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CARVEDILOL AND THE HEART – A PROMISING THERAPY

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Chronic myxomatous degeneration of the mitral valve causing left ventricular and atrial volume overload is the leading cause of canine cardiac morbidity and mortality. Chronic degenerative AV valve disease (CVD, mitral endocardiosis) represents 80% of all canine cardiac disease. Clinical evidence of canine cardiac disease is reportedly present in 25% of all primary care veterinary canine appointments. CVD is most common is small breed older dogs but affects all breeds with some frequency. It is characterized by a protracted asymptomatic course. There are currently no recognized medical therapies to delay the progression of this disease. Symptomatology is characterized by signs of cardiogenic pulmonary edema, which is managed with traditional heart failure therapy including furosemide, angiotensin converting enzyme inhibition, and spironolactone, with or without digoxin. However, despite medical management mortality rates remain high and there is limited experience with mitral valve repair in veterinary medicine thus medical management remains the cornerstone of therapy.

CVD is easily diagnosed in its early stages by the presence of a characteristic murmur. The grade of the murmur has been shown to positively correlate with disease severity. Although not all dogs with CVD develop clinical signs all dogs experience disease progression. In two previously reported clinical trials, approximately 40% of asymptomatic small breed dogs with CVD and moderately loud murmurs developed clinical signs with 4-5 years of follow-up.

Reduced left ventricular (LV) systolic function has been demonstrated in an experimental canine model of chronic MR and in human primary MR. The proposed mechanism for systolic dysfunction characteristic of primary MR is related to elevations in sympathetic nervous system (SNS) tone, resulting in a reduction in both the absolute number of cardiomyocytes as well as the number of contractile elements within each cardiomyocyte. Selective and non-selective β-blockers including carvedilol (Coreg®) have been shown to significantly improve systolic function and survival in human patients with heart failure secondary to both ischemic and idiopathic dilated cardiomyopathy. Additionally, high dose atenolol (2-5 mg/kg PO q 24hr), a 2nd generation selective β₁-blocker, improved LV systolic function in an experimental canine model of chronic MR. The improvement was associated with enhanced innate contractile function of isolated cardiomyocytes due to an increase in the absolute number of contractile elements. The reported beneficial effects of gradual β blockade on systolic function represent a biologic effect that is not immediate upon initiation of therapy.

Elevated concentrations of circulating norepinephrine (NE) is characteristic of chronic heart failure in humans, and has been documented in canine patients with symptomatic CVD and in an experimental canine model of chronic MR. However, circulating NE does not appear to accurately identify the magnitude of organ specific SNS tone and thus does not identify the onset of organ specific SNS up regulation. Evaluation of cardiac specific SNS tone has demonstrated early adrenergic nervous system enhancement that precedes elevations in circulating NE in human primary MR. Furthermore, augmented SNS tone and may act as a deleterious signal in the progression of this disease. These data suggest β blockade may be beneficial in asymptomatic dogs with CVD. Initial evaluation of β blockade for the treatment of heart failure focused on second generation β₁ selective agents (metoprolol, atenolol) to avoid increases in afterload characteristic of nonselective β blockade. However, β₁ and β₂ receptors are present in the myocardium and both are important in mediating adrenergic effects in cardiomyocytes. Additionally, in human heart failure, cardiac β₁ receptors are down regulated while β₂ receptor numbers remain unchanged. Therefore, due to the increased proportion of β₂ receptors, more comprehensive cardiac adrenergic blockade can be achieved with the use of nonselective β-blockers. However, non-selective β blockade may increase afterload by blocking the vasodilatory effects of peripheral vascular β₂ receptors. Although afterload reduction has failed to demonstrate a favorable effect on the progression of asymptomatic human primary MR and CVD, it has demonstrated favorable short term hemodynamic effects and is a cornerstone of pharmacotherapy for CVD. Carvedilol is a 3rd generation non-selective β-blocker with ancillary α₁ blocker and antioxidant properties. Unlike high dose metoprolol, the potential risk of afterload augmentation due to the non-selective nature of carvediols β blockade appear to be offset by its α₁ blocking properties. Finally, carvedilol has important in vivo antioxidant properties and in vitro endothelial and cardiomyocyte anti-apoptotic effects. Reductions in free radical oxidative stress and apoptotic cellular loss may delay the progression of many forms of heart disease.

The goal of β blockade in the treatment of human heart failure is to achieve maximum tolerable continuous blockade. This clinical goal reflects the concern that β receptors intermittently available to endogenous stimulation may facilitate arrhythmogenesis, tachycardia and enhance myocardial oxygen consumption, all of which increase the risk of an adverse outcome. However, the relative risk of short-term decompensation due to the negative inotropic and chronotropic properties of these agents mandate gradual initiation of therapy in the form of an up-titration protocol based on canine pharmacokinetic and pharmacodynamic data.