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B-type natriuretic peptide in Parkinson's disease: a novel biomarker of dysautonomia

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ABSTRACT

Background: The presence of cardiac diseases in Parkinson's disease (PD) patients opens the debate on the identification of early biomarkers of heart damage. N-terminal pro-brain natriuretic peptide (NT-proBNP) may be involved in cardiac autonomic denervation.
Objectives: i) to investigate whether there is a relationship between NT-proBNP and measures of cardiovascular autonomic function in PD patients; ii) to elucidate the discrimination power of NT-proBNP levels to identify PD patients with dysautonomia.
Methods: Thirty-one consecutive PD patients were enrolled. NT-proBNP levels were measured and cardiovascular autonomic function tests were performed, including the Head-up Tilt test (HUTT), Valsalva Maneuver (VM), Hand Grip (HG), and Deep Breathing (DB). ROC curve analysis was performed to explore the discriminatory power of NT-proBNP levels. Non-collinear independent variables associated with autonomic parameters were examined using multivariable linear regression models.
Results: we found: i) high levels of NT-proBNP in patients with neurogenic orthostatic hypotension (adj. $P = 0.001$) and pathologically absent overshoot in VM (adj. $P = 0.001$) along with significant associations with the difference (Δ) in the HUTT between 10' values of the systolic and diastolic blood pressure (ΔSBP, ΔDBP) and baseline values ($P = 0.011$, $P = 0.027$), ΔBP of the VM phase III ($P = 0.024$), and the E/I of the DB ($P = 0.019$); ii) significant correlations with self-reported measures of cardiovascular manifestations; iii) high discriminatory power of NT-proBNP levels in detecting PD patients with dysautonomia (AUC = 0.917, $P < 0.0001$).
Conclusion: This is the first study exploring the relationship between NT-proBNP and cardiovascular autonomic function test measures, suggesting its role as a suitable biomarker of dysautonomia in PD patients.

1. Introduction

Parkinson's disease (PD), one of the most common neurodegenerative diseases, is no longer viewed solely as a movement disorder or a neurodegenerative condition confined to the brain. The pathological process in PD extends beyond the central nervous system and affects autonomic functions. This leads to a range of systemic issues, including impaired cardiovascular, gastrointestinal, and urological function regulation, ultimately reducing patients' quality and duration of life [1]. Among these, cardiac dysautonomia is one of the most common and disabling conditions. The altered function of the heart and vessels seen in cardiovascular dysautonomia generates various manifestations in response to stimuli, mainly postural, including orthostatic hypotension, supine hypertension, and changes in heart rate variability. In addition, PD promotes arrhythmias, myocardial infarction, and heart failure, and is associated with an increased risk of death [2,3].

The mechanisms underlying the interplay between PD and cardiovascular diseases remain unclear, but cardiac dysautonomia may be a

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contributing factor, as already well documented in patients with dysautonomia due to metabolic disorders such as diabetes [4]. The role of the pathological hallmark of PD, α-synuclein, has been investigated in dysautonomia: it has been shown that up to 82 % of patients with synucleinopathies presented intracardiac α-synuclein at pathological examination [5]. Furthermore, in patients with neurogenic orthostatic hypotension (nOH), the accumulation of α-synuclein within sympathetic ganglia correlated with the loss of cardiac noradrenaline [6].

The emergence of cardiac diseases in a relatively large number of PD patients opens the debate on the identification of early biomarkers of heart damage. Several serum markers have been studied to aid cardiovascular risk stratification in patients with PD, i.e., vitamin D, C-reactive protein, DJ-1, coenzyme Q10, homocysteine, and advanced oxidized protein products [7]. Indeed, other biomarkers from different pathophysiological pathways may be incorporated to better elucidate the risk of cardiovascular events. Among them, N-terminal pro-brain natriuretic peptide (NT-proBNP) has been extensively studied in the context of cardiovascular diseases. Several lines of evidence support the role of NT-proBNP in cardiac autonomic denervation in patients with diabetes, with elevated NT-proBNP levels significantly associated with the presence and severity of cardiac autonomic dysfunction [8].

BNP is secreted by the cardiac ventricles in response to increased ventricular stretch or wall stress, playing a role in volume homeostasis and cardiovascular remodeling [9]. ProBNP is cleaved into active BNP and more stable NT-proBNP within cardiomyocytes. The role of BNP in diagnosing heart failure and predicting cardiovascular death in patients with acute coronary syndromes, type 2 diabetes mellitus (T2DM), and hypertension has been established [10,11]. Nonetheless, the usefulness of this biomarker in PD has been poorly investigated. A study by Watanabe et al. evaluated serum BNP levels in patients treated with ergot-derived dopamine agonists and found significantly higher levels compared to the non-ergot group, accompanied by significant correlations with measures of valvular heart disease [12]. Another study [13] evaluated NT-proBNP in 285 patients with PD and 570 age-, sex-, and cardiovascular risk factor-matched healthy controls. In nearly 50 % of this cohort, NT-proBNP levels exceeded the clinical cut-off value of 125 ng/L, and significant correlations were observed with poorer motor functions. However, no differences were detected between PD patients with and without dysautonomia. These findings could be explained by the heterogeneity in the definition of dysautonomia as well as the lack of a standardized assessment of cardiovascular autonomic function.

In the present study, we aimed to fill this gap by investigating: i) the relationship between NT-proBNP as a biomarker of subclinical cardiomyopathy and measures of cardiovascular autonomic function; ii) the discrimination power of NT-proBNP levels to identify parkinsonian patients with dysautonomia.

2. Methods

2.1. Study population and clinical assessment

This cross-sectional study involves a cohort of 31 consecutive PD patients, enrolled from January 2023 to January 2024 at the Parkinson Institute of Milan (Italy) by neurologists experienced in movement disorders and contributing to the Parkinson Institute Biobank. The local Ethics Committee approved the study procedures (CE 3499/23), and this research was conducted following the principles of the Declaration of Helsinki and its later amendments. All patients gave their written informed consent. The inclusion and exclusion criteria are reported in the Supplementary Material.

Motor impairment was assessed in the "on" condition using the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) [14], and the Hoehn and Yahr scale (HY). PD medication was also recorded, and the levodopa equivalent daily dose (LEDD) was calculated according to Ref. [15]. Other relevant data were collected, including the presence and duration of non-motor symptoms: hyposmia (according to medical reports), probable REM sleep behavior disorder (pRBD) (defined as a cut-off score $\geq$6 on the RBD Screening Questionnaire (RBDSQ), constipation, urinary and sexual dysfunction, anxiety or depression, dementia, and hallucinations. Specific questionnaires were used to explore non-motor domains and dysautonomia, more in detail: the Scales for Outcomes in Parkinson's Disease - Autonomic Dysfunction (SCOPA-AUT), the Composite Autonomic Symptom Score 31 Questionnaire (COMPASS-31), the Orthostatic Hypotension Symptom Assessment (OHSA), and the Orthostatic Hypotension Daily Activity Scale (OHDAS). Using medical records, we evaluated the prevalence of cardiovascular diseases, including arterial hypertension (AH), T2DM, atrial fibrillation (AF), kidney disease (KD), and obesity.

2.2. Laboratory analysis

At enrollment, patients underwent peripheral venous blood collection after overnight fasting. NT-proBNP hormone levels were measured on the Cobas e411 analyzer using an electrochemiluminescence immunoassay (proBNPII, ECLIA, Roche Diagnostics). The analytical range was 5–35,000 pg/mL.

2.3. Cardiovascular autonomic function tests (CAFTs)

CAFTs were performed within one month of clinical and laboratory assessments, following standard operating procedures as reported in the Supplementary Material.

Continuous beat-to-beat measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were recorded with a non-invasive integrated device, the ANScovery System, with a Tutor Monitor guiding patients to perform the maneuvers correctly and in a standardized manner. The protocol included: 20 min of lying recumbent, 10 min 60° Head-up Tilt test (HUTT), Valsalva Maneuver (VM) (3 trials with analysis of the best one), Hand Grip (HG), and Deep Breathing (DB). Patients rested for at least 5 min between tests to allow cardiovascular parameters to stabilize.

The following measures were automatically calculated for each test by the ANScovery software: 1) basal SBP, DBP, and HR as the mean value of the last 10 min of supine rest, as an estimate of supine hypertension; 2) SBP, DBP, and HR responses to HUTT (difference (Δ) between values at 3, 5, and 10 min of tilting, and 5 min after tilting down, compared to basal values); 3) blood pressure (BP) responses to VM (phase I, phase II early (IIE), phase II late (IIL), phase III, and phase IV/overshoot) and the difference between average BP values in each phase and average baseline BP values (ΔBP); 4) HR responses to VM (Valsalva ratio, VR); 5) BP responses to 3 min HG (Δ SBP, Δ DBP); 6) HR responses during DB (average of the 10 shortest R–R intervals during inspiration (I) – average of the 10 longest R–R during expiration (E), Δ I-E and I/E ratio). Adrenergic function indexes are BP responses to VM and HUTT, and cardiovagal indexes are HR responses to DB and VM. nOH was defined as a sustained decrease in SBP >20 mmHg and/or DBP drop >10 mmHg within 3 min of HUTT or as a fall in SBP >30 mmHg and/or DBP >15 mmHg in the case of concomitant supine hypertension [16]. The responses in VM, HG, and DB tests were age-adjusted and considered normal according to Ref. [17]. To improve the detection of cardiovascular dysautonomia, a modified composite autonomic scoring scale (mCASS) with the cardiovagal (points from 0 to 3) and adrenergic (points from 0 to 4) subscores of Low's original CASS [18] was employed. Parkinsonian patients with dysautonomia (PD-Dys) were identified with a mCASS score $\geq$1 in either the cardiovagal or adrenergic domains, whereas patients without dysautonomia (PD-NoDys) had a mCASS score = 0.

2.4. Statistical analysis

This is a cross-sectional hypothesis-generating study. The number of participants was determined by both *a priori* sample size estimation and

practical availability. Specifically, we considered the correlation between NT-proBNP values and cardiovascular autonomic measures as the primary outcome. Assuming a correlation coefficient r = 0.5, a two-tailed type I error = 5 %, and power = 80 %, we estimated a sample size of at least 28 patients ("pwr" package, RStudio 2022.07.2 + 576). All the analyses performed in the study are reported in the Supplementary Material.

3. Results

The analyzed PD cohort consisted of 31 patients, with a mean age of 71.84 ± 1.57 years, predominantly male (77.4 %), and an average disease duration of 10.94 ± 1.32 years. Regarding motor symptoms, the mean UPDRS-III score was 13.29 ± 1.36, and most patients were classified between 1 and 2.5 on the HY scale. Regarding non-motor symptoms, the average duration of non-motor PD symptoms was 13.29 ± 2.28 years. At the time of enrollment, the most prevalent non-motor symptoms were: hyposmia (48.4 %), pRBD (61.3 %), constipation (74.2 %), anxiety/depression (45.2 %), nOH (48.4 %), urinary dysfunction (83.9 %), and sexual dysfunction (56.7 %). Concerning cardiovascular diseases, the most common was AH (38.7 %). See Table 1 for complete demographic and clinical data. The mean serum NT-proBNP levels were 176.95 ± 29.10 pg/mL, with 17/31 patients (54.5 %) displaying a pathological value above the cut-off of 125 pg/mL. A direct correlation between NT-proBNP levels and age was found (r = 0.387, $P = 0.032$), whereas no differences were observed when stratifying the population by sex. No significant correlations were found between NT-proBNP levels and clinical measures, except for a direct relationship with PD duration (r = 0.367, $P = 0.043$). However, this correlation was not confirmed after controlling for the effect of age. No differences in NT-proBNP levels were found when stratifying the cohort by hyposmia, pRBD, constipation, anxiety/depression, urinary and sexual dysfunction, dementia, or hallucinations.

3.1. Testing of cardiovascular adrenergic function and NT-proBNP levels

3.1.1. HUTT

Detailed cardiovascular testing measures are reported in Supplementary Table S1. Regarding baseline resting values, we found that 15/31 patients (48.4 %) had neurogenic supine hypertension (nSH), defined as SBP of ≥140 mmHg and/or diastolic BP of ≥90 mmHg, measured after at least 5 min of rest in the supine position [19]. However, no differences in NT-proBNP levels were found when stratifying the PD population according to nSH.

After 3 min of tilting, 12/31 patients (38.7 %) exhibited nOH. Patients with nOH had significantly higher NT-proBNP levels than those without nOH (in the ANCOVA model adjusted for age and disease duration, $P = 0.001$). Significant correlations were also found between NT-proBNP levels and both ΔSBP (r = −0.650, $P < 0.001$) and ΔDBP (r = −0.535, $P = 0.007$) at 10 min of HUTT. This association between HUTT measures and NT-proBNP was confirmed in multivariable regression models, using age and disease duration as independent variables for ΔSBP and ΔDBP (β = −0.550, $P = 0.011$; β = −0.530, $P = 0.027$). To account for potential chronic dopaminergic effects, we conducted secondary analyses by repeating the multivariable regression models, substituting disease duration with total LEDD. NT-proBNP remained a significant predictor of ΔSBP (β = −0.638, $P = 0.006$) and ΔDBP (β = −0.522, $P = 0.045$), whereas LEDD and age were not significant, confirming the robustness of these associations. Significant inverse correlations were observed between NT-proBNP levels and DBP/HR (r = −0.383, $P = 0.049$; r = −0.471, $P = 0.013$) 5 min after tilt-down, although these associations were not confirmed in the multivariable regression models. Fig. 1 summarizes all significant associations between NT-proBNP and HUTT measures.

Table 1
Clinical and demographic characteristics of the study population.

Variables	PD cohort (N = 31)
Demographic and clinical characteristics	
Age, years, mean (SD)	71.84 (1.57)
Sex (male), n (%)	24 (77.4)
Age at PD onset, years, mean (SD)	61.29 (1.80)
PD duration, years, mean (SD)	10.84 (1.32)
NTproBNP levels, pg/mL, mean (SD)	176.95 (29.10)
Motor symptoms	
HY stage	29 (93.5 %)
1–2.5, n (%)	2 (6.5 %)
3, n (%)	
UPDRS-III, score (on), mean (SD)	13.29 (1.36)
Non-motor symptoms	
Number of NMS at PD onset	11 (35.5 %)
0, n (%)	9 (29.0 %)
1, n (%)	10 (32.3 %)
2, n (%)	1 (3.2 %)
3, n (%)	
NMS duration, years, mean (SD)	13.29 (2.28)
Hyposmia, n (%)	15 (48.4 %)
Hyposmia duration, years, mean (SD)	17.18 (2.58)
pRBD, n (%)	19 (61.3 %)
pRBD duration, years mean (SD)	7.81 (2.22)
Constipation, n (%)	23 (74.2 %)
Constipation duration, years, mean (SD)	9.92 (2.67)
Anxiety/Depression, n (%)	14 (45.2 %)
Anxiety/Depression duration, years, mean (SD)	11.88 (5.64)
Orthostatic hypotension, n (%)	15 (48.4 %)
Orthostatic hypotension duration, years, mean (SD)	3.36 (0.88)
Urinary dysfunction, n (%)	26 (83.9 %)
Urinary dysfunction duration, years, mean (SD)	4.82 (1.37)
Sexual dysfunction, n (%)	17 (56.7 %)
Sexual dysfunction duration, years, mean (SD)	5.30 (2.15)
Dementia, n (%)	5 (16.1 %)
Dementia duration, years, mean (SD)	1.40 (0.60)
Hallucinations, n (%)	4 (12.9 %)
Hallucinations duration, years, mean (SD)	3.00 (1.35)
Pharmacological therapy	
LEDD L-DOPA mg/day, mean (SD)	589.23 (49.82)
LEDD DA mg/day, mean (SD)	68.10 (18.32)
LEDD MAOBIs mg/day, mean (SD)	45.16 (8.79)
LEDD total, mg/day, mean (SD)	709.84 (58.04)
Cardiovascular comorbidities	
Arterial hypertension, n (%)	12 (38.7 %)
Atrial fibrillation, n (%)	1 (3.2 %)
Diabetes mellitus, n (%)	1 (3.2 %)
Valvular heart disease, n (%)	2 (6.5 %)
Obesity, n (%)	2 (6.5 %)

Abbreviations: *HY*, Hoehn and Yahr; *NMS*, non-motor symptoms; *UPDRS*, Unified Parkinson's Disease; *pRBD*, probable REM sleep behavior disorder; *LEDD*, Levodopa Equivalent Daily Dose; *DA*, dopamine agonists; *MAOBIs*, Monoamine Oxidase-B Inhibitors.

3.1.2. Valsalva Maneuver

No correlations were observed when considering phase I of the VM measures. We found a non-statistically significant correlation between NT-proBNP levels and ΔBP of phase IIE and phase IIL (r = −0.433, $P = 0.056$; r = −0.439, $P = 0.053$). Significant correlations were observed between NT-proBNP levels and ΔBP in phases III and IV (r = −0.472, $P = 0.041$; r = −0.644, $P = 0.003$). However, NT-proBNP was a significant predictor only in the multivariable regression model with ΔBP of phase III as the dependent variable (β = −0.691, $P = 0.024$; see Fig. 2A). We then used LEDD instead of disease duration as an independent variable. NT-proBNP remained significant for ΔBP phase III (β = −0.400, $P = 0.045$), and LEDD also showed a significant effect (β = −0.480, $P = 0.019$). When stratifying our PD cohort according to the presence or absence of overshoot (OV) in phase IV, we found that patients with pathologically absent OV displayed significantly higher levels of NT-proBNP (281.54 ± 180.12 *vs* 101.41 ± 95.03 pg/mL; $P = 0.001$). This difference was confirmed after controlling for the potentially confounding effect of age and disease duration in the ANCOVA analysis (F

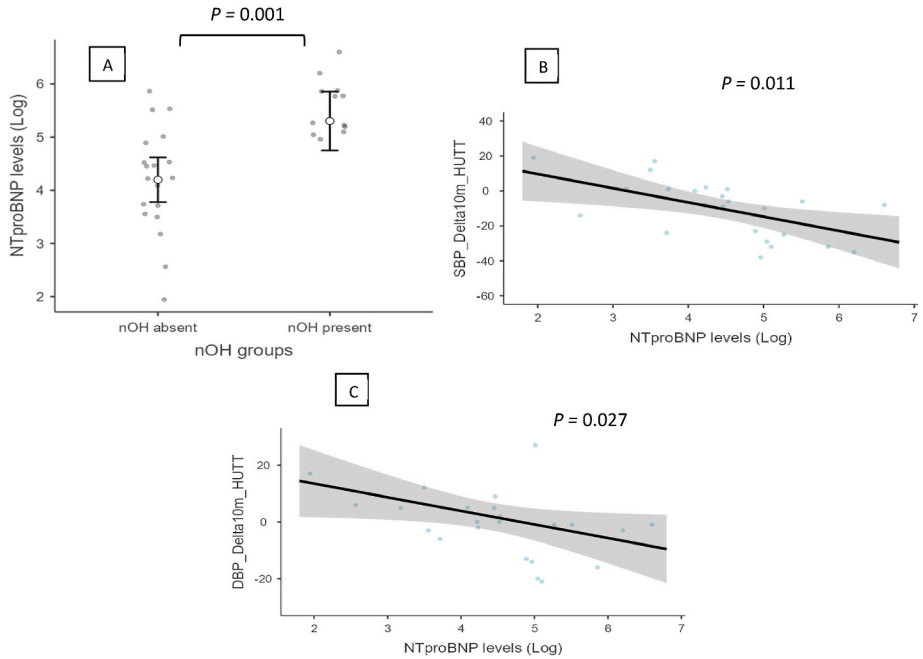

Fig. 1. A: Estimated marginal means (ANCOVA analysis adjusting for age and disease duration) for NT-proBNP levels by nOH subgroups. Error bars represent the 95 % confidence interval. **B-C:** Multivariable regression models including NT-proBNP, age, and disease duration as predictors and HUTT measures as dependent variables. Grey-shaded areas around each regression line represent the 95 % confidence intervals.

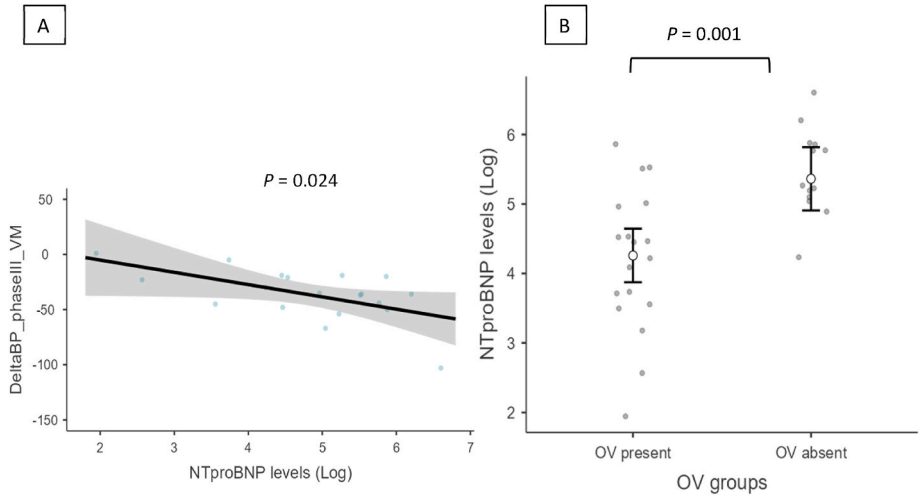

Fig. 2. A: Multivariable regression model including NT-proBNP and age as predictors and Valsalva maneuver's measures as the dependent variable. **2B**: Estimated marginal means (ANCOVA analysis adjusting for age and disease duration) for NT-proBNP levels by overshoot subgroups. Error bars represent the 95 % confidence interval.

= 14.56, $P = 0.001$); see Fig. 2B.

3.1.3. Handgrip test

When considering the correlation between NT-proBNP levels and the HG test as a measure of sympathetic function, we found significant correlations with ΔSBP and ΔDBP (r = −0.632, $P = 0.001$; r = −0.551, $P = 0.006$). However, the multivariable regression model, which included age and disease duration as independent variables, did not confirm this association.

3.2. Testing of cardiovagal function and NT-proBNP levels

3.2.1. Valsalva ratio and heart rate variability during deep breathing

We found a trend toward an inverse relationship between NT-proBNP levels and VR values (r = −0.412, $P = 0.071$). Similarly, when stratifying patients according to pathological VR values, higher levels of NT-proBNP were observed in those patients with pathological VR, even though statistical significance was not reached (242 ± 122.93 *vs* 177.07 ± 231.24; $P = 0.096$).

Considering the DB test, we observed a significant relationship between NT-proBNP levels and the E/I ratio (r = −0.460, $P = 0.012$). This association was confirmed in the multivariable regression model, which included age and disease duration as predictors (β = −0.519, $P = 0.019$), see Fig. 3. Secondary analysis using LEDD confirmed NT-proBNP as a significant predictor (β = −0.503, $P = 0.035$).

3.2.2. mCASS score and NT-proBNP levels

Finally, we confirm the correlation between NT-proBNP and

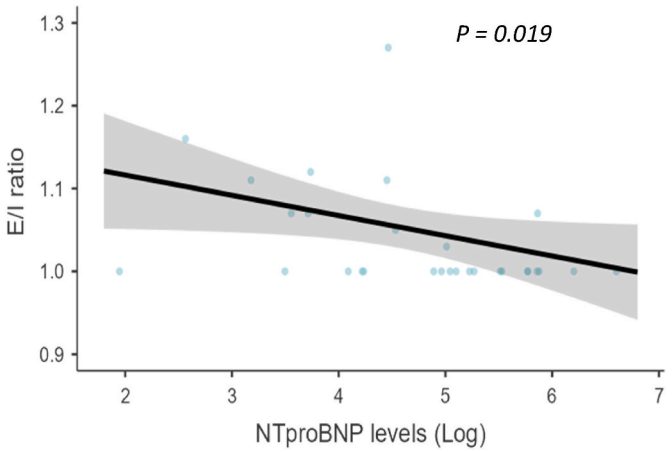

Fig. 3. Multivariable regression model including NT-proBNP, age, and disease duration as predictors and E/I ratio as the dependent variable.

adrenergic and cardiovagal function indices, expressed as mCASS scores. More specifically, NT-proBNP levels showed a direct correlation with mCASS total score (r = 0.622, $P = 0.0003$), adrenergic subscore (r = 0.544, $P = 0.004$), and cardiovagal subscore (r = 0.654, $P = 0.0001$).

3.2.3. Autonomic symptoms questionnaires and NT-proBNP levels

Autonomic symptoms were also evaluated using specific questionnaires. We focused on the relationship with NT-proBNP levels and observed: i) a direct correlation with the OH subitem of the SCOPA-AUT scale (r = 0.461, $P = 0.036$); ii) a direct correlation with subitem 5 ("trouble concentrating") of the OHSA (r = 0.460, $P = 0.036$).

3.2.4. Evaluation of NT-proBNP in PD with and without dysautonomia

The cohort of parkinsonian patients was then divided into two subgroups according to the presence of dysautonomia, as previously described. Regarding clinical-demographic measures, PD with dysautonomia (PD-Dys; N = 16) and PD without dysautonomia (PD-NoDys; N = 15) were similar. As reported in Supplementary Table S2, we found a higher prevalence of dementia in PD-Dys than PD-NoDys ($P = 0.04$), but no other statistically significant differences were observed. On the other hand, significant differences in cardiovascular autonomic testing were observed in all tests, as expected. PD-Dys showed higher NT-proBNP values than PD-NoDys (269 ± 165 *vs* 78.8 ± 84.5; $P < 0.001$). Notably, this difference was confirmed in ANCOVA analysis controlling for age and disease duration (F = 17.51, $P < 0.001$); see Fig. 4A. When conducting a ROC curve analysis to evaluate the discriminatory power of NT-proBNP levels to identify PD-Dys, we found an AUC of 0.917 (95 % CI 0.804–1), $P < 0.0001$; see Fig. 4B. A cut-off value ≥ 113 pg/mL showed 93.8 % sensitivity and 86.7 % specificity. Supplementary Tables S3 and S4 display, respectively, the average scores of questionnaires and autonomic function test measures in PD-Dys and PD-NoDys subgroups.

4. Discussion

This study highlighted the potential role of NT-proBNP as a biomarker of dysautonomia in Parkinson's disease. Specifically, we found: i) higher levels of NT-proBNP in patients with cardiovascular dysautonomia, along with significant associations with autonomic tests assessing both adrenergic and cardiovagal functions; ii) significant correlations between NT-proBNP levels and self-reported measures of cardiovascular manifestations; iii) high sensitivity and specificity of NT-proBNP levels in distinguishing PD patients with dysautonomia from those without dysautonomia.

Regarding cardiovascular test measures, we report significant associations with both adrenergic and cardiovagal function indices. Higher levels of NT-proBNP were found in patients with nOH within 3 min (classical OH) and correlated with lower SBP and DBP after 10 min of tilting. Delayed OH is defined as a fall in blood pressure beyond 3 min of standing or upright tilt table testing [20]. Classical OH is commonly observed in PD patients, whereas delayed OH is under-recognized but carries the same symptoms, risks, and high mortality rate as classical OH. Both forms share the same pathophysiological basis: dysfunction or degeneration of baroreceptors, along with reduced cardiac output or impaired peripheral vascular resistance, leads to a drop in blood pressure within or after 3 min. It has been theorized that delayed OH represents a milder form of OH and an early expression of autonomic nervous system dysfunction in individuals with neurodegenerative diseases. Intriguingly, a previous study found that patients with OH (both classical and delayed) exhibited more advanced cardiac sympathetic denervation than patients without OH [20].

Regarding other measures of cardiovascular sympathetic dysfunction, we found significantly higher levels of NT-proBNP in patients with absent phase IV overshoot during the VM. Previous studies have reported that a lack of BP increase in phase IV is a very sensitive early sign of sympathetic dysfunction [21] and may be associated with other

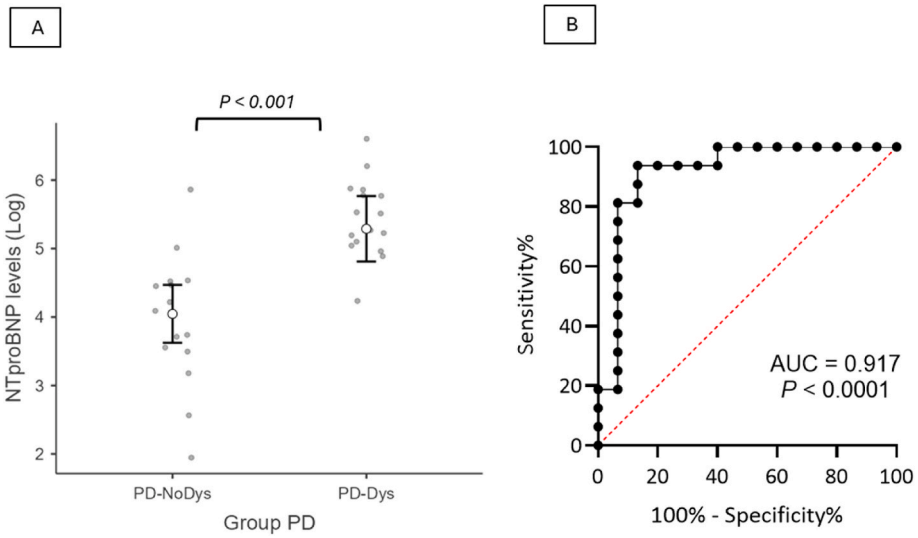

Fig. 4. A: Estimated marginal means (ANCOVA analysis adjusting for age and disease duration) for NT-proBNP levels by dysautonomia subgroups. Error bars represent the 95 % confidence interval. Fig. 4B: ROC curve analysis of NT-proBNP levels to discriminate between PD-Dys and PD-NoDys.

non-motor symptoms. A significant relationship between olfactory dysfunction and the magnitude of blood pressure overshoot during phase IV was detected in early-stage PD patients [22]. We also report an intriguing association between NT-proBNP levels and ΔBP in phase III. It is known that at the end of VM, the sudden fall in intrathoracic and abdominal pressure results in a transient fall in BP lasting 1–2 s, which is mostly a mechanical phase of the VM. Two-dimensional echocardiography clarified [23] that during the strain phase of the VM, both the left ventricular (LV) and right ventricular (RV) areas progressively decrease. After strain release, the RV end-diastolic area increases suddenly, while the LV end-diastolic area decreases further. The overloaded RV and associated septal shift alter the LV shape, further reducing the LV cross-sectional area. Thus, the resulting drop in the stroke volume from the LV may contribute, along with pulmonary blood pooling, to the abrupt systemic blood pressure drop characteristic of phase III [23]. In the case of T2DM, systolic function reduction occurs slowly, without changes in cardiac structure and function in the early stages. A recent study [24] involving diabetic patients with normal left ventricular ejection fraction (LVEF) and normal myocardial perfusion found abnormal left ventricular systolic dyssynchrony (LVSD) compared to healthy controls. Interestingly, in these patients, BNP levels were positively associated with LVSD, linking BNP to early myocardial damage even when a normal LVEF was observed.

Our results also support the association between NT-proBNP and cardiovagal measures, specifically the E/I ratio during the DB test. Previous evidence [25] observed that the DB test is the most effective among all subtests in the diagnostic panel for cardiac autonomic neuropathy. From a neuropathological perspective, as an index of the vagal efferent pathway, the DB test reflects the degeneration of the dorsal motor vagal (DMV) nucleus, which is almost always involved in the early stage of the disease. Furthermore, we found correlations between NT-proBNP levels and both the mCASS total score and the adrenergic/cardiovagal subscores, which align with other findings reported in the present study. Interestingly, an association with questionnaires investigating dysautonomia was also observed.

Taken together, these results support the hypothesis that NT-proBNP is an easily accessible biomarker for detecting cardiovascular dysautonomia in PD patients. Other available biomarkers, such as 123I-metaiodobenzylguanidine (MIBG) cardiac scintigraphy, can be used in clinical practice to evaluate cardiac sympathetic innervation. In line with the association between autonomic function tests and MIBG parameters, a previous study [26] found a positive correlation between the DBP response to the HG test and MIBG measures. A possible explanation is that the HG test explores efferent sympathetic pathways to the vessels, which serve as an index of peripheral noradrenergic activity, similar to MIBG cardiac scintigraphy. In the present study, we did not find any significant association between NT-proBNP levels and HG test measures, but we did observe a strong relationship with HUTT and VM measures. In this regard, it should be noted that blood pressure responses to HUTT and VM are not solely mediated by efferent pathways, as the baroreceptor reflex is also involved. Therefore, we hypothesize that the NT-proBNP may reflect the functioning of both central and afferent connections, thus broadening the spectrum of sympathetic adrenergic alterations detected by this biomarker compared to MIBG cardiac scintigraphy. It is important to emphasize that although MIBG scintigraphy is a useful diagnostic tool for differentiating pre-ganglionic from post-ganglionic damage, it may lack specificity in the early stages of the disease, and certain confounders should be carefully considered [27]. Furthermore, since MIBG scintigraphy is quite expensive, it may not be available in many facilities. In contrast, NT-proBNP is a highly cost-effective or cost-saving diagnostic option in patients with chronic heart failure, and it could provide similar diagnostic benefits in PD and other synucleinopathies. NT-proBNP is considered the most valuable and reliable biomarker for diagnosing heart failure and cardiac dysfunction caused by ischemic heart disease, different types of arrhythmias, and cardiomyopathy. In addition, it is responsible for the determination of the severity, guiding relevant treatment strategies, and assessing the prognosis of heart disease [28]. Lastly, recent research has highlighted the potential therapeutic role of recombinant human BNP (rh-BNP) in congestive heart failure: Luo and colleagues reported an improvement in venous return [29], and novel natriuretic peptide-based drugs are currently being investigated [30].

This study has several weaknesses: i) the absence of healthy controls for autonomic testing; ii) the lack of other imaging biomarkers (e.g., MIBG cardiac scintigraphy), which were not required for study enrollment; iii) the small sample size, which limited the statistical power of the analyses; iv) the cross-sectional design.

Despite these limitations, our population of parkinsonian patients was carefully selected, with both a confirmed clinical diagnosis of PD and the exclusion of subjects with relevant comorbidities that could have potentially affected the assessment of biomarker evaluation and autonomic function testing. Additionally, although the sample size was relatively small, we were able to assess the role of significant confounders in the ANCOVA and multivariable regression analyses.

5. Conclusions

In conclusion, to the best of our knowledge, this is the first study to explore the potential role of NT-proBNP as a promising diagnostic tool for detecting early dysautonomia in PD patients. Future studies should assess the strength of this biomarker in larger, prospective patient cohorts and elucidate its relevance in other synucleinopathies.

CRediT authorship contribution statement

Elena Contaldi: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marta Corradi:** Resources, Project administration, Investigation, Data curation. **Marco Percetti:** Investigation, Data curation. **Manuela Pilleri:** Supervision, Data curation, Conceptualization. **Daniela Calandrella:** Writing – review & editing, Supervision. **Ioannis U. Isaias:** Writing – review & editing, Supervision. **Gianni Pezzoli:** Writing – review & editing, Supervision. **Francesca Del Sorbo:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation.

Consent to participate

Written informed consent was obtained from all participants.

Availability of data and material

Anonymized data presented in this article will be shared by request from any qualified investigator.

Ethical approval

The study was performed following the ethical standards as laid down in the 1964 Declaration of Helsinki and following the international research ethical principles involving human subjects. The local Ethics Committee of Milan approved the study procedures (CE 3499/23).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2025.108079.

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