Trimetazidine in heart failure with preserved ejection fraction: a randomized, double-blind cross-over trial


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Introduction: Impaired myocardial mitochondrial function plays an important role in the pathophysiology of heart failure with preserved ejection fraction (HFpEF). Left ventricular relaxation has a high energy demand, and there is evidence indicative of a causal relationship between observed impaired energy homeostasis and diastolic dysfunction. Improvement of mitochondrial function with metabolism-modulating drugs may be a promising novel therapeutic approach in HFpEF. Trimetazidine – a fatty acid oxidation inhibitor – shifts mitochondrial metabolism towards glucose oxidation, which results in higher mitochondrial oxygen efficiency. In this study we investigated whether trimetazidine improves diastolic function during exercise in HFpEF by improving the myocardial energy homeostasis.

Methods: The DoPING-HFpEF trial was a phase II single-center, double-blind, placebo-controlled, randomized cross-over trial. The study consisted of two treatment periods of three months separated by a 2-week wash-out period (Figure 1). Patients were treated with placebo or trimetazidine three times a day (or twice daily in case of an impaired kidney function). The primary endpoint was change in pulmonary capillary wedge pressure (PCWP) measured with right heart catheterization at multiple stages of exercise. Secondary endpoint was change in phosphocreatine (PCr)/adenosine triphosphate (ATP) ratio, an index of the myocardial energy status, measured with phosphorus-31 magnetic resonance (MR) spectroscopy. Additional exploratory endpoints were 6-minute-walking-distance, diastolic and systolic parameters measured with echocardiography or cardiac MR, NT-proBNP levels, and quality of life.

Results: Twenty-five HFpEF patients were included and completed the trial, 80% of which were included based on previously established elevated (exercise) PCWP, and 20% were included based on diastolic dysfunction grade ≥II on echocardiography and elevated NT-proBNP levels. There was no effect on the primary outcome PCWP at multiple levels of exercise, with an average change in PCWP of 0±4 (SD) mmHg (Figure 2A, P=0.97). Myocardial PCr/ATP in the trimetazidine arm was similar to placebo (Figure 2B, P=0.08). There was no change by trimetazidine in the exploratory parameters 6-minute walking distance, NT-proBNP, overall quality of life, or other parameters for diastolic function measured with echocardiography and cardiac MR. There was no indication of period or cross over effect.

Conclusion: Trimetazidine did not improve diastolic function or myocardial energy homeostasis in patients with HFpEF.

Figure 1. Study design and data examples

Figure 2. Primary and secondary outcomes