Heart failure therapy: testosterone replacement and its implications

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This editorial refers to ‘Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial’† by C.J. Malkin et al., on page 57

Heart failure: therapeutic targets

Chronic heart failure (CHF) is a serious health care problem, associated with a high hospitalization rate and poor prognosis. CHF treatment means modern combination therapy, nevertheless, its associated mortality is higher than that of most cancers. Patients with CHF also have a poor quality-of-life.

The majority of today’s therapeutic knowledge is based on evidence from large-scale multi-centre, double-blind, placebo-controlled intervention trials. During the last 20 years, a remarkable evolution of therapeutic concepts has taken place with ACE-inhibitors, beta-blockers, and aldosterone receptor antagonists marking milestones of CHF therapy. The therapeutic targets in patients with CHF are two-fold: first, an increase of life expectancy, and, secondly, improvements in quality-of-life.

First, prolongation of lifespan can be reached if the progression of the disease can be stopped, delayed, reversed, or if the risk for sudden cardiac death can be reduced. Secondly, and equally important is to keep patients with CHF in a good quality-of-life.1 Quality-of-life can be improved in CHF if therapeutic interventions lead to a reduction of exertional dyspnoea, to the cessation of peripheral or central oedema, and/or to an improvement of exercise capacity. Malkin et al.2 followed the latter approach, focusing on testosterone as an important determinant of anabolic function that is impaired in CHF and linked to reduced exercise tolerance. In their randomized, double-blind, placebo-controlled single-centre trial, 76 male patients with moderate severity of CHF were included (age 63 vs. 65 years, LVEF 34% vs. 33%, BMI 28 vs. 28 kg/m², BNP 206 vs. 161 pg/mL, and ISWT 280 vs. 298 m, verum vs. placebo group, respectively). They received testosterone replacement therapy (5 mg skin patch with replacement every 24 h) over a period of 12 months, which significantly improved exercise capacity in the active treatment group (ISWT: increase of 25 ± 15 m, i.e. 15 ± 11%, P = 0.006 vs. baseline). Clinical severity of CHF as assessed by NYHA class improved by at least one class in 13 (35%) patients in the testosterone group compared with three (8%) on placebo (P = 0.01).

To date, this is the largest published study on testosterone replacement therapy in CHF patients. Previous studies have shown testosterone deficiency in men with CHF, which may be responsible for some of the features of CHF such as reduced muscle mass, abnormal energy expenditure, wasting, depression, and fatigue. In a short-term, randomized, placebo-controlled study in men with CHF intramuscular depot testosterone treatment was associated with significant increases in effort tolerance and improvement of symptoms.3

Testosterone replacement therapy and its implications

Markin et al.2 targeted a metabolic surrogate marker, i.e. testosterone. In their patients, mean bioactive testosterone concentrations were at the lower limit of normal at baseline (4.7 vs. 4.6 nmol/L, verum vs. placebo, respectively) and increased significantly in the active treatment group (+2.3 vs. 0 nmol/L, P = 0.003, verum vs. placebo, respectively). From the results presented in the article, we can see that there was no direct relationship between the change in serum bioactive testosterone and subsequent response to testosterone replacement with regards to changes in walking distance, handgrip strength, cross-sectional area, BNP, haematologic parameters, or tumour necrosis factor-alpha at the end of follow-up.

Serum testosterone concentrations reflect one aspect of anabolic insufficiency, that adds to the emerging picture of a general anabolic failure with superseding catabolic stimulation as the major underlying mechanism for tissue wasting seen in advanced CHF.4 Beyond the lack of anabolic steroid hormones, also GH resistance, insulin resistance, lack of serum IGF-I, and muscular levels of proinflammatory...
cytokines correlate with a reduced expression of insulin-like growth factor-I, all of which reflect aspects of anabolic dysfunction seen in CHF.

Whether testosterone replacement therapy finds a way into general clinical practice for CHF seems somewhat doubtful. The known cardiotoxic effects of anabolic steroids and the substantial number of skin reactions (seen in 55% of cases in the present study) may negatively impact on the wider acceptance of this therapeutic option. The authors report the key results for patients who completed the therapy, however, this excludes 34 patients from the analyses. Accordingly, for this phase-II proof-of-concept study this approach may be acceptable. Clearly, in an intention-to-treat analysis the therapeutic benefit observed by the authors would have been less.

The importance of the trial beyond the direct effect of testosterone replacement may be two-fold. First, the trial supports the muscle hypothesis suggesting that therapeutically targeting peripheral maladaptations could be clinically relevant in CHF. As observed by Malkin et al., peripheral abnormalities may be more important than the degree of myocardial dysfunction in determining a patients' symptomatic status. CHF is a progressive disorder in which complex interactions of haemodynamic, neurohormonal, immunological, and metabolic pathways lead to a systemic manifestation of the disease. The dramatic culmination of the CHF syndrome is the development of cardiac cachexia. Body wasting is also a severe clinical problem in other chronic conditions such as cancer, chronic lung disease, chronic liver, and renal failure as well as in ageing. Cachexia is particularly well recognized in cancer where the use of anabolic steroids is more common.

We believe the second important feature of the trial by Malkin et al. to be the provision of data enabling us to compare supportive therapies in CHF with those in cancer. We may consider that between 1970 and 2000, cancer research has been far less successful in reducing overall mortality than CHF research. When improvement of life expectancy is not a realistic goal, palliative treatment and supportive care are being placed in the centre of cancer therapy. The image of palliative care is one of being used on a potentially long journey. Quality-of-life issues increasingly play an extraordinary role in the care for patients with CHF, i.e. irreversible heart disease, and hence, palliative therapeutic concepts should increasingly be considered for CHF patients not only in end-stage heart failure.

Heart failure and cancer: two completely different entities?

Beyond its epidemiology and the concept of palliative and supportive care, there are more similarities between cancer and CHF. The recently introduced staging of CHF by the AHA/ACC follows to some extent the oncological approach by grading the patients from stage A to D, thereby virtually introducing TNM-staging for CHF patients (Table 1).

Following the concept of palliative therapy in patients with CHF aiming to improve quality-of-life, there are promising approaches available, but they will not be without risks and higher costs and their application may be limited to certain subgroups of patients as in the case of the study by Malkin et al. Therefore, in our opinion, in the future it will not be enough to only monitor cardiac function and symptomatic status of CHF patients. The patients' metabolic status should also be taken into account, together with assessments of exercise capacity, body composition, and hormonal status. Hence, the best translation of 'TNM' for CHF may be 'MFH', i.e. metabolic, functional, and haemodynamic staging.

It is time to advocate for an inter-disciplinary approach for CHF therapy. Learning from the successes and failures of other specialties may cross-stimulate our own therapeutic research. Interestingly, this appears not to be a one-way street. ACE-inhibitors and beta-blockers are widely used in CHF patients and both have been suggested to reduce the frequency of weight loss in CHF. Now the first ACE-inhibitor trial in oncology is taking place, which aims to reduce the occurrence of muscle wasting in cancer patients taking imidapril. Targeting peripheral pathways not directly linked to the pathophysiology in CHF patients has the potential to restore metabolic pathways, may reduce immunological imbalance, and in general may benefit CHF patients with regards to their symptoms and quality-of-life. Whether testosterone will be part of the arsenal of future CHF therapies is not yet clear. The study by Malkin et al. is a first step on a potentially long journey.

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References


Clinical vignette
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Anatomical features of congenital right atrial diverticulum on 3D-transoesophageal echocardiography

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A 9-year-old female was referred to our institution with a history of palpitations at rest. She had no comorbidities or history of cardiovascular disease. Previous electrocardiograms (ECGs) and 24 h Holter monitoring failed to record any arrhythmias. The physical examination revealed a blood pressure of 100/60 mmHg, pulse of 85 b.p.m., and normal findings on auscultation. The 12-lead ECG was normal for age and sex. A transthoracic echocardiogram revealed an abnormal chamber connected to the lateral wall of the right atrium consistent with a large congenital right atrial aneurysm/diverticulum. A transoesophageal echocardiogram was then performed (Panel A) along with 3D off-line reconstruction. Mutiplane 3D views showed a large diverticulum connected to the free wall of the right atrium with a 1 × 1.5 cm orifice (Panel B–E) with several trabeculae consistent with septation within the diverticulum (Panel D). The patient was referred for surgery owing to the increased risk of supraventricular arrhythmias and thrombus formation. Surgical exploration confirmed all the echocardiographic findings (Panel F). Excision of the diverticulum and direct suture of the connecting orifice was then performed. The patient was discharged 7 days after surgery and remains asymptomatic at 6-month follow-up.

This case illustrates how improvements in both transthoracic and transoesophageal real-time 3D echo are likely to be useful for presurgical and intraoperative evaluation of cardiac anatomy.

Panel A. Transoesophageal echo at 0° midoesophageal plane. The transducer is slightly rotated rightward to enhance the visualization of the right cardiac chambers. A large diverticulum is seen lateral to the right atrium and extending inferiorly towards the right ventricle. D: diverticulum; TV: tricuspid valve; RA: right atrium; RV: right ventricle.

Panels B and C. 3D-echo reconstructions from the right atrium (view from a virtual atriotomy). The diverticulum is connected to the lateral wall of the right atrium. The orifice (small arrows) connecting to the right atrium to the diverticulum is well defined. D: diverticulum; TV: tricuspid valve; RA: right atrium.

Panel D. 3D-echo reconstruction in a longitudinal plane. The large diverticulum with multiple trabeculae (arrowheads) is connected to the lateral wall of the right atrium. D: diverticulum; TV: tricuspid valve; RA: right atrium; RV: right ventricle.

Panel E. 3D-echo reconstruction en-face from the diverticulum (view from a virtual diverticulotomy). Notice the orifice (1 cm × 1.5 cm) connecting the diverticulum (demarcation by arrowheads) to the lateral wall of the right atrium.

Panel F. Surgical images of the large diverticulum confirming the 3D-echo findings. The orifice (1 cm × 1.5 cm) is directly connected to the lateral wall of the right atrium. A large trabecula is seen within the diverticulum.