Steroid Characteristics of Mineralocorticoid Adrenocortical Hypertension

Edward G. Biglieri and Claudio E. Kater

Adrenocortical causes of hypertension are established by examining the mineralocorticoid hormones produced in the zona glomerulosa and zona fasciculata. In the zona glomerulosa, aldosterone excess leads to hypertension, hypokalemia, and suppressed plasma renin activity, with increased concentrations of urinary aldosterone (either as the 18-glucuronide or free aldosterone) as an index of its production. Identifying a tumor by computed tomography scan verifies the diagnosis of a correctable lesion. If no tumor is found, several maneuvers are used to identify primary adrenal hyperplasia, a disorder with autonomous aldosterone production, for which reduction of adrenal mass is curative. The zona fasciculata has two major pathways: the 17-deoxy pathway, where deoxycorticosterone (DOC) and corticosterone are the significant steroids, and the 17-hydroxy pathway, which leads to cortisol production. Tumors of the 17-deoxy pathway, DOC-producing adenomas, have increased concentrations of DOC and its precursor steroids, normal concentrations of cortisol, and suppression of aldosterone production secondary to suppression of the renin system. Two enzymatic defects in the zona fasciculata, 11β- and 17α-hydroxylase deficiency, can be readily identified by the virilization in the former, hypogonadal features in the latter. Steroid patterns are diagnostic. DOC is produced in excess in both deficiencies and is the cause of the hypertension. Deficient or impaired 11β-hydroxy steroid dehydrogenase in the apparent mineralocorticoid excess syndrome or after licorice ingestion retards the conversion of cortisol to inactive cortisone in the kidney, leading to mineralocorticoid hypertension; this leads to suppression of the renin system and subsequently of aldosterone.

Although the history, physical examination, and laboratory confirmation are the necessary ingredients of a diagnosis of hormonal disorders, the measurement of specific steroids is required to accurately identify the disorder. The history is of paramount importance in patients with pheochromocytoma, the physical examination singles out Cushing syndrome, and the laboratory confirms the diagnosis of the former and establishes the diagnosis of hypermineralocorticoidism.

Each of the major zones of the adrenal cortex—zona glomerulosa, zona fasciculata (ZF), and zona reticularis—have orderly sequences of steroid production.

The zonal products result in a unique clinical type of steroid hypertension (Figure 1). Virtually all adrenocortical forms of hypertension display evidence of hypermineralocorticoidism attributable to different steroids. The hallmarks of hypermineralocorticoidism are hypertension (mild to severe), hypokalemia (renal potassium wasting), and suppression of the renin—angiotensin system (Table 1) (1, 2).

Hypertension may well be labile, with normal blood pressure values often being achieved in a research or hospital setting or with ingestion of low-sodium diets. However, this situation is rare, as is malignant hypertension. The conditions for measuring electrolytes in serum or plasma must be consonant with the conditions under which normal values are established. A measurement after overnight fasting is the more ideal setting. Potassium concentrations may be decreased because of restricted dietary intake, while on diuretic therapy, or may be falsely increased because of previous spironolactone therapy, a recent meal, or vigorous fist clenching before phlebotomy (1). Although measurements of plasma renin activity can also vary with posture, diet, activity, and medications (e.g., β-blockers, converting enzyme inhibitors), if a hypermineralocorticoid state is present and the patient is not taking renin-modifying drugs, the plasma renin will be decreased regardless of physiological modifiers.

**General Characteristics of Hypermineralocorticoid Hypertension**

All patients with confirmed hypertension and hypokalemia are suspect for hypermineralocorticoid hypertension (Figure 2); suppression of plasma renin establishes this state (Figure 3). The assessment of increased production of urinary aldosterone confirms

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1 Nonstandard abbreviations: ZF, zona fasciculata; PAH, primary adrenal hyperplasia; IHA, idiopathic hyperaldosteronism; APA, aldosterone-producing adenoma; DOC, deoxycorticosterone; 18-OHB, 18-hydroxycorticosterone; 21-OH, 11β-OHD, 17α-OHD, deficiencies of 21-, 11β-, and 17α-hydroxylases, respectively.

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Table 1. Zona Glomerulosa Disorders

Primary aldosteronism
Aldosterone-producing adenoma
Primary adrenal hyperplasia
Glucocorticoid-suppressible hyperaldosteronism
Secondary aldosteronism
Idiopathic hyperaldosteronism

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Plasma K</th>
<th>PRA</th>
<th>Syndrome of Primary Hypermineralocorticidism</th>
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<tr>
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<td>PRA, plasma renin activity; Dx, diagnosis</td>
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</table>

**Fig. 2. Differential diagnosis of mineralocorticoid excess disorders**

PRA, plasma renin activity; Dx, diagnosis

**Fig. 3. Mean plasma renin activity (PRA) in primary aldosteronism**

Bars indicate 1 SD. Figs. 3, 4, 7: NCS, normal control subjects

Hyperaldosteronism; suppression of urinary aldosterone excludes aldosterone as the causative steroid but suggests other mineralocorticoid hormones such as deoxycorticosterone (DOC) or in some situations, cortisol. Under the conditions of this laboratory, 24-h urine samples for aldosterone determination are obtained after an intake of salt (NaCl) >120 mmol/d. The mean ± SEM of urinary aldosterone in 94 patients with aldosterone-producing adenoma (APA) under these conditions was 45.2 ± 6.01 (normal 10.3 ± 3.0) μg/24 h (Figure 4). The 18-glucuronide metabolite of aldosterone is routinely measured. HPLC separation of urinary free aldosterone followed by RIA quantification will eventually be preferred because this approach has the advantage of detecting lower concentrations of aldosterone in such disorders as adrenal insufficiency and renal disorders with hyporeninemic hypoaldosteronism.

The absence of a demonstrable adrenal lesion (unilateral adenoma) by computed axial tomography or magnetic resonance imaging requires additional testing to establish autonomy of production and identification of primary adrenal hyperplasia (PAH). Both conditions (APA and PAH) can be corrected by removal of an adenoma or reduction of adrenal mass (3, 4). Nonautonomy of production indicates a nonsurgically correctable type of hyperaldosteronism, idiopathic (IHA).

Tests for autonomy in primary aldosteronism involve measuring the following: plasma aldosterone response to upright posture; 18-hydroxycorticosterone (18-OHB)/cortisol ratio after intravenous saline; and plasma renin and aldosterone production after spironolactone treatment.

**Postural study.** The plasma aldosterone response to the upright posture is a reliable test to discriminate autonomous aldosterone secretion in a patient with an adenoma, PAH, or IHA. Ideally, the test should be performed after overnight recumbency after a sodium chloride intake >7 g. An overnight recumbent sample is obtained at about 0800 hours, and a second sample is taken after 2 h in an upright posture or normal sitting position. Under these conditions, the occurrence of no change or of a decrease in the concentration of plasma aldosterone with the normal circadian decreases in cortisol is diagnostic of an APA (Figure 5). Slight increases in cortisol may invalidate the postural maneuver, but this interference can be eliminated by subtracting the percentage increase in cortisol from the percentage increase in aldosterone. Percentage increases <30% are 85% specific in APA and PAH (5, 6).

**18-OHB or aldosterone/cortisol ratio after intravenous**
Saline. Saline infusions of various quantities have been used to separate hyperaldosteronism states from essential hypertension by the demonstration of a decrease of plasma aldosterone concentrations to <60 ng/L (0.166 nmol/L) in most laboratories (7). The usefulness of this procedure can be extended to provide additional discriminating evidence between APA, PAH, and IHA. Our procedure is to infuse 250 mL of isotonic saline (NaCl, 150 mmol/L) for the first 30 min followed by 1000 mL of isotonic saline for the next 90 min. Concentrations of plasma 18-OHB, cortisol, and (or) aldosterone are measured at the end of the infusions. Patients with APA or PAH have virtually absent renin concentrations, which therefore do not decrease with saline infusion. Concentrations of plasma aldosterone remain above-normal, and cortisol follows its normal circadian pattern decrease. An aldosterone: cortisol ratio >3 suggests a surgically correctable lesion, whereas ratios ≤3 are seen in normal subjects and patients with IHA (8).

Spironolactone treatment. Spironolactone, an antagonist of specific mineralocorticoid receptors, has been used to obtain presumptive evidence of primary aldosteronism (Figure 6) (2). Treatment with 100–400 mg daily for one month usually reduces blood pressure in hyperaldosteronism. However, the specific effects of spironolactone on tumor production of hormones has added importance to this treatment. Spironolactone can correct or ameliorate hypertension but also normalizes plasma potassium concentrations and restores plasma renin to normal values. Despite these corrections, autonomous tissue (in APA and PAH) does not show any increase in plasma concentrations or urinary excretion of aldosterone metabolites in response to spironolactone (3, 9).

Steroids of confirmatory value. With activation of the mineralocorticoid hormone pathway, it is not unusual to observe a spillover of precursors of aldosterone into the peripheral circulation: e.g., DOC, corticosterone, and particularly 18-OHB in APA and PAH (1, 4). Although circulatory DOC and corticosterone originate in the ZF, their increase in the presence of cortisol implies primary adrenal disease because they are not increased in secondary (renin-driven) aldosteronism. 18-OHB is a normal product of the zona glomerulosa, with concentrations always two- to threefold that of aldosterone.

18-Hydroxycortisol and its reduced product, 18-oxocortisone, are normal products of the adrenal cortex (10), cortisol being the precursor. These compounds possess mineralocorticoid activity but their contribution to the hypertensive process is not clear. 18-Hydroxycortisol is increased in three conditions: APA, PAH, and glucocorticoid-suppressible hyperaldosteronism. These unique abnormalities of excretion give clues as to the mechanisms involved. In autonomous lesions (APA and PAH), 18-hydroxylation is an active process not seen in secondary forms of hyperaldosteronism (Figure 7) (3, 4, 11). Not only is 18-hydroxylation increased in glucocorticoid-suppressible hyperaldosteronism, but also 18-dehydrogenation of 18-OHB, which acts to form aldosterone, occurs uniquely in the ZF.

Recommendations on therapy. The results of these maneuvers provide evidence of autonomous secretion, be it a microadenoma or PAH. The surgical treatment remains the same—the removal of an adenoma or reduction of adrenal mass; unilateral right adrenalectomy if no apparent abnormality of adrenal configuration is detected. Sustained cures or amelioration of hypertension are expected in >75% of these patients (11). Total or subtotal removal of adrenal tissue in IHA is no longer performed because, although hyperaldosteronism may be cured by bilateral adrenalectomy, hypertension is little affected (12, 13).

Glucocorticoid-Suppressible Hyperaldosteronism

The exact lesion in this disorder is not firmly established but the implications are that enzymatic derangements in the ZF permit 18-hydroxylation of cortisol and corticosterone and 18-dehydrogenation of 18-OHB to form aldosterone (14). Whether additional regulators exist for the ZF besides corticotropin is still not resolved. This disorder is an autosomal dominant form of hyperaldosteronism that has the unusual feature of correcting the hyperaldosteronism, the renal potassium wasting, and the suppression of plasma renin when corticotropin-suppressive doses of a glucocorticoid are administered (e.g., 0.5 mg of dexamethasone every 6–8 h) (15). Glucocorticoid administration only transiently suppresses

![Diagram](https://via.placeholder.com/150)

Fig. 6. Response of urinary aldosterone concentrations after spironolactone therapy (●)

![Diagram](https://via.placeholder.com/150)

Fig. 7. 18-Hydroxycortisol/cortisol metabolites (18-OHF/F) in primary aldosteronism
AP-RA, aldosterone-producing adenoma–renin-responsive adenoma

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aldosterone production in normal subjects and in patients with APA or IHA, but sustains correction of hypermineralocorticoidism in glucocorticoid-suppressible hyperaldosteronism indefinitely. This suggests that ZF cells have the capacity to dehydrogenate 18-OHB to aldosterone, a function of corticosterone methyl oxidase type II, an enzyme of the zona glomerulosa.

The ZF has two distinct biosynthetic pathways and each one can result in hypertension (Table 2). The normal regulator of this zone is corticotropin. The 17-deoxy steroids (corticosterone, 18-hydroxydeoxycorticosterone, and DOC) are all mineralocorticoids to various degrees, DOC being the most potent. They have few glucocorticoid properties. Corticosterone concentrations >550 nmol/L can suppress corticotropin. On the other hand, the 17-hydroxy pathway produces cortisol, the primary glucocorticoid secreted by the adrenal cortex, which, at concentrations >1390 nmol/L, possesses mineralocorticoid properties.

**Primary hyperDOCism.** Primary hyperDOCism is an unusual finding. The rare DOC-secreting tumor has all the metabolic consequences seen in primary aldosteronism. DOC, present in excess, suppresses the renin system and aldosterone production. The steroid patterns are illustrated in Figure 8. Regardless of etiology—e.g., benign adenoma, hyperplasia, or carcinoma—aldosterone concentrations are suppressed. The 17-deoxy pathway steroids are increased, including 18-OHB, because of the high concentration of corticosterone in the ZF. Only in patients with carcinoma have the concentrations of corticosterone reached amounts that suppress cortisol (16).

A unique observation was made on the ZF steroid response of the remaining adrenal gland to corticotropin after the removal of a unilateral benign DOC-producing tumor. Determination of plasma steroid concentrations before and 1 h after intravenous administration of 250 μg of cosyntropin (Cortrosyn®) showed a normal basal cortisol concentration and stimulated responses. However, DOC concentrations, although ordinarily staying basal after surgery, revealed a considerably blunted response to cosyntropin. Full recovery took eight weeks. This dissociation between DOC and other steroids in the 17-deoxy pathway is unusual, because both are ZF steroids under corticotropin regulation. These findings suggest that DOC and its distal steroids suppressed a potential 17-deoxysteroid regulator that was not corticotropin. Similar dissociations were observed in patients with severe burns or AIDS. Intramuscular administration of 20 mg of DOC acetate every 12 h for three days in normal subjects did not suppress cortisol but did suppress other steroids of the 17-deoxy pathway (corticosterone, 18-hydroxydeoxycorticosterone) by 50%. Dexamethasone (2 mg daily) in normal subjects suppresses cortisol within 24 h, but DOC concentrations are not completely suppressed even after four days (17). The presence of such a putative factor could sustain DOC increases without changes in cortisol.

**Secondary hyperDOCism.** Secondary hyperDOCism is a common feature of the three major types of congenital adrenal hyperplasia: 21-hydroxylase deficiency (21-OHD), 11β-hydroxylase deficiency (11β-OHD), and 17α-hydroxylase deficiency (17α-OHD). Only in the 11β- and 17α-OHD types is hypertension observed because salt-losing factors counteract the mineralocorticoid hormone effect of DOC in 21-OHD. The site of each deficiency (Figure 1) reduces cortisol formation, resulting in increased concentrations of corticotropin. Only steroids proximal to the deficiency and under corticotropin stimulation are increased. Thus, DOC and 11-deoxycorticisol are increased, and the distal steroids (those beyond the deficiency point in the pathway) are decreased in the 17-deoxy and 17-hydroxy pathway and respond poorly to corticotropin in 11β-OHD (Figure 9) (18). In 17α-OHD, all steroids of the 17-deoxy pathway are increased and the concentrations of the 17-hydroxy steroids are decreased (Figure 9) (19). Aldosterone is suppressed because DOC causes increased intravascular volume and suppression of the renin system. Also, because 17-hydroxylation and 17,20-desmolase activities are probably contained in the same enzyme protein, cleavage of the side chain 20,21 is not possible, which is key to the

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**Table 2. Zona Fasciculata Disorders**

<table>
<thead>
<tr>
<th>Hyperdeoxycorticosteronism (hyperDOCism)</th>
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<tr>
<td><strong>Primary</strong></td>
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<td>Congenital adrenal hyperplasia</td>
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<td>17α- and 11β-hydroxylase deficiency</td>
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<td><strong>Hypercortisolism</strong></td>
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<td>Cortisol-producing adenoma</td>
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<td>Cushing disease</td>
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<tr>
<td>Ectopic corticotropin syndrome</td>
</tr>
<tr>
<td>Apparent mineralocorticoid hormone excess (11β-hydroxy steroid dehydrogenase deficiency)</td>
</tr>
<tr>
<td><strong>Other mechanisms</strong></td>
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<tr>
<td>Exogenous administration of mineralocorticoid hormones</td>
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<td>Excessive licorice ingestion</td>
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production of gonadal steroids. Androgen concentrations are increased in 11β-OHD, but no gonadal steroids are produced in 17α-OHD. Measurement of concentrations of the 18-hydroxylated steroids can be useful in the diagnosis of ambiguous cases of congenital adrenal hyperplasia (Figure 10). The diagnosis of 17α-OHD can often be confused with congenital adrenal hyperplasia (20). When glucocorticoid suppressive therapy is stopped in 17α-OHD patients, the resurgence of corticotropin causes an increase in aldosterone to excessive amounts until overproduction of DOC suppresses renin and aldosterone after several weeks. During this period, the high concentrations of aldosterone can be associated with falsely high cortisol concentrations because of the lack of specificity for cortisol assays in the presence of major increases of corticosterone (19).

**Hypercortisolism.** Hypertension occurs in 85% of patients with Cushing syndrome. Cortisol at high concentrations does possess mineralocorticoid properties and plasma renin concentrations are invariably normal to low with corresponding normal or low amounts of aldosterone production. The dissociation between aldosterone and cortisol is particularly noted in the ectopic corticotropin syndrome, where aldosterone production can be extremely low. In addition to low concentrations of plasma renin, cortisol concentrations appear to have an inverse effect on aldosterone production over a wide range of concentrations. Local inhibition of cytochrome P450 enzymes in the zona glomerulosa can be operative. In both Cushing disease and the ectopic syndrome, corticotropin also stimulates the 17-deoxy steroids, which can contribute to the frequent hypokalemia and hypertension.

**Apparent mineralocorticoid hormone excess syndrome (11β-hydroxysteroid dehydrogenase deficiency).** This rare disorder, occurring primarily in children, has had a major influence in our appreciation of the mineralocorticoid hormones and how they operate through their receptors. This disorder presents as an excess of mineralocorticoid hormones, with hypokalemia, hypertension, suppressed plasma renin, and decreased aldosterone secretion. Other mineralocorticoid hormones, e.g., DOC, are not increased. Concentrations of cortisol and corticotropin are normal but cortisol degradation is delayed (21–25). Novel ideas for the explanation of cortisol as a local mineralocorticoid have emerged.

The major types of this disorder have a deficiency of 11β-hydroxysteroid dehydrogenase. This enzyme is critically placed near receptors for mineralocorticoid hormones, especially in the kidney, and function to convert cortisol (an equivalent competitor for this receptor) to the inactive cortisone; thus, in the renal tubule, the mineralocorticoid receptor is protected from the potentially high concentrations of cortisol. In the apparent mineralocorticoid hormone excess syndrome, this enzyme is deficient, so that excessive amounts of cortisol now act like a mineralocorticoid hormone and cause profound mineralocorticoid hormone-related effects (19–25).

Therefore, this disorder is characterized by increased amounts of free cortisol in the urine with normal concentrations of cortisol in plasma, and by an abnormally high ratio of the metabolites of cortisol to those of cortisone (usually 1.0 in healthy subjects). Management usually consists of cortisol reduction with dexamethasone and treatment with inhibitors to mineralocorticoid.
hormone receptors such as spironolactone. The major impact of this mechanism is that a paracrine function can modify the steroid that the hormone receptor "sees."

New mechanisms are being described for mineralocorticoid hormone-related hypertension. Perhaps we should be searching not for new mineralocorticoid hormones but for the conditions under which recognized hormones more effectively express their actions.

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References