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Heart Failure

Trimetazidine, a Metabolic Modulator, Has Cardiac and Extracardiac Benefits in Idiopathic Dilated Cardiomyopathy

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Abstract

Background— The anti-ischemic agent trimetazidine improves ejection fraction in heart failure that is hypothetically linked to inhibitory effects on cardiac free fatty acid (FFA) oxidation. However, FFA oxidation remains unmeasured in humans. We investigated the effects of trimetazidine on cardiac perfusion, efficiency of work, and FFA oxidation in idiopathic dilated cardiomyopathy.

Methods and Results— Nineteen nondiabetic patients with idiopathic dilated cardiomyopathy on standard medication were randomized to single-blind trimetazidine (n=12) or placebo (n=7) for 3 months. Myocardial perfusion, FFA, and total oxidative metabolism were measured using positron emission tomography with [^{15}O]H_2O, [^{11}C]acetate, and [^{11}C]palmitate. Cardiac function was assessed echocardiographically; insulin sensitivity was assessed by the homeostasis model assessment index. Trimetazidine increased ejection fraction from 30.9±8.5% to 34.8±12% (*P*=0.027 versus placebo). Myocardial FFA uptake was unchanged, and β-oxidation rate constant decreased only 10%. Myocardial perfusion, oxidative metabolism, and work efficiency remained unchanged. Trimetazidine decreased insulin resistance (glucose: 5.9±0.7 versus 5.5±0.6 mmol/L, *P*=0.047; insulin: 10±6.9 versus 7.6±3.6 mU/L, *P*=0.031; homeostasis model assessment index: 2.75±2.28 versus 1.89±1.06, *P*=0.027). The degree of β-blockade and trimetazidine interacted positively on ejection fraction. Plasma high-density lipoprotein concentrations increased 11% (*P*<0.001).

Conclusions— In idiopathic dilated cardiomyopathy with heart failure, trimetazidine increased cardiac function and had both cardiac and extracardiac metabolic effects. Cardiac FFA oxidation modestly decreased and myocardial oxidative rate was unchanged, implying increased oxidation of glucose. Trimetazidine improved whole-body insulin sensitivity and glucose control in these insulin-resistant idiopathic dilated cardiomyopathy patients, thus hypothetically countering the myocardial damage of insulin resistance. Additionally, the trimetazidine-induced increase in ejection fraction was associated with greater β1-adrenoceptor occupancy, suggesting a synergistic mechanism.

Key Words:
- fatty acids
- heart failure
- metabolism
- positron emission tomography
- trimetazidine

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