Medical Treatment of Heart Failure with Reduced Ejection Fraction – Improving Clinical Status and Functional Capacity

Cristiana Vitale¹ and Giuseppe MC Rosano²,³

1. IRCCS San Raffaele Pisana, Roma, Italy
2. Cardiovascular Clinical Academic Group, St George’s NHS Trust Medical School, Cranmer Terrace, London SW17 0RE, UK
3. Department of Medical Sciences, IRCCS San Raffaele, Roma, Italy

Corresponding author:
Giuseppe MC Rosano, Cardiovascular Clinical Academic Group, St George’s NHS Trust Medical School, Cranmer Terrace, London SW17 0RE, UK
Email: giuseppe.rosano@gmail.com

Abstract

A contemporary review of treatments that have been shown to improve functional capacity in patients with Heart Failure and reduced Ejection Fraction (HFrEF). The improvement of functional capacity is one of the main goals of treatment in patients with HFrEF. In the past, despite significant effects on exercise capacity some drugs (e.g. ibopamine, flosequinan) have shown detrimental effects on long-term outcomes in patients with HFrEF. It is perhaps notable that both of these drugs had shown signals of increased safety concerns during the earlier clinical phases of their development. The challenge is to encourage a timely identification of effective treatments that can enhance functional performance in HF without the more difficult and more expensive path to prove all drugs also reduce mortality. It is valuable to have approved and effective treatments that can do the first without the need for the second in all cases, provided adequate safety can be assured. Ivabradine, trimetazidine, ferric carboxymaltose and diuretics have consistently shown to improve functional capacity and symptoms in patients with HFrEF because of their effect on long term prognosis these drugs should always be considered in patients with heart failure. Diuretics improve functional capacity and should be prescribed in patients with signs and symptoms of congestions. Cardiac resynchronisation therapy improves functional capacity in patients with HFrEF in whom it is appropriately applied (QRS >130/150 msec according to morphology).

Keywords: Heart Failure; Guidelines; Treatment

Citation: Vitale C, Rosano GMC. Rosano GMC. Medical Treatment of Heart Failure with Reduced Ejection Fraction - Improving Clinical Status and Functional Capacity. International Cardiovascular Forum Journal 2017;10:22-28 DOI 10.17987/icfj.v10i0.425

Introduction

The improvement of functional capacity is one of the main goals of treatment in patients with HFrEF.¹ In the past, despite significant effects on exercise capacity some drugs (e.g. ibopamine, flosequinan) have shown detrimental effects on long-term outcomes in patients with HFrEF.²,³ It is perhaps notable that both of these drugs had shown signals of increased safety concerns during the earlier clinical phases of their development.⁴,⁵ The challenge is to encourage a timely identification of effective treatments that can enhance functional performance in HF without the more difficult and more expensive path to prove all drugs also reduce mortality. It is valuable to have approved and effective treatments that can do the first without the need for the second in all cases, provided adequate safety can be assured.

It is now clear that stabilisation or improvement of exercise capacity reflects the ability of effective treatments to slow or prevent progressive worsening of HF and are important patient related outcomes. Amongst the drugs effective in improving prognosis in patients with heart failure some have a neutral or sometime negative effect on exercise capacity while some others have shown a significant improvement in exercise capacity. ACEi, ARBs and MRAs have a neutral effect on exercise capacity in patients with HFrEF while beta-blockers tend to reduce exercise tolerance. There are no data available on the effect of LCZ696 on exercise capacity in patients with HFrEF.

The only pharmacological treatments with a significant effect on cardiovascular prognosis that have consistently shown to improve exercise capacity are ivabradine, trimetazidine, intravenous iron and diuretics. Amongst devices CRT has been consistently
shown to improve prognosis and improve exercise capacity in patients with HFrEF, and cardiac contractility modulation (CCM) have been shown to improve exercise capacity in one study and a comprehensive individual patient data meta-analysis.[6–7]

There are no adequate surrogate measures for mortality in heart failure, however once the drug has been shown to have a positive effect on prognosis it is important to assess its effect on well being. This can be difficult because of both patient and researchers biases in assessing well-being. Indeed, patients’ perceptions may be affected by their state of health, by their expectations, by related co-morbidities and by their personal priorities. Similarly, the medical assessment of patient general status is influenced consciously or unconsciously by information on the severity of the disease derived from investigations, and the doctors’ perceptions of likely prognosis derived from these. Exercise capacity, when reliably measured, represents a good measure of the effect of a given treatment on functional status of patients with heart failure.

Exercise tests using both bicycle or treadmill have been used to assess the effects of therapy in heart failure.[8] More objective assessment of true maximal exercise capacity utilising respiratory gas exchange to establish a close to maximal effort improves reliability of exercise capacity assessment. This allows the assessment of maximal oxygen consumption as the best available measure of functional capacity. This has been used for the pre-transplant assessment of patients with heart failure and assessing the effects of heart failure interventions. However, exercise testing and assessment of gas exchange may be difficult to administer in all patients as patients may be unable to exercise on a bicycle or to breathe into a gas exchange mask. Heart failure patients, however, can perform a self-paced 6 min walk test (6MWT). This test has long been used as an outcome measure in clinical trials and its results have been shown to be concordant with changes in symptoms, suggesting that it is a good indicator for symptom benefit.[8] A significant increase in 6MWT has been observed with cardiac resynchronization and CCM for example.[6–7]

ACE-inhibitors and ARBs
Despite their prognostic benefits ACE inhibitors have failed to show significant effects on functional capacity and no difference between ACE-I and ARBs has been ever demonstrated.

In general the adequately sized studies aimed at assessing the effect of ACE-I on exercise capacity have reported a neutral effect on functional status. One large multicentre, placebo-controlled trial testing captopril and cilazapril failed to show any effect of ACE-inhibition.[9] (Figure 1) One study testing the effect of perindopril showed a significant improvement in exercise capacity.[10] One adequately sized study compared candesartan with placebo and showed no effect (Figure 2).[11] Four studies have compared the effect of ARBs with the ACEI enalapril, and found no differences in functional capacity nor on patient reported outcomes.[12–15] Therefore, the overall effect of RAAS inhibitors on functional capacity and symptoms appears to be neutral.

Beta-blockers
Beta-blockers have a neutral or negative effect on exercise capacity.[8] A small effect has been shown with carvedilol in some studies but this effect has not been consistently demonstrated and confirmed. Only 3 of 20 trials and only one of five multicentre studies investigating the effect of beta-blockers on 6MWT showed an improvement.[8,16–20] When detected, this effect has been marginal (Figure 3). Two trials compared the effect of metoprolol and carvedilol on 6MWT and showed no difference between these two beta-blockers.[21,22] Carvedilol and bisoprolol have consistently been shown to be inferior to ivabradine in their effects on symptomatic improvement and on exercise capacity in separate well sized studies.[23,24]

Therefore, despite their prognostic benefits beta-blockers do not improve symptoms and functional tolerance in patients with heart failure, but other treatments may do so. Higher doses of beta-blockers are associated with fatigue and with reduced exercise tolerance and therefore it is unlikely that merely increasing the dose of beta-blockade will improve functional capacity in HF.
patients. Therefore, we may consider down-titration of beta-blocker dose in patients reporting fatigue or a decrease in exercise capacity and replacing this with the alternative heart rate reducing agent, ivabradine that does not decrease (and may actually increase) exercise capacity in HF patients.

Ivabradine

The prognostic benefits of ivabradine in patients with heart failure are coupled with a significant improvement in functional capacity and well-being. In one early randomised study in patients with underlying coronary artery disease, the combination of ivabradine and bisoprolol was found to be more effective at improving exercise capacity than doubling the bisoprolol dose in patients receiving bisoprolol 5mg at baseline (Figure 4). A further study showed a similar effect with ivabradine added to carvedilol being more effective than up-titrating the dose of carvedilol in patients with HFrEF (Figure 5).[23]

In another large randomised study Volterrani et al compared the effect of heart rate reduction with carvedilol, ivabradine, and their combination on exercise capacity in patients with HFrEF receiving maximal dose of ACE inhibitors.[24] The maximal dose of study treatment was more frequently tolerated in patients receiving ivabradine than in those receiving carvedilol. Heart rate was reduced in all three groups, but to a greater extent by combination therapy and the distance walked on the 6-min walking test improved significantly only in patients receiving ivabradine alone or in association with carvedilol while it did not change with carvedilol. (Figure 6) The effects observed on the 6MWT were mirrored by similar improvements on MVO$_2$. Patients receiving ivabradine alone or in combination had better quality of life compared with carvedilol that did not change quality of life compared to baseline values.[24]

The effect of ivabradine on exercise capacity and maximal oxygen consumption was confirmed by another randomised study in patients with ischemic heart failure receiving background beta-blockers. In this study exercise capacity increased doubled and maximal oxygen consumption increased by nearly 30% with ivabradine.[25] These data show that heart rate reduction with ivabradine leads to a better exercise capacity compared to beta blockers alone and that the association of ivabradine with a beta-blocker is effective in improving functional capacity and quality of life compared to beta-blocker alone suggesting that combination therapy is more beneficial than simple beta-blockade. The better effect of ivabradine compared to beta blockers on exercise capacity seems related not only to heart rate reduction, but may also be due to the differing effects of ivabradine and beta-blockers on skeletal muscle perfusion.
and performance during exercise. It is well known that beta-blockers impair the alpha-adrnergic-mediated dilation that occurs during exercise while ivabradine preserves the exercise-induced increase in blood flow.[26–28] These effects reflect a better muscle performance during exercise with ivabradine compared to beta-blockers. Given the prognostic effect of ivabradine and its effect on functional capacity and patients related outcomes this drug should always be considered for the treatment of patients with HFrEF. It should always be considered in patients in sinus rhythm. Furthermore, its implementation, associated with an adjustment of the beta-blocker dose, in patients receiving full beta-blockade, especially when reporting fatigue or limited exercise tolerance, may lead to an improved functional status.

ARNI – Angiotensin receptor neprilysin inhibitor
There are no data on the effect of LCZ696 on functional capacity in patients with heart failure. The PARADIGM-HF study showed that the drug was associated with a reduction of the worsening of functional status as assessed by KCCQ change from baseline to month 8. During the first eight months of the study patients receiving LCZ696 had a worsening of the clinical score of –2.99 points compared to –4.63 points in the enalapril group with a significant between-group difference of 1.64 points.[29]

Mineralocorticoid/aldosterone receptor antagonists [MRAs]
While the effect of MRAs on exercise capacity in patients with HFrEF has been extensively investigated, this effect has not been systematically tested in patients with HFrEF. In one randomised study the adjunct of spironolactone to ACEi and diuretics did not increase exercise capacity in HFrEF.[30]

Digoxin and other digitalis glycosides
The effect of digoxin on exercise capacity is neutral. Indeed, only one of four trials showed an improvement in exercise capacity.[31–34] Of importance, the largest of these studies that by itself included more patients than all other studies together (580 patients), did not show any benefit of digoxin on exercise capacity compared to placebo.[35] Whether the effect of digoxin differs between patients in sinus rhythm and those in atrial fibrillation has not been investigated.

Diuretics
Diuretics improve symptoms of congestion in patients with HFrEF.[1] The available data from small trials suggest that in patients with HFrEF conventional diuretics appears to improve exercise capacity when compared to a placebo or to an active comparator. Four trials compared diuretics to active control and showed that diuretics improved exercise capacity in participants. [36–39] Whether the effect of diuretics on exercise capacity was dependent upon the degree of congestion at baseline is not known. All these studies have reported an improvement in symptoms with diuretic therapy.

Metabolic agents
It is well known that altered cardiac metabolism plays an important role in the pathophysiology of heart failure. In particular, chronic HF may be conceived as “a ketosis-prone state” with a switch towards free fatty acid utilisation in the heart. Trimetazidine is an inhibitor of free fatty acid oxidation that shifts cardiac metabolism from free fatty acids to glucose utilisation resulting into a greater production of high-energy phosphates. This translates into a greater myocardial efficiency. Trimetazidine added to standard therapy improves symptoms and exercise capacity in patients with HFrEF of ischaemic and non ischaemic aetiology. The effect of trimetazidine on symptoms and functional capacity has been tested in several studies in patients with HFrEF. Three meta-analyses of the available data suggest that Trimetazidine improves symptoms, exercise capacity and prognosis in patients with HFrEF.[40–42] The effect of trimetazidine on exercise capacity and symptoms are concordant in all studies and suggest an additive effect on top of medical therapy and on top of cardiac rehabilitation programmes. (Figure 7 and 8) It has been observed that trimetazidine improves skeletal muscle metabolism.[43–45] This suggests that the main effect of trimetazidine on functional capacity in patients with heart failure may be dependent upon cardiac metabolic effects more than by other mechanisms. Given its positive effect on prognosis in patients with heart failure and its significant effect on symptoms and functional capacity trimetazidine should
Iron deficiency occurring in patients with heart failure is associated with impaired functional capacity, poor quality of life, and increased mortality.[46–47] The effect of correction of iron deficiency on exercise capacity has been tested in a few clinical studies. The Ferric Iron Sucrose in Heart Failure (FERRIC-HF) study was one of the first placebo-controlled studies that used iron sucrose to replenish iron stores, irrespective of the presence of anaemia. Thirty-seven patients were randomised in a 2 to 1 ratio (either iron sucrose or placebo) according to their haemoglobin values. Therapy was continued until iron status was normalised. Patients with iron deficiency who received intravenous iron improved their exercise capacity by a mean change in maximal oxygen uptake of almost 2 mL/kg/min.

More recently intravenous administration of ferric carboxymaltose has been consistently shown to improve exercise capacity in patients with HFrEF and low ferritin levels regardless of the presence of anaemia in the FAIR-HF and in the CONFIRM-HF studies (Figure 9 and 10).[48–49] The FAIR HF study reported a significant improvement with ferric carboxymaltose in the quality of life as measured by the self-reported Patient Global Assessment, improvement (20 metres) in exercise capacity and in the assessment of quality of life measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).[48] The CONFIRM-HF study showed that ferric carboxymaltose administration in iron-deficient HFrEF patients with and without anaemia caused a sustained improvement in functional capacity over a 12 month period. Of importance patients treated with ferric carboxymaltose showed a significantly reduced risk of hospital admission due to worsening HF during a 1-year follow-up.

A recent meta-analysis of the studies conducted with ferric carboxymaltose in patients with HFrEF with or without anaemia has suggested that this iron formulation reduces re-hospitalisation rates. Therefore, intravenous administration of ferric carboxymaltose is indicated in all patients with HFrEF with ferritin levels <299 μg/l. Oral administration of iron is inadequate to correct low ferritin levels and should not be considered as an alternative to intravenous iron.

**Testosterone**

Testosterone supplementation in patients with HFrEF has been shown to improve exercise capacity regardless of the baseline testosterone levels in both men and women.[50–51] (Figure 11) Randomised controlled studies have shown that the effect of testosterone supplementation is related to the improvement in muscle strength and not to any effect on central haemodynamics. A meta-analysis of the available data support the significant benefit of testosterone supplementation in improving exercise capacity in patients with heart failure.[52] The effect is more evident when testosterone supplementation is associated with cardiac rehabilitation programmes. Supra-physiological and supra-therapeutic testosterone supplementation does not have any additional effect on functional capacity and may worsen clinical status. Testosterone supplementation can be considered in patients with muscle wasting or with cachexia. Supplementation therapy will need adequate monitoring of prostate health and fluid retention.

**Calcium channel blockers.**

Worsening of heart failure has been reported with all classes of calcium channel blockers. An early small study suggested that amlodipine had a minimal effect on exercise tolerance in heart failure. However, 2 subsequent multicentre studies including patients assessed the effect of amlodipine on exercise capacity and quality of life in patients with HFrEF. Although no statistically significant excess of adverse events were reported the episodes of worsening heart failure were higher in amlodipine-treated patients (10% vs 6.3%). Amlodipine had no effect on exercise tolerance, increasing exercise time less than placebo (53 ± 9 seconds vs 66 ± 9 seconds).[53] Therefore, calcium channel blockers have no effect on exercise tolerance in patients with heart failure. These drugs should not be used in patients with heart failure unless there is a compelling need.

In conclusion, ivabradine, trimetazidine, ferric carboxymaltose and diuretics have consistently shown to improve functional capacity and symptoms in patients with HFrEF because of their effect on long term prognosis these drugs should always be considered in patients with heart failure. Diuretics improve functional capacity and should be prescribed in patients with signs and symptoms of congestions. Cardiac resynchronisation therapy improves functional capacity in patients with HFrEF in whom it is appropriately applied (QRS >130/150 msec according to morphology).

**Declarations of Interest**

The authors declare no conflicts of interest.

**Acknowledgements**

The authors state that they abide by the requirements for ethical publishing in biomedical journals. [53]

**References**


54. Shewan LG, Coats AJS, Henein M. Requirements for ethical publishing in biomedical journals. International Cardiovascular Forum Journal 2015:2:2 dx.doi.org/10.17987/icfj.v2i1.4