

Corrigendum: Advances in the understanding of the pathogenesis, progression and diagnosis of myxomatous mitral valve disease in dogs



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The author Johan P. Schoeman has requested that the initial of his second name be included on the article 'Advances in the understanding of the pathogenesis, progression and diagnosis of myxomatous mitral valve disease in dogs', published in 2014.

This has been amended under the author section of the corrigendum, to read Johan P. Schoeman.

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Advances in the understanding of the pathogenesis, progression and diagnosis of myxomatous mitral valve disease in dogs

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A number of key questions remain unanswered in the pathogenesis of myxomatous mitral valve disease (MMVD). As MMVD typically afflicts small-breed dogs, a genetic basis has been implied. In addition, the fact that not all dogs within a risk group develop MMVD is still unexplained. Research into the pathogenesis of MMVD typically falls under three categorical divisions, namely genetic factors, mechanical factors of the valve and systemic factors. Genetic studies have implicated certain loci in the pathogenesis of MMVD. Of particular interest is the insulin-like growth factor (IGF)-1 locus, as IGF-1 is also associated with growth. The mechanical structure and function of the mitral valve have also received much attention in recent years. What has emerged is the notion of a highly complex dynamic structure, which has an uneven distribution of stress and strain according to the flow of blood. Research efforts have also identified a number of systemic factors such as cytokines and signalling pathways that may contribute to the failure of the valve. Serotonin remains an area of interest in this field. Taken together, the amalgamation of research efforts in these three areas will go a long way towards resolving the understanding of this disease. Another area of focus in MMVD has been the development of clinical tests to diagnose the onset of congestive heart failure. To this end, echocardiographic indices and biochemical markers have been investigated. Echocardiographic indices such as left atrial to aortic ratio and the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) have been identified as specific risk factors to predict progression. Advanced imaging studies such as cardiac magnetic resonance imaging have enabled investigators to determine the earliest remodelling changes that occur in MMVD.

Introduction

Pathogenesis of myxomatous mitral valve disease

Genetic factors

Despite intense research efforts, a complete understanding of the processes governing the development of myxomatous mitral valve disease (MMVD) remains elusive (Orton 2012). A number of key questions remain to be resolved; in particular the genetic associations that have been inferred by the occurrence of breed and size predispositions to MMVD (Parker & Kilroy-Glynn 2012). The fact that a distinct signalment of patient appears to be predisposed to MMVD tends to emphasise the fact that a significant part of the pathogenesis of the disease must lie in the unique genotype of these individuals. Genome-wide association studies (GWAS) have increasingly demonstrated genetic loci associated with many diseases; however, in many cases these loci are not directly related to the pathogenesis of the disease (Brookfield 2010). The mere presence of a characteristic genome does not necessarily mean that a certain individual will develop the disease phenotype (Kitsios & Zintzaras 2009). As a result, newer research methodologies have sought to characterise the expression of genes.

Using GWAS in patients with MMVD and small-breed dogs predisposed to MMVD, a number of interesting loci have been determined (Parker & Kilroy-Glynn 2012). One of the questions GWAS have sought to answer is whether MMVD is associated with or directly related to the genetics of small size. One hypothesis is that small size may contribute to MMVD due to 'crowding' of the chest cavity (Parker & Kilroy-Glynn 2012). Studies in humans have shown that shorter people are more likely to succumb to heart disease than their taller counterparts, which is believed in part to be due to altered thoracic wall shape (Raggi *et al.* 2000). Therefore, small dogs may also experience similar anatomical constraints that may contribute to their heart disease. Alternatively, genes that regulate growth may also be responsible for cardiac development and thus genetic recruitment for small size may also affect cardiac development. Insulin-like growth factor (IGF) has been

implicated in cardiac development in dogs and people and is also important in terms of regulation of growth (Donath *et al.* 1994). In a study of Portuguese water dogs in which radiographic skeletal measurements were performed, a strong correlation was found between a mutation on chromosome 15 and overall body size (Chase *et al.* 2002). This mutation was within the IGF locus. Subsequent genetic studies using single nucleotide polymorphism (SNP) technology demonstrated that a consistent haplotype within the IGF locus was preserved in all small breeds assessed (Parker & Kilroy-Glynn 2012). Thus it was inferred that all small breeds share at least one common ancestor. It is therefore tempting to speculate that the IGF mutation may be central to the pathogenesis of MMVD, given its consistent presence within the small dog genome and the fact that it is known to regulate cardiac development. Unfortunately, complex disease processes seldom have simple monogenic abnormalities. Additional GWAS have been performed correlating body size indices with genetic loci and an additional eight loci have been identified (Parker & Kilroy-Glynn 2012). Of these eight loci, five are particularly interesting, including IGF, high mobility group AT hook (high-mobility group AT-hook 2 [HMGA2]), insulin growth factor 2 mRNA binding protein (IGF2BP2) and mothers against decapentaplegic homolog 2 (SMAD 2) (Parker & Kilroy-Glynn 2012). Of these five loci, four are associated with cardiac development. The candidate gene SMAD2 is of particular interest due to its association with transforming growth factor beta (TGF β), which has also been implicated in the pathogenesis of MMVD (Parker & Kilroy-Glynn 2012). Aberrant TGF β signalling has been observed in heart valve disease associated with Marfan's disease in people and along with other inflammatory mediators is believed to contribute to the pathology of the extracellular matrix of the mitral valves (Parker & Kilroy-Glynn 2012).

The role of inflammatory mediators

Another area of research interest dealing with the pathogenesis of MMVD is the role of inflammatory mediators (Orton, Lacerda & MacLea 2012). Throughout the lifespan of the mitral valve it undergoes shear stresses as a result of repeated opening and closing. The ensuing wear and tear will stimulate reparative processes to restore the integrity of the valve, or to preserve the functioning of the valve by altering the structure. All of these processes are controlled by inflammatory mediators, chemokines and molecular signalling pathways (Orton *et al.* 2012). It has been observed that the mitral valve undergoes matrix and cellular changes as it ages, including a decrease in the number of valve endothelial cells, increased activation of valve interstitial cells (VICs), decreased innervation and decreased elastin (Aupperle & Disatian 2012). These changes increase the stiffness and thickness of the valve (Connell, Han & Grande-Allen 2012). There is considerable overlap between the molecular processes of ageing and MMVD but the lesions of MMVD are considerably more severe and ultimately lead to failure of the valve (Connell *et al.* 2012). It is therefore intuitively logical that aberrant cellular signalling may be involved in the pathogenesis of MMVD. Two of these

signalling pathways that will be discussed further are TGF β and serotonin. One of the hypotheses of MMVD is that valves predisposed to disease elaborate different molecular signature pathways in association with normal mechanical stresses (Orton *et al.* 2012). Mechanical strain studies have shown that when mitral valves are subjected to cyclic strain *in vitro*, valves exposed to TGF β undergo cellular differentiation and the VICs transform into a myofibroblast phenotype (Waxman *et al.* 2012). The resultant VIC phenotype causes increased collagen synthesis. Other studies have shown enzymatic up-regulation of tryptophan hydroxylase (TPH-1) which is a rate-limiting enzyme in the synthesis of serotonin, which also has been implicated in the pathogenesis of MMVD (Lacerda *et al.* 2012). Serotonin is of particular interest given the fact that human patients with high serotonin levels (such as in carcinoid syndrome) are known to develop valvulopathies (Fox & Khattar 2004). Right-sided heart valves are normally affected due to serotonin clearance in the lungs. Serotonin signalling activates a number of pathways, including extracellular signal-regulated kinases (ERK) $\frac{1}{2}$, which in turn results in the production of TGF β . Therefore, up-regulated TPH-1 secondary to strain, attachment of platelets to damaged valves (which are known to be rich in serotonin) and the subsequent elaboration of TGF β secondary to serotonin signalling may be key players in the development of weakened valves in MMVD (Orton *et al.* 2012).

A number of other pathways have been implicated in the pathogenesis of MMVD, many of which overlap with the pathways discussed so far. Proponents of the inflammatory mediator theory suggest that the mitral valve can undergo pathological changes in response to normal loading due to the presence or abundance of certain inflammatory mediators (Orton *et al.* 2012).

The mechanical function of the mitral valve

The notion that the mitral valve is anatomically equivalent to a mechanical flap has been debunked (Richards *et al.* 2012). The mitral valve is now known to be a complex structure, with a dynamic mechanical structure that is able to withstand the normal forces applied to it during the cardiac cycle in a complex manner. In addition, the presence of a rich nerve supply and smooth muscle fibres implies that its mechanical function is not entirely passive (Blevins *et al.* 2008; Eckert *et al.* 2009; Grande-Allen & Liao 2011; Richards *et al.* 2012). The biomechanics of the mitral valve have also been implicated in the pathogenesis of MMVD. The observation that the tensile strength of the valve varies in different anatomical locations of the valve and that certain regions of the valve undergo more strain than others has led to the suggestion that subtle mechanical variations may lead to pathology (Blevins *et al.* 2008; Eckert *et al.* 2009; Grande-Allen & Liao 2011; Richards *et al.* 2012). It has been suggested that altering loads on the valve due to mechanical factors may up-regulate cell signalling that results in transformation of the VICs to a myofibroblast phenotype (Richards *et al.* 2012). This in turn could result in the up-regulation of metalloproteinase enzymes (MMP) and collagenolytic enzymes, all of which

can alter the extracellular matrix of the valve and lead to valve pathology. Complex mechanobiology models and the observation that the normal mitral valve operates at stress strain levels that are at 10% of the stress strain curve have led to the speculation that MMVD may be part of a mechanical failure of the valve (Richards *et al.* 2012). The paradigm shift in the understanding of the mechanical function and complexity of the mitral valve raises the question as to what differences may be present in valves that develop pathology (Richards *et al.* 2012).

Diagnosis of myxomatous mitral valve disease and assessing risk of progression

Diagnosis of myxomatous mitral valve disease

Diagnosing MMVD is not challenging in most cases, as the presence of a murmur in a dog of the correct signalment, together with identification of mitral valve regurgitation and left atrial enlargement in an echocardiographic evaluation, are typically sufficient to make the diagnosis. The challenge of diagnosis in MMVD is to determine the early onset of congestive heart failure and decide on the point at which to initiate treatment. It is the opinion of the authors that this is an academic exercise without an added benefit to the patient. In the light of our current knowledge there appears to be little to no benefit in treating preclinical MMVD (Atkins *et al.* 2009; Kwart *et al.* 2002) in terms of delaying the onset of congestive heart failure (CHF) or prolonging the life of the patient. Whilst there is no complete consensus on this matter (Atkins *et al.* 2009; Atkins & Häggström 2012), without firm evidence to prove the benefit of early detection of cardiac remodelling it becomes an expensive clinical exercise that is difficult to justify. In addition, in spite of the development of advanced cardiac imaging such as cardiac magnetic resonance imaging (cMRI) and tissue Doppler imaging (TDI) (Arques *et al.* 2006), a simple clinical parameter such as respiratory rate (Schober *et al.* 2010), which costs nothing to measure, remains one of the most sensitive predictors of CHF. Therefore, advanced cardiac imaging or indeed exhaustive echocardiographic measurements are still more suited to research than clinical medicine. Notwithstanding the fact that early subtle remodelling is of little value to the general practitioner, echocardiography remains an indispensable tool in the assessment and clinical management of MMVD. Firstly, echocardiography is able to confirm the source of the murmur and rule out other cardiac diseases that may mimic MMVD clinically, such as dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM). Both DCM and HCM are uncommon in small-breed dogs, but both can result in murmurs and CHF similar to MMVD and whilst the treatment of CHF due to DCM is very similar to that of MMVD (Olsen, Häggström & Petersen 2010), the treatment of HCM is not. In addition, if treatment is instituted and the patient fails to respond adequately, the veterinarian cannot be certain that the treatment failure is due to refractory CHF secondary to MMVD or due to the fact that the disease is not MMVD, especially if thoracic radiographs are not

typical of MMVD. Radiographic changes consistent with MMVD include left atrial enlargement, dorsal displacement of the left mainstem bronchus and left-sided cardiomegaly (Olsen *et al.* 2010). Furthermore, some echocardiographic indices (measurements of chamber sizes) have been shown to predict the onset of CHF. For example, the left atrial to aortic ratio (La:Ao) has been shown to be an independent predictor of progression to CHF in MMVD (Borgarelli *et al.* 2012; Chetboul & Tissier 2012; Hezzell, Boswood, Moonarmart & Elliott 2012; Reynolds *et al.* 2012; Serres *et al.* 2009). Another area in which the utility of echocardiography has been investigated is in the assessment of systolic function of the ventricles (Bonagura & Schober 2009). Early systolic dysfunction would precede the onset of CHF and therefore be of value to the veterinarian. Indeed, researchers have sought to use advanced echocardiographic indices and modalities to diagnose early CHF (Chetboul & Tissier 2012). As yet, there are no standard two-dimensional echocardiographic variables that are able to diagnose CHF and radiography remains the gold standard for this (Chetboul & Tissier 2012). Human studies have shown that selected Doppler echocardiographic measurements are able to diagnose early CHF in dyspnoeic patients, prior to the development of radiographic signs (Arques *et al.* 2006). Tissue Doppler imaging in veterinary cardiology has been shown to be a more sensitive test for systolic dysfunction, but as yet is not able to differentiate patients with and without CHF (Chetboul & Tissier 2012). In addition, TDI is technically demanding and beyond the reach of many practitioners. Furthermore, as stated, there is as yet no firm imperative to support the necessity for early diagnosis of CHF in terms of providing a better prognosis for the patients. In addition, modalities such as cMRI are far more sensitive in assessing cardiac remodelling than echocardiography (Dillon *et al.* 2012).

Prediction of progression of myxomatous mitral valve disease

Detection of a murmur in an old dog at a routine clinical examination is a common scenario for the general practitioner. Owners are often distressed to learn that their pet has heart disease and would like information as to the potential course of the disease process. This remains a challenge in veterinary practice. A number of publications have found clear clinical (Schober *et al.* 2010), echocardiographic (Borgarelli *et al.* 2012; Borgarelli *et al.* 2008) and biochemical parameters (Ferasin *et al.* 2013; Hezzell, Boswood, Chang, Moonarmart, Souttar & Elliott 2012; Moonarmart *et al.* 2010) associated with MMVD course and outcome. However, practitioners are cautioned to understand how to apply these variables in the assessment of an individual patient. There are two different scenarios in which clinical, imaging and biochemical data have been used to assess MMVD, namely in the prediction of progression and in the assessment of risk of cardiac-related death. Studies normally make use of relative risk, odds ratio or hazard ratio to compare the variable in a group of dogs that do not experience an event (death or worsening of cardiac disease). In-depth discussion of these statistical measures is beyond the scope of this review; however, all of these

measures are relative assessments of an outcome. Simply stated: if the outcome is progression of heart failure, these measures express the likelihood that an individual with an enlarged La:Ao ratio (for example) will progress to a worse stage of heart failure than an individual with a normal La:Ao ratio (below a certain cut-off value). Continuing with this example, it has been reported that a La:Ao ratio above 1.40 is associated with an increased likelihood of progression of heart failure with an adjusted hazard ratio of 2.64 (Borgarelli *et al.* 2012). Considering that in this study only 8% of the dogs (of a total of 256) progressed to heart failure, this finding is fairly unimpressive. Therefore, over the course of the study, at any given time there were 2.64 times as many patients likely to progress to CHF in the group with elevated La:Ao ratio. However, overall only 8% in both groups combined progressed. Whilst this is a significant reduction, the fact remains that the overall risk of progression remains low and indeed the conclusion of the authors in this study was that MMVD is a relatively benign disease (Borgarelli *et al.* 2012).

In another study, the risk of death due to MMVD was assessed using the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) (BNP) in dogs with mitral valve regurgitation and various stages of CHF (Moonarmart *et al.* 2010). These authors found a significant increase in the BNP values in the non-survivor group versus the group of dogs that were alive at a 6-month follow-up. They also suggested cut-off values to serve as a predictor of survival in dogs (1500 pmol/L). Careful scrutiny of the article showed that there is considerable overlap in the values between the survival group and the non-survival group. Therefore, veterinarians should remember not to make absolute recommendations based on these results alone. Notwithstanding these limitations, there is some value in measuring BNP, as both a low value and a decrease in the BNP associated with treatment are associated with a greater chance of survival (Chetboul *et al.* 2009; Hezzell, Boswood, Chang, Moonarmart, Souttar & Elliott 2012; Moonarmart *et al.* 2010; Serres *et al.* 2009; Wolf *et al.* 2012).

Holistic view of mitral pathology

As research efforts in different areas of MMVD pathogenesis converge, it appears likely that key insights into the pathogenesis of MMVD will be elucidated. A number of questions still remain unanswered, such as why only some dogs with the same genetic make-up develop MMVD, whilst others do not? Why are there varying severities of lesions and progression? Answering these questions will go a long way towards understanding the disease process.

Conclusion

Whilst the aetiology of MMVD remains incompletely understood, great strides have been made in the elucidation of the complex mechanisms driving this process. A thorough understanding of the mechanisms driving the pathology of MMVD may provide insight into how the disease can be prevented or suggest early treatment regimens. Finally,

contrary to the assertion of many drug companies, MMVD is a relatively benign disease. Predicting progression remains a challenge given the low numbers of patients that progress in many cases. Notwithstanding this observation, a number of tools, such as echocardiography and NT-proBNP, which provide valuable insight into the natural course of MMVD in patients, are available to veterinarians. However, advanced diagnostics need to be weighed with the overall clinical picture.

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Competing interests

The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this article.

Authors' contributions

R.K.B. (University of Pretoria) read the reference material and wrote the review. J.S. (University of Pretoria) read the reference material, collated key literature and envisioned the review, recognising the need for a paper to summarise and interpret the current literature.

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