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Student: Stockner Alina

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Regulation of lipid alterations in heart failure with preserved ejection fraction

Alina Stockner; Viktoria Trummer-Herbst; Mahmoud; Abdellatif; Simon Sedej

Obesity and aging are major risk factors contributing to the pathogenesis of heart failure with preserved ejection fraction (HFpEF), a predominant form of cardiac insufficiency with only a limited number of therapies. High levels of fatty acids and toxic lipid species which are present in obesity have been associated with HFpEF. Recently, the interorgan crosstalk between the white adipose tissue (WAT) and the heart has emerged as a novel therapeutic target to reduce the growing burden of this disease. In this regard, we hypothesize that pharmacological inhibition of adipose triglyceride lipase (ATGL) by Atglistatin (ATGLi) and thus reducing rates of lipolysis in WAT decreases lipotoxic effects and ameliorates the HFpEF phenotype. For this purpose, to generate experimental HFpEF driven by obesity and hypertension, respectively, 6-weeks-old C57BL6/J mice were administered a high-fat diet (HFD) and the nitric oxide synthase inhibitor L-NAME in the drinking water for 8 weeks. Upon the development of HFpEF phenotype, mice fed HFD and L-NAME were treated or not with ATGLi for 4 weeks. In vivo examinations, including weekly monitoring of body weight, transthoracic echocardiography and non-invasive blood pressure measurements, were used to analyze the effect of ATGLi on cardiometabolic health. Compared to control mice fed standard diet, HFpEF mice had significantly increased body weight gain, which was markedly reduced by ATGLi. Preliminary data from echocardiography showed improved diastolic dysfunction in response to ATGLi treatment, suggesting that inhibition of lipolysis in WAT has the potential to ameliorate the pathogenesis of HFpEF in mice. Future studies will focus on the mechanisms by which ATGL improves cardiometabolic health in experimental HFpEF.