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Programme VCS MEETING

PRE-BSAVA DAY MEETING- 3rd April 2013

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Speakers:

Mark Rishniw BVSc MS PhD DACVIM (Cardiology & IM)

Mark Rishniw obtained his veterinary degree from the University of Melbourne in 1987. Following several years in general mixed practice in Australia and England, he completed residencies in internal medicine and then cardiology, and was certified as a Diplomate of the American College of Veterinary Internal Medicine in both disciplines. He was employed as a registrar of small animal medicine at Melbourne University for 1 year, and then moved to Ithaca, NY, where he was acting section chief of cardiology for 3 years. In 2000, Mark enrolled in a PhD program in physiology, examining esophageal muscular development, which he concluded in 2009. During this period, he began consulting for Veterinary Information Network (VIN), becoming a full-time employee in 2005. He is currently a VIN employee and a visiting scientist at Cornell University.

His interests are diverse. Mark has published over 80 peer-reviewed manuscripts, focusing mostly on cardiology. His current interests are to develop simple, practical tools for clinicians and clients to better manage their cardiac patients. He has a perverse interest in biostatistics, competitive cycling and restoring antique wooden boats. He is happily married with an over-exuberant yellow Labrador.

Clarke Atkins DVM DipACVIM

Clarke Atkins, DVM, the Jane Lewis Seaks Distinguished Professor of Companion Animal Medicine at North Carolina State University and 2004 Norden Award Winner, is board-certified by the ACVIM (Medicine & Cardiology). His research involves canine and feline heartworm disease and treatment of cardiovascular disease in dogs, cats, and horses. He has over 150 publications and has provided well over 1000 hours of continuing education in the U.S. and many countries around the world.

Sonja Fonfara Dr med vet CertVC DipECVIM-CA (Cardiology) MRVCS

Sonja graduated from the University in Hannover, obtained a doctoral thesis in veterinary pathology, and worked for several years in a first opinion practice in Germany. This was followed by a post doctoral position at the GKSS research centre and University of Kiel investigating the effect of anthropogenic stressors on the immune system of marine mammals. In 2006 she came to the UK for an internship and residency, followed by a lectureship, in veterinary cardiology at the University of Liverpool. Sonja obtained the certificate in veterinary cardiology in 2007 and board certification from the European College of Veterinary Internal Medicine in Cardiology in 2010. After a brief spell in Germany, she was appointed as Senior Lecturer in Small Animal Cardiorespiratory Medicine at the University of Bristol in July 2012. Her main research interest is cardiac inflammation and remodelling in canine and feline cardiac and systemic diseases.

Alex Smith BVetMed MRCVS

Alex graduated from the RVC in 2009, and subsequently stayed on for a further 6 months to undertake a research position based on canine and feline abdominal imaging. He then moved into general practice, working at a small animal hospital in Cambridgeshire, before starting the small animal rotating internship at the RVC in 2011. Since finishing the internship he has been working for Vets Now Emergencies in Salisbury, Wiltshire.

Domingo Casamian DVM CertSAM CertVC DipECVIM-CA MRCVS

Domingo graduated from the University of Zaragoza (Spain). After an internship at the Animal Medical Centre (Manchester) he worked in two large hospitals in Nottingham and Bristol. He combined this work with frequent visits/externships at Mike Martin Referrals. It was here, where motivated by the pioneering clinical work and outstanding clinical research environment; he developed his interest/passion for respiratory medicine and cardiology on top of his overall interest in Internal Medicine. He joined the University of Bristol in January 2007 where he still works as a clinician/clinical teacher at the Small Animal Hospital /Langford Cardiorespiratory Unit. Domingo holds the RCVS Certificates in Small Animal Medicine and Veterinary Cardiology and the European Diploma in Small Animal Internal Medicine. He is also working towards the RCVS diploma in Cardiology. His research interests include several areas of respiratory medicine and cardiology.

Hannah Stephenson BVMS (Hons) CertSAM DipECVIM-CA (Cardiology) MRCVS

Hannah graduated from the University of Glasgow in 2005 and spent 2 years in mixed practice in Lancashire. She undertook a small animal Junior Clinical Training Scholarship at the RVC before being employed as a research assistant at the University of Liverpool in 2008. This research was part of the LUPA project, investigating dilated cardiomyopathy in dogs, and she has continued this research during her residency and beyond, particularly focusing on DCM in Great Danes. During her residency at the University of Liverpool she obtained the RCVS Certificate in Small Animal Medicine, and was recently awarded the ECVIM Diploma in Cardiology. She is now working as a part-time clinical lecturer in cardiology at the University of Liverpool and part-time milk maid at her farm in Lancashire.

Geoff Culshaw BVMS DVC MRCVS

Geoff graduated from Glasgow in 1994 and spent 11 years in general practice. He joined the R(D)SVS, University of Edinburgh in 2005 and is currently Senior Lecturer in Cardiopulmonary Medicine. He obtained the RCVS Diploma in Veterinary Cardiology in 2008 and is an RCVS Recognised Specialist in Veterinary Cardiology and a Clinical Research Associate of The Roslin Institute.

Geoff's clinical/research interests include the pathogenesis of MMVD, the genetics of accessory pathways and radiofrequency ablation.

He is currently studying towards a PhD investigating the role of endothelin in the renal handling of salt in diabetic nephropathy, at the Queens Medical Research Institute, University of Edinburgh.

Simon Dennis BVetMed MVM MRCVS FHEA DipECVIM-CA (Cardiology)

Simon graduated from the RVC in 2000. Following an internship and general practice he completed a cardiology residency at the RVC from 2005 to 2008 and was a lecturer in cardiology at the RVC from 2008 to 2011. He is a European Veterinary Specialist in Small Animal Cardiology and an RCVS Recognised Specialist in Veterinary Cardiology. Simon currently works at North Downs Specialist Referrals. He is the cardiology associate editor for the *Journal of Small Animal Practice*, an editor for the BSAVA Manual of Canine and Feline Cardiorespiratory Medicine, module leader for the RCVS CertAVP C-VC examinations at the RVC, and chair of the ECVIM-CA (Cardiology) Diploma certifying examination committee.

Echo estimates of left atrial size and function

Mark Rishniw
College of Veterinary Medicine, Cornell University, Ithaca, USA

Left atrial size is considered one of the better estimates of severity of diseases causing left-sided volume overload, and has been shown to correlate with outcomes. Measuring the size of the left atrium (LA) by echocardiography is standard practice in cardiology, and seemingly simple. However, many factors influence the validity of LA measurements – beam angle, positioning, timing and non-atrial structures. Consequently, multiple methods have been evaluated to better estimate LA size. However, no strict guidelines exist to maximize consistency of measurement, and individual preferences often dictate the method used without a firm basis for the choice. This makes comparisons of data between studies and between observers difficult to interpret. Inter-observer variability in LA measurement is substantial, with considerable disagreement about the semi-quantitative assessment of LA size. More complex imaging techniques, such as MRI and 3D echocardiography have begun to examine the clinical importance of this variability in assessing LA size. Finally, estimates of LA function are being evaluated, and might provide important insight into severity of left-sided heart disease that complement simple estimates of size.

This talk will highlight the issues facing veterinary cardiology in measuring LA size echocardiographically and attempt to offer resolutions for some of these issues.

Evidence for use bimodal RAAS suppression in canine heart failure: Aldosterone Breakthrough

Clarke Atkins DVM, Andrea Lantis[1] DVM and Marisa Ames DVM
College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA

Cardiovascular disease in dogs produces significant morbidity and mortality and ranks second in importance, behind only neoplastic disease, as a cause of non-traumatic death in dogs.[1] The most important non-parasitic cardiovascular disease affecting dogs is degenerative mitral valve disease with mitral insufficiency/regurgitation (MR).[1] An ACVIM consensus panel has unanimously indicated that chronic pharmacologic management of heart failure in dogs caused by MR should include furosemide, pimobendan, and an angiotensin converting-enzyme inhibitor (ACE-I), with the majority of panelists also recommending a mineralocorticoid receptor blocker (MRB), such as spironolactone.[2] The use of the latter 2 drug groups (ACE-I and MRB) demonstrates the priority placed upon suppression of the renin-angiotensin-aldosterone system (RAAS) in canine cardiovascular disease. The ACE-I, utilized in veterinary medicine, blunt plasma ACE activity maximally by approximately 75%, when administered as directed, and the benefits of ACE-inhibition have been demonstrated in multiple clinical trials in dogs with heart failure due to chronic degenerative valve disease and dilated cardiomyopathy.[3-7]

Definition and Incidence. These above-mentioned benefits are also appreciated in human cardiovascular and renal patients.[8] It is recognized in human heart failure-patients, however, that a percentage of the population experiences a recrudescence of aldosterone and angiotensin II secretion with chronic ACE-inhibition.[9] Persistent or recrudescent aldosterone secretion, despite ACE-inhibition or angiotensin II receptor blockade (ARB), is referred to as "aldosterone escape" or preferably, "aldosterone breakthrough".[10] Aldosterone breakthrough has been defined in the human literature as any increase in serum aldosterone concentration that exceeds a baseline value after initiation of RAAS-blocking therapy.[11] To date, no study has been reported which precisely assesses the time from onset of treatment until breakthrough or the percentage of patients affected. Therefore, there is no consensus within the human literature, regarding the time course of aldosterone breakthrough. Confusion exists because some authors describe this phenomenon based on a serum aldosterone level that exceeds a baseline (pre-ACEI and/or -ARB therapy) value 6-12 months after initiation of RAAS-blocking therapy[11], while others have defined aldosterone breakthrough in human patients 4-6 weeks after initiation of an ACEI.[11-13] Additional variation in the definition of breakthrough arises when a pre-determined serum aldosterone cut-off value (rather than a patient's baseline value) is used to define aldosterone breakthrough. Bomback and Klemmer addressed the role of dosage and method of RAAS blockade and found no apparent differences in the frequency of aldosterone breakthrough.[11] The frequency, degree, and importance of aldosterone breakthrough are poorly understood in humans, even more-so, in animals. Nevertheless, scrutiny of several historical studies reveals the likelihood of the existence of aldosterone breakthrough in veterinary patients and in experimental animals.[15-17, a] In a clinical study of

[1] Dr. Lantis' current address is Veterinary Emergency and Referral Group, Brooklyn, NY, USA

22 Cavalier King Charles Spaniels with naturally-occurring MR and "early" signs of heart failure (modified NYHA class III), 12 dogs receiving enalapril monotherapy (0.4 mg/kg PO,q12h) had significant reductions in plasma ACE activity at 3 weeks (83%). Furosemide was subsequently added to the treatment regimen at the time of the 3-week re-evaluation. Significant reductions in plasma ACE activity (81%) were again noted 6 months after the initial examination. However, while administration of enalapril led to a significant decrease in plasma aldosterone concentration after 3 weeks of treatment, the 6-month plasma aldosterone concentration in dogs receiving enalapril and furosemide were significantly increased, as compared to the initial and 3-week examination ($P<0.05$).[15] This demonstrates aldosterone breakthrough coincident with the addition of the known RAAS-activator, furosemide.

Mechanism. The mechanism(s) by which aldosterone breakthrough occur(s) are not yet well understood and the phenomenon is probably multifactorial in origin.[8,11,18] The most popular explanation is that alternative pathways and enzymes for conversion of angiotensin I to angiotensin II are evoked, including chymase and cathepsin G. Renin plasma concentrations are elevated in the presence of ACE-I therapy with subsequent elevations in angiotensin II concentrations, which may contribute to aldosterone breakthrough. Increase in blood potassium values has also been suggested as a potential mechanism for aldosterone breakthrough, but the available evidence does not support this hypothesis. Three studies reported that serum potassium levels remain unchanged during ACEI therapy longer than 6 months, regardless of breakthrough status.[19-21] Endogenous factors, such as corticotrophin, catecholamines, endothelin, prolactin, iserotonin, and vasopressin, as well as diuretics, sodium restriction and vasodilators stimulate aldosterone secretion and may therefore contribute to aldosterone breakthrough.[22] Lastly, we have shown that the inodilator, pimobendan, does not significantly activate RAAS, nor does suppress it.[23,24, a] To the authors' knowledge, compliance failure has not been evaluated as a contributor to aldosterone breakthrough.

Clinical Relevance. Chronic exposure to high concentrations of aldosterone results in excessive sodium retention with expansion of extracellular volume, favors potassium and magnesium wasting, inhibits myocardial norepinephrine uptake, diminishes heart rate variability, produces cardiac arrhythmias, decreases baroreceptor sensitivity, contributes to endothelial dysfunction and vascular inflammation, and is independently associated with renal, vascular and cardiac remodeling and heart failure.[11,25-28] Plasma aldosterone levels at presentation are known to be significantly predictive of mortality after myocardial infarction in humans.[29]

Increasing evidence links aldosterone excess and/or activation of mineralocorticoid receptors to the development and progression of various cardiovascular disease processes in humans.[29,30] The Randomized Aldactone Evaluation Study (RALES) revealed a 31% reduction in cardiac mortality in human patients with NYHA class III and IV heart failure, receiving spironolactone in addition to conventional therapy (ACE-I, loop diuretic, and digoxin), as compared to a placebo-treated control group, receiving only conventional therapy. Pro-collagen markers decreased in the spironolactone-treated group, but did not change in the placebo cohort, indicating that the benefits of aldosterone blockade paralleled the reduction of cardiac fibrosis. Serum levels of three pro-collagen markers were independently associated with increased risk of death and the beneficial effects of spironolactone on patient survival were predominantly seen among patients with the highest baseline levels of collagen markers.[30,31] The EPHESUS study compared the second-

generation MRB, eplerenone, to placebo, each with standard therapy (including a beta blocker), in post-infarct human patients with diminished left ventricular function, resulting in significant survival benefit (17% reduction in cardiovascular mortality).[32] This benefit was noted early, within 30 days of initiation of therapy. Finally, the EMPHASIS-HF study demonstrated that eplerenone, in a population of mild (NYHA II) heart failure patients with left ventricular dysfunction, significantly reduced cardiac death and hospitalization, as compared to placebo.[33] This study is important because it demonstrated benefits of MRB early in the course of heart failure.

The use of renin antagonists may play a future role in treatment of cardiovascular disease, although the direct renin inhibitor aliskiren did not prevent aldosterone breakthrough in people with chronic kidney disease and clinical trials involving aliskiren have been terminated due to an increased risk of non-fatal stroke, renal complications, hyperkalemia and hypotension.[34]

Evidence of the harmful effects of RAAS activation and the benefits of RAAS suppression are evident in veterinary patients as well. In a prospective veterinary study by Hezzell et al[b], urinary aldosterone concentrations were found to be negatively associated with survival (P=0.005) in 54 dogs with mitral valve disease. A recent double-blinded, field study in 212 dogs demonstrated a 69% reduction in risk of cardiac morbidity and mortality in dogs with chronic degenerative mitral valve disease that were treated with spironolactone, in addition to an ACEI with furosemide, +/- digoxin, when compared to furosemide, an ACEI, +/- digoxin, without spironolactone.[35]

Previous studies in cats[16], experimental models of heart failure in dogs,[17,36] and dogs with naturally occurring chronic degenerative valve disease[15] have revealed persistent aldosterone secretion despite ACE-inhibition. Studies in authors' laboratory revealed that furosemide-induced RAAS activation of 10 days duration was not always attenuated with concomitant benazepril administration.[c] Similar results were found with enalapril.[d] In both of these studies, failure to suppress aldosterone excretion was associated with successful inhibition of angiotensin-converting enzyme. Overall, our experimental data suggest that aldosterone breakthrough occurs in over 70% of dogs with amlodipine- or furosemide-activated RAAS, treated with benazapril or enalapril.

Though we have demonstrated aldosterone breakthrough in an experimental model of RAAS activation in our laboratory, the prevalence of aldosterone breakthrough in canine patients remains an important unknown. We are now striving to determine the prevalence of aldosterone breakthrough in canine patients receiving ACE-I and/or ARB for heart failure and for proteinuric renal disease.[e]

Dogs with cardiac disease and with protein-losing renal disease were prospectively enrolled and classified into 6 groups: Group A: acute heart failure prior to treatment, Group B: heart failure with less than 2 weeks of 'standard treatment' (at a minimum ACE-I, furosemide and pimobendan but not spironolactone), Group C: chronic heart failure on 'standard treatment' for greater than 2 weeks; Group D: chronic heart failure with 'standard treatment' and spironolactone; Group EF: asymptomatic MR or DCM; and Group G: proteinuric renal disease. Urine A:C was determined for each dog.

A "working definition" of aldosterone breakthrough was created by using the mean UA:C from a population of normal dogs from NCSU (mean urine A:C of 0.44 ug/g, ± 0.26). Aldosterone breakthrough was defined using two 'cut-off' values: 1) urine A:C greater than

the upper 99% confidence limit of the reference interval of our normal population (>0.54 ug/g) and 2) urine A:C greater than the mean plus two standard deviations (>0.96 ug/g). As many patients did not have a baseline urine A:C, a definition depending on baseline values could not be used. A urine A:C ratio above these 'cut-off' values in any dog not yet on an ACE-I (Group A and sporadic cases in other groups) was considered to merely indicate RAAS activation.

A total of 66 dogs are currently enrolled, with 69 data points. Underlying heart disease includes chronic valvular disease (MR), dilated cardiomyopathy, heartworm disease and patent ductus arteriosus with tricuspid valve dysplasia (n=1). Thirty samples were obtained from dogs in heart failure. Preliminary results indicate that ~47% of these patients with chronic heart failure fit the first definition of aldosterone breakthrough. These data are preliminary and further study is necessary before firm conclusions can be drawn.

Our clinical data suggest that aldosterone breakthrough does occur in dogs receiving ACEI for heart failure, and that its prevalence likely approximates that observed in human patients, early in the course of heart failure therapy. In addition, RAAS activation is demonstrated in some dogs with preclinical MR and in proteinuric renal disease. These data argue for the addition of MRB to current RAAS suppression strategies in dogs with heart failure and some form of RAAS suppression in dogs with proteinuric renal disease.

In summary, both aldosterone and angiotensin II contribute to progression of cardiac, vascular and renal disease and worsen the signs of heart failure. Aldosterone breakthrough, apparently occurring in animals as it does in man, is an important negative prognostic indicator for dogs and humans suffering from cardiac disease and failure. To counteract this, an MRB, such as spironolactone, is probably necessary in many/most heart failure patients and may be necessary earlier than previously thought. These conclusions are supported by the above-mentioned trial of Bernay, et al.[35], in which spironolactone improved survival and by a subsequent safety study[f], which demonstrated, not only a lack of adverse side effects with spironolactone therapy, but a reduction in cardiorenal adverse events using this MRB. Furthermore, the FILIT[g] study of the combination of benazepril and spironolactone in the management of heart failure due to MR, has demonstrated clinical improvement in a variety of cardiac signs and quality of life scores. Spironolactone has received approval in the European Union as a single agent (Prilactone®) and in combination with benazepril (Cardalis®) for the treatment of heart failure due to MR.

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Footnotes:

[a]Ames, M, Atkins, C, Lantis, A. The effect of high-dose pimobendan on furosemide-induced renin-angiotensin-aldosterone system (RAAS) (abst). J Vet Intern Med 2012; 26:715-716.

[b]Hezzell MJ, Boswood A, Elliott J. Relationships between serum and urinary aldosterone, ventricular remodeling and outcome in dogs with mitral valve disease (abst). J Vet Intern Med 2010;24(3):672.

[c]Lantis A, Atkins CE, DeFrancesco TC, Keene BW. Aldosterone escape in furosemide-activated circulating renin-angiotensin-aldosterone system (RAAS) in normal dogs (abst.). J Vet Intern Med 2010;24(3):672.

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The role of pimobendan in cardioprotection

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Pimobendan is a benzimidazole pyridazinone derivate with combined inotropic and peripheral vasodilatory properties, which are attributable to selective inhibition of Phosphodiesterase III (inotropic and vasodilatory effects) and sensitation of cardiac myofilaments to intracellular calcium (inotropic effect).

It is licensed as treatment of canine congestive heart failure (CHF) originating from valvular insufficiency (mitral and/or tricuspid regurgitation) or dilated cardiomyopathy (DCM)[1]. This license is based on studies performed in veterinary medicine, where pimobendan added to heart failure treatment resulted in an increase in quality and quantity of life in dogs with degenerative valvular disease (DVD) and DCM[2-4]. Furthermore, a recent study did show extended survival of Dobermans with progressed preclinical DCM treated with pimobendan[5].

The potential role of pimobendan in reducing the progression of myocardial damage was lately added to the vetmedin licence[6]. The background for this additional license is pimobendans haemodynamic effects[7], and the results of several experimental studies. Pimobendan was reported to inhibit Nuclear Factor κ B activation, pro-inflammatory cytokine and nitric oxide production, and iNOS gene expression *in vitro* and in mouse models[8-11]. It was also associated with a reduction of plasma noradrenalin (NA) levels in a dog model with mitral regurgitation[12].

These studies about potential anti-cytokine and immunomodulating properties of pimobendan are *in vitro* studies and murine models. Transferring those results to clinical situations has its limitations. The reported NA reductions were detected during a period of four weeks[12]. A pimobendan induced reduction of NA levels was also observed in human patients after four weeks, but not anymore after six months, despite continuous treatment[7,13].

However, further factors involved in reducing or even preventing myocardial damage, include myocardial oxygen supply, adaptation of metabolic flow rates to demand, reserve capacity of important function and control of protective and adaptive mechanisms[14].

In cardiac disease left ventricular (LV) remodelling, which is associated with changes in LV mass, volume, shape and composition, occurs[15,16]. LV dilatation, present in DVD and DCM, results in increased wall stress, which might lead to subendocardial hypoperfusion and ischaemia, increased oxidative stress and activation of genes sensitive to free radical generation (i.e. inflammatory cytokines), and stretch activation of hypertrophic signalling pathways[15,16].

PROTECT and also human studies did report a reduction in LV dimension, end-diastolic and – systolic volumes and pressure in dogs and people treated with pimobendan[5,7,17]. The improved LV geometry and pimobendans vasodilatory effect causing a reduction in pre- and

afterload, are associated with a reduction in myocardial wall stress. Furthermore, despite pimobendans positive inotropic effect the myocardial oxygen demand does not increase and pimobendan was shown to enhance myocardial oxygen delivery[18,19]. The resulting improved myocardial oxygen supply/demand ratio ameliorates the energy expenditure in heart failure[18-20]. Pimobendan increases right ventricular function, which contributes to improved LV function and reduces coronary sinus pressure[21], further optimising myocardial function and oxygen supply.

Even if the studies about pimobendans potential anti-cytokine and immunomodulating properties might not be convincing, pimobendan as inodilator drug is likely to be involved in several cardioprotective mechanisms.

Cardiac remodelling is an important, but complex and incompletely understood process[15,16]. Most of our knowledge is based on *in vitro* studies and models of cardiac diseases. To improve the understanding of pimobendans role in myocardial preservation, further studies investigating clinical patients or samples of these would be needed. It is likely that pimobendans positive effect on quality and quantity of life in dogs with CHF caused by DVD or DCM, is not just caused by its inodilator effects, especially considering that we struggle to prove systolic dysfunction in dogs with DVD[22], and that hypertension, which is a problem in human medicine is rarely a problem in our canine patients.

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Management of a PDA with pulmonary hypertension

Alex Smith

This case study describes a 13 week old Chihuahua with a patent ductus arteriosus and concurrent pulmonary hypertension. The patient was found to have bi-directional ductal flow on echocardiographic examination, which was successfully converted to uni-directional left-to-right flow with sildenafil treatment, and subsequently ligated surgically. The management of this case is presented along with the potential risks and complications, and the associated human literature is discussed for consideration of alternative treatment strategies in veterinary patients.

Electrocardiographic J-waves associated with hypoglycaemia and insulinoma in a dog

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Electrocardiographic presence of J-wave deflections (Osborne waves or J-waves) were consistently observed in an 8-year old Boxer dog with hypoglycaemia caused by an insulinoma, which resolved after surgical removal of the tumour. In humans, J-wave syndromes are observed as inherited or acquired disorders. Inherited disorders are caused by channelopathies and include three types of early repolarisation syndromes and the Brugada syndrome. Hypothermia is the most common cause of acquired J-waves in people and was also reported in hypothermic dogs in experimental conditions. Other underlying causes for acquired J-waves such as hypercalcaemia, myocardial ischaemia or disorders affecting the central and peripheral nervous system have also been sporadically reported in human medicine. To the authors' knowledge hypoglycaemia, hyperinsulinism or insulinoma have previously not been associated with J-waves.

The case will be fully described during the talk and potential electrophysiological mechanisms and a review of the literature will be discussed.

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Arrhythmias in UK Great Danes

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The Great Dane is one of the most common breeds affected by dilated cardiomyopathy (DCM).[1-4] In some breeds, such as the Dobermann, ventricular arrhythmias are commonly seen as part of the DCM phenotype, with sudden death occurring frequently as a result.[5] The most commonly reported arrhythmia in Great Danes with DCM is atrial fibrillation, with ventricular premature complexes occurring occasionally.[1] The Great Dane has the shortest median survival time of all breeds of dogs with DCM, in the UK.[6]

Over the last 5 years we have prospectively screened over 150 Great Danes aged from 4 to over 12 years. During this screening we identified a high prevalence of DCM in the UK population, estimated to be 35-47% (depending on the classification system used).[7] As part of our ongoing longitudinal screening study, owners were invited to bring asymptomatic dogs, for echocardiographic screening. Initially these dogs were unrelated, but latterly dogs with a known family history of sudden death or DCM were also invited to attend. Pedigree, clinical and ECHO data were collected from these Great Danes and their relatives. A single lead ECG was recorded throughout ECHO examination, and a six lead ECG was performed if an arrhythmia was identified on physical examination or during ECHO. 24 hour ambulatory ECG (Holter) monitors were fitted to some dogs.

Many of the asymptomatic Danes presenting for screening (30%) had ventricular arrhythmias (defined as at least one VPC during screening), with and without echocardiographic evidence of DCM. In addition, information from owners and breeders of Great Danes in the UK indicated a high incidence of sudden death in this breed, with increased incidence in certain family lines. We have therefore collected pedigree data from families affected by sudden death, and started screening these and other Danes by Holter monitoring, in addition to the echocardiographic screening, to determine if ventricular arrhythmias (VA) are associated with dilated cardiomyopathy and/or sudden death in Great Danes.

Holter monitors have now been fitted to over 40 Danes. Data were analysed from the first 24 Holters. Of the 24 dogs assessed, 6 had VA on ECG during screening. 13/24 had significant VA on Holter. 7 dogs with VA on either ECG or Holter died suddenly. Data from one extended family group were analysed due the ready availability of dogs for screening (19 members screened), and pedigree and historical data from members of this family. Sudden death occurred frequently in this family (26 members known to have died suddenly), in multiple generations, and in both male and female dogs. Ventricular arrhythmias were identified in some dogs by Holter monitoring, and preclinical DCM was identified in some by echocardiography. Some dogs with ventricular arrhythmias died suddenly. Post-mortem analysis is now available from 9 dogs, some of which died suddenly, and some which were euthanased due to congestive heart failure. Fibrofatty infiltrate was noted on histopathological examination in the majority of cases.

Our data shows that malignant ventricular arrhythmias and DCM occur in the same

extended family of Great Danes in the UK, as well as in other, unrelated individuals. The high prevalence of sudden death in this family, and the high prevalence of ventricular arrhythmias on Holter suggest that VA may be an important cause of sudden death in Great Danes in the UK.

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Accessory pathways in UK Labrador retrievers: presentation, management and genetics

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INTRODUCTION

Accessory pathways consist of electrically conducting cardiac muscle fibres that cross the electrically insulating annulus fibrosus of the heart, thus allowing electrical communication between the atria and ventricles other than through the atrioventricular node (AV node). Their presence can potentially lead to an electrical short-circuit or "macro re-entrant" circuit consisting of atrial tissue, AV node, ventricular tissue and accessory pathway and consequently the possibility of a narrow QRS tachycardia or supraventricular tachycardia (SVT) called orthodromic atrioventricular reciprocating tachycardia (OAVRT).

Accessory pathways exhibit a range of electrical properties which probably reflects their mixed myocardial/Purkinje cell phenotype. They usually lack the rate-modifying properties of the AV node and therefore conduct more rapidly but take longer to repolarise. Often, though, the rapid conduction is only in one direction. When identified, this is usually retrograde, ie from the ventricles to the atria, but some can conduct in both directions. Unidirectional retrograde conducting pathways are termed "concealed" because when in sinus rhythm, only dominant AV nodal conduction is apparent. Bidirectional pathways compete with the AV node for dominance. When conduction from atria to ventricles is via the accessory pathway, pre-excitation occurs (see below). The level of pre-excitation is variable according to the relative rates that the accessory pathway and AV node repolarise, the heart rate and the degree of autonomic tone affecting the AV node eg pre-excitation might only be apparent when the dog is asleep or during the expiratory phase of a sinus arrhythmia.

OAVRT can occur in a rapid onset-offset manner resulting in rapid reductions in cardiac output. Where it is sustained for a period of time, it can result in congestive heart failure due to tachycardia-induced cardiomyopathy (TICM), which may be very difficult to distinguish from dilated cardiomyopathy (DCM).

OAVRT can induce secondary narrow and wide QRS tachyarrhythmias in the short term from electrolyte imbalances within cardiac cells caused by rapid pacing (eg calcium overload) or in the long term as a result of the remodelling of TICM. Pre-excitation is not normally problematic unless it allows conduction of atrial fibrillatory or flutter waves through into the ventricle. This can result in acute, severe reduction in cardiac output, syncope and even sudden death. Because people are more prone to lone atrial fibrillation than small animals, all airline pilots are screened for pre-excitation.

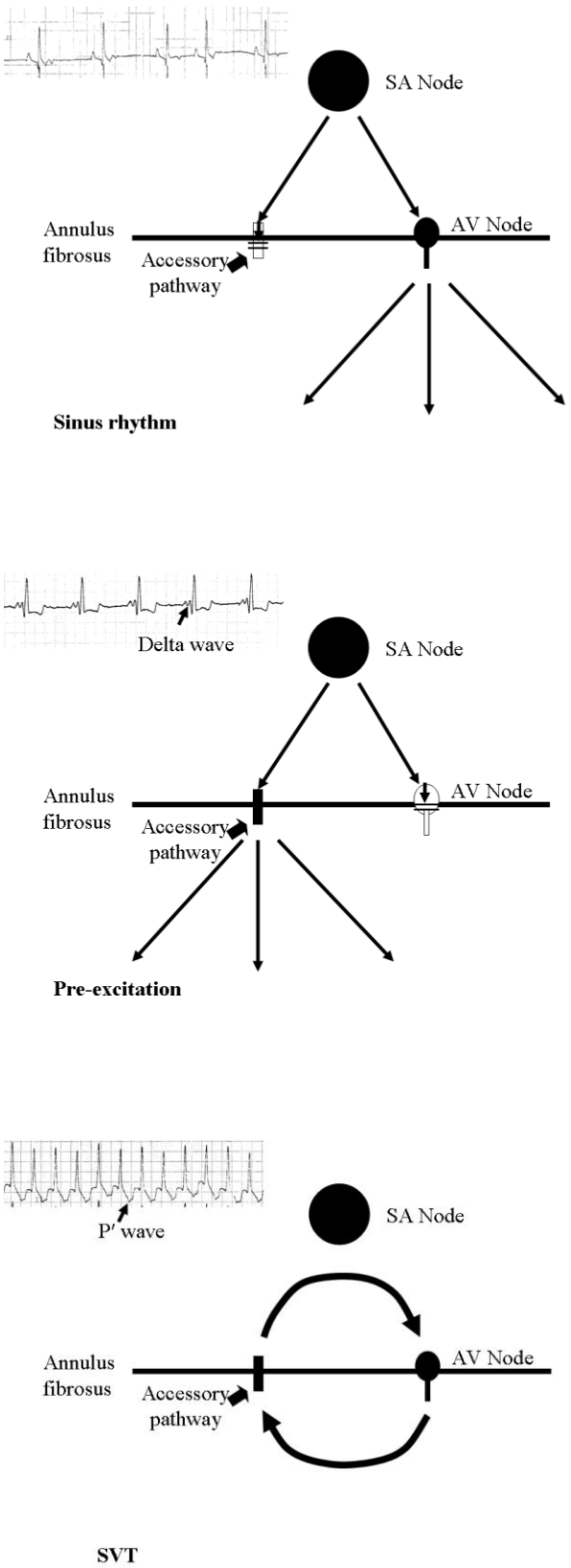

Figure 1. Schematic representations of accessory pathways with sinus rhythm, pre-excitation and OAVRT.

PRESENTATION

Signalment

Previously published reports on dogs with OAVRT have suggested a predisposition in Labrador retrievers, boxers and in male dogs[1-4]. In the UK, the canine breed most represented with OAVRT is the Labrador retriever and there may be an association with chocolate and black coated members of this breed (see below). OAVRT is seen less frequently in golden retrievers and other breeds, predominantly gundogs. According to the records of the R(D)SVS over a 12 year period, the age range for initial detection of a tachycardia by a veterinary surgeon is 3 months – 9 years although most dogs first present within the first 18 months of life.

Cats can present also at a very young age but we have not identified a breed pre-disposition.

Humans also tend to present for the first time as teenagers or adults. The reason for this common age of onset across the species probably relates to maturation of the autonomic nervous system altering AV node conduction capability and the growth of the heart altering the physical distance between the pathway and the AV node that creates the correct anatomo-physiological conditions for OAVRT to occur.

History and Clinical Findings

Dogs not in congestive heart failure typically present with a history of insidious onset lethargy, or with rapid onset exercise intolerance. Many owners notice an extremely rapid, vigorous apex beat. Gastrointestinal signs at the time of SVT are common and a rapid tachycardia in a weak dog with poor cardiac output and GI signs can be mistaken for an abdominal catastrophe. If in congestive heart failure, dogs present with signs of either left, right or biventricular failure. For both groups of dogs, the tachycardia may not be present at the time of initial examination.

When in tachycardia, heart rates tend to be extremely high. Lower rates in comparison to another form of SVT called focal atrial tachycardia (FAT) have been reported[4] but in UK Labrador retrievers, in common with other reports[1,2,5], the rates tend to be higher, ranging from 280-400 beats/min.

What is surprising though, is how well some dogs tolerate sustained rapid SVT. Firstly, syncope does not appear to occur in OAVRT, it does occur in cats in which it can degenerate into a seizure. Secondly, many dogs in sustained SVT do not show signs of lethargy until they have developed TICM. In the author's experience, dogs that fluctuate between OAVRT and sinus rhythm tend to show more signs of lethargy, presumably due to the acute fluctuations in blood pressure, whereas in dogs in sustained OAVRT, long term neuroendocrine compensatory mechanisms have been activated that help maintain blood pressure. Thirdly, Labradors tend to be rather gregarious and stoic so that clinical signs may not be apparent to owners.

Diagnosis

Definitive diagnosis requires an electrophysiological study (EPS) but there are certain ECG features that give a high index of suspicion and differentiate OAVRT from FAT. These include ventricular pre-excitation, rapid onset-offset of SVT, initiation or termination of the

SVT by an atrial premature complex (APC) or ventricular premature complex (VPC) [6], echo beats and the appearance of a P′ wave in the ST segment of SVT[4].

Pre-excitation either on resting ECG or 24 hour Holter ECG either before or after starting therapy occurs in approximately two thirds of affected UK Labradors. It occurs in pathways with bidirectional conduction when a normal impulse generated from the sinoatrial node is conducted through the pathway to the ventricles rather than through the AV node. It appears as a short PQ interval with, typically, an abnormal QRS and a deflection called a delta wave. Care should be taken not to confuse pre-excitation with Isorhythmic AV dissociation, also seen in Labradors.

Because OAVRT is due to a macro re-entrant circuit, appropriately-timed stimulation at any point along that circuit by an APC or VPC can either trigger or terminate an SVT. Macro re-entrant circuits tend to either be "on" or "off" and so the gradual slowing of SVT before conversion into sinus rhythm observed in FAT does not occur.

Analysis of the termination of the SVT is often the most useful way of diagnosing OAVRT. Spontaneous termination of the SVT is usually due to refractoriness of the AV node breaking the macro re-entrant circuit. This is immediately preceded by depolarisation of the atria, observed as a P′ wave in the ST segment of the final QRST of the SVT. The P′ wave is usually negative in polarity on lead II[4] and its presence detected by comparison of this ST segment with the ST segment of the first normal sinus beat. The ST segment of the first normal sinus beat is less negative or even positive. Additionally, the P′ wave in OAVRT is usually positive on lead aVR[4]. With FAT, on the other hand, the P′ wave during SVT is not within the ST segment but lies much closer to the QRS that follows it[4, 6]. Care, however, should be taken though to assess several terminations of the tachycardia if an abnormal ST termination is not observed, especially if the dog is already receiving anti-arrhythmic therapy. This is because the OAVRT may be terminated if the accessory pathway becomes refractory, in which event the ST segment will appear normal.

Echo beats are also useful clues. They are observed where an SVT almost occurred but was stopped by the AV node. Because an impulse travelled retrograde up the accessory pathway into the atria and reset the SA node, the ECG displays an apparent sinus rhythm with occasional more negative ST segments (the P′ echo beat) followed by a non compensatory pause. Overall, this may appear at first glance to be a sinus arrhythmia so any periods of sinus arrhythmia on a Holter ECG in a dog for which OAVRT is a differential should be closely scrutinised.

MANAGEMENT

It should be remembered that most anti-arrhythmic or rate controlling medication is negatively inotropic. Therefore, dogs in congestive heart failure should have this stabilised first using conventional therapy such as furosemide and pimobendan. In most cases, only 1-2 hours of parenteral therapy is required. Once congestion is under control or if congestive failure is not present, then medical cardioversion can be attempted.

Drug Management

Dogs presented to the R(D)SVS have been treated with a range of anti-arrhythmic medications prior or subsequent to referral which reflects the variable success of drug

management, the development of drug refractoriness and the multiple therapeutic target sites within the macro re-entrant circuit. For rapid cardioversion, intravenous medications include lidocaine, verapamil and esmolol. Approximately 50% of Labradors at the R(D)SVS have responded to intravenous lidocaine despite the fact that lidocaine theoretically should not affect SVTs[5] although there is also evidence for its efficacy on acutely fibrillating atrial myocardial cells[7]. It presumably also works on the ventricular and accessory pathway components of the circuit. When lidocaine is ineffective, slow intravenous verapamil is usually successful although several doses may be required. For oral medication, mexiletine has been effective if lidocaine has been efficacious, and diltiazem is usually effective if the SVT has responded to verapamil. Mexilitene is sadly now no longer readily available and we have only very limited experience of the use of flecainide in dogs. Another useful drug is sotalol because of its multiple effects on the macro re-entrant circuit but in our experience it is only effective in approximately 50% of cases. Very often combination therapy is employed such as mexiletine plus diltiazem, or sotalol plus diltiazem. It should be remembered though that use of these medications is not without risk. They are usually negatively inotropic so caution should be exercised when administering to patients with myocardial failure. Drugs such as diltiazem and sotalol should be titrated to effect. In our experience vagal manoeuvres are ineffective in these dogs and drug efficacy is reduced where congestive heart failure is present, presumably due to enhanced conduction through the AV node caused by elevated sympathetic tone. Digoxin is theoretically contra-indicated but, again in our experience, can be considered where dogs are refractory and medical management the only option.

Long term (possibly lifelong) medical management is often problematic because of development of drug refractoriness and the use of polypharmacy with associated drug side effects and cost. Labradors tend to be indiscriminate foragers with gastrointestinal upsets commonly resulting in reduced drug absorption and relapse into SVT. Monitoring control of SVT may be difficult as it may only occur at night or because many Labradors may not show overt clinical signs when in SVT and so frequent 24 hour Holter ECG monitoring is required. For many patients, permanent cure is desirable and this can be achieved through radiofrequency ablation (RFA).

Radiofrequency Ablation

RFA consists of passing an alternating electrical current through a small, well defined area of cardiac tissue (in this case, the accessory pathway) via a special ablating catheter inserted transvenously. The resistive properties of the cardiac muscle result in heating of the area to the point of thermal destruction of the tissue[8]. There are 4 stages to RFA:

- Electrophysiological testing to establish AV node health and refractoriness
- Pacing tests to induce SVT and determine the presence of OAVRT or FAT
- Mapping to identify the location of the accessory pathway
- Ablation of the accessory pathway followed by repeat testing 30-40 minutes later[5].

Multi-polar electrode catheters are inserted into the femoral and jugular veins, advanced into the heart and located in the right atrium, coronary sinus, bundle of His and the right ventricle. These catheters are also capable of pacing. Catheter placement is guided both fluoriscopically and by intracardiac ECG.

On the intracardiac ECG, atrial impulses are denoted as A and ventricular impulses as V. Therefore 3 normal sinus beats would appear as AV AV AV deflections while OAVRT appears as VA VA VA . RFA can be performed during SVT where termination of the VA cycle on V confirms the pathway has been damaged, during ventricular pacing when VA dissociation confirms the pathway has been damaged or during pre-excitation when loss of pre-excitation should confirm the correct area has been targeted. Ablation during SVT is preferable as it allows assessment of the AV nodal conduction during ablation. During ablation attempts, the power of the current and the temperature of the catheter are closely monitored. Evidence of accessory pathway damage should appear within 10-15 seconds. If it does then the ablation is continued for one minute to permanently damage the pathway.

Although left-sided and multiple pathways have been occasionally described in dogs[3,6], all of the Labradors that have undergone RFA at the R(D)SVS have had a single right-sided accessory pathway, usually on the right posteroseptal wall of the atrioventricular groove.

Minor complications of RFA include induction of atrial fibrillation which is usually self-limiting, skin burns if the dog is not electrically earthed and wound seroma formation. The major potential complication is inadvertent damage of the AV node by ablation leading to temporary or permanent AV block. This risk is reduced by careful mapping of the location of the pathway and the bundle of His, lower power ablation and ablation during SVT if possible. Consent should be obtained beforehand for pacemaker implantation if required so that this can be performed at the time of the procedure if AV nodal damage occurs.

Follow-up

Follow-up echocardiography after RFA usually shows complete or partial reversal of TICM as previously reported[2,9]. If RFA is successful, there is usually no requirement for long term cardiac medication. We are close to completing analysis of follow-up echocardiographic data of dogs that we have ablated, some with follow-up of greater than 3 years and we intend to submit for publication soon. **Many of these scans have been performed by VCS members and we are very grateful for their help in this.**

GENETICS

The R(D)SVS is currently the only centre in the UK to offer RFA in dogs. Because of this, we receive cases from throughout the UK. None of the cases presenting since 1999 has been a boxer and therefore the incidence of OAVRT in boxers may be lower in the UK than in other countries. In the UK, darker coated Labrador retrievers appear predisposed to OAVRT. It was therefore decided to undertake a genetic study of this population of dogs.

In humans, accessory pathways that cause pre-excitation and SVT result in Wolff-Parkinson-White (WPW) Syndrome. WPW Syndrome is termed “sporadic” with an incidence of 0.15-0.25%. However, children of affected individuals have a higher incidence of up to 3.4%[10]. There is also a male predisposition in humans (2:1). WPW Syndrome may also be observed in combination with HCM for which a genetic mutation on chromosome 7 has been identified[11,12] and as part of multisystemic disorders[10]. It is also seen in humans with Ebstein anomaly which is of interest as Labrador retrievers are predisposed to tricuspid

valve dysplasia.

Pedigree Analysis

We have acquired pedigrees and DNA of Labradors diagnosed with OAVRT at the R(D)SVS or by other veterinary cardiologists within the UK. Common ancestry has been found in all the dogs where we have sufficient pedigree information. This may reflect the narrow gene pool of coloured Labradors within the UK but could indicate a founder effect leading to inheritance of a common mutation for accessory pathways. A small number of lines appear more than once in most affected dogs and on both the sides of the sire and dam. Affected dogs can be classified into 2 closely related groups. No direct link between the 2 groups closer than 5 generations back has been found as yet but some of the pedigrees are incomplete. European and American ancestry is also within these groups. Pedigree analysis suggests either an autosomal recessive or autosomal dominant with reduced penetrance pattern of inheritance.

Determination of Linkage with Coat Colour

The hypothesis that OAVRT is a recessive trait linked to coat colour is being tested. In Labradors there are 2 main genes responsible for coat colour. They are *MC1R* and *TYRP1*[13]. *MC1R* encodes an "on/off" switch for pigment production. Yellow Labradors (and most pale coloured dogs) are homozygous for a recessive mutation in this gene and produce only yellow or red phaeomelanin pigment. Black and chocolate Labradors are either heterozygous or homozygous for the original dominant form of *MC1R* so produce dark (eumelanin) pigment in their coat. *TYRP1* determines the colour and amount of dark pigment produced. It too has dominant and recessive forms. If homozygous or heterozygous for the original dominant form of *TYRP1*, the dog is black. If homozygous for the recessive form, the dog is chocolate.

If the mutation for accessory pathways is recessive and linked to coat colour, then affected dogs must be homozygous for the gene it is linked to. This means that it cannot be linked to any form of *TYRP1* as both black and chocolate dogs are affected. Also, if the trait is linked to *MC1R*, affected dogs must be homozygous for the dominant form of the gene. Sequencing of the MC1R genes in known affected dogs is currently under way.

The hypothesis that OAVRT is a trait that is autosomal dominant with reduced penetrance (that is, not all animals carrying the mutation show the condition) linked to coat colour is also being tested. In order for this to be valid, the disease mutation must be linked to the recessive allele of *TYRP1* so all affected black dogs would be heterozygous for *TYRP1*. Sequencing of the *TYRP1* genes in known affected dogs is also under way.

It is possible that there is only a chance association without linkage between accessory pathways and coat colour in Labradors. Breeders of black and chocolate Labrador retrievers tend not to use yellow Labrador breeding stock and a random mutation within black and chocolate Labrador lines would result in such an association.

Further Genetic Investigation

Investigation is under way to identify the causative gene(s) in UK Labrador retrievers, working from the assumption that the condition is autosomal recessive. There are several aspects to this investigation:

- Screening of Labradors to determine phenotype and establish a control group.

Phenotype will be determined by presence of OAVRT, pre-excitation or echo beats on 24 hour Holter ECG. It is accepted that some of the control group may be incorrectly phenotyped by this method but this will be minimised by preferentially choosing older dogs with no history of heart disease/arrhythmia and by having as large a control group as possible. It should be remembered that accessory pathways are believed to be uncommon.

- Screening of siblings of known affected dogs.

Eight members of a known affected litter have been screened. Members of another known affected litter will be screened soon. **All screening is funded by the RCVS Trust.**

- Genome Wide Association Study (GWAS)

This compares affected and control dogs to look for common single nucleotide polymorphisms (SNPs) where specific alleles are associated with disease status. Candidate genes closely linked to these SNPs can then be sequenced to determine whether significant mutations are present. **This work is funded by the Roslin Institute.** Preliminary results are expected soon.

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