Obesity Research & Clinical Practice 18 (2024) 226–231

Contents lists available at ScienceDirect

Obesity Research & Clinical Practice

journal homepage: www.elsevier.com/locate/orcp

Association between N-terminal pro-brain natriuretic peptide and maximal functional capacity in heart failure with preserved ejection fraction: The modifying role of obesity

Patricia Palau [a,*,1], Gonzalo Núñez [a,1], Rafael de la Espriella [a], Gema Miñana [a,e], Eloy Domínguez [a,b], Miguel Lorenzo [a], Laura López [a,c], Cristina Flor [c], Paloma Marín [a,d], Antoni Bayés-Genís [f], Juan Sanchis [a,e], Julio Núñez [a,e,*]

[a] Cardiology Department, Hospital Clínico Universitario, INCLIVA, Universitat de València, Valencia, Spain
[b] Universitat Jaume I, Castellón, Spain
[c] Facultad de Fisioterapia, Universitat de València, Valencia, Spain
[d] Facultad de Enfermería, Universitat de València, Valencia, Spain
[e] CIBER Cardiovascular, Spain
[f] Cardiology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Universitat Autònoma de Barcelona, Barcelona, Spain

ARTICLE INFO

Keywords:
HFpEF
Maximal functional capacity
PeakVO$_2$
NT-proBNP
Obesity

ABSTRACT

This study investigates the association between maximal functional capacity (peakVO$_2$) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in 133 ambulatory patients with heart failure with preserved ejection fraction (HFpEF), focusing on patients with obesity. Across all participants, NT-proBNP inversely correlated with peakVO$_2$. However, this association varied based on obesity status. In patients without obesity, there was an inverse relationship between NT-proBNP and peakVO$_2$, while no significant correlation was observed in patients with obesity. These findings suggest that in stable ambulatory HFpEF, NT-proBNP did not predict peakVO$_2$ in patients with obesity.

1. Introduction

Reduced maximal functional capacity and exertional dyspnea are the main hallmarks in patients with heart failure (HF) with preserved ejection fraction (HFpEF) [1]. Exercise intolerance and higher levels of circulating N-terminal pro-brain natriuretic peptide (NT-proBNP) identify patients at higher risk of adverse outcomes [2,3]. However, it is known that patients with HF and obesity show lower-than-expected NT-proBNP values, probably due to increased clearance by adipose tissue [4]. This study aimed to examine the association between maximal exercise capacity, assessed by peak oxygen consumption (peakVO$_2$), and NT-proBNP in symptomatic stable patients with HFpEF and whether this association was influenced by obesity.

2. Methods

2.1. Study sample and procedures

This study prospectively included 133 consecutive outpatients with HFpEF and stable NYHA functional class II-III who performed cardiopulmonary exercise testing (CPET) from June 2012 to January 2019. The study was conducted in a single third-level center. All patients provided informed consent, and the research ethics committee approved the protocol following the principles of the Declaration of Helsinki and national regulations. Candidates were selected from the outpatient specialized HF unit. All patients met the following inclusion criteria: a) a previous history of symptomatic HF (New York Heart Association functional class II–III); b) normal left ventricular ejection fraction (ejection fraction > 0.50 by the Simpson method and end-diastolic

Abbreviations: BMI, body mass index; CPET, Cardiopulmonary exercise testing; HFpEF, Heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PeakVO$_2$, Peak oxygen consumption at maximal exercise.

* Correspondence to: Servicio de Cardiología, Hospital Clínico Universitario, INCLIVA, Universitat de Valencia, Av. de Blasco Ibáñez, 17, 46010 Valencia, Spain.
E-mail addresses: patricia.palau@uv.es (P. Palau), juenuvi@uv.es (J. Núñez).

[1] Both authors contributed equally.

https://doi.org/10.1016/j.orcp.2024.05.005
Received 20 February 2024; Received in revised form 7 May 2024; Accepted 31 May 2024
Available online 12 June 2024

Table 1
Baseline characteristics of population stratified by the presence of obesity.

	Total (n = 133)	Non-obese (n = 52)	Obese (n = 82)	p-value
Demographic and clinical variables				
Age, years	73.2 ± 10.5	73.4 ± 13.2	73.1 ± 8.4	0.883
Women, n (%)	75 (56.4)	23 (45.1)	52 (63.4)	0.038
BMI, kg/m^2	31.4 ± 4.9	26.6 ± 2.3	34.3 ± 3.6	< 0.001
NYHA III, n (%)	45 (33.8)	13 (25.5)	32 (39)	0.109
Hypertension, n (%)	120 (90.2)	43 (84.3)	77 (93.9)	0.070
Past smoker, n (%)	41 (30.8)	17 (33.3)	24 (29.3)	0.622
Dyslipidemia, n (%)	102 (76.7)	41(80.4)	61 (74.4)	0.267
IHD, n (%)	41 (30.8)	19 (37.3)	22 (26.8)	0.206
COPD, n (%)	13 (9.8)	4 (7.8)	9 (11)	0.554
Diabetes, n (%)	59 (44.4)	19 (37.3)	40 (48.8)	0.193
History of stroke, n (%)	9 (6.8)	5 (9.8)	4 (4.9)	0.271
Smoker, n (%)	6 (4.5)	4 (7.8)	2 (2.4)	0.144
Atrial fibrillation, n (%)	68 (51.1)	26 (51)	42 (51.2)	0.979
Charlson index, n	2 (1–3)	2 (1–3)	2 (1–3)	0.755
Echocardiographic parameters				
LVEF, %	66 (60–74)	65 (57–71)	67 (62–76)	0.021
TAPSE, mm	22 (19.4–25)	22 (19–25)	22 (20–25)	0.348
E/e′ ratio	13 (10.2–16.3)	13 (9.5–18.8)	13 (10.4-15.8)	0.569
LVEDV, mL/m^2	45.7 (37.8–56.1)	47.2 (41.8–60.2)	43.5 (34.8–53.8)	0.067
LVEDV, mL/m^2	52 (42.8–65.8)	51.5 (42.7–64.8)	53.5 (41.2–66.5)	0.957
LVESV, mL/m^2[a]	14.9 (11.1–18.8)	16.2 (12–20.3)	14.6 (9.3–17.6)	0.049
LVESV, mL/m^2[b]	17.9 (12.5–21.4)	17.9 (12.8–22.8)	18.1 (11.3-21.4)	0.637
Left atrial volume, mL	80 (70–90.2)	80 (61–92)	80 (70–90.2)	0.284
CPET parameters				
HR at rest, bpm	68.3 ± 12.4	66.9 ± 12.3	69.2 ± 12.4	0.309
PeakVO$_2$, mL/kg/min	10.9 ± 2.9	11.8 ± 3.1	10.4 ± 2.6	0.006
VE/VCO2 slope	34.8 ± 6.8	35.4 ± 6.6	34.5 ± 6.8	0.456
SBP at rest, mmHg	126 (120-140)	125 (120–140)	127 (120–140)	0.993
Chronotropic index	0.4 (0.3–0.55)	0.4 (0.3–0.6)	0.4 (0.3–0.5)	0.751
Laboratory parameters				
Hemoglobin, mg/dL	13.0 (11.7–14.1)	13.0 (11.6–14.6)	12.9 (11.7–13.8)	0.622
NT-proBNP, pg/mL	556 (288–1399)	873 (288–2309)	525.5 (283–1208)	0.046
CA125, U/mL	12 (8–19)	16 (10.7–37)	10 (7–15)	< 0.001
Sodium, mEq/L	141 (139–142)	141 (139-143)	141 (139–142)	0.433
eGFR, mL/min/1.73 m^2	58.4 (43.6–74.2)	60.7 (46.9-74.7)	58.4 (43.6–74.2)	0.271
Medical treatment				
ACEI or ARB, n (%)	91 (68.4)	32 (62.7)	59 (72)	0.267
MRA, n (%)	29 (21.8)	9 (17.6)	20 (24.4)	0.360
β-blockers, n (%)	118 (88.7)	44 (86.3)	74 (90.2)	0.482
Loop diuretics, n (%)	112 (84.2)	42 (82.4)	70 (85.4)	0.643

Continuous variables are expressed as means (± 1 SD) or medians (interquartile range [IQR]), and discrete variables as frequencies and percentages.
ACEI, angiotensin-converting enzyme inhibitor; AFib, atrial fibrillation; ARB, angiotensin-receptor blocker; BMI, body mass index; CA125, antigen carbohydrate 125; COPD: chronic obstructive pulmonary disease; E/e′, ratio between early mitral inflow velocity and mitral annular early diastolic velocity; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricular end-systolic volume; MRA, mineralocorticoid receptor antagonist; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; VE/VCO2 slope, ventilatory efficiency.

[a] Indexed to body surface area.
[b] Indexed to height^2.

diameter < 60 mm); c) structural heart disease (left ventricular hypertrophy/left atrial enlargement) and diastolic dysfunction estimated by 2-dimensional echocardiography; and d) clinical stability, without hospital admissions in the past t3 months. Patients were excluded if they could not perform a valid baseline CPET; had amyloid cardiomyopathy, genetic or restrictive cardiomyopathies; presented angina or ischemia during maximal CPET; had a history of pulmonary disease (including pulmonary arterial hypertension, chronic thromboembolic pulmonary disease, or moderate to severe chronic obstructive pulmonary disease) or moderate to severe valvular heart disease; or any other comorbidity with a life expectancy of less than one year.

Maximal functional capacity was evaluated using incremental and symptom-limited CPET on a bicycle ergometer, using a ramp protocol of 10 W increments every 1 min. We defined maximal functional capacity as when the patient stops pedaling because of symptoms, and the respiratory exchange ratio (RER) was ≥ 1.

The heart rate (HR) was evaluated at rest (rest-HR) and peak effort (peak-HR). The HR response during CPET was evaluated following the chronotropic index (CIx) formula = peak HR-rest HR/[(220-age)-rest-HR)].

2.2. Biomarkers and body mass index assessment

Circulating levels of NT-proBNP and body mass index were assessed immediately before CPET assessment. Obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2.

2.3. Statistical analysis

Continuous variables are expressed as mean (standard deviation, SD) or median (inter interquartile range, IQR), and categorical variables are presented as numbers (percentage, %). Spearman correlation index was used to test the correlations between NT-proBNP and peakVO$_2$. A multivariate regression model was performed to test the independent association between peakVO$_2$ and NT-proBNP in all the samples and across obesity. Baseline age, sex, hemoglobin, BMI, glomerular filtration rate, atrial fibrillation, chronotropic index, RER, left ventricular ejection fraction, the presence of non-severe mitral regurgitation, tricuspid annular plane systolic excursion, Charlson comorbidity index, and beta-blocker dosing were included as covariates into the multivariate model. Stata 17.0 (StataCorp LP, College Station, TX, USA) was used for the analyzes.

3. Results

3.1. Baseline characteristics

The mean age of the participants in the study was 73.2 ± 10.5 years. Among the participants, 56.4 % were female, 49.9 % were in sinus rhythm, and 66.2 % were in stable NYHA class II. The mean peakVO$_2$ and BMI values were 10.9 ± 2.9 mL/kg/min and 31.4 ± 4.9 kg/m^2, respectively. The median (IQR) of NT-proBNP was 556 (288–1399) pg/mL. Table 1 summarizes the baseline characteristics stratified by the presence of obesity status. Overall, HFpEF patients with obesity were predominantly women and showed higher left ventricular ejection fraction and lower indexed left ventricular end-systolic volumes. Likewise, patients with obesity showed lower levels of NT-proBNP and peakVO$_2$.

3.2. Relationship between maximal exercise capacity and NT-proBNP

In the whole sample, NT-proBNP showed a moderate negative correlation with peak VO$_2$ (r = − 0.437, p < 0.001). Multivariate analysis

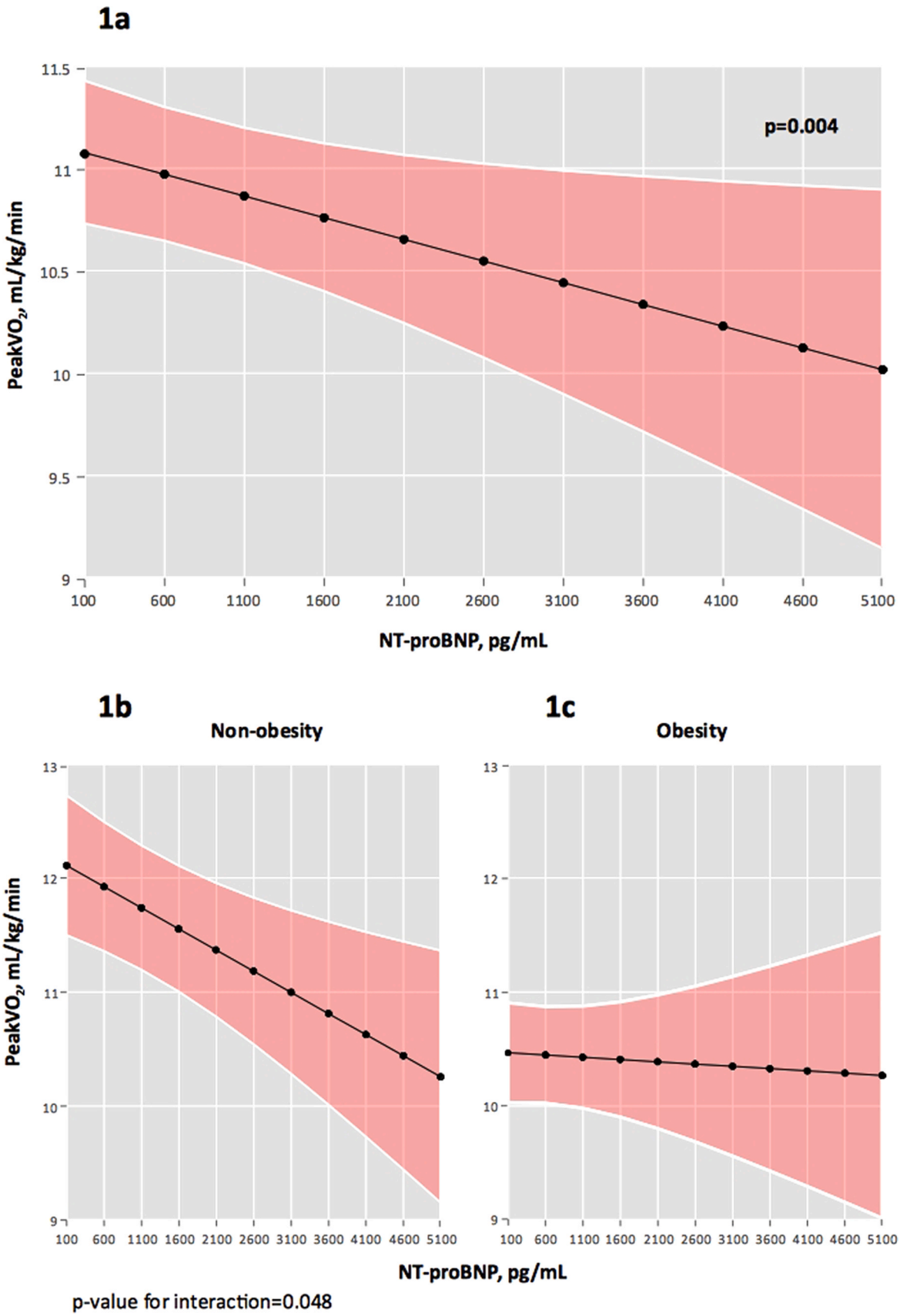

Fig. 1. Relationship between NT-proBNP and peakVO_2 in the whole sample (1a), the relationship between NT-proBNP and peakVO_2 in patients without obesity (1b) and those with obesity (1c). Nt-proBNP, N-terminal pro-brain natriuretic peptide; peakVO_2, peak oxygen consumption.

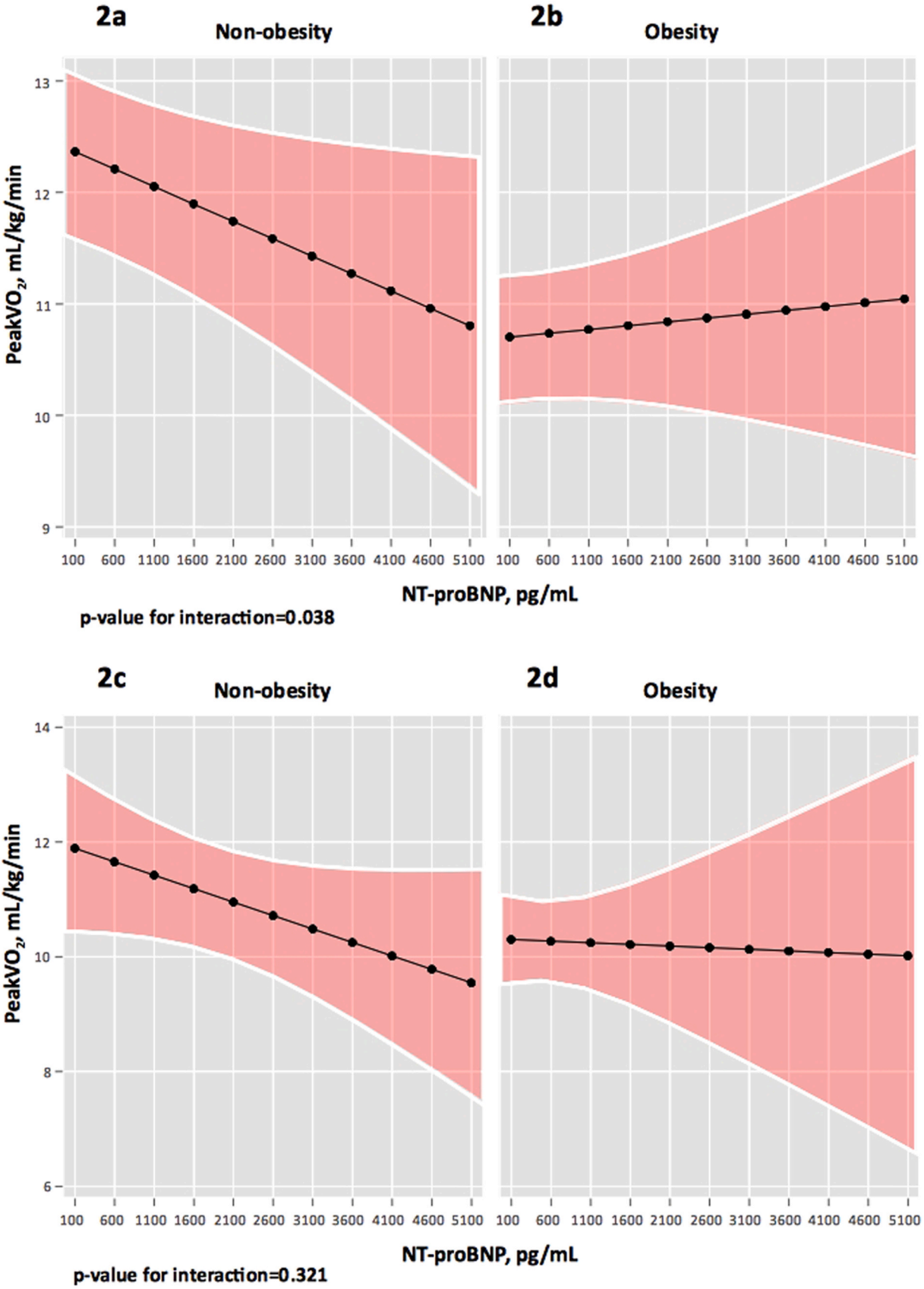

Fig. 2. Relationship between NT-proBNP and peakVO_2 across the type of rhythm in patients with and without obesity. Relationship between NT-proBNP and peakVO_2 in patients with sinus rhythm (2a and 2b) and those with atrial fibrillation (2c and 2d). Nt-proBNP, N-terminal pro-brain natriuretic peptide; peakVO_2, peak oxygen consumption.

confirmed that NT-proBNP was linear and inversely related to peakVO_2 (see Fig. 1a). Per increase in 500 pg/mL of NT-proBNP, we inferred a − 0.11 mL/kg/min decrease in peakVO_2 (CI 95 %: − 0.20 to − 0.01, p = 0.027). The contribution of NT-proBNP to the variability of the model (R2) was 4.3 %.

3.3. NT-proBNP and functional capacity: the role of obesity

Multivariate analysis showed a differential association between NT-proBNP and peakVO_2 across obesity (p-value for interaction = 0.048), as depicted in Figs. 1b and 1c. In patients without obesity, NT-proBNP exhibited a linear, inverse, and significant relationship with peakVO_2. Indeed, per increase in 500 pg/mL of NT-proBNP, we found a − 0.19 mL/kg/min in peakVO_2 (CI 95 %: − 0.31 to − 0.06, p = 0.004) (Fig. 1b). This relationship was no longer significant in patients with obesity (Fig. 1c). Thus, per increase in 500 pg/mL of NT-proBNP, a non-significant change of − 0.02 mL/kg/min in peakVO_2 was estimated (CI 95 %: − 0.15 to 0.11, p = 0.762).

We found similar results when stratifying the sample across the type of rhythm (sinus rhythm-SR- and atrial fibrillation- AF-), as shown in Fig. 2. In SR, higher NT-proBNP (per increase in 500 pg/mL) was significantly associated with a decrease of − 0.16 mL/kg/min in peakVO_2 (CI 95 %: − 0.30 to − 0.01, p = 0.033) (Fig. 2a) in patients with BMI < 30 kg/m^2 but not when BMI≥ 30 kg/m^2 (Fig. 2b). In patients with AF, higher NT-proBNP (per increase in 500 pg/mL) was borderline associated with a decrease of − 0.23 mL/kg/min in peakVO_2 (CI 95 %: − 0.51 to 0.03, p = 0.091) in patients without obesity (Fig. 2c) but not in those with obesity (Fig. 2d).

4. Discussion

In this analysis that enrolled 133 ambulatory symptomatic and stable patients with HFpEF, the main findings were: a) in the entire sample, higher NT-proBNP was significantly but marginally associated with lower peakVO_2, and b) the association between NT-proBNP and peakVO_2 largely differed across obesity, being non-significant in patients with obesity. Similar findings were found when the sample was stratified by sinus rhythm or atrial fibrillation.

Objective estimation of cardiorespiratory fitness is of utmost clinical importance in HF [1]. Prior evidence shows how reduced peakVO_2 is associated with greater disease severity, worse quality of life, and worse outcomes in HFpEF [1,2,5]. Estimating maximal functional capacity using widely available circulating biomarkers is a pertinent goal. In patients with HFrEF, there is literature endorsing a strong relationship between NT-proBNP and maximal functional capacity [6]. However, there is limited evidence exploring the ability of NT-proBNP levels to predict exercise capacity among stable patients with HFpEF [7]. The reasons for this divergence are not fully explained; however, the complex pathophysiology of HFpEF and the many prevalent conditions that influence natriuretic peptides in HFpEF (older age, renal dysfunction, atrial fibrillation, and obesity) might be playing a relevant role.

In this regard, previous research has indicated that patients with HFpEF and obesity commonly exhibit reduced circulating levels of NT-proBNP due to increased clearance of adipose tissue, and this fact may potentially result in false-negative findings [4,8,9]. In HFrEF, the HF-ACTION trail showed that NT-proBNP was the most potent predictor of peakVO_2; however, as in this report, the authors found heterogeneous findings across obesity (p = 0.04), indicating a higher correlation between NTproBNP and peakVO_2 in patients without obesity vs. those with obesity (R = − 0.48 for BMI ≤ 30 kg/m^2 vs. − 0.36 for BMI < 30 kg/m^2, respectively) [6]. The current report's results align with these prior findings but expand to HFpEF, a syndrome in which obesity is highly prevalent [1,4]. Under the premise that our findings need further validation with prospective trials, we believe that our results will help us to understand better the mechanisms underlying the heterogeneity of the HFpEF syndrome and support the need for further studies analyzing the ability of natriuretic peptides to distinguish different pathophysiological groups in HFpEF. These findings endorse the limitations of natriuretic peptides in assessing patients with HFpEF and obesity [3,7–9].

4.1. Study limitations

We acknowledge that the main limitations of this study are the small sample size and the fact that this is an observational single-center study. Second, the current findings applied only to symptomatic patients with stable HFpEF. They cannot be extrapolated to other clinical scenarios, prevalent subgroups, or milder forms of the syndrome. Third, we did not register the longitudinal changes in the NT-proBNP levels or peakVO_2 during the follow-up.

5. Conclusion

In patients with stable ambulatory HFpEF, NT-proBNP did not predict maximal functional capacity in patients with obesity.

Funding sources

This work was supported by grants from the Spanish Ministry of Economy and Competitiveness through the Carlos III Health Institute (PI17/01426) and co-funded with EDRF Funds and CIBER Cardiovascular Funds (16/11/00420 and 16/11/00403).

Ethical statement

This statement is to certify that all authors declare that all experiments on human subjects were conducted in accordance with the Declaration of Helsinki, http://www.wma.net, and that all procedures were carried out with the adequate understanding and written consent of the subjects.

CRediT authorship contribution statement

Eloy Domínguez: Writing – review & editing, Supervision, Investigation, Data curation. **Miguel Lorenzo:** Writing – review & editing, Data curation. **Laura López:** Writing – review & editing, Methodology, Investigation. **Cristina Flor:** Writing – review & editing, Methodology, Data curation. **Paloma Marín:** Writing – review & editing, Data curation. **Antoni Bayés-Genís:** Writing – review & editing, Methodology. **Juan Sanchis:** Writing – review & editing, Resources. **Patricia Palau:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Julio E. Núñez:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Gonzalo Núñez:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Rafael de la Espriella:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Gema Miñana:** Writing – review & editing, Supervision.

Declaration of Competing Interest

Authors declare no conflict of interest.

References

[1] Pandey A, Shah SJ, Butler J, et al. Exercise intolerance in older adults with heart failure with preserved ejection fraction: JACC state-of-the-art review. J Am Coll Cardiol 2021;78:1166–87. https://doi.org/10.1016/j.jacc.2021.07.014.
[2] Palau P, Domínguez E, Núñez E, et al. Peak exercise oxygen uptake predicts recurrent admissions in heart failure with preserved ejection fraction. Rev Esp Cardiol (Engl Ed) 2018;71:250–6. https://doi.org/10.1016/j.rec.2017.05.022.
[3] Verbrugge FH, Omote K, Reddy YNV, et al. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. Eur Heart J 2022;43:1941–51. https://doi.org/10.1093/eurheartj/ehab911.

[4] Patel RB, Shah SJ. Inclusion criteria for heart failure with preserved ejection fraction clinical trials: making the case for precision diagnosis and greater inclusivity. J Card Fail 2022;28:732–5. https://doi.org/10.1016/j.cardfail.2022.03.345.
[5] Lee K, Jung JH, Kwon W, et al. The prognostic value of cardiopulmonary exercise testing and HFA-PEFF in patients with unexplained dyspnea and preserved left ventricular ejection fraction. Int J Cardiol 2023;386:74–82. https://doi.org/10.1016/j.ijcard.2023.05.038.
[6] Felker GM, Whellan D, Kraus WE, et al. N-terminal pro-brain natriuretic peptide and exercise capacity in chronic heart failure: data from the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study. Am Heart J 2009;158:S37–44. https://doi.org/10.1016/j.ahj.2009.07.011.
[7] Fudim M, Kelly JP, Jones AD, et al. Are existing and emerging biomarkers associated with cardiorespiratory fitness in patients with chronic heart failure? Am Heart 2020; 220:97–107. https://doi.org/10.1016/j.ahj.2019.11.006.
[8] Buckley, Canada LF, Del Buono JM, et al. Low NT-proBNP levels in overweight and obese patients do not rule out a diagnosis of heart failure with preserved ejection fraction. ESC Heart Fail 2018;5:372–8. https://doi.org/10.1002/ehf2.12235.
[9] Francis GS, Felker GM, Tang WH. A test in context: critical evaluation of natriuretic peptide testing in heart failure. J Am Coll Cardiol 2016;67:330–7. https://doi.org/10.1016/j.jacc.2015.10.073.