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Endocrinopathies and hypertension

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In dogs and cats, the importance of hypertension was first recognized about 15 – 20 years ago. In 2007 guidelines similar to those established for humans have been published as Consensus Statement of the ACVIM. As blood pressure rises, there is progressive risk of damage to the so called end organs or target organs, such as brain, heart, kidney and eye. The most common adverse effects, which include hypertensive retinopathy, intraocular hemorrhage and hypertensive encephalopathy, are seen when the systolic blood pressure exceeds 180 mmHg, particularly when the increase is acute. Hypertension is classified as idiopathic (primary, essential) or secondary. The latter is the most prevalent form and is subclassified into renal and endocrine hypertension. The presentation will focus on the most common causes of endocrine hypertension in dogs and cats.

Primary aldosteronism

The first case of feline primary aldosteronism was described in 1983. Since then, the disease has been diagnosed with increased frequency, and a little more than 30 cases have now been reported. Although no data are available concerning the true prevalence of the disease in the feline population, it is assumed that the disease is more common than initially thought. This hypothesis is based on data from human medicine, where a more systematic screening revealed a higher than estimated prevalence. The majority of human patients diagnosed today have normal potassium levels. The two central mechanisms responsible for the development of hypertension are expansion of plasma and extracellular fluid volume and increase in total peripheral vascular resistance. Clinical signs are weakness with associated cervical ventroflexion, mydriasis and blindness because of hypertensive retinopathy; some cats also have polyuria/polydipsia. Almost all cats described to date have been hypokalemic at the time of diagnosis. However, as in human medicine, it may be possible that aldosteronism is overlooked in cats with normal potassium levels. The prevalence of hypertension in cats with primary aldosteronism is high. Blood pressure was recorded in 30 cases, 26 of which were hypertensive. The severity ranged from mild to severe (185 – 270 mmHg), and the most common sequels were retinal detachment and ocular bleeding. Initial treatment should be directed towards alleviation of hypertension and hypokalemia by using an aldosterone antagonist (spironolactone 2.5

mg/kg q24h or 6.25 mg/cat q12h PO) and a calcium channel blocker (amlodipine 0.625-1.25 mg/cat q24h PO), and substituting potassium as needed. Subsequent adrenalectomy is the treatment of choice.

Hyperadrenocorticism

Hyperadrenocorticism is one of the most common endocrine disorders in dogs. In people hypertension is a common complication with a prevalence of between 55% and 80%. The mechanisms by which glucocorticoids are involved in the etiology of hypertension are (1) their intrinsic mineralocorticoid activity, (2) activation of the renin-angiotensin-aldosterone system (RAAS), (3) enhancement of cardiovascular inotropic and pressor activity of vasoactive substances, including catecholamines and/or vasopressin and angiotensin II, and (4) suppression of the vasodilatory system, including the nitric oxide (NO) synthase, prostacyclin and kinin – kallikrein systems. In dogs with hyperadrenocorticism the prevalence of hypertension is similar to that in humans ranging from 59% to 86%. We recently showed that dogs with experimentally-induced hypercortisolism have significantly higher plasma levels of endothelin-1 compared to control dogs. It was also seen that the concentration of the ANP precursor (proANP) is lower than that of control dogs. In contrast to current data in human medicine, there is no evidence to support reduced NO availability as a cause of increased blood pressure.

A significant proportion of dogs with hyperadrenocorticism (approximately 40%) remain hypertensive despite adequate control of the disease. In human medicine, persistent hypertension is treated with substances belonging to various classes of drugs, including angiotensin II blockers, ACE inhibitors and/or aldosterone antagonists. The use of these drugs in dogs with persistent hypertension despite adequate control of hyperadrenocorticism needs to be evaluated.

Pheochromocytoma

Pheochromocytoma is an uncommon catecholamine-secreting neuroendocrine tumor. In human pheochromocytomas, norepinephrine is the predominant catecholamine secreted and in some tumors it may be the only catecholamine produced. On rare occasions tumors may secrete only epinephrine. The secretory patterns of canine and feline pheochromocytomas have not yet been investigated. Catecholamines bind to two types of receptors: ∀- and β-adrenergic receptors, which are further subdivided into subtypes. The $\forall_1$ receptor subtype mediates vascular and smooth muscle contraction

and stimulation of the receptor causes vasoconstriction and increased blood pressure. Activation of $\forall_2$ receptors inhibits norepinephrine release, suppresses sympathetic outflow and decreases blood pressure. Stimulation of β_1 receptors results in positive inotropic and chronotropic effects on the heart. β_2 stimulation causes bronchodilatation and vasodilatation, and β_3 receptors regulate energy expenditure and lipolysis.

The clinical presentation is highly variable and ranges from complete absence of signs to dramatic and life-threatening signs; the latter is usually the result of a hypertensive crisis. Clinical signs depend on the type of catecholamine produced by the tumor and the amount and frequency of catecholamine release into the circulation. Ninety to 95% of human patients with pheochromocytoma have hypertension. Current information on blood pressure values is limited to less than 50 dogs, approximately half of which had hypertension. Similar to the situation in human medicine, the increase in blood pressure in dogs may range from mild to severe; the maximum systolic pressure reported was 325 mmHg.

Adrenalectomy is the treatment of choice; however, there is a high risk of hypertensive and hypotensive crises, cardiac arrhythmias and hemorrhage. α-adrenergic blockade (phenoxybenzamine) should be used prior to surgery to reverse vasoconstriction and hypovolemia and control fluctuations of blood pressure and heart rate during anesthesia. The starting dose of phenoxybenzamine is 0.25 mg/kg BID, which is gradually increased until signs of hypotension or adverse drug reaction occur or the maximum dose of 2.5 mg/kg BID is attained. A recent study showed that dogs treated with phenoxybenzamine had a significantly decreased mortality compared with untreated dogs after adrenalectomy.

Hyperthyroidism

Hyperthyroidism is the most common feline endocrine disease with an estimated prevalence of 2% but is rare in dogs.

In humans with hyperthyroidism systolic arterial pressure is almost always increased. However, the disease usually has only minor effects on mean arterial pressure because the increase in systolic blood pressure is offset by the decrease in diastolic pressure. Excessive levels of circulating thyroxine cause a 40 – 60% decrease in systemic vascular resistance. This decline is accompanied by a decrease in diastolic blood pressure, which in turn causes a reflex increase in heart rate, stroke volume and cardiac output. The effect of these changes on renal physiology is considerable: a fall in

systemic vascular resistance induces a decline in renal perfusion pressure, and this stimulates the release of renin, leading to increased production of angiotensin. The sum of these changes is augmentation of renal sodium reabsorption and expansion of total body sodium content and blood volume. An excess of thyroid hormones also leads to increased sensitivity to circulating catecholamines resulting in direct induction of inotropy and chronotropy. The prevalence of systemic hypertension in the hyperthyroid feline population is estimated to be between 5% and 22%. Severe hypertension has been considered uncommon and if documented, concomitant diseases like renal failure should be suspected. Chronic kidney disease may be masked at initial presentation because the increased glomerular filtration rate induced by hyperthyroidism will maintain urea and creatinine levels in the reference range. Azotemia will therefore only become obvious after hyperthyroidism is treated, occurring in 17 – 39% of cats.

Some cats which had been normotensive at the time of diagnosis will develop hypertension during the treatment of hyperthyroidism. All of them and the majority of initially hypertensive hyperthyroid cats will need additional medication (e.g. amlodipine) to control blood pressure.

Diabetes mellitus

Diabetes mellitus is one of the most common endocrine diseases in humans as well as dogs and cats. In diabetic people, hypertension is a frequently encountered comorbid condition, affecting 10 – 30% of patients with type 1 and 30 – 50% of patients with type 2 diabetes mellitus. Possible causes of hypertension are loss of the normal vasodilator effect of insulin (e.g. loss of insulin-induced NO generation), increase in sodium and water retention, increase in intracellular calcium levels enhancing contractility of vascular smooth muscle, proliferation of vascular smooth muscle and stimulation of sympathetic outflow.

Information on blood pressure in diabetic dogs and cats is scarce. It has been shown in dogs with newly diagnosed diabetes that although blood pressure is higher than in healthy dogs, most of them are not hypertensive. It is possible that hypertension is of greater importance in dogs with long-standing diabetes. In 50 dogs treated for diabetes for a median of six months, hypertension was detected in 23 (46%), a number which compares to the prevalence in human diabetics. There is currently no convincing evidence that diabetic cats have hypertension.