Understanding Mitral Valve Disease

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Acquired mitral valve disease is the single most common heart disease of the dog and is a major cause of illness and early death in many dogs. It is also a disease that causes significant levels of distress to owners, in addition to the financial burden of caring for their beloved pet.

The disease is known by several names including, chronic mitral valve disease, degenerative mitral valve disease, mitral valve endocardiosis and myxomatous mitral valve disease (MMVD). The latter term is the preferred scientific name as it best describes what happens to diseased valves.

MMVD is so common that all dogs will have evidence of the disease if they live long enough, but for many of these dogs their quality of life will not be affected. This close association with age is interesting in that it may reflect changes that normally would be expected to occur with age. What is most striking about MMVD is that it occurs much earlier in life in certain breeds of dogs, and it is in some of those breeds that it is most devastating. While all dogs, including cross-breeds, may have evidence of the disease, it is the small pedigree breeds and the cavalier King Charles spaniel in particular (CKCS) that are most adversely affected. In some small breed dogs where the valve pathology can be extensive resulting in a very loud murmur, there often are no adverse consequences and these dogs can live into old age unaffected. An important question in veterinary cardiology is why different breeds of dogs with the same severity of valve pathology can have completely different disease progression and outcome? Furthermore, adverse outcome (heart failure and death) is not just restricted to pedigree breeds, but can occur with equal devastation in mixed breed dogs. Lastly, there is a lot of interest in dog MMVD and its similarities to an equivalent disease in humans, and the possibilities of better understanding of the disease in both species by comparing the similarities and contrasting the differences.

Since MMVD is clearly recognised to be a problem in the CKCS, clubs in the UK and North America, and the Kennel Club of England and the American Kennel Club have actively supported research at the University of Edinburgh Veterinary School over recent years in an attempt to better understand the disease and hopefully identify the cause, improve treatments and even identify a cure. It is worth noting that by supporting MMVD research the CKCS breed societies benefit not only the CKCS breed but all dogs, both pedigree and mixed, and indirectly are helping our understanding of the same disease in humans. The veterinary community know a lot about MMVD, how it presents and progresses, how to diagnose the disease and have developed better treatments in the last few years. What is less clearly understood is what damage occurs in the leaflet at the microscopic and sub-microscopic (molecular level). Edinburgh vet school has been very active the last 10 years in trying to elucidate the pathological mechanisms that set the disease in motion, and other researchers worldwide are now also putting effort into MMVD research. This is all good news because while medical research is a slow process the more centres that are involved the quicker that process becomes and the sooner are significant discoveries made.

At Edinburgh we have been researching a variety of features of MMVD. The mitral valve separates the two chambers on the left side of the heart and when open allows blood from the left atrium to enter the left ventricle, and when closed allows the left ventricle to push blood out into the circulation. If the valve becomes damaged, as occurs with MMVD, a proportion of the blood that should pass around the body goes in the wrong direction back into the left atrium (referred to as regurgitation) (Figure 1). This regurgitation generates the heart murmur typical of MMVD and is the first abnormality noted by the veterinary surgeon. As a mechanical device the mitral valve is a very important structure and when viewed it has the appearance of a leather-like flap working by a simple hinge mechanism. In fact, it is a much more complex structure than it appears. The valve itself consists of four distinct layers, but also has important anchoring points to the space between the two chambers and to the heart muscle (papillary muscles). Combined together, all these elements are referred to as the mitral valve complex. The layers include two outer cell layers (endothelium) sandwiching a layer of dense fibrous tissue (fibrosa) and a layer of loose connective tissue (spongiosa) (Figure 2). The valve contains a lot of collagen and a lesser quantity of elastin, but together these proteins allow the valve to flex and bend and also allow it to cope with the large pressures placed on in it by the heart contracting. This layered arrangement is crucial to its proper mechanical function and any damage to the valve can affect function or precipitate changes that in time would irreparably damage the valve (typically what occurs with MMVD).

From our work at Edinburgh we have shown that damage to the lining cell layer of the valve occurs with MMVD and we suspect this is an important trigger event that contributes to the start of valve change (Figure 3). This damage is likely to be due to repeated trauma to the valve edges, and it is at the edge of the leaflets that the most dramatic changes indeed occur. In association with the damage to the endothelium, cells deep in the valve change their type and function and begin to migrate towards the valve surface (Figure 4). Some of these cells (valvular interstitial cells or VICs) develop close contacts with the endothelial cells, some squeeze between the gaps caused by the damage, some show evidence of apoptosis (the phenomenon of programmed cell death where cells automatically self-destruct), and others even incorporate themselves into the endothelium itself. We know that damage occurs to the endothelium in normal valves and suspect that this becomes too extensive in the diseased valve for it to cope. The valve attempts to repair the damage, but in the process and over time is overwhelmed by the continual trauma to the valve edge. The VICs in their attempt to heal the damage may actually be contributing to the damage that occurs deeper in the valve.

VICs are the cells that produce the collagen and elastin and the cement that holds it all together, glycosaminoglycans. Together all these constituents are known as the valve matrix. In the healthy valve, the VICs sit quietly in a collagen rich environment and it is thought they produce more matrix as needed and constantly remodel the matrix, but apart from that remain reasonably quiescent (Figure 5). When the valve is injured, the VICs become more active and start to migrate towards the site of damage (see above), but by being activated they probably cause damage to the matrix and fail in their main task of maintaining matrix integrity. In time the normally tight collagen bundles start to break apart and any new collagen formed is either of an abnormal type or fails to organise (Figure 6). The valve now begins to loose its mechanical strength, becomes

distorted and starts to leak. Once this degenerative process begins it appears to be unstoppable and the valve continues to change over time. This whole process may take several years which would fit in with how the disease is seen in affected dogs.

So the process of maintaining the integrity and structure of the valve is ongoing and is believed to be part of a process of normal life-long remodelling. In young dogs and during maturity into early adulthood this process is maintained and successful, but as on entering middle age the reparative processes appear to fail or possibly become overwhelmed. The production of collagen, elastin and the other important matrix proteins is very complex and not completely understood. It also depends on close interaction and inter-play between a wide range of different proteins and all this is controlled by cellular activity. It is the balanced interaction between all these elements that is crucial for maintaining a healthy valve. Work at Edinburgh has shown that this balanced interaction is not maintained and thereby contributes to disease development. For example, production of collagen alone is not sufficient, but it has to be organised into fibrils and bundles and has to develop maturity. Using nuclear facilities in Darnesbury in the UK, Grenoble, France and Trieste, Italy, we have shown that there is a failure of collagen organisation in MMVD such that the collagen is not of the right type, fails to bind tightly to form strong bundles, and is aligned in the wrong direction. All this contributes to the mechanical failure of the valve, which in itself leaves the valve prone to further damage (perpetuating the problem) and results in valve leaking (Figure 7.).

To complicate the problem further, using a technique called Proteomics, we have identified the loss of crucial proteins in diseases valves, some of which are important in matrix production and organisation and others that are necessary for normal VIC function. Together, all these findings suggest MMVD is a dyscollagenesis problem that is abnormality of collagen production rather than a loss of collagen.

From all the work carried out at Edinburgh we have a much clearer picture of what is happening in the valves of dogs with MMVD, but there are still many unanswered questions with this disease. The issue of why certain breeds are more rapidly and more severely affected by MMVD is being addressed through the European LUPA project which is attempting to identify genes that may be involved in the disease. Complimentary to that work, in Edinburgh we are using similar techniques to look at the inheritance of the disease in CKCS and possible gene involvement. Other groups in the USA are looking at the type of tissue and cellular changes we have been concentrating on in recent years, and all told a large amount of high quality scientific research is being brought to bear on the problem of MMVD in the dog. From our own work in Edinburgh, a favoured hypothesis at present is that the normal damage that occurs to the valve during its constant use eventually overwhelms the systems in place for self-repair. This raises the possibility that what we are seeing is a normal aging process, but what is of major concern is why this process should be accelerated in some dogs and not other. There is much more work that needs to be done.

Figure 1. A colour Doppler echocardiographic image of blood regurgitating back through the mitral valve of a dog with MMVD. The regurgitation is show by the large patch of blue colour with the rainbow coloured core. This generates the murmur typical of MMVD.

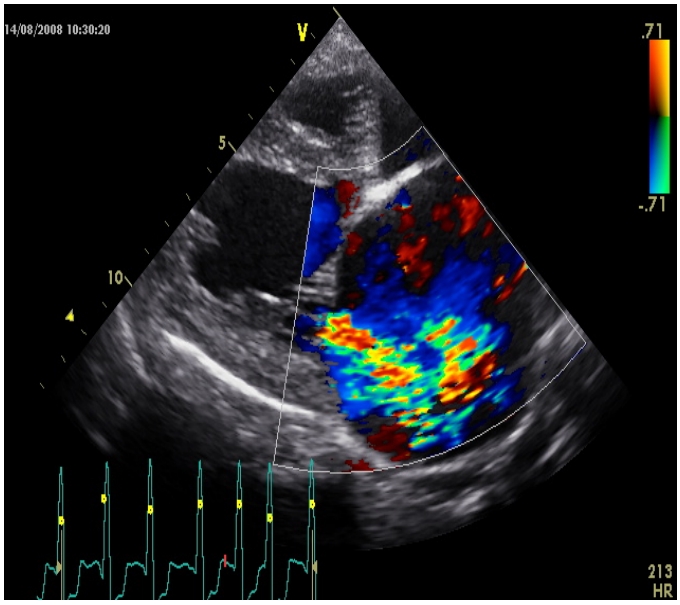

Figure 2. Normal (upper) and abnormal (lower) dog mitral valves. Note how the valve consists of layers, but in particular how the leaflet becomes markedly thickened toward the free edge (right side of pictures).

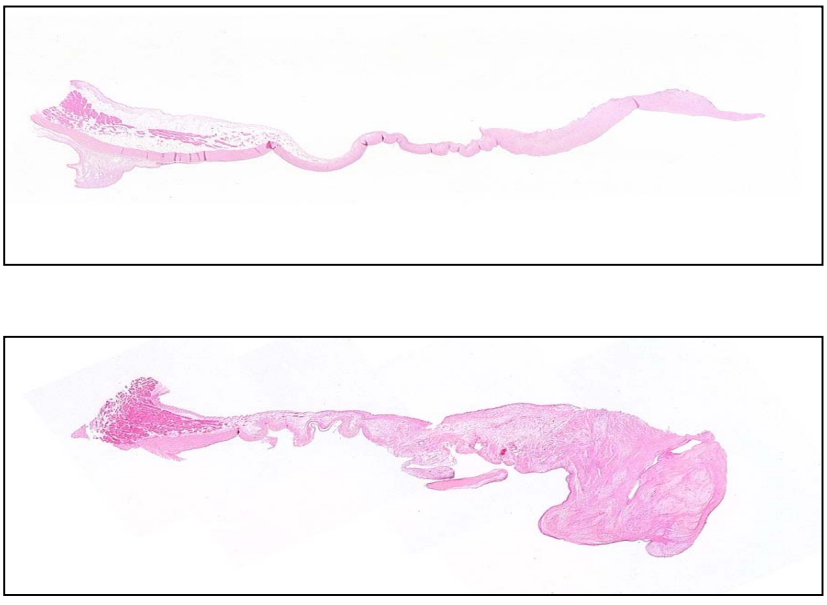

Figure 3. High powered electron microscopy image of a disease leaflet showing damage to the endothelial lining. The lower part of the images shows where the cells have been removed exposing the underlying valve tissue.

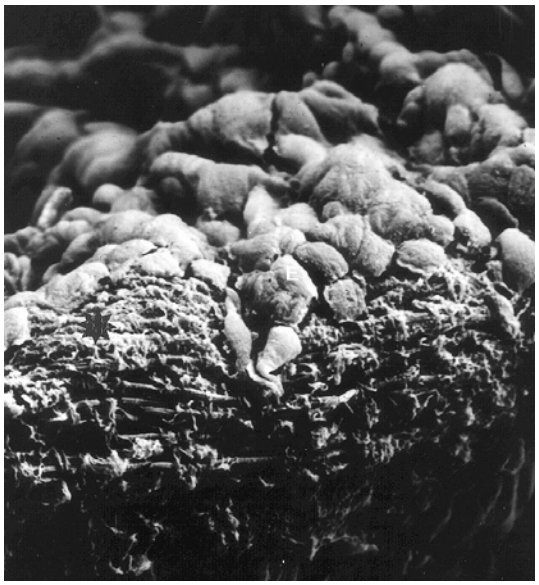

Figure 4. A high powered electron microscopy image of the damaged valve showing a valvular interstitial cell (ic) migrating from the extracellular matrix (ecm) and pushing between two endothelial cells (e). The interstitial cell is very unhealthy and is in the process of dying.

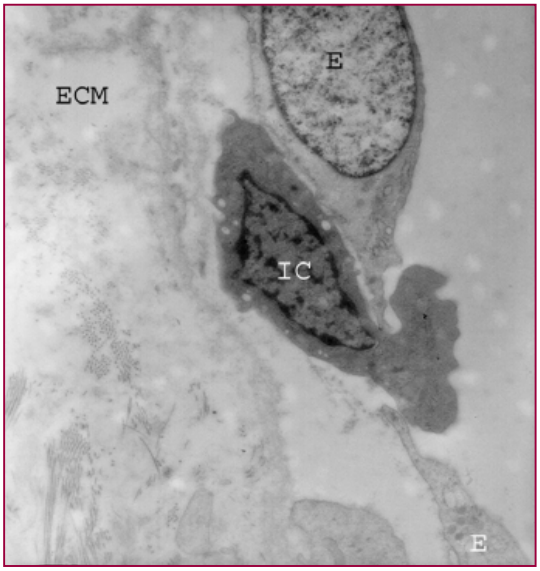

Figure 5. High powered electron microscopy image of the normal appearance of the centre of the dog mitral valve. In the centre is a valvular interstitial cell and surrounding it are packed bundles of well organised collagen.

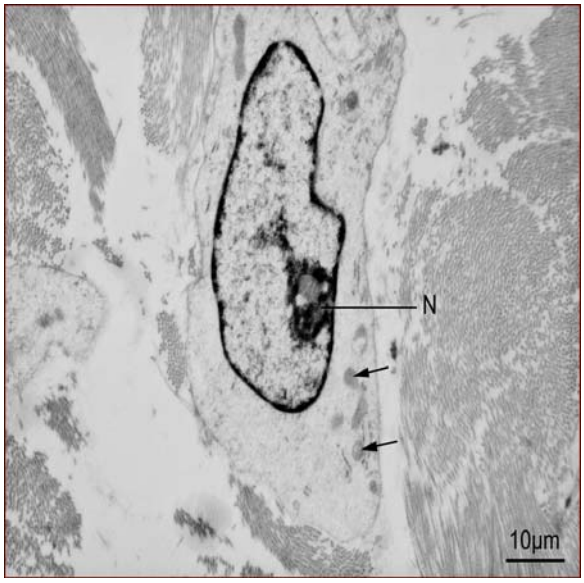

Figure 6.

An electon microscopy image showing poorly organised and thread-like collagen in an affected dog mitral valve

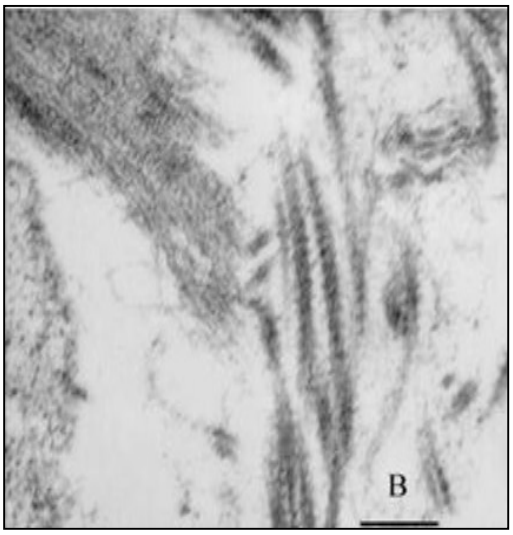

Figure 7. A nuclear diffraction image, showing loss of organised collagen close to the valve edge (blue), contrasting with relatively normal collagen away from the valve edge (green/orange/red).