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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, spiroergometry 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 m, $p = 0.003$) 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 s (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.

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].

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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 241,558 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 ≥50% on echocardiography and dilated left atrium (left atrial volume index ≥34 mL/m^2 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 Corporation 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 m, 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 s, p = 0.03), lower VE/VCO_2 (31 ± 6 *vs.* 37 ± 4, p = 0.01) on spiroergometry testing (see Table 1, Table 2, Fig. 1a–b).

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 3). The same applied for handgrip strength in both hands (Fig. 2a), and knee extension strength measurements (Fig. 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 s, 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; Fig. 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, Fig. 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], Fig. 5a and b).