Impact of exercise training and testosterone replacement on skeletal muscle atrophy and muscle sympathetic nerve activity in heart failure patients with hypogonadism

Purpose: Testosterone deficiency is common in advanced heart failure (HF) leading to skeletal muscle atrophy. Our hypothesis was that aerobic training alone or associated with testosterone replacement, could reduce skeletal muscle fiber atrophy and muscle sympathetic nerve activity (MSNA), improve body composition, functional capacity and quality of life (QoL) in patients with HF and hypogonadism. **Methods:** Twenty-four patients, functional class III, total testosterone (<271 ng/dL) and free testosterone (<131pmol/L), ejection fraction (EF) <45% (Echocardiography), were randomized into 3 groups: Training (TR, n=9), Testosterone (T, n=8) and Training+Testosterone (TR+T, n=7). Patients performed pre and post 4 months: 1) MSNA, microneurography; 2) Biopsy, immunohistochemistry (vastus lateralis; type I and IIX fibers); 3) Body composition, dual X-ray absorptiometry; 4) Cardiopulmonary exercise on a bike and 5) QoL, Minnesota questionnaire. Exercise training on bicycle, 3 times/week, between anaerobic threshold and respiratory decompensation point, and undecylate testosterone (intramuscular). **Results:** There was no difference between TR, T and TR+T groups for age (54±4, 51±4 and 52±3 years) and EF (28±2, 28±4 and 22±2%), respectively. MSNA decreased within TR+T (49±4 vs. 34±3 bursts/min; P<0.05) and TR (61±4 vs. 32±2 bursts/min; P<0.05). MSNA in bursts/100 heart beats decreased within TR+T group (80±7 vs. 50±4 bursts/100HB; P=0.05). Cross-sectional area (CSA) of type I fibers increased within TR+T group (2.487±329 vs. 3.637±347 µm, P=0.04). CSA of type I fibers increased in TR+T group compared to TR and T (3.637±347 vs. 2.567±238 vs. 2.628±178 µm; P <0.03, respectively). CSA of type IIX fibers was not different between groups. Lean mass increased within TR+T group (58±3 vs. 63±4 kg; P=0.02). Lean mass increased both TR and TR+T groups compared to T group (57±3 vs. 50±3 kg; P <0.001 and 63±4 vs. 50±3 kg; P<0.001, respectively). VO2 peak increased in TR, T and TR+T groups (14.76±1.60 to 18.06±2.26; 18.31±1.87 to 20.34±2.08 and 17.61±1.37 to 20.63±2.72 ml/kg/min; P <0.01, respectively). However, maximal power (Watts) increased in TR+T group (75±6 to 129±20 Watts; P=0.001) and it was higher compared to TR and T groups (129±20 vs. 87±8 vs. 73±18 Watts; P<0.01, respectively). QoL improved in TR and TR+T groups (57±7 to 23±6 and 70±7 to 13±3 score; P<0.03, respectively). **Conclusion:** Although functional capacity improved in all groups, TR+T

reduced skeletal muscle atrophy, decreased MSNA, improved lean muscle mass and QoL. This combined therapy signals a new approach to clinical management in HF patients.