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Thyroid

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Treatment of Heart Failure with Preserved Ejection Fraction (HFpEF) with Low and High Dose of Triiodothyronine: an Animal Model of Metabolic Syndrome with HFpEF

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Introduction: Low levels of triiodothyronine (T3) are common in patients with heart failure (HF). It has been proposed that the decreased levels of T3 contribute to metabolic and cardiac dysfunction in HF. We aimed to evaluate the effects of treatment with low dose and high dose of T3 in an animal model of HF with preserved ejection fraction (HFpEF). **Materials and Methods:** We evaluated four groups: ZSF1 Lean (Lean-Ctrl, n=8), ZSF1 obese (rat model of metabolic syndrome with HFpEF, HFpEF-Ctrl, n=13), ZSF1 obese supplemented with a replacement dose of T3 (initially 0.04mg/ml, increased to 0.06mg/ml after 4 weeks; HFpEF-T3high, n=8), and ZSF1 Obese supplemented with a low-dose of T3 (0.03mg/mL; HFpEF-T3low, n=8). T3 was supplemented in drinking water from week 13 to 24. The animals were submitted to anthropometric and metabolic evaluation, echocardiography, VO2max evaluation, hemodynamic evaluation, single cardiomyocyte evaluation, and myocardial tissue collection at 24 weeks. **Results:** HFpEF-Ctrl animals had lower serum and myocardial thyroid hormone levels than Lean-Ctrl. Treatment with low dose and high dose of T3 did not correct serum T3 levels, but increased myocardial T3 levels, with normalization of myocardial T3 levels in the HFpEF-T3high group. In comparison to HFpEF-Ctrl, body weight was significantly decreased in HFpEF-T3low and HFpEF-T3high groups (616±39g, 572±24g and 535±18g respectively, $p<0.001$). An improvement in glucose metabolism was observed only in HFpEF-T3high, with a decreased AUC of glucose during OGTT and insulin tolerance test. Both treated groups presented an improvement in diastolic function (with decreased isovolumetric relaxation time) and systolic function (with increased peak systolic velocity and decreased ejection time) comparing to HFpEF-Ctrl. These results were supported by enhanced Ca2+ transients during diastole and sarcomere relaxation. Comparing with

HFpEF-Ctrl, animals treated with T3 had higher myocardial expression of the calcium transporter RYR2, of the transcriptional coactivator PGC-1α, and of the α-myosin heavy chain (MHC), with a lower expression of β-MHC. VO2max was improved with low-dose and high-dose T3 compared with HFpEF-Ctrl. Comparing with HFpEF-Ctrl, heart rate was increased with high-dose (277.9±30.2 vs 313.5±35.8, p=0.049) but not significantly with low-dose (277.9±30.2 vs 299.8±30.9 bpm, p=0.13). Mortality was increased in the HFpEF-T3high comparing with the other groups (no animals died during the protocol in the Lean-Ctrl, HFpEF-Ctrl and HFpEF-T3low groups; three animals had sudden death in the HFpEF-T3high group). **Conclusion:** Treatment with T3 improves metabolic function, myocardial calcium handling, diastolic and systolic function, and exercise capacity in this animal model of HFpEF. While the low dose was well tolerated and safe, the high dose was associated with increased heart rate and a higher risk of sudden death. Modulation of thyroid hormones may be a potential therapeutic target in HFpEF; however such approaches must take into account a narrow therapeutic window of T3 in HFpEF.

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