Correlation Between N-Terminal Pro-Brain Natriuretic Peptide Levels and Cardiopulmonary Exercise Testing in Patients With Pre-Capillary Pulmonary Hypertension: A Pilot Study

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ABSTRACT

BACKGROUND: N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiopulmonary exercise testing (CPET) are useful for severity assessment in patients with pulmonary hypertension (PH). Correlations between these tests in pre-capillary PH patients is less well studied.

METHODS: We studied 23 patients with pre-capillary PH: 8 with idiopathic pulmonary arterial hypertension (IPAH), 6 with systemic sclerosis-associated PAH (SSc-PAH), and 9 with chronic thromboembolic pulmonary hypertension (CTEPH). Clinical evaluation, NT-proBNP levels, six-minute walking test (6MWT), spirometry, and CPET were evaluated on the same day. Correlation between NT-proBNP levels and CPET parameters were investigated.

RESULTS: In all patients, NT-proBNP levels were significantly correlated with peak oxygen uptake (VO_2) ($r = -0.47$), peak oxygen pulse ($r = -0.43$), peak cardiac output (CO) ($r = -0.57$), peak end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) ($r = -0.74$), ventilatory equivalent to carbon dioxide (VE/VCO_2) at anaerobic threshold (AT) ($r = 0.73$), and VE/VCO_2 slope ($r = 0.64$). Significant correlations between NT-proBNP levels and peak $P_{ET}CO_2$ and VE/VCO_2 were found in IPAH and CTEPH subgroups, and a significant correlation between NT-proBNP levels and VO_2 at AT was found in the CTEPH subgroup. No significant correlation was found in the SSc-PAH subgroup.

CONCLUSION: NT-proBNP levels were significantly correlated with CPET parameters in patients with IPAH and CTEPH subgroups, but not in SSc-PAH subgroup. A further study with larger population is required to confirm these preliminary findings.

KEYWORDS: N-terminal pro-brain natriuretic peptide, cardiopulmonary exercise testing, pulmonary hypertension, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension

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Introduction

Pulmonary hypertension (PH) is a hemodynamic condition which is traditionally defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg.[1] PH is further classified as pre-capillary PH when associated with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg. Pulmonary arterial hypertension (PAH, Group 1 PH) and chronic thromboembolic pulmonary hypertension (CTEPH, Group 4 PH) are important subclasses of pre-capillary PH, due to the availability of potential therapies for patients in these subclasses. Both PAH and CTEPH share similar pathophysiology, in which obliteration of pulmonary arterioles, vascular inflammation and remodeling, and endothelial dysfunction can lead to increased pulmonary vascular resistance (PVR) and consequently cause right ventricular failure.[2,3] Furthermore, therapeutic intervention with PAH-specific drugs is also an option for both groups.[1]

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a cardiac biomarker that plays a significant role in PH. Elevation of right ventricular wall stress due to PH triggers a release of NT-proBNP from cardiomyocytes. NT-proBNP level is therefore a non-invasive marker of right ventricular dysfunction.[4] In PAH and CTEPH patients, NT-proBNP levels are correlated with functional capacity, six-minute walking test (6MWT) distance, echocardiography-derived and cardiovascular magnetic resonance-derived indices of right ventricular function, and hemodynamics from right heart catheterization (RHC).[5-7]

NT-proBNP level has also been shown to be an independent predictor of mortality.[5,6] Recent evidence showed that

monitoring of NT-proBNP levels in patients with PAH during treatment with PAH-specific drugs can further guide prognosis.[8] Currently, NT-proBNP level is widely used for screening of particular forms of PAH,[9] and is a crucial component of a multiparameter risk assessment for patients with PAH.

Cardiopulmonary exercise testing (CPET) is a noninvasive test that assesses exercise capacity, and has emerged as a new prognostic tool for PH patients.[10,11] CPET provides integrated data about cardiovascular, ventilatory and gas exchange, metabolic, and skeletal muscle response to physical effort. CPET has a potential role in diagnosis, differentiating causes, assessing prognosis, and guiding therapy in PH.[12] Studies in PH patients, including those with PAH and CTEPH, suggest that CPET parameters predict prognosis, survival,[13] and add a prognostic value over 6MWT. Currently, CPET is also one component of multiparameter risk assessments for patients with PAH.[1]

Both NT-proBNP levels and CPET test results reflect the severity of PH (especially in PAH and CTEPH patients), and correlations between NT-proBNP levels and several risk markers of PH have been demonstrated. However, information regarding correlation between NT-proBNP levels and CPET in patients with PH is limited. Andreassen and colleagues[6] described a significant inverse correlation between NT-proBNP levels and peak oxygen uptake (VO_2) from CPET in various classes of patients with pre-capillary PH before treatment. In addition, Berghaus and colleagues[14] described a higher correlation between NT-proBNP levels and CPET parameters in therapy-naïve PAH patients than in CTEPH patients. Nevertheless, correlation between NT-proBNP levels and CPET in specific subgroups of PAH or in PH patients after receiving PAH-specific drugs has never been studied. Characterizing this correlation could help improve screening and risk assessment for PH in clinical practice. We therefore investigated this correlation in patients with idiopathic PAH (IPAH), systemic sclerosis-associated PAH (SSc-PAH), and CTEPH following treatment with PAH-specific drugs.

Methods

Study design and patients

We conducted a cross-sectional study in 84 PH patients aged 20 years old and over who came for a follow-up at the Cardiovascular Clinic of Srinagarind hospital and Queen Sirikit Heart Center of the Northeast, Khon Kaen University, Thailand between January 2018 and January 2019. Diagnosis of PH was made by RHC with a traditional criterion of mPAP ⩾ 25 mmHg. PH patients were classified into IPAH, SSc-PAH, and CTEPH subgroups according to standard practice guidelines.[1] Sixty one PH patients with history of cardiovascular diseases (eg, coronary artery disease, myocardial infarction, and acute heart failure), history of systemic infection in the previous 3 months, history of respiratory tract infection 6 weeks prior to the study, who were not able to perform CPET, or who had absolute contraindications for CPET were excluded. Out of the 23 patients recruited, 8, 6, and 9 were diagnosed with IPAH, SSc-PAH, and CTEPH, respectively (Figure 1). On the day of the study, serum NT-proBNP level was measured in the morning, followed by 6MWT. Spirometry and CPET were done at least 3 hours after 6MWT for a washout period for cardiopulmonary parameters. Appropriate background therapy for PH was considered for each particular patient and all patients received PAH-specific drugs promptly after definite diagnosis of PAH or CTEPH was made from RHC. Clinical outcomes (mortality and heart failure hospitalization) were recorded from the start of the study until December 31, 2019. The study protocol was reviewed and approved by the Khon Kaen University Ethics Committee for Human Research (HE591467) and informed consent was obtained from each participant.

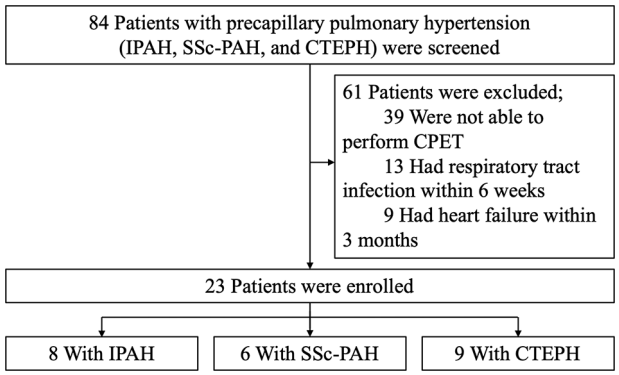

Figure 1. Flow diagram of patient recruitment.
Abbreviations: CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; SSc-PAH, systemic sclerosis-associated pulmonary arterial hypertension.

NT-proBNP

Serum NT-proBNP level was measured using the Elecsys proBNP ELISA assay (Elecsys® ProBNP, Roche Diagnostics, Indianapolis, IN, USA). According to the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines, NT-proBNP levels were categorized as low, intermediate, or high risk of 1-year mortality for patients with PAH by using thresholds of <300, 300 to 1400, or >1400 pg/mL, respectively.[1]

6MWT

6MWT was performed according to American Thoracic Society (ATS) guidelines.[15] Patients were made to sit for at least 15 minutes while the aim and methods of the test were explained. The hallway in which the test was conducted was a flat, point-to-point track that was 30 m in length. Patients were instructed to walk back and forth as far as possible for 6 minutes at their own pace. Patients were instructed to stop walking if they develop chest pain, intolerable dyspnea,

light-headedness, legs cramp, extreme legs muscle fatigue, diaphoresis, staggering, or paleness, and to restart walking as soon as they could. Distance covered in 6 minutes was recorded, and blood pressure, heart rate (HR), O_2 saturation (SpO_2), and dyspnea score (Borg scale) were also measured prior to and after the test.

Spirometry

Spirometry was performed as per ATS/ERS guidelines[16] just prior performing CPET. Lung function parameters measured were forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) using a turbine spirometer (Stationary CPET, Cosmed, Quark CPET, Rome, Italy).

CPET

CPET was performed per ATS/American College of Chest Physicians (ACCP)) guidelines.[17] Incremental exercise was done on a treadmill (Stationary CPET, Cosmed, Quark CPET, Rome, Italy) with a modified Naughton protocol. The test was done in an air-conditioned room at 25°C. Patients were encouraged to exercise until symptoms were intolerable. The test could be interrupted either by patients due to dyspnea, leg fatigue, leg cramping, or disabling symptom, or by a physician for any safety reason. Continuous electrocardiography, blood pressure, SpO_2, and gas exchange measurements were obtained throughout the baseline rest, exercise, and recovery periods. VO_2, minute ventilation (VE), and carbon dioxide production (VCO_2) were measured breath-by-breath in expiratory flow using a Cosmed Face Mask (Quark CPET, Rome, Italy). HR and SpO_2 were measured using pulse-by-pulse filtering fingertip oximeters. The peak VO_2 was defined as the highest average VO_2 for a given 15- or 20-second interval within the last 60 seconds of exercise. The ventilatory equivalent to carbon dioxide (VE/VCO_2) slope was determined with the linear regression slope of VE and VCO_2 from the first second of exercise period until the respiratory compensation point, where acidemia stimulated ventilation and end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) began to decrease. The anaerobic threshold (AT) was defined as the VO_2 level where the VE/VCO_2 decreased or remained constant while the ventilatory equivalent to oxygen (VE/VO_2) persistently increased. The ΔSpO_2 was defined as peak SpO_2 minus rest SpO_2.

RHC

RHC was performed under fluoroscopy in a catheterization laboratory with local anesthesia. Patients were placed in a supine position and breathing on ambient air. A 7-French, balloon-tipped, Swan-Ganz thermodilution pulmonary artery catheter (Edwards Lifesciences, Irvine, USA) was inserted via right femoral vein. Hemodynamic measurements were taken at rest, including; right atrial pressure (RAP), right ventricular pressure (RVP), PAP, PAWP, cardiac output (CO), and mixed venous O_2 saturation (SVO_2). The CO was obtained using thermodilution technique, in which 10 mL of iced-cold, isotonic saline was used as an injectate to inject through proximal port of the catheter. The drop of temperature was then detected at distal thermistor. The injection was done at least 3 times in each patient which an average value was calculated from 3 measurements that fell within 10% variation from a median value. The cardiac index (CI) and pulmonary vascular resistance (PVR) were calculated using standard formulas [CI = CO/body surface area; PVR = (mPAP – PAWP))/CO].

Statistical analysis

Descriptive statistics are presented as mean ± standard deviation (SD) for continuous data and frequency (percentage) for categorical data. The clinical characteristics, NT-proBNP levels, 6MWT distances, spirometry parameters, CPET parameters, and hemodynamics of RHC were compared between each subgroup using one-way ANOVA followed by a Bonferroni's post-hoc comparison test for continuous data and a Chi-square test for categorical data. Correlation analysis between NT-proBNP levels and CPET parameters was done using Pearson's correlation coefficient. Distribution of data were checked using the Shapiro-Wilk test, and NT-proBNP values were log-transformed to base 10 in order to achieve normality. All statistical tests were 2 sided and a P value $<.05$ was considered statistically significant. All analyses were done using STATA for Windows version 10.0 (StataCorp, College Station, TX, USA).

Results

Baseline clinical and hemodynamics characteristics

Table 1 summarizes baseline clinical and hemodynamics characteristics of the PH patients and subgroups. It was observed that the majority of the PH patients were middle age females and were symptomatic. Among all PH patients, 70% were in World Health Organization (WHO) functional class II (mildly symptomatic), whereas 13% were in WHO functional class III (significant symptoms). Cardiovascular risk factors were present in small proportion. Baseline hemodynamics from RHC indicated characteristics of severe PH, with high RAP, mPAP, and PVR, and low CI and SVO_2. All patients received PAH-specific drugs, including phosphodiesterase type 5 (PDE5) inhibitor. Most patients were treated with monotherapy. Patients with IPAH were significantly younger than other 2 subgroups, having significantly higher mPAP than patients with SSc-PAH, and received combination therapy in a significantly higher proportion than other 2 subgroups. Patients with SSc-PAH had similar clinical and hemodynamic characteristics to patients with CTEPH.

Table 1. Baseline clinical and hemodynamic characteristics of patients.

	ALL PATIENTS (N = 23)	IPAH SUBGROUP (N = 8)	SSC-PAH SUBGROUP (N = 6)	CTEPH SUBGROUP (N = 9)	*P* VALUE[a]	*P* VALUE[b]	*P* VALUE[c]
Age (years)	50 ± 11	40 ± 9	57 ± 7	54 ± 8	.01	.01	.97
Female	16 (70)	5 (63)	4 (67)	7 (78)	.83	.86	.12
BMI (kg/m^2)	23 ± 4	21 ± 4	24 ± 1	23 ± 4	.77	.98	.97
Comorbidity							
Systemic hypertension	3 (13)	1 (13)	1 (17)	1 (11)			
Hypercholesterolemia	1 (4)	0	1 (17)	0			
Diabetes mellitus	2 (9)	0	1 (17)	1 (11)			
WHO FC							
I	4 (17)	1 (13)	1 (17)	2 (22)			
II	16 (70)	6 (75)	4 (67)	6 (67)	.66	.67	.91
III	3 (13)	1 (13)	1 (17)	1 (11)			
Estimated GFR (mL/min/1.73 m^2)	85	86	81	89	.61	.74	.53
LVEF (%)	72 ± 7	75 ± 3	72 ± 13	71 ± 4	.98	.97	.99
RHC hemodynamics							
mRAP (mmHg)	11 ± 6	12 ± 5	5 ± 2	12 ± 6	.17	.96	.11
sPAP (mmHg)	81 ± 16	89 ± 16	70 ± 16	80 ± 10	.12	.72	.75
dPAP (mmHg)	32 ± 10	40 ± 9	27 ± 6	28 ± 7	.04	.02	.89
mPAP (mmHg)	50 ± 11	58 ± 10	43 ± 9	46 ± 8	.04	.06	.95
PAWP (mmHg)	11 ± 3	11 ± 3	11 ± 4	11 ± 2	.96	.95	.93
CO (L/min)	3.3 ± 1.4	3.2 ± 2.0	4.2 ± 1.0	2.8 ± 0.5	.74	.96	.27
CI (L/min/m^2)	2.1 ± 0.7	2.1 ± 0.9	2.7 ± 0.5	1.8 ± 0.3	.27	.95	.059
PVR (Wood units)	14 ± 8	19 ± 10	8 ± 4	13 ± 5	.07	.36	.83
Mixed venous O_2 saturation (%)	52 ± 11	50 ± 12	62 ± 6	49 ± 9	.14	.97	.10
NT-proBNP at RHC (pg/mL)	1473 ± 1311	2026 ± 1454	351 ± 219	1605 ± 1142	.08	.97	.25
PAH-specific drugs							
PDE5 inhibitor	23 (100)	8 (100)	6 (100)	9 (100)	.81	.84	.75
Prostaglandins	8 (35)	6 (75)	1 (17)	1 (11)	.01	.02	.74
ERA	5 (22)	5 (63)	0	0			
Monotherapy	15 (65)	2 (25)	5 (83)	8 (89)	.02	.03	.41
Dual therapy	3 (13)	1 (13)	1 (17)	1 (11)	.58	.66	.54
Triple therapy	5 (22)	5 (63)	0	0			
Combination therapy (dual therapy + triple therapy)	8 (35)	6 (75)	1 (17)	1 (11)	.001	.001	.65

Data are presented as mean ± standard deviation or n (%).
Abbreviations: BMI, body mass index; CI, cardiac index; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; dPAP, diastolic pulmonary arterial pressure; ERA; endothelin receptor antagonist; GRF, glomerular filtration rate; IPAH, idiopathic pulmonary arterial hypertension; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PDE5; phosphodiesterase type 5; PVR, pulmonary vascular resistance; RHC, right heart catheterization; sPAP, systolic pulmonary arterial pressure; SSc-PAH, systemic sclerosis-associated pulmonary arterial hypertension; WHO FC; World Health Organization Functional Class.
[a]Comparison of IPAH versus SSc-PAH.
[b]Comparison of IPAH versus CTEPH.
[c]Comparison of SSc-PAH versus CTEPH.

Table 2. Results of investigations performed in the study.

	ALL PATIENTS (N = 23)	IPAH SUBGROUP (N = 8)	SSC-PAH SUBGROUP (N = 6)	CTEPH SUBGROUP (N = 9)	*P* VALUE[a]	*P* VALUE[b]	*P* VALUE[c]
NT-proBNP (pg/mL)	718 (236-2466)	2361 (354-2858)	244 (236-550)	799 (550-2549)	.49	.84	.52
NT-proBNP (log_{10} pg/mL)	6.4 ± 1.2	6.5 ± 1.4	5.8 ± 0.6	6.7 ± 1.2	.96	.94	.73
6MWT distance (m)	343 ± 58	368 ± 28	323 ± 75	348 ± 74	.90	.91	.95
Spirometry parameters							
FEV1 (% predicted)	71 ± 16	67 ± 12	67 ± 21	76 ± 15	.93	.87	.94
FVC (% predicted)	64 ± 16	62 ± 14	66 ± 23	66 ± 13	.91	.94	.93
FEV1/FVC	87 ± 12	94 ± 10	84 ± 4	83 ± 13	.38	.12	.90
CPET parameters							
Peak VO_2 (mL/min)	680 ± 182	690 ± 162	623 ± 90	704 ± 225	.91	.95	.89
Peak VO_2 (mL/min/kg)	13.3 ± 4.0	15.0 ± 5.3	11.1 ± 1.4	13.0 ± 2.8	.32	.98	.95
VO_2 at AT (mL/min/kg)	12.5 ± 3.5	13.8 ± 4.0	10.0 ± 1.5	13.0 ± 3.3	.17	.94	.33
Peak RER	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.2	1.0 ± 0.1	.86	.76	.78
Peak METs	3.6 ± 1.3	4.2 ± 1.7	2.7 ± 0.6	3.5 ± 0.9	.21	.93	.84
Peak HR (bpm)	124 ± 18	131 ± 21	122 ± 16	120 ± 15	.98	.85	.96
Peak oxygen pulse (mL/beat)	5.4 ± 1.9	5.6 ± 1.8	4.4 ± 0.9	5.7 ± 2.2	.94	.93	.73
Peak CO (L/min)	4.3 ± 1.1	4.5 ± 1.0	3.6 ± 0.6	4.5 ± 1.3	.60	.93	.52
Peak VE (L/min)	31 ± 8	32 ± 8	26 ± 7	33 ± 7	.44	.93	.38
Peak $P_{ET}CO_2$ (mmHg)	27 ± 6	27 ± 7	28 ± 4	25 ± 6	.91	.93	.92
Δ O_2 saturation (%)	−5.7 ± 6.4	−7.1 ± 4.8	−8.0 ± 5.5	−2.6 ± 6.8	.97	.51	.43
VE/VCO_2 at AT	48 ± 12	49 ± 13	47 ± 8	49 ± 14	.93	.92	.95
VE/VCO_2 slope	48 ± 13	47 ± 13	48 ± 7	48 ± 16	.92	.95	.92

Data are presented as mean ± standard deviation or median (interquartile range).
Abbreviations: 6MWT, six-minute walking test; AT, anaerobic threshold; CO, cardiac output; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; IPAH, idiopathic pulmonary arterial hypertension; METs, metabolic equations; NT-proBNP, N-terminal pro-brain natriuretic peptide; $P_{ET}CO_2$, end-tidal pressure of carbon dioxide; RER, respiratory exchange ratio; SSc-PAH, systemic sclerosis-associated pulmonary arterial hypertension; VE, minute ventilation; VE/VCO_2, ventilatory equivalent for carbon dioxide; VO_2, oxygen consumption; Δ O_2 saturation, peak O_2 saturation – rest O_2 saturation.
[a]Comparison of IPAH versus SSc-PAH.
[b]Comparison of IPAH versus CTEPH.
[c]Comparison of SSc-PAH versus CTEPH.

Investigations performed in the study

NT-proBNP levels, 6MWT distance, spirometry, and CPET parameters in the PH patients are summarized in Table 2. The median NT-proBNP levels in all patients was 718 pg/mL. Such NT-proBNP levels were highly elevated in patients with IPAH, moderately elevated in patients with CTEPH, and mildly elevated in patients with SSc-PAH, although these differences were not statistically significant. Amongst all patients, the lowest, average, and highest 6MWT distance were 250, 343, and 478 m, respectively, and FEV1 and FVC were 71% and 64% predicted, respectively. Additionally, there were no significant differences among 3 patient subgroups. Regarding the CPET parameters in all patients, mean peak VO_2 was 13.3 mL/min/kg, mean oxygen pulse was 5.4 mL/min/beat, mean $P_{ET}CO_2$ was 27 mmHg, and mean VE/VCO_2 slope, and VE/VCO_2 at AT were equal at 48. There was no significant difference in any CPET parameters between any of the 3 patient subgroups.

Table 3. Correlation between log NT-proBNP and CPET parameters.

	ALL PATIENTS (N=23)		IPAH SUBGROUP (N=8)		SSC-PAH SUBGROUP (N=6)		CTEPH SUBGROUP (N=9)	
	R	*P* VALUE	*R*	*P* VALUE	*R*	*P* VALUE	*R*	*P* VALUE
Peak VO_2 (mL/min)	−0.47	.02	−0.53	.17	−0.20	.69	−0.58	.10
Peak VO_2 (mL/min/kg)	−0.41	.054	−0.50	.19	0.11	.82	−0.65	.056
VO_2 at AT (mL/min/kg)	−0.08	.72	0.13	.76	−0.06	.90	−0.70	.03
Peak METs	−0.38	.07	−0.54	.16	0.05	.91	−0.54	.12
Peak HR (bpm)	−0.18	.40	0.07	.85	−0.30	.55	−0.42	.25
Peak oxygen pulse (mL/beat)	−0.43	.04	−0.62	.09	−0.07	.88	−0.57	.10
Peak CO (L/min)	−0.57	.004	−0.70	.050	−0.15	.77	−0.79	.01
Peak VE (L/min)	0.17	.44	0.15	.71	0.16	.75	0.04	.90
Peak $P_{ET}CO_2$ (mmHg)	−0.74	.0001	−0.73	.03	−0.74	.08	−0.74	.02
Δ O_2 saturation (%)	0.29	.20	−0.52	.22	−0.06	.93	0.87	.002
VE/VCO_2 at AT	0.73	.0001	0.77	.02	0.74	.15	0.72	.02
VE/VCO_2 slope	0.64	.001	0.81	.01	0.15	.76	0.60	.08

Abbreviations: AT, anaerobic threshold; CO, cardiac output; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; HR, heart rate; IPAH, idiopathic pulmonary arterial hypertension; METs, Metabolic Equations; NT-proBNP, N-terminal pro-brain natriuretic peptide; $P_{ET}CO_2$, end-tidal pressure of carbon dioxide; SSc-PAH, systemic sclerosis-associated pulmonary arterial hypertension; VE, minute ventilation; VE/VCO_2, ventilatory equivalent for carbon dioxide; VO_2, oxygen consumption; Δ O_2 saturation, peak O_2 saturation – rest O_2 saturation.

Correlations between NT-proBNP levels and CPET parameters

Table 3 shows correlations between NT-proBNP levels and CPET parameters. In all patients, NT-proBNP levels were inversely correlated with peak VO_2 ($r = -0.47$, $P = .02$), peak oxygen pulse ($r = -0.43$, $P = .04$), peak CO ($r = -0.57$, $P = .004$), and peak $P_{ET}CO_2$ ($r = -0.74$, $P = .0001$). NT-proBNP level were linearly correlated with VE/VCO_2 at AT ($r = 0.73$, $P = .0001$) and with VE/VCO_2 slope ($r = 0.63$, $P = .001$) (Figure 2). In patients with IPAH, NT-proBNP levels were significantly and strongly correlated with peak $P_{ET}CO_2$ ($r = -0.73$, $P = .03$) and VE/VCO_2 [both at AT ($r = 0.77$, $P = .02$) and slope ($r = 0.81$, $P = .01$)], and were also correlated with peak CO ($r = -0.70$, $P = .050$). In patients with CTEPH, NT-proBNP levels were significantly correlated with VO_2 at AT ($r = -0.70$, 0.03), peak CO ($r = -0.79$, $P = .01$), peak $P_{ET}CO_2$ ($r = -0.74$, $P = .02$), VE/VCO_2 at AT ($r = 0.72$, $P = .02$), and ΔSpO_2 with a strong correlation ($r = 0.87$, $P = .002$), and had a trend of correlation with peak VO_2/kg ($r = -0.65$, $P = .056$) and VE/VCO_2 slope ($r = 0.60$, $P = .08$). In patients with SSc-PAH, there was no significant correlation between NT-proBNP levels and CPET parameters demonstrated, however, a trend of correlation between NT-proBNP levels and peak $P_{ET}CO_2$ ($r = -0.74$, $P = .08$) was observed.

Clinical outcomes

During the observation period, there were 2 deaths (1 in a SSc-PAH subgroup and 1 in a CTEPH subgroup) and 2 hospitalizations for heart failure (1 in a IPAH subgroup and 1 in a SSc-PAH subgroup). The risk of death or heart failure hospitalization was not statistically different among each subgroup, with $P = .87$ and .84, respectively.

Discussion

In this study, we enrolled 23 patients with a specific class of pre-capillary PH (ie, IPAH, SSc-PAH, and CTEPH) after treatment with PAH-specific drugs to evaluate the correlation between NT-proBNP levels and CPET parameters. The NT-proBNP levels of each subgroup did not differ significantly despite of 3 different prognostic categories. The overall CPET parameters, current WHO functional class, and 6MWT distances were not different significantly among patient subgroups. These characteristics indicated that the patients we enrolled included a comparable degree of PH severity across all subgroups.

Amongst all patients with pre-capillary PH, we demonstrated a significant correlation between NT-proBNP levels and parameters of aerobic capacity, circulatory efficiency, and ventilatory efficiency from CPET. Our findings agree with the results from a study of Andreassen and colleagues,[6] which included patients

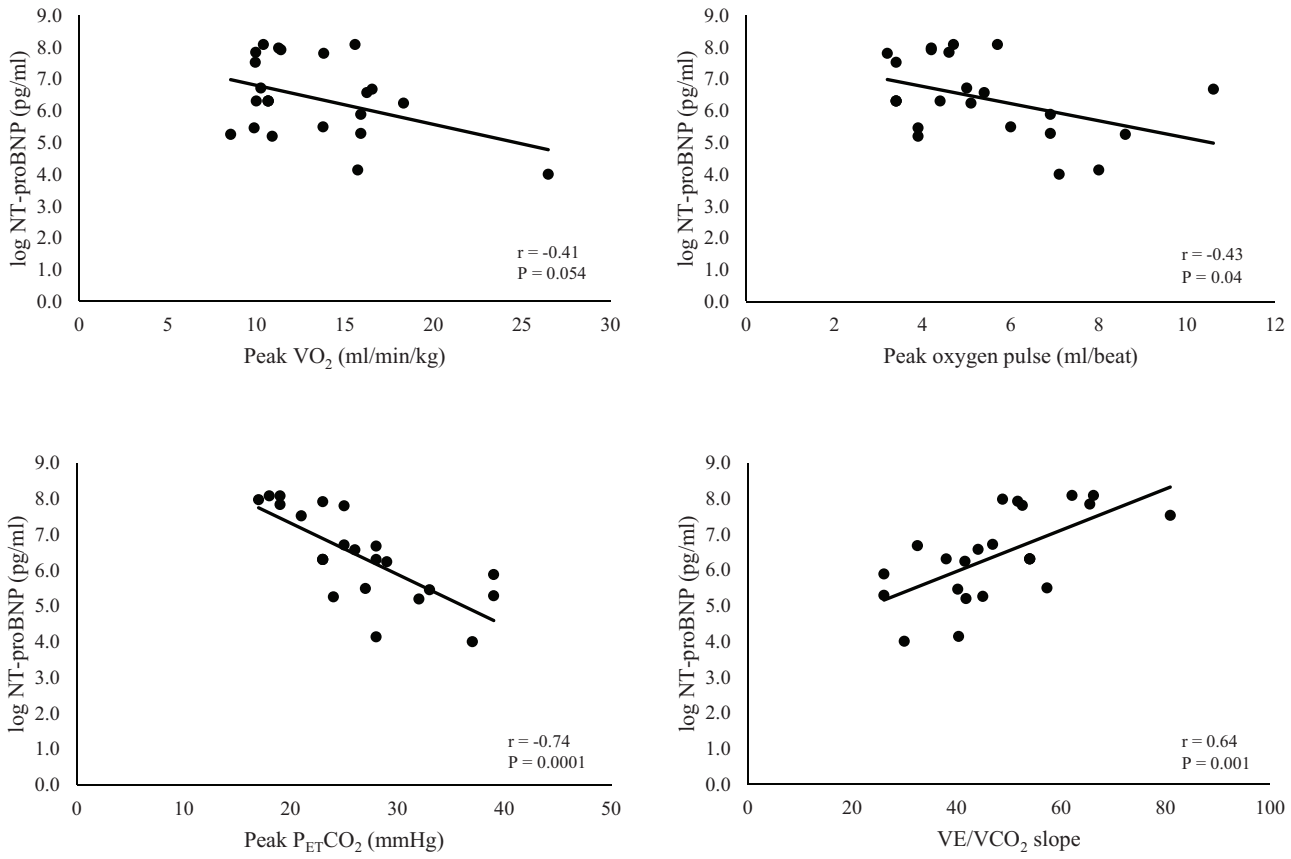

Figure 2. Correlation between NT-proBNP level and peak VO_2, peak oxygen pulse, peak $P_{ET}CO_2$, and VE/VCO_2 slope in precapillary pulmonary hypertension patients.
Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide; $P_{ET}CO_2$, end-tidal pressure of carbon dioxide; VE/VCO_2 slope, ventilatory equivalent for carbon dioxide slope; VO_2, oxygen consumption.

from various groups of PAH, pulmonary-veno occlusive disease (PVOD), and CTEPH, and a study of Berghaus and colleagues,[14] which included patients with PAH and CTEPH (sub-classification of PAH was not defined). Although there was heterogeneity in patients with respect to PH classification between studies, it could be conservatively stated that correlation between NT-proBNP levels and CPET parameters was confirmed in patients with pre-capillary PH.

In subgroups of pre-capillary PH, the significant correlation between NT-proBNP and CPET parameters was partially retained and quite similar between patients with IPAH and patients with CTEPH, but not in patients with SSc-PAH. This discrepant finding was new and warranted further investigation. We hypothesized that the characteristics of PH and comorbidity in each patient subgroup could be the main explanation of this discrepancy. In PH, pathology of the pulmonary vessel leads to right ventricular dysfunction. The presence of pulmonary vascular disease could be detected by ventilatory inefficiency and the presence of right ventricular dysfunction could be detected by cardiovascular inefficiency and rising NT-proBNP level.[10,11] In patients with IPAH and CTEPH, evidence of similarities regarding histopathology, microvascular diseases, hemodynamics, and pathophysiology were reported,[18] although macrovascular obstruction by organized thrombus was noted only in patients with CTEPH.[3] No other significant comorbidity was involved in either IPAH and CTEPH, hence exercise capacity was mainly limited by the function of the pulmonary vasculature-right ventricle unit. Thus, disorder of pulmonary vasculature and right ventricle were parallel, which caused the correlation between NT-proBNP levels and CPET parameters in patients with IPAH and CTEPH. However, pulmonary vasculature-right ventricular unit dysfunction might not be the only perturbation that limits exercise capacity in SSc-PAH. Indeed, SSc is known to be an auto-immune disease manifested by microvascular disorders and fibrosis of skin and internal organs. Interstitial lung disease (ILD) is recognized as a main pulmonary involvement in SSc. Significant ILD was detected by chest imaging in 5 out of 6 patients with SSc-PAH in our study (data not shown). The presence of ILD could affect CPET parameters even without the presence of combined-PH.[19] Musculoskeletal disorders are also a hallmark of SSc, and the presence of such disorders inevitably limits the exercise capacity, and previous studies have shown that peripheral muscle dysfunction contributes to exercise intolerance in patients with PAH.[20] ILD and musculoskeletal disorders are frequently present in SSc, and both limit exercise capacity and disturb CPET parameters independent of right ventricular dysfunction resulting from

PAH. Consequently, this could lead to nonparallel changes of NT-proBNP levels and CPET parameters, and therefore might explain the lack of correlation between both tests in patients with SSc-PAH in our study. However, as a result of skeletal muscle impairment, an independent association between skeletal muscular disorder and exercise capacity was also demonstrated in IPAH and CTEPH[21-23] (though the magnitude of such association could not be compared between each patient subgroup). Therefore, our explanation should be viewed as hypothesis generating, and a large, comprehensive assessment should be conducted to clarify this speculation.

A previous study of Berghaus and colleagues[14] showed a stronger correlation between NT-proBNP levels and CPET parameters in patients with PAH compared to patients with CTEPH. Our results showed a similar significant correlation in patients with IPAH and CTEPH, although we observed a significant correlation with aerobic capacity (VO_2 at AT) only in the CTEPH subgroup. However, comparison in this regard between both studies could not be clearly done because PAH subclassification in the prior study was not available. Further information from a large study with clear clarification of PAH subgroup should be conducted to elucidate this issue. The age- and gender-dependent correlation were also demonstrated from the aforementioned study, in which a stronger correlation was found in patients age > 65 years and female. Since there was only 1 patient in our study with age > 65 years, a similar subgroup analysis regarding age could not be reliably done and the character of age-dependent correlation in our study could not be explored. Furthermore, since there was no statistical difference regarding proportion of females between each patient subgroups, therefore the effect of gender-dependent correlation across patient subgroups in our study could be omitted.

Our study is the first to demonstrate a correlation between NT-proBNP and CPET in specific subgroups of patients with PH who received treatment with PAH-specific drugs. Moreover, we observed patterns and differences in correlation between the patient subgroups. Considering these correlations might improve the multiparametric risk assessment in PH by optimizing the use of risk parameters among patients, since NT-proBNP and CPET may not produce value on top of each other in patients with IPAH or CTEPH. Performing CPET may be unnecessary in evaluation of disease severity among such patients if information about NT-proBNP level is available. On the other hand, since no correlation was observed between NT-proBNP and CPET in SSc-PAH patients, both tests might be necessary when the risk of PH or causes of exercise intolerance needed to be clearly elucidated. Such speculations need to be proved in a large patient cohort.

There were a few limitations in our study: (1) we enrolled a small sample size, although we still detect a significant correlation between NT-proBNP levels and CPET parameters in patients with IPAH and CTEPH. A larger sample size of patients, especially patients with SSc-PAH, would allow more definitive conclusions to be drawn, (2) a CPET program had just been initiated at our center at the time the study was conducted, so the limited expertise in performing CPET may raise some concerns, and (3) we lacked data about right ventricular function from either echocardiography or RHC, so an accurate evaluation of disease severity in relation to right ventricular function could not be conducted. Such information may enhance our understanding about correlation between NT-proBNP levels and CPET parameters in different levels of disease severity.

Conclusion

NT-proBNP levels were correlated with aerobic capacity, circulatory efficiency, and ventilatory efficiency of CPET parameters in PH patients with pre-capillary PH who received treatment with PAH-specific drugs. The correlation, especially for ventilatory efficiency, existed in subgroup of patients with IPAH and CTEPH, but not in patients with SSc-PAH.

These results indicate further challenge on optimization of combined use of NT-proBNP and CPET in evaluation of PAH severity among different classes of PAH though further study with larger population is required to confirm these preliminary findings.

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Author Contributions

SA, WK, and BP contributed to literature review, study design, data acquisition, statistical analysis, data interpretation, and writing manuscript. UK, OP, PR, and CW contributed to study design and editing manuscript.

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