Title: Updates in Canine Mitral Valve Disease Part 1

Session description:

This presentation will be a practical review of canine myxomatous mitral valve disease (MMVD), diagnostics and the renin-angiotensin-aldosterone system (RAAS). While the RAAS system is a life-saver in acute, hypovolemic situations such as blood loss, this system causes deleterious effects when left unchecked long term. The canine MMVD patient has decreased cardiac output which triggers RAAS activation. We will review the RAAS cascade and discuss the importance of its management along with a practical review of the diagnostic approach to canine mitral valve disease.

Lecture notes:

Myxomatous mitral valve disease (MMVD; also known as endocardiosis and degenerative or chronic valvular heart disease) is the most common cardiac condition in dogs with a higher incidence in male, small breed, older dogs. According to the 2019 American College of Veterinary Internal Medicine (ACVIM) consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs, 10% of dogs present to primary care veterinary hospitals with heart disease and of those, approximately 75% (more than 4.5 million dogs) have MMVD. Disease progression is typically slow but certain breeds are predisposed to rapid progression and a worse prognosis.

Besides the thorough physical examination, radiographs should be the first diagnostic step in suspected MMVD cases. As these dogs often have concurrent tracheobronchial disease, baseline radiographs are ideal to differentiate future cardiac from noncardiac etiologies of coughing. Additionally, pulmonary edema associated with congestive heart failure (CHF) is a radiographic diagnosis.

Parameters to monitor:

- Vertebral heart score (VHS) and/or vertebral left atrial size (VLAS)
- Baseline and serial blood pressure
- Echocardiography
    - LA: Ao
    - LVIDDn
- Baseline laboratory tests (at a minimum PCV, TP, Creatinine, BUN, electrolytes, urine specific gravity
- Resting respiratory rate

One consequence of MMVD is activation of the renin-angiotensin-aldosterone system (RAAS). The RAAS is a primal, lifesaving mechanism meant to detect and adjust for changes in body homeostasis. For instance, in situations where blood loss or dehydration occur, the kidneys detect decreased perfusion and release renin, thus beginning the cascade that causes vasoconstriction and retention of sodium and water. These functions work to expand blood volume and maintain organ perfusion. When the bleeding is stopped or dehydration is corrected, the cascade is deactivated. Short-term, the RAAS activation is good. This is not the case if you're a dog with MMVD. Long-term, chronic, unchecked activation of the RAAS occurs with MMVD due to decreased cardiac output. Negative consequences occur when this

system is activated chronically. These negative consequences include chronic vasoconstriction which leads to raised arterial pressures, increased afterload which further depresses systolic function, and limited perfusion at smaller arterioles. Sodium and water retention and cardiac remodeling are also associated with chronic RAAS activation.

Due to decreased cardiac output, renin is released from the kidneys. Renin cleaves a piece off angiotensinogen to create angiotensin I. Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II causes the adrenal glands to release aldosterone, norepinephrine, and epinephrine. Angiotensin II bind with the AT1 and AT2 receptors in the vessel walls and (along with norepinephrine and epinephrine) cause vasoconstriction. Aldosterone causes retention of sodium and water at the nephron which acts to further expand blood volume. While this can be lifesaving in cases of acute blood loss, it contributes to pulmonary congestion in the MMVD patient. Aldosterone and angiotensin II excess contributes to cardiac muscle remodeling or fibrosis. This fibrosis causes stiffening and dysfunction of the heart muscle which contributes to further decreased cardiac output and arrhythmias in the MMVD patient. For these reasons, suppression of RAAS is a key strategy in the management of canine cardiovascular disease. Angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) are all used to suppress the effects of RAAS.

Because furosemide, both when administered alone and in combination with pimobendan, has been shown to activate the RAAS, its use as a sole agent or with pimobendan alone is not appropriate. When loop diuretics are used for CHF treatment, mitigation of the RAAS cascade with ACEIs, ARBs, and MRAs is necessary.

Now well accepted (although poorly understood) as a human and canine phenomenon, the concept of aldosterone breakthrough (ABT) was first described by Bertram Pitt in 1995. ABT is the condition in which ACEIs and/or ARBs fail to fully suppress the activity of the RAAS. In one study, ABT occurred in approximately 30% of dogs (32% in CHF and 30% not in CHF) despite ACEI administration. This phenomenon is the reason spironolactone, a mineralocorticoid receptor antagonist (MRA), is recommended to augment the traditional triple-therapy approach to CHF management in dogs.

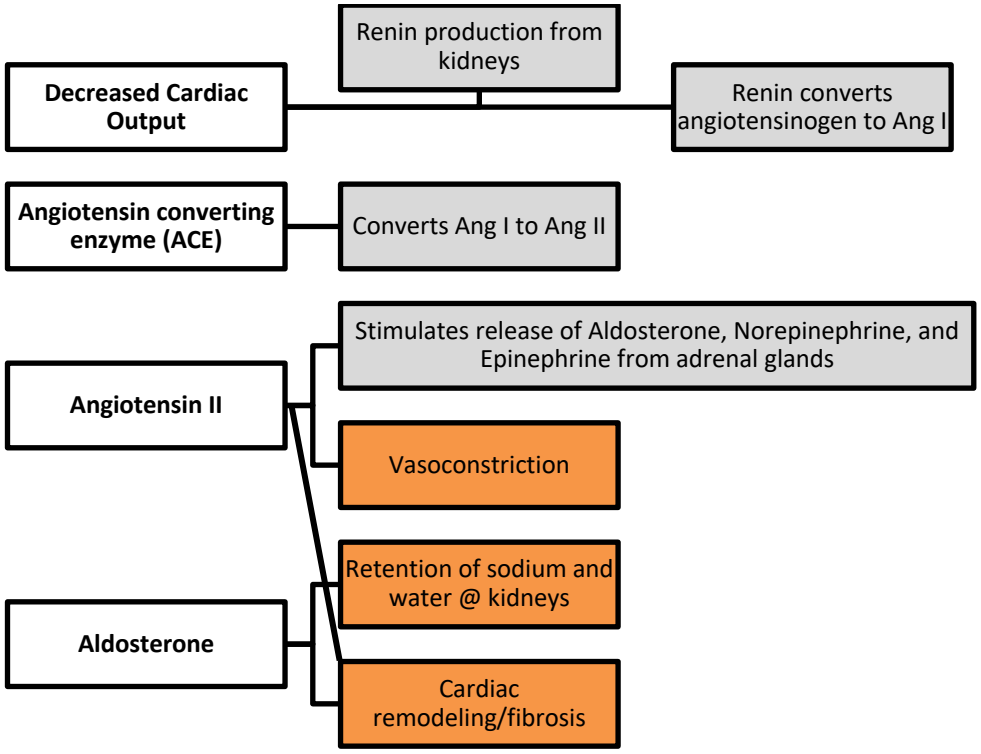

Figure 1: The renin-angiotensin-aldosterone system cascade

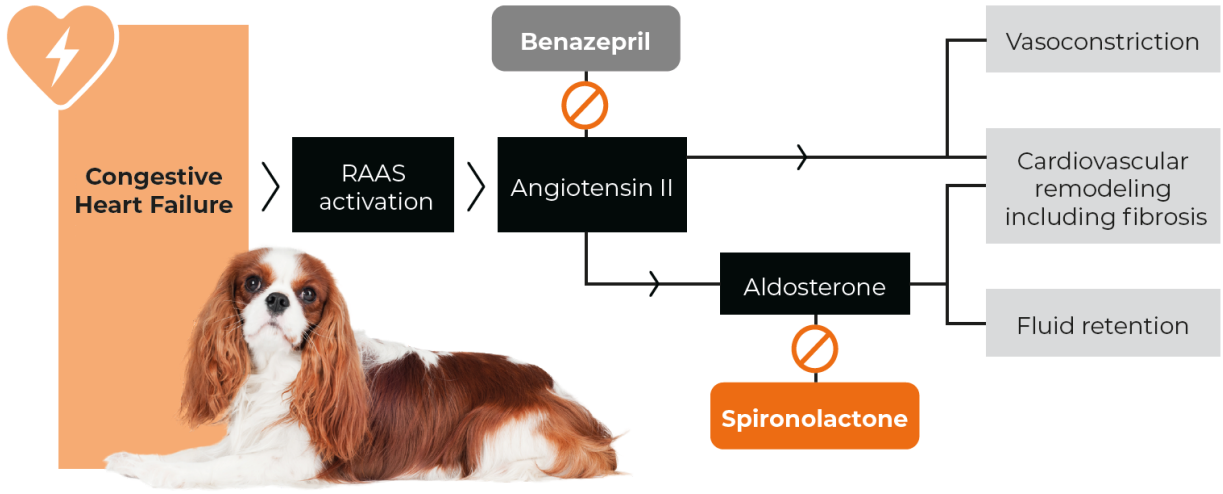

Figure 2: Therapeutic management of RAAS

References:

- Keene, BW, Atkins, CE, Bonagura, JD, et al. ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. J Vet Intern Med. 2019; 33: 1127– 1140. https://doi.org/10.1111/jvim.15488
- Borgarelli M, Häggström J. Canine degenerative myxomatous mitral valve disease: natural history, clinical presentation and therapy. Vet Clin North Am Small Anim Pract. 2010; 40:651-663.
- Häggström J, Höglund K, Borgarelli M. An update on treatment and prognostic indicators in canine myxomatous mitral valve disease. J Small Anim Pract. 2009; 5:25-33.
- Lantis A, Atkins C, Defrancesco T, Keen B, Weere S. Effects of furosemide and the combination of furosemide and the labeled dosage of pimobendane on the circulating renin-angiotensin-aldosterone system in clinically normal dogs. Am J of Vet Research 2011; 72. 1646-51. 10.2460/ajvr.72.12.1646.
- Pitt B. "Escape" of aldosterone production in patients with left ventricular dysfunction treated with an angiotensin converting enzyme inhibitor: implications for therapy. Cardiovasc Drugs Ther. 1995;9(1):145-149. doi:10.1007/BF00877755
- Ames MK, Atkins CE, Eriksson A, Hess AM. Aldosterone breakthrough in dogs with naturally occurring myxomatous mitral valve disease. J Vet Cardiol. 2017;19(3):218-227. doi:10.1016/j.jvc.2017.03.001
- Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression [published correction appears in J Vet Intern Med. 2019 Sep;33(5):2551]. J Vet Intern Med. 2019;33(2):363-382. doi:10.1111/jvim.15454
- Freedom of Information Summary, NADA #141-538 (July 27, 2020)