THE EFFECT OF SYSTEMIC DISEASE ON THE HEART
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As one accrues more clinical experience, the notion that heart disease does not exist as a single condition, especially a dog with mitral valve disease (MVD), becomes apparent. Dogs with MVD are often older small breed dogs with many concurrent conditions. Concurrent conditions or co-morbidities are common not only in MVD but in all types of heart disease and patients. In this seminar presentation, we will explore just a few conditions commonly affecting dogs and cats with heart disease in a case based approached. The notes below should serve as a reference for the various co-morbid conditions.

AZOTEMIA:
The finding of an increased blood urea nitrogen (BUN) and serum creatinine is always concerning in the setting of heart failure or heart disease since it represents reduced glomerular filtration, either as a result of organ dysfunction (heart or kidney) or complication of heart failure therapy. Renal impairment in human heart failure patients is common and is increasingly recognized as an independent risk factor for morbidity and mortality. The Acute Decompensated Heart Failure National Registry (ADHERE), a large database of > 100,000 human patients with heart failure reported that approximately 30% had concurrent chronic renal disease at admission. Furthermore, approximately one fourth of human patients hospitalized for treatment of heart failure will experience significant worsening of their renal function. In a recent canine study, the prevalence of renal dysfunction in chronic valvular disease was also surprisingly high, 50% overall. Additionally, as functional class of heart failure increased so did the percentage of azotemic dogs which may also suggest that azotemia may also be a poor prognostic indicator. In another canine study of spontaneous heart failure, an increase in BUN was associated with worsening severity of heart failure and diuretic usage. Common causes of azotemia associated with heart failure can be divided into prerenal and renal etiologies.(See Table)

Table. Causes of azotemia commonly associated with heart failure

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<th>Category of azotemia</th>
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| Prerenal                   | Severe “forward” heart failure associated with low cardiac output       | • Advanced end stage heart disease, cardiac tamponade due to pericardial effusion and symptomatic complete heart block are examples of heart diseases that can cause “forward” heart failure and azotemia.  
• Many times the combination of low cardiac output due to advanced heart disease and pre-existing renal disease can lead to azotemia |
| Hypovolemia and volume contraction associated with diuretic administration | • Diuretics, but in particular furosemide, can lead to potent diuresis and volume contraction and subsequent azotemia.  
• Concerned about pre-existing occult renal disease when azotemia develops with appropriate diuretic therapy  
• Reduction in diuretic dose, if possible, usually improves azotemia |                                                                                                                                                                                                                       |
| Decreased renal perfusion pressure associated with excessive vasodilation | • Hypotension associated with vasodilators can lead to azotemia  
• As with diuretics, reduction in dose can improve azotemia |                                                                                                                                                                                                                       |
| Renal                  | Pre-existing chronic renal disease                                      | • May be more common than previously recognized, particularly in older animals with heart disease  
• Many times becomes apparent with heart failure drug therapy. |
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<td>Acute renal failure due to ischemic renal ischemic renal injury</td>
<td>• If the prerenal azotemia of any etiology is severe and sustained can lead to ischemic renal injury.</td>
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<td>Renal thrombosis associated with feline arterial thromboembolism</td>
<td>• Many cats with arterial thromboembolism have evidence of previous renal infarcts leading to renal impairment</td>
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| Glomerulonephropathy (GN) associated with advance heartworm disease (HWD) | • Many dogs with severe HWD have proteinuria associated with GN.  
• Severe GN can lead to renal tubular loss and azotemia |                                                                                          |

It’s important to emphasize that the renal impairment may result from a combination of causes: concurrent renal disease and advanced heart disease are not uncommon. Additionally, severe hypoperfusion of the kidneys (prerenal azotemia) of any etiology can lead to acute renal failure, potentially irreversible, due to ischemic injury (renal azotemia) if the insult is severe and sustained.

**Renal function, electrolytes and blood pressure should be assessed both before and after initiation of therapy of heart failure.** The time interval between assessments is dependent on the severity of HF and the intensity of management. For the typical outpatient heart failure case, reassessment in 5-7 days is sufficient while the management of an intense in-patient heart failure case requiring high dose diuretics may benefit from daily or every other day reevaluation of BUN, creatinine and electrolytes until stabilized.

**Management of azotemia in heart failure patients is somewhat dependent on understanding it’s etiology. In general, though, improving cardiac output and decreasing diuretic dose, if possible, are vital to improving renal function.**

If the renal impairment is primarily due to poor cardiac output and “forward” heart failure then immediate maneuvers to improve cardiac output are necessary. For example, urgent removal of pericardial effusion causing cardiac tamponade and intravenous (IV) fluid therapy should improve the azotemia. Similarly, azotemia associated with severe and symptomatic complete heart block should improve with urgent pacing to increase heart rate and initiating IV fluids. The rate of fluid administration is dependent on the acuteness of the illness (i.e., how long has the animal not been eating or drinking) as well as if any previous diuretic or vasodilating therapy had been overzealously administered.

Aside from these previous examples of primarily forward heart failure, the majority of heart failure associated with azotemia is a combination of backwards (edema, effusion) as well as forward failure (low cardiac output). In these cases, it’s important to decrease diuretic dose to a minimum as well as to optimize cardiac output. In the author’s experience, for severe in-hospital management of congestive heart failure with azotemia, furosemide dose can be minimized by constant reassessing of the patient’s respiratory rate and titrating the dose to the patient. A furosemide continuous rate infusion (CRI) after an initial bolus is a nice way to titrate the dose to the patient. The CRI can be stopped as soon as the animal’s respiratory rate is nearing normal rather than giving several larger scheduled bolus doses. In some cases of erroneously diagnosed pulmonary edema, the diuretics can be stopped entirely. Occasionally, a dog with respiratory disease, pulmonary hypertension and cor pulmonale will be misdiagnosed with left sided congestive heart failure. These dogs are especially at risk for developing azotemia with aggressive diuretic therapy as they are usually older dogs with likely some underlying renal insufficiency. Additionally many of these dogs will have pulmonary hypertension to a sufficient degree that left heart preload and cardiac output will be decreased. In addition to discontinuation of furosemide, these dogs with pulmonary hypertension may benefit from pulmonary arterial vasodilation to improve cardiac output. Vasodilators such as sildenafil, pimobendan and amiodipine have all shown improvement of
clinical signs associated with pulmonary hypertension. Certain drugs such as digoxin, atenolol, sotolol, enalapril, are cleared by the kidneys and should be dose reduced or avoided.

**Therapeutic removal of pleural effusion or ascites will also help lower the diuretic dose, both during initial and chronic management, in heart failure animals prone to azotemia.** Although long term, ascites and pleural effusion should ideally be managed medically. However, some animals with concurrent renal disease do not tolerate high dose diuretics and periodic removal of body cavity effusion will provide relief of symptoms and extension of quality life. In addition to minimizing diuretic dose, strategies to improve cardiac output and azotemia will include the cautious use of vasodilators (ACE-I) and positive inotropic drugs.

Recent studies have shown, in addition to the author’s anecdotal experience, the use of pimobendan is quite helpful in managing azotemia in heart failure patients. The addition of pimobendan should be considered in all cases of symptomatic canine heart failure especially in the face of azotemia. **The pimobendan will allow reductions in the diuretic dose and even the ACE-I, if needed.** Although not approved for use in cats, the author has used pimobendan in severe refractory heart failure with generally good results. Dobutamine, an intravenous catecholamine, is another positive inotrope that can lead to short term improvement of cardiac output and azotemia especially if the patient is unable to take oral medications. In addition to positive inotropes, appropriate use of vasodilators, particularly angiotensin enzyme inhibitors (ACE-I), will improve cardiac output and renal blood flow. Adjusting the dose of vasodilators in the presence of azotemia and heart failure can be challenging. **It’s important to emphasize that vasodilators, in general, improve cardiac output by decreasing systemic vascular resistance so one should be a bit resistant to discontinuing the vasodilator, especially ACE-I, unless the azotemia or hypotension is severe, creatinine > 3 mg/dl or systolic blood pressure < 100 mmHg, respectively.** The author is more likely to reduce the dose of the vasodilators rather than discontinue them in mild to moderate azotemia. Additionally the diuretic dose is carefully examined and decreased, if possible. Remember, diuretics never improve cardiac output. Vasodilator therapy is particularly important in managing the acutely decompensated heart failure dog with chordae tendinae rupture. As previously stated, these dogs, in general, are not markedly hypervolemia and may be more predisposed to azotemia with aggressive diuretic therapy. The fulminant and severe pulmonary edema in these dogs are primarily due to increase pulmonary venous pressure from sudden worsening of mitral valve regurgitation. In the author’s experience, IV nitroprusside, a balanced vasodilator, is quite helpful in these cases to improve the dyspnea, reduce the diuretic dose and improve cardiac output.

In addition to manipulating preload, afterload and cardiac output with cardiac medications, the management of azotemia in a heart failure patient may include the use of parenteral fluids. In general, one is resistant to administering, either subcutaneous or IV fluids, in a heart failure animal if it is eating or drinking on its own. However, there are several instances when parenteral fluids may be needed. In general, IV fluids serves two purposes. One is to replete or maintain intravascular fluid volume, and two, is to maintain or replete free water, electrolyte, blood component or protein concentration derangement. Ultimately the purpose of fluid administration is to maintain cardiac preload and cardiac output, oxygen delivery and tissue perfusion to maintain cellular homeostasis. Most animals in heart failure are hypervolemia when showing clinical signs of heart failure thus initial management in general, with some exceptions, should not include IV fluids. In addition to careful consideration of the rate or amount of fluids to administer, one should be aware of the sodium concentration of the fluids. For example, if one in administering IV fluids to a heart failure patient primarily to maintain hydration or to replete potassium, a lower sodium content fluid (e.g., 0.45% NaCl + 2.5% dextrose) should be administered. 5% dextrose in water is often used to deliver IV drugs such as nitroprusside or dobutamine: the rate of fluid administration ideally should be a low rate (e.g., 1-10 ml/hr) that can be easily measured and delivered with the available fluid or syringe pump. These situations are contrasted to a heart failure patient with severe gastrointestinal fluid loss due to digoxin toxicity: this patient should initially be administered high sodium content fluids (e.g., Lactated Ringer’s solution) to replace the vomiting and diarrhea fluid losses. The fluids can be switched to a lower sodium containing fluid as soon as the vomiting and diarrhea cease. The rate and amount of parenteral fluids to administer is a case by case consideration. In general, although there are no studies to support this but many experienced cardiology clinicians consider subcutaneous or even oral fluids less likely to worsening clinical signs of congestion. However, some cases are sick enough with either concurrent disease or overzealous off-loading medications (diuretics, vasodilators) that administering IV fluids will be needed. To minimize the risk of volume overload, monitoring of vascular volume and cardiac output will also be helpful to determine rate and amount of fluids to administer. The gold standard to determine pulmonary venous pressure and cardiac output is pulmonary artery catheterization with thermodilution cardiac output monitoring. This technique has been associated with some morbidity (ref), and is not readily available at most veterinary practices, even referral centers. Other more practical and frequently used monitoring techniques include: hourly respiratory rate and effort monitoring, frequent body weight measurement, central venous pressure (CVP) and systemic blood pressure measurement, echocardiography and thoracic radiography. Closely monitoring respiratory rate and breath sounds by an experienced veterinary nurse or clinician may
be pickup on accumulation of pulmonary edema or pleural effusion in a heart failure patient receiving fluids. Twice or three times daily body weight measurement on an accurate scale may be helpful in IV fluid management as acute changes in body weight are most likely due to acute changes in body water. Central venous pressure can be helpful in administering fluids to a heart failure patient but it also has some significant drawbacks. It’s important to recognize that CVP measures the preload of the right heart and there can be significant disconnect between CVP and left sided filling pressures in a patient with heart disease. Over reliance of CVP monitoring can lead to over zealous fluid administration and accumulation of pulmonary edema in a patient with heart disease. Normal CVP measurement is 0-5 mmHg but can be greater > 5 mmHg in a heart failure patient. In the author’s experience, the goal for fluid administration in a heart failure patient is to not increase the baseline CVP unless the initial CVP is markedly decreased. In addition to monitoring both systemic and venous pressures, periodic imaging of the heart and lungs with either echocardiogram or radiograph may provide valuable information regarding heart size, edema or effusion formation and venous tone. Both techniques are non invasive however the echocardiogram has the advantage of being a potentially "cageside" technique. For most non- cardiologist echocardiographers, the most important images are those that assess left atrial and ventricular size. Many charts of normal chamber dimensions relative to body size exist. If the size of the left atrium is normal in an azotemic dog with chronic mitral valvular heart disease, this suggests that cautious IV fluids may be well tolerated. Alternatively, if the echocardiogram shows a marked enlarged left atrial size with dilation of the pulmonary veins, IV fluids may worsen pulmonary edema and this dog’s azotemia may be better served with manipulation of cardiac output with drugs such as positive inotropes and vasodilators. The echocardiogram is also quite helpful in assessing accumulation of body cavity effusions. Similarly the thoracic radiograph will also assess heart size and pleural effusion reaccumulation. Additionally, the thoracic radiograph will assess pulmonary parenchyma and pulmonary venous size which may pick up on impending pulmonary edema prior to overt clinical signs. This information can be quite helpful in monitoring the heart failure patient receiving IV fluids.

Systemic hypertension is another important condition, commonly associated with intrinsic renal disease, that can negatively affect the heart. Increased blood pressure can increase the work load of the heart leading to left ventricular hypertrophy and worsening mitral valve insufficiency. Cardiac remodeling secondary to mitral valve disease can be accelerated by systemic hypertension. For this reason, every dog with a murmur should get a blood pressure measurement. The greater challenge, of course, is the interpretation of the blood pressure in a nervous animal. Please refer to the ACVIM consensus statement on diagnosis and treatment of systemic hypertension. That said, I do think it’s important to treat systemic hypertension in a dog with preclinical and clinical heart disease.

CHRONIC ANEMIA:
Anemia has recently emerged as a relatively common and independent risk factor for worse outcome in humans with heart disease. Even small reductions in hemoglobin are associated with worse outcomes. The causes of anemia in advanced heart failure are not entirely clear. Renal dysfunction, neurohormonal and proinflammatory cytokine activation appear to contribute to the anemia of chronic disease. Under normal conditions, tissue hypoxemia due to poor cardiac output would stimulate the bone marrow to increase red blood cell production but but erythropoesis appears to be defective in heart failure. Chronic anemia, regardless of the etiology, will induce a vasodilation-mediated high output state associated with plasma volume expansion and neurohormonal activation. The high-output state initially helps to increase oxygen transport however the hemodynamic and neurohormonal alterations will have long-term deleterious effects and may exacerbate congestive heart failure. Our understanding of the prevalence and clinical significance of anemia in animals with heart disease is poor. There is one case report of a kitten with severe flea anemia-associated congestive heart failure. Dog with moderate to severe congestive heart failure have been shown to have decreased hematocrit when compared to normal healthy controls. Additionally, one recent canine study failed to demonstrated a link between anemia and worsening of heart failure severity. Nevertheless, familiarity with the cardiovascular effects of chronic normovolemic anemia is important in the management of a heart failure patient with concurrent anemia. Heart failure patients with normovolemic anemia are at risk for developing pulmonary edema with blood transfusions. A couple of classic examples are the middle-aged cocker spaniel with immune medicated hemolytic anemia with concurrent compensated mitral valve disease; and the older cat with chronic anemia due to long standing renal disease with concurrent hypertrophic cardiomyopathy. Despite the decline in hematocrit and oxygen carrying capacity in these patients, they should be euvoletic if no concurrently bleeding or fluid losses are present. Thus, if these patients required a blood transfusion, slow administration of ideally packed red blood cells with close monitoring of respiratory rate is recommended. Packed red blood cells delivers the component of the blood that is most needed and minimizes the risk for volume overload.

SEPSIS AND SEPTIC SHOCK:
In an emergency and critical care setting, severe sepsis and septic shock is commonly associated with myocardial depression and decreased contractility. This is why a dog with pre-existing heart disease is extremely fragile when it
develops severe sepsis and its associated cardiac dysfunction. Severe sepsis causes left ventricular dilation and decreased contractility most likely due to cytokine activation, primarily TNF alpha. An important treatment goal for severe sepsis is to administer IV fluids to improve blood pressure and cardiac output however in a patient with pre-existing heart disease, IV fluids may cause circulatory overload and pulmonary edema. To maintain blood pressure and cardiac output, dobutamine and low dose nor epinephrine infusion may be needed in addition to cautious fluid administration.

References:
1. ACC/AHA 2005 Guideline Update for the Diagnosis and Treatment of Chronic Heart Failure in the Adult. J Am Coll Cardiol