Per Hellman *Editor*

Primary Aldosteronism

Molecular Genetics, Endocrinology, and Translational Medicine

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Preface

Primary aldosteronism (PA) may be the best treatable risk factor for cardiovascular disease besides to quit smoking. The discovery of the disease is described in Prof. Gordon's chapter in this book, and the understanding of its prevalence and the epidemiology behind it as well. Thus, PA is common, and millions and millions of individuals worldwide most likely suffer from undiagnosed PA as an underlying reason for their hypertension. To improve the diagnose of PA, understand the derangements and what consequence untreated PA lead to is crucial for development of care of individuals with PA.

Consequences of PA are bearing the risk factor not only for cardiovascular disease but also on life quality. Drs. Stowasser and Ahmed describe the important QoL assessments that have been done until now in one section of this book. It is clear that improvement of QoL is the effect of medical as well as surgical treatment, with a more rapid effect after surgical treatment. Besides the positive effects seen by the reduced blood pressure per se, also less need of medication with reduced negative side-effects with benefits surgery. Reversal of PA also leads to positive effects on various psychological measures, caused by so far unknown mechanisms. Aldosterone is a risk factor for cardiovascular disease, which may be reduced by proper treatment of PA. Thus, there is a higher incidence of cardiovascular events in PA-associated hypertension than in age- and sex-matched populations with essential hypertension.

The diagnostic procedures for PA are discussed in several chapters in this book, commenting on the aldosterone–renin ratio (ARR), confirmatory testings, and the adrenal venous sampling. In clear cases the diagnosis is easy, but in the majority these methods may certainly be beyond the sensitivity level. Thus, a major issue is identification and treatment of early or "subclinical" PA, among patients with essential hypertension. Indeed, there seems to be a continuum of this disease into the entity denoted low-renin hypertension, which in many cases is a mild form of early or subclinical PA. Indices state that this form of the disease is also associated with increased risk for cardiovascular complications and possibly reduced QoL. Today, the method of choice to identify PA is the aldosterone/renin ratio, which has been

used also for screening of populations with essential hypertension. However, this method has a number of drawbacks as being sensitive for ongoing medications, posture, diet, etc. In addition, assays of aldosterone and, especially, renin have been unsensitive. Although the ARR still is the most available method to possibly identify also early PA, a continuous search for alternative diagnostic methods to increase the possibility to identify also early "subclinical" PA is needed.

If performing the ARR is a problem, also the confirmatory testings are sometimes difficult with far less than 100 % sensitivity and specificity. Moreover, lateralization may be determined by adrenal venous sampling, but it also has its well-known technical difficulties. Recent development in using positron emission tomography (PET) by, for instance, ^{11}C-metomidate as tracer after Dexamethasone suppression is promising in distinguishing aldosterone-producing from hormonally inactive adenomas.

The recent developments in understanding the genetics behind sporadic PA may lead to novel methods to diagnose the disease in the future. Although no success has been described yet in identifying, for instance, mutated KCNJ5 in plasma samples, further investigations are needed. The identification of mutations in KCNJ5, ATP1A, ATP2B3, and CACNA1D has also made understanding of the pathophysiology of the zona glomerulosa cells more clear. The importance of the membrane potential and depolarization for release of aldosterone is obvious.

Treatment of PA is either medical or surgical. The medical treatment of PA is limited to spironolactone and eplerenone, where the latter has considerably less side effects. This is recommended especially in idiopathic hyperaldosteronism (IHA) where surgery has limited effect due to its bilateral cause. However, in certain cases with assymetrical nodular hyperplasia, a unilateral adrenalectomy may still be beneficial. Interestingly, Dr. Takeda and coworkers comment on the possible epigenetic factors influencing the disease, by proposing that the methylation of CpG islands in the CYP11B2 promoter region may regulate the activity of transcription of this gene, and consequently the amount of aldosterone produced and the level of PA. Long-term treatment with, for instance, spironolactone has in some cases induced, or being associated with, remission of the PA, possibly due to a changed methylation status.

While medical treatment in cases with IHA or milder forms may be successful, surgical treatment has an excellent outcome, and today the laparo- or retroperitoneoscopic approach is an easy procedure for the patient who may leave the hospital the following day. Reversal of PA is instant after surgery, with a dramatic reduction of the number of hypertensive drugs and no need for potassium supplementation, as well as improved QOL and reduction of risk for cardiovascular complications.

The present book presents the disease of primary aldosteronism from pathophysiology to quality-of-life aspects, covering genetics, diagnostics, and different treatments in a truly translational manner.

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Contents

Chapter 1
Primary Aldosteronism: Molecular Mechanisms and Diagnosis

Gian Paolo Rossi and Livia Lenzini

Abstract Primary aldosteronism (PA) is the most common endocrine form of high blood pressure (BP) and causes excessive organ damage to the heart, vessels, and kidneys, which translates into an excess of cardiovascular events.

When the diagnosis is made early on and an appropriate therapy is timely instituted, the hyperaldosteronism and the hypokalemia can be cured in practically all the cases, while the arterial hypertension is cured in about 40 % of the cases and BP control markedly ameliorated in the rest. Thus, an aggressive diagnostic approach in hypertensive patients is justified.

The recent discoveries with molecular biology techniques have led to the identification of some mechanisms that can explain the persistent hyperaldosteronism in spite of the high BP, the hypokalemia, and the suppression of renin, all factors that would be expected to shut down aldosterone secretion.

The purpose of this chapter is to provide updated information on molecular genetics of PA and the diagnostic strategy for case detection and subtype differentiation of PA. While a cost effective strategy for the screening of patients with PA can be exploited at most centers, the identification of its subtypes involves adrenal vein sampling, which is a procedure technically difficult to perform and interpret. Therefore, it should be undertaken at tertiary referral centers with experience in performing and interpreting this test.

Keywords Arterial hypertension • Aldosterone • Primary aldosteronism • Diagnosis

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Introduction

Primary aldosteronism (PA) is a common, albeit markedly under diagnosed, cause of curable arterial hypertension, which is characterized by an increased secretion of aldosterone that is apparently autonomous of the renin–angiotensin system (RAS), because renin is suppressed. This translates into sodium and water retention and potassium loss with hypokalemia. In the presence of a high-to-normal sodium intake, the hyperaldosteronism exerts several detrimental effects [1–19] on the cardiovascular system, which ultimately translate into an excess rate of atrial fibrillation, ischemic stroke [19–21], and cerebral hemorrhage [22], "flash" pulmonary edema, and myocardial infarction [21]. The early identification PA followed by diagnosis of its subtypes, which entail surgically curable and surgically incurable causes (Table 1.1) [23], is key since in the former adrenalectomy cures PA and in the latter institution of specific drug treatment can avoid the ominous consequences of PA, including prominent target organ damage and cardiovascular events.

Molecular Mechanisms of PA

Aldosterone is synthesized from cholesterol in the mitochondria of the adrenocortical zona glomerulosa (ZG) cells. The regulation of this biosynthesis occurs acutely through the increase of cholesterol entry into the mitochondria and chronically by changing the expression of enzymes involved in ZG steroidogenesis, such as the aldosterone synthase, which is responsible for the final step of aldosterone biosynthesis and is encoded by the CYP11B2 gene. When systematically investigated in

Table 1.1 Forms of primary aldosteronism

Surgically curable
Aldosterone-producing adenoma (aldosteronoma)
Unilateral
Bilateral
Primary unilateral adrenal hyperplasia
Multinodular unilateral adrenocortical hyperplasia
Ovary aldosterone-secreting tumor
Familial type II hyperaldosteronism
Familial type III hyperaldosteronism (requiring bilateral adrenalectomy)
Aldosterone-producing adenoma or bilateral adrenal hyperplasia with concomitant pheochromocytoma
Aldosterone-producing carcinoma
Surgically not curable
Bilateral adrenal hyperplasia
Unilateral aldosterone-producing adenoma with bilateral adrenal hyperplasia
Familial type I hyperaldosteronism (also known as glucocorticoid-remediable aldosteronism)

aldosterone-producing adenoma (APA), unexpectedly this gene was not found to be consistently overexpressed as these tumors exhibited heterogeneous levels of the CYP11B2 transcript, indicating a high degree of complexity in the regulation of aldosterone production in PA [24].

It is well established that the major regulators of aldosterone production are angiotensin II, ACTH, endothelin-1, and the extracellular level of potassium (K^+). The former three stimuli were not found to be activated in human PA and therefore are unlikely to play a key role in maintaining the hyperaldosteronism in PA. At variance, the role of K^+ has been emphasized by recent findings: K^+ is a key modulator of aldosterone secretion as small elevations in its serum levels even within the physiological range increase the sensitivity of ZG cells to angiotensin (Ang) II and other secretagogue stimuli. These K^+ oscillations are held to depolarize the cell leading to opening of T-type-low-voltage-activated calcium channels, and thereby to Ca^{2+}-triggered aldosterone synthesis and cell growth. Recently, molecular variants of K^+ Channels genes have been associated with phenotypes mimicking PA in animal models and in humans [25–47].

Moreover, a germinal mutation in the KCNJ5 gene coding for the Kir3.4 potassium channel has recently been described to cause a rare familial form of PA featuring severe drug-resistant high BP and massive bilateral hyperplasia that required bilateral adrenalectomy (Familial Hyperaldosteronism type III) [29, 34, 38, 42]. Besides this exceedingly rare germinal variant, several somatic KCNJ5 mutations were found to occur in approximately one-third of the APA [25, 27, 28, 31–33, 39–42]. All of these variants are located in the selectivity filter of the channel, e.g., the region that confers selectivity for K^+. They were found to be functional in that they cause loss of ion specificity of the channel leading to Na^+ entry and thus to cell depolarization with subsequent opening of T-type Ca^{2+} Channels [35–37, 42]. Besides these mutations, exome sequencing recently revealed additional mutations in the ATP1A1 and ATP2B3 [48] and in the calcium channel CACNA1D [49, 50]. The common denominator of all these changes would be enhanced Ca^{2+} entry with ensuing stimulation of steroidogenesis. However, the reasons for the occurrence of these mutations remain unknown although at this stage it would seem that they represent a mechanism whereby hyperaldosteronism once developed is maintained rather than the initial trigger of the disease. It remains unclear if these mutations are responsible also for enhanced cell proliferation leading to APA development or only for persistent aldosterone excess, as in vitro experiments in transfected cells would support the latter but not the former contention [35, 37, 42].

Overall available data allow the conclusion that molecular alterations of cell handling of K^+ are instrumental in maintaining overproduction of aldosterone in a subset of APA, in spite of the high BP, the suppression of Angiotensin II and the hypokalemia, all factors that occur in PA and by themselves would be expected to blunt aldosterone production. This contention is supported by findings in different animal models in which inactivation of other K^+ channels, the Twik Related Acid Sensitive K^+ (TASK) 1 and/or 3 created a phenotype similar to human PA featuring hyperaldosteronism, sodium-dependent high blood pressure, low plasma renin and low K^+ [45]. These channels generate background, or "leak," K^+ currents that are

essential for maintaining a negative resting membrane potential. The homozygous knockout of only one of these channels generated two distinct forms of hyperaldosteronism: the inactivation of TASK-1 caused a severe hyperaldosteronism with low-renin hypertension and a defective adrenocortical zonation, which were glucocorticoid-remediable, albeit only in females [46]. At variance, the knockout of TASK-3 in mice caused a low-renin and salt-sensitive form of hypertension [44, 47].

Recent discoveries, however, have drawn attention also to other molecular mechanisms that can drive aldosterone overproduction in APA. An elevated serum titer of angiotensin-II type-1 receptor auto-antibodies (AT1AA) in patients with an APA, and not with bilateral adrenal hyperplasia was discovered [51]. The peculiar increase of AT1AA in APA patients could have both functional and clinical consequences. In fact, these tumors were found to express functional AT1 receptors and moreover, a considerable proportion of them are responsive to Ang-II. Hence, it might be that these agonistic autoantibodies against type-1 angiotensin-II receptor stimulate aldosterone secretion and trigger the development of hyperplastic changes in the ZG of PA patients. From the clinical standpoint the unique increase in APA and not in IHA can be helpful in selecting the patients to be submitted to adrenal vein sampling.

Another recent study from our group showed that patients with APA have a 31 % higher parathormone (PTH) levels than demographically comparable primary (essential) hypertension patients with similarly elevated blood pressure values [52]. A mild increase of PTH can therefore be a further, albeit hitherto unappreciated, feature of APA that can be useful in pinpointing the patients with these tumors [52]. Moreover, the increase of PTH could be a factor contributing to the persistent hyperaldosteronism in that PTH was shown to concentration-dependently increase aldosterone secretion from human ZG and APA cells in primary culture [53].

In summary, the past 5 years have witnessed unprecedented progresses in the understanding of the molecular mechanisms responsible of human PA. The impact of this novel knowledge in terms of prevention and treatment of this common cause of human hypertension is yet to be fully deployed.

Implications for Case Detection of the High Prevalence of PA

Notwithstanding the fact that normokalemic PA was described in 1965 [54–56], most doctors still believe that hypokalemia is a *conditio sine qua non* of the disease. Hence, they are alerted to search for PA only if hypertensive patients are hypokalemic, which implies that many patients who can have PA, but are not hypokalemic, are not subjected to any investigations to detect PA. This can explain why PA has been markedly under diagnosed and therefore its prevalence has been underestimated among hypertensive patients.

The first large prospective survey designed to furnish solid data on PA prevalence, the PAPY (*P*rimary *A*ldosteronism *P*revalence in h*Y*pertensives) Study, was eventually reported in 2006 [57].

Table 1.2 Cohorts of patients with increased chance of primary aldosteronism

• Resistant hypertension
• Grade 2 or 3 hypertension
• Spontaneous or diuretic-induced hypokalemia
• Incidentally discovered apparently nonfunctioning adrenal mass (incidentaloma)
• Early onset (juvenile) hypertension and/or stroke (<50 years)

Patients with hypertension who also have one or more of these conditions have an increased pretest probability of primary aldosteronism

Using a thorough diagnostic workup and a rigorous set of criteria aimed at establishing the presence of PA, and of its subtype [58], this study evidenced that PA involves 11.2 % of consecutive newly diagnosed hypertensive patients referred to hypertension centers. More importantly, it showed that 4.8 % of the 1,125 patients that were recruited had a surgically curable subtype, which led, the investigators to conclude that PA is the most common endocrine form of hypertension and can be curable in almost half of the cases.

Knowledge of the exact prevalence rate of a disease is fundamental for estimating, along with clinical assessment, the prior probability of PA in individual patients, which in turn is key for deciding whether to proceed with further diagnostic tests. The incremental gain of a diagnostic test is in fact maximized when the patient's prior probability of a disease is between 10 and 30 %. Hence, with a documented high prevalence of PA of 11.2 % in hypertensive patients [57, 59–73] by selecting the categories of patients to be screened (Table 1.2) [74], one could enrich the PA prevalence and therefore make the screening cost-effective.

Screening Strategy

The Endocrine Society guidelines [74] suggested a case detection strategy, which is based on the aforementioned considerations (reviewed in [75]), according to which the screening tests should be performed only in patients with a higher pretest probability of PA (Table 1.2).

However, considering the high prevalence rate of PA [57], and the possibility of preventing cardiovascular complications with an early diagnosis and specific treatment [76], other experts favor a wider strategy, e.g., screening of all newly presenting hypertensive patients. Implementation of this strategy could be too challenging on the health care system of many countries and therefore the decision on what to do depends on several aspects, some of which related to the patient's features and some to the level of health care that a given country can provide.

Nonetheless, the screening is mandatory in the categories of patients listed in Table 1.2, particularly if the patients are reasonable candidate for adrenalectomy and/or have resistant hypertension. Some additional categories of patients could be included in this list, because of a higher risk of PA, including those with evidence of target organ disproportionate to their blood pressure levels, those with obstructive sleep apnea syndrome and patients with hypertension and overweight/obesity [77, 78].

Biochemical Diagnosis

In all these patients the first step for the diagnosis of PA requires the demonstration of a hyperaldosteronism that is autonomous from the RAS. The aldosterone-to-renin ratio (ARR) represents a simplified approach to this goal [79], but its proper use requires consideration to several issues that are discussed in depth elsewhere [80]. Since the ARR value depends on plasma aldosterone concentration (PAC) and on renin, a suppressed renin value will increase the ARR even when PAC is normal. Therefore, a high ARR should be considered as diagnostic for PA only if the PAC is elevated, e.g., ≥15 ng/dL.

Currently available assays for plasma renin activity (PRA) and for direct active renin (DRA) lose their precision in the low range. Therefore, to avoid overinflating the ratio ARR when renin is very low, it is common to fix the lowest renin value at a minimum (which is 0.2 ng/mL/h for PRA and 0.6 mIU/dL (0.36 ng/mL) for DRA) [57, 58]. These precautions are fundamental in the elderly and the population of African origin who usually have low PRA values. Thus, the ARR should not be used in a purely arithmetic manner, but rather interpreted as indicative of PA if a combination of increased ARR and a PAC > 15 ng/dL is found. It has indeed to be acknowledged that the ARR is a crude bivariate analysis. Based on strong theoretical considerations multivariate discriminant analysis strategies can achieve a more accurate identification of PA [63]. They have the additional advantage of furnishing an estimate of the individual patient's probability of PA, which enables clinicians to decide on whether to proceed with further testing [57].

It is worth reckoning that the ARR was shown to be reproducible when repeated under carefully standardized conditions [57, 81], and carries quantitative information. Therefore, an ARR value that was properly determined and resulted to be markedly elevated represents a strong indication of the presence of PA. An ARR value that is not markedly elevated, particularly when a carryover effect of drug treatment cannot be ruled out, should be confirmed at retesting under proper conditions, before being considered as an indication to proceed to AVS [81].

Finally, some important points must to be made concerning the assay to be used for renin measurement. The DRA assay is gaining popularity because it requires handling the samples at room temperature (for review [75]) [82, 83]. On the other hand, when using the PRA assay, handling plasma at room temperature can lead to angiotensin I generation and angiotensinogen consumption, and thus to underestimation of renin. If the samples are properly collected for each assay, the DRA and PRA values show a good correlation; which is and stronger when renin is stimulated weaker in the low range values [84], where the PA patients typically are, because the precision of either assay diminishes in this low range [84]. Moreover, it has, however, to be acknowledged that only one study has prospectively documented the feasibility of using the ARR based on the DRA for identifying APA to date [84], and therefore further experience should be gained before replacement of the PRA could be advised.

Conditions for Testing

A careful preparation of the patient is a key step in the screening because several factors and most antihypertensive drugs affect either PAC or renin values or both, and thereby the ARR (Table 1.3). Treatment must therefore be modified before measuring these hormones.

Importantly, some agents have negligible effects on the ARR: the alpha$_1$-receptor blocker doxazosin minimally affect the renin–angiotensin–aldosterone system, while the long-acting calcium channel blockers (CCB) have a small blunting effect on aldosterone secretion [57, 85, 86]. These agents can therefore be used, alone or in combination, to control blood pressure at screening if withdrawal of the antihypertensive treatment is harmful [57]. If the patient needs a more complex treatment, knowledge of the effect of the different drugs on the ARR and its components (Table 1.4) can assist in interpreting the ARR and making the correct diagnosis: a high PAC in a patient on drugs that should lower aldosterone, and/or a blunted renin value on agents that are expected to raise renin secretion are strong clues to the presence of PA.

Table 1.3 Suggestions for the correct use of the ARR as a screening test

Factors affecting ARR	Suggestion
Serum levels of potassium	Correct hypokalemia, if present, before performing the test to avoid false negative ARR values
PAC	Be aware that high PAC might originate from low salt intake or use of diuretics
	Prepare patient with adequate salt intake, measure 24 h urinary sodium excretion
	Withdraw diuretics at least 3–4 weeks before testing; mineralocorticoid receptor antagonists at least 6 weeks before testing
Renin assay	Because of low precision of the PRA or DRA assay for low renin values, fix the lowest level of renin to be used in the ARR
Patient position and blood sampling	Standardize the position of the patient and sampling conditions at your center
Handling of the samples	Be aware that handling and storage of plasma samples differ for PRA and DRA assays
Drugs	α_1-receptor blocker doxazosin and long-acting calcium channel blockers are allowed
ARR accuracy	The cutoff value that provides the best combination of sensitivity and specificity should be identified at each center by ROC curves
	Be aware that the ARR is a crude bivariate analysis and that multivariate logistic discriminant analysis might provide better diagnostic accuracy

ARR aldosterone–renin ratio, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *DRA* direct active renin, *ROC* receiver operating characteristic

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