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Role of exercise in arrhythmogenic cardiomyopathy

Martherus R, Jain R, Takagi K, Mendsaikhan U, Turdi S, Osinska H, et al. Accelerated cardiac remodeling in desmoplakin transgenic mice in response to endurance exercise is associated with perturbed Wnt/β-catenin signaling. **Am J Physiol Heart Circ Physiol 2015 [Epub ahead of print] http://doi.org/9w5**

Arrhythmogenic ventricular cardiomyopathy is one of the most frequent causes of sudden death, especially during endurance exercise. Forty percent of cases present with mutations, mostly in genes encoding for desmosomal proteins, generally by dominant autosomic inheritance and variable penetrance. The remaining 60% is estimated to be associated with unidentified genes or acquired causes. Despite its clinical relevance, the pathophysiological mechanisms involved have not been fully elucidated.

Desmosomes are structures which participate in cellular adhesion and are abundant in tissues subject to constant mechanical tension, as the skin and myocardium. The expression of anomalous proteins in desmosomes of patients with cardiomyopathy decreases their adhesivity favoring myocyte loss, fibroadipose substitution and inflammation. One of the most important desmosome components is desmoplakin. Studies performed in mice with mutated forms of this protein have shown the development of characteristics similar to ventricular arrhythmogenic cardiomyopathy. Originally described in the right ventricle, arrhythmogenic cardiomyopathy has expanded to forms affecting mainly the left ventricle, called left-dominant arrhythmogenic cardiomyopathy.

In the present study, the team led by Dr. Jeffrey Towbin used transgenic mice expressing desmoplakin point mutation. These animals developed arrhythmogenic cardiomyopathy at 6 months of life, similar to the one affecting humans. In this model, the authors attempted to establish whether endurance exercise in mice overexpressing desmoplakin point mutation accelerated the emergence of arrhythmogenic cardiomyopathy.

Transgenic animals submitted to exercise revealed a dilated right ventricle and wall thinning. In addition, focal lipid infiltrations in the right ventricle and cytoplasmic desmoplakin, plakoglobin and connexin-43 aggregates were observed. These aggregates were coincident with intercalated disk, intermediate filament and microtubule disruption.

The research performed by Dr. Towbin shows another interesting finding: during exercise signicant changes were observed in the Wnt/β-catenin signaling pathway, which is implied in the promotion of new cell growth and prevention of fat deposits.

The study suggests that changes in cell-to-cell binding occur before functional disturbances in the heart. This may help identify subjects carrying the mutation before developing symptoms of arrhythmogenic cardiomyopathy, providing the opportunity of better strategies to prevent complications induced by exercise. In addition, it opens a window for the development of pharmacological strategies targeting Wnt/β-catenin.