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Heart Failure

RELATIVE IMPORTANCE OF TITIN AND COLLAGEN FOR MYOCARDIAL STIFFNESS IN METABOLIC RISK-INDUCED HEART FAILURE WITH PRESERVED EJECTION FRACTION

Poster Contributions
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Background: High diastolic left ventricular (LV) stiffness is an important contributor to Heart Failure with preserved Ejection Fraction (HFpEF). Metabolic comorbidities such as obesity and diabetes type 2 increase diastolic LV stiffness. How metabolic risk affects molecular mechanisms responsible for diastolic LV stiffness remains unclear.The relative contributions of the sarcomeric protein titin and collagen were therefore investigated in a type 2 diabetes HFpEF rat model.

Methods: Obese Zucker spontaneously hypertensive diabetic fatty rats were fed with normal (ZSF1 Ob) or high fat diet (ZSF1 ObHF) and sacrificed at 20 weeks of age. Hypertensive lean ZSF1 and Wistar Kyoto rats served as controls. ZSF1 Ob and ZSF1 ObHF rats had developed HFpEF evident from high LVEDP at identical LVEDV. Passive tension (Fpassive) was measured in single cardiomyocytes before and after protein kinase G (PKG) administration. Expression and phosphorylation of titin was assessed by electrophoresis. PKG activity and cyclic guanosine monophosphate (cGMP) concentration were determined in tissue homogenates. In LV papillary muscle strips, Fpassive was measured before and after depolymerization of thick and thin filaments to discern contributions of titin and collagen to Fpassive.

Results: Fpassive was higher in ZSF1 Ob and ZSF1 ObHF cardiomyocytes compared to controls. PKG lowered Fpassive to control value. Titin expression was unaltered, while total titin phosphorylation was lower in ZSF1 Ob and ZSF1 ObHF. PKG activity and cGMP concentration were lower in obese rats. In strips, titin-based Fpassive was increased in both obese groups. Collagen-based Fpassive was similar in all groups at sarcomere lengths 1.9 to 2.2μm, but rose sharply at higher lengths. A ratio reflecting the relative contributions of titin and collagen to Fpassive fell at larger sarcomere lengths in all groups and was lower in obese rats at each sarcomere length.

Conclusions: A titin phosphorylation deficit importantly contributes to the high myocardial stiffness in a metabolic risk-induced HFpEF model. Metabolic risk also affects collagen deposition evident from a larger relative contribution of collagen at each sarcomere length.