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SHORT COMMUNICATION

Low NT-proBNP levels in overweight and obese patients do not rule out a diagnosis of heart failure with preserved ejection fraction

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Abstract

Background Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome that presents clinicians with a diagnostic challenge. The use of natriuretic peptides to exclude a diagnosis of HFpEF has been proposed. We sought to compare HFpEF patients with N-terminal pro-brain natriuretic peptide (NT-proBNP) level above and below the proposed cut-off.

Methods Stable patients (n = 30) with left ventricular (LV) ejection fraction $\geq$ 50% were eligible if they had a diagnosis of HF according to the European Society of Cardiology diagnostic criteria. Characteristics of patients with NT-proBNP below ($\leq$125 pg/mL) and above ($>$125 pg/mL) the diagnostic criterion were compared.

Results There were 19 (66%) women with median age 54 years. Half were African American (16, 53%), and most were obese. There were no significant differences in clinical characteristics or medication use between groups. LV end-diastolic volume index was greater in high NT-proBNP patients (P = 0.03). Left atrial volume index, E/e′ ratio, and E/e′ ratio at peak exercise were not significantly different between NT-proBNP groups. Peak oxygen consumption (VO_2), VO_2 at ventilatory threshold, and ventilatory efficiency measures were impaired in all patients and were not significantly different between high and low NT-proBNP patients.

Conclusions NT-proBNP was below the proposed diagnostic cut-off point of 125 pg/mL in half of this obese study cohort. Cardiac diastolic dysfunction and cardiorespiratory fitness were not significantly different between high and low NT-proBNP patients. These data indicate that excluding the diagnosis of HFpEF based solely on NT-proBNP levels should be discouraged.

Keywords Heart failure with preserved ejection fraction; Cardiorespiratory fitness; Natriuretic peptides

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Background

Due to heterogeneity, the heart failure with preserved ejection fraction (HFpEF) syndrome presents clinicians with a diagnostic challenge. The recently updated 2016 European Society of Cardiology (ESC) guidelines mandate an elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) to diagnose HF, departing from prior recommendations.[1–5]

Indeed, evidence cited in the guidelines on the diagnostic utility of NP derives from patients with predominantly systolic dysfunction.[5–9] Studies on the diagnostic utility of NP in HFpEF patients are conflicting.[10–13] Moreover, elevated NP levels do not predict the response to treatment among

HFpEF patients and treatment response may be greatest in patients with low NP levels.[14,15]

Aims

The aim of the current study was to determine whether an NT-proBNP level below the ESC-recommended diagnostic cut-off of 125 pg/mL excludes a diagnosis of HFpEF.

Methods

We included stable HFpEF outpatients who were enrolled prospectively for a clinical trial (NCT02173548) as described previously.[16] Patients were eligible according to 2007 ESC criteria,[3] which did not mandate an elevated NP level for diagnosis, and were excluded if they had recent (within 1 month prior) hospitalization or were unable to complete cardiopulmonary exercise (CPX) testing.

Plasma NT-proBNP levels were determined using a Elecsys proBNP II platform and a electrochemiluminescence immunoassay 'ECLIA' (Roche Diagnostics, Indianapolis, IN, USA). The assay reports a range of accuracy between 5 and 35 000 pg/mL. Patients were categorized as low or high NT-proBNP levels based upon the 2016 ESC diagnostic cut-off[5] of 125 pg/mL. All patients underwent maximal CPX according to a conservative ramping treadmill protocol and achieved a peak respiratory exchange ratio $>$ 1.0 (preferably $\geq$1.1).[17,18]

Venous whole blood samples were drawn prior to CPX. Serum was separated, and NT-proBNP level quantification was conducted on the same day as blood sample acquisition. Body composition was assessed via bioelectrical impedance analysis (Quantum IV Body Composition Analyzer, RJL Systems, Clinton, MI, USA) as previously described.[19]

Transthoracic Doppler echocardiography was performed by a cardiologist according to current recommendations.[20–22]

Summary statistics are reported as median and interquartile range (IQR). Comparisons between patients with high and low NT-proBNP were conducted with the Mann–Whitney U-test for continuous variables and Fisher's exact test for categorical variables. Spearman's ρ was calculated to determine whether NT-proBNP correlated with cardiac structure or cardiorespiratory fitness. A two-sided *P*-value $<$0.05 was considered statistically significant. All analyses were conducted with SPSS 24.0 (IBM, Armonk, NY, USA).

Results

Table 1 summarizes characteristics of included patients. All patients had New York Heart Association (NYHA) functional class II (9, 30%) or III (21, 70%) symptoms. All patients were obese except one that was overweight [body mass index (BMI) of 27]. Median BMI was 42 (38–48) kg/m^2. There were no differences in fat mass, % fat mass, or fat mass index between low and high NT-proBNP patients ($P > 0.50$ for each measure). Clinical characteristics and medication use were not different between patients with a low NT-proBNP and patients with a high NT-proBNP ($P > 0.13$ for each comparison) (*Table 1*). Patients with low NT-proBNP reported greater self-assessed activity levels compared with high NT-proBNP patients ($P = 0.02$). Many patients with low NT-proBNP level reported NYHA functional class III symptoms (9, 60%), indicating marked limitation of physical activity.

All patients achieved a maximal effort during CPX as measured by peak respiratory exchange ratio. Exercise time during maximal CPX was shorter in patients with high NT-proBNP levels compared with low NT-proBNP levels 7.2 vs. 9.5 min ($P = 0.007$) (*Figure 1*). Cardiorespiratory fitness was significantly impaired in all patients. Peak oxygen consumption (VO_2) was 13.3 mL/kg/min (IQR, 11.7–17.2) and 16.0 mL/kg/min (IQR, 13.5–17.8) in the high and low NT-proBNP groups, respectively ($P = 0.19$ for between-group comparison). These achieved peak VO_2 represented 49% and 64% of the value predicted based upon age, sex, and weight ($P = 0.12$ for between-group comparison). Impairments were also observed in VO_2 at ventilatory threshold, peak O_2 pulse, and oxygen uptake efficiency slope for both high and low NT-proBNP groups (*Table 2*).

Left ventricular (LV) end-diastolic and end-systolic volume indices as well as left atrial volume index (each adjusted for body surface area) were smaller in patients with low NT-proBNP levels (*Table 2*). Stroke volume index was smaller in low NT-proBNP patients. Median ratio of early mitral inflow velocity to mitral annular early diastolic tissue velocity (E/e') was 12.6 (IQR, 8.3–18.4) and 11.3 (8.2–11.7) in the high and low NT-proBNP groups, respectively.

Conclusions

Abnormalities of cardiac structure, cardiac diastolic function, and cardiorespiratory fitness were present in this cohort of mostly obese patients with HFpEF regardless of NT-proBNP level. Clinicians should avoid excluding a diagnosis of HFpEF in obese patients with a low NT-proBNP level who otherwise meet diagnostic criteria. Future studies should assess the prevalence of 'low NP HFpEF' in a more diverse cohort.

The use of NP levels was first introduced as a requirement for the diagnosis of HFpEF in the 2016 ESC HF guidelines.[5] The mandate to assess NP levels departed from a prior ESC consensus statement in 2007 and other recommended

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Table 1. Patient characteristics in the overall cohort and according to N-terminal pro-brain natriuretic peptide level

Characteristic	All patients (n = 30)	NT-proBNP > 125 pg/mL (n = 15)	NT-proBNP ≤ 125 pg/mL (n = 15)	P-value
Age (years, IQR)	54 (48–62)	58 (51–66)	54 (48–57)	0.23
Female gender (n [%])	19 (66)	7 (47)	12 (80)	0.13
African American (n [%])	16 (53)	8 (53)	8 (53)	1.0
Diabetes (n [%])	23 (77)	13 (87)	10 (67)	0.39
Hypertension (n [%])	30 (100)	15 (100)	15 (100)	1.0
Hyperlipidaemia (n [%])	22 (73)	10 (67)	12 (80)	0.68
Shortness of breath (n [%])	30 (100)	15 (100)	15 (100)	1.0
Orthopnoea (n [%])	14 (50)	8 (57.1)	6 (42.9)	0.71
Paroxysmal nocturnal dyspnoea (n [%])	6 (20)	3 (21.4)	3 (21.4)	1.0
Peripheral oedema (n [%])	11 (37)	8 (57.1)	3 (21.4)	0.12
Systolic blood pressure (mm Hg)	130 (119–137)	130 (120–140)	125 (112–134)	0.35
Diastolic blood pressure (mm Hg)	70 (62–74)	70 (62–80)	68 (62–72)	0.33
Heart rate (beats/min)	75 (62–83)	63 (58–88)	78 (67–83)	0.25
C-reactive protein (mg/L)	6.1 (3.7–16.2)	6.9 (4.1–17)	4.6 (2.7–14.5)	0.38
Body composition				
Body mass index (kg/m^2, IQR)	42 (38–48)	42 (40–54)	42 (36–45)	0.22
Normal weight	1 (7)	1 (7)	0	0.26
Class 1 obesity (n [%])	2 (13)	0	2 (13)	
Class 2 obesity (n [%])	8 (27)	3 (20)	5 (33)	
Class 3 obesity (n [%])	19 (63)	11 (73)	8 (53)	
Fat mass (kg)	55 (47–61)	54 (43–63)	55 (49–59)	0.92
Fat mass (% total body weight)	48 (38–52)	40 (37–49)	50 (37–53)	0.50
Fat mass index	19 (16–23)	19 (15–23)	19 (17–23)	0.77
New York Heart Association functional class				
Class II	9 (30)	3 (20)	6 (40)	0.43
Class III	21 (70)	12 (80)	9 (60)	
Quality of life assessment (score [IQR])				
MLHFQ	61 (35–73)	67 (44–74)	60 (27–67)	0.44
DASI	23 (16–33)	16 (11–27)	26 (19–40)	0.02
Heart failure therapies (n [%])				
ACE-I or ARB	17 (57)	8 (53)	9 (60)	0.99
Beta-blocker	25 (83)	13 (87)	12 (80)	0.99
Aldosterone antagonist	17 (57)	8 (53)	9 (60)	0.99
Hydralazine	8 (27)	6 (40)	2 (13)	0.22
Nitrates	2 (7)	2 (13)	0	0.48
Loop diuretic	30 (100)	15 (100)	15 (100)	1.0
Loop diuretic dose (mg furosemide)	80 (40–160)	80 (40–160)	80 (20–160)	0.82
NT-proBNP (pg/mL, IQR)	127 (48–251)	248 (174–318)	48 (24–90)	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DASI, Duke Activity Status Index; IQR, inter-quartile range; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide.

diagnostic approaches, which recommend optional use of NPs.[3,22] This mandate was included despite a lack of evidence to support the diagnostic precision and accuracy of NPs in patients with HFpEF. Indeed, the majority of available data on the diagnostic utility of NPs are derived from studies that were designed to identify LV systolic dysfunction,[6–9] mixed cohorts that included few patients with HFpEF[10] or reported conflicting results.[11,12] The data presented herein further challenge the use of NPs to rule out HFpEF in overweight or obese patients with signs and symptoms of HF and objective cardiac diastolic dysfunction or elevated filling pressure.

However, while elevated NP levels have very high positive predictive value for HFpEF, low NP levels have very low negative predictive value in obese patients who otherwise meet criteria for a diagnosis of HFpEF: in the cohort presented here, 50% of patients of HFpEF diagnosed according to strict Doppler echocardiographic or haemodynamic criteria had NT-proBNP < 125 pg/mL and showed severe impairment in exercise capacity associated with 7diastolic dysfunction.

Importantly, we enroled patients according to 2007 ESC consensus statement criteria.[3] Had we applied 2016 ESC guideline criteria and mandated an elevated NT-proBNP level to confirm diagnosis, 50% of patients in our cohort would no longer be considered to have HFpEF and an alternative diagnosis would have been pursued erroneously to explain cardiac signs and symptoms.

Obesity is associated with low NP levels due to increased adipose tissue.[23] It is unclear whether our results will generalize to non-obese cohorts. However, we did not find any differences in fat mass between the high and low NT-proBNP groups, suggesting that body composition alone cannot explain our findings. We believe that our results

Figure 1 Cardiac structure and function and cardiorespiratory fitness according to N-terminal pro-brain natriuretic peptide (NT-proBNP) level for each patient is presented. The vertical dashed line separates patients with NT-proBNP level above and below 125 pg/mL, the diagnostic cut-point recommended by the European Society of Cardiology. E/e′ ratio, early diastolic mitral inflow velocity to mitral annular velocity ratio; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; OUES, oxygen uptake efficiency slope; pVO_2, peak oxygen consumption.

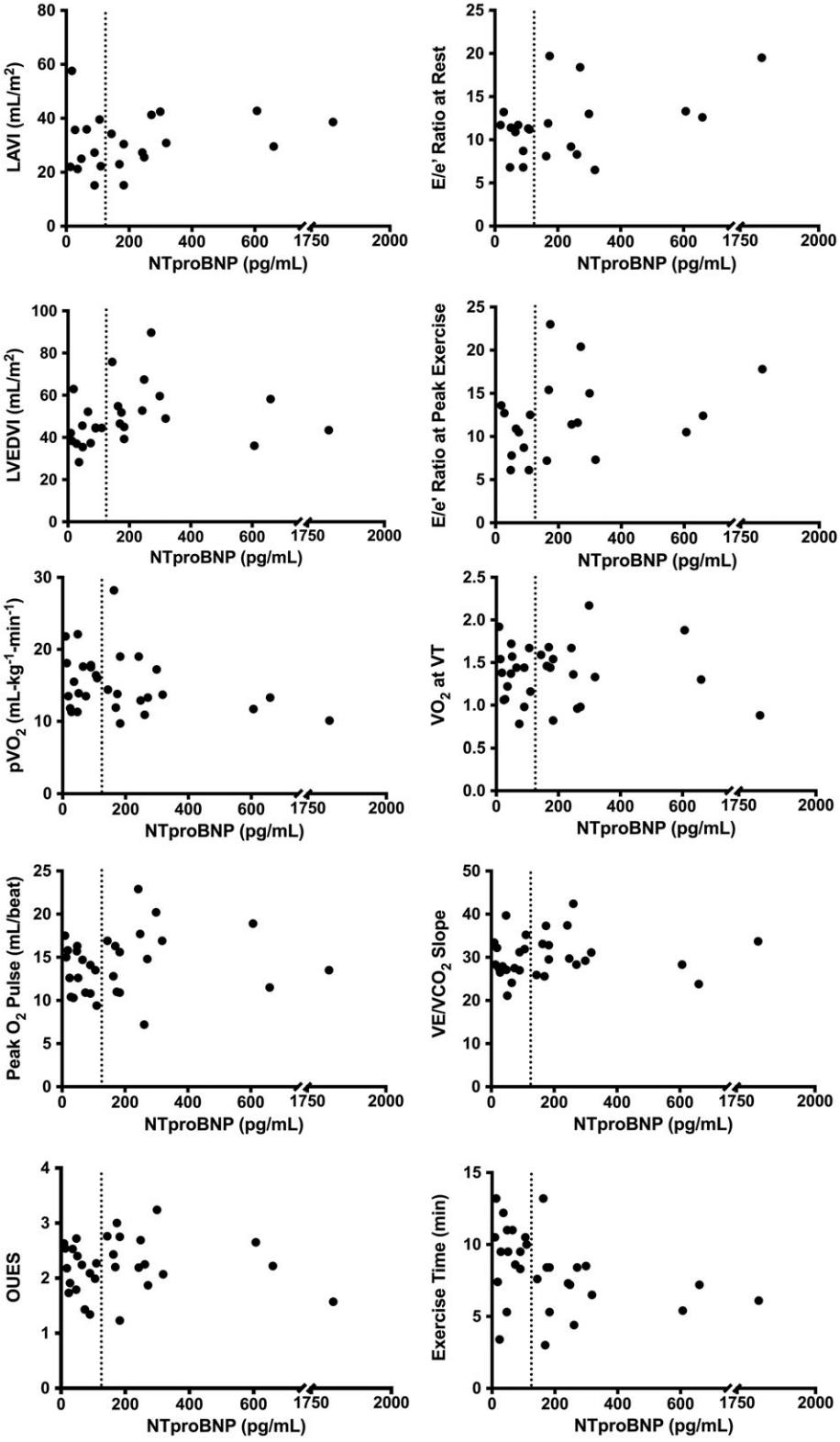

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Table 2. Cardiac structure and function and cardiorespiratory fitness in the overall cohort and according to N-terminal pro-brain natriuretic peptide level

Parameter	All patients (n = 30)	NT-proBNP > 125 pg/mL (n = 15)	NT-proBNP ≤ 125 pg/mL (n = 15)	P-value
Doppler echocardiography				
LVEF (%)	60 (56–63)	60 (53–63)	60 (57–62)	0.78
LVEDV index (mL/m^2)	46 (39–58)	52 (45–62)	43 (37–51)	0.03
LVESV index (mL/m^2)	18 (14–26)	21 (16–30)	16 (14–21)	0.08
SV index (mL/m^2)	29 (23–34)	30 (28–34)	24 (23–30)	0.02
LAV index (mL/m^2)	30 (23–39)	30 (26–41)	26 (22–37)	0.35
E/A ratio	1.1 (0.9–1.4)	1.2 (0.9–1.6)	1.0 (0.9–1.2)	0.16
DT (ms)	230 (188–270)	230 (190–280)	229 (151–250)	0.31
e′ (cm/s)	7.9 (5.7–9.2)	6.2 (5–6.6)	7 (6.5–8.8)	0.05
E/e′ ratio	11.4 (8.5–13.1)	12.6 (8.3–18.4)	11.3 (8.2–11.7)	0.20
e′ at peak exercise (cm/s)	9.6 (8.4–12.1)	8.6 (7.7–10.6)	10.5 (9.6–13.3)	0.08
E/e′ ratio at peak exercise	11.5 (8.0–14.7)	12.4 (10.5–17.8)	10.5 (7.0–12.6)	0.10
Change in E/e′ with exercise	0.4 (−1.1 to 2.1)	2.0 (−0.9 to 3.3)	−0.5 (−2.5 to 1.6)	0.10
LV s′ (cm/s)	7.6 (6.9–8.5)	7.5 (6.2–8.5)	9.8 (9.4–11.3)	0.46
RV s′ (cm/s)	13 (9.6–14.6)	13.5 (9.8–15.5)	12.4 (9.6–13.5)	0.53
TAPSE (cm)	2.5 (2.0–2.7)	2.3 (2.0–2.9)	2.5 (2.2–2.6)	0.76
Cardiopulmonary exercise testing				
Exercise time (min)	8.4 (6.4–10.1)	7.2 (5.4–8.4)	9.5 (8.3–11.0)	0.007
Peak respiratory exchange ratio	1.10 (1.04–1.15)	1.09 (1.04–1.15)	1.10 (1.03–1.16)	0.99
Peak VO_2 (mL/kg/min)	13.9 (11.9–17.7)	13.3 (11.7–17.2)	16 (13.5–17.8)	0.19
Predicted peak VO_2 (%)	51 (43–65)	49 (42–54)	64 (43–71)	0.12
Peak VO_2 (L/min)	1.7 (1.4–2.1)	1.9 (1.5–2.2)	1.8 (1.4–2.2)	0.78
Predicted peak VO_2 (%)	79 (67–88)	74 (63–82)	84 (67–101)	0.17
VO_2 at VT (L/min)	1.41 (1.07–1.61)	1.44 (0.98–1.67)	1.38 (1.07–1.57)	0.81
Peak O_2 pulse (mL/beat)	14.4 (11.0–16.5)	15.6 (11.5–17.7)	13.5 (10.8–15.7)	0.11
VE/VCO_2 slope	29 (27–33)	30 (28–34)	28 (27–32)	0.31
OUES	2.23 (1.90–2.64)	2.25 (2.07–2.75)	2.18 (1.79–2.53)	0.20
Rating of perceived exertion	17 (15–17)	17 (15–17)	17 (15–18)	0.54
Borg dyspnoea score	7 (4–9)	7 (4–9)	7 (3–9)	0.51

DT, deceleration time; E, early diastolic mitral annular inflow velocity; e′, early diastolic mitral annular velocity; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; IQR, inter-quartile range; OUES, oxygen uptake efficiency slope; RV, right ventricular; s′, peak systolic annular velocity; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion VO_2, oxygen consumption; VE/VCO_2 slope, minute ventilation-carbon dioxide production slope; VT, ventilatory threshold.

retain a high degree of relevance for population of patients with HFpEF as obesity is an important and highly prevalent co-morbidity in this group.[24]

These data, however, do not support elimination of NP assessment as part of routine management of HFpEF patients. Indeed, NPs remain strong markers of LV wall stress[25] and prognosis.[26] Our own data indicate that abnormalities in cardiac structure and cardiorespiratory fitness are likely worse in patients with high NT-proBNP levels compared with those with low NT-proBNP levels.

These results have important implications for the use of elevated NP level as an inclusion criterion in clinical trials.[27–29] Our data support the use of a lower threshold for inclusion compared with prior trials in order to enrol patients with HFpEF and obesity. Of note, even many of the patients in the high NT-proBNP group would have failed to meet the inclusion criteria for recent HFpEF studies,[30] and thus overweight and obese patients are likely to be largely under-represented in contemporary HFpEF study with NT-proBNP-driven enrolment criteria.

Nevertheless, it should be noted that our study is limited by a small sample size and by the single-time-point determination of NT-proBNP. All patients had been treated for HFpEF by the time of blood sampling and therefore it is possible that untreated NT-proBNP levels would have been higher in newly diagnosed patients, yet this is likely to occur in clinical practice in which thiazide diuretics are commonly used for the treatment of arterial hypertension. Finally, our results may not generalize to other ethnicities or to normal weight individuals. However, results similar to ours have been reported previously in various settings.[11–13]

In summary, excluding the diagnosis of HFpEF based solely on NT-proBNP levels should be discouraged in overweight and obese patients.

Conflict of interest

None declared.

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