Mitral valve regurgitation

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Mitral valve disease (MVD) is the most common acquired cardiac disease of dogs and is a very common reason for the presentation of dogs to veterinarians. The condition is progressive and will lead to signs of congestive heart failure in the majority of patients, provided they will survive long enough and not die from an unrelated disease at a premature age. The disease is easily recognized by its characteristic systolic heart murmur, heard best on the left side of the thorax. MVD has a long preclinical period (several years, somewhat breed dependent) during which cardiac remodeling occurs. Echocardiography and radiography are the methods of choice to document such remodeling during the asymptomatic period, where the mitral valve leaflets thicken and the left atrium and left ventricle become progressively larger over time. If the underlying degenerative valvular disease (endocardiosis) affects the tricuspid valve leaflets, the same progressive cardiac enlargement/hypertrophy can also be recorded on the right side. Endocardiosis affects primarily small dogs such as Cavalier King Charles Spaniels, Poodles, Terriers, Schnauzers, Spitz, Chihuahua etc., and many mixed-bred dogs. The disease may affect larger dogs over 15 to 20 kg such as German Shepherds and Labrador Retrievers, but seems to have other characteristics and different progression pattern in those dogs. As the disease has an increased incidence in certain family lines of e.g. Cavalier King Charles Spaniels, an underlying genetic predisposition is strongly suspected, but hasn't been proven yet. Offspring of affected parents clearly showed a higher frequency of heart murmurs. Eliminating dogs based on the presence of a heart murmur at a young age at dog shows is problematic, as many more dogs without murmurs at a young age still develop MVD at a later stage in life, i.e. between 8 and 15 years of age.

Clinical signs and progression. Many affected dogs have heart murmurs of mitral regurgitation and no outward signs of cardiac disease whatsoever. They behave normally, can exercise without problem and appear totally normal to their owners. Only at middle age, generally between 5 and 10

years, do mild signs of cardiac disease develop. Some of the earliest signs of beginning decompensation are difficult to measure and manifest themselves as progressive exercise intolerance, tachypnea/ dyspnea during and after heavy exercise, as well as a prolonged recovery period. As they progress with the ageing of the patient, owners frequently do not recognize these signs or attribute them to a normal ageing process of their pet. Once pulmonary congestion develops, the respiratory signs become more evident with coughing during exercise, after periods of resting and starting to move again, during and after drinking and at night (nocturnal restlessness, inability to sleep through the night, waking up the owner etc. As dogs in this age bracket have frequently concomitant disease of the respiratory tract such as chronic bronchitis, collapsing tracheas, interstitial pulmonary fibrosis etc., it may be difficult to clearly correlate the respiratory signs unequivocally to either cardiac or respiratory disease, even with high quality radiographs.

In order to get a grip on the severity of the clinical stages of MVD, the ISACHC classification scheme is commonly used (1994) Though not perfect, it allows the differentiation from asymptomatic to symptomatic animals, and among the latter ones the separation of mild and moderately affected from severely affected ones. The system is based mostly on symptoms of the patient, similar to human systems such as the NYHA-score, but would benefit from additional input from measurement techniques such as radiography, electrocardiography and echocardiography, which were not incorporated in the original publication. Nevertheless, the ISACHC-classification is used to justify therapeutic interventions for the different grades of severity, and is used for the grouping of patients in research trials looking for drug effects and/or increased survival.

ISACHC-classification of congestive heart failure

Class I	Asymptomatic
	Ia : No evidence of cardiac compensation
	Ib : Signs of remodeling are present (radiography, echocardiography)
Class II	Mild to moderate signs of heart failure, but still normal at rest.
	Signs include shortness of breath with and after exercise, eventual mild cough, prolonged recovery time, diminished peak exercise capabilities and tolerance
Class III	Signs of advanced heart failure (elevated respiratory and heart rates, dyspnea and eventual cough at rest or with minimal exercise, nocturnal dyspnea, jugular vein distension, ascites)
	IIIa : home therapy possible
	IIIb : patient needs to be hospitalized for intensive care and stabilization

Electrocardiography. In early and even middle grades of severity of mitral regurgitation, electrocardiography is not useful and doesn't bring important additional information, unless arrhythmias heard on auscultation are analysed. The normal respiratory sinus arrhythmia of dogs is preserved for a long time and likely a good indicator of full compensation of the cardiac problem. Studies of the progression of heart failure with mitral regurgitation and dilated cardiomyopathy have shown a parallel progressive loss of heart rate variability. Arrhythmias such as atrial premature beats, paroxysmal supraventricular tachycardias or atrial fibrillation usually occur only in late stages such as ISACHC III, with severely dilated atrias. Some dogs with MVD may be followed over years, and their ECG will change from normal to enlarged P-waves to atrial fibrillation, when the left atrium has become severely enlarged. Sensitivity and specificity of ECG-sigs of left atrial enlargement (widened and notched P-waves, also called P-mitrale) and of left ventricular hypertrophy (LVH, widened QRS-complexes, increased R-wave amplitudes) are not very high, unfortunately. Ventricular tachyarrhythmias are rare with mitral regurgitation. If present, possible other causes for these should be investigated.

Radiography. This time honored technique is probably the most useful tool for the evaluation of mitral regurgitation in dogs, especially for the progression of the disease. It is also the most objective tool to prove the presence of congestive heart failure, by showing cardiomegaly, enlargement of the pulmonary vessels as well as pulmonary infiltrates as signs of pulmonary congestion due to increased left atrial and pulmonary vein pressures. Buchanan and Bucheler introduced the concept of the vertebral heart scale (VHS) in the year 1995. With this simple measurement technique, where only a good quality lateral thoracic radiograph is needed, more objective assessment of the heart size or cardiomegaly has become possible. While the absolute values are not so important, documentation of the progression of the cardiomegaly over time within the same dog makes this technique very valuable, especially for the therapeutic decisions. Besides the cardiac and vascular structures, evaluation of the tracheobronchial tree and pulmonary parenchyma may reveal important information about concomitant other diseases that could be responsible for respiratory signs such as dyspnea or cough: collapsing trachea, chronic bronchitis, and pulmonary fibrosis are the most important ones. In older dogs, rule-out of pulmonary neoplasms (primary or metastatic) also becomes important.

Echocardiography. The value of this extremely useful tool of cardiology lies in its ease of application, non-invasiveness and repeatability. It provides direct visual evidence of mitral (and eventual tricuspid regurgitation) with color Doppler echocardiography. The color jets of mitral (and

tricuspid) regurgitation have been assessed semiquantitatively, by planimetry (Ratio of the jet area and the surface area of the left atrium). Draw-back of such a method is its limitation to 2 dimensions and therefore lack or at least uncertainty of the true volumetric regurgitation. An elegant, but technically demanding way of obtaining volumetric information of the regurgitant volume RV (or regurgitant fraction RF as percentage of the stroke volume) is the PISA- technique (proximal isovelocity surface area).

There are many more simpler and useful echocardiographic measurements available for the assessment of dogs with mitral regurgitation. In a decreasing order of importance (also based on the volume of avaible information and publications) are:

The LA/Ao-ratio (unfortunately, different measurement techniques by M-mode and 2D exist),
Ventricular diastolic and systolic dimensions (LVIDd and LVIDs)
Shortening Fraction of the LV (LVIDd - LVIDs / LVIDd)
Septal and LV-wall thickness (IVSd and LVWd)

Volumetric calculations from the above dimensions derived from a ventricular short axis with the so-called Teichholz equation (and some modifications of the formula) have serious geometric limitations and have not properly been validated for dogs, especially not in advanced stages of excentric volume overload where the shape of the ventricular lumen may change considerably. The Simpson biplane method of calculating volume by adding discs is an improvement over the Teichholz method. The gold standard would be volume-derived ejection fractions by the radionuclide technique; this is however not practicle or available for veterinary patients on a routine base. The search for easily obtainable parameters of the myocardial function (systolic and diastolic) during mitral regurgitation continues. Finally, assessment of the thickness of the valves leaflets themselves, or 2-dimensional evidence of mitral valve prolapse, are supportive causative evidence of mitral regurgitation, but do not lend themselves for more than very gross monitoring of the progression of the disease.

There is general agreement that the systolic myocardial function during MVD is preserved over a long period of time, which causes endless discussions of the use of positive inotrope therapy versus vasodilatator therapy in this disease. Systolic function may be roughly assessed by the maximal velocity of mitral regurgitation. More important are likely measurements of diastolic dysfunction, by assessing inflow patterns, relaxation indices, and possibly tissue Doppler information. The latter

is only applied by a few specialized veterinary centers of expertise in Europe and the United States. And hardly any useful information is available about the positive influence of the currently used veterinary drugs onto these indices, which would provide evidence about the usefulness/benefits and justification of these drugs or therapies.

Blood pressure measurement and vasodilatator drugs. This technique is unfortunately still in its infancy with respect to routine application in cardiac patients, because of the lack of accurate measurement devices that are easy to use. Because the lack of cooperation from the patients side, another source of great variability of the blood pressure results is evident. Promising new techniques are based on high definition oscillometry, which should improve the accuracy of measurements and the time needed to register them. Nevertheless, in order to properly apply vasodilatator drugs such as ACE-Inhibitors and 3rd generation Ca-channel antagonists (Amlodipine) during the therapy of MVD, the blood pressure should be monitored carefully and drug dosages adjusted accordingly. The goal of therapy in these cases is to diminish mean arterial pressure into the range of 70-90 mmHg, warranting a real decrease of the afterload, but of course only if tolerated by the patient.

Therapeutic considerations

It would be desirable to have clear and proven information about effective drug therapy (single or combination) for each ISACHC-severity class of heart failure. This unfortunately does not exist, as historical developments of drug recommendations were targeting primarily symptomatic relief of the most severe and debilitating signs, i.e dyspnea due to pulmonary edema. Diuretics are unquestionably suited for this purpose and are a time honored pillar of combination therapy of late stages of heart failure. It is remarkable to mention that not a single blinded and placebo-controlled study exists in veterinary cardiology proving this benefit of diuretics!

Therapy of heart failure has mainly been guided by combating/alleviating the predominant signs of failure. This occurs obviously in the late stages of the diseases (ISACHC classes II and III), where the relief of signs can be monitored. Studies about the improvement of signs, acceptable quality of life and prolongation of survival are more recent developments; they followed essentially the landmark CONSENSUS study (1987) from human medicine, where Enalapril was shown to diminish mortality in human subjects in heart failure due to various causes. The similar veterinary blinded and placebo-controlled studies were : LIVE (1998) showing the benefits of adding Enalapril to dogs with heart failure treated conventionally with diuretics and some with digoxin as well. And BENCH

(1999) with a broader severity range of subjects with heart failure, but still 86% of patients on diuretics, unfortunately without indicating dose levels. A study from Scandinavia (SVEP 2002) revealed no benefits of treating asymptomatic (ISACHC class I) dogs with Enalapril.

The arrival of the new inodilator drug Pimobendan changed the situation considerably. Pimobendan has vasodilator as well as positive inotrope effects and makes the drug ideally suited to treat congestive heart failure caused by dilated cardiomyopathy. This was put in evidence by the PiTCH-study (2003), that contained some dogs with MVD as well. That doubleblinded, placebo-controlled study looked for symptomatic improvement and prolongation of survival, in direct comparison with Benazepril, and provided some evidence of better performance. The follow-up VETSCOPE study (2006) was restricted to MVD dogs with moderately severe to severe disease, and revealed again improvement of clinical signs and longer survival of Pimobendan-treated dogs in comparison with Benazepril treated ones. The latest study in this series (QUEST 2008) dealt with a better defined stage of MVD dogs, that had to have suffered a bout of congestive heart failure to be admissible. The study very tightly controlled drug dosages and allowed very high (up to 12 mg/kg/day) diuretic therapy. Again, a superior performance of Pimobendan over Benazepril was put in evidence with respect to survival.

These results from different drug trials may be confusing for the practitioner who would like clear guidelines about which drug or drug combination to use at the different stages of severity of MVD. The enclosed table is our present recommendation for therapy of MVD. Please notice that the majority of decisions, especially for class ISACHC II, are based on clinical impressions, experience and frequent monitoring of the individual dog, and not so much on hard facts from drug trials.

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Table 1: Therapy for the different stages of MVD

Drug or management	ISACHC class I	ISACHC class II	ISACHC class III
Pimobendan	no	Individual: based on Echo indices LA/Ao > 2.0, moderate cardiomegaly, diminishing MR velocity	YES (Quest-study)
ACE-inhibitor	No evidence (SVEP-trial)	May give as monotherapy (no evidence):	YES (inferior to Pimobendan in QUEST study): Combination in most severe cases?
Digoxin	No evidence	Only with atrial fibrillation	Only with atrial fibrillation
Diuretic: Furosemide	No evidence	Individual: Based on symptoms, with radiographic evidence of congestion, LA/Ao > 2.2	YES (individualize dosage, may increase up to 12 mg/kg/day)
Diuretic: Spironolactone	No evidence	No evidence	As add-on to Furosemide: sequential nephron blockade when Furosemide > 4mg/kg/day
Bronchodilatator	No evidence	Individual (no evidence)	As Individual add-on
Amlodipine	No evidence	Individual: based on blood pressure evidence, LA/Ao > 2.0, high MR-velocities	As individual add-on with elevated blood pressures
Exercise restriction	No evidence	Avoid severe exercise	Yes
Low sodium diet	No evidence	No evidence	Individualize