European Journal of Heart Failure

Skeletal muscle alterations and exercise intolerance in heart failure with preserved ejection fraction patients: ultrasonography assessment of diaphragm and quadriceps.

--Manuscript Draft--

Manuscript Number:	EURJHF-21-1164R1
Full Title:	Skeletal muscle alterations and exercise intolerance in heart failure with preserved ejection fraction patients: ultrasonography assessment of diaphragm and quadriceps.
Article Type:	Research Letter
Keywords:	heart failure with preserved ejection fraction; Exercise intolerance; Diaphragm; Skeletal muscles
Corresponding Author:	Maria Andriopoulou National and Kapodistrian University of Athens Faculty of Medicine: Ethniko kai Kapodistriako Panepistemio Athenon Iatrike Schole Athens, GREECE
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	National and Kapodistrian University of Athens Faculty of Medicine: Ethniko kai Kapodistriako Panepistemio Athenon Iatrike Schole
Corresponding Author's Secondary Institution:	
First Author:	Maria Andriopoulou
First Author Secondary Information:	
Order of Authors:	Maria Andriopoulou
	Niki Dimaki
	Manolis S. Kallistratos
	Eftihia Chamodraka
	Edison Jahaj
	Alice G Vassiliou
	Georgios Giokas
	Anastasia Kotanidou
	Athanasios J. Manolis
	Massimo F. Piepoli
	Gerasimos Filippatos
Order of Authors Secondary Information:	
Manuscript Region of Origin:	GREECE

Skeletal muscle alterations and exercise intolerance in heart failure with preserved ejection fraction patients: ultrasonography assessment of diaphragm and quadriceps.

Maria Andriopoulou[1,2], Niki Dimaki[2], Manolis S. Kallistratos[2], Eftihia Chamodraka[2], Edison Jahaj[1], Alice G Vassiliou [1], Georgios Giokas[3], Anastasia Kotanidou[1], Athanasios J. Manolis[2], Massimo F. Piepoli[4], Gerasimos Filippatos[5]

1. First Critical Care Department, Evangelismos University Hospital, Medical School, National and Kapodistrian University of Athens, Greece.

2. Department of Cardiology and Cardiac Rehabilitation, Asklepieio General Hospital, Athens, Greece

3. Second Department of Surgery, Aretaeion University Hospital, Medical School, National and Kapodistrian University of Athens, Greece.

4. Heart Failure Unit, Cardiac Department, G. da Saliceto Hospital, Piacenza, Italy.

5. Heart Failure Unit, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Greece.

Corresponding authors:

Maria Andriopoulou

Cardiac Rehabilitation Department, Aklepieio Voulas,

Vasileos Pavlou 1, 16673 Voula, Athens Greece

Ph: +306932353879, +302132163107

Email: mariandriop@yahoo.gr,

Keywords: Heart failure with preserved ejection fraction; Exercise intolerance; Diaphragm; Skeletal muscles

It is estimated that 40-50% of heart failure (HF) patients have preserved ejection fraction (HFpEF). HFpEF prognosis remains poor and the underlying pathophysiologic mechanisms of the origin of exercise limitation are still unclear (1). Exercise intolerance, measured by peak oxygen uptake (VO_2) during cardiopulmonary exercise testing (CPET), is a prognostic factor of morbidity (2). Peak VO_2, which is computed as the highest VO_2 reached on a given test, is depended on several central and peripheral factors. It has been suggested that peripheral limitations, including skeletal muscles abnormalities, contribute to exercise intolerance in HFpEF patients and may be improved after exercise training (3). There is some evidence that quadriceps abnormalities are associated with impaired exercise capacity in HFpEF (4, 5). However, less is known about inspiratory function and the relationship between diaphragm, the most important inspiratory muscle, with exercise intolerance.

Thus, the evaluation of skeletal muscles and diaphragmatic function may contribute to better understanding of the pathophysiology of exercise intolerance in HFpEF, providing potential therapeutic interventions.

The objective of the present study was to investigate 1. the difference of diaphragm function and quadriceps parameters measured by ultrasound, in HFpEF patients compared to healthy controls and 2. the relation between the aforementioned parameters with exercise intolerance measured by peak VO_2 uptake.

In this cross-sectional study patients with HFpEF and matched controls were included. The subjects did not participate in any regular exercise program for the last 12 months. Patients were on NYHA class II–III, with preserved ejection fraction (>45%) and no evidence of significant anemia or coronary artery, valvular, infiltrative, pericardial, pulmonary, or renal disease. Age-gender matched control subjects were recruited, screened and excluded if they had any chronic medical illness, current symptoms or an abnormal physical examination. Other exclusion criteria were: current treatment with oral corticosteroids, long-term oxygen therapy or any other co morbid conditions that would prevent exercise training. The study was approved by hospital Ethics Committee and was carried out in accordance with the Declaration of Helsinki (1989). A written informed consent was obtained from all participants prior to study entry.

Ultrasound assessment of skeletal muscles and CPET were performed the same day for all participants in this study. Signos portable ultrasound device was used to assess the motion of the right hemidiaphragm, during quiet (QBr) and deep breathing (DBr), rectus femoris cross-sectional area (RFcsa) and quadriceps thickness (Qt) of the dominant limb. Three consecutive measurements were taken for each variable and the average was used in statistical analysis.

Quantitative variables were expressed as mean values (SD), while qualitative variables were expressed as absolute and relative frequencies. Independent samples Student's t-tests were used for the comparison of mean values between the two groups. For the comparison of proportions chi-square and Fisher's exact tests were used. Partial correlations coefficients were used to explore the association among ultrasound and ergospirometry parameters, after adjusting for group, age and gender. Multiple linear regression analysis was used to examine the ultrasound and ergospirometry parameters associated with peak VO_2. Peak VO_2 was the dependent variable and all other ultrasound and ergospirometry parameters were inserted in the model as independent variables in a stepwise method (p for entry 0.05, p for removal 0.10). All reported p values were two-tailed. Statistical significance was set at $p<0.05$ and analyses were conducted using SPSS statistical software (version 22.0).

Sample consisted by 50 participants (25 HFpEF patients and 25 controls). Mean age for controls was 64.1±11.9 years and for the HFpEF patients was 63.5 ±12 years ($p=0.859$). Mean body mass index (BMI) for controls was 28.98±5.2 Kg/m^2 and 30.6±6.07 Kg/m^2 ($p=0.488$) for HFpEF patients.

All ultrasound and ergospirometry parameters differ significantly between HFpEF patients and controls, except for ratings of perceived exertion (RPE) ($p=0.088$) (Table 1). More specifically, peak VO_2, respiratory exchange ratio (RER), ventilatory anaerobic threshold (VAT), rectus femoris cross-sectional area (RFcsa), quadriceps thickness (Qt) and the motion of the right hemidiaphragm, during quiet (QBr) and deep breathing (DBr), were significantly lower in HFpEF patients. On the contrary, VE/VCO_2 slope and ratings of perceived dyspnea (RPD) were significantly higher in HFpEF patients.

The partial correlation coefficients among ultrasound and ergospirometry parameters, were adjusted for group, age and gender. Peak VO_2 was negatively correlated with ratings of perceived dyspnea ($r=-0.60$, $p<0.001$) and positively correlated with rectus femoris cross-sectional area ($r=0.31$, $p<0.05$), quadriceps thickness ($r=0.36$, $p<0.05$), diaphragmatic motion during quiet ($r=0.47$, $p<0.01$) and deep breathing ($r=0.71$, $p<0.001$). Higher QBr was significantly associated with greater Rfcsa ($r=0.30$, $p<0.05$), Qt ($r=0.37$, $p<0.05$) and DBr ($r=0.38$, $p<0.01$). Also, higher Rfcsa was significantly associated with greater DBr ($r=0.44$, $p<0.01$).

In order to examine which of the ultrasound and ergospirometry parameters are mostly associated with peak VO_2, multiple linear regression was conducted, in the total sample and in each group separately. In all participants, DBr ($b=2.53$, $SE=0.51$, standardized b=0.5, $p<0.001$), QBr (b=5.5, SE=1.92, standardized b=0.25, p=0.006) were significantly associated with VO_2 peak and comparing the absolute values of the standardized regression coefficients, it can be concluded that DBr was of higher importance (Figure 1). In controls, DBr (b=2.98, SE=0.61, standardized b=0.62, $p<0.001$) and Qt (b=1.93, SE=0.65, standardized b=0.38, p=0.007), while in HFpEF patients, DBr (b=2.48, SE=0.98, standardized b=0.35, p=0.019) were significantly associated with VO_2 peak.

To the best of our knowledge, this is the first study demonstrating that there is an ultrasound proven diaphragm and quadriceps muscles dysfunction in HFpEF patients compared to matched controls and both are associated with exercise intolerance during cardiopulmonary exercise testing.

Although it is well established that HF with reduced ejection fraction patients have multiple skeletal muscle abnormalities affecting both limb and inspiratory muscles, there is sparse and controversial evidence available in HFpEF. The present study assessed, directly by the use of ultrasound, the excursion of diaphragm during quiet and deep breathing, the rectus femoris cross-sectional area and quadriceps thickness in HFpEF patients compared to healthy matched controls and demonstrated statistically significant differences. Furthermore, all the aforementioned variables were positively correlated to VO_2 peak, an important prognostic factor of morbidity (2). Concerning quadriceps muscle, our findings are consistent with previous evidence reported that abnormalities in older HFpEF patients are related to lower VO_2 peak (4) and six-minute walking distance (5).

Regarding inspiratory muscle function, previous studies using maximal inspiratory pressure (MIP) assessment or ultrasonographic diaphragmatic evaluation, of both thickness and excursion, reported positive correlation with exercise intolerance measured by 6MWD (5, 6). Further strengthening this concept, our results indicated that diaphragm excursion, during quiet and deep breathing, is positively correlated with VO_2 peak, the gold standard parameter to assess exercise tolerance in HF. However, the only study that assessed the relation between inspiratory muscle function and peak VO_2, used MIP assessment and demonstrated no correlation (7). Maximal inspiratory pressure is not a direct assessment of diaphragm muscle function that may be underestimated since it can be compensated by accessory muscles. Furthermore, in contrast to ultrasonographic assessment of diaphragm, MIP includes volitional mouth pressure maneuvers which many subjects find difficult to perform.

Another important finding of this study is that, diaphragm excursion during deep breathing is highly correlated to VO_2 peak in all participants, after adjusting for group, age and gender and in each group separately. Specifically, in HFpEF patients, diaphragmatic motion during deep breathing is of higher importance, while in controls is DBr and quadriceps thickness. This finding indicates that underlying diaphragm atrophy might affect exercise intolerance more than quadriceps deterioration in HFpEF patients and it requires special attention.

Hence, specific diaphragmatic exercises may be included in cardiac rehabilitation programs for all HFpEF patients independently of MIP. A recent multicentered randomized controlled trial in HF with reduced ejection fraction found that a combination of aerobic training, resistance exercise training and inspiratory muscle training (ARIS) was superior to other exercise programs (8).

Notably, while previous observations were in older, hospitalized HFpEF patients (5) our results highlight the existence of alterations even in younger patients.

However, the results of this study should be interpreted considering the limitations. The relatively small sample size and that this study focused on ambulatory, able to perform an exercise testing, clinical stable, not hospitalized and without advanced pulmonary disease HFpEF patients and matched controls. Another limitation is that diaphragmatic function was assessed by measuring only right hemidiaphragm excursion. Left hemidiaphragm excursion was decided to be excluded since visualization is more difficult. Measurement of diaphragm thickening also has been proposed, but both thickening and excursion are suggested to represent diaphragm dysfunction (9). Further studies with larger sample size are needed to confirm diaphragm and skeletal muscles dysfunction and exercise intolerance in HFpEF as well as the results of therapeutic interventions.

In conclusion, the high correlation of diaphragm and quadriceps muscle status with exercise intolerance supports the role of skeletal muscles in the pathophysiology of symptom generation in HFpEF patients.

Funding: None

Conflict of interest: None declared.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2021;42(36):3599-726.

2. Sato T, Yoshihisa A, Kanno Y, Suzuki S, Yamaki T, Sugimoto K, et al. Cardiopulmonary exercise testing as prognostic indicators: Comparisons among heart failure patients with reduced, mid-range and preserved ejection fraction. Eur J Prev Cardiol. 2017;24(18):1979-87.

3. Upadhya B, Haykowsky MJ, Eggebeen J, Kitzman DW. Exercise intolerance in heart failure with preserved ejection fraction: more than a heart problem. J Geriatr Cardiol. 2015;12(3):294-304.

4. Kitzman DW, Nicklas B, Kraus WE, Lyles MF, Eggebeen J, Morgan TM, et al. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Physiol Heart Circ Physiol. 2014;306(9):H1364-70.

5. Yamada K, Kinugasa Y, Sota T, Miyagi M, Sugihara S, Kato M, et al. Inspiratory Muscle Weakness is Associated With Exercise Intolerance in Patients With Heart Failure With Preserved Ejection Fraction: A Preliminary Study. J Card Fail. 2016;22(1):38-47.

6. Spiesshoefer J, Henke C, Kabitz HJ, Bengel P, Schütt K, Nofer JR, et al. Heart Failure Results in Inspiratory Muscle Dysfunction Irrespective of Left Ventricular Ejection Fraction. Respiration. 2021;100(2):96-108.

7. Palau P, Domínguez E, Núñez E, Ramón JM, López L, Melero J, et al. Inspiratory Muscle Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction. J Card Fail. 2017;23(6):480-4.

8. Laoutaris ID, Piotrowicz E, Kallistratos MS, Dritsas A, Dimaki N, Miliopoulos D, et al. Combined aerobic/resistance/inspiratory muscle training as the 'optimum' exercise programme for patients with chronic heart failure: ARISTOS-HF randomized clinical trial. Eur J Prev Cardiol. 2020.

9. Boussuges A, Rives S, Finance J, Brégeon F. Assessment of diaphragmatic function by ultrasonography: Current approach and perspectives. World J Clin Cases. 2020;8(12):2408-24.

Table 1. Ultrasound and ergospirometry parameters for each study group

	Group				Mean difference (SD)	P Student's t-test	Cohen's effect size
	Control		HFpEF patients				
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)			
VO_2 peak, ml/kg/min	24.5 (4.5)	24 (21.3 — 27.7)	17.1 (4.1)	17 (14.7 — 19.9)	-7.4 (4.3)	<0.001	1.74
VE/VCO_2slope	27.6 (2.7)	27 (26 — 29)	29.6 (4.5)	29 (27 — 34)	2.1 (3.7)	0.050	0.56
RER	1.23 (0.14)	1.2 (1.15 — 1.26)	1.15 (0.14)	1.14 (1.1 — 1.25)	-0.1 (0.1)	0.046	0.58
VAT ml/kg/min	69.9 (9.9)	72 (64 — 77)	55.5 (13)	54 (46 — 66)	-14.4 (11.5)	<0.001	1.25
RPD	0.3 (0.6)	0 (0 — 0)	4 (2)	4 (2 — 6)	3.7 (1.5)	<0.001++	2.52
RPE	15.7 (1.1)	15 (15 — 17)	16.3 (1.1)	17 (15 — 17)	0.6 (1.1)	0.088	0.49
Rfcsa mm^2	433.6 (24.6)	430 (420 — 450)	374 (34.5)	370 (350 — 400)	-59.6 (30)	<0.001	1.99
Qt mm	21.5 (0.9)	21.3 (21.1 — 21.8)	20.1 (1)	20.1 (19.2 — 20.9)	-1.4 (0.9)	<0.001	1.50
QBr cm	1.36 (0.22)	1.32 (1.25 — 1.48)	1.09 (0.23)	1.04 (0.9 — 1.18)	-0.3 (0.2)	<0.001	1.23
DBr cm	5.8 (0.9)	5.8 (5.4 — 6.3)	4.2 (0.6)	4.2 (3.7 — 4.6)	-1.6 (0.8)	<0.001	2.08

HFpEF, heart failure with preserved ejection fraction; VO_2 peak, peak oxygen uptake; VE/VCO_2, minute ventilation/carbon dioxide production; RER, respiratory exchange ratio; VAT, ventilatory anaerobic threshold; RPD, ratings of perceived dyspnea; RPE, ratings of perceived exertion; Rfcsa, rectus femoris cross-sectional area; Qt, quadriceps thickness; QBr, motion of the right hemidiaphragm during quiet breathing; DBr, motion of the right hemidiaphragm during deep breathing

Supplementary table: Baseline characteristics by each study group

	Group		P[‡]
	Controls	HFpEF patients	
	N (%)	N (%)	
Age, years, mean (SD)	64.1 (11.9)	63.5 (12.0)	0.859[+]
Gender			
male	17 (68.0)	17 (68.0)	1.000
female	8 (32.0)	8 (32.0)	
BMI, Kg/m^2			
Normal	7 (28.0)	6 (24.0)	0.488
Overweight	8 (32.0)	5 (20.0)	
Obese	10 (40.0)	14 (56.0)	
Systolic blood pressure, mmHg, mean (SD)	124.6 (8.5)	132.6 (10.8)	0.003[+]
Diastolic blood pressure, mmHg, mean (SD)	76.4 (6.2)	83.6 (9.4)	0.003[+]
Heart rate, bpm, mean (SD)	80 (6.0)	73.6 (8.2)	<0.001[+]
Hypertension	0 (0.0)	17 (68.0)	<0.001
Dyslipidemia	0 (0.0)	7 (28.0)	0.010[++]
Diabetes	0 (0.0)	9 (36.0)	0.002[++]
Atrial Fibrillation	0 (0.0)	10 (40)	<0.001
NYHA			
II	n/a	20 (80.0)	-
III	n/a	5 (20.0)	
Beta-blockers	4 (16.0)	18 (72.0)	<0.001
ACEi	0 (0.0)	10 (40)	<0.001
ARBs	0 (0.0)	12 (48)	<0.001
Diuretics	0 (0.0)	17 (68.0)	<0.001
CCBs	0 (0.0)	6 (24)	0.022[++]
MRAs	0 (0.0)	9 (36)	0.002[++]
LVEF, %, mean (SD)	63.4 (2.8)	53.3 (7.1)	0.308[+]
IVS, mm, median (IQR)	9 (9 — 9)	11 (11 — 12)	<0.001‡‡
PS, mm, median (IQR)	9 (9 — 9)	11 (11 — 11.5)	<0.001‡‡
E, m/sec, median (IQR)	0.7 (0.6 — 0.8)	0.7 (0.5 — 0.8)	0.521‡‡
A, m/sec, median (IQR)	0.5 (0.5 — 0.6)	0.7 (0.6 — 0.8)	<0.001‡‡
E', m/sec, median (IQR)	9 (9 — 10)	7 (6 — 7)	<0.001‡‡
DT, msec, median (IQR)	200 (185 — 210)	230 (200 — 282)	0.004‡‡

[‡]Pearson's chi-square test; [+]Student's t-test; [++]Fisher's exact test; HFpEF, Heart failure with preserved ejection fraction; SD, Standard deviation; BMI, Body mass index; bpm, beats per minute; NYHA, New York Heart Association; ACEi, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin receptor blockers; CCBs, Calcium channel blockers; MRAs, Mineralocorticoid receptor antagonists; LVEF, Left ventricular ejection fraction; IVS, Interventricular septum; PS, Posterior wall; E, E-wave mitral velocity; A, A-wave mitral velocity; E', Early diastolic mitral annular velocity; DT, Deceleration time