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

Leo F. Buckley1, Justin M. Canada2,3, Marco G. Del Buono2, Salvatore Carbone2,4, Cory R. Trankle2, Hayley Billingsley2, Dinesh Kadariya2, Ross Arena5, Benjamin W. Van Tassell1 and Antonio Abbate2*

1Department of Pharmacotherapy and Outcomes Science, Virginia Commonwealth University, Richmond, VA, USA; 2VCU Pauley Heart Center, Virginia Commonwealth University, 1200 E Broad Street, 5th Floor Rm 520, Richmond, VA 23298, USA; 3Department of Kinesiology and Health Sciences, Virginia Commonwealth University, Richmond, VA, USA; 4Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy; 5Department of Physical Therapy, College of Applied Health Sciences, University of Illinois at Chicago, Chicago, IL, USA

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 diagnostic criterion.

Methods  Stable patients (n = 30) with left ventricular (LV) ejection fraction ≥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 (≤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/e0 ratio, and E/0 ratio at peak exercise were not significantly different between NT-proBNP groups. Peak oxygen consumption (VO2), VO2 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
HFpEF patients and treatment response may be greatest in patients with low NP levels.\textsuperscript{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.\textsuperscript{16} Patients were eligible according to 2007 ESC criteria,\textsuperscript{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 an 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\textsuperscript{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 ≥1.1).\textsuperscript{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.\textsuperscript{19}

Transthoracic Doppler echocardiography was performed by a cardiologist according to current recommendations.\textsuperscript{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 $\rho$ 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.\textsuperscript{5} The mandate to assess NP levels departed from a prior ESC consensus statement in 2007 and other recommended
diagnostic approaches, which recommend optional use of NPs.3,23 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 HFpEF10 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 enrolled 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

### 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/m², 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)               | 2 (13)                         | 0                              | 0       |
| 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]) | 61 (35–73)           | 67 (44–74)                     | 60 (27–67)                     | 0.44    |
| MLHFQ                                  | 23 (16–33)           | 26 (19–40)                     | 26 (19–40)                     | 0.02    |
| DASI                                   |                      |                                |                                |         |
| 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.
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\(^0\) ratio, early diastolic mitral inflow velocity to mitral annular velocity ratio; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; QUES, oxygen uptake efficiency slope; pVO\(_2\), peak oxygen consumption.
Doppler echocardiography

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 |
|-----------|-----------------------|---------------------------------|---------------------------------|---------|
| LVED (%)  | 60 (56–63)            | 60 (53–63)                      | 60 (57–62)                      | 0.78    |
| LVEDV index (mL/m²) | 46 (39–58)            | 52 (45–62)                      | 43 (37–51)                      | 0.03    |
| LVESV index (mL/m²) | 18 (14–26)            | 21 (16–30)                      | 16 (14–21)                      | 0.08    |
| SV index (mL/m²) | 29 (23–34)            | 30 (28–34)                      | 24 (23–30)                      | 0.02    |
| LAV index (mL/m²) | 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)                 | 0.05    |
| 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 oxygen consumption ratio | 1.10 (1.04–1.15) | 1.09 (1.04–1.15) | 1.10 (1.03–1.16) | 0.99 |
| Peak VO₂ (ml/kg/min) | 13.9 (11.9–17.7) | 13.3 (11.7–17.2) | 16 (13.5–17.8) | 0.19 |
| Predicted peak VO₂ (%) | 51 (43–65) | 49 (42–54) | 64 (43–71) | 0.12 |
| Peak VO₂ (L/min) | 1.7 (1.4–2.1) | 1.9 (1.5–2.2) | 1.8 (1.4–2.2) | 0.78 |
| Predicted peak VO₂ (%) | 79 (67–88) | 74 (63–82) | 84 (67–101) | 0.17 |
| VO₂ 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 O₂ pulse (ml/beat) | 14.4 (11.0–16.5) | 15.6 (11.5–17.7) | 13.5 (10.8–15.7) | 0.11 |
| VE/VO₂ 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 VO₂, oxygen consumption; VE/VO₂ slope, minute ventilation-carbon dioxide production slope; VT, ventilatory threshold.

retain a high degree of relevance for population of patients with HFP EF 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 HFP EF patients. Indeed, NPs remain strong markers of LV wall stress25 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 HFP EF 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 HFP EF studies,30 and thus overweight and obese patients are likely to be largely under-represented in contemporary HFP EF 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 HFP EF 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 HFP EF based solely on NT-proBNP levels should be discouraged in overweight and obese patients.

Conflict of interest

None declared.

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