Heart failure is a condition in which the heart has lost the ability to pump enough blood to the body’s tissues. With too little blood being delivered, the organs and other tissues do not receive enough oxygen and nutrients to function properly. Heart failure is a general term that can often be separated into low-output and congestive heart failure. Low-output heart failure in the absence of congestive heart failure or arrhythmic disease is relatively uncommon, but can be seen with some frequency in diseases associated with poor systolic function. Low-output heart failure results in low blood pressure, weakness, exertional dyspnea, and can be seen in combination with congestive heart failure. Congestive heart failure is a clinical syndrome wherein heart failure results in sodium and water retention, culminating in pulmonary edema or systemic congestion, which manifests as cough, tachypnea, dyspnea, cavitary effusions, or peripheral limb or ventral swelling. Arrhythmogenic cardiac disease may not involve either of these processes. This type of cardiac disease may simply result in asymptomatic disease, or be severe enough to cause sudden cardiac death.

Reduced systolic function is found in patients with idiopathic or heritable disorders, resulting in structural or functional abnormalities of the myocardium, as well as secondary cardiomyopathies associated with tachycardia, valvular heart disease, ischemic, nutritional, metabolic, drug toxicity, toxins, infiltrative, or infectious/inflammatory disease. We have traditionally been very limited in our ability to treat this type of heart failure. Many attempts have been made to develop an oral medication that would greatly increase the systolic function of the heart, but most of these strategies have failed due to their tendency to induce ventricular arrhythmias and sudden death. Angiotension converting enzyme (ACE) inhibitors have been shown to preserve systolic function by reducing myocardial fibrosis and detrimental hypertrophy in cardiac disease states, but aldosterone production and release can be mediated by other stimuli that allow for continued negative cardiovascular effects. Chronic adrenergic stimulation can also result in down regulation of beta-1 and beta-2 adrenergic receptors, reducing overall systolic and diastolic myocardial function. Digoxin has been used chronically for decades as a chronotrope and inotrope, and has been our only chronic oral option for restoring some positive inotropic activity. However, more recently drugs have come on the market that may help improve our treatment of these patients. These include spironolactone, beta-blocker therapy, and pimobendan (Vetmedin®).

The benefits of ACE-inhibitor therapy in cardiac disease are well known once the patient has developed signs of heart failure. These benefits include increased survival, improved quality of life, improved exercise capacity, relief of congestive signs, decreased need for large diuretic doses, and decreased rate of disease progression. The exact reason for these benefits was not always clear. Initial theories in human medicine suggested that afterload reduction was the essential component of these benefits, but more potent afterload reducers (arteriovasodilators) did not fair as well when compared directly to the less potent ACE-inhibitors. Inhibition of the renin-angiotensin-aldosterone system (RAAS) produces a reduction in afterload via arteriodilation, reduced preload via decreased renal sodium resorption, and increased venous capacitance, and positively affects the remodeling process at the tissue and structural level in the heart. Inhibition of negative remodeling is now suspected to be the main engine driving the benefits of RAAS inhibition. However, there is some evidence, especially in patients with dilated cardiomyopathy, that aldosterone blood levels can be elevated despite ACE-inhibitor therapy. Aldosterone is produced and released in response to angiotensin II, adrenocorticotropic hormone (ACTH), elevated blood potassium levels, plasma catecholamines, vasopressin, and endothelin-1. Thus, inhibiting the production of angiotensin II with an ACE-inhibitor seems unlikely to result in complete circulating and tissue aldosterone. This “aldosterone escape” can result in sodium and water retention, replacement, and interstitial fibrosis as well as significant increases in myocyte cross-sectional area, a measure of myocyte hypertrophy. With this theory in mind, large human trials have been performed showing that sub-diuretic doses of spironolactone could reduce myocardial fibrosis and hypertrophy, when given in addition to an ACE-inhibitor. However, aldosterone breakthrough has not been shown in all human patients with heart failure, and evidence is lacking even more in dogs.

Improved human survival data in patients with low systolic function that are on chronic beta-adrenergic antagonist therapy has prompted considerable interest in its use for our cardiac patients that have reduced ventricular contractility. There is clear evidence in humans of an improvement in ejection fraction and ventricular remodeling after chronic treatment with various beta-adrenergic antagonists. Heart failure patients typically have chronic
sympathetic stimulation by direct innervation to the myocardium and via circulating catecholamines. This overstimulation results in detrimental effects that experimentally can be reversed or reduced by administration of a beta-adrenergic antagonist (beta-blocker). The particular mechanism of the survival benefit in humans is not known, but is likely a combination of positive effects. These advantageous changes include upregulation of available beta-1 receptors, improved coupling of the beta-2 receptors with their G protein signaling complex, decreased plasma renin concentration, and decreased heart rate and myocardial oxygen demand. Specific studies in dogs showing clinical efficacy are lacking. The best clinical trial regarding the use of carvedilol in dogs with degenerative valve disease concluded that carvedilol did not improve the sympathetic activation and echocardiographic variables over 3 months of chronic oral treatment. However, the results suggested a beneficial effect on the quality of life score, functional classification, and a reduction of systolic blood pressure. Another study in naturally occurring dilated cardiomyopathy showed that carvedilol treatment did not result in significant changes in neurohormonal activation, echocardiographic indicators of heart function, radiographic heart size, heart rate, or owner-perceived quality of life. Critiques that can be made about both of these studies are that the dose may have been too low (maximum of 0.3mg/kg q12hr). However, to date the major benefits seen in humans have yet to be shown in our clinical canine patients. The other disadvantage of beta-blocker therapy is that some patients cannot tolerate the initial reduction in systolic function and can decompensate during the titration phase. Slow titration often eliminates this complication. Drugs with proven benefit in humans include metoprolol and carvedilol. Metoprolol is a Beta-1 specific antagonist, while carvedilol is a non-specific blocker of Beta-1, Beta-2, and Alpha-1 adrenergic receptors. Dogs are generally started at 0.1mg/kg every 12 hours and increased by 25% every week until a dose of 1mg/kg q12hr is achieved. Patients should be monitored for changes in heart rate and decompensated heart failure about every 2 weeks during the titration phase. Human studies suggest that it generally takes up to 3 months to see an improvement in ejection fraction, and as long as 11 months to see a survival benefit. Thus, many of our dilated cardiomyopathy patients may die before any expected survival benefit. However, beta-blocker use is often considered in occult cases of dilated cardiomyopathy, compensated dilated cardiomyopathy, and degenerative valve patients with systolic dysfunction.

Pimobendan is a benzimidazole-pyridazinone derivative with positive inotropic and vasodilatory properties, thus the classification as an inodilator. The inotropic activity is thought to be mainly due to its calcium sensitizing effect, which improves the use of calcium by the myocardium without the need to increase intracellular calcium. The improvement in systolic function is also due to inhibition of phosphodiesterase III (PDE III) in the myocardium, which reduces the breakdown of cyclic adenosine monophosphate (cAMP). This improves myocardial contraction and relaxation by enhancing the adrenergic phosphorylation pathways, which affect the increase release and uptake of calcium in the cytosol of the myocyte. The inhibition of PDE III and PDE V also results in peripheral dilation of the systemic and pulmonary arterioles. This reduces afterload and results in increased perfusion to the tissues. The half-life of pimobendan is only 30 minutes, and that of its metabolite is 2 hours. The duration of effect is over 8 hours. Its peak effect is reached in about 45 minutes after oral administration. The drug has been marketed to veterinarians in Europe as Vetmedin® for almost a decade. FDA approval in the United States was not obtained until September 2007. Some of the safety concerns about pimobendan stemmed from a large human trial (Pimobendan in Congestive Heart Failure PICO Trial). This study of pimobendan improved exercise capacity in patients with chronic heart failure who were also on conventional treatment. It did not show any proarrhythmic effects on 24-hour electrocardiography, but in both pimobendan groups combined, the hazard of death was 1.8 (95% confidence interval 0.9 to 3.5) times higher than in the placebo group. There is one published paper showing IV pimobendan increased the incidence of ventricular fibrillation after acute myocardial infarction. These are the warnings we were initially giving owners before we started our heart failure patients on pimobendan. However, there is now a recent study that shows survival data in patients on chronic oral dosing of pimobendan called the QUEST Trial. This is a multicenter study in Europe, Canada, and Australia that took 7 years to complete. It was a prospective single-blind study with dogs randomized to PO receive furosemide and pimobendan (0.4–0.6 mg/kg/d) or furosemide and benazepril hydrochloride (0.25–1.0 mg/kg/d). The primary endpoint was a composite of cardiac death, euthanized for heart failure, or treatment failure. 260 dogs with degenerative mitral valve disease and left-sided congestive heart failure were entered in the study. None of the individual endpoints reached a statistically significant difference between the 2 groups, but pimobendan trended toward a benefit in each category, so that when combined, the median time to the combined endpoints was 267 days (pimobendan group) vs. 140 days (benazepril group), which indicates that the median time in the pimobendan group was prolonged by 91% (127 days, 4.2 months) of the benazepril group. This study helps us build a powerful defense for our use of pimobendan in degenerative valve patients. We are not advocating its use as a replacement for enalapril or benazepril, but as an adjunct to conventional therapy (furosemide and ACE-inhibitor). The pimobendan dose used in the QUEST trial was 0.2–0.3mg/kg q12hr. Pimobendan is indicated in any form of systolic dysfunction in the absence of a fixed
outflow obstruction such as subaortic stenosis. It is a natural fit for patients with dilated cardiomyopathy, and studies have shown increased survival and reduced symptoms in dobermans with dilated cardiomyopathy on pimobendan therapy. There are no clinical studies evaluating its use in an acute setting of congestive heart failure, but if a CRI of nitroprusside or dobutamine is not feasible or blood pressure cannot be monitored, pimobendan can be used orally to function as a combination of inotropy and vasodilator. Pimobendan is absorbed rapidly (less than 1 hour in most patients). Excessive pimobendan can cause hypotension that could be excessive, so measuring blood pressure is still warranted.

References


