Heart lipomatosis in domestic animals: a review

C.F. Agudelo, M. Svoboda, R. Husnik, S. Dvir

Faculty of Veterinary Medicine, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic

ABSTRACT: Heart lipomatosis represents a group of diseases leading to fatty tissue changes and their accumulation in the heart. Though the morbidity is relatively low, fatty changes are believed to take part in many processes that can cause death, and in fact fatty tissue is a normal component in healthy human and animal hearts. Several diseases that produce fatty changes in human hearts may possibly cause the same syndromes in animals but many of these conditions remain undiscovered. The aim of this paper is to review the typical conditions leading to fatty changes in human hearts and to delineate their relationship with animal pathologies.

Keywords: heart disease; fatty tissue; animals

List of abbreviations

ARVC = arrhythmogenic right ventricular cardiomyopathy, ***xmd* dog** = X-linked muscular dystrophic dog, **DMD** = duchenne-type muscular dystrophy, **PAS** = persistent atrial standstill

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1. Introduction

Heart lipomatosis is an uncommon clinical condition in humans and animals, which describes a variable degree of fat deposition in between and in some instances in place of the cardiac myocytes (Sowmya 2004). In humans it has been observed primarily in arrhythmogenic right ventricular cardiomyopathy (ARVC) and as a secondary finding in various conditions such inherited muscular dystrophies, chronic ischaemia, myocarditis, pressure and volume overload or associated with obesity and alcohol abuse (Sowmya 2004; Tansey et al. 2005; Lucena et al. 2007; Schmitt et al. 2007). Fatty infiltration of the myocardium is sometimes an incidental finding during surgery or necropsy. It can also be present in healthy subjects and reflects a normal physiological process of involution that occurs with ageing (Pantanowitz 2001; Tansey et al. 2005; Poirier et al. 2006). Interestingly, as an autopsy finding, it is detected in approximately 50% of cases (Lucena et al. 2007). Heart lipomatosis is also found in animals. Findings in caged birds can show some similarities with those seen in human necropsies (Krautwald-Junghanns et al. 2004). In dogs and cats, with the exception of a single case of atrial adipofibrosis in a dog (Une et al. 1998), ARVC is the only described type of heart lipomatosis. It can lead to heart failure, arrhythmia and in rare cases, sudden death. The purpose of this review is

to describe heart lipomatosis in domestic animals with reference to the updated human classification.

2. Heart lipomatosis

Adiposity of the heart, also known as *adipositas cordis, adipomatosis cordis, cor adiposum* and *lipomatosis cordis* is described as a progressive and degenerative diffuse infiltration of adipose tissue in the myocardium (Sowmya 2004; Lucena et al. 2007). Fatty replacement of the myocardium is a peculiar condition that has been reported to occur primarily in the right side of the heart (Macedo et al. 2007). Fatty tissue is normally present on the epicardial surface of the right ventricle and around the coronary blood vessels in humans and animals (Figure 1) (Fontaine et al. 1999; Macedo et al. 2007). Furthermore, minor foci of fat are also located subepicardially in the free walls of the atria and around the two appendages. As the amount of epicardial fat increases, it progressively fills the space between the ventricles, sometimes covering the entire epicardial surface (Tansey et al. 2005). Abundant fat can be found in guinea pigs, rabbits, larger mammals (i.e., pigs) and humans. This is not true, however, for all species. In laboratory rats and mice, epicardial fat is either absent, or found sparingly (Iacobellis et al. 2005; Tansey et al. 2005). In the past, it was assumed that epicardial fat had a role in mechanically protecting the heart from blunt trauma (Iacobellis et al. 2005). However, this view has changed in the last few years, after the discovery of the importance of the epicardium in metabolic activities, due to its richness in free fatty acids, a number of bioactive molecules, such as adiponectin, resistin, and inflammatory cytokines (Iacobellis et al. 2005).

The proportion of fatty tissue varies with age and nutritional status (Basso and Thiene 2005; Tansey et al. 2005); in some instances the ratio of fat to myocardium weight in the right side of the heart is more than three times that of the left side (Iacobellis et al. 2005). Interestingly, there is little evidence of a correlation between the extent of epicardial fat and overall adiposity. There is no

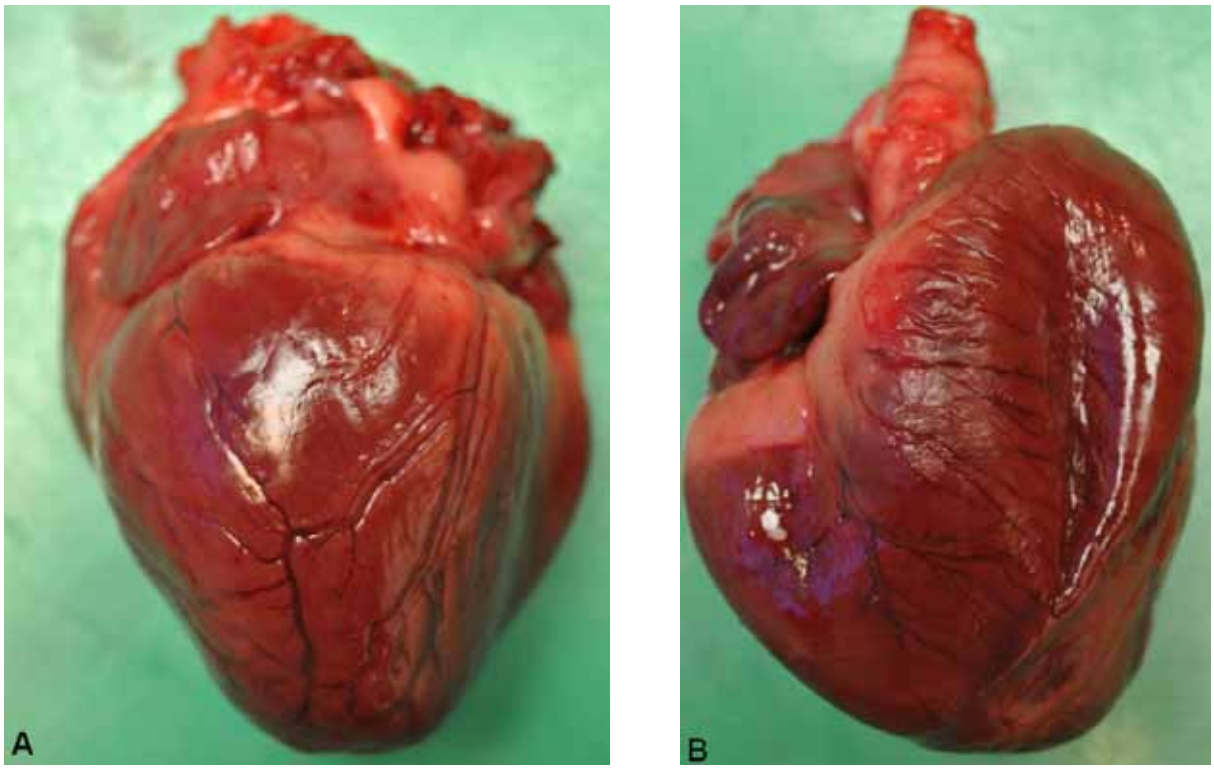

Figure 1. Macroscopic appearance of the epicardial surface in a young dog. **A** = left side, **B** = right side. In both views the fat distribution is limited to the atrioventricular and interventricular grooves, and along the major coronary branches; however, a large area of fatty tissue is visible on the right side (courtesy of Dr. Pyszko. Institute of Anatomy, Histology and Embryology, Faculty of Veterinary Medicine, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic)

relationship between epicardial fat mass and the abundance of adipose tissue in other fat depots in a variety of wild and domesticated animals (Tansey et al. 2005; Verberkmoes et al. 2007).

For many years, the "fatty heart" has been considered the most frequent cause of cardiac sudden death in humans; in fact, fatty infiltration of the right ventricle has been considered *per se* a sufficient morphologic hallmark for certain diseases like ARVC (Basso and Thiene 2005), and it is know recognised that total ventricular fat weight is significantly greater in diseased hearts (Tansey et al. 2005). However, it is still undetermined how much fatty replacement is necessary to justify the diagnosis of heart lipomatosis since some degree of adipose tissue is considered normal (Gerlis et al. 1993).

Heart lipomatosis is seen more commonly in elderly people and animals, and is usually not accompanied by any other major abnormal findings. In these cases, fatty tissue can be found minimally interspersed within the right ventricular myocardial fibres without evidence of fibrosis or inflammation (Tansey et al. 2005; Macedo et al. 2007). The cause of the abundance of right ventricular fat is unknown. It is found in more than half of normal hearts at necropsy (Lucena et al. 2007), and is possibly associated with obesity (metabolic syndrome) and sedentary lifestyle (Iacobellis et al. 2005; Macedo et al. 2007). A similar proportion has been reported for psittacine caged birds due in part to high-energy diets or excessive food combined with restricted exercise (Krautwald-Junghanns et al. 2004).

3. Pathophysiology

The initial presence of fatty tissue in the heart is most likely not caused by an infiltrative process but rather by a metaplasic phenomenon (Fontaine et al. 1999). The fatty tissue can be interspersed within the right ventricular myocardial fibres without causing fibrosis or signs of inflammation (fat dissociation syndrome) (Fontaine et al. 1999; Macedo et al. 2007). Fat gradually accumulates between muscle fibres resulting in myocyte degeneration and cardiac dysfunction. Small irregular aggregates and bands of adipose tissue can separate myocardial cells, which is a potential result of pressure-induced atrophy from the intervening fat. It is believed that diffuse and massive fatty infiltration mainly in the sub-epicardial fat might interfere with ventricular relaxation and ventricular diastolic filling, leading to haemodynamic changes similar to restrictive cardiomyopathy (Pantanowitz 2001; Sowmya 2004).

Fatty tissue infiltration in all susceptible species can cause electrical instability, resulting in life-threatening supraventricular and ventricular arrhythmias, and in some instances valvular dysfunction (Pantanowitz 2001). These phenomena can lead to progressive structural and functional abnormalities of the myocardial tissue. These changes eventually lead to chronic heart failure and in some patients to sudden cardiac death (Ochoa 1972; Kittleson 1998; Pantanowitz 2001; Protonotarios and Tsatsopoulou 2004; Sowmya 2004; Maxie and Robinson 2007; Oxford et al. 2007). The mechanism by which fatty infiltration promotes arrhythmogenicity and causes sudden death has never been well addressed. However, it is thought that the infiltrating fat may enhance automaticity. Also, there is atrophy and degeneration of adjacent myocardial cells, reducing the number of sites or area of intercellular communication, which can cause a delay in the intraventricular transmission of impulses, with subsequent development of re-entrant ventricular arrhythmias (Pantanowitz 2001; Oxford et al. 2007). Additionally, the fatty tissue can induce myocardial toxicity due to the release of certain free fatty acids that can induce arrhythmias and apoptosis of cardiomyocytes, a process known as *cardiomyopathy of obesity* (Poirier et al. 2006).

3.1. Lipomatous hypertrophy

Lipomatous hypertrophy (LH) is a benign infiltration of non-encapsulated adipose tissue (both foetal and adult type) within the atrial septum (Xanthos et al. 2007). This abnormality has no clear cause; however, the condition has been associated with age and obesity, and is more frequent in female patients. It can be an incidental finding during a variety of cardiac imaging procedures or at necropsy (Cunningham et al. 2006; Verberkmoes et al. 2007; Xanthos et al. 2007). These lesions have been associated with atrial arrhythmias, sudden cardiac death, congestive heart failure, compromised vascular structures, and valvular disruption. Furthermore, it is possible for LH in the heart to even undergo malignant transformation (Pantanowitz 2001). The condition has not been described in animals.

3.2. Fatty tissue tumours

Primary heart tumours are very rare. Primary cardiac lipomas are thus extremely rare benign tumours of the heart that originate in the subepicardial, subendocardial, pericardial or intramural adipose tissue, and are usually encapsulated (Wiese et al. 2001; Gaerte et al. 2002). The most common sites of cardiac lipomas are the right atrium, left ventricle, and interatrial septum (Wiese et al. 2001).

Lipomatous lesions are initially identified as incidental masses or from clinical sequelae caused by mass effect, arrhythmia, vascular obstruction, or valvular compromise (Wiese et al. 2001). The risk of incidence increases with age (Baker and Kreeger 1987; Kolma et al. 2002). In the veterinary literature, such lesions have only been described in dogs and horses in which infiltrative processes were the defining feature.

Malignant lipomas (liposarcomas), which originate from the right side of the heart, are probably one of the rarest sarcomas of the heart. Liposarcomas metastatic to the heart have been reported, and are likely far more frequent than primary cardiac liposarcomas (Cunningham et al. 2006). Hibernomas are neoplasms derived from foetal brown adipose tissue. In spite of the fact that they often originate from skeletal muscles and subcutaneous tissues (Ochoa 1972) they can also be located periaortally (Gaerte et al. 2002). Reports of hibernomas in animals are scant. They have been reported in the dog (Ochoa 1972), rhesus monkey and rat (Al Zunaidy and Finn 1983). Since adult domestic animals do not have brown fat, or intracapsular tissue (the so-called hibernating gland), it is probable that these tumours resembling brown fat represent a variant of lipomas.

3.3. Arrhythmogenic right ventricular cardiomyopathy

ARVC is a localised-to-diffuse fatty infiltration of the myocardium leading to fibrosis, myocarditis and degenerative changes in myocytes (Mallat et al. 1996; Basso et al. 2004; Sowmya 2004). This disease has been described in humans, dogs and cats. It is progressive, starting in the epicardium and eventually extending to the endocardium, becoming transmural (Corrado et al. 2000). At the initial stages, the abnormalities in the right ventricle, such as dilatation and aneurysms are localised to the "triangle of dysplasia" (right ventricular outflow tract, posterior wall and apex) (Gerlis et al. 1993; Fontaine et al. 1998; Corrado et al. 2000; Protonotarios and Tsatsopoulou 2004; Fernandez del Palacio et al. 2001).

In humans, dogs and cats, ARVC may also be associated with infiltration of the left ventricle; however, because of its minor involvement, left ventricular failure is not often observed (Fontaine et al. 1998). Involvement of the ventricular septum is rare, probably because it is not a subepicardial structure (Thiene et al. 2007). Involvement of the atria has also been only reported in human beings, dogs and cats (Fernandez del Palacio et al. 2001; Maxie and Robinson 2007; Agudelo et al. 2011).

Two types of ARVC have been suggested: one characterized by a 'fatty pattern', in which fat infiltration and dilatation of the right ventricle are the main features (Basso et al. 2004; Tansey et al. 2005), and the other, characterised by a 'fibrofatty pattern' where fat infiltration, and inflammation lead to degeneration and necrosis of myocytes. An alternate view, suggests that these two types may represent consecutive stages of the disease, where myocarditis with consequent myocyte death and repair by fibrosis may transform the purely fatty to the fibrofatty form (Tansey et al. 2005). In a retrospective study of human cases, the two pathological patterns (fatty (40%) and fibrofatty (60%) were identified (Basso et al. 1996). In dogs, the 'fatty pattern' represents two thirds of reported cases (Kittleson 1998). On the other hand, in cats the 'fibrofatty pattern' predominates, and is associated with extensive right ventricular myocardial loss, replacement fibrosis, wall thinning and aneurysms (Basso et al. 2004; Harvey et al. 2005). In humans certain viruses (picornavirus, retrovirus, hepatitis C virus, adenovirus, herpesvirus, coxsackie A-B, influenza A-B, flavivirus, among others) (Wang et al. 2007) have been detected in the myocardium of some ARVC patients leading to the claim of an infective aetiology of the disease.

Familial occurrence, genetic abnormality and activated apoptosis are proposed as aetiological factors for this condition in humans, dogs and cats (Mallat et al. 1996; Fox et al. 2000; Basso et al. 2004; Oyama et al. 2008). In humans an autosomal dominant mode of inheritance has been demonstrated in nearly 50% of ARVC cases (Corrado et al. 2000). The same genetic pattern of inheritance has been identified in Boxer dogs (Hyun and Filippich 2006). Loss of myocardial cells through apoptosis is, at

least in part, a primary process that precedes the filling of the acellular space with fat and fibrous tissue in the absence of an inflammatory reaction. The triggering factors for apoptotic myocardial cell death in ARVC remain to be elucidated. Some evidence from *in vitro* and *in vivo* studies in animals suggests that hypoxia, reperfusion injury, inflammation (related to the production of inflammatory cytokines), and myocardial dystrophy (which might reflect a genetically determined atrophy and abnormal levels of resting tension), are possible triggers for apoptosis in cardiomyocytes (Mallat et al. 1996; Corrado et al. 2000; Fox et al. 2000; Protonotarios and Tsatsopoulou 2004).

Myocardial cells are differentiated bipolar cells, connected by intercalated discs where adherence junctions, desmosomes and gap junctions are located. Adherence junctions and desmosomes provide mechanical connection, while gap junctions connect the cells electrically. Plakoglobin is an intracellular protein component of adherence junctions and desmosomes. Plakophilin is another desmosomal protein with properties similar to plakoglobin. Desmoplakin is also a cytoplasmic protein of the desmosomes that interlinks plakoglobin or plakophilin with desmin intermediate filaments. Defects in these proteins can result in reduced cell adhesion, particularly under conditions of increased mechanical stress, leading to cell isolation and death, progressive loss of myocardium and fatty replacement (Meurs 2004; Protonotarios and Tsatsopoulou 2004). Several studies in humans have located two recessive forms of the genes encoding the proteins plakoglobin and desmoplakin, and three genes for the dominant form, encoding desmoplakin, plakophilin and ryanodine. Apart from their role in mechanical connection these proteins have also been shown to have a role in signalling to the nucleus, which can even lead to apoptosis. Mutations within the desmosomal genes associated with the development of ARVC in humans do not appear to cause ARVC in Boxer dogs (Basso et al. 2004; Meurs 2004; Meurs et al. 2007).

Ryanodine is sarcoplasmic reticulum protein that contributes to intracellular calcium transport, and is required mainly for cardiac excitation-contraction. Calstabin2 stabilises ryanodine preventing Ca^{2+} leakage from the sarcoplasmic reticulum during diastole, which can trigger ventricular tachyarrhythmias, and abnormal excitation-contraction coupling (Protonotarios and Tsatsopoulou 2004; Maxie and Robinson 2007; Oyama et al. 2008). More recently, a depletion of calstabin2 was found in the hearts of Boxer dogs with ARVC indicating a specific molecular mechanism with direct pathophysiological implications for the canine disease (Maxie and Robinson 2007; Meurs et al. 2007).

3.4. Muscular dystrophies

Uhl's disease is an anomaly characterised by severe attenuation and fibrosis of the right ventricular myocardium (referred to as parchment heart) and in some instances leading to apposition of endocardium with epicardium without intervening myocardium and minimal fatty tissue deposition within (Une et al. 1998; Sowmya 2004). It is a cause of cardiac failure and sudden death in human neonates and young adults. In animals this condition has been found in a cat and in a Coon Pastel mink; however, the pathological descriptions resemble ARVC rather than Uhl's disease. Recently, apoptosis was reported as a possible mechanism for the loss of myocardial cells in human beings with Uhl's anomaly (Mallat et al. 1996; Fontaine et al. 1998).

In other progressive muscular dystrophies, myocardial fibrosis and adiposis are often observed (atrioventricular dystrophy). A cardiomyopathy has been recognized in the *xmd* dog (X-linked muscular dystrophic dog), used as an animal model of human Duchenne-type muscular dystrophy (DMD) (Cooper at al. 1988). DMD is characterized by skeletal muscle fibrosis and adiposis, and is caused by a defective dystrophin (X chromosome) gene. Becker muscular dystrophy is a milder form of DMD, with defects in the same gene (Valentine et al. 1989). However, in affected humans and dogs, lesions are reportedly most severe in the left ventricular papillary muscle and the apical free wall, whereas the right ventricular free wall and atria are rarely involved (Valentine et al. 1989; Une et al. 1998). Other dystrophies such as fascioscapulohumeral-type muscular dystrophy and Emery-Dreifuss muscular dystrophy also lead to enlargement of the left atrium and attenuation of the atrial wall with fibrosis and fatty tissue deposition in rats, dogs and cats (Une et al. 1998; Gavaghan et al. 1999; Hyun and Filippich 2006).

Persistent atrial standstill (PAS) is a very rare outcome in human beings and animals with marked atrial lesions secondary to chronic cardiac disease, or neuromuscular disease involving both cardiac and skeletal muscles (Gavaghan et al. 1999). It can involve degen-

eration (fibrosis and fatty infiltration) of the specialised conduction tissue, including the sinus node, AV node, and His-Purkinje system. PAS has been associated with fascioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophy and Charcot-Marie-Tooth muscular dystrophy in humans (Gavaghan et al. 1999). The clinical presentation also includes arrhythmias (predominantly heart blocks, and atrial and ventricular arrhythmias), mitral valve prolapse (related to papillary muscle dysfunction).

3.5. Other heart lipomatoses

Alaskan sled dogs, which died suddenly during racing, were found to have marked fibrosis or fatty infiltration of the sinus node, AV node, AV bundle, and bundle branches, and focal scarring of the left ventricle. These were similar to the pathological findings in and around the conduction system in cases of sudden death in humans (Bharati et al. 1997; Maxie and Robinson 2007). Fatty metaplasia describes the replacement of fat in the myocardium by scar tissue. Metaplasia can be a consequence of hypoxia, ischaemia or infarction. Fatty changes can be seen in the presence of myocardial fibrosis. In addition there may be a decrease and in some instances disappearance of myocardium that also can occur secondary to cardiac inflammation (Schmitt et al. 2007). A relationship between fatty infiltration of the myocardium and chronic hypoxia has also been found. Under hypoxic conditions, fatty acid oxidation decreases, and when intracellular lipids are no longer metabolised by mitochondria, they are extruded and subsequently phagocytosed (Pantanowitz 2001). This condition rarely is associated with acute heart failure; however, it is a common histological finding in explanted hearts of patients with ischaemic heart disease, idiopathic dilated cardiomyopathy, or chronic valvulopathy (Schmitt et al. 2007).

4. Conclusions

With a few exceptions, there are enormous similarities in the cardiac fatty changes observed in human beings and domestic animals. This offers a unique opportunity for observing the natural process of this special group of diseases in animal models that can widen our understanding of their pathophysiology, diagnostics and therapeutics.

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Corresponding Author:

Carlos F. Agudelo, University of Veterinary and Pharmaceutical Sciences, Faculty of Veterinary Medicine, Clinic of Dog and Cat Diseases, Department of Internal Medicine, Palackeho 1/3, 612 42 Brno, Czech Republic
E-mail: cagudelo@vfu.cz