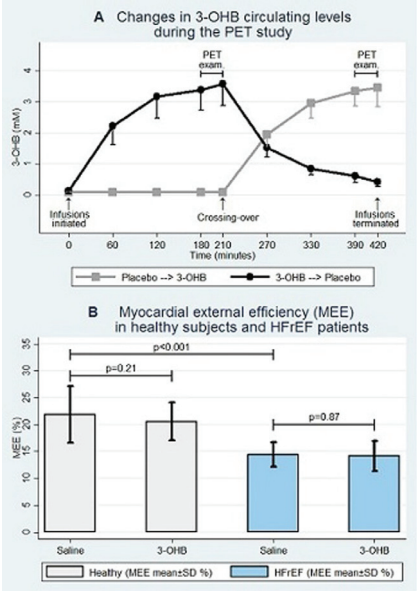
(HFrEF). 3-OHB fuels myocardial ATP production during fasting and metabolic stress, but the mechanoenergetic effects of this metabolic shift are unknown.
Purpose: To investigate the effects of short-term 3-OHB infusion on left ventricular (LV) external stroke work (EW), myocardial oxygen consumption (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.
Funding Acknowledgements: Lundbeck foundation

P3194
Discriminating sarcopenia in male patients with heart failure: the influence of body mass index

M.R. Dos Santos[1], G.W.P. Fonseca[1], F.R. Souza[1], V.M. Castro[1], L. Takayama[2], R.M.R. Pereira[2], C.E. Negrao[1], M.J.N.N. Alves[1]. *[1]Instituto do Coração (InCor), Sao Paulo, Brazil; [2]University of Sao Paulo, Bone Laboratory Metabolism, Rheumatology, Sao Paulo, Brazil*

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.
Funding Acknowledgements: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 2016/24306-0)

P3195
Impaired functioning and low mass of skeletal muscles in men with heart failure with reduced ejection fraction are reflected by reduced muscle-derived irisin

M. Kasztura[1], M. Dziegala[1], K.A. Kobak[1], M. Tkaczyszyn[1], M. Drozd[1], K. Wegrzynowska-Teodorczyk[2], K. Josiak[3], J. Bania[4], L. Kiczak[5], W. Banasiak[6], P. Ponikowski[3], E.A. Jankowska[1]. *[1]Wroclaw Medical University, Department of Heart Diseases, Laboratory for Applied Research on Cardiovascular System, Wroclaw, Poland; [2]University School of Physical Education of Wroclaw, Faculty of Physiotherapy, Wroclaw, Poland; [3]Wroclaw Medical University, Department of Heart Diseases, Wroclaw, Poland; [4]Wroclaw University of Environmental and Life Sciences, Department of Food Hygiene and Consumer Health, Wroclaw, Poland; [5]Wroclaw University of Environmental and Life Sciences, Department of Biochemistry, Pharmacology and Toxicology, Wroclaw, Poland; [6]Military Hospital of Wroclaw, Cardiology Department, Centre for Heart Diseases, Wroclaw, Poland*

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.

Funding Acknowledgements: Financially supported by National Science Centre (Poland) grant no: SONATA 2012/05/E/NZ5/00590

P3196

Anorexia coexisted in frailty predicts 1-year prognosis in patients with heart failure: a multicenter prospective cohort study

T. Adachi[1], T. Abe[2], T. Mizuno[3], Y. Iida[4], T. Yamada[5], S. Uchiyama[6], M. Nishi[6], T. Nagao[7], K. Sakamoto[8], T. Ito[9], N. Fujimoto[10], K. Kobayashi[11], T. Okumura[12], S. Yamada[13]. *[1]Nagoya University Graduate School of Medicine, Department of Rehabilitation, Nagoya, Japan; [2]Aichi Medical University Hospital, Department of Rehabilitation, Nagakute, Japan; [3]Aichi Medical University Hospital, Department of Cardiology, Nagakute, Japan; [4]Kainan Hospital, Department of Rehabilitation, Yatomi, Japan; [5]Kainan Hospital, Department of Cardiology, Yatomi, Japan; [6]New Tokyo hospital, Department of Rehabilitation, Matsudo, Japan; [7]Hoshi General Hospital, Department of Rehabilitation, Koriyama, Japan; [8]Hoshi General Hospital, Department of Cardiology, Koriyama, Japan; [9]Mie University Hospital, Department of Rehabilitation, Tsu, Japan; [10]Mie University Graduate School of Medicine, Department of Cardiology, Tsu, Japan; [11]Nagoya University Hospital, Department of Rehabilitation, Nagoya, Japan; [12]Nagoya University Hospital, Department of Cardiology, Nagoya, Japan; [13]Nagoya University, Department of Health Sciences, Nagoya, Japan.* On behalf of FLAGSHIP collaborators

Background: Anorexia often coexists with heart failure (HF) and leads to malnutritional status. Particularly in fragile HF patients, anorexia may carry poor prognosis, however, detailed insight has been remained unknown.
Purpose: This study aimed to examine the relationship between the presence of frailty and anorexia and 1-year prognosis in HF.
Methods: This prospective study was performed as a multicenter cohort study in Japan (FLAGSHIP). We analyzed 1,606 ambulatory patients admitted for acute HF or exacerbation of chronic HF. From data at discharge, we collected data on frailty, anorexia, age, gender, New York Heart Association class, brain natriuretic peptide, depression (5-item Geriatric Depression Scale $\geq$2) and medications for HF treatment. Frailty was defined as $\geq$3 of the followings based on our previous publication: usual walking speed $<$0.8 m/s; grip strength $<$26 kg (men) or $<$17 kg (women); Performance Measure of Activity in Daily Living-8 $\geq$21; body mass index $<$20 kg/m^2. Anorexia was defined as Simplified Nutritional Appetite Scale $<$14. Study outcome is a composite outcome of HF re-hospitalization or all-cause mortality within one year after discharge. Cox proportional hazards model was used to examine the association between measured variables and study outcome.
Results: A total of 257 events (16.0%) were observed (209 HF re-hospitalization, 27 cardiac death, 21 non-cardiac death). There was a significant difference in event-free survival across the groups stratified by frailty and anorexia (Log-rank test, p$<$0.001) (Figure). As the result of Cox proportional hazards model adjusted for all variables, coexistence of both frailty and anorexia was independently associated with 1-year prognosis (hazard ratio [HR] 1.73, 95% confidence interval [CI] 1.08–2.75), whereas frailty without anorexia was not (HR 1.28, 95% CI 0.84–1.96).

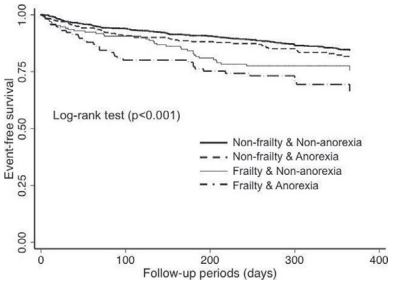


Figure 1. Kaplan-Meier curve analysis

Conclusion: The results of this study indicate that anorexia leads to poor prognosis in fragile HF patients and should be assessed along with frailty in clinical practice.
Funding Acknowledgements: This study is supported by a Grant-in-Aid for Scientific Research (A) from the Japanese Society for the Promotion of Science [16H01862].

P3197

Frailty predicts short-term heart failure re-hospitalization independently from other known prognostic indicators in patients with heart failure: a multicenter prospective cohort study

S. Yamada[1], T. Adachi[2], K. Iwatsu[3], R. Fujita[4], K. Kamisaka[5], E. Nakane[6], D. Sakui[7], I. Kawamura[8], K. Shibata[9], M. Ehara[10], H. Ohtake[11], T. Shimozato[12], N. Iritani[13], M. Terashima[14]. *[1]Nagoya University Graduate School of Medicine, Department of Health Sciences, Nagoya, Japan; [2]Nagoya University Graduate School of Medicine, Department of Rehabilitation Science, Nagoya, Japan; [3]Hirakata Kohsai Hospital, Department of Rehabilitation, Hirakata, Japan; [4]Hirakata Kohsai Hospital, Department of Cardiology, Hirakata, Japan; [5]Kitano Hospital, Rehabilitation Center, Osaka, Japan; [6]Kitano Hospital, Cardiovascular Center, Osaka, Japan; [7]Gifu Heart Center, Department of Rehabilitation, Gifu, Japan; [8]Gifu Heart Center, Department of Cardiology, Gifu, Japan; [9]Nagoya Heart Center, Department of Rehabilitation, Nagoya, Japan; [10]Nagoya Heart Center, Department of Cardiology, Nagoya, Japan; [11]Nagoya Tokushukai General Hospital, Department of Rehabilitation, Kasugai, Japan; [12]Nagoya Tokushukai General Hospital, Department of Cardiology, Kasugai, Japan; [13]Toyohashi Heart Center, Department of Rehabilitation, Toyohashi, Japan; [14]Toyohashi Heart Center, Department of Cardiology, Toyohashi, Japan.* On behalf of FLAGSHIP collaborators

Background: As prognostic impact of frailty in heart failure (HF) has been published, indistinct clinical consensus that fragile HF patients tend to be re-hospitalized earlier than the patients without frailty has been raised. To establish clinical availability, short-term prognostic value of frailty need to be examined.
Purpose: This study aimed to examine the predictive ability of frailty-based assessment for HF re-hospitalization within six months.
Methods: This prospective study was conducted as a part of a multicenter cohort study in Japan to develop frailty-based diagnostic criteria of frailty in HF patients (FLAGSHIP). We analyzed 1,606 ambulatory HF patients using data of discharge and follow-up. Study outcome was HF re-hospitalization within six months. Frailty was assessed with following three items; usual walking speed (UWS), grip strength (GS) and Performance Measure of Activity in Daily Living-8 (PMADL-8) $\geq$21. A cut-off value of each indicator was identified using receiver operating characteristic (ROC) analysis to predict study outcome, and the number of frailty items was calculated for each subject. Additionally, from data set at discharge, we collected age, women, left ventricular ejection fraction $<$40%, history of HF hospitalization, brain natriuretic peptide $\geq$200 pg/ml, geriatric nutritional risk index (calculated using height, weight and albumin), anemia ($<$13 g/dl for men, $<$12 g/dl for women), high-sensitivity C-reactive protein, sodium, chronic kidney disease (CKD, estimated glomerular filtration rate $<$30 ml/min/1.73m^2), depression (5-item geriatric depression scale $\geq$2), Mini-Mental State Examination and medications for HF treatment. Cox proportional hazards model was performed including all variables to identify independent predictors of short-term HF re-hospitalization.
Results: A total of 173 HF re-hospitalization were observed (10.8%). Cut-off value of each frailty item was as follows; UWS $<$0.911 m/s; GS $<$26.8 kg (men), 16.5 kg (women); PMADL-8 $\geq$21. As the results of Cox proportional hazards model, independent predictors of 6-month HF re-hospitalization were the number of frailty items (0 vs 3, hazard ratio [HR] 1.95; 95% confidence interval [CI] 1.16–3.28), history of HF hospitalization (HR 2.27; 95% CI 1.63–3.16), anemia (HR 1.48; 95% CI 0.99–2.20), CKD (HR 1.66; 95% CI 1.16–2.38), oral inotropic agent (HR 1.97; 95% CI 1.35–2.87).
Conclusion: Our results demonstrate that frailty becomes a novel short-term prognostic indicator for HF re-hospitalization independently from other known prognostic factors.
Funding Acknowledgements: This study is supported by a Grant-in-Aid for Scientific Research (A) from the Japanese Society for the Promotion of Science [16H01862].

ROLE OF NON CODING RNAS IN CARDIOVASCULAR DISEASES

P3198

Long noncoding RNA NEAT1 controls ROS production in macrophages and is suppressed in post-myocardial infarction patients

W. Poller[1], M. Gast[1], S. Nakagawa[2], J. Haas[3], N. Nath[4], C. Mueller[5], T. Hirose[6], U. Rauch[1], C. Skurk[1], B. Rauch[7], S. Blankenberg[5], A. Kuss[8], B. Meder[3], U. Landmesser[1], T. Zeller[5]. *[1]Charité - Universitätsmedizin Berlin, Cardiology, Berlin, Germany; [2]Hokkaido University, Faculty of Pharmaceutical Sciences, Sapporo, Japan; [3]University Hospital of Heidelberg, cardiology, Heidelberg, Germany; [4]University Medicine of Greifswald, Bioinformatics, Greifswald, Germany; [5]University Heart Center Hamburg, Hamburg, Germany; [6]Hokkaido University, genetic Medicine, Sapporo, Japan; [7]University Medicine of Greifswald, Institute for Pharmacology, Greifswald, Germany; [8]University Medicine of Greifswald, Genetics and Functional Genome Research, Greifswald, Germany*

Background: Inflammation is a key driver of atherosclerosis and myocardial infarction (MI), and beyond proteins and microRNAs, long noncoding RNAs (lncRNAs) have been implicated in inflammation control. In a previous study of circulating immune cells (PBMCs) from post-MI patients, we identified distinctive anomalies in the patients by comprehensive RNA-sequencing (RNA-seq) based transcriptome mapping (protein-coding transcripts, lncRNAs). Among deregulated lncRNAs, NEAT1 was the most highly expressed and the only one significantly suppressed in patients.
Methods and results: We subsequently investigated NEAT1 knockout (NEAT1–/–) mice as a model of the NEAT1 deficiency observed in post-MI patients, and thus evaluated if NEAT1 depletion may directly and causally alter immunoregulation. NEAT1–/– mice displayed a massive (6.6-fold, p$<$0.001) increase in the ROS production from NEAT1–/– macrophages ex vivo in response