Pharmacological Interventions Effective in Improving Exercise Capacity in Heart Failure

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Abstract
Heart failure (HF) is characterised by exercise intolerance, which substantially impairs quality of life (QOL) and prognosis. The aim of this review is to summarise the state of the art on pharmacological interventions that are able to improve exercise capacity in HF. Ivabradine, trimetazidine and intravenous iron are the only drugs included in the European Society of Cardiology HF guidelines that have consistently been shown to positively affect functional capacity in HF. The beneficial effects on HF symptoms, physical performance and QOL using these pharmacological approaches are described.

Keywords
Exercise tolerance, heart failure, intravenous iron, ivabradine, trimetazidine

Exercise intolerance is a typical symptom of heart failure (HF), impairing patients’ ability to perform activities of daily living and affecting quality of life (QOL).1 Chronic HF is characterised by a progressive reduction in exercise capacity, increasing fatigue and shortness of breath.2 In addition, exercise intolerance is often accompanied by increased blood pressure and chronotropic incompetence.1

According to European Society of Cardiology (ESC) guidelines on HF,1 the goals of treatment are to improve functional capacity and QOL, as well as clinical status, in order to prevent hospital admission and reduce mortality. For these reasons, pharmacological and non-pharmacological interventions have been developed to improve exercise capacity in HF. According to ESC guidelines, exercise training is an integral component of the management of patients with this condition.1 In fact, there is considerable evidence that exercise not only is safe but also leads to physical and psychological benefits in HF patients.2

As for pharmacological intervention, in past decades this has been mainly focused on improving mortality and morbidity, and has added little to exercise capacity and QOL in people with HF. Interventions with effects on exercise capacity have not been considered in the therapeutic algorithm of HF, mainly because early interventions such as flosequinan and ibopamine have been associated with neutral or unfavourable outcomes.3,4 However, more recently, it has become evident that drugs with a positive effect on functional capacity may also positively affect prognosis in HF. With this in mind, the aim of this review is to summarise the state of the art on pharmacological interventions that are able to improve exercise capacity in HF.

Intravenous Iron
Iron deficiency is a common comorbidity of HF, affecting up to 50 % of patients.2–4 It can lead to anaemia and/or skeletal muscle dysfunction without anaemia in HF patients. Iron is a critical component of peroxide- and nitrous oxide-generating enzymes that are critical for mitochondrial function. As a consequence of iron insufficiency, impaired oxygen transport occurs, altering the metabolism of cardiac and skeletal muscle. Owing to these effects on skeletal muscle, iron deficiency is associated with reduced exercise capacity and poor prognosis. In fact, increased morbidity and mortality is associated with this condition.5

For these reasons, the ESC guidelines indicate that ferric carboxymaltose (FCM; intravenous iron) should be considered in symptomatic patients (serum ferritin <100 μg/l, or serum ferritin 100–299 μg/l with transferrin saturation <20 %).6 This recommendation is based on evidence showing that treatment with intravenous FCM decreases symptoms and improves functional capacity and QOL in HF patients.

Earlier studies suggested that in anaemic patients with chronic HF, iron alone (without erythropoietin) increased haemoglobin count, reduced symptoms and improved exercise capacity.6,8 In patients with moderate-to-severe congestive HF and chronic kidney insufficiency, improvements in New York Heart Association (NYHA) class and echocardiographic indices were observed.9

Consistently with this, a double-blind, randomised, placebo-controlled study in anaemic patients with chronic HF and renal insufficiency demonstrated that FCM reduced N-terminal probrain natriuretic peptide (NT-proBNP) levels, and that this reduction was associated with an improvement in exercise capacity as well as left ventricular ejection fraction (LVEF), NYHA functional class, renal function and QOL.10 In addition, the Effect of FCM on Exercise Capacity in Patients with Iron Deficiency and Chronic HF (EFFECT-HF) study further clarified that FCM led to repletion of iron stores and improved HF severity and QOL.11
A single-blind, randomised controlled study demonstrated that FCM improved exercise tolerance, functional class and HF symptoms in patients with chronic HF and evidence of abnormal iron metabolism, with these effects being more evident in anaemic patients.13

Independently of the presence of anaemia, the Ferinject Assessment in Patients with Iron Deficiency and Chronic HF (FAIR-HF) trial showed the benefits of FCM on symptoms, functional capacity and QOL, with an acceptable side-effect profile.14 The Ferric Carboxymaltose Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic HF (CONFIRM-HF) trial showed that the observed improvements in functional capacity, symptoms and QOL were also associated with a decreased risk of hospitalisation for worsening HF at 1 year.15 Two meta-analyses in iron-deficient patients with systolic HF indicated that FCM improved HF symptoms, outcomes, exercise capacity and QOL,16 and that this intervention was associated with a reduction in recurrent cardiovascular hospitalisations.17

On the other hand, the recent Iron Repletion Effects on Oxygen Uptake in HF (IRONOUT-HF) trial, conducted in patients with HF and reduced ejection fraction (HFrEF) and iron deficiency, showed that high-dose oral iron did not improve exercise capacity over 16 weeks.18 These results suggest that oral intake does not provide adequate replacement of iron in HF patients.

Three recently initiated double-blind, placebo-controlled clinical trials (AFFIRM-AHF, FAIR-HF2 and HEART-FID) will investigate the effects of intravenous FCM versus placebo on morbidity and mortality outcomes and will further clarify the impact of intravenous FCM supplementation on functional capacity and clinical outcomes.

Ivabradine

The efficacy of ivabradine in HF is now well established.19–22 ESC guidelines indicate ivabradine for the treatment of HFrEF patients who are in sinus rhythm, have ischaemic HF and heart rate ≥70 BPM was found to lead to a shorter beta-blocker up titration period, higher final beta-blocker dose, greater heart rate reduction and better exercise capacity.22

Most of the effects of ivabradine on functional capacity are related to the haemodynamic improvements provided by ivabradine in HF, and not only through heart rate reduction.22 In fact, ivabradine provides an anti-remodelling effect, improves left ventricular structures and function, and reduces NT-proBNP levels.23 When compared with beta-blockers, ivabradine, for the same degree of heart rate reduction, does not impair the neuromuscular junction, thereby affecting muscular contraction. For all these reasons, ivabradine is effective in improving functional capacity, relieving symptoms and increasing QOL in patients with HF.24 These effects also translate into prognostic benefits.

Trimetazidine

Trimetazidine is a relatively old agent but relatively new in the treatment of HF. It has been shown to improve LVF, exercise capacity and prognosis in patients with mainly ischaemic HF.25–30

Trimetazidine improves cardiac metabolism by inhibiting free fatty acid oxidation and improving glucose utilisation. This metabolic switch leads to a greater production of high-energy phosphate per mol of oxygen and, therefore, to more energy for contraction. This improved metabolic efficiency translates into greater efficiency of sarcolemmal/endolesomal reticulum Ca2+ ATPase and of the actin–myosin interactions.31,32

Several studies have shown that modulation of myocardial metabolism with trimetazidine and drugs acting on the same metabolic pathway, such as perhexiline, may improve left ventricular remodelling and prognosis in patients with HFrEF. Although metabolic modulators have been used in clinical practice for decades, they have been only recently introduced in HF management.

Metabolic agents improve cardiac metabolism without altering haemodynamics.34 Among metabolic agents acting on cardiac myocytes, only perhexiline and trimetazidine are available for clinical use. Trimetazidine is the metabolic agent with the most data in patients with HF, while only a few reports, mainly preclinical, are available for perhexiline.

In chronic HF, trimetazidine improves LVF, normalises myocardial metabolism and improves endothelial dysfunction.25–29 A collaborative, multicentre study has shown that trimetazidine improves mortality in patients with HFrEF.25 A meta-analysis investigating the effects of trimetazidine as add-on treatment in patients with chronic HF demonstrated that the agent improves clinical symptoms and cardiac function, reduces hospitalisations for cardiac causes, and decreases serum levels of BNP and C-reactive protein.30

Finally, there is evidence that modified trimetazidine may yield fewer benefits than the original form in terms of LVF enhancement, which may be because of the difference in pharmacokinetics.34,35
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**Conclusions**

A substantial body of evidence for their beneficial effects supports the use of ivabradine, trimetazidine and intravenous iron to improve functional capacity and prognosis in HF. In particular, treatment with ivabradine up to 7.5 mg twice daily has been found to improve functional parameters and exercise capacity in HF patients, with improvements in QOL scores and better outcomes. Similarly, treatment with trimetazidine is associated with improvements in exercise tolerance, NYHA functional class, QOL and LV function. Intravenous FMC has been found to improve exercise capacity, functional class, HF status and symptoms, and QOL, as well as reducing hospitalisation rates for worsening HF. Ongoing trials will further clarify the impact of intravenous FCM supplementation on functional capacity and clinical outcomes.