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Sarcopenia in patients with heart failure with preserved ejection fraction: Impact on muscle strength, exercise capacity and quality of life

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Abstract

Background: To describe the prevalence of sarcopenia in ambulatory patients with heart failure with preserved ejection fraction (HFpEF) and its relation to reduced exercise capacity, muscle strength, and quality of life (QoL).

Methods and Results: A total of 117 symptomatic outpatients with HFpEF were prospectively enrolled in Germany, England, and Slovenia as part of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). Appendicular skeletal muscle (ASM) mass (the sum of muscle mass in both arms and legs) was assessed by DEXA. Echocardiography, 6-minute walk testing (6-MWT), muscle strength assessment, spirometry and QoL evaluation using EQ-5D Questionnaire were performed. Sarcopenia was defined as ASM 2 standard deviations below the mean of a healthy reference group aged 18-40 years. Patients were divided into 3 groups according to the E/e' value: ≤ 8 , 9-14, and ≥ 15 . Sarcopenia was detected in 19.7% of all patients. These patients performed worse during 6-MWT (404 ± 116 vs. 307 ± 145 meters, $p=0.003$) and showed lower absolute peak oxygen consumption (1579 ± 474 vs. 1211 ± 442 ml/min, $P<0.05$). Both ASM and muscle strength were lowest in patients with $E/e' > 15$ ($P<0.05$). Higher values of muscle strength/ASM were associated with a better QoL ($r=0.5$, $p<0.0005$). Logistic regression showed ASM to be independently associated with reduced distance walked during the 6-MWT adjusted for NYHA, height, left atrium diameter, ferritin and forced expiratory volume in 1 second (FEV1) (odds ratio 1.2, $p=0.02$).

Conclusion: Sarcopenia affects a clinically relevant proportion of patients with HFpEF. Low ASM is strongly linked to reduced muscle strength, exercise capacity and QoL in these patients.

Keywords

Heart failure with preserved ejection fraction - muscle wasting – sarcopenia - exercise capacity - quality of life.

1. Introduction

Heart failure (HF) is a major public health problem. About 50% of all patients with HF present with preserved left ventricular ejection fraction (HFpEF) on imaging tests (1,2). The main symptom of these patients with HFpEF is dyspnea or early fatigue (3-5). The underlying causes are heterogeneous and not well understood. Several mechanisms might have a role in explaining the pathophysiology, as for example reduced left ventricular (LV) longitudinal strain function (6), and higher LV filling pressures (7). Recent studies suggest that peripheral factors such as skeletal muscle abnormalities may contribute to decreased maximal oxygen consumption (peak VO_2) and may explain its improvement after exercise training (8-12).

After the age of 50, muscle mass declines by 1-2% annually (13) and muscle strength by about 1.5%; this process accelerates to as much as 3% per year after age 60 (14). Such age-related loss of skeletal muscle mass and function is part of the normal aging process and has been termed sarcopenia or muscle wasting (15), and it affects about 10% of elderly healthy subjects aged 60-70 years (12,16-17). The 2016 HF guidelines of the European Society of Cardiology acknowledge sarcopenia as an important co-morbidity of HF that requires particular attention (18), because wasting processes are accelerated and more pronounced in chronic diseases including HF (19). The prevalence of sarcopenia in a mixed cohort of patients with symptomatic chronic HF was found to be 19.5% in a recently published study by our group (10). However, its prevalence in a highly selected HFpEF cohort and its association with exercise capacity and muscle strength in these patients have not been investigated yet.

The Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) were designed as an observational study into the co-morbidities of HF, whether with reduced or preserved ejection fraction (20). The project was jointly funded by the European Commission

and the Russian Ministry of Health. Using data from SICA-HF, the present study aimed to investigate the prevalence and clinical effects of sarcopenia in patients with HFpEF.

2. Methods

2.1. Study population

We included symptomatic out-patients with HFpEF enrolled between March 2010 and September 2013 into SICA-HF, a European observational multi-center study investigating the prevalence, incidence and impact of key co-morbidities of HF in out-patients with a clinical diagnosis of chronic HF. For this sub-study, subjects were recruited from the Departments of Cardiology at the Charité Medical School, Campus Virchow-Klinikum, Berlin, Germany (n=61, 52.1%); Hull University Hospital, Hull, England (n=32, 27.4%); and Golnik University Hospital, Golnik, Slovenia (n=24, 20.5%). All subjects provided written informed consent at enrolment, and the protocol was approved by the responsible ethical review boards (20). The study was funded by the European Commission's 7th Framework program (FP7/2007-2013) under grant agreement number 241558 and fulfilled all principles of the Declaration of Helsinki. The protocol is registered at clinicaltrials.gov under the unique identifier number NCT01872299.

HFpEF was defined as the presence of signs and symptoms of HF combined with an LVEF $\geq 50\%$ on echocardiography and dilated left atrium (left atrial volume index ≥ 34 ml/m² as assessed using the Du Bois formula for estimating the body surface area) and/or evidence of diastolic dysfunction on tissue doppler examination (septal e' <8, and/or lateral e' <10) (21-22). Patients with severe valve abnormalities were excluded in the present analysis. Overall, 117 patients fulfilled these criteria. Patients were further sub-grouped into one of three groups according to E/e' value with e' being the average of septal and lateral values in this equation as ≤ 8 (group A), 9-14 (group B), ≥ 15 (group C) (21-22).

2.2. Assessment of muscle strength, muscle function, and functional capacity

Body composition analysis was performed using dual energy X-ray absorptiometry (DEXA) with a Lunar Prodigy device together with Lunar en Core 2002 software (both from GE Medical Systems, Madison, WI, USA). Appendicular skeletal muscle mass (ASM) that includes non-fat and non-bone tissue in both arms and legs combined in grams was analyzed in all patients to evaluate skeletal muscle mass according to the definition of sarcopenia (muscle wasting) (23-24). In accordance with previously published consensus statements and using reference values (7.26 kg in men vs. 5.45 kg in women) from the previously published younger (age range: 18-40 years) Rossetta cohort (25-26), sarcopenia was defined as muscle mass 2 standard deviations below the mean of the reference values in this reference population. The ratio resulting from indexing appendicular lean mass to body height (in meters squared) was used to separate patients with and without sarcopenia (27).

Muscle strength was assessed in 54 patients as handgrip strength (HGS) using a handgrip dynamometer (Saehan Coporation Korea Hydraulic Hand Dynamometer, model SH5001). Knee extension (quadriceps) strength was measured in 54 patients using isokinetic dynamometer (Multitrace 2, Lectromed, Jersey, Channel Islands) in both legs in a sitting position with the patient's legs hanging freely, the ankle fixed by a pressure transducer (kilograms). The best of three measurements was used in each of the hand- and knee extension strength tests as defined in the protocol (20). The maximum uptake of oxygen (peak VO_2 in mL/kg/min or absolute peak VO_2 in mL/min) was measured using spiroergometry with a treadmill and the modified Bruce protocol (50 patients) (28). In selected patients, the modified Naughton protocol was used (29). In addition, a 6-minute corridor walk test (6-MWT) was performed in 86 patients. As part of the co-morbidities work-up, patients were

also screened for the presence of iron deficiency, defined as ferritin < 100 µg /L or 100-299 µg/L and transferrin saturation (TSAT) < 20%

2.3. Quality of life assessment

Quality of life was assessed using the VAS (Visual Analogue Scale), which is part of the European Quality of Life–5 Dimensions (EQ-5D) questionnaire (30). This questionnaire captures a self-rating of health status on a 20-cm vertical VAS, anchored at 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom the score. EQ-5D (VAS) ratings are a quantitative measure, and differences in this scale can be used as a measure of outcome, as judged by the individual respondents (31-32).

2.4. Statistical analysis:

Data are presented as mean ± standard deviation (SD) or median with percentiles. StatView 5.0 (SAS Institute, inc., Cary, USA) and the Statistical Package for the Social Sciences (version 21, IBM Cop. Armonk, NY, USA) were used for statistical analysis. Analysis of variance (ANOVA), Student's unpaired *t*-test, Fisher's exact test, Pearson's simple and logistic regression were used as appropriate. A two-tailed *p*-value ≤0.05 indicates statistical significance.

3. Results

We enrolled a total of 117 patients with HFpEF who were symptomatic with a mean New York Heart Association (NYHA) class NYHA 2.4±0.5 with most patients (60.2%) being in NYHA class II (Table 1). Of all patients, 38 (32.5%) were female, and 22 were found to

have E/e' values ≤ 8 , 79 had moderately elevated E/e' between 9 and 14, and 16 had elevated values E/e' ≥ 15 . Twenty-three of all patients with HFpEF (19.7%) were found to fulfill the criteria of sarcopenia, 87% of them were males. Patients with sarcopenia performed worse on the 6-MWT (404 ± 116 vs. 307 ± 145 meters, $p=0.003$), showed lower absolute peak VO_2 (1579 ± 474 vs. 1211 ± 442 mL/min, $p<0.05$) and had shorter exercise time (604 ± 177 vs. 477 ± 152 seconds, $p=0.03$), lower VE/VCO_2 (31 ± 6 vs. 37 ± 4 , $p=0.01$) on spiroergometry testing (see Table 1, Figures 1a-1b).

By dividing the HFpEF cohort into subgroups according to E/e' we found that there was a steady reduction of appendicular lean mass (ASM/BMI) with increased severity of diastolic dysfunction (group A 0.84 ± 0.19 vs. group B 0.76 ± 0.16 vs. group C: 0.71 ± 0.11 , $p=0.03$) (Table 2). The same applied for handgrip strength in both hands (Figure 2a), and knee extension strength measurements (Figure 2b). A trend was noted with regards to exercise time on spiroergometry testing with patients with more severe diastolic dysfunction having shorter exercise duration values (group A 705 ± 170 vs. group B 552 ± 169 , vs. group C 576 ± 201 seconds, $p=0.06$).

3.1. Correlation analyses

Lower values for appendicular lean mass were associated with more severe diastolic dysfunction as measured by E/e' ($r=-0.22$, $p<0.02$; Figure 3). Using simple regression, we found higher values of ASM to be positively associated with a higher value of absolute peak VO_2 ($r=+0.67$, $p<0.0001$, Figure 4), muscle strength in hands and legs in both sides ([right hand: $r=+0.59$, $p<0.0001$; left hand: $r=+0.62$, $p<0.0001$], [right leg: $r=+0.37$, $p<0.006$; left leg: $r=+0.47$, $p=0.0003$]), exercise time ($r=+0.33$, $p=0.01$), and 6-MWT ($r=+0.30$, $p=0.003$). Furthermore, higher peak VO_2 was seen in patients with higher values of muscle strength in arms ($p<0.001$) and legs ($p<0.01$). Higher muscle strength/muscle mass (both in kg) was

associated with higher quality of life in HFpEF patients estimated by the VAS-Score ([left leg: $r=+0.5$, $p=0.001$], right leg: [$r=+0.38$, $p=0.01$], Figures 5a and 5b).

3.2. Exercise Capacity

A 6-MWT distance was covered by 86 (73.5%) of all patients, 19 (22.1%) of those with sarcopenia and 67 (77.9%) of those without ($p=0.003$). Univariate logistic regression showed that FEV1, FVC, NYHA class, height, ferritin, left atrium diameter, quadriceps strength and ASM were all associated with reduced exercise capacity evaluated by 6-MWT, defined as a distance walked <400 m during the test (all $p<0.05$). This was not the case for age, sex, E/e', LVEF, anemia, Hb, or the presence of iron deficiency. Multivariable logistic regression showed that appendicular lean mass remained independently associated with reduced exercise capacity after adjustment for parameters found to be statistically significant predictors on univariate analysis (odds ratio 1.2- per 500g increase of appendicular lean mass, 95% confidence interval 1.03-1.33, $p=0.02$) (Table 3).

4. Discussion

The main symptom in patients with HFpEF is exercise intolerance whose etiology has been deemed multifactorial. The role of peripheral factors, such as skeletal muscle mass, strength and function, is poorly understood. This is the first multicenter European study that describes the prevalence of sarcopenia in patients with HFpEF and its impact on exercise capacity, muscle strength, and quality of life. Overall, 19.7% of the symptomatic stable HFpEF out-patients in our cohort presented with sarcopenia, *i.e.* muscle wasting. These patients showed reduced exercise capacity, measured objectively in the cardiopulmonary exercise test as well as in 6-MWT. Furthermore, scores of the VAS (Visual Analogue Scale)

derived from the EQ-5D showed higher quality of life in patients with higher values of the ratio muscle strength/muscle mass. In addition, there was a steady increase in absolute peak VO_2 in parallel to the increased values of ASM. This could support the supposed role of muscle mass in explaining reduced exercise tolerance in patients with HFpEF and its improvement after exercise training (11).

In our previously published study of a mixed cohort of patients with HF, we described the prevalence of sarcopenia (muscle wasting) in patients with chronic HF with either HF with reduced LVEF or HF with dilated atrium (diameter >40 mm) and LVEF $>40\%$ (20). The prevalence of muscle wasting in the overall cohort was 19.5%, with lower values in the group with only mildly reduced or normal LVEF. However, using a more restrictive definition of HFpEF in the present study, we found the prevalence of sarcopenia in patients with HFpEF as defined by the European and American Societies of Cardiology and Echocardiography to be very similar to that of the mixed cohort (21-22). Patients in the present cohort had typical characteristics of HFpEF. Most of the patients with severe diastolic dysfunction ($E/e' \geq 15$) were women, had higher cardiac muscle mass index, left atrium volume index (LAVI), and estimated systolic pulmonary artery pressure. The prevalence of sarcopenia among patients with enlarged atrium and LVEF $>40\%$ in the mixed cohort was lower than that of patients with reduced ejection fraction. We believe that the difference in the prevalence of sarcopenia between the two studies is due to the different definitions and more sophisticated characteristics of HFpEF in the present study.

It is known that muscle undergoes changes such as decline in muscle mass and muscle strength as part of the pathophysiology of the ageing process (12). These changes include a switch in the muscle fibers types from fast type II to the slow type I fibers and a reduction in capillary density (33,34). This may result in reduced physical performance. The prevalence of muscle wasting described in healthy adults aged 60-70 years is 5-13% (12). Our finding of

almost 20% of HFpEF patients to have sarcopenia is considerably higher than what was expected according to the age category alone. Sarcopenia can be observed in many other chronic diseases like chronic obstructive pulmonary disease (COPD). One study found that 14.5% of patients of COPD had sarcopenia, and prevalence was higher with worsening of COPD status (35). The pathophysiology of muscle wasting in patients with chronic diseases is not entirely clear yet. Signaling pathways may be different in healthy aging and in patients with chronic diseases with higher inflammatory load and thus more pronounced proteasome activity in patients with chronic disease, thus serving as a basis for active myofibril degeneration (34,39). Indeed, one of the hypotheses holds that inflammatory processes, which accompany many chronic diseases, may lead to metabolic changes. These, in turn, lead to an imbalance between anabolic and catabolic signals (36). The stimulation of catabolic pathways induces protein breakdown and as a result affects skeletal muscle (37). Pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) intensify catabolism (38,39). We detected significantly elevated serum levels of IL-6 among HF patients with muscle wasting already in our previously published study in patients with chronic HF (10). Our results could open a new horizon in the treatment targets of patients with HFpEF through developing new nutritional or hormonal treatments (40) or by developing special exercise training programs as recommended from the European Society of Cardiology in patients with HF (41). This may lead to improve muscle mass, muscle strength, exercise capacity (11,42), and as a result the quality of life in this group of patients.

5. Conclusions:

This multi-center study shows that patients with HFpEF are at least as frequently affected by sarcopenia as patients in mixed cohort described previously that predominantly embraced patients with reduced ejection fraction. Patients with HFpEF and sarcopenia have

worse exercise capacity as assessed in the cardiopulmonary test and in the 6-MWT as well as worse QoL.

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7. Conflict of interest:

SvH is consulting and has received honoraria for speaking from Solartium Dietetics, Professional Dietetics, Vifor, Novartis, Chugai, Respocardia, Sorin, and Pfizer. SDA is consulting, has received honoraria for speaking and/or attended advisory boards for Amgen Inc, Professional Dietetics, Psioxus Therapeutics, GTx, Helsinn, GSK, Sanofi, Regeneron, Novartis, Takeda, Servier, Chugai and Vifor. All other authors report no conflict of interest.

8. Figure legends:

Figure 1a: Exercise capacity assessed by the distance walked in 6-min walk test in patients with and without muscle wasting.

Figure 1b: Absolute peak VO_2 assessed by a treadmill in the spiroergometry test in patients with and without muscle wasting.

Figure 2a: Handgrip strength as assessed by a handgrip dynamometer in patients of different severities of diastolic dysfunction.

Figure 2b: Quadriceps strength assessed by an isokinetic dynamometer in patients of different severities of diastolic dysfunction.

Figure 3: Simple regression analysis of appendicular lean mass and E/e' .

Figure 4: Simple regression analysis of appendicular lean mass and absolute peak VO_2 .

Figure 5a-5b: Simple regression analysis of Muscle strength/muscle mass (both in kg) of both legs and quality of life assessed by VAS-Score.

9. Tables:

Table 1: Baseline characteristics of patients with muscle wasting vs. without muscle wasting:

Variable	All Patients (n=117)	Patients without muscle wasting (n=94)	Patients with muscle wasting (n=23)	P-Value
Sex (m/f %)	67.5/32.5	62.8/37.2	87/13.0	0.03
Age (years)	69.8±8.5	69.1±8.4	72.3±8.5	0.11
Weight (kg)	89.27±19.53	92.75±18.40	75.05±17.78	< 0.0001
BMI (kg/m ²)*	30.95±6.57	32.18±6.36	25.69±4.68	< 0.0001
Hip circumference (cm)	112.11±12.69	113.42±12.87	105.29±9.33	0.02
NYHA	2.4±0.5	2.3±0.5	2.7±0.5	0.002
Hypertension (present)	89%	89%	90%	>0.99
Diabetes mellitus (present)	48%	50%	33%	0.48
Atrial fibrillation (present)	25%	28%	10%	0.15
Hemoglobin (g/dL)	13.5±1.6	13.4±1.6	13.8±1.7	0.33
Creatinin (mg/dL)	1.1±0.4	1.1±0.4	1.1±0.5	0.82
LDL-Cholesterol (mg/dL)	102.3±42.5	102.1±44.0	100.1±36.8	0.85
Ferritin (ng/mL)	186.9±194.9	197.6±201.3	142.1±162.1	0.24
LVEF %‡	58.8±7.3	58.5±6.8	59.9±9.3	0.42
Left ventricular mass index (gm/m ²)	126.94±36.26	127.94±38.30	122.73±26.35	0.55
LAVI (ml/m ²)§	37.44±13.57	38.07±13.94	32.71±9.61	0.24

PAP (mmm/Hg)†	35.61±10.24	35.06±10.17	38.14±10.89	0.45
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*BMI: Body Mass Index, ‡LVEF: Left ventricular ejection fraction. §LAVI: Left atrium volume index, †PAP: Pulmonary artery pressure.

Table 2: Baseline characteristics of HFpEF patients

Variable	Group A E/e' ≤8 n=22	Group B E/e' 9-14 n=79	Group C E/e' ≥15 n=16	p Value ANOVA
Age (years)	67.9±8.5	70.2±8.4	70.0±9.1	0.53
Sex (m/f %)	77.3/22.7	70.9/29.1	37.5/62.5	0.02
BMI (kg/m ²)	29.88±6.75	31.02±6.82	31.21±5.14	0.70
NYHA	2.22±0.43	2.46±0.50	2.31±0.48	0.14
Left ventricular mass index (gm/m ²)	111.30±28.54	127.33±35.55	145.57±41.21	0.02
LAVI(ml/m ²)*	35.00±18.36	36.21±9.48	45.43±16.34	< 0.05
E/A	0.98±0.52	0.99±0.59	1.5±0.98	0.04
PAP (mmHG)†	34.27±7.85	34.08±10.45	47.43±5.23	0.02
LVEDVI (ml/m ²)§	52.69±16.51	51.27±15.37	52.76±16.79	0.92
LVESVI (ml/m ²)¶	23.23±9.16	22.33±8.20	21.23±8.95	0.79
LVEF (%)‡	57.68±5.81	58.81±7.62	60.00±7.77	0.63

*LAVI: Left atrium volume index, †PAP: Pulmonary artery pressure, §LVEDVI: Left ventricular end diastolic volume index, ¶LVESVI: Left ventricular end systolic volume index. ‡LVEF: Left ventricular ejection fraction.

Table 3: Logistic regression model with reduced exercise capacity (defined as 6-MWT below 400 m) serving as the dependent variable.

	Univariate			Multivariate		
	OR	95% CI	P-Value	OR	95% CI	P-Value
Age (per year increase)	1.01	0.96-1.06	0.72			
Sex (female)	0.60	0.24-1.51	0.27			
NYHA (per 1 class increase)	9.37	3.22-27.20	<0.0001	13.29	2.73-64.62	0.001
Height (per 10 cm increase)	0.49	0.29-0.84	0.009	0.52	0.16-1.72	0.28
BMI (per kg/m ² increase)	1.02	0.95-1.09	0.63			
Atrial fibrillation (present)	1.25	0.64-5.44	0.86			
Left atrium diameter (per 1 mm increase)	0.27	0.12-0.64	0.003	0.4	0.09-1.78	0.23
E/e' (per 1 unit increase)	0.99	0.91-1.09	0.88			
Peak VO ₂ (per 1 ml/kg/min increase)	0.37	0.19-0.72	0.003			
FEV1 (per 1 L/s increase)	0.21	0.1-0.46	<0.0001	0.1	0.02-0.26	0.006
FVC (per 1 L increase)	0.44	0.24-0.79	0.006			
Anemia (present)	0.98	0.37-2.61	0.97			
Iron deficiency (present)	0.57	0.23-1.38	0.21			
Ferritin (per 1ng/mL increase)	1.0	0.99-1.00	0.02	1.0	0.99-1.00	0.5

ASM (per 500 g increase)	0.95	0.91-1.00	0.03	1.2	1.03-1.33	0.02
Left quadriceps strength (per 1kg increase)	0.91	0.86-0.98	0.009			
Right quadriceps strength (per 1 kg increase)	0.92	0.86-0.98	0.01			

Table 4: Patients' medication at study entry

	All patients % (n=117)	Patients with muscle wasting % (n=23)	Patients without muscle wasting % (n=94)	P- value
Beta-blocker	79.2	88.9	77.9	0.68
ACE-inhibitors	63.6	54.0	63.3	>0.99
Angiotensin receptor blockers	29.9	33.3	29.4	>0.99
Digitals	13.0	11.1	13.2	>0.99
Loop diuretics	48.05	33.3	50.0	0.84
Aspirin	54.5	66.6	52.9	0.5
Statins	68.8	77.8	67.6	0.71
Calcium channel blocker	22.1	44.4	19.1	0.1
Anticoagulants	29.9	11.1	32.4	0.27

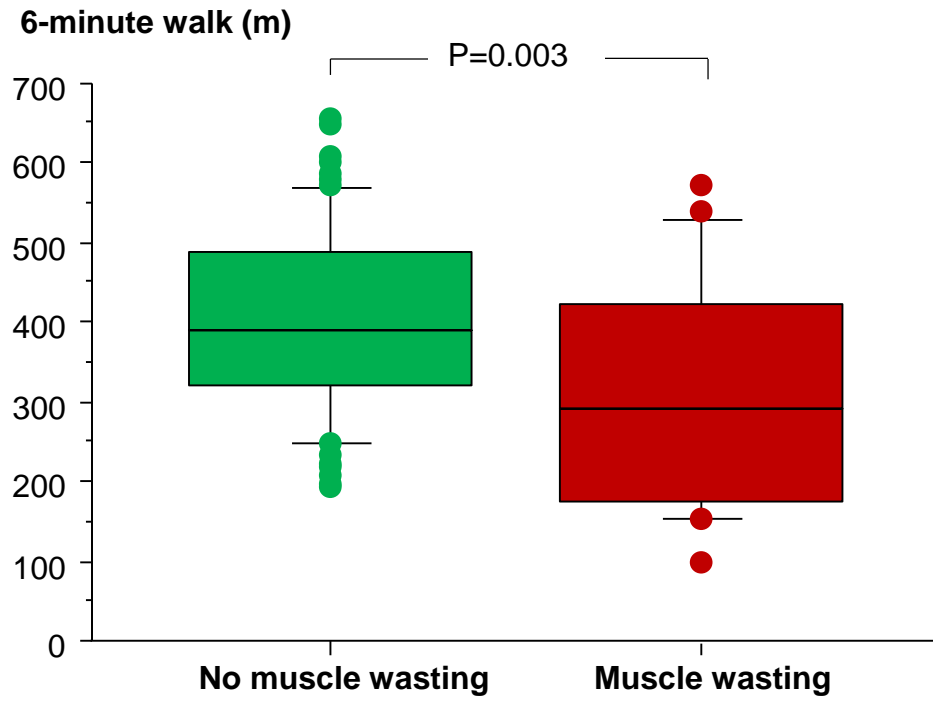


Figure 1a

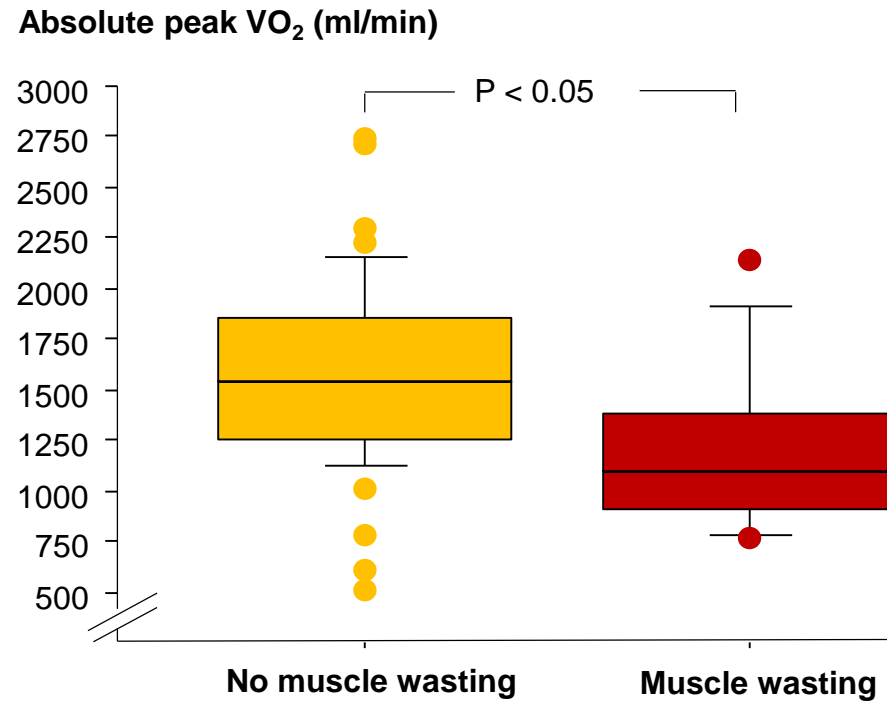


Figure 1b

Right handgrip strength (kg)

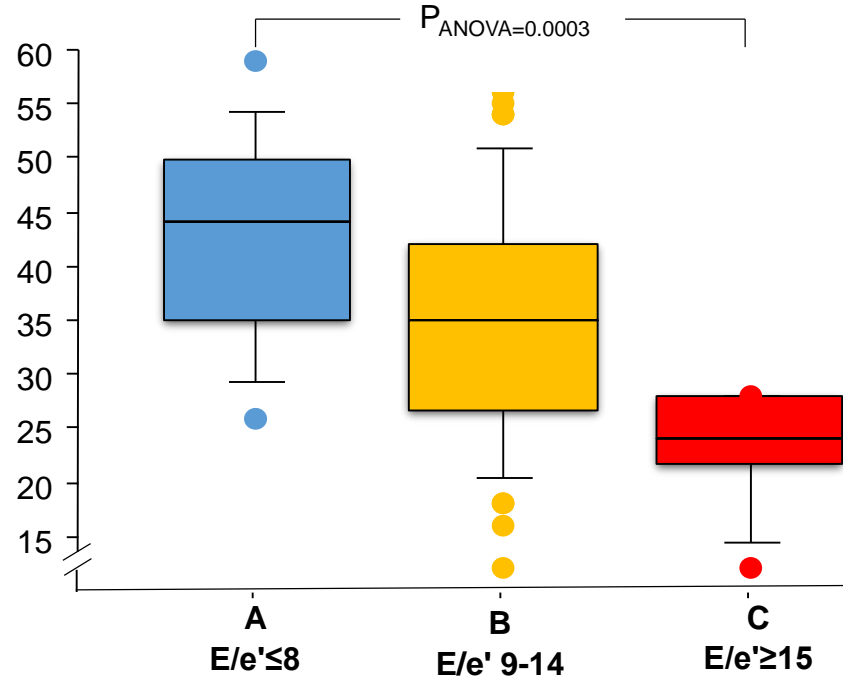


Figure 2a

Right quadriceps strength (kg)

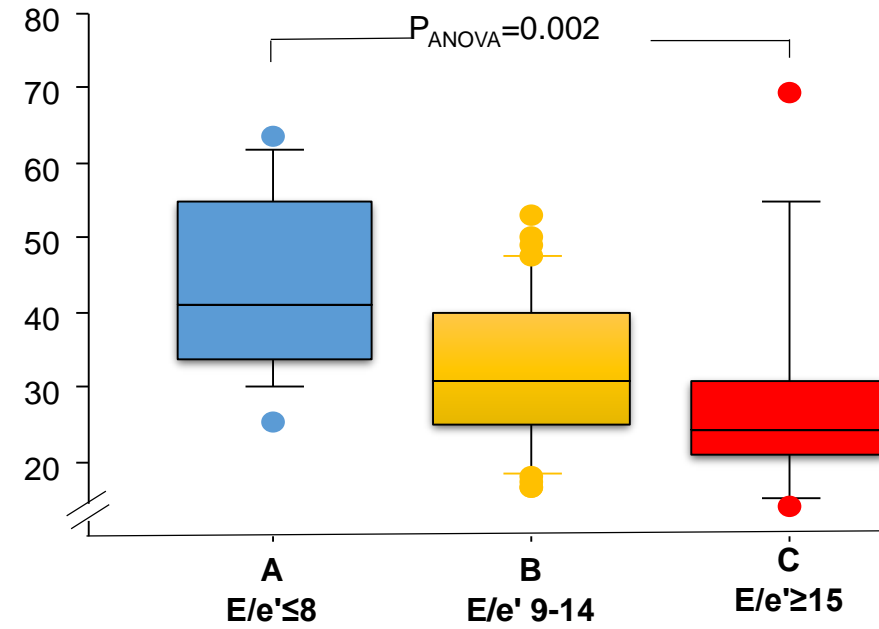


Figure 2b

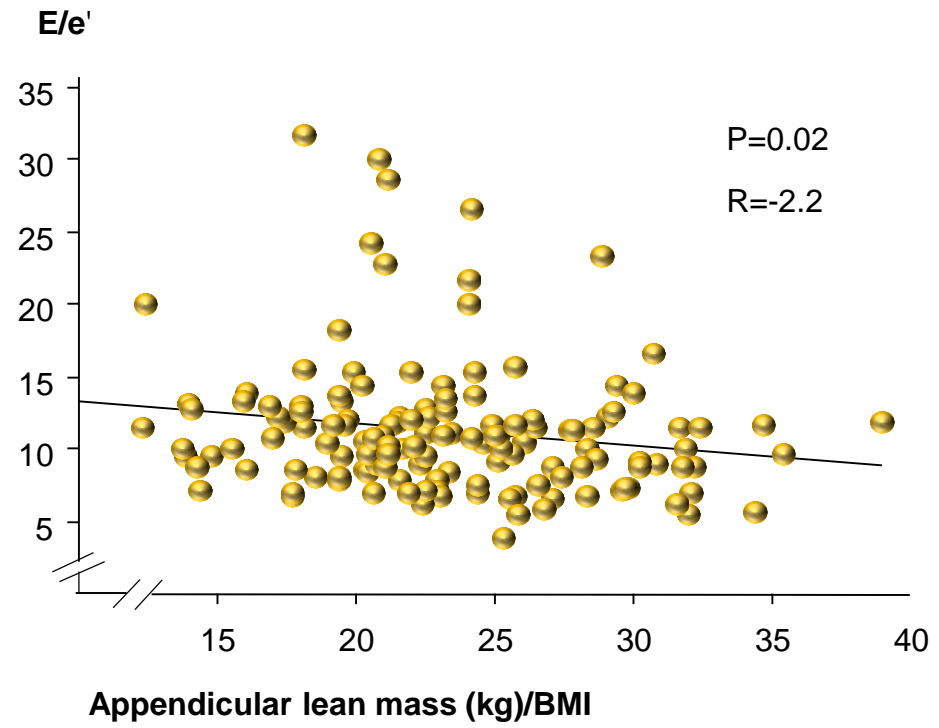


Figure 3

Absolute peak VO₂ (ml/min)

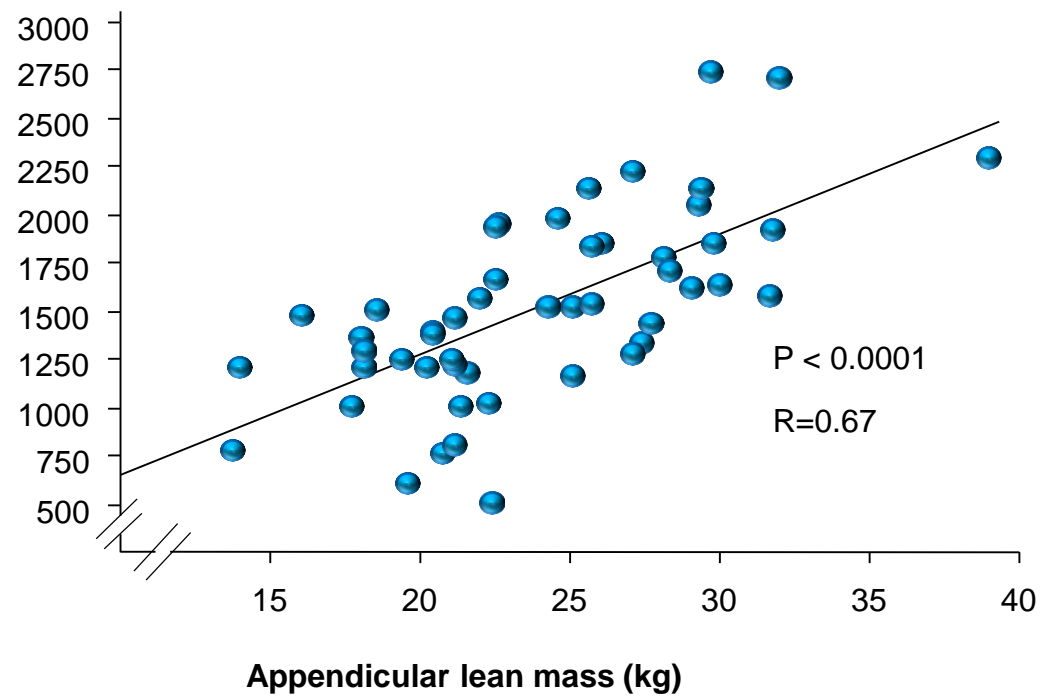


Figure 4

Vas-Score

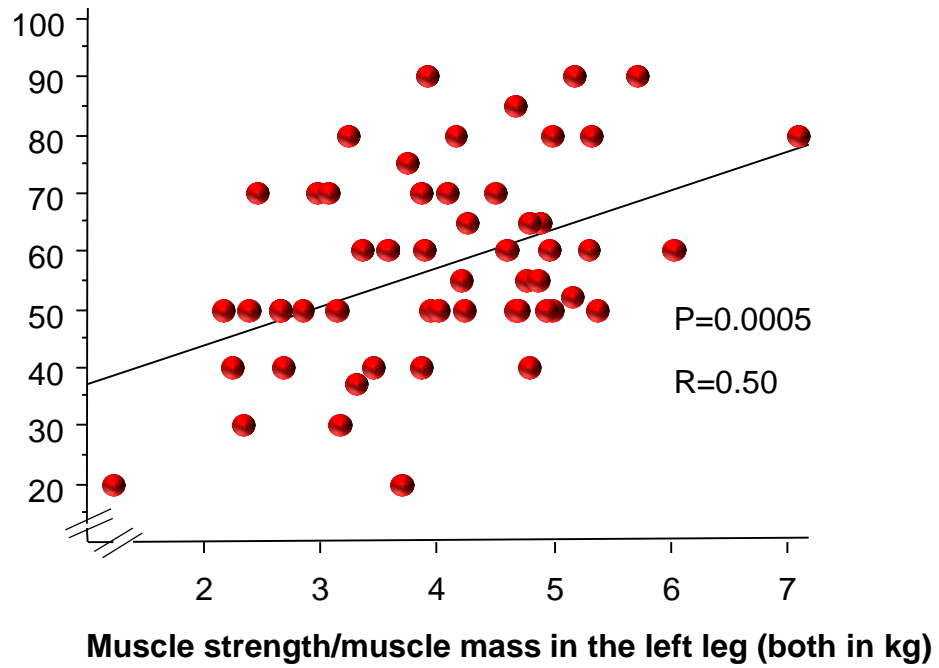


Figure 5a

Vas-Score

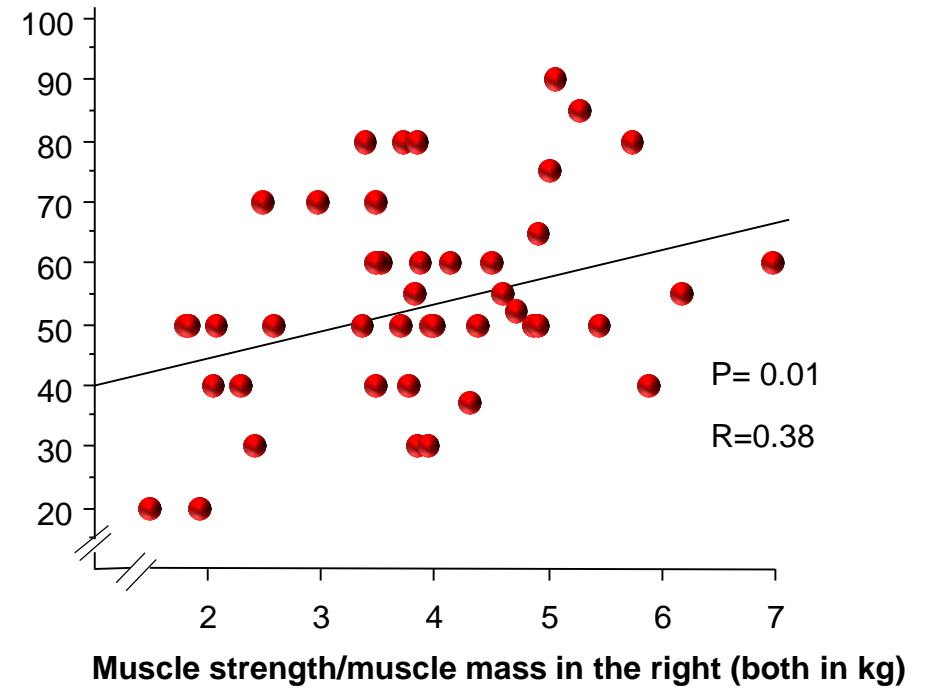


Figure 5b