Testosterone Therapy in Women With Heart Failure

“Why Can’t a Woman Be More Like a Man?”*

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In the near half-century since Alan Jay Lerner posed his famous question in the play *My Fair Lady*, investigators have vigorously pursued the basis for sexual dimorphism (1). Behavioral diversity, health outcomes, and longevity are only some of the distinctive features of the sexes often attributed to hormonal differences (2). The dramatic reduction in estradiol in women associated with menopause led to the—apparently obvious—conclusion from epidemiologic and observational studies that estrogen replacement would enhance post-menopausal cardiovascular health. When the converse was shown to be true in a randomized trial, this enhancement was shown to be true in a randomized trial, this conclusion led to a remarkable reversal in the guideline recommendations on hormone replacement therapy (3,4). Because testosterone also declines with age, its replacement has garnered substantial attention, especially among men, where it has been used to enhance lost muscle mass and sexual prowess as well as to augment athletic performance in competitive sport. By contrast, in the therapy of prostate cancer, androgen deprivation therapy is used (5). The conventional excess of neurohormones as an apt descriptor of the heart failure syndrome has undergone substantial revision as new evidence points to down-regulation of a variety of contributors, including steroid hormones. As outlined by Sacca (6), testosterone is decreased in proportion to heart failure severity, an independent predictor of death, and when replaced, seems to exert a beneficial metabolic affect on insulin resistance. The observations from Italian researchers, reported by Caminiti (7), using intramuscular injections of testosterone added to optimal medical therapy in elderly men with chronic heart failure support this paradigm, because they showed in a randomized placebo-controlled trial that this therapy improved exercise capacity, muscle strength, and glucose metabolism. Because androgens also decline in aging women, Iellamo et al. (8) (from the same Italian group who studied this issue in men) undertook a proof-of-concept investigation to assess whether low-dose testosterone supplementation would benefit women with chronic heart failure.

In this issue of the *Journal*, they report the results of transdermal testosterone supplementation in 36 elderly women. Patients were randomized in a 2:1 ratio to receive either a transdermal patch of 300-μg testosterone or a placebo, applied twice weekly for 24 weeks; the primary end points were distance traversed in a 6-min walk test and insulin sensitivity by the homeostasis model. A significant 23% relative increase in 6-min walking time coupled with a parallel increase in peak oxygen consumption (VO2) was achieved, analogous to that found in their previous study of men. So too was there a decline in insulin resistance in the treated group, confirming the anticipated metabolic changes.

Although the authors of the current study assert a positive correlation between the change in free testosterone levels and the increase in walking time, much unexplained variance in this relationship exists. It would have been more useful to have seen confirmation of their previous findings that demonstrated a relationship between change in testosterone levels and peak VO2 and maximal isometric muscle strength. Therapies that improve lower limb muscle strength and thus have the potential to improve exercise tolerance and reduce fatigue are sorely needed in heart failure. This need is greatest in elderly persons, who constitute a growing segment of the heart failure population. Additional benefit to upper body strength (thus allowing potential improvement in activities of daily living) would be a certain “win” for this treatment if assessed by standardized tools used in other fields. Fatigue remains the single most difficult symptom to treat—limited improvement in this troubling and pervasive symptom is seen with current evidence-based therapies. Because there was no parallel improvement in cardiac function or structure as demonstrated by echocardiography in this and previous studies, it seems that a purely peripheral mechanism accounted for the enhanced exercise performance, akin to what might be expected with exercise training (7,8). At least 2 other potential factors might have contributed to the functional improvement associated with testosterone therapy in the current study: 1) because there was a 1.7-g rise in hemoglobin (and a commensurate 0.5-g decline in the placebo group), an improved oxygen-carrying capacity that has been previously shown to modulate enhanced exercise performance and peak VO2 in heart failure could have been operative (9); and 2) baroreceptor sensitivity might have...
improved, as demonstrated in previous studies; this has the potential to improve muscle sympathetic nerve activity with concomitant increased muscle arteriole vasodilation and function (7). Additionally, androgens are known to possess both anti-inflammatory and immunosuppressive effects (10). Future studies should include an examination of these possibilities.

No major side effects were evident with the 300-μg patch applied twice weekly in the current trial, but it is noteworthy that this is a much smaller dose than that used in men, and long-term surveillance in larger numbers of patients will be required to evaluate its potential therapeutic role.

Figure 1 provides a suggested construct for the assessment of novel heart failure therapies such as employed in the current study. With this “bottom-up approach,” we have arbitrarily scored the evidence acquired from the innovative and interesting work of Iellamo et al. (8), which represents a promising start for this new therapeutic direction. However, we have travelled down the path of potential new treatments for heart failure many times and been disappointed more often than pleased. To that end, more work needs to be done. We require further understanding of the optimal degree of androgen replacement—physiologic or supraphysiologic—and how best to identify those requiring it; we also need to know which clinically available metric is the best gauge to follow. Hence, future studies should systematically examine both differing doses and routes of administration of testosterone, include much larger patient populations of both sexes, explore other correlates that would provide insight into the mechanism and benefit, and finally collect meaningful clinical outcome data that can establish its role and its potential promise in clinical practice.

Perhaps adding some androgens to women with heart failure will fulfill the hopes of Henry Higgins as expressed in *My Fair Lady*!

**References**


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**Figure 1** Construct and Score Card for Evaluation of Novel Therapies in Chronic HF

ED = emergency department; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.


Key Words: congestive heart failure • exercise capacity • female • insulin resistance • testosterone.