

Android to gynoid fat ratio and its association with functional capacity in male patients with heart failure

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Abstract

Aims We studied the association between android (A) to gynoid (G) fat ratio and functional capacity (peak VO_2) in male patients with heart failure with reduced ejection fraction (HFrEF).

Methods and results We enrolled 118 male patients with HFrEF with left ventricular ejection fraction (LVEF) <40%. Body composition (by using dual x-ray absorptiometry) and peak VO_2 (by cardiopulmonary exercise testing) were measured. Sarcopenic obesity was defined according to the Foundation for the National Institutes of Health criteria (FNIH). Blood sample for metabolic and hormonal parameters were measured. Fifteen patients (12.7%) showed sarcopenic obesity (body mass index > 25 kg/m² with FNIH index < 0.789). The median A/G ratio was 0.55. A/G ratio > 0.55 was detected in 60 patients. Relative peak VO_2 was lower in patients with A/G ratio > 0.55 than in patients with A/G ratio < 0.55 (18.7 ± 5.3 vs. 22.5 ± 6.1 mL/kg/min, $P < 0.001$). Logistic regression analysis showed A/G ratio > 0.55 to be independently associated with reduced peak VO_2 adjusted for age, body mass index, LVEF, presence of sarcopenia, anabolic hormones, and haemoglobin (odds ratio 3.895, 95% confidence interval 1.030–14.730, $P = 0.045$).

Conclusions Body fat distribution, particularly android and gynoid fat composition, together with other cofactors, might have an important adverse role on functional capacity in male patients with HFrEF. Future studies are needed to address possible mechanisms involved in this relationship.

Keywords Body composition; Fat distribution; Heart failure; Oxygen consumption

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Introduction

Heart failure with reduced ejection fraction (HFrEF) is a worldwide problem affecting 1–2% of the total population.¹ HFrEF is characterized by breathlessness, swelling, and exercise intolerance.¹ Moreover, comorbidities such as anaemia, diabetes, and sarcopenia/cachexia syndrome might be associated with HFrEF.² In fact, sarcopenia, which is a process of skeletal muscle loss with no change (or even an increase) in fat mass,³ is associated with poor outcome and affects around 20% of patients with HFrEF and preserved ejection

fraction (HFpEF).⁴ However, little is known about regional fat distribution and its consequence in patients with HFrEF.

Obesity is associated with several metabolic and cardiovascular diseases, including the development of heart failure.⁵ Curiously, overweight/obesity may have a protective role in patients with HFrEF, a phenomenon known as obesity paradox.⁶ However, some patients can also present sarcopenic obesity with similar exercise intolerance as lean patients with muscle wasting.⁶ Recently, it was shown that older, obese patients with HFpEF have larger composition of abdominal fat than healthy controls.⁷ Interestingly, this abdominal fat

deposition was associated with lower relative peak oxygen consumption (peak VO_2) after adjusting for cofactors such as age and sex. However, the impact of body fat distribution, mainly the central adiposity on exercise intolerance in HFrEF is unknown.

For instance, in the general population visceral adiposity is linked to the progression of sarcopenia, inflammation, and insulin resistance.³ Moreover, in patients with type 2 diabetes, visceral fat is an independent risk factor for cardiovascular disease.⁸ Fukuda and collaborators found that android to gynoid fat ratio (A/G ratio) was a good predictor of cardiovascular risk in patients with type 2 diabetes.⁸

Excess of adipose tissue, which contains the enzyme aromatase, metabolizes testosterone to oestrogen with consequent reduction of testosterone concentrations.⁹ These anabolic hormone alterations could also be responsible by the reduction of exercise capacity in patients with HFrEF.¹⁰ However, these important factors together (adipose distribution, anabolic hormones, and body composition) on exercise tolerance have never been studied in patients with HFrEF.

The aim of this study was to investigate the impact of A/G ratio on functional capacity (peak oxygen consumption) in patients with HFrEF. In addition, we tested the relationship between A/G ratio and anabolic parameters such testosterone, insulin-like growth factor-1 (IGF-1), and dehydroepiandrosterone (DHEA).

Methods

Study population

This is a unicentric, cross-sectional study, where we recruited 118 ambulatory male patients with clinically stable HFrEF. All subjects provided written informed consent at enrolment, and the local ethics committee approved the protocol. Part of the participants of this study is registered at Clinical Trials (NCT01852994 and NCT03190304).

Inclusion criteria were as follows: patients with HFrEF older than 18 years old; history of HFrEF greater than 6 months before the study; signs and symptoms suggestive of HF along with a clinical diagnosis; ischemic and non-ischemic aetiology; left ventricular ejection fraction (LVEF) <40%; New York Heart Association functional Class I–III; and compensated HFrEF with optimal medication.

Patients with previous hormonal treatment (testosterone replacement), heart transplantation, a history of unstable angina, myocardial infarction, stroke, cardiovascular revascularization within 6 weeks, biventricular pacemaker with or without implantable cardioverter-defibrillator, severe kidney dysfunction (under haemodialysis), and liver disease were excluded.

Maximal cardiopulmonary exercise test

The maximal cardiopulmonary test (Vmax, Mod. 29 S serie YL012278C, Sensor Medics Corporation) was performed on a cycloergometer (Medifit 400L, Medical Fitness Equipment) using a ramp protocol with workload (5 or 10 W) increment every minute. The patients were instructed to pedal at 60 rpm, and workload was increased progressively. The completion of the test occurred when, despite verbal encouragement, the patient could no longer maintain the exercise intensity and the maximal respiratory exchange ratio reached greater than 1.10.¹¹ Heart rate was continuously recorded at rest and during the graded exercise testing using a 12-lead digital electrocardiogram (ERGO PC 13, MICROMED Biotechnology Ltda).

Body composition

A dual X-ray absorptiometry (DXA) was used (Lunar iDXA, GE Medical Systems Lunar, Madison, USA) to measure body composition. Dual energy X-ray absorptiometry measures total mass, fat mass, and fat-free mass (estimate of muscle mass). Android and gynoid fat were measured, and the ratio between them was calculated (A/G ratio).

Appendicular lean mass (in kilograms) was calculated as the lean muscle mass of both arms and legs divided by the height (in metre) squared. Sarcopenic obesity was defined according to FNIH criteria (appendicular lean mass adjusted for body mass index < 0.789 for men),¹² and only those patients with body mass index (BMI) higher than 25 kg/m² were considered either overweight (25.0 to 29.9 kg/m²) or obese (30 kg/m² or higher). Patients with BMI lower than 25 kg/m² and with index <0.789 were not considered sarcopenic. Muscle strength was assessed using the handgrip dynamometer (cutoff point for sarcopenia was defined as proposed by European Working Group on Sarcopenia in Older People).¹³

Left ventricular ejection fraction evaluation

Left ventricular ejection fraction was evaluated (Teicholz) using two-dimensional imaging according to standard methods.¹⁴

Blood test

All patients had blood drawn in the morning (7:00–11:00 a. m.). Sodium, potassium, creatinine, total cholesterol, high density cholesterol, low density cholesterol, glycaemia,

thyroid stimulating hormone, and haemoglobin were measured. In addition, total testosterone, free testosterone, DHEA, and IGF-1 were measured in all patients. In our local laboratory, serum level of total testosterone (intra-assay coefficient of variation, $\leq 5.5\%$; interassay coefficient of variation, $\leq 5.4\%$) and sex hormone-binding globulin level (normal range, 12–75 nmol/L; intra-assay coefficient of variation, $\leq 2.3\%$; interassay coefficient of variation, $\leq 6\%$) were determined using standard laboratory techniques. Total testosterone and sex hormone-binding globulin levels were used to estimate free testosterone level by using the validated formula.¹⁵

Statistics analysis

Data are presented as mean \pm standard deviation or median and interquartile range (25–75%). The Shapiro–Wilk test was used to assess normality of distribution and Levene's test to assess homogeneity. Paired Student's *t*-test or Mann–Whitney test were used to assess the within group differences. Pearson's chi-square test and logistic regression were used as appropriate. The Hosmer and Lemeshow test was used to evaluate the goodness of fit of logistic regression

models. A two-tailed *P* value < 0.05 indicates statistical significance. For statistical analysis, the Statistical Package for the Social Sciences Version 23 was used.

Results

We enrolled 118 male patients with HF_{rEF}, 15 (12.7%) of whom showed sarcopenic obesity. These patients with sarcopenic obesity showed lower functional capacity as measured by peak VO_2 when compared with non-sarcopenic patients (1.26 ± 0.35 vs. 1.50 ± 0.47 L/min, $P = 0.026$ and 18.3 ± 5.3 vs. 21.2 ± 6.1 mL/kg/min, $P = 0.047$). In our cohort, the median A/G ratio was 0.55. A/G ratio > 0.55 was detected in 60 patients, while 58 patients presented A/G ratio < 0.55 (Table 1). The average age of all patients was 56 ± 7 years, and the mean LVEF was $28 \pm 7\%$. Baseline characteristics of patients are summarized in Table 1. Diuretics and statin were more used in patients with A/G ratio > 0.55 , while no differences were observed for other medications between patients with A/G ratio lower or higher than 0.55 (Table 1).

In our cohort, the median VO_2 in L/min of all patient was 1.41 ± 0.45 L/min. Absolute peak VO_2 was similar between patients with A/G ratio lower or higher than 0.55 ($1.48 \pm$

Table 1 Baseline characteristics

Variable	All patients (n = 118)	A/G < 0.55 (n = 58)	A/G > 0.55 (n = 60)	P-value
Age (years)	56 \pm 7	55 \pm 8	57 \pm 6	0.115
Weight (kg)	70.89 \pm 11.52	65.90 \pm 10.24	75.70 \pm 10.68	<0.001
BMI (kg/m ²)	25.51 \pm 3.67	23.48 \pm 3.15	27.48 \pm 3.03	<0.001
LVEF (%)	28 \pm 7	29 \pm 7	28 \pm 7	0.707
SBP (mmHg)	102.8 \pm 17.6	102.6 \pm 13.7	102.9 \pm 21.4	0.917
DBP (mmHg)	67.8 \pm 10.9	67.7 \pm 11.0	67.8 \pm 10.7	0.951
Ischemic/no ischemic (%)	24/75	31/55	69/44	0.032
NYHA-class I/II/III/IV (%)	40/39/19/2	51/40/7/2	28/40/30/2	0.009
Sodium (mmol/L)	139 \pm 2	140 \pm 3	140 \pm 2	0.707
Potassium (mmol/L)	4.5 \pm 0.5	4.6 \pm 0.3	4.5 \pm 0.6	0.307
Creatinine (mg/dL)	1.2 \pm 0.5	1.1 \pm 0.2	1.3 \pm 0.7	<0.001
eGFR (mL/min/1.73m ²)	70 \pm 20	74 \pm 18	67 \pm 22	0.063
Total cholesterol (mmol/L)	174 \pm 43	180 \pm 37	168 \pm 47	0.119
HDL (mg/dL)	47 \pm 16	53 \pm 19	42 \pm 11	<0.001
LDL (mg/dL)	104 \pm 36	107 \pm 31	101 \pm 41	0.374
hs-CRP (mg/L)	2.27 (3.86–7.16)	1.71 (1.02–2.38)	3.17 (2.03–4.99)	0.010 ^a
TSH (μ IU/mL)	3.53 \pm 4.97	3.15 \pm 2.85	3.89 \pm 6.39	0.422
Haemoglobin (g/dL)	14.0 \pm 1.6	14.1 \pm 1.3	14.0 \pm 1.8	0.756
IGF-1 (ng/mL)	152 \pm 57	155 \pm 57	148 \pm 58	0.503
Peak VO_2 /lean mass (mL/kg/min)	29.1 \pm 9.6	30.5 \pm 9.1	27.8 \pm 10.1	0.125
Medications				
Beta blocker (%)	100	100	100	1.000
ACEi/ARB (%)	92.4	47.5	44.9	0.163
Loop diuretics (%)	76.3	31.4	44.9	0.002
Statins (%)	58.5	21.2	37.3	0.001
Spirolactone (%)	77.1	37.3	39.8	0.828
Aspirin (%)	38.1	16.9	21.2	0.453

A/G, android/gynoid ratio; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FT, free testosterone; HDL, high density lipoprotein; hs-PCR, high sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; NYHA, New York Heart Association; TSH, thyroid-stimulating hormone; TT, total testosterone; VO_2 , oxygen consumption.

^aMann–Whitney test with median and interquartile range.

0.40 vs. 1.43 ± 0.40 L/min, $P = 0.559$; *Figure 1A*), while relative peak VO_2 was lower in patients with A/G ratio >0.55 (18.7 ± 5.3 vs. 22.5 ± 6.1 mL/kg/min, $P < 0.001$; *Figure 1B*).

Fasting glucose was higher in male patients with A/G ratio > 0.55 when compared with patients with A/G ratio < 0.55 (*Figure 2A*). We found that 53 (44.9%) patients had pre-diabetes (glycaemia between 100–125 mg/dL) and 17 (14.4%) had diabetes (glycaemia > 126 mg/dL) according to the American Diabetes Association. In the other hand, total testosterone and DHEA were significantly decreased in male patients with A/G ratio > 0.55 when compared with patients

with A/G ratio < 0.55 (*Figure 2B,D*). We observed a declining trend in free testosterone in patients with A/G ratio > 0.55 (*Figure 2C*).

Fat mass was higher in arms, legs, trunk, and in the total body in male patients with A/G > 0.55 when compared with patients with A/G < 0.55 (*Table 2*). Moreover, patients with A/G > 0.55 have increased adipose visceral tissue (mass and volume) when compared with patients with A/G < 0.55 (*Table 2*). Lean mass in the arms and trunk were similar between patients with lower or higher A/G ratio, while we observed a trend to lower lean mass in the legs ($P = 0.057$)

Figure 1 (A) Absolute peak oxygen consumption (VO_2 in L/min) and (B) relative peak VO_2 in mL/kg/min in patients with heart failure with reduced ejection fraction with lower or higher A/G ratio.

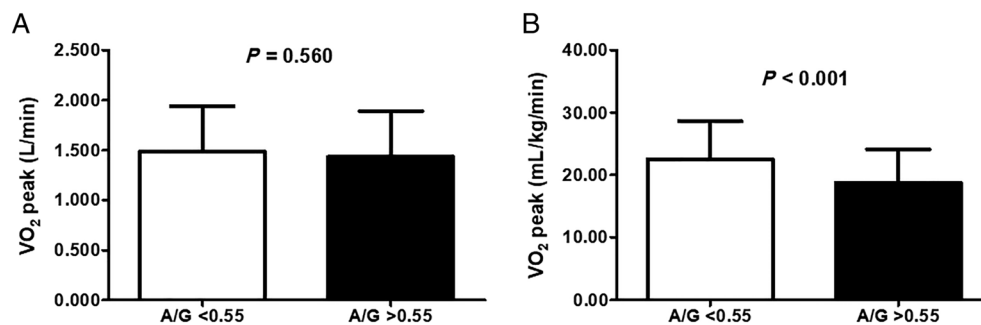


Figure 2 (A) Glycaemia, (B) total testosterone, (C) free testosterone, and (D) dehydroepiandrosterone (DHEA) in patients with heart failure with reduced ejection fraction with lower or higher A/G ratio. Dashed lines indicate the cutoff point for normality—(A) Glycaemia: 99 mg/dL, (B) total testosterone: 249 ng/dL, and (C) free testosterone: 131 pmol/L. * = Mann–Whitney test with median and interquartile range.

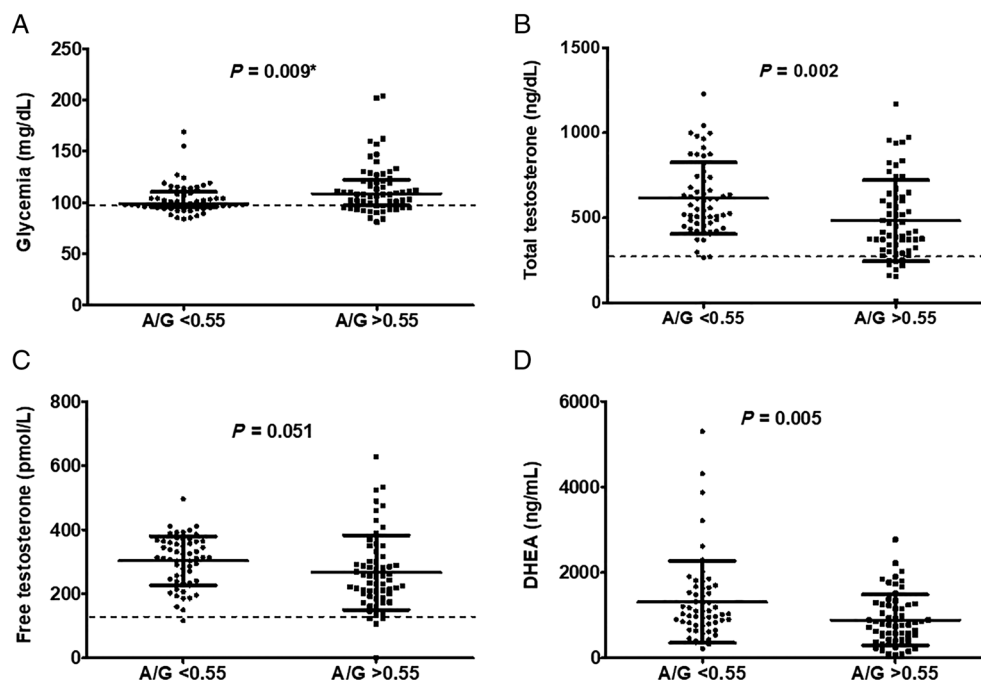


Table 2 Body composition

Variable	All patients (n = 118)	A/G < 0.55 (n = 58)	A/G > 0.55 (n = 60)	P-value
Upper body composition				
Arms fat mass (g)	1.94 ± 0.63	1.67 ± 0.54	2.22 ± 0.72	<0.001
Arms lean mass (g)	6.00 ± 1.04	5.85 ± 1.07	6.15 ± 1.02	0.116
Trunk fat mass (g)	11.20 ± 4.26	8.27 ± 3.69	14.13 ± 4.82	<0.001
Trunk lean mass (g)	23.55 ± 3.12	23.08 ± 3.13	24.02 ± 3.11	0.104
Lower body composition				
Legs fat mass (g)	5.39 ± 1.57	4.88 ± 1.56	5.91 ± 1.58	0.001
Legs lean mass (g)	15.78 ± 2.50	15.34 ± 2.47	16.23 ± 2.54	0.057
Total body composition				
Total fat body mass (g)	19.45 ± 6.23	15.69 ± 5.66	23.20 ± 6.80	<0.001
Total lean body mass (g)	48.64 ± 6.32	47.51 ± 6.45	49.77 ± 6.19	0.055
Adipose visceral tissue				
AVT mass (g)	1.28 ± 0.65	0.68 ± 0.45	1.88 ± 0.86	<0.001
AVT volume (cm ³)	1.34 ± 0.68	0.68 ± 0.45	1.99 ± 0.91	<0.001

A/G, android/gynoid ratio; AVT, adipose visceral tissue.

and total lean body mass ($P = 0.055$) in patients with A/G < 0.55 when compared with patients with A/G > 0.55 (Table 2).

In the logistic regression analysis, in which peak VO_2 was used as dependent variable, we found that age, BMI, LVEF, A/G ratio >0.55, presence of sarcopenia, and haemoglobin were associated with peak VO_2 in L/min (all $P < 0.05$, Table 3). In multivariate analysis, age, LVEF, A/G ratio > 0.55, presence of sarcopenia, and haemoglobin remained independently associated with peak VO_2 in L/min ($P < 0.05$, Table 3). During the construction of logistic regression models (using peak VO_2 as the dependent variable), we included all variables that had been shown to be significantly different between A/G groups. In the univariate analysis, we tested total testosterone [($P = 0.819$, odds ratio (OR) 1.000 (0.998–1.001)], statins [($P = 0.434$, OR 2.000 (0.352–11.364)], creatine [($P = 0.195$, OR 0.586 (0.261–1.315)], high density cholesterol-C [($P = 0.225$, OR 1.015 (0.991–1.040)], glycaemia [($P = 0.662$, OR 1.004 (0.987–1.022)], and diuretic [($P = 0.037$, OR 2.598 (1.058–6.382)]. Only diuretic was correlated in the univariate analysis; however, diuretic did not show statistical significance after adjusting for cofactors such as age, BMI, LVEF, A/G ratio, sarcopenia, and haemoglobin [($P = 0.451$, OR 1.654 (0.447–6.114)].

In the second logistic regression analysis, we used peak VO_2 in mL/kg/min as the dependent variable. In the univariable logistic regression, we found that age, LVEF, A/G ratio > 0.55, and haemoglobin were associated with peak VO_2 in mL/kg/min (all $P < 0.05$, Table 3). In multivariate analysis, age, LVEF, A/G ratio > 0.55, and haemoglobin remained independently associated with peak VO_2 in mL/kg/min ($P < 0.05$, Table 3).

Discussion

This is the first study to show an association between android and gynoid fat on functional capacity in male patients

with HFREF. The main findings were that male patients with higher A/G ratio (>0.55) have lower peak VO_2 when adjusted by total weight, but not in absolute value (in L/min). In a logistic regression model adjusted by cofactors, A/G ratio was strong associated with lower VO_2 . In addition, similarly observed in patients with obesity or metabolic syndrome,¹⁶ those patients with HFREF and higher central fat deposition have a slightly increase in glycaemia with lower anabolic hormones such as testosterone and DHEA. However, after adjusting for cofactors, anabolic hormones did not correlate with VO_2 .

Comorbidities in patients with HFREF are prevalent, and it is associated with worse quality of life and poor outcome.^{2,4,17} Sarcopenia in patients with HFREF has been shown an important marker of mortality, affecting approximately 20% of this population.¹⁸ Moreover, several patients with HFREF can also present an overlap in wasting syndromes (cachexia and sarcopenia),¹⁹ and cachexia is associated with an increased rate of mortality (50% of mortality in 18 months of follow-up).¹⁷ Interestingly, obesity may have a protective effect in patients with HFREF because higher body weight prevents loss of muscle mass.⁶ However, this phenomenon known as obesity paradox should be more explored, because greater abdominal, cardiac, and intermuscular fat are associated with lower physical function in patients with HFREF.⁷ Moreover, an increased waist-to-hip ratio is associated with a higher risk of mortality in female but not in male patients with HFREF.²⁰ For these reasons, regional adipose-induced exercise intolerance in HFREF should be more studied. Several studies suggest that the use of VO_2 adjusted by lean body mass (cutoff < 19 mL O_2 /kg of lean body mass/min) should be used for timing transplantation, particularly in women and in patients with excess adiposity,^{21,22} because peripheral skeletal muscle dysfunction meaningfully contribute to the development of sarcopenia, sarcopenic obesity, and cachexia.²³ In our study, we extend this knowledge to the possible role of central fat and its influence on exercise intolerance in patients with HFREF.

Table 3 Logistic regression model defined as the absolute peak VO₂ in L/min below the median (1.41 ± 0.45 L/min) serving as the dependent variable

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (per year increase)	0.913	0.860–0.970	0.003	0.922	0.853–0.996	0.039
BMI (per kg/m ² increase)	1.121	1.009–1.245	0.034	1.036	0.832–1.289	0.754
LVEF (per 1% decrease)	1.061	1.009–1.115	0.021	1.103	1.032–1.180	0.004
TT (per 1 ng/dL decrease)	1.000	0.998–1.001	0.819			
FT (per 1 mmol/L decrease)	1.002	0.999–1.006	0.819			
A/G ratio > 0.55 (present)	2.094	0.996–4.405	0.050	3.895	1.030–14.730	0.045
Sarcopenia (present)	7.269	2.693–19.618	<0.001	8.373	1.743–40.221	0.008
Haemoglobin (per 1 g/dL decrease)	1.910	1.406–2.596	<0.001	1.815	1.269–2.598	0.001
Diabetes >126 mg/dL (present)	1.168	0.391–3.489	0.781			
Absolute peak VO₂ in mL/kg/min below the median (19.90 ± 6.03 mL/kg/min)						
Age (per year increase)	0.939	0.888–0.992	0.026	0.945	0.886–1.008	0.012
BMI (per kg/m ² increase)	0.966	0.873–1.068	0.497			
LVEF (per 1% decrease)	1.063	1.011–1.118	0.018	1.084	1.023–1.147	0.006
TT (per 1 ng/dL decrease)	1.001	1.000–1.003	0.136			
FT (per 1 mmol/L decrease)	1.003	0.999–1.007	0.140			
A/G ratio > 0.55 (present)	3.020	1.414–6.453	0.004	3.024	1.276–7.170	0.012
Sarcopenia (present)	1.649	0.721–3.769	0.236			
Haemoglobin (per 1 g/dL decrease)	1.575	1.200–2.067	0.001	1.606	1.180–2.185	0.003
Diabetes > 126 mg/dL (present)	1.637	0.528–5.075	0.393			

Hosmer and Lemeshow Test, Chi-squared: 4.427, *df*: 8, *P*-value = 0.817.

A/G, android/gynoid ratio; BMI, body mass index; CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; TT, total testosterone; FT, free testosterone.

Adipose-induced inflammation is a hallmark of adverse effects including endothelial dysfunction and impaired skeletal muscle mitochondrial function, with consequent reduction of skeletal muscle oxygen delivery and extraction.^{24–26} In an experimental model, accumulation of visceral fat led to generation of reactive oxygen species and markedly lower maximal VO₂.²⁷ In patients with heart failure, exercise training reduced visceral adipose tissue with significant correlation with exercise capacity improvement.²⁸

These findings point out abdominal adipose-induced exercise intolerance in heart failure, and exercise training, which plays a role on anti-inflammatory process, increases expression of interleukin-10 and decreases interleukin-6.²⁹ Furthermore, exercise improves adiponectin and insulin resistance in obese individuals with diabetes, favouring cardiac energy metabolism via AMP-activated protein kinase.^{30,31} These mechanisms may be involved in the relationship between visceral adipose tissue and exercise capacity in patients HFrEF. However, these mechanisms should be investigated in future studies.

Obesity per se decreases mitochondrial oxidative capacity through reduced expression of electron transport chain components and/or their enzymatic capacity.³² Subcutaneous depots obtained from obese patients revealed a reduced membrane potential, inorganic phosphate utilization, and the activities of respiratory chain complexes I–IV in isolated mitochondria from subcutaneous depots.³³ Taken together, impaired mitochondrial oxidative capacity, mainly in white adipose tissue, and generation of reactive oxygen species

might be the mechanisms involved in the blunted energetic production and exercise intolerance in patients with HFrEF.

In conclusion, our data suggest that in addition to well-known cofactors such as age and the presence of sarcopenia in functional capacity worsening, body fat distribution, particularly android and gynoid fat composition, might have an important adverse role on functional capacity in male patients with HFrEF.

This study has limitations. First, adipose visceral fat was estimated by DXA. Computed tomography (CT) and magnetic resonance imaging are the gold standard method to measure visceral fat. However, DXA has a strong correlation with CT (0.949 for males) to estimate adipose visceral fat³⁴ with minimal bias from CT or magnetic resonance imaging.³⁵ Second, we studied only male patients with HFrEF. Therefore, our results are restricted to this population.

Conflict of interest

None declared.

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Author contributions

Marcelo Rodrigues dos Santos and Guilherme Wesley Peixoto da Fonseca carried out the conceptualization, data curation, formal analysis, investigation, project administration, methodology, writing of the original draft, reviewing & editing. Letícia Pironato Sherveninas and Francis Ribeiro de Souza did

the data curation, formal analysis, investigation, and writing—review & editing. Antônio Carlos Battaglia Filho and Caio Eduardo Novaes carried out data curation, writing—review & editing. Rosa Maria Rodrigues Pereira did the data curation, methodology, writing—review & editing. Carlos Eduardo Negrão and Antônio Carlos Pereira Barretto performed the investigation, project administration, methodology, writing—original draft—and review & editing. Lastly, Maria Janieire de Nazaré Nunes Alves carried out the conceptualization, data curation, formal analysis, investigation, project administration, methodology, writing—original draft—review & editing.

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