



# Heart failure: a cardiac or a systemic disease?

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According to the American Heart Association, heart failure may be defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or to eject blood. Five million people are estimated to suffer from heart failure worldwide, with over 1 million hospitalizations per year. About 65 000 new cases are diagnosed every year and the estimated economic burden amounts to \$40 billion/year.

The main manifestation of heart failure is fluid retention, leading to pulmonary congestion and peripheral edema, which results in dyspnea and fatigue that may limit exercise tolerance. The first hospitalization for heart failure is associated with a 4% in-hospital mortality rate. After discharge, 30% to 50% of patients die or are rehospitalized within 60 days of admission. Mortality is 20% to 30% after one year and 40% to 50% after 5 years.

This issue of *Heart and Metabolism* offers a great opportunity for a better understanding of the central and peripheral abnormalities contributing to the natural history of heart failure.

The central role of skeletal muscles on symptoms and clinical outcomes is clearly described in the article by **Mario Marzilli** and in the article by **Stephan von Haehling**. Skeletal muscle wasting, which is present in almost 20% of ambulatory patients with chronic heart failure, is associated with reductions in exercise capacity, quadriceps strength, handgrip strength, distance walked during a 6-minute corridor walk, and gait speed.

**Patricia Iozzo** confirms that heart failure is accompanied by defects in muscle oxidative and glucose metabolism, together with a loss in muscle mass and a remarkable intramuscular fat infiltration. These features are related to the degree of exercise intolerance and are partially restored by chronic exercise training. They are also typically present in conditions that predispose to the development of heart failure, indicating that skeletal muscle should be an early prevention target.

**Romualdo Belardinelli** suggests that exercise training is able to maintain peak oxygen consumption (peak  $\dot{V}O_2$ ) at more than 60% of the  $\dot{V}O_{2max}$  in heart failure patients. He also suggests that exercise training is associated with a reduction in major cardiovascular events, including hospitalizations for chronic heart failure and cardiac mortality.

**Gabriele Fragasso** agrees that muscle factors limit exercise capacity independently from central hemodynamics, and suggests that pharmacological manipulation of cardiac substrate utilization with agents that directly inhibit fatty acid oxidation could improve cardiac function and, accordingly, global metabolism efficiency. Trimetazidine, a 3-ketoacyl-coenzyme A thiolase (3-KAT) inhibitor, shifts the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by 3-KAT inhibitors and could be an effective adjunctive treatment in patients with heart failure.

**Marco Guazzi** proposes the cardiopulmonary exercise test as the gold standard for assessing the pathophysiological derangements behind heart failure. Cardiopulmonary exercise tests allow for a

global evaluation of the pulmonary, cardiovascular, muscular, and cellular oxidative systems, which are not adequately reflected through the measurement of individual organ-system function. Accordingly, cardiopulmonary exercise testing is now being used in a wide spectrum of clinical settings for evaluation of undiagnosed exercise intolerance. The test's popularity is increasing due to recent statements and official documents that have provided simplified easy-to-apply reports that may consistently help the practicing clinician with their interpretations and clinical directions.

**Alda Huqi** contributes to this issue with a stimulating analysis of the role of obesity in heart failure. Obesity is often presented as a “starting point” toward negative outcomes; conversely, when an “interventional attitude” with purposeful weight loss is adopted, the tendency can be inverted.

So, with this issue, *Heart and Metabolism* offers, once again, the readers a valuable tool to better understand a relevant clinical problem—heart failure. ■