Cardiac mitochondrial and cytoskeletal changes in feline hypertrophic cardiomyopathy: An ultrastructural study

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Feline hypertrophic cardiomyopathy (fHCM) is the most common heart disease in cats. HCM is considered an inherited disease of the sarcomere and fHCM has been linked to mutations in one sarcomere protein i.e. MYBPC3. However, the pathophysiologic mechanisms behind disease development and progression are largely unknown. In this study we investigate whether mitochondrial morphological changes in the myocardium accompany the findings of mitochondrial dysfunction and enhanced oxidative stress formation that we have recently done in fHCM.

Myocardial tissue from the left ventricle (LV) was obtained immediately after euthanasia from 7 cats, diagnosed with primary HCM on echocardiography (3 Maine Coon, 2 British Shorthair, 1 Exotic Shorthair, 1 Norwegian Forest cat) and eight age-matched control (CON) cats (5 Maine Coon, 3 Norwegian Forest cats). Ultrastructural examination was performed by the use of transmission electron microscopy.

In HCM cats, marked ultrastructural changes of the cardiomyocytes were observed. The population of subsarcolemmal mitochondria (SSM) was absent in large cellular areas in cats with moderate and severe LV hypertrophy. Flattening of the sarcolemma was a common finding, causing disorganization of the T-tubular system. There were no apparent changes of the interfibrillar mitochondria (IFM) in HCM cats. Additional changes in cardiomyocytes from cats diagnosed with fHCM included disorganization of myofibrils, remodeling of sarcomeres, convolution of gap junctions, accumulation of intracellular Z-disc material, perinuclear lipofuscin granula and extensive extracellular deposits of collagen.

In healthy mammalian cardiomyocytes, the T-tubular system upholds cellular structure, prevents mitochondrial reticulum formation and provides calcium, oxygen and substrates, necessary for the normal functioning muscle. Disorganization of the sarcolemma and T-tubular system may cause the depletion of SSM. Possible mechanisms are induction of disruption or atrophy of the mitochondria or, alternatively, by changing mitochondrial fusion-fission dynamics.

Moreover, calcium cycling and substrate supply are likely compromised by the observed structural changes. We propose this to be related to mitochondrial dysfunction and oxidative stress formation that occurs in fHCM, however a causative relationship remains unknown.

In conclusion, morphological changes of mitochondria and extra-sarcomeric structures are common in fHCM, regardless of breed, genotype and phenotypic disease expression. Moreover, mitochondrial subpopulation-specific changes occur in fHCM with depletion of SSM.

Ultrastructural and functional changes of cardiac muscle mitochondria are considered important molecular mechanisms, responsible for the development and progression of fHCM and may be relevant future treatment targets.