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MITRAL VALVE DISEASE – ALTERNATIVE THERAPIES SUCH AS BETA BLOCKERS, AMLODIPINE AND PIMOBENDAN

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Mitral valve (and tricuspid valve) regurgitation (MR) due to degenerative valvular disease is undoubtedly the most common disease in small animal cardiology. Over approximately the last 25 years, therapy with ACE-inhibitors and additional diuretics, when needed, has become the most established way to treat this disease which represents a combination of volume overload and systolic myocardial failure. Additional digoxin therapy has been advocated in cases with supraventricular tachyarrhythmias and congestive heart failure, especially right sided with chronic ascites. Systolic failure is difficult to document in the early stages of the disease, but is definitely present in advanced stages of MR. Different opinions have arisen with respect to treating asymptomatic and mildly symptomatic stages, i.e. ISACHC classes I and II. Advances in laboratory techniques today allow the determination of NT-proBNP as indicators of volume overload and atrial wall stress, troponins as indicators of cardiomyocyte damage, and aldosterone as indicators of activation of the RAAS. Unfortunately, there are not any clinical studies documenting the incidence of aldosterone-escape (Ang.II-breakdown into aldosterone by alternative pathways other than the converting enzyme ACE) in dogs with naturally occurring mitral regurgitation. ACE-inhibitors have only slight blood pressure lowering and therefore afterload-reducing effects in dogs. Therefore, knowledge about their sustained Ang. II and aldosterone blockage is required and essential to determine why they have beneficial effects in chronic mitral regurgitation. Enalapril was not able to reduce the regurgitant fraction in dogs with experimentally induced MR (1). On the other hand, aldosterone-inhibitor drugs (Spironolactone) was recently licensed for the use in dogs in many European countries. Its use may prevent or at least reduce the damage (mostly fibrosis) of aldosterone in the myocardium and vascular walls. Mitral regurgitation could be treated in 3 different ways: Firstly with pure afterload reduction to reduce the regurgitant fraction, secondly with drugs increasing the efficiency of myocardial contraction (part of the inodilator effect), and thirdly with beta blockers protecting the heart from the damaging effects of chronic overstimulation by endogenous catecholamines.

Betablocker therapy is well established in human cardiology to protect the myocardium from the damaging catecholamine effects and to prolong survival with heart failure, as an add-on with classical heart failure...
therapy. Procedures are usually to up-titrate patients in early stages of heart failure to the maximum tolerable levels of the drug. Downregulation of beta 1 receptors has been documented in humans in heart failure, mostly due to idiopathic cardiomyopathy, and restoration of beta 1 receptor levels after prolonged beta blocker therapy (selective and nonselective) has also been shown. Many opinions exist on the “best” drug to use, and on advantages of non-selective versus selective beta blockade, without uniformly accepted opinion. Carvedilol (a partially selective beta blocker) has additional antioxidant effects and is amongst the most frequently prescribed drug for the purpose of cardioprotection. Studies on Carvedilol pharmacokinetics, -dynamics and dosing recommendations have been derived from studying mainly healthy dogs or dog models with artificially induced mitral regurgitation. It is debatable if these recommendations can universally be applied to dogs with naturally progressing MR. As shortened survival has been shown in MR-dogs when using Carvedilol in ISACHC class II MR-dogs, we prefer to begin Carvedilol therapy in ISACHC class I b, and titrate it up (4 weeks protocol) to a dose of 0.8 to 1mg/kg twice daily. This titration has served us well without significant alterations of heart rate and blood pressure. By doing so, the drug is well tolerated over prolonged periods of time, in many cases years, even in Cavalier King Charles Spaniels. We recommend to keep giving the beta blocker until early signs of CHF appear (ISACHC IIIa), and then continue it while adding Pimobendan, diuretics and ACE-inhibitors. Based on very promising results with Aldosterone blockade in moderate stages of MR, we speculate that a combination of Carvedilol with Spironolactone will turn out to be a very effective therapy for early stages of MR.

Therapy with Amlodipine

Potent vasodilator therapy certainly reduces the regurgitant fraction by reducing afterload and ventricular pressure, but also activates the RAAS if it is not already turned on, depending upon the MR-severity of the particular patient. One short-term study only measured various parameters in 16 dogs with moderate or severe MR that were on different therapies. Treatment resulted (average follow-up time 20 days only) in reduction of the systolic BP (10%), the regurgitant fraction (15%) and the LVEDd (4%). No significant change of the echographic LA/Ao-ratio was detectable (2). Amlodipine may cause gingival hyperplasia with chronic administration in dogs with a reported incidence of 8.5% (3). We therefore see the current role of Amlodipine in MR-dogs as an add-on measure in advanced MR-stages with heart failure, where BP-measurements indicate a sufficient “reserve” above the minimum level required for sufficient renal perfusion, i.e. a mean pressure of around 70-80 mmHg. The drug needs to be given with frequent reevaluations of the BP, renal values and, if possible, NT-proBNP measurements.

Therapy with Pimobendan

Pimobendan in combination with moderate to high doses of furosemide was compared to Benazepril with equal doses of furosemide and clearly outperformed the ACE-inhibitor: Pimobendan achieved significantly longer survival. Entry criteria were evidence of congestive heart failure (clinical and radiographic), i.e. the severity of admitted dogs was ISACHC class III (4). The question of added benefits by combining both drugs at that severity-stage was not addressed by the study and remains speculative. A smaller and shorter study (5) documented Pimobendan-induced benefits on quality of life and reduction of pulmonary hypertension (PH, assessed by the severity of tricuspid regurgitation) in dogs that had developed PH as a consequence of severe, chronic MR. Pimobendan seems indicated in MR because of its inotropic and vasodilatory effect. We look at the inotropic effect as not purely an increase of contractile force (which would tend to increase the regurgitant fraction), but rather a more effective work of the contractile apparatus by increasing the sensitivity of calcium
binding, and therefore working more economically. This may explain the benefit of Pimobendan over an ACE-inhibitor in 2 separate studies when given to MR-dogs in moderate MR without signs of CHF at entry (equivalent to early ISACHC II). Both studies used Pimobendan in conjunction with diuretics. Better quality of life, longer survival and reduction of heart size was documented by radiographs (6). Better quality of life, reduced need for hospitalization due to heart failure or reaching endpoint of the study (death, intractable heart failure) was evident in the other study(7). Pimobendan does not activate the RAAS when given to healthy dogs, in contrast to furosemide (8), but was unable to offset the furosemide-induced RAAS-activation when given together. Therefore, coverage of dogs with an additional ACE-inhibitor when giving Pimobendan and diuretics has been advocated by some veterinary cardiologists, but not by others. We belong to the latter group, using the above mentioned QUEST study as a counter-argument, without having exact data including neurohormonal measurements to prove this theory.

The question if Pimobendan could be used as monotherapy in MR-dogs in ISACHC classes Ib and II is very intriguing to us. While arguing that a more economical cardiac function should delay the onset of congestive heart failure, other arguments have been that Pimobendan could induce adverse effects such as cardiac hypertrophy and increased regurgitant fraction in dogs without MR or only mild stages(9)The same group of authors (10) gave either Pimobendan or Benazepril over a period of 512 days to asymptomatic Beagle dogs with MR (equal to ISACHC class Ia, MR identified by soft heart murmurs and Doppler color jets in the left atrium, 6 dogs per group), but totally normal conventional echocardiographic and tissue Doppler (TDI) parameters. Heart rates and BP remained unchanged in both groups, the loudness of heart murmurs increased by an average of 2 grades in the Pimobendan group. Conventional and TDI echographic variables remained unchanged in the Benazepril group; in the Pimobendan group, an increase of the shortening fraction (SF), a decrease of LVEDs, an increase in septal and LVW-thickness, and no change in LVEDd and LA/Ao-ratio was seen. Systolic TDI-variables were significantly increased in the Pimobendan group, as was the thickness of the anterior mitral valve leaflet, and the increased ratio of the ARJ/LAA (area of regurgitant jet/left atrial area assessed by Color Doppler). In addition, more severe valvular lesions and histologic alterations dominated in the Pimobendan group in comparison with the Benazepril group. These studies were unfortunately performed without the use of biomarkers to have additional indicators of adverse effects.

In contrast, a small study of 4 dogs with surgically induced mild MR documented unchanged stroke volume and heart rate, and decreased MR and systolic blood pressure over a 4 week period (11). In 19 dogs with natural, asymptomatic MR(class Ib equivalent) receiving Pimobendan therapy and studied over a 6 month period, systolic function increased only transiently, and other echocardiographically derived MR-parameters remained unchanged (12). Some Pimobendan effects could have been influenced by ACE-inhibitor-therapy that was inconsistent among participants in that study.

It appears therefore that sustained effects of Pimobendan therapy MR-dogs with a mild degree of regurgitation are not clear cut and to some extent contradictory. At present, if used at mild to moderate stages of MR, frequent monitoring with echocardiography appears essential. A direct comparative study (monotherapy, longterm, blind, with carefully selected endpoints) of an ACE-inhibitor against Pimobendan in ISACHC class Ib dogs seems necessary to clear this confusion using these drugs early in MR.
References