

Sudden cardiac death in dogs, cats and humans: a comparative review

Word count: 10 934

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A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Veterinary Medicine

Academic year: 2018 - 2019

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Voorwoord

Bij deze wil ik graag enkele personen uitdrukkelijk bedanken. In de eerste plaats Prof. Pascale Smets (DVM, PhD, EBVS[®] European Veterinary Specialist in Small Animal Cardiology) voor de uitstekende begeleiding bij het hele proces dat tot dit uiteindelijke werk heeft geleid. De grenzeloze passie voor het uitbreiden en verder op de kaart zetten van de veterinaire cardiologie was hetgene waar ik me meteen in herkende en zorgde voor een uiterst aangename en productieve samenwerking.

Verder wens ik ook Prof. Em. Dr. Pedro Brugada (Scientific Director, Cardiovascular Division, Free University of Brussels (UZ Brussel) VUB., CEO Medical Centre Prof. Brugada, Aalst, Belgium., Director, Arrhythmia Unit, Hospiten Estepona, Spain) en tevens mijn vader, van harte te bedanken voor alle steun en hulp bij het schrijven van deze Masterproef. Zijn oeverloze kennis en jarenlange ervaring zijn van onschatbare waarde gebleken tijdens het tot stand komen van dit werk. Het was een fantastische ervaring om als vader en dochter hieraan te kunnen samenwerken.

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1. List of abbreviations

- AF: atrial fibrillation
- AP: action potential
- AMI: acute myocardial infarction
- ARVC: arrhythmogenic right ventricular cardiomyopathy
- ARVD: arrhythmogenic right ventricular dysplasia
- ATE: arterial thromboembolism
- BrS: Brugada syndrome
- BSA: body surface area
- CAD: coronary artery disease
- CASQ2: cardiac -specific isoform of calsequestrin gene
- CDA: catecholamine dependent arrhythmias
- CHF: congestive heart failure
- CPVT: catecholaminergic polymorphic ventricular tachycardia
- CTE: coronary thrombo-embolism
- cTnI: cardiac troponin I
- DCM: dilated cardiomyopathy
- DLVOTO: dynamic left ventricular outflow obstruction
- DRVOTO: dynamic right ventricular outflow obstruction
- ECG: electrocardiogram
- EF: ejection fraction
- HCM: hypertrophic cardiomyopathy
- ICD: implantable cardioverter-defibrillator
- IDC: idiopathic cardiomyopathy
- IVF: idiopathic ventricular fibrillation
- LA: left atrium
- LV: left ventricle
- LVEDV: left ventricle end diastolic volume
- LQTS: long QT syndrome
- NT-proBNP: N-terminal prohormone of brain-natriuretic peptide
- PTE: pulmonary thrombo-embolism
- RA: right atrium
- RV: right ventricle
- RyR2: cardiac ryanodine receptor
- SAM: systolic anterior motion
- SCD: sudden cardiac death
- SVPC: supraventricular premature complex
- SQTS: short QT syndrome
- TdP: torsades de pointes
- VF: ventricular fibrillation
- VPC: ventricular premature complex

2. Summary

Plotse dood is een van de meest voorkomende doodsoorzaken bij de mens in Westerse landen. Naar schatting 85% van al deze gevallen zijn van cardiale aard (Magi et al., 2017). Ventriculaire tachyarritmieën zijn de meest voorkomende oorzaak van plotse cardiale dood (Kirchof et al., 2006). Ook bij dieren komt dit vaak voor. In vergelijking met de humane geneeskunde is er heel wat minder geweten over de pathogenese en onderliggende genetica van plotse cardiale dood bij dieren.

In deze review zullen we de meest voorkomende oorzaken van plotse cardiale dood bespreken. Dit zullen we doen voor zowel de mens als verschillende diersoorten zijnde hond en kat. De focus zal vooral op de pathogenese liggen, en meer specifiek op de gekende gelijkenissen en verschillen tussen de mens en dieren, en zelfs tussen verschillende rassen. We hopen uiteindelijk nieuwe inzichten te verwerven wat betreft de pathogenese en diagnose van plotse cardiale dood bij dieren.

Deze vergelijking zal twee kanten opgaan. Langs de ene kant zullen we informatie uit klinische studies uit de humane geneeskunde halen, maar ook uit meer experimentele studies gebaseerd op dierproeven. Deze vinden plaats met behulp van onder andere knock-out muizenstammen en ingeteelde kolonies (Camacho et al., 2016), maar ook van grote zoogdieren zoals katten en honden (Duncker et al., 2015; Hamlin, 2007). Langs de andere kant zullen we ook data uit humane studies gebruiken in een poging tot het beter begrijpen van de pathogenetische mechanismes van plotse cardiale dood bij dieren.

Sudden cardiac death is one of the most common causes of death in humans in Western countries. Approximately 85% of all these cases are of cardiac origin (Magi et al., 2017). Ventricular tachyarrhythmias are the most common cause of sudden cardiac death (Kirchof et al., 2006). In animal SCD also commonly occurs. When compared to human medicine, a lot less information is currently available concerning pathogenesis and underlying genetics of SCD in animals.

In this review the most common causes of sudden cardiac death will be discussed. This will be the case for human but also several other species being cats and dogs. The focus will be put on pathogenesis and more specifically on the known differences and similarities between humans and animal, and even between several breeds. We hope to create new insights on pathogenesis and diagnostics concerning sudden cardiac death in animals.

This comparison will be two folded. On one side information will be gathered from clinical studies in human medicine, but also from more experimental studies based on animal testing. These usually rely on for example knock-out strains of mice and in-bred colonies (Camacho et al., 2016), but also on larger animal models such as dogs and cats (Duncker et al., 2015; Hamlin, 2007). On the other hand, data from human studies will be used in order to try and better understand pathogenetic mechanisms of sudden cardiac death in animals.

3. Introduction

The following paragraphs represent a summary of the current information regarding sudden cardiac death (SCD) in humans, dogs and cats. The main goal of the literature review will then be to further analyze every condition and make a comparison between humans and animals considering main components of the origin of the diseases such as genetics and pathophysiology.

Humans

First of all, a few well-known diseases in humans will be discussed. There is an overwhelming body of scientific data emphasizing the importance of coronary artery disease (CAD) as the most important cause of SCD in humans. However, other causes of SCD not related to CAD are for example other structural heart diseases such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC). On the other side, human SCD can occur in individuals with a pure cardiac electrical disease without structural abnormalities. The most common of these diseases are Brugada syndrome (BrS), long QT syndrome (LQTS), short QT syndrome (SQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) (Papadakis et al., 2018).

Apart from pure electrical diseases, several forms of structural heart disease can predispose to ventricular tachycardia or ventricular fibrillation and thus possibly cause SCD. Many of these structural diseases are inherited disorders and are transmitted according to Mendelian patterns (autosomal dominant or recessive). They can be responsible for up to 26% of SCDs (Sweeting, 2018). In humans, CAD is the most common cause of SCD at advanced age, but other structural heart diseases play also a role.

The LQTS (Romano-Ward syndrome) was the first syndrome described in humans as a pure electrical disorder without structural abnormalities. The first description dates back more than 50 years. For years, it was widely accepted that the long QT syndrome was the number one cause of sudden cardiac death in humans with a normal structural heart on autopsy. More than 15 different forms are currently known (Pérez-Riera, 2018). One form of this syndrome (type 3) is caused by a gain-of-function mutation in the SCN5A gene. This gene encodes for the alpha subunit of the cardiac sodium channel. The syndrome is characterized by abnormal sodium influx in the cardiomyocytes with a prolonged QT interval as a result (Wilde, 2018). Prolongation (as well as shortening) of the QT interval is strongly linked to ventricular tachyarrhythmias. These are a direct cause for sudden cardiac death (Tse, 2017). In the long QT syndrome, the typical polymorphic tachycardia is known as 'torsades de pointes' (TdP) (Shimizu, 2012; Bezzina, 2001).

Besides the long QT syndrome, there is also the short QT syndrome. Just like in long QT syndrome, several mutations have been linked to the disease. In general, there is either hyperfunction of potassium channels, or hypofunction of the calcium channels. This causes shortened atrial and

ventricular refractory periods, shortening of the action potential and short QT intervals on ECG. These then typically predispose for atrial or ventricular fibrillation and thus SCD¹.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) leads to SCD also because of ventricular arrhythmias. These occur because of mutations in the ryanodine receptor encoded by the gene RYR2. The calcium transport and handling are disrupted by these mutations. Typically, the arrhythmias occur during exercise because of the increased sensitivity of the calcium handling to catecholamines.

The idea that long QT syndrome is the leading cause of arrhythmic death caused by a channelopathy, has recently been debunked. The results of a prospective study concluded that it was not long QT syndrome, but Brugada syndrome that is the leading cause of these sudden unexpected deaths. Approximately 28% of the studied families and 15% of the studied relatives were diagnosed with Brugada syndrome (Papadakis, 2018). This syndrome is also a primary electrical heart disease. When considering the pathophysiology behind these two channelopathies, Brugada syndrome is in some ways the mirror-image of long QT syndrome type 3. It is caused by a loss-of-function mutation in the SCN5A gene which causes the encoding of defective sodium channels. The decrease in sodium channel current leads to ventricular fibrillation and possible sudden death (Sweeting, 2018).

Dogs

The first species apart from humans that will be studied are dogs. Structural heart diseases have commonly been linked to SCD in dogs. The most important ones will be discussed.

After mitral valve disease (MVD), dilated cardiomyopathy (DCM) is the second most common heart disease in dogs. This structural heart disease frequently has a familial basis, just like in humans. Mostly large and giant breeds are affected (Simpson et al., 2015). Several breeds are strongly predisposed, such as the Doberman Pinscher with a 58% cumulative incidence for the disease (Wess et al., 2010). Also, the Irish Wolfhound, Newfoundlands, Portuguese Waterdog and German Shepherd are known to be often affected (Freeman et al., 2017). Inheritability was investigated in several breeds. In the Doberman Pinschers for example, an autosomal dominant transmission with incomplete penetrance is suggested, and in juvenile Portuguese Waterdogs an autosomal recessive transmission (Tidholm and Jönsson, 2005).

In dogs with DCM, the primary problem is a decreased systolic function (Simpson et al., 2015). Both left and right heart are usually affected. As a result of the myocardial damage, arrhythmias can occur. Also, the renin-angiotensin-aldosterone-system is activated because of the lacking 'pump'. This then leads to sodium retention, ventricular remodeling left ventricular dysfunction and dilation (Tripathi et al., 2017). This dilation can also affect the annulus of the valve. As a result, some dogs also obtain secondary valvular insufficiencies. Nevertheless, this has minor importance in the context of SCD.

¹ From: <https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-9/Short-QT-Syndrome>. Consulted lastly May 8th 2018.

Early diagnosis of structural heart disease and especially DCM is key in the prevention of its complications. It has been shown that Dobermans with systolic dysfunction treated with pimobendan (Vetmedin, Boehringer Ingelheim Vetmedica GmbH) stayed in the pre-clinical phase of disease 9 months longer than the placebo-treated dogs, stressing the need for early diagnosis and treatment (Summerfield et al., 2012). The problem is that there is often a very long occult phase with mild to absent clinical signs. This makes diagnosis a true challenge (Simpson et al., 2015). Apart from DCM, several other structural heart diseases associated with ventricular arrhythmias and SCD are known in dogs. For example, ARVC which was mostly studied in Bulldogs and Boxers (Boujon and Amberger, 2003; Hamlin, 2007; Simpson et al., 2015; Cunningham et al., 2018).

Dogs with DCM often display malignant ventricular arrhythmias, which is a very important complication because the arrhythmias can cause SCD. For example, about one-third of Doberman Pinschers in the occult stage of DCM can die from SCD (Klüser et al., 2016). Some of these arrhythmias can be detected during a 24-hour Holter monitoring (Simpson et al., 2015).

Electrical diseases can also cause SCD in dogs. For example, ventricular arrhythmias without a known underlying structural cause are described in young German shepherds (Moïse et al., 1994; Jesty et al., 2003; Hamlin, 2007; Pariaut et al., 2011; Ribas et al., 2018) and potentially Rhodesian ridgebacks (Meurs et al., 2016). There are suggestions that channelopathies could play a great role in sudden cardiac death in animals, like they do in humans, but data is scarce at the moment (Schwartz et al., 2017).

R on T phenomenon was described as a possible electrical dysfunction causing SCD in dogs. A Golden Retriever previously diagnosed with severe subaortic stenosis and LA dilation died suddenly while wearing a Holter monitor. The dog portrayed premature ventricular complexes occurring onto the T wave (R on T phenomenon). These further evolved into typical polymorphic ventricular tachycardia also known as torsades de pointes (Gunasekaran et al., 2017).

Also, it is generally believed that myocardial infarctions are very uncommon in cats and dogs, but recently a role in patients with symptoms of acute and severe heart failure is becoming more and more present (Wilson and Scheel, 1982; Vanoli et al., 1991; Driehuys et al., 1998). However, the cause of these myocardial infarctions may not be CAD, but rather systemic disease with enhanced thrombotic risk. A link with Duchenne muscular dystrophy is possible, but more research is required to confirm this suspicion (Schneider et al., 2016).

Cats

Cats will also be included in this study, because they are also a possible victim of SCD. Just like in dogs, several conditions are known to cause arrhythmias and sudden death. Here we will specifically discuss the best known and most common structural heart disease: hypertrophic cardiomyopathy. More research is still needed concerning primary electrical diseases causing SCD in cats.

Approximately 10-15% of pet cats have some form or degree of hypertrophic cardiomyopathy (Payne et al., 2015; Freeman et al., 2017). This primary structural heart disease affects cats of all ages and breeds, but mostly Domestic Shorthairs and males (Freeman et al., 2017). In some breeds such as the Maine Coon, Ragdoll and British Shorthair, HCM is often seen more in younger individuals (Lefbom et al., 2001). Other breeds are also predisposed such as the Sphynx, Scottish Fold, Persian and Burmese. In the Ragdoll and Maine Coone, an autosomal dominant transmission with incomplete penetrance was found. The mutation is seen in a gene responsible for the myosin-binding protein C in the sarcomeres of the myocardium. Recently, a new causative mutation was identified by Schipper et al. (2019) being the MYH7 c.5647G>A variant in a Domestic Shorthair. Most likely multiple other not yet identified mutations can cause the disease (Freeman et al., 2017).

Briefly, the pathogenesis of HCM is as follows. Because of the mutation, there is a defect in the sarcomeres. Compensatory hypertrophy of the myocardial walls and interventricular septum will take place as a result. Echocardiography shows that both the left as well as the right ventricle are usually involved in the hypertrophic process (Schober et al., 2016). Also, fibrosis and disarray of the myocardial fibres are typical findings, as is disturbed calcium transport in and out of myocardial cells (Ferasin, 2009).

What is important with regard to SCD, is that cats with asymptomatic HCM have significantly more frequent and complex ventricular and supraventricular arrhythmias than normal cats. This was proven based on echocardiography, ECG, Doppler blood pressure measurements and 24-h Holter monitoring (Jackson et al., 2014; Hanas et al., 2017). As we already stated, these could possibly lead to SCD like they do in dogs. More studies are needed to prove that these findings are directly linked to increased SCD in asymptomatic HCM cats (Jackson et al., 2014).

4. Literature review

4.1. Cardiomyopathies and associated arrhythmias

4.1.1. Dilated cardiomyopathy

4.1.1.1. Dogs

The pathogenesis of DCM in dogs is very similar to that in humans. It can be defined as a classic structural cardiomyopathy, which implies there is an aberrant structure of the heart. The disease can be primary and thus genetically inherited or can be secondary attained. The primary form is caused by genetic defects that encode for defective myocardial cells, who typically portray decreased inotropy and thus cause systolic dysfunction of the myocardium. Phenotypically, it is characterized by progressive dilation and thinning of the myocardial wall and possibly interventricular septum.

In the Doberman Pinscher a cumulative incidence of 58% was noted (Wess et al., 2010). Also, the Irish Wolfhound, Newfoundland, Boxers, Great Dane, St. Bernard, Portuguese Waterdog and German Shepherd are high risk breeds (Freeman et al., 2017; Simpson et al., 2015). In humans several responsible mutations were already identified, but in dogs no exact causative gene defect were found yet. An autosomal recessive pattern is likely in juvenile Portuguese Waterdogs, whereas autosomal dominant transmission was suspected in the Doberman Pinscher (Tidholm and Jönsson, 2005). In Great Danes transmission is probably linked to the X-chromosome (Wess et al., 2010).

Secondary DCM is often seen a result of nutritional deficiency, such as taurine-deficiency. Taurine is a free amino acid and is not considered an essential amino acid in dogs. It is highly important for numerous physiological processes such as proper retinal function (which will be discussed later in cats), reduction in platelet aggregation, anti-oxidant in all cells including cardiac cells and most importantly for us, is responsible for adequate myocardial function. The exact ways in which taurine operates as an aid in myocardial cell function are still unknown, but it is suspected it helps modulate tissue calcium concentrations and availability. Also, taurine is a direct antagonist of angiotensin II and thus interacts with the RAAS activation which plays a huge role in DCM progression (Sanderson, 2006). Knowing this, it is no surprise taurine deficiency can lead to (severe) myocardial dysfunction. The link between taurine and DCM was first noticed in foxes (Moise N.S., 1989; Sanderson, 2006). Rapidly, the pathogenesis of DCM in dogs was reconsidered, and experts found that 17% of 75 dogs with DCM in a study had low taurine plasma levels. These dogs with low taurine levels were mostly 'unusual DCM breeds' such as American Cocker Spaniels and Golden Retrievers, which led to the idea of a non-primary DCM (Kramer et al., 1995). Lately, newer and unconventional diets such as grain-free and 'boutique' diets are getting more and more attention. These diets typically contain very different nutrient sources compared to more classical balanced diets. The exact link is not yet identified but causes including dietary deficiency or reduced bioavailability of taurine or its precursors are suggested. Also, a different processing of the dietary taurine or increased faecal excretion are possible (Tidholm and Jönsson, 2005; Kaplan et al., 2018).

Secondary DCM can also be tachycardia-induced. This form of DCM is usually reversible and is also seen in humans. As in other forms of DCM, myocardial contractility is also decreased. Apart from this, other consequences are increased afterload/peripheral vascular resistance. Diastolic function is also affected. Very typical is the incomplete relaxation of the myocardium because of abnormal increase in calcium levels in the sarcoplasmic reticulum during tachycardia resulting in diastolic contracture. The

left ventricle usually displays 'normal' DCM characteristics with the most prominent one being dilation of the lumen, whereas the right ventricle also develops eccentric hypertrophy (Gupta and Figueredo, 2014).

Infectious and toxic agents such as doxorubicin were also related to secondary dilatory changes of the heart in dogs. Doxorubicin is an antitumor antibiotic used to treat for example lymphoma. Especially in already at-risk breeds such as Boxers, the incidence of DCM during chemotherapy with doxorubicin was quite remarkable with 15.4%, whereas in other breeds a rather low incidence of 3% was noticed (Hallman et al., 2018). Not all dogs showed clinical symptoms, but when they did, they usually emerged 6 months after doxorubicin use. Duration of infusion with doxorubicin had no influence on the incidence of cardiotoxicity. Mostly premature contractions and decreased fractional shortening were seen, but also decreased systolic function and arrhythmias (Hallman et al., 2018). This last finding is important when considering sudden death.

Since ventricular contractions are responsible for adequate circulation of the blood and along with it sufficient cardiac output, the renin-angiotensin-aldosterone-system will be activated in order to maintain correct arterial blood pressure. This is a result of the decreased systolic dysfunction. The activation of this cascade results in expression of renin by the kidney granular cells, which hydrolyses angiotensinogen to angiotensin I. After, angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II which has smooth muscle contracting properties promoting vasoconstriction. Another effect of renin is the activation of the sympathetic nervous system. Also, angiotensin II will stimulate aldosterone secretion, which is responsible for sodium-potassium homeostasis in the body (Patel et al., 2017). Retention of sodium results in fluid retention, which eventually causes volume overload of the heart. The main issue here is the resulting dilation of both left and right ventricles which then predisposes to arrhythmias. From human studies, we know that myocardial scarring is the main trigger for arrhythmias (Horowitz et al., 1980). This is a direct cause for SCD.

Whether a patient is affected by primary or secondary DCM, the consequences often remain the same and are usually quite serious. The dilation of the left and often also the right ventricle has several effects. First of all, systolic function will further decrease, and also the annulus of the valves can be affected by the dilation, resulting in a secondary valve insufficiency. As already stated, this is less important concerning SCD, although it will contribute to the volume overload. What is important, is the fact that most dogs with DCM display malignant arrhythmias and thus have a direct link to SCD. This can easily be explained: when the myocardium is damaged it is more likely that arrhythmias occur because of the disrupted cell function. Often ectopic foci will start firing signals resulting into (supra)ventricular premature complexes. These can then easily evolve to for example ventricular tachycardia and/or fibrillation and death (Simpson et al., 2015).

What is absolutely essential in this story, is to recognize DCM usually has three stages concerning the clinical progression of the disease. During the first stage no morphological or electrical abnormalities can be detected. This stage can last several years. In the second stage, also called the occult or preclinical phase, there are still no or very subtle clinical signs but there may be morphological or electrical abnormalities such as an enlarged left ventricle or arrhythmias on ECG such as VPCs. For the owner, the dog will appear practically normal during this phase which makes diagnosis very challenging. Eventually when the dog reaches the third stage, clinical signs of heart failure such as

ascites, coughing, exercise intolerance, lethargy and pulmonary edema will be noticeable (Wess et al., 2010; Simpson et al., 2015).

In high risk breeds, such as Doberman Pinschers and Great Danes, diagnostic tools such as echocardiography, ECG and 24-hour Holter monitoring are essential in the battle against congestive heart failure. Especially these types of dogs should be screened from a young age on to make sure that structural or electrical changes are noticed as early as possible. This suspicion was confirmed in the Protect study showing that pimobendan (Vetmedin, Boehringer Ingelheim Vetmedica GmbH) treatment in Dobermans with systolic dysfunction prolonged their time in the occult phase with 9 months as opposed to placebo-treated dogs, thus stressing the importance of an early diagnosis (Summerfield et al., 2012).

Most dogs from at risk breeds such as Doberman Pinschers are diagnosed with occult DCM are between 5 and 7 years old, but dogs as young as 2 years old can already be affected. Screening should start at the age of 3. Ideally, according to Wess et al. (2017) these screenings using echocardiography and Holter monitoring should be repeated yearly to make timely diagnosis possible. This way we can also try and eliminate affected male dogs as soon as possible from breeding programs so less affected puppies will be born in the future. When performing Holter monitoring, 24h monitoring is advised in order to get a complete and thorough idea of the ECG. In Doberman Pinschers a maximum of 50 VPC's per 24h is considered normal and more than 300 VPC's per 24h is diagnostic for occult DCM (O'Sullivan et al., 2007; Wess et al., 2017). Because risk factors for SCD were poorly defined Klüser et al. (2016) investigated predictive parameters for SCD in Doberman Pinschers diagnosed with DCM. They found that the ejection fraction (EF) alone, as is used in human medicine as a predictive factor, is insufficient. This is mainly due to the fact that not all dogs with DCM suffer from decreased systolic dysfunction. They evaluated the prognostic value of echocardiographic and Holter-ECG variables, but also cardiac Troponin I (cTnI) and N-terminal prohormone of brain-natriuretic peptide (NT-proBNP) and tried to provide conditional inference trees based on these variables. Volume overload of the left ventricle (which was expressed as a Left Ventricle End Diastolic Volume (LVEDV) on Body Surface Area (BSA)) was found to be the best predictor for SCD. EF and left ventricular end-systolic volume were strongly linked to the LVEDV/BSA.

4.1.1.2. Humans

Many of the structural diseases are inherited disorders and are transmitted according to Mendelian patterns (for example autosomal dominant or recessive). They can be responsible for up to 26% of SCDs (Sweeting, 2018). Also in humans DCM is a well-known cardiomyopathy. Just like in dogs, the condition is characterized by progressive thinning of the myocardial wall and decreasing systolic function.

It is usually seen as an inherited primary structural disease but can also occur as a secondary phenomenon due to for example coronary artery disease. It is considered a mixed (genetic and non-genetic) condition according to Wexler et al. (2009) but the disease is familial in approximately 25% of the cases (Collis and Elliott, 2017). Mutations are usually seen in genes that encode for cytoskeletal proteins, sarcomeres, intercalated discs and nuclear membranes (Collis and Elliott, 2017). DCM is the most common cardiomyopathy seen in humans (Sweet et al., 2015). The incidence is approximately 5 in 100 000 adult and 0,57 in 100 000 children, which is probably an underestimation since many cases remain unrecognized (Wexler et al., 2009; Collis and Elliott, 2017). Blacks and males have a 2,5 times higher risk compared to whites and women (Dec and Fuster, 1994). Symptoms may present as

shortness of breath, fatigue, cough, orthopnea, paroxysmal nocturnal dyspnea and edema (Wexler et al., 2009).

When considering primary inherited DCM, in 30-40% of the cases a causative genetic mutation is found. Mutations were already detected in more than 50 different genes such as for example SCNA5A or DSP. For several of these genes genetic screening is possible. Other primary cases are considered of idiopathic origin. A confirmed family history of DCM is the only clinical phenotype available to distinguish between familial and idiopathic primary DCM (Sweet et al., 2015). In most of the cases, the pattern seems to be autosomal dominant, but also autosomal recessive, X-linked recessive and mitochondrial inheritance were reported (Dec and Furster, 1994).

DCM can also occur as a secondary result of viral myocarditis or other cytotoxic insults, for example Coxsackie virus B3 antibodies were often found in large amounts in patients with both Idiopathic Cardiomyopathy (IDC) and myocarditis. The exact link between the two still remains unknown, but an autoimmune response triggered by induction difficulties in the MHC gene could possibly play a role (Dec and Fuster, 1994). Also, immune abnormalities, and metabolic, energetic and contractile abnormalities such as abnormalities of cardiac high-energy phosphate substrate of abnormal actin-myosin interaction could lead to secondary myocardial dilatory changes (Dec and Fuster, 1994).

Diagnostic criteria for DCM on echocardiography are fractional shortening <25% and/or ejection fraction <45%, and also left ventricular end diastolic diameter >117% after excluding any known cause of myocardial disease. (Sweet et al., 2015). Also, screening is very important in humans, just like in dogs, since the occult phase exists here too. In human medicine multiple techniques are used to do this, such as echocardiography, ECG and genetic testing.

Exactly like in dogs, pathogenetic pathways in humans lead to RAAS-activation, but most importantly in our study predispose for possible (malignant) arrhythmias that can cause SCD. The mechanism behind this revolves around myocardial ischemia. This ischemia can be explained by defective myocardial perfusion, decreased wall motion and abnormal cell metabolism that are often present in patient with DCM. Ischemia can be a direct cause of arrhythmias: we could state it is a structural defect turning into an electrical defect (Fang et al., 2010).

4.1.1.3. Cats

DCM in cats is very rare. It is most frequently caused by taurine deficiency, but as Pion et al. (1987) stated, the incidence drastically reduced when the importance of taurine supplementation in cat food was recognized. In this case DCM is usually reversible but irreversible retinal degeneration can be seen. Nowadays, cats with taurine related DCM are usually fed a non-traditional diet (Pion et al., 1987). Hambrook and Bennett (2012) studied the effect of pimobendan in thirty-two cats with non-aurine responsive DCM and concluded that the mean survival time was four times higher in the pimobendan treated cats than in the non-pimobendan treated cats. A gender or breed predisposition was not confirmed (Pion et al., 1992).

Symptoms and consequences for cats with DCM are much similar to those in dogs and humans. It also predisposes for malignant arrhythmias and thus SCD since it compromises normal myocardial structure. An important side note is that since systolic function is impaired in DCM patients, symptoms

of left heart failure will emerge, but in some cats also the right heart is affected. In dogs and humans, we would suspect clinical signs such as lung edema, coughing, exercise intolerance, but in cats also pleural effusion is seen in cases of left-sided CHF. This is probably due to a different anatomy of the pulmonary venous system and different porosity of subpleural capillary beds in the thorax of the cat (Johns et al., 2012). Also gallop rhythm (third and fourth heart sounds), murmurs and (aortic) thromboembolism can be a sign of DCM in cats (Pion et al., 1992).

Recently, DCM was diagnosed in a juvenile Pallas cat (a wild feline species) with dyspnea based on echocardiography and was confirmed at necropsy. Both atria and ventricles were dilated and histologically fibroelastosis of the endocardium was seen (Gudenschwager et al., 2019).

4.1.2. Hypertrophic cardiomyopathy

4.1.2.1. Cats

Hypertrophic cardiomyopathy (HCM) is also a primary structural disease of the heart. It is characterized by diastolic dysfunction, caused by hypertrophy of the free walls and interventricular septum leading to impaired filling of the ventricles and atrial dilation. This concentric hypertrophy is of compensatory origin, since genetic mutations cause decreased function of the myocardial cells. Mostly disarray of the myocardial sarcomeres is seen, along with fibrosis and impaired calcium transport in and out of the myocardial cells (Ferasin, 2009). Also, enlargement of the left atrium (LA) is very often seen, which is a direct hemodynamic result of the diastolic dysfunction that causes volume overload of the LA. Echocardiography shows that also the right ventricle is involved in the hypertrophic process in about 50% of the cats with HCM. Also, severity of LV and RV hypertrophy are related (Schober et al., 2016).

A striking 10-15% of all cats is affected by HCM (Payne et al., 2015; Freeman et al., 2017). There is a clear predisposition in Domestic Shorthairs and males, but also the Sphynx, Scottish Fold, Persian and Burmese are often diagnosed with HCM, but all genders, ages and breeds can be affected (Freeman et al., 2017). Important to note is that even though male cats are predisposed for HCM, they are at no higher risk to develop CHF or SCD than female affected cats (Fuentes and Wilkie, 2017). In British Shorthairs, Ragdolls and Maine Coons, the disease is also often seen in younger individuals (Lefbom et al., 2001).

As we already stated, the disease is primary inherited and just like in DCM, a lot of research is still required to identify exact causative mutations. In the Ragdoll and Maine Coon an autosomal dominant transmission with incomplete penetrance in the gene encoding for myosin-binding protein C (MYBPC3) is very likely to be one of the causes, just like in humans, but others still need to be identified (Maron and Fox, 2015). Recently, a new causative mutation for HCM in cats was identified by Schipper et al. (2019). It was a MYH7 c.5647G>A variant in a Domestic Shorthair of which the orthologous variant already was reported in a human with HCM.

Often cats with HCM are first recognized because of a systolic heart murmur (20-60%) which may have been noticed on routine examination, but many cats have innocent heart murmurs or murmurs caused by other heart diseases (Fuentes and Wilkie, 2017). Gallop rhythm is actually a much more specific finding for HCM than a murmur and is heard when diastolic filling is audible. It is usually typical for diastolic dysfunction as it is heard when the left ventricle is less flexible and pressures in the LA rise. Audible gallop rhythm or arrhythmia are markers for high-risk HCM (Fuentes and Wilkie, 2017). Due to

pulmonary oedema, pleural effusion and even ascites also dyspnea and/or tachycardia can be seen as symptoms, but the cat can have no symptoms at all (Ferasin et al., 2003). Sometimes, arterial thromboembolism or even sudden death can be the first manifestation of HCM in cats (Freeman et al., 2017). ATE is a consequence of stasis of blood in the enlarged left atrium. The flow is slower and coagulability increases. This way thrombi can be formed and can follow arterial circulation. Often the thrombus then gets stuck at the level of aortic bifurcation, causing the classic symptoms such as paresis/paralysis of the hind limbs, acute severe pain, decreased rectal temperature and pale and cold hind limbs (Borgeat et al., 2013). Even though this is the classical presentation, the syndrome is not solely caused by arterial occlusion only, since Imhoff (1961) found that experimental ligation of the feline distal aorta does not reproduce this exact clinical syndrome. Prostaglandins and serotonin along with vasoactive mediators probably also play a critical role in the onset of the phenomenon.

HCM is normally diagnosed on echocardiography by measuring the left ventricular free wall and interventricular septum thickness. Commonly seen in HCM cats is systolic anterior motion of the mitral valve, often accompanied by dynamic left ventricular outflow obstruction. Around 30% of cats with HCM are affected by this. In this case, the mitral valve moves towards the interventricular septum during systole, which causes a dynamic obstruction of the left ventricular outflow area, i.e., of the aorta. Normally this occurs due to deviant implantation of papillary muscles and abnormal chordae tendineae (Fuentes and Wilkie, 2017). When the RV is involved, an obstruction of its outflow area can also occur due to the interventricular septum and RV free wall moving towards each other. This phenomenon increases in severity with increase of heart rate and/or contractility and of course when the concentric hypertrophy is more pronounced. Important to note is that no increased risk for cardiac death was seen in cats with accompanying outflow obstructions, but since these usually cause a murmur and thus are more easily noticed and have a higher chance of being treated appropriately, these cats will have a greater chance at positive outcome than HCM affected cats without a murmur (Fox et al. 1995; Rush et al., 2002). Mean survival time after HCM diagnosis was 1276 days (Payne et al., 2010).

When performing ECG on these cats, not all of them show arrhythmias, but when they do it is usually episodes of VPCs. Côté and Jaeger (2008) found that 96% of all cats with ventricular tachyarrhythmias in their study had underlying structural heart disease, indicating the importance of the search for an underlying cause when arrhythmias are seen. On the other hand, they investigated the hypothesis that ventricular tachyarrhythmias could serve as a possible predictor for underlying cardiomyopathy. In addition to this hypothesis, it became clear that ventricular tachyarrhythmias were linked much more frequently to myocardial disease than they were to congenital heart malformations. This may occur due to the high arrhythmogenicity of cardiomyopathies or simply due to their higher prevalence.

Some causes of SCD cannot be classified strictly into the previously mentioned categories. For example, other causes of arrhythmia in cats include hyperthyroidism, restrictive and/or unknown cardiomyopathy, cardiac neoplasia and bacterial endocarditis. These usually cause secondary left ventricle hypertrophy similar to HCM findings, but strictly cannot be put under the same primary cardiomyopathic category (Côté and Jaeger, 2008).

4.1.2.2. Humans

The prevalence of HCM in humans is about 1 in 500 is affected when considering screening data and the disease is usually inherited by an autosomal dominant pattern with age-related penetrance (Shah, 2017). Mutations in 11 genes are known but about 70% them occur in the genes encoding for the myosin-binding protein C and the beta-myosin heavy chain of the sarcomeres (Maron and Maron, 2013). Unfortunately, in only about 50% of clinically affected probands the causative mutation is found. The typical disarray of the muscle fibres and fibrosis which we see in cats, are also known in humans (Maron and Maron, 2013; Maron and Fox, 2015; Shah, 2017).

The disease can possibly lead to CHF, stroke (embolic and usually associated with AF, syncope and of course SCD, but in most cases is completely asymptomatic (Maron and Maron, 2013; Shah, 2017). Spontaneous ventricular fibrillation is the most common direct cause for SCD in these patients (Collis and Elliott, 2017). Even when no risk factors are present, a patient with HCM still has an annual 0,6% mortality chance of SCD and the risk peaks in age group 8 to 16-year-old. Major risk factors include previous cardiac arrest, sustained and non-sustained ventricular tachycardia, unexplained syncope, family history of SCD and maximal left ventricular wall thickness > 3cm (Shah, 2017).

4.1.2.3. Dogs

HCM in dogs is extremely rare. When it does occur, it has a very similar pathogenesis to HCM in cats and humans. LV free wall and interventricular septum hypertrophy is seen. Although most dogs remain asymptomatic, signs of CHF and even syncope or SCD can be seen. Diagnosis still remains difficult and requires echocardiography to reveal myocardial hypertrophy (Liu et al., 1979).

Most diagnosed cases were in male dogs under 3 years of age. Since reported cases are so sparse, it is difficult to draw a conclusion about predisposition. Breeds that already have been diagnosed with HCM include mostly Rottweilers and Dalmatians, but also the German Shepherd, Doberman Pinscher, Pointer, Walker hound, Airedale terrier, Great Dane, Cocker Spaniel, Bull dog, Boston Terrier, Pembroke Corgi, Rhodesian Ridgeback and a Shih Tzu were reported (Liu et al., 1979; Washizu et al., 2003).

Also, Washizu et al. (2003) reported a 14-year-old Yorkshire Terrier with cardiac murmur and convulsive seizures who was diagnosed with HCM and had typical myocardial disarray and fibrosis. The suspected late onset of the disease in this dog is even more rare.

Liu et al. (1979) fully examined 10 dogs on necropsy with findings of heart disease resembling HCM. What is striking is that 3 out of 10 dogs suffered from sudden death, with no symptoms of heart failure prior. Also, 3 dogs showed signs of complete heart block. The main difference with cats and humans is that no causative genetic mutation was found yet in dogs. There is a high suspicion these genetic defects will also lay in sarcomere proteins, but there is no evidence today. What is remarkable is Liu et al. (1979) also found that only 2 out of 10 dogs had typical findings on histology like in cats and humans, being myocardial cell disarrange. Left ventricular free wall thickness varied between 10 and 19mm. We have to keep in mind that the findings on necropsy were only resembling HCM and histological exam did not often fit the usual findings. Since HCM is not a disease solely diagnosed on ECG, this means these dogs could have possibly been affected by secondary HCM and not the primary inherited form.

4.1.3. Arrhythmogenic right ventricular cardiomyopathy

ARVC was first described in humans and is characterized by atrophy and fibrofatty infiltration of the right ventricular myocardium. The right ventricular free wall is affected, mostly in the typical 'triangle of dysplasia' being the subtricuspid outflow tract, infundibular inflow tract and apex (Boujon and Amberger, 2003; Stadiotti et al., 2017). It is a primary genetically inherited structural heart disease, which also eventually leads to electrical deficiencies of the heart in a similar way to HCM and DCM. Usually it follows a Mendelian autosomal dominant pattern. Mutations in over 13 genes were already found in humans. Most of these mutations occur in the genes encoding for desmosomes, a protein containing structure specialized in cell-to-cell adherence, for example PKP2 (Stadiotti et al., 2017). Besides these mutations it is also suspected that myocardial atrophy can be induced by patchy myocarditis, in this case it is not known whether the inflammation is secondary to myocardial death or if it is the cause (Basso et al., 1996). Patients with ARVC, also called ARD (arrhythmogenic right ventricular dysplasia), are very susceptible to malignant arrhythmias and thus SCD. Especially the young are often affected (Fox et al., 2000). Apart from SCD, ARVC can also lead to CHF. Symptoms of right-sided CHF like exercise intolerance, syncope and ascites are frequently seen. Usually the right heart is affected, but in 16-76% percent of cases also the LV is involved (Miles et al., 2019). The most important thing to remember is that ARVC can cause arrhythmias even in the early stage of the disease, which again stresses the need for screening and early diagnosis (Leren et al., 2016).

ARVC is also known in dogs. Several cases were reported, among which were a Boxer, Weimaraner and a Husky. The findings are also very similar to the ones in humans and cats, suggesting that it probably is the almost the same exact disease (Simpson et al., 1994; Boujon and Amberger, 2003; Eason et al., 2015). Cunningham et al. (2018) studied 31 cases of English Bulldogs with presumed ARVC and found that mostly male dogs around the age of 9 were being diagnosed with the disease. Exactly like in humans, there was a wide spectrum of the disease in dogs, with 15 out of 31 dogs suffering from clinical or subclinical arrhythmias and 15 out of 31 dogs displaying symptoms of congestive heart failure. English Bulldogs usually are affected by quite a specific form of ARVC, with typical lesions found in the area of the right outflow tract (Santilli et al., 2009; Cunningham et al., 2018)

Also, cats can be affected. Fox et al. (2000) identified 12 cats with symptoms of right CHF with great suspicion of ARVC. Very similar findings to human ARVC were noted. For example, histopathologically, fibrous, fibrofatty or fatty infiltration and loss of myocardial cells was found. Also, RV free wall thinning and typical echocardiographic findings such as enlargement and hypokinesis of the RA and RV were seen in all studied cats.

4.2. Primary electrical cardiac dysfunctions

4.2.1. Channelopathies

4.2.1.1. Humans

Data emphasize the importance of coronary artery disease (CAD) as the most important cause of SCD in humans. However, there are other causes of SCD not related to CAD. As mentioned above, human SCD can be caused by other structural heart diseases such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC). In contrast, human SCD also occurs in individuals with a pure cardiac electrical disease without structural abnormalities. The most common of these diseases are Brugada syndrome (BrS), long QT syndrome (LQTS), short QT syndrome (SQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) (Papadakis et al., 2018).

The LQTS was the first syndrome described in humans as a pure electrical disorder without structural abnormalities. The first description dates back more than 50 years (Ward O.C., 1964). There are several forms of this syndrome, one being the autosomal recessive form which presents with prolonged QT interval on ECG and also congenital deafness. This form is also known as Jervell and Lange-Nielsen syndrome. The autosomal dominant form, which occurs much more often, typically presents without deafness and is known as the Romano-Ward syndrome. It is diagnosed on ECG when QT intervals exceed >470 ms in males and >480 ms in females (after correction for heart rate when needed) (Bohnen et al., 2017).

For years, it was widely accepted that the long QT syndrome was the number one cause of sudden cardiac death in humans with a normal structural heart on autopsy. More than 15 different forms are currently known (Pérez-Riera, 2018). One form of this syndrome (type 3) is caused by a gain-of-function mutation in the SCN5A gene. This gene encodes for the alpha subunit of the cardiac sodium channel. The syndrome is characterized by abnormal sodium influx in the cardiomyocytes with a prolonged QT interval as a result (Wilde, 2018). Voltage-gated sodium channels which are activated by depolarization initiate action potentials (AP) in cardiac myocytes. The rate of conduction of the AP through the myocardium is strictly related to the speed at which the cardiac AP rises. This is therefore dependent of the density of active sodium channels and their rate of activation. (Catterall, 2018). The mutations in LQTS result in an increase of depolarizing currents over repolarizing ones and thus will cause increased refractory periods from channels that remain depolarized longer. This will create pockets of functional block (Martin et al., 2012). Prolongation (as well as shortening) of the QT interval is strongly linked to ventricular tachyarrhythmias. These are a direct cause for sudden cardiac death (Tse, 2017). In the long QT syndrome, the typical polymorphic tachycardia is known as 'torsades de pointes' (Shimizu, 2012; Bezzina, 2001). Torsades de pointes can also be drug-induced, for example after use of dofetilide (Tkosyn, Pfizer) or tedisamil (Pulzium, Solvay Pharmaceuticals), which are both class III anti-arrhythmic drugs used for chemical cardioconversion after atrial fibrillation Barrett et al., 2001).

Besides the long QT syndrome, there is also the short QT syndrome. Just like in long QT syndrome, several mutations have been linked to the disease. In general, there is either hyperfunction of potassium channels, or hypofunction of the calcium channels. Three different gain-of-function mutations in genes encoding for cardiac potassium channels (KCNH2, KCNQ1, and KCNJ2) were already found (Borggreffe et al., 2005). This causes shortened atrial and ventricular refractory periods, shortening of the action potential and short (shorter than 300 to 320 ms) QT intervals on ECG. These

then typically predispose for atrial or ventricular fibrillation and thus SCD¹. Increased transmural repolarization gradients were shown to be the underlying cause in the arrhythmogenic mechanism (Martin et al., 2012).

The idea that the long QT syndrome is the leading cause of arrhythmic death caused by a channelopathy, has recently been debunked. The results of a prospective study concluded that it was not the long QT syndrome, but the Brugada syndrome that is the leading cause of these sudden unexpected deaths. Approximately 28% of the studied families and 15% of the studied relatives were diagnosed with Brugada syndrome (Papadakis, 2018). This syndrome is also a primary electrical heart disease. When considering the pathophysiology behind these two channelopathies, Brugada syndrome is in some ways the mirror-image of the long QT syndrome type 3. It is caused by a loss-of-function mutation in the SCN5A gene which causes the encoding of defective sodium channels (Fig. 1). This can be seen as no expression of the sodium channel, disrupted current of the sodium channel due to a shift in the voltage and time dependence of the channel during activation, inactivation or reactivation, or even early inactivation of the sodium channel (Hyun and Phillipich, 2006). This way, there is a delay of the action potential, causing a greater transmural voltage gradient between endocardium and epicardium leading to the typical ST-elevation (Fig. 2). The decrease in sodium channel current leads to ventricular fibrillation and possible sudden death (Brugada and Brugada, 1992; Brugada et al., 2009; Sweeting, 2018).

Another cause of SCD in humans is idiopathic ventricular fibrillation (IVF) or tachycardia. Since the pathology is still very poorly understood we cannot correctly categorize it. IVF can only be diagnosed by exclusion which implies that no common diagnostic means were able to identify the underlying cause of the arrhythmia. By definition no structural heart disease was unmasked, no abnormalities were seen on ECG nor echocardiography nor MRI. Ajmaline tests are also negative, as is genetic testing. The disease can also manifest as a non-lethal syncope, cardiac arrest or seizures and is characterized by transient spontaneous polymorphic ventricular fibrillations/tachycardia (Visser et al., 2016).

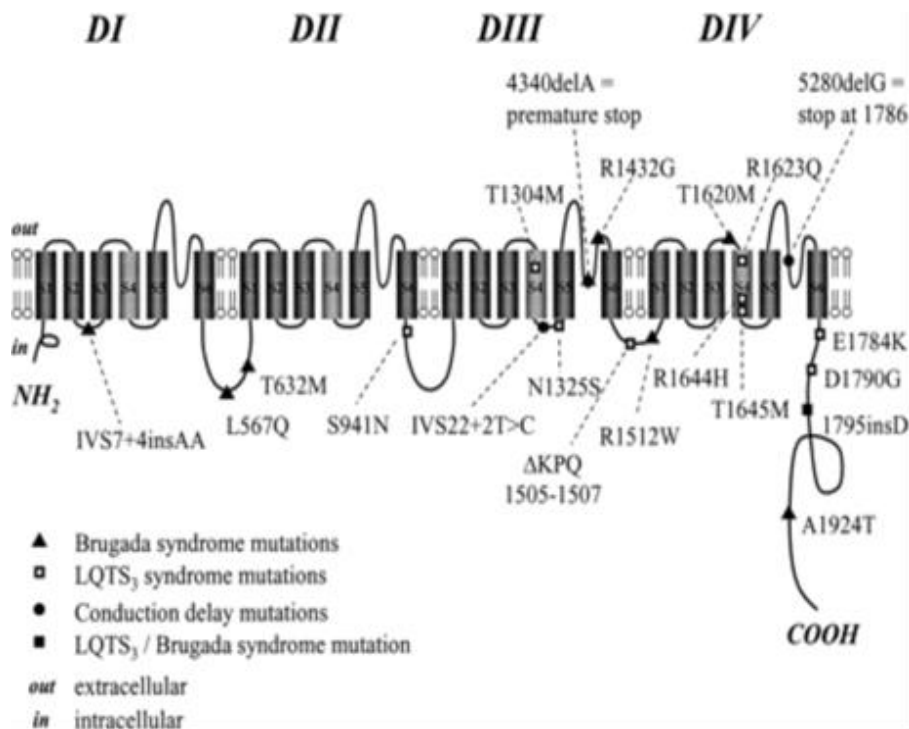


Fig. 1 Diagrammatic representation of the human cardiac sodium channel displaying location of mutations associated with the long QT syndrome type 3, the Brugada syndrome and isolated cardiac conduction defects. From: Cardiac sodium channel and inherited arrhythmia syndromes, Cardiovasc RES. 2001; 49(2):257-271. doi, 2000 European Society of Cardiology

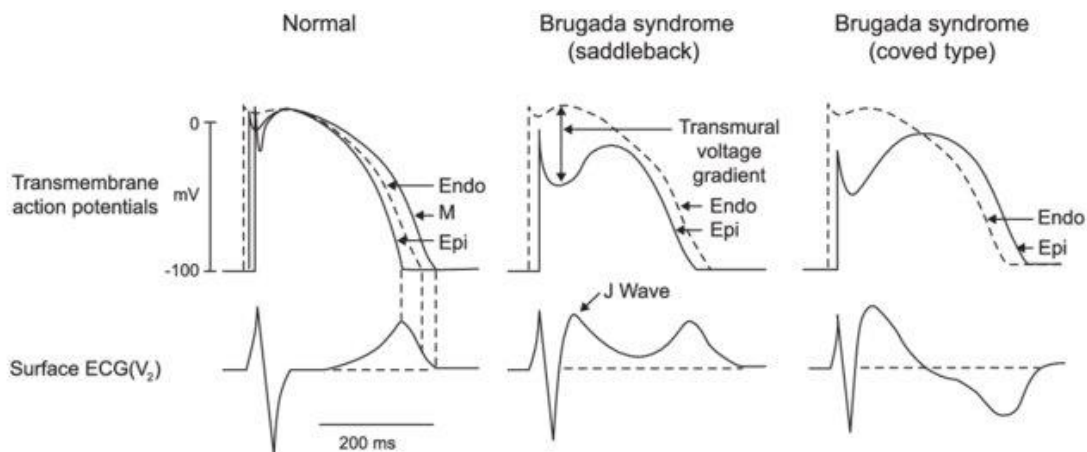


Fig. 2 schematic explanation of the typical ST elevation and possible negative T wave seen on ECG in a patient with Brugada syndrome. From: Brugada, P., Benito, B., Brugada R., Brugada, J., 2009. Brugada Syndrome: update 2009. Hellenic Journal of Cardiology 5; 352-372.

4.2.2.2. Channelopathies in dogs and cats

Data on channelopathies causing primary electrical cardiac disease in cats and dogs is almost non-existent, but recently their importance as a component of SCD has got more and more attention. In small animals no genetic mutations were found yet despite several cases of sudden cardiac death being reported seemingly caused by these conduction defects as will be discussed further on. Channelopathies in animals were described in other medical fields concerning other pathologies such as in neurology, e.g. canine myotonia and achromatopsia (Tanaka et al., 2015; Lowrie and Garosi, 2017).

Several cases of sudden death suspected to be caused by channelopathies in dogs were reported. For Meurs et al. (2016) SCD of 4 young related Rhodesian Ridgebacks was motive for further investigation since no structural heart disease nor previous symptoms were found. Holter, echocardiography and necropsy were performed on as many related animals as possible, in order to try and analyze possible inheritance patterns. Since males and females were almost equally affected and unaffected parents did sometimes produce affected offspring, an autosomal recessive inheritance pattern was strongly suspected. Yet, an autosomal dominant pattern with incomplete penetrance could not be completely ruled out. Important to note is that Meurs et al. (2016) does not conclude on any etiopathogenesis, but a cardiac channelopathy is mentioned as one of the possible underlying diseases.

Also, in the English Springer Spaniel SCD with no evident underlying structural heart disease was reported. This was the first case report where inherited LQTS in dogs was suspected (Ware et al., 2015). LQTS in dogs is already known to be caused by toxins, certain drugs or electrolyte imbalances. An otherwise healthy 5-year old Springer Spaniel who recently delivered her first litter died suddenly after activity. Three of her puppies also suffered SCD and in several other offspring Holter and ECG monitoring revealed abnormal elongation of the QT interval and biphasic T-waves. Gene sequencing revealed that the puppies displaying these prolonged QT intervals had mutations in the KCNQ1 gene, which was a defect that most likely appeared de novo in the dam. These findings are very similar to LQTS known in humans, where mutations in the KCNQ1 gene are the number one cause for the disease. In humans this syndrome was the first channelopathy to be described causing SCD and it is still a major cause of SCD in humans without structural heart disease (Ware et al., 2015).

Even though not much has been described about cardiac channelopathies in dogs, in cats even less is known. Feline fatal arrhythmias are mostly caused by underlying structural heart disease such as HCM. Currently, there are no reports about primary electrical disorders caused by channelopathies in cats.

4.2.2. German Shepherd genetic arrhythmias

German Shepherds are known to suffer SCD (Ribas and Pariaut, 2018). An inherited disease that follows a sex-linked or autosomal dominant pattern is suggested but is not confirmed to date. Typically, SCD occurs during sleep or after exercise and is induced by ventricular tachycardia that evolves to ventricular fibrillation and eventually asystole. The abnormal ventricular repolarization is actually very similar as is seen in LQTS and Brugada syndrome in humans. Moise et al. (1994) stated that all dogs studied died between the age of 4 and 30 months old and polymorphic non-sustained ventricular tachycardia was present in all of them. Yet, no prolonged QT interval is seen nor are there usually any previous echocardiographic abnormalities found. Normally no histopathological anomalies are present

when investigated post-mortem. Since there are no structural causes found, a purely electrical disorder is very likely, but the pathology remains very poorly understood (Moise et al., 1994; Hyun and Phillipich, 2006). Jesty et al. (2013) found that German Shepherd dogs with these ventricular arrhythmias had lower ATP2A2/SERCA2a expression. The SERCA pump plays a big role in the calcium homeostasis within the cardiomyocyte. It is known that abnormal calcium kinetics can lead to abnormal Aps and thus can contribute to these arrhythmias. Of course, no provocative pharmacological tests such as ajmaline or procainamide are available to exclude Brugada syndrome.

4.2.3. Catecholamine dependent arrhythmias

4.2.3.1. Catecholaminergic polymorphic ventricular tachycardia in humans

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited electrical dysfunction of the heart leading to arrhythmias, syncope and possible SCD. It was first described in 1960 by Berg. The disease is characterized by bidirectional ventricular tachycardia or polymorphic ventricular tachycardia seen on ECG. It typically occurs during exercise or periods of emotional stress (Liu et al., 2007). The cause of this increased risk during these periods is release of catecholamines: these increase the sensitivity of calcium handling. The incidence of the disease is estimated at 15% of all cases of SCD without structural heart disease (Lieve et al., 2016).

The causative mutations behind this genetic deficiency are two folded. One form of the disease is inherited with an autosomal dominant pattern and is caused by mutations in the gene encoding for the cardiac ryanodine receptor (RyR2). Another form is inherited recessively and originates in defective cardiac-specific calsequestrin genes (CASQ2). Both genes regulate efflux from the sarcoplasmic reticulum into the cardiomyocyte and thus play an important role in cardiac excitability and contractility (Venetucci et al., 2012).

The disease usually has its onset during childhood or adolescence with most patients being around 10 years old. Without accurate treatment the mortality rate is around 30% before 40 years of age (Lieve et al., 2016). Sometimes supraventricular arrhythmias can be seen in these young patients preceding the actual ventricular tachycardia. This occurs probably due to the disrupted calcium handling in the atrium (Di Pino et al., 2014).

4.2.3.2. Catecholamine dependent arrhythmias in dogs and cats

Currently no analogue disease as seen in humans is described in dogs or cats. Further research is required to exclude whether it actually does not occur or is just not yet recognized.

4.3. Ischemic myocardial events

4.3.1. Ischemic myocardial infarctions in humans

Arteriosclerosis leading to coronary artery occlusion and causing ischemia of the myocardium is currently the most common cause of death in humans (Scansen, 2017). These myocardial infarctions are usually of the ischemic and not the hemorrhagic type. It is a very commonly occurring problem affecting approximately 4% of the population in their lifetime (Antman and Loscalzo, 2018). It is a local thrombus formed in the coronary arteries mostly as a result of atherosclerosis (Hackel and Jennings, 1988). Atherosclerosis is characterized by fatty degeneration of the extramural coronary arteries (Falk and Jönsson, 2000). This atherosclerotic plaque then weakens and partially breaks off. When coming into contact with the circulating blood, prothrombotic factors are activated and a local thrombus is formed. This causes occlusion of the vessels and thus creates an ischemic zone in the part of the myocardium being perfused by this vessel.

Classical risk factors in humans are well studied. The Framingham risk factors (the algorithm analyzing the 10-year risk of cardiovascular disease for an individual) include: diabetes, smoking, hyperlipidemia, hypertension and unhealthy diet but also hormonal factors such as polycystic ovary syndrome and psychological impact for example due to depression (Mehta et al., 2016).

It is of great importance to recognize signs of an acute myocardial infarction (AMI) as soon as possible in order to be able to intervene quickly for the best prognosis possible and minimize myocardial damage. Typical symptoms are acute heavy chest pain, dyspnea and collapse. Coventry et al. (2011) even found significant differences in symptoms between men and women by which AMI presented. Women had much lower odds to present with chest pain than men, whereas men showed much less signs such as neck pain, nausea and syncope.

4.3.2. Possible role in SCD in dogs and cats

Not much attention was given to typical myocardial insults as we know them in human medicine to be a cause of possible SCD in animals. Recently, more information is being obtained.

Coronary thrombosis or thrombo-embolism is the classical phenomenon causing myocardial infarcts: occlusion of the arterial blood supply by an embolus causing ischemia. As for the mechanisms causing coronary occlusions in cats and dogs, still a lot of pathophysiological factors have to be clarified. What we do know is that this disease is very seldomly diagnosed in veterinary practice. Dogs tend to have a left dominant coronary circulation, which imposes more unique collaterals than in species with right dominant coronary circulation like humans (Scansen, 2017). This imposes a question: do these occlusions really occur much less in dogs and cats or is it just that they have much less consequences when they do occur?

Atherosclerosis, the most common cause of ischemic heart disease in men, is very rare in dogs (Falk and Jönsson, 2000). Also, Falk and Jönsson (2000) found no gender or breed predisposition but concluded that intramural arterial arteriosclerosis is in fact a very common finding on necropsy in dogs. They also saw that 87 percent of dogs in their study group that suffered SCD had hyaline arteriosclerosis, of which half had concurrent myocardial infarctions. Although, Liu et al. (1968) stated that dogs are naturally resistant to the development of atherosclerosis and rarely experience any clinical issues from it. Predisposing factors for AMI in dogs are unknown (Driehuys et al., 1998).

Most of the myocardial ischemic events in cats and dogs are described as being secondary to structural heart disease and/or its hemodynamic consequences. Induced hypercoagulability or hypofibrinolytic state is usually the underlying trigger for thrombi to be formed. Common related conditions include neoplasia, disseminated intravascular coagulation, sepsis, hyperadrenocorticism and glucocorticoid use (Driehuys et al., 1998; Machen and Sleeper, 2015). Underlying structural heart disease such as HCM and DCM can also cause myocardial infarction in the end-stage (Machen and Sleeper, 2015).

Symptoms usually include lethargy, weakness, anorexia, dyspnea, collapse and vomiting. Affected dogs often have history of hypercholesterolemia and lipidemia like in humans, but also hypothyroidism was commonly previously diagnosed (Liu et al., 1986).

Methods for diagnosis of possible myocardial ischemic events include echocardiography where typical signs as local hypokinesis of the muscle, hyperechoic fibrosis and wall thinning can be noticed (Park et al., 2012). As for detection of the often-underlying hypercoagulability, D-dimers are not quite sensitive enough, with a sensitivity of D-dimer concentrations $>2,000$ ng/ml to predict thrombo-embolism only being 36% (Nelson and Andreasen, 2003). Thromboelastography would make for a much better option but is currently rarely available in veterinary medicine practice.

5. Discussion and conclusions

A lot of similarities and interesting possibilities for further research were found for cardiac disease in humans and in animals.

Structural heart disease causing SCD

Duncker et al. (2015) described the exponential increase in knowledge about cardiomyopathies mostly due to advanced research on genomic levels in both humans and animals. New technologies like CRISPR/Cas9 allow us to investigate mutations in animal models like zebrafish but also larger animals such as pigs. The goal is to use this information in order to better understand pathogenesis in a variety of species. Sleeper et al. (2009) concluded that therapeutic gene transfer using adeno-associated viral vector seems to be very interesting as a therapy for several cardiomyopathies such as HCM, DCM and ARVC. This therapy is used to normalize metabolic state (e.g. calcium handling and apoptosis) of aberrant myocardial cells.

As for DCM, it is certain that dogs can act as a spontaneous model for human DCM. With exact mutations in dogs still remaining unknown, affected dogs can act as a naturally occurring model for testing new therapies, but also as subject for genetic screening (Duncker et al., 2015). High-risk breeds for DCM such as Doberman Pinschers and Great Danes serve as ideal candidates. Especially Portuguese Waterdogs, known for their rapid progression of DCM, could serve as an excellent spontaneous model in hopes to directly transfer results of suppression of phospholamban (a membrane protein of the cardiac calcium pump) expression onto human cardiomyopathies (Sleeper et al., 2009).

The exact mechanism underlying familial arrhythmias in Boxers remains unknown (Spier et al., 2001), but since there are a lot of similarities with findings in human ARVC, the Boxer has been proposed as a model for ARVC in humans (Hamlin, 2007). Also, cats present a very interesting spontaneous model

for human ARVC just like they do for HCM. Especially since the pathogenesis of this disease is not yet completely resolved, findings in cats could lead to new insights in the disease in humans. Several papers confirmed the huge similarities in findings concerning the disease in cats, dogs and humans such as the typical 'triangle of dysplasia' (Simpson et al., 1994; Fox et al., 2000; Boujon and Amberger, 2003; Eason et al., 2015). This term describes the three typical locations to find histological abnormalities in patients suffering from ARVC, being that the right ventricular wall was thinner in subtricuspidal, apical and infundibular locations (Boujon and Amberger, 2003).

As already stated, cats were already used as a model for human HCM for years. Pathogenesis is strikingly similar to that in cats which implies cats can serve as a spontaneous model for human HCM (Maron and Fox, 2015). Maine Coon cats are especially interesting given the fact that their identified autosomal dominant MYBPC3 mutation very much resembles the human form. Both species have lower cMyBP-C protein, whether affected homogenous or heterogenous (Duncker et al., 2015). Also, Ragdolls were identified with mutations in this same gene. Cats can serve as models for exploring new therapies in order to prevent heart failure of SCD. &We can conclude that as for now cats have better potential for serving as spontaneous models for HCM in humans since there are much more affected individuals and the basics of genetic defaults are already known in this species. Unfortunately, genetic research in identifying causative genetic mutations causing HCM in animals is still on the low rise.

Electrical dysfunctions causing SCD

Naturally occurring models of ventricular arrhythmias include the non-ischemic arrhythmias in sleeping or resting German Shepherd puppies. As already stated above, the disease usually starts to manifest as occasional VPCs and then rapidly progresses towards ventricular tachycardia (Moïse et al., 1994; Jesty et al., 2003; Hamlin, 2007; Pariaut et al., 2011; Ribas et al., 2018). This type of spontaneous model could serve as an excellent base for further research of many diseases in man such as the LQTS but also dysautonomic arrhythmias (Hamlin, 2007).

Since not a vast amount of information is currently available concerning channelopathies in cats and dogs, it could be very interesting to check whether mutations as are already known in humans, also exist in these animals. One was already found when Ware et al. (2015) described a family of English Springer Spaniels who suffered SCD had a mutation in the KCNQ1 gene, just like is known in human LQTS. Unfortunately, in cats no cases of SCD allegedly caused by channelopathies were described. Regarding CVPT, currently no analogue disease as seen in humans is described in dogs or cats. Further research is required to exclude whether it actually does not occur or is just not yet recognized.

Dogs with ventricular arrhythmias due to gastric dilation/volvulus are known to resemble those secondary to dysautonomia in humans. By further researching the exact pathogenesis of these arrhythmias more insights could be obtained concerning diagnosis and treatment in both humans and animals (Hamlin, 2007).

Ischemic myocardial infarctions

Atherosclerosis, the most common cause of ischemic heart disease in men, is very rare in dogs. Myocardial infarctions are very seldomly diagnosed in practice, but Falk and Jönsson (2000) found that intramural arterial arteriosclerosis is in fact a very common finding on necropsy in dogs and 87 percent of dogs that suffer SCD have hyaline arteriosclerosis, of which half have concurrent myocardial

infarctions. Although, Liu et al. (1968) stated that dogs rarely experience any clinical issues from atherosclerosis. For now, we can conclude that most dogs or cats suffering myocardial infarctions, do so secondary to systemic disease like neoplasia which cause hypercoagulability or hypofibrinolytic state (Driehuys et al., 1998; Machen and Sleeper, 2015). More research is warranted to confirm or deny this suspicion. With further development and higher availability of diagnostic tools like thromboelastography in the future, hopefully better and faster diagnostics will be possible.

Conclusions

The most interesting benefits of using larger mammals like cats and dogs instead of more classical test animals like mice and rats, is that cats and dogs are a spontaneous model of these diseases. This means they develop the disease naturally, not by manipulated processes in laboratories. In mice, usually knock-out strands are used to create lines artificially affected by certain pathologies (Camacho et al., 2016). The main issue with these researches lays in extrapolating the results to humans which for a number of reasons is not always accurate. For example, the MHC protein which plays an important role in sarcomeric function completely differs in humans and mice (Duncker et al., 2015). Also, larger animals have a more heterogenous genetic background and their size allows easier surgical interventions and clinical evaluation compared to smaller species (Sleeper et al., 2009). Furthermore, large animals live in the same environment as humans and thus are exposed to the same environmental factors, making results more reliable for extrapolation.

There are still some important difficulties that are encountered when trying to analyse underlying genetics. Genetic testing through DNA sequencing is already available, yet sometimes new genetic mutations are identified for which pathogenesis is not yet fully understood. This can cause problems concerning interpretation and is of little use for familial screening. Also, for example in only about 50% of clinically affected human HCM probands the causative mutation is found (Maron and Maron, 2013). Since these are all problems that are encountered in human medicine, we can state that this will also be the case in the veterinary field.

In humans often the preferred treatment for serious arrhythmias that can lead to SCD is an implantable cardioverter-defibrillator or ICD (Borggreffe et al., 2006). Of course, this option is still very rare and unusual in animals even though the first defibrillator to be implanted was in a dog in 1970. After that, two more cases of ICD implantation were reported (Nelson et al., 2006; Coats et al., 2010; Pariaut et al., 2011). The main issue with this treatment in animals is the price of the intervention, but also the non-fitting algorithms of the device since they were originally designed for human use. For example, rapid sinus tachycardia (>250 bpm) which occurs frequently in dogs with ventricular arrhythmias, can be a reason for inappropriate therapy. This is because the decision for defibrillation is made based on rate and duration of the tachycardia, but usually maximum programmable rate for detection of this ventricular arrhythmia is 250 bpm (Pariaut et al., 2011). On the other hand, animals displaying arrhythmias secondary to primary cardiomyopathies such as DCM can serve as a subject of investigation concerning arrhythmias and anti-arrhythmic drugs (Hamlin, 2007). Considering what is presently known, it is clear that further research on SCD in animals is more than warranted.

6. References

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