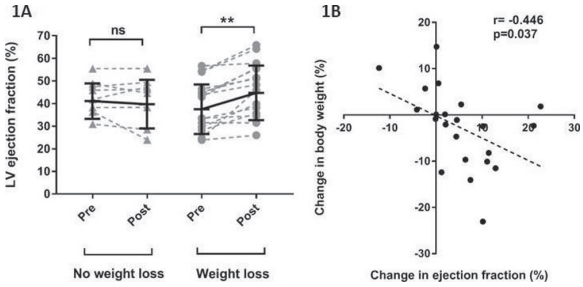

Figure 1

creased mortality with unintentional weight loss, we demonstrate here, for the first time in a prospective trial, that successful weight loss in obese HFrEF patients is not only safe, but results in major improvements in LV systolic function. Further study is required to reproduce these findings in an unselected heart failure population, and assess long-term outcomes. Irrespective, this data provides a strong mandate to consider intentional weight loss as a potentially powerful therapeutic intervention in obese heart failure.

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Impact of cardiorespiratory fitness in the obesity paradox in heart failure with reduced ejection fraction

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Background: High body mass index (BMI) is associated with improved outcomes in heart failure with reduced ejection fraction, a finding leading to the concept of an obesity paradox.
Purpose: We aim at investigating the impact of exercise tolerance and cardiorespiratory capacity on the obesity paradox.
Methods: Ambulatory patients with symptomatic heart failure and left ventricular ejection fraction ≤40%, followed in our center, prospectively underwent a baseline comprehensive evaluation including clinical, laboratorial, electrocardiographic, echocardiographic, and cardiopulmonary exercise testing parameters. Peak VO2 (pVO2) was normalized for body mass and in obese patients adjusted to lean body mass. The study population was divided according to BMI (<25, 25–30, >30 kg/m^2). A sub-analysis of patients of the BMI <25 kg/m^2 group, differentiating BMI <20 and 20–25 kg/m^2 was also performed. All patients were followed for 60 months and the combined endpoint was defined as cardiac death, urgent heart transplantation or need for mechanical circulatory support.
Results: In the 263 enrolled patients (75% male, 54±12 years, LVEF 28±7%, BMI 27±4 kg/m^2), 74 events occurred. Patients with higher BMI had better LVEF (p 0.003), percentage of predicted pVO2 (p<0.001), ventilation equivalent of carbon dioxide (VE/VCO2) slope (p 0.006), serum sodium concentration (p 0.021) and Heart Failure Survival Score (p 0.046) compared with the lower BMI groups. At univariable analysis, both BMI, pVO2 and VE/VCO2 slope were significant predictors of outcome (HR 0.940, CI 0.886–0.998, p 0.042; HR 0.791, CI 0.742–0.842, p<0.001 and HR 1.164, CI 1.135–1.194, p<0.001, respectively). In the sub-analysis of patients with BMI <25 kg/m^2, very low BMI was associated with worse outcomes (log-rank p 0.014). At multivariable Cox regression analysis adjusting for pVO2 or for VE/VCO2 slope, the protective role of BMI disappeared (p 0.101 and p 0.786, respectively).
Conclusion: These results suggest that exercise tolerance affects the relationship between BMI and survival. Thus, cardiorespiratory fitness may mitigate the obesity paradox in heart failure patients.

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Muscle-derived follistatin and decorin levels in men with heart failure with reduced ejection fraction and different iron status

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Background: The functioning of skeletal muscle in heart failure (HF) patients is impaired upon disturbed iron status. Thanks to its secretory capacity skeletal muscle produces various, mainly contraction-induced proteins (myokines). These bioactive factors trigger local responses, affecting energy metabolism, hypertrophy and regeneration of the muscle.
Purpose: We aimed to determine whether patients with HF and iron deficiency (ID) had the altered the production of decorin which exerts pro-hypertrophic effect, and follistatin, a myokine promoting muscle regenerative potential. Further, we investigated whether the intravenous iron repletion influenced the exercise-induced production of these myokines.
Methods: Study population comprised of 53 men with heart failure with reduced ejection fraction (LVEF ≤40%; mean age: ±64 years; NYHA class I-II: 87%) and of 15 middle-aged healthy men. We assessed follistatin and decorin levels in plasma samples from peripheral blood from all patients by ELISA. Further, we analyzed samples taken from antecubital veins draining the forearm muscle before and after physical local exercise (standardized 5-minute handgrip exercise) for the myokines. Additionaly iron-deficient HF patients (serum ferritin<100μg/L or serum ferritin 100–300 μg/L with Tsat<20%) and were randomized in a 1:1 fashion (double-blind scheme) to receive either intravenous ferric carboxymaltose (FCM) or saline (comparator) (24-week dosing protocol according to CONFIRM-HF trial).
Results: We observed no differences in concentrations of both myokines measured in peripheral samples between HF patients and controls, and between HF patients with and without ID. There were no correlations between myokine levels in peripheral and forearm samples. In forearm samples levels of decorin and follistatin assessed both before and after handgrip were significantly lower in HF patients with ID as compared to those with preserved iron status (all p<0.001). Moreover, both before and after exercise the lower levels of decorin in forearm samples of men with HF were associated with lower mean handgrip strength (R=0.45, p<0.01; R=0.46, p<0.01). In HF patients during exercise there was a correlation between a reduced netto decorin and higher netto lactate formation in forearm samples (R= -0.38, p<0.01). Notably, the netto muscle production of follistatin in forearm samples was significantly increased in men with HF and ID treated with FCM as compared to those who received saline (p<0.01).
Conclusions: In patients with HF and ID decreased decorin and follistatin secretion assessed in forearm blood, but not in peripheral blood, reflects the lower pro-hypertrophic and regenerative potential. Lower secretion of decorin in HF patients during exercise is associated with altered muscle metabolic activity. In patients with HF and ID iron repletion therapy partially restitutes the follistatin production during exercise.

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Absolute and functional iron deficiency in heart failure defined and described

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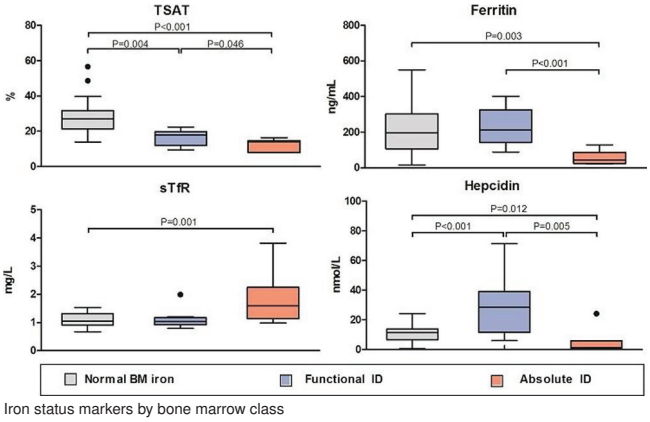
Background: Iron deficiency (ID) is very prevalent in heart failure (HF) patients. Absolute and functional ID are considered to be two distinct aetiologies. However, they are not defined by criteria and, as a consequence, studied and treated as if they are the same.
Purpose: To define both absolute and functional ID in HF patients using the gold standard of bone marrow iron staining and subsequently validate and describe biochemical, clinical and prognostic characteristics in a large cohort of HF patients.
Methods: Bone marrow aspiration with iron staining was performed in 42 HF patients with reduced ejection fraction (LVEF≤45%) undergoing median sternotomy for coronary artery bypass grafting. Both iron stores and iron incorportation were assessed to be able to differentiate between functional and absolute ID. Subsequently, a large cohort of patients with worsening HF and a LVEF≤45% (n=1.807) was used to study baseline associates and follow-up. The primary end-point was defined as a combined endpoint of all-cause mortality or HF hospitalizations.
Results: Patients in the bone marrow cohort were predominantly male (n=32.



Iron status markers by bone marrow class