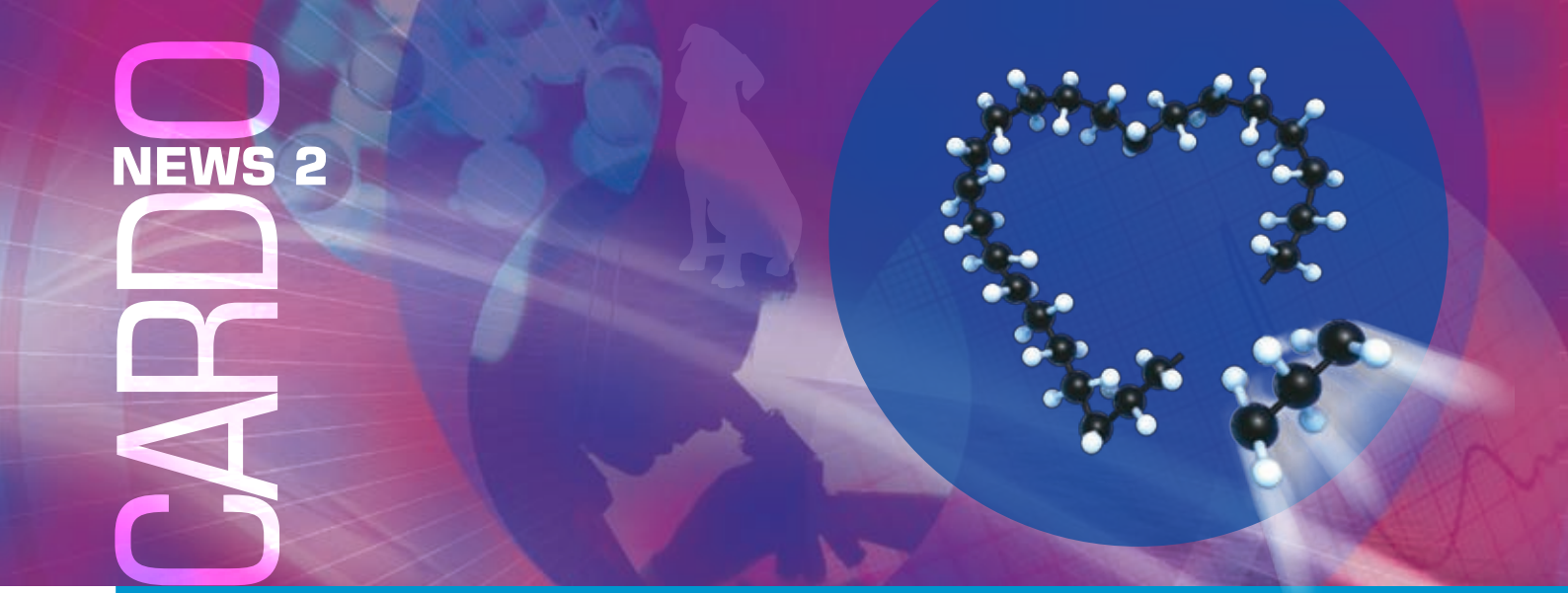
CARDIO NEWS 2



CEVA ANIMAL HEALTH | AT THE HEART OF INNOVATION

The link between fibrosis and survival time in canine heart failure

AUTHOR:

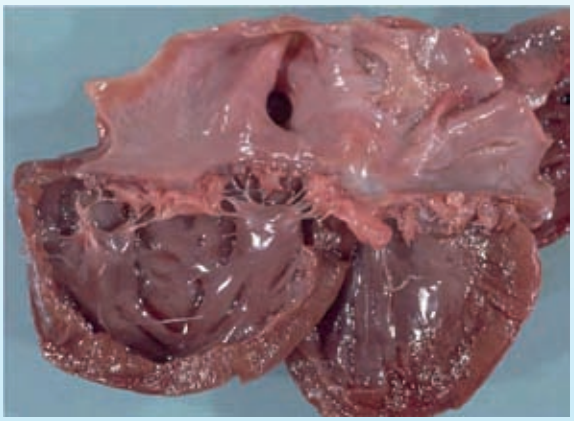
Pr T. Falk DVM PhD
Department of Basic Animal and Veterinary Sciences, The Royal Veterinary and Agricultural University, Frederiksberg, Denmark

For this second edition of Cardionews, professor Falk (from the Veterinary University in Copenhagen) discusses the effects of fibrosis on the progression of canine heart failure and survival time. The article describes how fibrosis has been an under-diagnosed pathological change in canine congestive heart failure and one that adversely affects systolic function, disease progression and survival time. Aldosterone has been shown to cause fibrosis in the dog[1,2] and this effect may help to explain the dramatic benefits associated with adding the aldosterone antagonist spironolactone as part of first-line heart failure therapy in dogs.

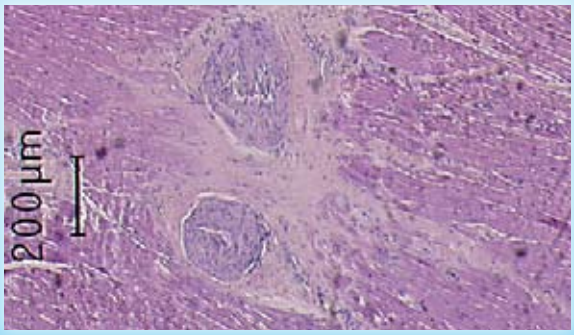
Introduction

It has been a general opinion among veterinarians that arteriosclerosis (thickening and narrowing of the intra-myocardial arteries) and myocardial fibrosis are of minor significance in dogs with heart failure, and this notion is also supported by some veterinary textbooks[3]. However, in early work on heart disease in older dogs, arteriosclerosis and fibrosis are described as common findings[4-8]. Their clinical relevance had previously not been proven, but most authors seemed to be fairly certain that the changes were of clinical significance. In a previous study, we have also demonstrated that arteriosclerosis and fibrosis are significantly more common and severe in dogs with severe myxomatous mitral valve disease (MMVD) and congestive heart failure (CHF) than in age, sex and weight matched control dogs with no or minor MMVD[9]. These changes can also affect the papillary muscles which attach to the mitral valve (see figure 1).

Unlike in man, however, the arteriosclerotic changes in the dog are virtually never seen in the extra-myocardial coronary arteries. Instead, the changes occur almost exclusively in the smaller intra-myocardial blood vessels. This explains why the dramatic acute infarcts, resulting in a large acute myocardial injury, that are so commonly seen in humans, very rarely occur in dogs with heart disease



Heart from a dog with MMVD. The mitral valve is thickened with nodular changes and the heart is dilated from volume overload.



Severe arteriosclerosis of the intra-myocardial arteries from the papillary muscle.

Figure 1: Macro and microscopic aspects of myxomatous mitral valve disease

Material and Methods

Our hypothesis was that, although different from the vascular pathology in humans, the changes in smaller vessels may result in more myocardial hypoxia and fibrosis which, over time, may impair myocardial function and affect the progression of heart failure.

To study this hypothesis, we performed standardised autopsies on 58 dogs that died or were euthanised because of chronic congestive heart failure. It was a prospective study, so all the dogs had undergone a standardised clinical examination at regular intervals before they died. This included:

- Electrocardiography (ECG)
- Radiography
- Echocardiography

The cardiac pathology protocol involved assessing the following parameters in a standardised fashion:

- Intra-myocardial vessel narrowing was measured in different locations by dividing luminal area by total vessel area (lumen area ratio - LAR)
- Myocardial fibrosis was scored at various locations according to a 5-grade scale
- Valvular lesions were measured according to Whitney's 5-grade scale[10]
- Myocardial atrophy was scored according to a 5-grade scale

Myocardial atrophy, where myocardial fibres are below 6µm in thickness, is the histopathological hallmark of most cases of dilated cardiomyopathy in the dog[11].

Results

23 breeds were represented (n=58). The two most common breeds studied were Cavalier King Charles Spaniels (n=19) and Dachsunds (n=10), both breeds with a known predisposition for myxomatous mitral valve disease[12]. The dogs in the study could be divided into three different groups according to the degree of myocardial atrophy and myxomatous mitral valve disease (MMVD), as shown on figure 2.

Group	Degree of atrophy	Degree of MMVD	Number	Median age at inclusion (yrs)	Median weight at inclusion (kg)	Fractional shortening on inclusion (%)	Mean survival time (days)
1	Grade 0 - 1	Whitney grade 3 - 4	47	10.3	11.6	33.2	272.8
2	Grade 2 - 4	Whitney grade 2 - 4	5	7	21.6	22	332.6
3	Grade 2 - 4	Whitney grade 0 - 1	6	5.6	37.7	12.5	83.6

Figure 2: Table to show the different groups according to the degree of myocardial atrophy and MMVD

Group 1 represents the older small breed dogs with **"classic" myxomatous mitral valve disease** whereas dogs within group 3 have a poorer prognosis and, from a clinical viewpoint, would be referred to as **"classic" dilated cardiomyopathy**.

The association between pathological changes, systolic function and survival

Groups 2 and 3 contain too few animals to achieve any statistically significant data whereas for group 1, the largest group, statistical analysis can be carried out. **Within group 1, indices of systolic function on echocardiography (fractional shortening and ejection fraction) were significantly associated with arteriosclerosis and fibrosis**. For example, in a multivariate analysis:

- Vessel narrowing (LAR) and fibrosis were a strong predictor of reduced fractional shortening (p=0.002 and p=0.0001 respectively). This association was particularly strong in dogs with no atrophy compared to dogs with mild (Grade 1) atrophy (p = 0.03)

Other interesting findings from this study include:

- The greater the degree of papillary muscle fibrosis, the greater the indices of regurgitation in the mitral valve (PISA-radius method, p = 0.03)
- The greater the degree of overall fibrosis, the shorter the survival time (time elapsed from start of medication to death, p = 0.002)

The link between the degree of arteriorsclerosis/fibrosis, fractional shortening and mean survival time within group 1 is highlited in figure 3.

Degree of arteriosclerosis/fibrosis	Severe (LAR < 0.15)	Less severe (LAR >0.15)
Fractional shortening (%)	22.1	37.0
Mean survival time (days)	156.1	312.8

Figure 3: Table showing the link between arteriorsclerosis/fibrosis, fractional shortening and mean survival time

Discussion

Link between fibrosis and survival time

An important finding is that **the degree of arteriosclerosis/fibrosis is associated with decreased systolic function (contractility) in dogs with congestive heart failure**. This may affect the progression of congestive heart failure and may also be of importance when considering the differential diagnosis, since, on echocardiography, advanced arteriosclerotic/fibrotic changes may mimic dilated cardiomyopathy. The fact that dogs with a high degree of myocardial fibrosis had a significantly shorter survival time, as shown in figure 4, is interesting, bearing in mind that the study was not designed to assess survival primarily, and it is always debatable from which starting point survival should be measured.

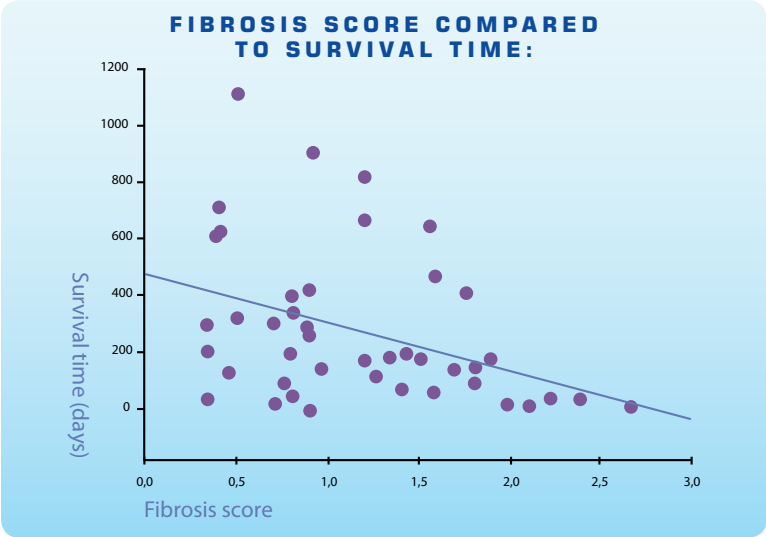


Figure 4: Graph to show the link between fibrosis score and survival time

Link between fibrosis and mitral incompetence

It is well established in humans that myocardial infarction may cause or worsen mitral regurgitation and this is often referred to as ischeamic mitral regurgitation (IMR). Dysfunction of the papillary muscle caused by ventricular dilatation is believed to be a major cofactor in IMR[13,14]. Since ventricular dilatation is an early change in the development of myxomatous mitral valve disease in dogs due to volume overload, this is probably of importance in the pathogenesis of canine congestive heart failure as well. We have previously demonstrated that arteriosclerosis/fibrosis is significantly more pronounced in the papillary muscles of dogs with congestive heart failure compared to control dogs (figure 1)[9]. **The association between fibrosis in the papillary muscle and the degree of mitral incompetence** (measured by the proximal isovolumetric surface area (Pisa) method) is therefore interesting, although this method to assess mitral incompetence does have technical limitations[15].

Limits of fibrosis detection

In this study, we demonstrated vessel changes and fibrosis in histopathology samples. **How these changes could be detected *ante-mortem*, in a clinical setting, is a difficult question that will require further research**. An attempt was made in this work to measure myocardial echogenicity (density) by pixel density, but this did not correspond to myocardial fibrosis, probably due to technical limitations. Maybe other imaging techniques or serum biomarkers for fibrosis will be more successful in detecting these changes in the future. In earlier studies, we have demonstrated that arteriosclerosis/fibrosis is more prevalent in dogs with myxomatous mitral valve disease[7], and Detweilers hypothesis of the triad of valve changes, arteriosclerosis and fibrosis[16] seems to find some validation in this material. It is also possible that the puzzle becomes more complete if we add atrophy of myocardial cells as the fourth factor in the disease process. No previous attempts have been made to systematically measure arteriosclerosis, fibrosis, valve changes and atrophy from pathological samples. Further discussions about the significance of myocardial atrophy and the continuum of different pathological changes is planned to be discussed in a later newsletter.

CONCLUSION:

Canine intra-myocardial arteriosclerosis and fibrosis are probably a hithero under-diagnosed pathological change in canine congestive heart failure. There is evidence from this study that these changes may adversely affect systolic function, disease progression and survival time.

REFERENCES

1. Suzuki G et al, Effects of Long-Term Monotherapy With Eplerenone, a Novel Aldosterone Blocker, on Progression of Left Ventricular Dysfunction and Remodelling in Dogs with Heart Failure, Circulation 2002;106:2967 – 2972.
2. Yang et al, Effects of spironolactone on electrical and structural remodelling of atrium in congestive heart failure dogs, Chinese Medical Journal 2008;121(1):38-42
3. Kittleson M.D. Myxomatous atrioventricular valve degeneration. In: Kittleson MD, Kienle R.D., *eds. Small animal cardiovascular medicine.* St Louis: Mosby, 1998;273-282.
4. Detweiler DK, Patterson DF. The prevalence and types of cardiovascular disease in dogs. *Ann N Y Acad Sci* 1965;127(1):481-516.
5. Detweiler DK, Ratcliffe HL, Luginbuhl H. The significance of naturally occurring coronary and cerebral arterial disease in animals. *Ann N Y Acad Sci* 1968;149(2):868-881.
6. Jonsson L. Coronary arterial lesions and myocardial infarcts in the dog. A pathologic and microangiographic study. *Acta Vet Scand Suppl* 1972;38:1-80.
7. Kelly DF. Classification of naturally occurring arterial disease in the dog. *Toxicol Pathol* 1989;17(1 Pt 2):77-93.
8. Whitney JC. Some aspects of the pathogenesis of canine arteriosclerosis. *J Small Anim Pract* 1976;17(2):87-97.
9. Falk T, Jonsson L, Olsen LH, *et al*. Arteriosclerotic changes in the myocardium, lung, and kidney in dogs with chronic congestive heart failure and myxomatous mitral valve disease. *Cardiovasc Pathol* 2006;15(4):185-193.
10. Pomerance A, Whitney JC. Heart valve changes common to man and dog: a comparative study. *Cardiovasc Res* 1970;4(1):61-66.
11. Tidholm A, Jonsson L. Histologic characterization of canine dilated cardiomyopathy. *Vet Pathol* 2005;42(1):1-8.
12. Falk T. Canine arteriosclerosis occurrence and importance in different heart diseases. *Ph. D.Thesis* 2008;31-33.
13. Burch GE, De Pasquale N, Phillips JH. The Syndrome of Papillary Muscle Dysfunction. *American Heart Journal* 1968;75(3):399-415.
12. De Pasquale NP, Burch GE. Papillary Muscle Dysfunction in Coronary (Ischemic) Heart Disease. *Annual Review of Medicine* 1971;22:327-342.
13. Choi H, Lee K, Lee H, *et al*. Quantification of mitral regurgitation using proximal isovelocity surface area method in dogs. *J Vet Sci* 2004;5(2):163-171.
14. Detweiler DK. Spontaneous and induced arterial disease in the dog: pathology and pathogenesis. *Toxicol Pathol* 1989;17(1 Pt 2):94-108.

V5PRILA-1208

CEVA ANIMAL HEALTH LTD
90 The Broadway, Chesham, Bucks HP5 1EG
Tel: 01494 781510 Fax: 01494 781519

CEVA SANTE ANIMALE

www.ceva.uk.com