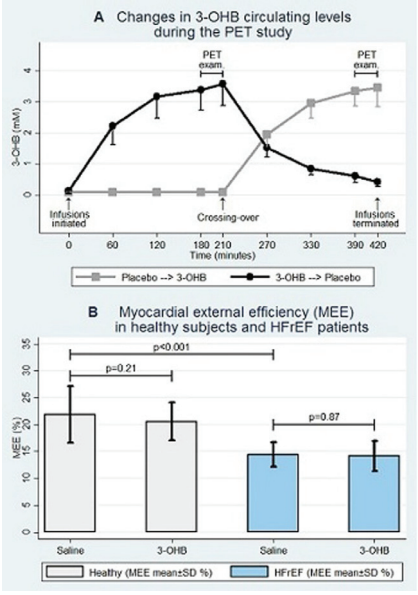
(HFrEF). 3-OHB fuels myocardial ATP production during fasting and metabolic stress, but the mechanoenergetic effects of this metabolic shift are unknown.
Purpose: To investigate the effects of short-term 3-OHB infusion on left ventricular (LV) external stroke work (EW), myocardial oxygen consumption (MVO2), and myocardial external efficiency (MEE) in stable HFrEF patients and age-matched control subjects.
Methods: HFrEF patients and healthy age-matched control subjects underwent 11-C-acetate positron emission tomography (11-C-acetate-PET). All participants received 3-OHB (0.18 g/kg/h) or saline (placebo) at an equivalent volume for 3 hours in a randomized single-blinded cross-over design. I) LV mechanical external work was calculated as EW = stroke volume (SV) x heart rate (HR) x mean arterial pressure (MAP), II) oxidative phosphorylation rate as MVO2, and III) mechanoenergetic coupling as MEE (%) = EW/MVO2 x LV mass. EW, MVO2 and MEE were all derived non-invasively based on 11-C-acetate-PET.
Results: We studied 10 HFrEF patients (LVEF 37±3%, NYHA 2–3, age 62±14 years) and 10 control subjects. Compared to placebo, 3-OHB infusion increased circulating 3-OHB levels from 0.2 [IQR:0.1–0.6]mM to 3.5 [IQR:3.1–3.6]mM. ($p<0.001$, figure 1A) with no difference between groups (p=0.82). Cardiac output increased approximately 40% due to an increase in SV and HR with a minor decrease in MAP (table). Accordingly, EW and MVO2 increased with an associated increment in myocardial blood flow ($p<0.001$). MEE was lower in HFrEF patients than in control subjects, but 3-OHB infusion had no effect on MEE (figure 1B).

PET measurements after saline and 3-OHB

	Healthy (n=10)		HFrEF (n=10)		P-value	P-value
	Saline	3-OHB	Saline	3-OHB	(2-way ANOVA)	(Interaction)
CO (L/min)	5.3±1.3	7.1±1.79	4.4±1.0	6.3±1.3	<0.001	0.64
SV (ml)	84±20	97±26	75±18	95±19	<0.001	0.11
MAP (mmHg)	87±10	83±9	78±10	75±8	0.02	0.11
Heart rate (bpm)	64±9	74±11	59±8	67±9	<0.001	0.36
MVO2 (O2/g/min)	0.10±0.05	0.14±0.04	0.08±0.02	0.12±0.12	<0.001	0.23
MEE (%)	21.8±4.9	20.7±4.0	14.4±2.3	14.2±3.1	0.31	0.44

CO: Cardiac output; SV: Stroke volume; MAP: Mean arterial pressure; MVO2: Myocardial oxygen consumption; MEE: Myocardial external efficiency.



3-OHB levels (A) and MEE (B)

Conclusion: 3-OHB demonstrates beneficial hemodynamic effects without deteriorating myocardial external efficiency. These findings suggest that 3-OHB may be valuable in the treatment of patients with HFrEF.
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Discriminating sarcopenia in male patients with heart failure: the influence of body mass index

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Background: The definition of sarcopenia based on the ratio between the appendicular skeletal muscle mass (ASM) divided by the height squared can underestimate the presence of muscle wasting in overweight patients with chronic heart failure (CHF).
Purpose: To evaluate sarcopenia by the ratio between the ASM and height squared and by ASM measurement adjusted for total fat mass.
Methods: We enrolled 113 male patients with HF with left ventricular ejection fraction <40%, mean age of 55±9 years old. Body composition was measured with dual x-ray absorptiometry (DXA) and ASM (in kg) was calculated as the lean muscle mass of both arms and legs divided by the height (in metre) squared. According to Baumgartner's criteria, sarcopenia was defined when the skeletal muscle mass index (SMI=ASM/height2) was lower than 7.26 kg/m^2. The Newman's criteria was based on ASM measurement adjusted for height, but also for total fat mass. Linear regression was used to model the association between ASM on height (in metre) and fat mass (in kg). The residuals from linear regression models were used to identify those individuals whose amount of ASM was lower than expected for a given amount of fat mass. The 20th percentile was defined as the cutoff point for sarcopenia for both criteria (Baumgartner's and Newman's). In addition, muscle strength was assessed using the handgrip dynamometer (handgrip <30 kg was used as the cutoff point for sarcopenia).
Results: The 20th percentile defined as the cutoff point for sarcopenia was 7.01 kg/m^2 and -0.90 for the criteria of ASM/h2 and ASM adjusted for fat, respectively. Of those 113 patients, 75 (66.3%) showed no sarcopenia by any of the methods (ASM/h2 or ASM adjusted for fat). In patients with body mass index (BMI) <25 kg/m^2, the criteria of ASM/h2 detected 22 (19.5%) patients with sarcopenia, whereas only 1 patient (0.9%) with BMI >25 kg/m^2 was detected with sarcopenia. On the other hand, the criteria of ASM adjusted for fat detected 6 (5.3%) patients with BMI <25 kg/m^2 with sarcopenia, whereas 9 (8%) patients with BMI >25 kg/m^2 were detected with sarcopenia.
Conclusion: Our data suggest that different definitions can be used to determine sarcopenia in patients with CHF. However, for patients with BMI higher than 25 kg/m^2, the sarcopenia determination should include adjustment for height and body fat mass by linear regression.
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Impaired functioning and low mass of skeletal muscles in men with heart failure with reduced ejection fraction are reflected by reduced muscle-derived irisin

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Background: Energy metabolism in adipose, bone and muscle tissues is integrated, among others, by irisin. This circulating hormone-like myokine at adequately high level secures optimal exercise capacity and metabolic homeostasis.
Purpose: The aim of the study was to assess the production of irisin in the blood draining exercising forearm muscles and in peripheral blood in relation to the mass and functioning of skeletal muscles in men with heart failure and healthy men.
Methods: We studied population comprised of 53 men with stable heart failure with reduced ejection fraction (HFrEF) (LVEF ≤40%); mean age: ±64 years; NYHA class I-II: 87%) and 15 middle-aged healthy men. Lean mass of upper extremities were determined by DEXA (dual-energy X-ray absorptiometry). We analysed the levels of irisin in plasma samples from peripheral blood from all patients by ELISA. Further, we analyzed samples taken from antecubital veins which drain the forearm muscle before and after local physical exercise (standardized 5-minute handgrip exercise) for the aforementioned myokine.
Results: We observed no differences in levels of irisin measured in peripheral blood samples between HF patients and healthy controls. There were no association between levels of irisin in peripheral blood and CRP, NTproBNP or eGFR in both men with HF and healthy controls. Reduced irisin concentrations in peripheral samples was related to both decreased fat content in the four extremities (R=0.35, $p<0.05$) and low lean tissue mass of the upper extremities (R=0.37, $p<0.05$). In HF patients an increased irisin level in peripheral samples was associated with longer distance in 6-minute walking test (R=0.37, $p<0.05$). There was correlation between concentrations of irisin in peripheral blood and in the forearm samples in HF patients (R=0.54, $p<0.001$) whereas such relationship was not observed in healthy controls. HF progression expressed as NYHA class was associated with decreased level of irisin measured in forearm samples (R= -0.28, $p<0.05$). There was no correlation between irisin and inflammatory marker IL-6 in forearm samples in HF patients. Both before and after exercise decreased concentrations of irisin assessed in forearm samples of men with HF were related to lower lean tissue mass of the upper extremities (R=0.47, $p<0.001$; R=0.39, $p<0.01$). Reduced irisin was associated with lower fat content both in upper extremities (R=0.37, $p<0.01$) and in all 4 extremities (R= 0.32, $p<0.05$).
Conclusions: Decreased irisin assessed in blood draining exercising muscles reflects decreased skeletal muscle mass and fat content in extremities subjected to physical effort in patient with HF.