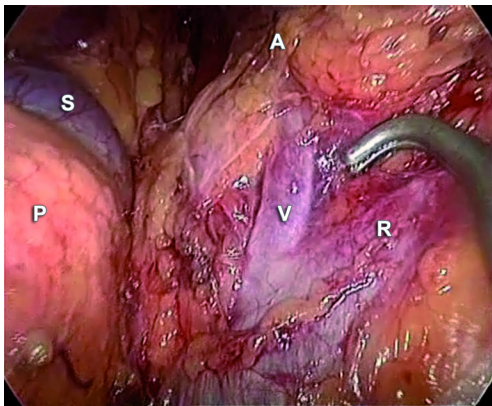


Figure 8 Intraoperative image of left transperitoneoscopic adrenalectomy. A, adrenal gland; P, pancreas; R, renal vein; S, splenic vein; V, main adrenal vein.

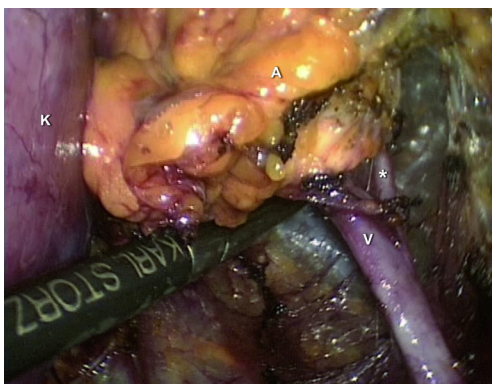


Figure 9 Intraoperative image of left retroperitoneoscopic adrenalectomy. A, adrenal gland; K, kidney; V, main adrenal vein; *, communicating vein between the inferior adrenal vein and left inferior phrenic vein.

For right adrenalectomy the liver is mobilized and retracted during the procedure. The renal vein represents the inferior margin of the dissection and the right main adrenal vein is identified by following the lateral edge of the vena cava. The dissection displays the inferior vena cava and nearby the adrenal gland (*Figure 7*). The main right adrenal vein is identified and divided early. Gland dissection is continued superiorly; the vascular branches from the inferior phrenic vessels, the aorta, and the renal vessels are divided.

On the left side the colonic flexure is mobilized, the splenorenal ligament is dissected to allow the spleen to fall away. As spleen fall medially, the tail of the pancreas and the splenic vein and artery are identified. The peritoneum along the inferior border of the pancreas is divided: an avascular plane separating the adrenal gland from the tail of the pancreas and the splenic vein is opened. The dissection and the traction of the splenic vein allow viewing the inferior adrenal vein, going into the left renal vein (*Figure 8*). The inferior adrenal vein is divided and then the gland is dissected and removed. The inferior phrenic vein runs close to the left adrenal gland and empties into the adrenal vein: it may be preserved or divided. Small arterial vessel from superior, medium and inferior pedicle can be easily coagulated. In all cases, the adrenal gland is removed via a retrieval bag.

In the retroperitoneoscopic approach, the procedure is performed with the patient in the prone position. A 1.5 cm transverse incision just below the tip of the 12th rib is performed. A small cavity is prepared digitally for insertion under finger guidance of one 5 mm trocar 4 to 5 cm laterally. In the same way, a 10 mm trocar is inserted 4 to 5 cm medial to the initial wound. A blunt trocar with an inflatable balloon is introduced into the initial incision and the capnoretroperitoneum is created (at 20-22 mmHg). Following creation of the retroperitoneal space by pushing down the fatty tissue, the upper pole of the kidney is retracted and the area of the adrenal gland exposed.

On the right side, lifting up the adrenal gland, the inferior vena cava is visualized posteriorly; the short right main adrenal vein running postero-laterally becomes visible; thus, it is divided. The preparation of the right adrenal gland is completed by lateral and cranial dissection. For left-sided retroperitoneoscopic adrenalectomy, the adrenal gland vein must be prepared in the space between the adrenal gland and the diaphragmatic branch, medial to the upper pole of the kidney (*Figure 9*). After dissection of the inferior main vein, the preparation of the adrenal gland

is continued medially, laterally, and cranially by lifting the gland at its venous stump. In all cases, the fully mobilized adrenal gland is placed in a retrieval bag and pulled through the initial incision.

Total vs. partial “sparing”adrenalectomy

For a long time, unilateral total adrenal excision has been considered the technique of choice in patients with surgically correctable PA. However, the routine unilateral partial adrenalectomy has also been advocated in order to preserve the remnant adrenal function and avoid potential adrenal insufficiency (77).

This strategy may expose the patient to increased risk of failures because of incomplete excision with subsequent persistent and recurrent PA. Furthermore, Honda *et al.* demonstrated that more than 80% of the adrenal reserve capacity is preserved also after unilateral total adrenalectomy in patients with APA without subclinical or overt Cushing's syndrome, making the risk of corticosteroid replacement after unilateral total adrenalectomy unlikely (78).

Hence, the indication to laparoscopic total or partial adrenalectomy in patients with unilateral PA remains controversial; the risk-to-benefit ratio must be weighed against the potential advantage of partial adrenalectomy.

Walz suggested that APA could be an ideal indication for partial adrenalectomy, because these tumors are almost always benign, small, and often lie eccentrically (79). An endoscopic ultrasound probe has been considered extremely useful for identifying the margin of normal and tumor tissue (73). Some studies suggest that partial adrenalectomy may achieve the biochemical cure of disease in almost all patients.

Nakada and Al-Sobhi reported the results of 26 and 7 adrenal sparing procedures at a mean follow up of 5 years and 1 year, respectively, without any recurrent hyperaldosteronism and with a greater reserve of normal ipsilateral adrenal tissue (80,81).

Jeschke *et al.* reported a series of laparoscopic partial adrenalectomy in 13 patients with APA with a low complication rate along with unremarkable postoperative BP and aldosterone levels (82).

In 2011, Fu *et al.* published the results of a multicenter randomized study comparing retroperitoneoscopic partial to total adrenalectomy for APA in 212 patients, with a mean follow up of 96 months in each group (77). No significant difference in age, gender, adrenalectomy site or tumor size between the two groups were found, although AVS was

performed only in patients with equivocal cross-sectional imaging findings (contralateral adrenal gland enlargement or an adrenal neoplasm smaller than 1 cm). Patients undergoing partial adrenalectomy (n=104) had short and long-term results similar to those who underwent total adrenal excision (n=108). However, they had a greater blood loss that did not require blood transfusions; the authors concluded that retroperitoneoscopic partial adrenalectomy is technically safe and effective in patients with PA due to APA.

By contrast, other authors have reported some failures following partial adrenalectomy. In 2003, Fendrich *et al.* reported a persistent hyperaldosteronism following incomplete adrenalectomy (83). In this case, CT clearly visualized two tumors in one adrenal gland; in the first operation, the nonfunctioning lesion was removed and a second operation was necessary to achieve the cure. In 2005, Ishidoya *et al.* performed a comparative, nonrandomized study of surgical outcomes in two groups of patients with APA who underwent laparoscopic partial and total adrenalectomy (84). The authors performed 29 partial adrenalectomies and experienced two cases in which hypertension and hyperaldosteronism failed to improve. Preoperative AVS and high resolution CT identified a unilateral single APA; thus, it was concluded that another functioning microadenoma was missed in the ipsilateral adrenal gland.

Hennings *et al.* reported two recurrences in nodular UAH after subtotal adrenalectomy; in one of these patients, relapse was caused by recurrent ipsilateral nodular disease in the remnant (16).

These failures may occur because APA cannot be predicted accurately before surgery, and UAH may be more common than expected (85). Subsequently, partial adrenalectomy in cases of unsuspected UAH may theoretically achieve an incomplete removal of abnormal adrenal tissue.

In fact, Shigematsu *et al.* found that aldosterone hypersecretion is not localized exclusively in the adenoma cells but also in the adjacent hyperplastic or micronodular tissue (86). However, little is known about how the cells expressing the enzyme for aldosterone synthase are distributed in the adrenal glands; new findings in immunohistochemistry and immunofluorescence may provide useful tools for diagnosis and treatment of adrenocortical adenomas (87,88).

KCNJ5 and surgery

Recently, important insights of the underlying cause of APA were presented. In 2011 Choi *et al.* identified three

mutations in the selectivity filter of the KCNJ5 (Kir 3.4) potassium channel (89). These mutations result in loss of channel selectivity followed by entry of Na⁺, chronic depolarization, constitutive aldosterone production, and cell proliferation.

In a recent paper, Dekkers *et al.* underline that most adrenal glands with supposedly unilateral aldosterone production display multinodular pathology (90). Somatic mutations in KCNJ5 and other genes (ATP1A1 or CACNA1D) are not limited to APAs but are also found in the more frequent multinodular adrenals. However, in multinodular glands, only one nodule (usually the largest) harbors a mutation. This suggests that the occurrence of a mutation and nodule formation are independent processes. However, the relevance of these findings for clinical management remains to be defined.

In a recent study including 28 patients, Arnesen *et al.* found that 36% of patients with PA displayed tumor mutations in KCNJ5 (91). The presence of KCNJ5 mutations was associated with lower BP and a higher chance for cure by surgery when compared to patients harboring the KCNJ5 wild type. Thus, a preoperative identification of the mutation status might have impact on surgical strategy.

Rossi *et al.* described that patients with APA carrying somatic mutations in the KCNJ5 showed more prominent cardiovascular damage than wild-type APA patients (92), presumably reflecting long-term exposure to higher aldosterone levels (93). However, the chances of these patients being cured from the hyperaldosteronism and high BP, and regression of left ventricular hypertrophy after adrenalectomy, were not compromised by the presence of these mutations.

KCNJ5 mutations are common among Japanese APA patients (69.4%) (94). Kitamoto *et al.* found that the KCNJ5-mutated patients demonstrated significant postoperative improvements in LVM index compared to patients harboring the KCNJ5 wild type, possibly due to strong autonomous aldosterone production (94).

Although not definitive, all these findings may have relevant implications for the management of PA.

Outcome of surgery

The goal of surgery in PA should be the cure of aldosterone excess because of its deleterious direct effect on the cardiovascular system (17,18). Interestingly, in several papers the outcomes of surgery focus only on BP changes and the normalization of serum potassium levels is often

used as a surrogate of PA recovery.

When unilateral disease has been unequivocally established, adrenalectomy achieves the correction of hypokalemia, if present before surgery, in virtually all patients (36); cure of hypertension is reported in about 30-60% of cases, and in the remaining patients a marked improvement of BP values is described (52,70,95).

The wide variation of BP outcome after adrenalectomy could be explained by the different criteria used to define cure and improvement, and even more by the fact that BP is a highly complex phenotype, deriving from several factors. For example, a patient with no cure of PA after adrenalectomy can become normotensive just for lifestyle measures and/or because of myocardial infarction. Conversely, a patient with concomitant essential hypertension is unlikely to be definitively cured even if the PA is fully corrected. Hence, we strongly advocate the need of considering the postoperative normalization of ARR as the main endpoint for determining outcomes of PA.

Several authors have suggested potential predictors of a postoperative hypertension cure in PA patients, including female sex, young age, no family history of hypertension, short duration of hypertension, low preoperative BP, few prescribed antihypertensive drug classes, low body mass index, and high estimated glomerular filtration rate (25,70,93,95-98).

Zarnegar *et al.* developed the Aldosteronoma Resolution Score, which was composed of four predictors (number of antihypertensive drugs, body mass index, duration of hypertension, sex) and roughly estimated postoperative hypertension cure according to 3 categories of likelihood (97).

Utsumi *et al.* have recently proposed a more accurate nomogram that could predict hypertension cure in PA patients after LA. Age, sex duration of hypertension, and number of antihypertensive drug classes are included in the nomogram (98). These scores/nomograms can help clinicians to calculate the probability of postoperative hypertension cure in PA patients and inform patients preoperatively.

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