Heart failure (HF) is a complex multisstep disease in which a number of physiological systems participate. Intense research aims at identifying novel therapeutic options in this disorder, and most of these efforts target pathological processes in the heart (i.e., ventricular remodeling) and the renewal of the failing heart by, for example, stem cell therapy. Additionally, therapeutic modalities targeting systemic mediators such as neurohormones and cytokines have also been developed. However, despite state-of-the-art cardiovascular treatment, chronic HF is a progressive disease with high morbidity and mortality, suggesting that important pathogenic mechanisms remain unmodified by the present treatment modalities.

Skeletal muscle manifestations of HF. Patients with HF experience impaired exercise capacity and muscle fatigue (8). However, this fatigue does not necessarily relate to the degree of myocardial dysfunction, indicating that mechanisms unrelated to a potential peripheral hypoperfusion are of importance. Several mediators of this skeletal muscle dysfunction have been suggested, including chronic beta-adrenergic stimulation and enhanced angiotensin II activity as well as the effects of inflammatory cytokines (e.g., tumor necrosis factor alpha and interleukin 6) and reactive oxygen species (8). Also, insulin resistance, leading to an inability of insulin to promote glucose transport into skeletal muscles, has been proposed as a mediator of skeletal muscle fatigue and wasting during HF, linking these processes directly to the metabolic disturbances in HF patients (7).

Testosterone: a new therapeutic option in HF? Chronic HF seems to be associated with decreased plasma testosterone levels (5), as mentioned in the preceding text. Thus, approximately 25% of men with chronic HF have biochemical evidence of testosterone deficiency, and low levels have been related to disease progression in HF. Moreover, myocardial cachexia, a syndrome with poor prognosis, is characterized by particularly low testosterone levels. On the basis of these issues as well as the suggested role of testosterone deficiency in insulin resistance and loss of muscle strength during HF, treatment that corrects this deficiency has become attractive. In this issue of the Journal, Caminiti et al. (9) show—in a double-blind, placebo-controlled, randomized trial in 70 elderly patients with chronic HF—that intramuscular testosterone supplementation on top of optimal therapy improves functional exercise capacity, muscle strength, insulin, and baroreflex sensitivity. Although the idea has been discussed for several years, only a few clinical trials have examined the effect of testosterone therapy in HF. The first, an uncontrolled open-label trial, found that treatment with oxymetholone improved cardiac function as determined by reduced left ventricular diameter and mass and reduced levels of brain natriuretic peptide (10). In a small double-blinded study, Pugh et al. (11) showed that HF

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patients receiving intramuscular testosterone injections had improved quality of life and functional capacity (walk test). In a follow-up to this pilot study, Malkin et al. (12) examined the effect of testosterone patches and found an improvement in New York Heart Association functional class and exercise capacity in HF patients. The study by Caminiti et al. (9) extends these previous findings in several ways. First, in contrast to some previous studies, they found no effects on left ventricular ejection fraction, suggesting that the effect of testosterone is not secondary to improved myocardial function. Second, although it has previously been reported that testosterone therapy might increase forearm muscle strength, the present study shows improved static and dynamic muscle performance in larger, weight-bearing muscles. Third, the improvement in muscle performance and functional capacity was accompanied by an increase in insulin sensitivity, further underscoring that testosterone deficiency, decreased insulin sensitivity, and impaired muscle performance might represent a pathogenic loop in the progression of the HF syndrome. The authors found that the improved insulin sensitivity was associated with a significant increase in body weight and body mass index, further underscoring that the mechanisms of decreased insulin sensitivity in HF are different from several other disorders, such as in obese patients with metabolic syndrome. Finally, heart failure patients have—simultaneously with neurohumoral activation—an increased peripheral chemoreflex and a decreased arterial baroreflex, and this impaired baroreceptor sensitivity has been associated with poor prognosis (13). Previous studies in animal models have shown that testosterone might improve baroreceptor sensitivity (14), and Caminiti et al. (9) show similar findings in HF patients. A disturbed interaction between CNS and the myocardium is an important feature of chronic HF, and the authors suggest that testosterone deficiency might be involved in the dysregulation of this important axis, potentially acting directly on androgen receptor within brainstem nuclei.

What’s next? The results of the testosterone studies performed thus far suggest a move forward to larger trials. However, several issues remain to be addressed before initiating such studies. First, is testosterone therapy in HF safe? High doses of testosterone might be cardiotoxic, and there are concerns that testosterone treatment might have adverse effects on coronary artery disease (5). However, with the low doses used in HF patients—many of them testosterone-deficient—these potential side effects might be negligible and, for coronary artery disease, possibly outweighed by positive effects on the “metabolic syndrome” of HF. Second, who should receive testosterone therapy? The treatment should most probably be restricted to men. But should a prerequisite be low testosterone levels? The results from the Caminiti et al. (9) study suggest that testosterone-deficient HF patients have a particularly good response to testosterone therapy. It is also conceivable that the side effect profile of testosterone will be better in this group as compared with patients with normal testosterone levels. Most of the patients that have been included in these studies so far have been elderly men, and the conclusions from these trials cannot necessarily be applied to a younger population of HF patients with testosterone levels within normal limits.

Conclusions. Testosterone treatment represents a new therapeutic approach in chronic HF that might have some potential. Studies performed thus far primarily demonstrate improved functional capacity and quality of life, with little or no effects on cardiac function, representing a more “palliative” therapeutic concept (15). However, it is not inconceivable, on the basis of the dynamic interaction between HF comorbidities and the myocardium, that these extra-cardiac effects, at least in the long-term, might translate into not only reduced morbidity but also into improved myocardial performance and reduced mortality. This aspect should be addressed in forthcoming studies.

Reprint requests and correspondence: Dr. Pål Aukrust, Section of Clinical Immunology and Infectious Diseases, Rikshospitalet, Oslo University Hospital, 0027 Oslo, Norway. E-mail: pal.aukrust@rikshospitalet.no.

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