

Primary aldosteronism: an update on screening, diagnosis and treatment

Gian Paolo Rossi^a, Achille Cesare Pessina^a and Anthony M. Heagerty^b

Background Primary aldosteronism is much more common than previously held; it implies an excessive organ damage to the heart, vessels and kidney, which translates into an excess of cardiovascular events. These two features, along with the fact that the arterial hypertension and the hypokalemia can be corrected with a timely diagnosis and an appropriate therapy, warrant an aggressive diagnostic approach in hypertensive patients.

Objectives To provide updated information on the screening and exclusion tests for primary aldosteronism and to illustrate the strategy that can be followed for primary aldosteronism subtype differentiation.

Design Review of the literature and personal experience of the authors.

Results The available evidence showed that a cost-effective strategy for the screening of patients with primary aldosteronism can be exploited at most centres. At variance, the identification of primary aldosteronism subtypes, for example, the differentiation of patients with an aldosterone-producing adenoma from those with idiopathic hyperaldosteronism should be undertaken at tertiary referral centres.

Conclusion The identification of a curable form of primary aldosteronism can be much rewarding for the patient and

the doctor. Thus, an aggressive diagnostic approach is mandatory at least in some subgroups of hypertensive patients who are at higher prior risk of primary aldosteronism or can benefit more from an accurate diagnosis. *J Hypertens* 26:613–621 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Journal of Hypertension 2008, 26:613–621

Keywords: diagnosis screening, primary aldosteronism, secondary hypertension

Abbreviations: 11βHSD2, 11β-hydroxysteroid dehydrogenase type 2; ACE, Angiotensin-converting enzyme; AME, Apparent Mineralocorticoid Excess; APA, aldosterone-producing adenoma; ARBs, angiotensin II receptor blockers; ARR, aldosterone renin ratio; aTHF, allotetrahydrocortisol; AVS, Adrenal vein sampling; BAH, bilateral adrenal hyperplasia; CCB, calcium channel blockers; FH-I, Familial hyperaldosteronism type I; FH-II, Familial hyperaldosteronism type II; IHA, idiopathic hyperaldosteronism; MR, mineralocorticoid receptor; MUAN, multiple unilateral nodular hyperplasia; NP59, adrenocortical scintigraphy with ¹³¹I-labelled cholesterol analogues; PA, Primary aldosteronism; PAC, plasma aldosterone concentration; PAH, primary adrenal hyperplasia; PAPY, PA Prevalence in hYpertensives Study; PCR, polymerase chain reaction; PRA, plasma renin activity; THE, tetrahydrocortisone; THF, tetrahydrocortisol (THF)

^aDMCS, Clinica Medica 4 and University of Padua, Padua, Italy and ^bCardiovascular Medicine, University of Manchester, Manchester, UK

Correspondence to Gian Paolo Rossi, MD, FACC, FAHA, DMCS, Clinica Medica 4, Policlinico Universitario, Via Giustiniani 2, 35126 Padova, Italy
Tel: +49 821 3304/2301; fax: +49 880 2252; e-mail: gianpaolo.rossi@unipd.it

Received 21 September 2007 Revised 6 November 2007
Accepted 20 November 2007

Introduction

Primary aldosteronism was originally reported in a woman with an adrenocortical tumour in 1955 by Conn [1,2]. The description of aldosterone and the identification of its biological actions followed shortly afterwards, thereby allowing Conn to establish a link between the autonomous excess production of aldosterone by the tumour, then defined as 'Conn's adenoma' or aldosterone-producing adenoma (APA), and the syndrome termed primary aldosteronism or Conn's syndrome.

Prevalence

After a decade of systematic screening of hypertensive patients Conn and co-workers [3–5] contended that primary aldosteronism affected more than 20% of them, even in the absence of hypokalemia, one of the hallmarks of the syndrome. Others, however, could not confirm this, which led most to believe that primary aldosteronism was rare. Eventually, Conn [6] conceded that 7.5% was a more realistic estimate of primary aldosteronism prevalence;

nevertheless, subsequent studies documented widely ranging (from 1.4% to 32%, median 8.8%) estimates of prevalence, probably explained by studies almost always being performed retrospectively in selected cohorts (for a review, see [7]). Yet reports [8–26] suggested that primary aldosteronism might be commoner than at first thought. This impression was supported by a large prospective survey of consecutive newly diagnosed hypertensive patients referred to hypertension centres in Italy, the Primary Aldosteronism Prevalence in hYpertensives (PAPY) study [27].

In this study [27], after a screening and a confirmatory test, patients underwent a comprehensive diagnostic work-up that allowed not only the unequivocal diagnosis of the presence or absence of primary aldosteronism, but also the identification of the primary aldosteronism subtype [28]. The criteria used for diagnosis of APA were the most rigorous ever used. The criteria used for diagnosing APA are as follows:

- (1) biochemical evidence of primary aldosteronism (see later);
- (2) lateralized aldosterone excess at adrenal vein sampling (AVS, see later) or, if unavailable, at adrenocortical mineralocorticoid scintigraphy;
- (3) identification of APA at surgery and/or pathology [29];
- (4) demonstration of correction of the hyperaldosteronism and cure, or marked improvement of the hypertension postadrenalectomy [27].

Primary aldosteronism patients without clear-cut lateralization of aldosterone excess were presumed to have idiopathic hyperaldosteronism (IHA), a condition usually associated with bilateral adrenocortical hyperplasia (BAH) and, therefore, not surgically curable. The overall prevalence of primary aldosteronism was 11.2%, with APA and IHA entailing 4.8% and 6.4%, respectively. Therefore, primary aldosteronism is likely to be by far the most common curable endocrine form of hypertension in newly diagnosed patients referred to tertiary centres. These rates of prevalence can impact on the strategy to be used in the investigation of the hypertensive patients because they might suggest that all newly diagnosed hypertensive patients should be screened for primary aldosteronism. The adoption of this strategy should be based on several considerations related to the patient's features and on the availability of diagnostic and healthcare resources. Also, screening could be considered mandatory in some categories of patients (discussed below).

Organ damage in primary aldosteronism

The importance of a timely diagnosis of primary aldosteronism followed by the identification of its underlying cause is emphasized by the fact that the cause of hypertension is associated with target organ damage. Compelling evidence suggests that, in the presence of excess salt intake, increased aldosterone is associated with oxidant stress [30,31], cardiovascular remodelling, hypertrophy and fibrosis [32–34], and ultimately an excess rate of cardiovascular events which are prevented by a blockade of the mineralocorticoid receptor or adrenalectomy [35–42]. Primary aldosteronism is associated with alterations in the left ventricular filling and diastolic dysfunction [43], prolongation of the cardiac PQ interval [44], stiffness of large arteries [45–47], widespread tissue fibrosis [48], alterations in the densitometry properties [49], and of the ultrasound backscatter of the left ventricular wall [50], even though systolic function is, at least initially, preserved [43], remodelling of resistance arteries [47,51], stroke [52], cerebral haemorrhage [53], and microalbuminuria [52,54–56]. A higher frequency of the metabolic syndrome has also been documented.

Whom to screen for primary aldosteronism

On the basis of the documented high prevalence rate [27], the excess rate of cardiovascular complications

which can be prevented with an early diagnosis, and the fact that arterial hypertension may be cured by adrenalectomy, it could be proposed that primary aldosteronism should be excluded systematically in all hypertensive patients; however, this remains controversial [57,58].

Notwithstanding the above-mentioned fact, there are certain categories of patients in whom screening for primary aldosteronism could be considered mandatory. The conditions that in a hypertensive patient make the search for primary aldosteronism mandatory are as follows:

- (1) unexplained hypokalemia (spontaneous or diuretic-induced);
- (2) resistant hypertension and grade 2 or 3 hypertension;
- (3) early onset (juvenile) hypertension and/or stroke (<50 years);
- (4) incidentally discovered apparently nonfunctioning adrenal mass (incidentaloma);
- (5) evidence of organ damage (left ventricular hypertrophy, diastolic dysfunction, atrioventricular block, carotid atherosclerosis, microalbuminuria, endothelial dysfunction) particularly if disproportionate for the severity of hypertension;
- (6) metabolic syndrome (this is still contentious).

Hence, there is no question that in these patients the pretest probability of primary aldosteronism is much higher and, therefore, the cost-effectiveness of the screening is more rewarding.

How to screen for primary aldosteronism

By definition, the diagnosis of primary aldosteronism entails the demonstration of an excess aldosterone secretion. Hence, the aldosterone/renin ratio (ARR) has been proposed as a simplified approach but its use requires careful consideration. First, because aldosterone secretion is directly related to plasma potassium, the ARR should be measured only after correction of hypokalemia by potassium supplement and the control of sodium intake. Second, because the ARR depends on plasma renin activity (PRA), patients with suppressed PRA will have an increased ARR regardless of the plasma aldosterone concentration (PAC). Therefore, the ratio must be interpreted in the light of the PAC itself, which should be higher than 15 ng/dl, and of the lowest detectable level of the PRA assay [59]. As current assays for PRA lose their precision in the low ranges, when calculating the ARR, it is the best practice to arbitrarily fix the lowest PRA value at 0.2 ng/ml/h to avoid overinflating the ratio [27]. This is of utmost importance in the elderly or black populations, who often have low PRA values. Therefore, the combination of PAC greater than 15 ng/dl and an increased ARR, rather than the latter alone, should be used as a screening test.

Ideally, the use of this ratio should be centre-based, with normal ranges established for salt intake in the local population and the type of assay used for aldosterone and renin. In recent years, the use of the direct active renin assay, instead of the PRA assay, has gained wider acceptance (for a review, see [60,61]). Indeed studies have shown a good correlation between the direct active renin and PRA values, but this correlation is weaker at the low ranges [60]. Furthermore, direct active renin and PRA values are differentially affected by pretest handling of the samples, owing to cryoactivation of the direct active renin [60,61]. Also, there has been no prospective study to assess the accuracy of direct active renin; therefore, the ARR, based on this renin assay as a screening test, is not validated for the diagnosis of primary aldosteronism.

Drug effects

Many antihypertensive drugs can affect the PAC and PRA values and, therefore, the ARR, which implies that drug treatment must be modified before measuring these hormones. Beta-blockers by decreasing the PRA and leaving the PAC relatively unaffected raise the ARR [27]; therefore, they should be stopped at least 2 weeks before the measurement of the PAC and renin. Conversely, diuretics and mineralocorticoid receptor antagonists should be withdrawn before 2 and 6 weeks, respectively, because they raise the PRA. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have an even more marked effect because they not only raise the PRA but also blunt aldosterone secretion, thus reducing the ARR and increasing false-negative results. Therefore, they should be withdrawn at least 2 weeks before performing the ARR.

By contrast, other agents have no or minimal effects on the ARR: the α_1 -receptor blocker doxazosin does not seem to have significant effects on the renin–angiotensin–aldosterone system. The long-acting calcium channel blockers (CCB) have a small blunting effect on aldosterone secretion [7,27], but short-acting CCB can blunt aldosterone secretion and raise the PRA and, therefore, can cause false-negative results.

Exclusion (confirmatory) tests

By definition, screening tests should be highly sensitive in order not to miss primary aldosteronism; in consequence, there will be a false-positive rate. False-positive cases need to be identified and excluded from AVS. The tests available are oral sodium loading, saline infusion test, fludrocortisone with salt loading, and the captopril test [8,13,62,63]. All are aimed at demonstrating nonsuppressible (autonomous) aldosterone excess and, therefore, must be performed only after correction of the hypokalemia. According to some experts [8], the

fludrocortisone and salt loading would be the most specific, but it requires hospitalization and careful surveillance of the patients for the possibility of severe hyperkalemia. Oral sodium loading is still widely used, but it gives inconsistent results because of the poor standardization and the variable adherence of the patients to the protocol [62].

Therefore, currently the most popular are the saline infusion [64,65] and the captopril tests [13,25,63]. Both have a moderate sensitivity and a high specificity in the patients on an adequate sodium intake, for example, greater than 133 mEq/day (6.3 g NaCl/day) [66]. At a lower sodium intake, however, the saline infusion is more accurate than the captopril test, which, therefore, should be used only after sodium repletion [66].

At optimal cut-off values both the saline infusion and the captopril test are more specific than sensitive [66,67]. Therefore, at the prevalence rates that are commonly encountered even at referral centres and after a positive screening test, both the saline and the captopril have a much higher negative than positive predictive value and, thus, are more useful to exclude rather than to confirm the presence of primary aldosteronism [66,67].

Identification of primary aldosteronism subtypes

The identification of primary aldosteronism (with the screening tests) and the exclusion of a false-positive result mark the beginning of a sometimes complex diagnostic work-up aimed at identifying whether the patient has surgically remediable primary aldosteronism. Surgically curable and not curable forms of mineralocorticoid excess, including primary aldosteronism, are as follows:

- (1) Surgically curable:
 - (a) aldosterone-producing adenoma (aldosteronoma, APA);
 - (i) unilateral
 - (ii) bilateral
 - (b) primary unilateral adrenal hyperplasia (PAH);
 - (c) multinodular unilateral adrenocortical hyperplasia (MUAN);
 - (d) ovary aldosterone-secreting tumour;
 - (e) APA or BAH with concomitant pheochromocytoma;
 - (f) aldosterone-producing carcinoma (APC).
- (2) Surgically not curable:
 - (a) BAH;
 - (b) unilateral APA with BAH;
 - (c) familial type I hyperaldosteronism, also known as glucocorticoid-remediable aldosteronism (GRA);
 - (d) familial type II hyperaldosteronism;
 - (e) apparent mineralocorticoid excess (AME):
 - (i) chronic liquorice intake
 - (f) carbenoxolone (antacid) use.

Some forms cause or mimic a hyperactivation of the mineralocorticoid receptor from the hormonal and haemodynamic standpoint but are not primary aldosteronism. They are mentioned here because they need to be considered in the differential diagnosis of surgically curable primary aldosteronism (see later). By far the two most common forms of primary aldosteronism are APA and BAH, also referred to as IHA. The other forms enlisted in above are very rare [68,69]. Cases of primary aldosteronism associated with pheochromocytoma and of APC are exceedingly rare [70–74].

Only the unilateral causes of primary aldosteronism are curable with adrenalectomy; thus, the identification of a surgically curable form of primary aldosteronism implies demonstrating the autonomous unilateral production of aldosterone excess. The diagnostic strategy for the differential diagnosis between APA and IHA, is difficult for three reasons: there are rare cases of unilateral autonomous hyperplasia, known as primary adrenal hyperplasia (PAH) [75] or MUAN, that can be cured by adrenalectomy [76]; the border between a microscopic APA and MUAN is undefined due to the lack of accepted histopathological criteria; and documented cases of bilateral APA and APA in a context of MUAN or BAH have been reported [77–80].

Demonstration of autonomous aldosterone excess

IHA would maintain the normal regulation of the adrenocortical zona glomerulosa; conversely, PAH and APA are held to be functionally autonomous from the renin-angiotensin system. Hence, some functional tests have been proposed to distinguish between these subtypes. They comprise standing-up, blood volume expansion, angiotensin II (Ang II) or adrenocorticotrophic hormone (ACTH) infusion, and administration of captopril, and losartan [13,27,81]. Experience has shown that the responses of PAC to these functional tests, albeit statistically significantly different, on average, between APA and IHA, show such a degree of individual values overlapping to render them obsolete.

Identification of unilateral causes of primary aldosteronism

Imaging

High-resolution computed tomography (CT) with fine (2–3 mm) cuts of the upper abdomen is the best available technique for the identification of adrenal nodules [82–84], which can be found in APA, less commonly in PAH [75], but also in BAH. Magnetic resonance (MR) can be slightly more sensitive, but at the price of a lower specificity and a greater susceptibility to motion artefacts [85]. Hence, it should be reserved for the patients with contraindications to X-ray contrast medium. Half of the APA is currently identified when smaller than 20 mm. Usually, PAH and MUAN are not detected by CT or MR.

Also, it must be acknowledged that an adrenal mass can coexist just by chance in a hypertensive patient with a biochemical picture of primary aldosteronism. In addition, an adrenal nodule in a patient with primary aldosteronism can be an APA, but also a macronodule of hyperplasia in a patient with IHA [86,87], a micronodule in a patient with PAH [75,76], or an apparently nonfunctioning incidentally discovered adenoma ('incidentaloma'). These are found in 2–10% of adults at autopsy and are common even in the normotensive population [88]. Adrenal imaging is insufficient to achieve discrimination between APA and IHA. This conclusion is supported by a study of 194 patients with primary aldosteronism who underwent both CT and AVS, in whom AVS was used as 'gold' standard for the diagnosis. CT mistakenly suggested an APA in 24.2% of the patients; identified correctly a unilateral or bilateral aldosterone excess only in 53%; falsely suggested a BAH in 21.2% of the patients with a unilateral source of aldosterone excess and showed the presence of an APA in the wrong adrenal in 12 patients [89]. Similar data on the fallibility of CT for diagnosing the surgically curable subtypes of primary aldosteronism have been reported by others [87]. Therefore, CT results are confounding in about half of the patients and can lead to useless and/or inappropriate adrenalectomy in 25% of the cases and to exclusion from adrenalectomy of roughly 25% of the patients who are potentially curable with this procedure.

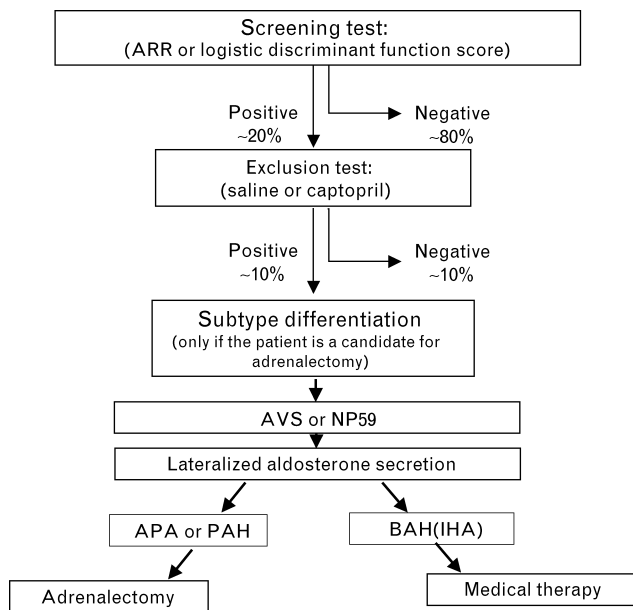
Adrenal vein sampling

Most experts [90] agree that the 'gold standard' for lateralization of aldosterone secretion is the measurement of PAC and plasma cortisol concentration in adrenal venous blood. This is technically demanding and carries a small, albeit not negligible, risk of adrenal vein rupture. It should be reserved for patients with a confirmed diagnosis of primary aldosteronism who are candidates for adrenalectomy (Fig. 1). AVS should be performed only in patients with normokalemia, for example, after correction of the hypokalemia and stopping of the confounding drugs [91].

Mineral corticoid adrenocortical scintigraphy (NP59)

An alternative approach to the demonstration of lateralization of aldosterone secretion entails the administration of ¹³¹I-labelled cholesterol analogues as 6β-[¹³¹I] methyl-19-norcholesterol (NP59). The assumption is made that NP59 would be taken up as cholesterol by the adrenal cortex in proportion to its degree of hyperfunctioning. Scanning (scintigraphy) is then performed after the removal of the ACTH drive to the zona fasciculata with dexamethasone (1 mg q.i.d.) for the preceding week. The sensitivity of NP59 scintigraphy is directly proportional to tumour size and also to the degree of hyperfunction. Therefore, this technique can demonstrate an adrenal gland, with a large (>1.5 cm) and markedly hypersecreting APA, but is

Fig. 1



Flow chart for the diagnostic work-up of primary aldosteronism. Aldosterone/renin ratio (ARR), plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio; AVS, adrenal vein sampling. Please refer to text for explanation and details.

insensitive for detecting the majority of APAs [82,92–95]. Moreover, the current shortage in the supply of the radio-tracer has impeded a wide use of NP59.

The cost-effectiveness of the diagnosis

The determination of the ARR is no more expensive than lipid measurements but can be far more rewarding for the long-term reduction of cardiovascular risk in the hypertensive patients who have a surgically curable form of primary aldosteronism. Nevertheless, the cost-effectiveness of the systematic screening for primary aldosteronism has been repeatedly challenged even recently [96]. Assuming a prevalence rate of 2% of APA and a diagnostic work-up based on the ARR for the screening, the fludrocortisone suppression test for confirming the diagnosis, CT for imaging and AVS for subtypes differentiation, Kaplan estimated that cure of one APA patient would cost roughly US\$250 000. This figure is unrealistic because (i) the prevalence of primary aldosteronism is more than five-fold higher (around 11%) and that of APA is about 5%, that is 2.5-fold higher than that assumed; (ii) roughly US\$100 000 were due to the cost of the fludrocortisone suppression test, which can be replaced by the much cheaper captopril or saline infusion test; and (iii) the costs of the imaging test (CT or MR) and AVS are much lower in Europe and other parts of the world than in the USA.

Thus, assuming a 5% prevalence of APA, use of the saline infusion test, a cost of CT similar to that in the USA but a cost for AVS of US\$3000 and by applying the same

mathematics, it can be calculated that the cost for cured patients would be US\$33 500 or US\$44 666, assuming a cure rate with adrenalectomy of 80% or 60%, respectively. The fact that long-term cure implies saving the costs of lifetime drug treatment of hypertension tests for monitoring the target organ damage, and the costs for treatment of complications should also be considered. Overall, an aggressive diagnostic strategy might be effective for both economic and morbidity reasons.

Differential diagnosis

Before selecting the patients for AVS, there are some rare forms of mineralocorticoid excess which need to be considered in the differential diagnosis of primary aldosteronism. Familial hyperaldosteronism type I, formerly known as GRA, is a monogenic form of hypertension inherited as an autosomal dominant trait that accounts for less than 1% of cases of primary aldosteronism [68]. It features early onset of moderate to severe hypertension, high incidence of premature stroke, and hyperaldosteronism with low renin values and, most importantly, its reversal by exogenous glucocorticoids.

Familial hyperaldosteronism type II is a familial type of primary aldosteronism unresponsive to glucocorticoids, which can present with either APA or BAH [97]. Hypertension was cured or markedly improved by adrenalectomy in each affected member [98]. An autosomal dominant mode of inheritance was observed in some families but the mode of inheritance remains indeterminate similar to the underlying variety of gene mutations [98]. Thus, the current diagnostic work-up for familial hyperaldosteronism type II requires demonstration of primary aldosteronism in two or more family members and exclusion of familial hyperaldosteronism type I by long-PCR [98].

AME is a rare monogenic form hypertension caused by loss of the activity of 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2) [99,100], the enzyme inactivating cortisol to cortisone in proximity of the mineralocorticoid receptor in the mineralocorticoid target tissues. This inactivation is crucial for allowing aldosterone to gain its access to the receptor, because it protects the mineralocorticoid receptor from binding cortisol, whose plasma concentrations are in the nanomolar range [101]. Over 30 mutations of the HSD11B2 gene leading to a blunted enzyme activity have been described [100,102,103]. They lead to cortisol-induced activation of the mineralocorticoid receptor, thus mimicking primary aldosteronism despite low PAC because of the renin suppression. AME is inherited as an autosomal recessive trait and is characterized by a close genotype–phenotype correlation: homozygous present all clinical signs (classic AME), whereas most heterozygous may show only mild hypertension and a moderately abnormal ratio of tetrahydrocortisol (THF) and allotetrahydrocortisol (aTHF)

to tetrahydrocortisone (THE) (THF : THE), or even a normal phenotype [104–106]. Classic AME usually presents early in life with severe hypertension, hypokalaemia, metabolic alkalosis, and low levels of renin and PAC. The diagnosis can be made by the demonstration of an increased (up to 33; normal values about 1) THF : THE, in a 24-h urine collection [100,107]. Spironolactone or amiloride, generally in doses higher than those used to treat primary aldosteronism, corrects hypertension and the biochemical alterations of AME [100].

Patients ingesting chronically large amounts of liquorices can present with AME, because of the inhibiting effect on 11 β HSD2 and the (weak) mineralocorticoid activity of glycyrrhizic acid and its hydrolytic product, glycyrrhizic acid [108,109]. Some of these patients may be heterozygous for some of the numerous mutations of the 11 β HSD2 gene, although this possibility has not been explored thus far.

Liddle's syndrome is an autosomal dominant form of hypertension induced by a point mutation in the genes coding for the β -subunit or γ -subunit of the epithelial sodium channel in the distal renal tubule with ensuing alteration or deletion in a conserved proline-rich sequence, called PY motif, in the cytoplasmic tails corresponding to the C-terminal ends of either subunits [110–113]. The disruption of the PY motif prevents internalization and inactivation of the channel that, in contrast to the wild type subunits, remain constitutively activated leading to excess tubular sodium re-absorption with ensuing salt-sensitive hypertension, suppression of renin and PAC [114]. These features of the syndrome, closely resembling those of AME, explain the peculiar sensitivity of Liddle's syndrome to amiloride and triamterene, as the epithelial sodium channel is inhibited by these drugs [115]. The demonstration of the mutations in the β -subunit or γ -subunit of the epithelial sodium channel allows to unequivocally diagnose Liddle's syndrome and can be useful for targeting the drug treatment [111,116,117].

Treatment

Regardless of the demonstration of an adrenal nodule at imaging, the best treatment that can be offered to primary aldosteronism patients with a lateralized aldosterone secretion currently is laparoscopic adrenalectomy, which can be performed with a 2-day hospital stay at a very low operative risk [118–120]. Hypertension is cured in about 33–72% of the cases and markedly ameliorated in 40–50% of the cases [121,122]. Attempts to identify the predictors of blood pressure outcome have given consistent results only for age and duration of hypertension [123], thus emphasizing the concept that early diagnosis and surgery are critical for a more favourable outcome. Failure to cure hypertension can be attributed to an inaccurate diagnosis, because of the lack of per-

forming or correctly interpreting AVS results, development of bilateral APA over time, or, more commonly, the concurrence of primary hypertension. Given the high prevalence of primary hypertension it can be anticipated that about one third of the patients with primary aldosteronism can in fact have concurrent primary hypertension [124]. Cure of the biochemical picture of primary aldosteronism but not of hypertension can conceivably identify these cases.

Mineralocorticoid receptor antagonists [125,126], as spironolactone, canrenone, potassium canrenoate, and in some countries, the more selective but more expensive eplerenone are a reasonable alternative to adrenalectomy for the patients who are not candidates for surgery or do not show lateralized aldosterone excess. The occurrence of gynecomastia and impotence, which can occur with the oldest mineralocorticoid receptor antagonists, is dose-dependent, thus suggesting the use of lower doses in combination, if necessary, with other agents such as long-acting CCB, ACE inhibitors or ARBs. Circumstantial evidence, however, suggests that they might be less effective in providing regression of target organ damage, although results from a large-scale randomized clinical trial are necessary.

Conclusion

Compelling evidence indicates that primary aldosteronism is far more common than usually perceived and represents the most common cause of secondary endocrine hypertension. The crucial importance of an early diagnosis of primary aldosteronism is underscored by its potential curability and the fact that, if not recognized timely, primary aldosteronism causes prominent cardiovascular damage and events [127]. Although a simplified screening protocol can be cost-effective and is feasible in most hypertensives, the search for primary aldosteronism is mandatory in certain categories of patients (enlisted in section 'Identification of primary aldosteronism subtypes') who have a higher pretest probability of the disease.

A positive screening test mandates use of an exclusion test which, if positive, requires an imaging test, as CT or MR, followed by AVS or, in the case of large tumours, by mineralocorticoid scintigraphy, to demonstrate lateralization of autonomous excess aldosterone and, therefore, to pose the indication for adrenalectomy. Therefore, if the patient represents a candidate to adrenalectomy and is eventually consenting to it, AVS should be used whenever available.

A timely identification of a surgically curable form of primary aldosteronism is much rewarding not only for the physician but also for the patient as it can prevent and/or regress the cardiovascular damages that imply a higher risk of ominous cardiovascular complications.

Acknowledgements

The research work described here was supported by research grants from the Foundation for Advanced Research in Hypertension and Cardiovascular Disease (FORICA) and the Società Italiana dell'Ipertensione Arteriosa (SIIA) to G.P.R. and the University of Padova '60%' and 'Progetti di Ateneo' to A.C.P. and G.P.R.

References

- Conn JW. Primary aldosteronism. In: *Hypertension: Pathophysiology and Treatment*, 1st ed. Anonymous, New York: McGraw-Hill; 1977. pp. 768–780.
- Conn JW. Part I. Painting background. Part II. Primary aldosteronism, a new clinical syndrome. *J Lab Clin Med* 1990; **116**:253–267.
- Conn JW, Cohen EL, Rovner DR, Nesbit RM. Normokalemic primary aldosteronism: a detectable cause of curable "essential" hypertension. *JAMA* 1965; **193**:200–206.
- Conn JW, Rovner DR, Cohen EL, Nesbit RM. Normokalemic primary aldosteronism: its masquerade as "essential" hypertension. *JAMA* 1966; **195**:21–26.
- Conn JW. Plasma renin activity in primary aldosteronism. *JAMA* 1964; **190**:222–225.
- Conn JW. A concluding response. *Arch Intern Med* 1969; **123**:154–155.
- Rossi GP. Primary aldosteronism: a needle in a haystack or a yellow cab on fifth avenue? *Curr Hypertens Rep* 2004; **6**:1–4.
- Gordon RD, Ziesak MD, Tunny TJ, Stowasser M, Klemm SA. Evidence that primary aldosteronism may not be uncommon: 12% incidence among antihypertensive drug trial volunteers. *Clin Exp Pharmacol Physiol* 1993; **20**:296–298.
- Anderson GH Jr, Blakeman N, Streeten DH. The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. *J Hypertens* 1994; **12**:609–615.
- Gordon RD, Stowasser M, Tunny TJ, Klemm SA, Rutherford JC. High incidence of primary aldosteronism in 199 patients referred with hypertension. *Clin Exp Pharmacol Physiol* 1994; **21**:315–318.
- Abdelhamid S, Muller-Lobeck H, Pahl S, Remberger K, Bonhof JA, Walb D, *et al.* Rockel A. Prevalence of adrenal and extra-adrenal Conn syndrome in hypertensive patients. *Arch Intern Med* 1996; **156**:1190–1195.
- Brown MA, Cramp HA, Zammit VC, Whitworth JA. Primary hyperaldosteronism: a missed diagnosis in 'essential hypertensives'? *Aust N Z J Med* 1996; **26**:533–538.
- Rossi GP, Rossi E, Pavan E, Rosati N, Zecchel R, Semplicini A, *et al.* Screening for primary aldosteronism with a logistic multivariate discriminant analysis. *Clin Endocrinol (Oxf)* 1998; **49**:713–723.
- Mosso L, Fardella C, Montero J, Rojas P, Sanchez O, Rojas V, *et al.* High prevalence of undiagnosed primary hyperaldosteronism among patients with essential hypertension. *Rev Med Chil* 1999; **127**:800–806.
- Rayner BL, Opie LH, Davidson JS. The aldosterone/renin ratio as a screening test for primary aldosteronism. *S Afr Med J* 2000; **90**:394–400.
- Loh KC, Koay ES, Khaw MC, Emmanuel SC, Young WF Jr. Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. *J Clin Endocrinol Metab* 2000; **85**:2854–2859.
- Denolle T, Hanon O, Mounier-Vehier C, Marquand A, Fauvel JP, Laurent P, *et al.* What tests should be conducted for secondary arterial hypertension in hypertensive patients resistant to treatment? *Arch Mal Coeur Vaiss* 2000; **93**:1037–1039.
- Cortes P, Fardella C, Oestreicher E, Gac H, Mosso L, Soto J, *et al.* Excess of mineralocorticoids in essential hypertension: clinical-diagnostic approach. *Rev Med Chil* 2000; **128**:955–961.
- Nishikawa T, Omura M. Clinical characteristics of primary aldosteronism: its prevalence and comparative studies on various causes of primary aldosteronism in Yokohama Rosai Hospital. *Biomed Pharmacother* 2000; **54** (Suppl 1):83s–85s.
- Fardella CE, Mosso L, Gomez-Sanchez C, Cortes P, Soto J, Gomez L, *et al.* Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. *J Clin Endocrinol Metab* 2000; **85**:1863–1867.
- Lim PO, Dow E, Brennan G, Jung RT, MacDonald TM. High prevalence of primary aldosteronism in the Tayside hypertension clinic population. *J Hum Hypertens* 2000; **14**:311–315.
- Rayner BL, Myers JE, Opie LH, Trinder YA, Davidson JS. Screening for primary aldosteronism: normal ranges for aldosterone and renin in three South African population groups. *S Afr Med J* 2001; **91**:594–599.
- Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension* 2002; **40**:892–896.
- Schwartz GL, Chapman AB, Boerwinkle E, Kisabeth RM, Turner ST. Screening for primary aldosteronism: implications of an increased plasma aldosterone/renin ratio. *Clin Chem* 2002; **48**:1919–1923.
- Rossi E, Regolisti G, Negro A, Sani C, Davoli S, Perazzoli F. High prevalence of primary aldosteronism using postcaptopril plasma aldosterone to renin ratio as a screening test among Italian hypertensives. *Am J Hypertens* 2002; **15**:896–902.
- Williams JS, Williams GH, Raji A, Jeunemaitre X, Brown NJ, Hopkins PN, *et al.* Prevalence of primary hyperaldosteronism in mild to moderate hypertension without hypokalaemia. *J Hum Hypertens* 2006; **20**:129–136.
- 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**:2293–2300.
- Giacchetti G, Ronconi V, Lucarelli G, Boscaro M, Mantero F. Analysis of screening and confirmatory tests in the diagnosis of primary aldosteronism: need for a standardized protocol. *J Hypertens* 2006; **24**:737–745.
- Rossi GP, Pitter G, Miotto D. To stimulate or not to stimulate: is adrenocorticotrophic hormone testing necessary, or not? *J Hypertens* 2007; **25**:481–484.
- Fritsch NM, Schiffrin EL. Aldosterone: a risk factor for vascular disease. *Curr Hypertens Rep* 2003; **5**:59–65.
- Pu Q, Neves MF, Virdis A, Touyz RM, Schiffrin EL. Endothelin antagonism on aldosterone-induced oxidative stress and vascular remodeling. *Hypertension* 2003; **42**:49–55.
- Brilla CG, Maisch B, Weber KT. Myocardial collagen matrix remodeling in arterial hypertension. *Eur Heart J* 1992; **13** (Suppl D):24–30.
- Brilla CG, Maisch B, Rupp H, Funck R, Zhou G, Weber KT. Pharmacological modulation of cardiac fibroblast function. *Herz* 1995; **20**:127–134.
- Brilla CG, Pick R, Tan LB, Janicki JS, Weber KT. Remodeling of the rat right and left ventricles in experimental hypertension. *Circ Res* 1990; **67**:1355–1364.
- Rocha R, Martin-Berger CL, Yang P, Scherrer R, Delyani J, McMahon E. Selective aldosterone blockade prevents angiotensin II/salt-induced vascular inflammation in the rat heart. *Endocrinology* 2002; **143**:4828–4836.
- Rocha R, Rudolph AE, Friedrich GE, Nachowiak DA, Kecek BK, Blomme EA, *et al.* Aldosterone induces a vascular inflammatory phenotype in the rat heart. *Am J Physiol Heart Circ Physiol* 2002; **283**:H1802–H1810.
- Rocha R, Funder JW. The pathophysiology of aldosterone in the cardiovascular system. *Ann N Y Acad Sci* 2002; **970**:89–100.
- Rocha R, Williams GH. Rationale for the use of aldosterone antagonists in congestive heart failure. *Drugs* 2002; **62**:723–731.
- Rocha R, Stier CT Jr. Pathophysiological effects of aldosterone in cardiovascular tissues. *Trends Endocrinol Metab* 2001; **12**:308–314.
- Rocha R, Stier CT Jr, Kifor I, Ochoa-Maya MR, Renne HG, Williams GH, *et al.* Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. *Endocrinology* 2000; **141**:3871–3878.
- Rocha R, Chander PN, Zuckerman A, Stier CT Jr. Role of aldosterone in renal vascular injury in stroke-prone hypertensive rats. *Hypertension* 1999; **33**:232–237.
- Rocha R, Chander PN, Khanna K, Zuckerman A, Stier CT Jr. Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. *Hypertension* 1998; **31**:451–458.
- Rossi GP, Sacchetto A, Pavan E, Scognamiglio R, Pietra M, Pessina AC. Left ventricular systolic function in primary aldosteronism and hypertension. *J Hypertens* 1997; **19** (Suppl 8):S147–S151.
- Rossi GP, Sacchetto A, Pavan E, Palatini P, Graniero GR, Canali C, *et al.* Remodeling of the left ventricle in primary aldosteronism due to Conn's adenoma. *Circulation* 1997; **95**:1471–1478.
- Holaj R, Zelinka T, Wichterle D, Petrak O, Strauch B, Widimsky J Jr. Increased intima-media thickness of the common carotid artery in primary aldosteronism in comparison with essential hypertension. *J Hypertens* 2007; **25**:1451–1457.
- Rizzoni D, Porteri E, Castellano M, Bettoni G, Muesan ML, Tiberio G, *et al.* Endothelial dysfunction in hypertension is independent from the etiology and from vascular structure. *Hypertension* 1998; **31**:335–341.
- Rizzoni D, Muesan ML, Porteri E, Salvetti M, Castellano M, Bettoni G, *et al.* Relations between cardiac and vascular structure in patients with primary and secondary hypertension. *J Am Coll Cardiol* 1998; **32**:985–992.
- Campbell SE, Diaz-Arias AA, Weber KT. Fibrosis of the human heart and systemic organs in adrenal adenoma. *Blood Press* 1992; **1**:149–156.

- 49 Rossi GP, Di Bello V, Ganzaroli C, Sacchetto A, Cesari M, Bertini A, *et al.* Excess aldosterone is associated with alterations of myocardial texture in primary aldosteronism. *Hypertension* 2002; **40**:23–27.
- 50 Kozakova M, Buralli S, Palombo C, Bernini G, Moretti A, Favilla S, *et al.* Myocardial ultrasonic backscatter in hypertension: relation to aldosterone and endothelin. *Hypertension* 2003; **41**:230–236.
- 51 Muesan ML, Rizzoni D, Salvetti M, Porteri E, Monteduro C, Guelfi D, *et al.* Structural changes in small resistance arteries and left ventricular geometry in patients with primary and secondary hypertension. *J Hypertens* 2002; **20**:1439–1444.
- 52 Nishimura M, Uzu T, Fujii T, Kuroda S, Nakamura S, Inenaga T, Kimura G. Cardiovascular complications in patients with primary aldosteronism. *Am J Kidney Dis* 1999; **33**:261–266.
- 53 Takeda R, Matsubara T, Miyamori I, Hatakeyama H, Morise T. Vascular complications in patients with aldosterone producing adenoma in Japan: comparative study with essential hypertension. The Research Committee of Disorders of Adrenal Hormones in Japan. *J Endocrinol Invest* 1995; **18**:370–373.
- 54 Halimi JM, Mimran A. Albuminuria in untreated patients with primary aldosteronism or essential hypertension. *J Hypertens* 1995; **13**:1801–1802.
- 55 Rossi GP, Bernini G, Desideri G, Fabris B, Ferri C, Giacchetti G, *et al.*, for the PAPY Study Participants. Renal Damage in Primary Aldosteronism: Results of the PAPY Study. *Hypertension* 2006; **48**:232–238.
- 56 Sechi LA, Novello M, Lapenna R, Baroselli S, Nadalini E, Colussi GL, *et al.* Long-term renal outcomes in patients with primary aldosteronism. *JAMA* 2006; **295**:2638–2645.
- 57 Kaplan NM. Is there an unrecognized epidemic of primary aldosteronism? *Con. Hypertension* 2007; **50**:454–458.
- 58 Calhoun DA. Is there an unrecognized epidemic of primary aldosteronism? *Pro. Hypertension* 2007; **50**:447–453.
- 59 Mulatero P, Dluhy RG, Giacchetti G, Boscaro M, Veglio F, Stewart PM. Diagnosis of primary aldosteronism: from screening to subtype differentiation. *Trends Endocrinol Metab* 2005; **16**:114–119.
- 60 Sealey JE, Gordon RD, Mantero F. Plasma renin and aldosterone measurements in low renin hypertensive states. *Trends Endocrinol Metab* 2005; **16**:86–91.
- 61 Rossi GP, Seccia TM, Pessina AC. Clinical use of laboratory tests for the identification of secondary forms of arterial hypertension. *Crit Rev Clin Lab Sci* 2007; **44**:1–85.
- 62 Agharazii M, Douville P, Grose JH, Lebel M. Captopril suppression versus salt loading in confirming primary aldosteronism. *Hypertension* 2001; **37**:1440–1443.
- 63 Castro OL, Yu X, Kem DC. Diagnostic value of the postcaptopril test in primary aldosteronism. *Hypertension* 2002; **39**:935–938.
- 64 Kem DC, Weinberger MH, Mayes DM, Nugent CA. Saline suppression of plasma aldosterone in hypertension. *Arch Intern Med* 1971; **128**:380–386.
- 65 Holland OB, Brown H, Kuhnert L, Fairchild C, Risk M, Gomez-Sanchez CE. Further evaluation of saline infusion for the diagnosis of primary aldosteronism. *Hypertension* 1984; **6**:717–723.
- 66 Rossi GP, Bellioren A, Bernini G, Desideri G, Fabris B, Ferri C, *et al.* Comparison of the captopril and the saline infusion test for excluding aldosterone-producing adenoma. *Hypertension* 2007; **50**:424–431.
- 67 Rossi GP, Bellioren 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 Hypertension* 2007; **25**:1433–1442.
- 68 Dluhy RG, Lifton RP. Glucocorticoid-remediable aldosteronism. *J Clin Endocrinol Metab* 1999; **84**:4341–4344.
- 69 Seccia TM, Fassina A, Nussdorfer GG, Pessina AC, Rossi GP. Aldosterone-producing adrenocortical carcinoma: an unusual cause of Conn's syndrome with an ominous clinical course. *Endocr Relat Cancer* 2005; **12**:149–159.
- 70 Wajiki M, Ogawa A, Fukui J, Komiya I, Yamada T, Maruyama Y. Coexistence of aldosteronoma and pheochromocytoma in an adrenal gland. *J Surg Oncol* 1985; **28**:75–78.
- 71 Gordon RD, Bachmann AW, Klemm SA, Tunny TJ, Stowasser M, Storie WJ, *et al.* Rutherford JC. An association of primary aldosteronism and adrenaline-secreting pheochromocytoma. *Clin Exp Pharmacol Physiol* 1994; **21**:219–222.
- 72 Tan GH, Carney JA, Grant CS, Young WF Jr. Coexistence of bilateral adrenal pheochromocytoma and idiopathic hyperaldosteronism. *Clin Endocrinol (Oxf)* 1996; **44**:603–609.
- 73 Mannhart M, Ludin H, Veyrat R, Ziegler WH. Secondary hyperaldosteronism caused by cervical pheochromocytoma cured by ablation of the tumor. *Helv Med Acta* 1971; **35**:479–483.
- 74 Kitajima W, Saruta T, Kondo K, Yamada R, Aoki S, Nagakubo I. A case of secondary aldosteronism induced by pheochromocytoma. *J Urol* 1975; **114**:141–143.
- 75 Goh BK, Tan YH, Chang KT, Eng PH, Yip SK, Cheng CW. Primary hyperaldosteronism secondary to unilateral adrenal hyperplasia: an unusual cause of surgically correctable hypertension. A review of 30 cases. *World J Surg* 2007; **31**:72–79.
- 76 Omura M, Sasano H, Fujiwara T, Yamaguchi K, Nishikawa T. Unique cases of unilateral hyperaldosteronemia due to multiple adrenocortical micronodules, which can only be detected by selective adrenal venous sampling. *Metabolism* 2002; **51**:350–355.
- 77 Haenel LC, Hermayer KL. A case of unilateral adrenal hyperplasia: the diagnostic dilemma of hyperaldosteronism. *Endocr Pract* 2000; **6**:153–158.
- 78 Morioka M, Kobayashi T, Sone A, Furukawa Y, Tanaka H. Primary aldosteronism due to unilateral adrenal hyperplasia: report of two cases and review of the literature. *Endocr J* 2000; **47**:443–449.
- 79 Katayama Y, Takata N, Tamura T, Yamamoto A, Hirata F, Yasuda H, *et al.* A case of primary aldosteronism due to unilateral adrenal hyperplasia. *Hypertens Res* 2005; **28**:379–384.
- 80 Hirono Y, Doi M, Yoshimoto T, Kanno K, Himeno Y, Taki K, *et al.* A case with primary aldosteronism due to unilateral multiple adrenocortical micronodules. *Endocr J* 2005; **52**:435–439.
- 81 Stowasser M, Klemm SA, Tunny TJ, Storie WJ, Rutherford JC, Gordon RD. Response to unilateral adrenalectomy for aldosterone-producing adenoma: effect of potassium levels and angiotensin responsiveness. *Clin Exp Pharmacol Physiol* 1994; **21**:319–322.
- 82 Gordon RD. Primary aldosteronism. *J Endocrinol Invest* 1995; **18**:495–511.
- 83 Stowasser M, Gordon RD, Rutherford JC, Nikwan NZ, Daunt N, Slater GJ. Diagnosis and management of primary aldosteronism. *J Renin Angiotensin Aldosterone Syst* 2001; **2**:156–169.
- 84 Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, *et al.* Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab* 2004; **89**:1045–1050.
- 85 Rossi GP, Chiesura-Corona M, Tregnaghi A, Zanin L, Perale R, Soattin S, *et al.* Imaging of aldosterone-secreting adenomas: a prospective comparison of computed tomography and magnetic resonance imaging in 27 patients with suspected primary aldosteronism. *J Hum Hypertens* 1993; **7**:357–363.
- 86 Fallo F, Barzon L, Boscaro M, Sonino N. Coexistence of aldosteronoma and contralateral nonfunctioning adrenal adenoma in primary aldosteronism. *Am J Hypertens* 1997; **10**:476–478.
- 87 Magill SB, Raff H, Shaker JL, Brickner RC, Knechtges TE, Kehoe ME, *et al.* Comparison of adrenal vein sampling and computed tomography in the differentiation of primary aldosteronism. *J Clin Endocrinol Metab* 2001; **86**:1066–1071.
- 88 Mantero F, Terzolo M, Arnaldi G, Osella G, Masini AM, Ali A, *et al.* A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. *J Clin Endocrinol Metab* 2000; **85**:637–644.
- 89 Young WF, Stanson AW, Thompson GB, Grant CS, Farley DR, van Heerden JA. Role for adrenal venous sampling in primary aldosteronism. *Surgery* 2004; **136**:1227–1235.
- 90 Omura M, Sasano H, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Clinical characteristics of aldosterone-producing microadenoma, macroadenoma, and idiopathic hyperaldosteronism in 93 patients with primary aldosteronism. *Hypertens Res* 2006; **29**:883–889.
- 91 Rossi GP. New concepts in adrenal vein sampling for aldosteronism in the diagnosis of primary aldosteronism. *Curr Hypertens Rep* 2007; **9**:90–97.
- 92 Hogan MJ, McRae J, Schambelan M, Biglieri EG. Location of aldosterone-producing adenomas with 131I-19-iodocholesterol. *N Engl J Med* 1976; **294**:410–414.
- 93 Nomura K, Kusakabe K, Maki M, Ito Y, Aiba M, Demura H. Iodomethylnorcholesterol uptake in an aldosteronoma shown by dexamethasone-suppression scintigraphy: relationship to adenoma size and functional activity. *J Clin Endocrinol Metab* 1990; **71**:825–830.
- 94 Vetter H, Fischer M, Galanski M, Stieber U, Tenschert W, Baumgart P, *et al.* Primary aldosteronism: diagnosis and noninvasive lateralization procedures. *Cardiology* 1985; **72** (Suppl 1):57–63.
- 95 Mansoor GA, Malchoff CD, Arici MH, Karimeddini MK, Whalen GF. Unilateral adrenal hyperplasia causing primary aldosteronism: limitations of I-131 norcholesterol scanning. *Am J Hypertens* 2002; **15**:459–464.
- 96 Kaplan NM. The current epidemic of primary aldosteronism: causes and consequences. *J Hypertens* 2004; **22**:863–869.

- 97 Gordon RD, Stowasser M, Tunny TJ, Klemm SA, Finn WL, Krek AL. Clinical and pathological diversity of primary aldosteronism, including a new familial variety. *Clin Exp Pharmacol Physiol* 1991; **18**:283–286.
- 98 Stowasser M, Gordon RD. Familial hyperaldosteronism. *J Steroid Biochem Mol Biol* 2001; **78**:215–229.
- 99 Ulick S, Levine LS, Gunczler P, Zancanato G, Ramirez LC, Rauh W, *et al.* A syndrome of apparent mineralocorticoid excess associated with defects in the peripheral metabolism of cortisol. *J Clin Endocrinol Metab* 1979; **49**:757–764.
- 100 New MI, Geller DS, Fallo F, Wilson RC. Monogenic low renin hypertension. *Trends Endocrinol Metab* 2005; **16**:92–97.
- 101 Stewart PM, Corrie JE, Shackleton CH, Edwards CR. Syndrome of apparent mineralocorticoid excess. A defect in the cortisol-cortisone shuttle. *J Clin Invest* 1988; **82**:340–349.
- 102 Edwards CR, Stewart PM, Burt D, Brett L, McIntyre MA, Sutanto WS, *et al.* Localisation of 11 beta-hydroxysteroid dehydrogenase: tissue specific protector of the mineralocorticoid receptor. *Lancet* 1988; **2**:986–989.
- 103 Funder JW, Pearce PT, Smith R, Smith AL. Mineralocorticoid action: target tissue specificity is enzyme, not receptor, mediated. *Science* 1988; **242**:583–585.
- 104 Wilson RC, Krozowski ZS, Li K, Obeyesekere VR, Razzaghy-Azar M, Harbison MD, *et al.* A mutation in the HSD11B2 gene in a family with apparent mineralocorticoid excess. *J Clin Endocrinol Metab* 1995; **80**:2263–2266.
- 105 Mune T, Rogerson FM, Nikkila H, Agarwal AK, White PC. Human hypertension caused by mutations in the kidney isozyme of 11 beta-hydroxysteroid dehydrogenase. *Nat Genet* 1995; **10**:394–399.
- 106 Stewart PM, Krozowski ZS, Gupta A, Milford DV, Howie AJ, Sheppard MC, *et al.* Hypertension in the syndrome of apparent mineralocorticoid excess due to mutation of the 11 beta-hydroxysteroid dehydrogenase type 2 gene. *Lancet* 1996; **347**:88–91.
- 107 Monder C, Shackleton CH, Bradlow HL, New MI, Stoner E, Iohan F, *et al.* The syndrome of apparent mineralocorticoid excess: its association with 11 beta-dehydrogenase and 5 beta-reductase deficiency and some consequences for corticosteroid metabolism. *J Clin Endocrinol Metab* 1986; **63**:550–557.
- 108 Stewart PM, Wallace AM, Valentino R, Burt D, Shackleton CH, Edwards CR. Mineralocorticoid activity of liquorice: 11-beta-hydroxysteroid dehydrogenase deficiency comes of age. *Lancet* 1987; **2**:821–824.
- 109 Farese RV Jr, Biglieri EG, Shackleton CH, Irony I, Gomez-Fontes R. Licorice-induced hypermineralocorticoidism. *N Engl J Med* 1991; **325**:1223–1227.
- 110 Canessa CM, Schild L, Buell G, Thorens B, Gautschi I, Horisberger JD, *et al.* Amiloride-sensitive epithelial Na⁺ channel is made of three homologous subunits. *Nature* 1994; **367**:463–467.
- 111 Shimkets RA, Warnock DG, Bosisis CM, Nelson-Williams C, Hansson JH, Schambelan M, *et al.* Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. *Cell* 1994; **79**:407–414.
- 112 Hansson JH, Nelson-Williams C, Suzuki H, Schild L, Shimkets R, Lu Y, *et al.* Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. *Nat Genet* 1995; **11**:76–82.
- 113 Hansson JH, Schild L, Lu Y, Wilson TA, Gautschi I, Shimkets R, *et al.* A de novo missense mutation of the beta subunit of the epithelial sodium channel causes hypertension and Liddle syndrome, identifying a proline-rich segment critical for regulation of channel activity. *Proc Natl Acad Sci U S A* 1995; **92**:11495–11499.
- 114 Luft FC. Molecular genetics of salt-sensitivity and hypertension. *Drug Metab Dispos* 2001; **29**:500–504.
- 115 Botero-Velez M, Curtis JJ, Warnock DG. Brief report: Liddle's syndrome revisited: a disorder of sodium reabsorption in the distal tubule. *N Engl J Med* 1994; **330**:178–181.
- 116 Persu A, Barbry P, Bassilana F, Houot AM, Mengual R, Lazdunski M, *et al.* Genetic analysis of the beta subunit of the epithelial Na⁺ channel in essential hypertension. *Hypertension* 1998; **32**:129–137.
- 117 Hummler E, Horisberger JD. Genetic disorders of membrane transport. V. The epithelial sodium channel and its implication in human diseases. *Am J Physiol* 1999; **276**:G567–G571.
- 118 Toniato A, Bernante P, Rossi GP, Piotto A, Pelizzo MR. Laparoscopic versus open adrenalectomy: outcome in 35 consecutive patients. *Int J Surg Investig* 2000; **1**:503–507.
- 119 Jeschke K, Janetschek G, Peschel R, Schellander L, Bartsch G, Henning K. Laparoscopic partial adrenalectomy in patients with aldosterone-producing adenomas: indications, technique, and results. *Urology* 2003; **61**:69–72.
- 120 Meria P, Kempf BF, Hermieu JF, Plouin PF, Duclos JM. Laparoscopic management of primary hyperaldosteronism: clinical experience with 212 cases. *J Urol* 2003; **169**:32–35.
- 121 Sawka AM, Young WF, Thompson GB, Grant CS, Farley DR, Leibson C, *et al.* Primary aldosteronism: factors associated with normalization of blood pressure after surgery. *Ann Intern Med* 2001; **135**:258–261.
- 122 Lumachi F, Ermani M, Basso SM, Armanini D, Iacobone M, Favia G. Long-term results of adrenalectomy in patients with aldosterone-producing adenomas: multivariate analysis of factors affecting unresolved hypertension and review of the literature. *Am Surg* 2005; **71**:864–869.
- 123 Obara T, Ito Y, Okamoto T, Kanaji Y, Yamashita T, Aiba M, *et al.* Risk factors associated with postoperative persistent hypertension in patients with primary aldosteronism. *Surgery* 1992; **112**:987–993.
- 124 Proye CA, Mulliez EA, Carnaille BM, Lecomte-Houcke M, Decouls M, Wemeau JL, *et al.* Essential hypertension: first reason for persistent hypertension after unilateral adrenalectomy for primary aldosteronism? *Surgery* 1998; **124**:1128–1133.
- 125 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341**:709–717.
- 126 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, *et al.* Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**:1309–1321.
- 127 Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* 2005; **45**:1243–1248.