Primary Hyperaldosteronism in Cats
An Underdiagnosed Disorder

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INTRODUCTION

Primary hyperaldosteronism, also referred to as Conn’s syndrome, is an adrenocortical disorder characterized by excessive, autonomous secretion of mineralocorticoids, mainly aldosterone, leading to systemic arterial hypertension and/or hypokalemia.1 After its first description in a woman in 1955,2 Conn suggested that primary hyperaldosteronism is the underlying cause in as many as 20% of people with arterial hypertension.3 A few years later, he changed this figure to 10%, which would still mean that primary hyperaldosteronism is a rather common disorder in humans. Nevertheless, primary hyperaldosteronism was considered rare for many decades. With improved screening methods, the disorder is diagnosed more often nowadays, and recent studies show that the prevalence of primary hyperaldosteronism is indeed...
much higher than previously thought. Primary hyperaldosteronism is found in about 6% of all human patients with arterial hypertension and in up to 11% of those with therapy-resistant arterial hypertension.  

Primary hyperaldosteronism is the most common adrenocortical disorder in cats and, as in humans, is associated with arterial hypertension. Although the cat is considered to be the domestic animal in which primary hyperaldosteronism is most prevalent, the disease is not often diagnosed in veterinary practice. It is underdiagnosed, as it is in humans, which excludes a potentially large number of cats from appropriate therapy and possibly a cure for the disease. This may in part be due to the frequent association of arterial hypertension and/or hypokalemia with chronic kidney disease. In many cases of arterial hypertension and/or hypokalemia, chronic kidney disease may be considered the causal disorder, thereby halting further diagnostic efforts, whereas in fact the chronic kidney disease may itself be a consequence of primary hyperaldosteronism. Arterial hypertension and hypokalemia are often treated symptomatically only, without a thorough search for the underlying cause. Moreover, arterial blood pressure is not measured routinely, if at all, in many veterinary practices.

ALDOSTERONE SYNTHESIS

The adrenal cortex consists of 3 layers: the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis. The difference in hormone production between the 3 adrenocortical zones is due to differences in expression of cytochrome P-450 enzymes. These cytochrome P-450 enzymes are responsible for most of the enzymatic conversions from cholesterol to steroid hormones (Fig. 1). The characteristic enzyme in the zona fasciculata and the zona reticularis is 17α-hydroxylase (17,20-lyase, CYP 17), which catalyzes the 17α-hydroxylation of pregnenolone and progesterone as well as the side-chain cleavage at C17 of 17α-hydroxy C21 steroids. In other words, the low expression of 17α-hydroxylase (CYP 17) in the zona glomerulosa is the main reason why cholesterol is converted into aldosterone instead of cortisol or androgens in the zona glomerulosa. The other steroidogenic enzymes are expressed in all 3 zones (see Fig. 1).

Aldosterone was historically considered to be a hormone produced exclusively in the adrenal cortex. However, recent research has revealed that aldosterone is also produced in tissues other than the adrenal cortex, including the heart, brain, and blood vessels. In these extra-adrenal tissues, aldosterone is thought to act in a paracrine or autocrine mode. These new insights may contribute to the understanding of a number of long-term complications of primary hyperaldosteronism.

ALDOSTERONE METABOLISM

Little is known about the metabolism of aldosterone in cats. The liver is generally considered to be the most important site for inactivation and conjugation of steroid hormones. In cats, cortisol, estradiol, and progesterone are excreted mainly or almost exclusively via the bile into the feces and, considering the structural similarities, it can be expected that this is the main excretion route for aldosterone, as well. This hypothesis is supported by a study by Syme and colleagues, who found that urinary excretion of free aldosterone in cats was 77 times less than in humans and 7 times less than in dogs.

REGULATION OF ALDOSTERONE SECRETION

The production and release of glucocorticoids and androgens by the middle and inner zones of the adrenal cortex are almost exclusively regulated by the plasma
adrenocorticotropic hormone (ACTH) concentration. In contrast, the 2 primary mechanisms controlling aldosterone release are the renin–angiotensin system and potassium. The renin–angiotensin system keeps the circulatory blood volume constant by promoting aldosterone-induced sodium retention during periods of hypovolemia and by decreasing aldosterone-dependent sodium retention during hypervolemia.
Potassium ions directly regulate aldosterone secretion, independent of the renin–angiotensin system. Thus, aldosterone secretion is regulated by negative feedback loops for both potassium and the renin-angiotensin system. In addition to these 2 regulatory mechanisms, aldosterone secretion is influenced by several other factors (ACTH, natriuretic peptides, and a variety of neurotransmitters), none of which is directly connected to a negative feedback loop. They have the common feature of usually responding to stress. ACTH is the classic representative of the group. Although ACTH is a very potent acute aldosterone secretagogue, its action is not sustained and it is not necessary to maintain normal glomerulosa cell function.

**PHYSIOLOGIC EFFECTS OF THE RENIN–ANGIOTENSIN SYSTEM**

The proteolytic enzyme renin is synthesized in the juxtaglomerular apparatus of the kidney. Stimulation of renal baroreceptors is the most potent mechanism for renin release by the juxtaglomerular cells. These stretch receptors in the afferent arteriole stimulate renin release in response to decreased renal perfusion pressure caused, for example, by hypovolemia. Additional regulation is provided by macula densa cells, a group of modified cells of the distal tubule near the end of the loop of Henle and intimately associated with the juxtaglomerular cells. The sodium concentration in the tubular lumen is monitored by the cells of the macula densa and low sodium levels trigger communication between the macula densa and the juxtaglomerular cells, resulting in renin release.

Angiotensinogen, the precursor of several angiotensin peptides, is produced mainly in the liver from its precursor preproangiotensinogen. In the circulation angiotensinogen is cleaved by renin and other enzymes to release angiotensin I. The angiotensin-converting enzyme converts the inactive decapeptide angiotensin I to the active octapeptide angiotensin II. Angiotensin-converting enzyme-inhibiting compounds are used clinically to disrupt the renin–angiotensin system, as in the treatment of heart failure.

The vast majority of the physiologic actions of the renin-angiotensin system are mediated by angiotensin II and one of its receptors (AT1-receptor). They include arteriolar vasoconstriction, cell growth, and aldosterone production. Angiotensin II increases vascular resistance and blood pressure. Angiotensin II also regulates the glomerular filtration rate and renal blood flow by constricting the efferent and afferent glomerular arterioles.

**PHYSIOLOGIC EFFECTS OF ALDOSTERONE**

Aldosterone has 2 important physiologic actions: (1) it regulates extracellular fluid volume and (2) it is a major determinant of potassium homeostasis. These effects are mediated by the binding of aldosterone to the mineralocorticoid receptor in the cytosol of epithelial cells. The epithelia of the kidneys, colon, and salivary glands are the classic target tissues for circulating aldosterone. Aldosterone easily passes through the plasma membrane of these epithelial cells and binds to the mineralocorticoid receptor in the cytoplasm. The aldosterone receptor has equal affinity for both aldosterone and cortisol. Circulating concentrations of cortisol are much higher than those of aldosterone. The mineralocorticoid receptor in the classic aldosterone target tissues is preferentially made available to aldosterone by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). This enzyme converts cortisol to cortisone, which has little affinity for the receptor. The aldosterone receptor complex moves from the cytosol to the nucleus, where it modulates the expression of multiple genes.
In the distal convoluted tubule, aldosterone increases sodium reabsorption and potassium excretion. In these tubular cells, the aldosterone receptor complex initiates a sequence of events leading to activation of sodium channels in the apical membrane. Subsequently, increased sodium influx stimulates the $\text{Na}^+,\text{K}^+$-ATPase in the basolateral membrane. As aldosterone increases active sodium reabsorption, an electrochemical gradient is established that facilitates the passive transfer of potassium from tubular cells into the urine. Thus, potassium is not excreted in direct exchange for sodium, but rather in a manner that depends directly on the active reabsorption of sodium.

In addition to its endocrine effects on classic epithelial target tissues, aldosterone has major effects on other epithelial and nonepithelial tissues. The effects of aldosterone on endothelial cells and on cardiac tissue contribute to blood pressure homeostasis. It seems that aldosterone may increase blood pressure through 2 main mechanisms: (1) expansion of plasma and extracellular fluid volume and (2) increased total peripheral resistance. With regard to the nonepithelial actions, it should be mentioned that long-term mineralocorticoid excess may lead to microangiopathies that contribute to fibrosis and proliferation of endothelial and smooth muscle cells in the heart, kidney, and other tissues. In cats, primary hyperaldosteronism has been reported as a mediator of progressive renal disease.

**PRIMARY HYPERALDOSTERONISM**

Two pathophysiologic mechanisms may lead to hypersecretion of aldosterone. A decrease in the effective arterial blood volume (eg, owing to heart failure or edema caused by hypoproteinemia), activates the renin–angiotensin system, which in turn stimulates aldosterone synthesis. This pathophysiologic response to hypovolemia is called secondary hyperaldosteronism or high renin hyperaldosteronism. In contrast, the autonomous and excessive aldosterone secretion in primary hyperaldosteronism is associated with suppressed plasma renin (activity) and is thus low renin hyperaldosteronism.

Primary hyperaldosteronism can be due to autonomous hypersecretion of aldosterone (and/or deoxycorticosterone) by an adrenocortical tumor or by nontumorous, hyperplastic zona glomerulosa tissue. In the majority of the reported cases, feline primary hyperaldosteronism was caused by a unilateral adrenocortical tumor of varying degrees of malignancy, ranging from well-capsulated adenomas to carcinomas with growth into the caudal vena cava and distant metastasis. These reported figures seem to differ markedly from those in humans, where bilateral hyperplasia of the zona glomerulosa accounts for 60% to 65% of cases and aldosterone-producing adenomas for 30% to 35%. However, the diagnosis of idiopathic primary hyperaldosteronism in humans can be established clinically, whereas in cats histopathologic examination of the adrenal glands is required. However, cats with hyperplasia of the zona glomerulosa are often treated medically, meaning that adrenal tissue is not examined histologically except in postmortem examinations. This practice probably means that idiopathic bilateral nodular hyperplasia of the zona glomerulosa occurs more often in cats than suggested by data based on histopathologic findings. In line with this hypothesis, Javadi and colleagues reported 11 cats with “idiopathic” primary hyperaldosteronism in which diagnostic imaging failed to demonstrate an adrenal tumor, suggesting that the cause was adrenocortical hyperplasia (Fig. 2).

**CLINICAL PRESENTATION OF PRIMARY HYPERALDOSTERONISM IN CATS**

Primary hyperaldosteronism mainly occurs in middle-aged and older cats. The pathophysiologic consequences of excessive aldosterone secretion are a consequence...
of increased sodium and water retention and increased renal potassium excretion, which may result in systemic arterial hypertension and potassium depletion, respectively. The progressive depletion of potassium and the development of hypokalemia affect several organ systems, but become particularly manifest in the neuromuscular system by affecting the polarization of nerve and muscle membranes. Muscle weakness is likely to occur at a plasma potassium concentration of less than 2.5 mmol/L, although the severity of muscle weakness is not strictly correlated with the plasma potassium concentration. Affected cats may have (episodic) muscle weakness that results in a plantigrade stance in the hind limbs, difficulty in jumping, and/or a characteristic ventroflexion of the neck (Fig. 3). In some cases there is progression to flaccid paresis with hyporeflexia, muscle hypotonia, and difficulty in breathing. In other cats, the presenting physical features of excessive aldosterone secretion are dominated by the consequences of arterial hypertension, that is, loss of vision owing to retinal detachment and/or intraocular hemorrhages. Not all cats with primary hyperaldosteronism present with both signs of hypokalemia and with signs of arterial hypertension.

Primary hyperaldosteronism, especially when owing to micronodular hyperplasia of the zona glomerulosa, is associated with cardiovascular and renal complications in both humans and cats. It has been hypothesized that mild hyperaldosteronism with incomplete renin suppression associated with micronodular hyperplasia of the zona glomerulosa results in the combined deleterious, proinflammatory, and profibrotic effects of elevated aldosterone and angiotensin II levels.

Fig. 2. Histologic sections of adrenals stained with neuron-specific enolase (NSE). In the healthy cat (left), the staining of the cortex (C) is mainly confined to the zona glomerulosa. In the cat with primary hyperaldosteronism (right), the cortex consists of multiple hyperplastic nodules, staining positively for NSE. Staining of the adrenal medulla (M) is similar in the 2 sections. Bar = 200 μm.
The most consistent routine laboratory finding is hypokalemia. Aldosterone excess also favors increased acid secretion, which may lead to (usually mild) hypokalemic metabolic alkalosis. Either hypophosphatemia or hypomagnesemia or both may develop in affected cats. Some cats may have increased plasma creatine kinase concentrations. In cats, idiopathic hyperaldosteronism is frequently associated with (slowly progressing) renal insufficiency, probably owing to aldosterone-induced arteriolar and glomerular sclerosis, tubular atrophy, and interstitial fibrosis and the deleterious effects of arterial hypertension.

DIAGNOSIS OF FELINE PRIMARY HYPERALDOSTERONISM

In primary hyperaldosteronism owing to an adrenocortical tumor, the plasma aldosterone concentration is usually quite high as well as the plasma concentration of aldosterone precursors, such as progesterone. In cats with idiopathic primary hyperaldosteronism, that is, owing to hyperplasia of zona glomerulosa tissue, the plasma aldosterone concentration is usually only slightly elevated or even within the (upper limit of the) reference range. Because hypokalemia is a predominant factor in decreasing aldosterone secretion, the combination of hypokalemia and a moderately increased aldosterone value should be considered inappropriately high and abnormal.

In primary hyperaldosteronism, the classic characteristics are an increased plasma aldosterone concentration with concomitant decreased plasma renin (activity). The combination of a high normal or elevated plasma aldosterone concentration and low plasma renin (activity) indicates persistent (autonomous) aldosterone synthesis in the presence of little or no stimulation by the renin–angiotensin system. In humans the plasma aldosterone to renin ratio is considered to be a very useful aid in diagnosing primary hyperaldosteronism. This also seems to be true for cats with primary hyperaldosteronism. The diagnostic value of the aldosterone to renin ratio is principally determined by the sensitivity of the renin assay. It is important to take into account that renin values should be interpreted in comparison with an appropriate control population. The accuracy of the aldosterone to renin ratio also depends on preservation of renin (activity) during sample collection and storage: blood samples should be collected in ice-chilled tubes and centrifuged in a chilled centrifuge, and the plasma should be kept in the refrigerator until assayed.
An alternative diagnostic approach may be measurement of the urinary aldosterone to creatinine ratio (UACR). Cats excrete smaller quantities of aldosterone and its 18-glucuronidated metabolite in urine than do humans or dogs, but nevertheless the UACR can be determined. It provides an integrated reflection of aldosterone secretion over time. It has the advantage that the urine sample for measurement of aldosterone does not have to be cooled and a urine sample can be collected quite easily by the owner. Unfortunately, the reference range for the UACR proved to be quite wide and did not easily facilitate differentiation between healthy cats and those with primary hyperaldosteronism, although a high UACR points to hyperaldosteronism.

A dynamic test using a suppressive agent that reduces aldosterone secretion in healthy cats but has little or no effect in those with primary hyperaldosteronism would seem to be the best method to show the presence of hyperfunctioning zona glomerulosa tissue. Oral administration of fludrocortisone has been shown to suppress circulating aldosterone concentration in healthy adult cats. In another study, it was shown that oral administration of sodium chloride (0.25 g/kg body weight, twice daily for 4 consecutive days) did not significantly lower the UACR in healthy cats, but oral administration of fludrocortisone acetate (0.05 mg/kg body weight, twice daily for 4 consecutive days) did reduce the UACR by more than 40% in healthy cats.

This fludrocortisone suppression test, using the UACR, was also used in a study with 19 client-owned cats with arterial hypertension caused by primary hyperaldosteronism (n = 9) or other causes (n = 10). The results of this study show that all cats with primary hyperaldosteronism had a basal UACR more than $7.5 \times 10^{-9}$. In all cats without primary hyperaldosteronism and a basal UACR of more than $7.5 \times 10^{-9}$, fludrocortisone administration induced more than 50% suppression of the UACR. In contrast, fludrocortisone administration resulted in less than 50% suppression in 6 of the 9 cats with primary hyperaldosteronism. The results suggest that measuring the UACR before and after 4 days of administering fludrocortisone is a practical method of confirming most cases of feline primary hyperaldosteronism, and especially of substantiating the absence of primary hyperaldosteronism in cats.

A suppression test using telmisartan, an angiotensin II receptor blocker, may also have the potential to diagnose primary hyperaldosteronism in cats. Theoretically, suppression of aldosterone secretion would be expected in healthy cats, whereas cats with primary hyperaldosteronism, that is, cats with autonomous aldosterone secretion, are not expected to have a significant decrease in aldosterone secretion. The fludrocortisone or telmisartan suppression test may prove to be a practical noninvasive diagnostic tool to diagnose primary hyperaldosteronism in cats, but further evaluation of these tests is required, particularly with regard to its discriminatory power in diagnosing “idiopathic” primary hyperaldosteronism.

**DIAGNOSTIC IMAGING**

Differentiating between tumorous and nontumorous mineralocorticoid excess, requires diagnostic imaging. Diagnostic imaging techniques such as ultrasound examination, MRI, and computed tomography scan are used to identify adrenal abnormalities and, in case of neoplasia, to evaluate for possible extension into blood vessels as well as evidence of distant metastases. Although the presence of visible tumor tissue in the caudal vena cava indicates that surgical removal may be difficult, failure to detect it by diagnostic imaging is no guarantee of its absence and does not necessarily predict an uncomplicated adrenalectomy.

There are more limitations to conventional diagnostic imaging in determining the optimal treatment strategy for primary hyperaldosteronism. Functional neoplasms of
the zona glomerulosa do not have to be large to cause clinically relevant hyperaldosteronism, and may therefore be well below the detection limit of ultrasound examination, computed tomography scan, or MRI. Similarly, clinically relevant hyperplasia of zona glomerulosa tissue may not be revealed by these conventional diagnostic imaging techniques. Failure to see an obvious mass for many endocrine tumors simply indicates that the tumor is small. Some nonfunctional adrenocortical neoplasms, that is, “incidentalomas,” may become quite large and be readily visualized with ultrasound examination, computed tomography scan, or MRI, but may not cause clinical signs. Therefore, a visible adrenal mass may not be a functional neoplasm of the zona glomerulosa, which is causing the clinical signs of primary hyperaldosteronism, and if surgery is planned on the basis of conventional diagnostic imaging alone, the wrong adrenal gland may be removed or the patient may be inappropriately selected for, or excluded from, adrenalectomy. It can be concluded that whatever imaging technique is used, the findings should be interpreted in conjunction with those of biochemical studies.

Adrenal vein sampling was introduced in human medicine in the late 1960s and, despite potentially severe complications, it has become the gold standard to determine the laterality (left or right adrenal) of excessive aldosterone production in humans. Each adrenal vein is cannulated in turn and samples are collected while peripheral venous blood samples are collected simultaneously. The plasma aldosterone and cortisol concentrations in the adrenal and peripheral venous samples are compared to detect the source of excess aldosterone. Unfortunately, the much smaller vascular dimensions in cats preclude adrenal venous sampling and thus determination of the laterality of primary hyperaldosteronism continues to rely on diagnostic imaging.

TREATMENT OF FELINE PRIMARY HYPERALDOSTERONISM

Unilateral adrenalectomy is the treatment of choice for confirmed unilateral primary hyperaldosteronism, at least when diagnostic imaging has not revealed metastases. Adrenalectomy can be performed via a ventral midline celiotomy or via a paracostal approach. In some centers, adrenalectomy in cats is now routinely performed by laparoscopy, with lower perioperative morbidity and mortality than by open transabdominal surgery. Laparoscopic adrenalectomy may become the surgical procedure of choice in veterinary medicine, but most surgeons still prefer transabdominal access because it provides maximal exposure of the adrenal and blood vessels. There have been several reports of successful surgical interventions in cats,17,18 including the excision of an adrenocortical carcinoma together with its extension into the vena cava.19

Preoperatively and perioperatively, hypokalemia should be controlled as well as possible, by oral or intravenous supplementation. During the first few weeks after surgery, a generous dietary intake of sodium can be provided to avoid the hyperkalemia that could develop from hypoaldosteronism as a consequence of chronic contralateral adrenocortical suppression. Analogous to the postoperative management of hypercortisolemia owing to an adrenocortical tumor, temporary fludrocortisone therapy could also be considered. However, in the reported cases such postsurgical measures have not been necessary and their omission does not seem to have had deleterious effects.

After complete removal of a unilateral, nonmetastasized, aldosterone-producing tumor, the prognosis is excellent, with no medication required in most cases. Most of the cats that survived the immediate postoperative period have continued to be clinically
asymptomatic for 1 to several years. However, perioperative complications have been reported, including intraoperative or postoperative intra-abdominal hemorrhage. Hemorrhage was not specifically related to the type of neoplasia, intravenous tumor extension, or the presence or absence of arterial hypertension as a presenting clinical sign. Therefore, all owners considering the surgical management of primary hyperaldosteronism in their cat should be informed of this potential complication.

Surgery may be contraindicated when the cat is diagnosed with bilateral hyperplasia of the zona glomerulosa, a nonresectable unilateral adrenocortical neoplasm, distant metastases, financial limitations, or comorbid conditions. These cats can be treated medically with a mineralocorticoid receptor blocker, together with potassium supplementation and antihypertensive drugs if needed. The aldosterone receptor blocker most often used in cats is spironolactone. The initial dose is 2 mg/kg body weight orally, twice daily, increased as needed to control hypokalemia. Persistent arterial hypertension can be treated with the calcium blocker amlodipine, at an initial oral dose of 0.1 mg/kg body weight, once daily. Telmisartan, being an angiotensin II receptor blocker, is less effective as an antihypertensive agent, because it does not block the effects of aldosterone.

In cats, hyperaldosteronism owing to bilateral adrenocortical hyperplasia is usually somewhat milder than that owing to neoplasia and normokalemia may be sustained for long intervals with spironolactone alone or combined with low doses of potassium. However, the prognosis may not be as favorable as that after complete removal of an aldosterone-producing neoplasm, because medical treatment does not permanently abolish the mineralocorticoid excess.

**DISCLOSURE**

The author does not have any commercial or financial conflicts of interest and no funding sources to disclose.

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