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SPONTANEOUSLY ARISING DISEASE

# Unexpected Cardiac Death During Anaesthesia of a Young Rabbit Associated with Fibro-fatty Replacement of the Right Ventricular Myocardium

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## Summary

A 6-month-old female pet rabbit was presented for routine ovariectomy. The pre-anaesthetic evaluation was unremarkable and no anaesthetic complications occurred during the procedure. However, at the end of the surgery, the rabbit suddenly showed acute bradycardia and cardiac death. Necropsy examination revealed marked dilation of the right ventricle, associated with diffuse thinning of the right ventricular free wall. Gross and histopathological findings were suggestive of a congenital dilated cardiomyopathy characterized by fibro-fatty replacement of the right ventricular myocardium. Similar myocardial lesions have not been previously described in rabbits, although they have been documented in myocardial diseases of man, dogs, cats, cattle, horses and chimpanzees.

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Cardiac disease is recognized increasingly in domestic rabbits and cardiomyopathy is a common post-mortem finding in older rabbits (Huston, 2004). Congenital heart disease in rabbits is reported rarely and little is known about the pathogenesis of naturally occurring heart disease in rabbits, since reports of spontaneously arising heart disease are usually sporadic (Huston, 2004).

The present case describes a 6-month-old female pet rabbit, 1.15 kg in body weight that was presented for routine ovariectomy. The animal had been vaccinated against myxomatosis and rabbit viral haemorrhagic disease and no previous signs of illness were reported. On physical examination, the rabbit was bright, alert and well hydrated. The mucous membranes were pink with normal capillary refill time.

Findings on oral examination, thoracic auscultation and abdominal palpation were within normal limits. The anaesthetic protocol included sedation and analgesia by subcutaneous administration of medetomidine (0.1 mg/kg), butorphanol (0.2 mg/kg) and ketamine (10 mg/kg), before isoflurane mask induction of anaesthesia. The patient was then intubated and maintained on isoflurane gas. No anaesthetic complications occurred during the procedure. However, at the end of surgery the rabbit suddenly developed acute bradycardia and died. The owner gave consent for necropsy examination, which revealed severe dilation of the right ventricular chamber (Fig. 1) associated with diffuse thinning (<1 mm) of the right ventricular free wall. An intense and diffuse, acute visceral congestion was also observed.

Samples of the heart and representative tissues of all major organs were fixed in 10% neutral buffered

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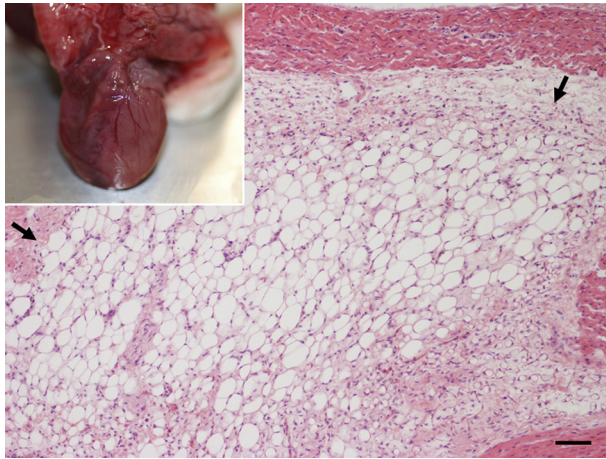


Fig. 1. Histopathology of the right ventricular myocardium. Severe, transmural myocardial replacement by fibro-fatty tissue (arrows). Residual areas of unaffected myocardium are visible at the top and right side of the image. HE. Bar, 66  $\mu$ m. Inset: gross appearance of the heart showing severe right ventricular dilation.

formalin, processed routinely and embedded in paraffin wax. Sections were stained with haematoxylin and eosin (HE) and Masson's trichrome. Histopathological examination of the right ventricular free wall revealed segmental, moderate to severe, transmural myocardial replacement by fibro-fatty tissue, predominantly extending from the subepicardium to the endocardium (Figs. 1 and 2). The remaining myocardial tissue had multiple myocyte abnormalities including wavy cell elongation with dysmetric and dysmorphic nuclei, segmentation of hypercontracted myofibres, myocyte hyper eosinophilia and focal necrosis (Fig. 3). In addition,

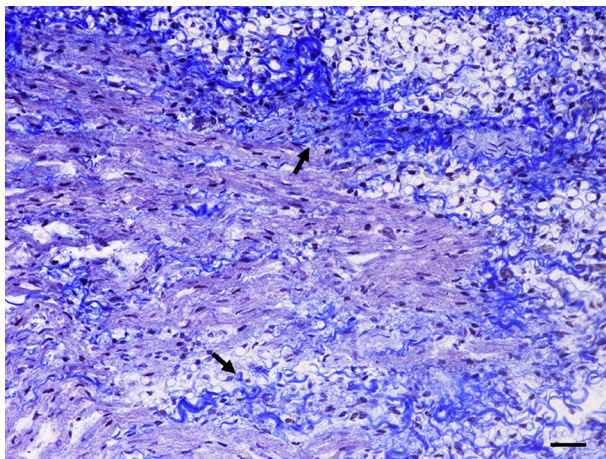


Fig. 2. Histopathology of the right ventricular myocardium. Severe myocardial replacement by fibro-fatty tissue (arrows), with admixed abnormal myocytes. Masson's trichrome. HE. Bar, 33  $\mu$ m.

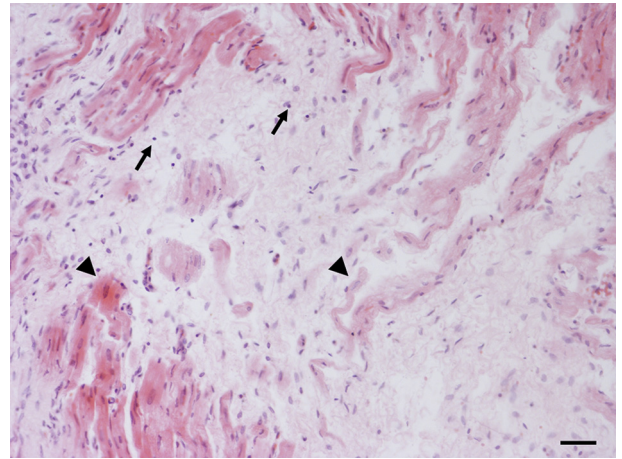


Fig. 3. Histopathology of the right ventricular myocardium. Higher magnification of myocyte abnormalities characterized by wavy cell elongation, myofibre segmentation and multifocal myocyte hyper eosinophilia (arrowheads). A few round inflammatory cells are also admixed with fibrous tissue (arrows). HE. Bar, 33  $\mu$ m.

tion, patchy, mild lymphocytic inflammatory infiltrates were admixed with the fibro-fatty tissue (Fig. 4). Multifocal areas of replacement-type fibrosis were also observed at the right side of the interventricular septum. The left ventricular free wall and the left side of the interventricular septum were not affected. The histopathological examination revealed no significant microscopical lesions in the other organs examined.

These findings, associated with the very young age of the rabbit, suggested a diagnosis of congenital dilated cardiomyopathy characterized by fibro-fatty replacement of the right ventricular myocardium.

Similar lesions have been reported in different myocardial diseases of man and animals. In this

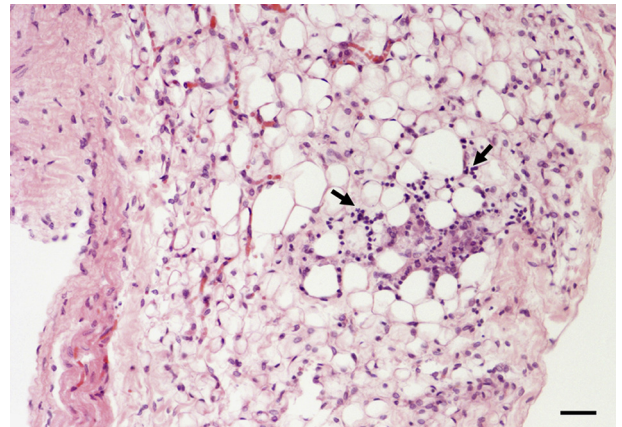


Fig. 4. Histopathology of the right ventricular myocardium. Patchy, mild lymphocytic inflammatory infiltrates (arrows) admixed with the fibro-fatty tissue. HE. Bar, 33  $\mu$ m.

respect, the ‘fatty infiltration—degenerative’ type is one of the two histologically distinct forms of canine dilated cardiomyopathy (Robinson and Robinson, 2016). A particular variant is arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC), an uncommon, spontaneously arising cardiomyopathy that has been described in man, dogs and cats (Ciamarella *et al.*, 2009; Hariu and Carpenter, 2010; Azaouagh *et al.*, 2011). ARVC can be inherited as an autosomal dominant disease with variable penetrance and polymorphic phenotypic expression in man and boxer dogs (Hariu and Carpenter, 2010; Azaouagh *et al.*, 2011). ARVC is a more recently recognized disorder of uncertain origin in cats, with no age or breed predisposition (Ciamarella *et al.*, 2009). ARVC is a unique myocardial disease, primarily affecting the right ventricle, with diffuse or segmental loss of myocytes and replacement by fatty or fibro-fatty tissue (Tabib *et al.*, 2003). The condition is characterized clinically by marked right ventricular dilation and thinning with ventricular arrhythmia, congestive heart failure and/or sudden cardiac death (Azaouagh *et al.*, 2011). It is a well-recognized cause of sudden unexpected death during exercise or perioperatively, especially in apparently healthy young canine and human patients (Basso *et al.*, 2004; Alexoudis *et al.*, 2009; Butcovan *et al.*, 2011). In the present case, sudden cardiac death under general anaesthesia was the first manifestation of the disease, since the rabbit did not previously show episodes of syncope or any other sign of cardiac disease. ARVC is frequently associated with ventricular tachycardia, although bradycardia and episodes of sinus arrest with prolonged ventricular asystole have been also reported in human patients (Takemura *et al.*, 2008).

A dilated cardiomyopathy characterized by myocardial fibro-fatty replacement also occurs in young adult to mature Holstein cattle, with clinical signs particularly referable to right-sided heart failure, although there is no indication of the presence of electrocardiographical abnormalities (Robinson and Robinson, 2016). Furthermore, a similar condition causing sudden and unexpected cardiac death has been described in horses (Freel *et al.*, 2010) and chimpanzees (Tong *et al.*, 2014).

Myocarditis characterized by patchy, mononuclear cellular inflammatory infiltrate has been reported in association with ARVC in human, canine and feline cases (Corrado *et al.*, 1997; Fox *et al.*, 2000; Basso *et al.*, 2004). Inflammation may represent a reactive process following myocyte death, or it could be the result of immune, toxic or infectious mechanisms (Calabrese *et al.*, 2006; Azaouagh *et al.*, 2011). Different types of

cardiotropic viruses have been identified in some sporadic forms of human ARVC, suggesting that these viruses may play a role in the progression of the disease or influence its adverse clinical course (Calabrese *et al.*, 2006). In this respect, infectious myocardial diseases are thought to be rare in pet rabbits, although coronavirus may be associated with cardiomyopathy in this species (Huston, 2004). In the present case, the history and clinical presentation, as well as the gross and histopathological lesions observed, were not compatible with the presence of a viral infection. Hypovitaminosis E, which may cause myocardial dystrophy (Huston, 2004), was also excluded, since the rabbit was fed with a well-balanced diet. Multiple anaesthetic episodes with ketamine combinations have been implicated in causing myocardial necrosis and fibrosis in rabbits (Heard, 2004). In this case, the rabbit did not undergo any previous anaesthetic procedure, making a role for anaesthetic agents as a cause of the lesions observed unlikely.

Although the origin of the cardiac lesions remains uncertain, the very young age of the rabbit is suggestive of a congenital myocardial disease, which should be taken into consideration in the differential diagnosis of sudden cardiac death in rabbits. In particular, when sudden unexpected or perioperative cardiac death occurs as a result of refractory arrhythmias or asystole in rabbits, necropsy and histopathological examinations should be performed in order to confirm/exclude the presence of myocardial lesions.

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### Conflict of Interest Statement

The authors declare that they have no conflict of interest with respect to the publication of this manuscript.

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