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Pulmonary Hypertension

Bendopnea and Its Clinical Importance in Outpatient Patients with Pulmonary Arterial Hypertension

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Purpose: Bendopnea is a recently reported novel symptom in patients with heart failure (HF) defined as shortness of breath when bending forward. It has been demonstrated that bendopnea is associated with advanced symptoms and worse outcomes. The aim of this study was to assess the presence of bendopnea and its clinical importance with regards to functional status, hemodynamic and echocardiographic characteristics in outpatient pulmonary arterial hypertension (PAH) patients.

Methods: We conducted this prospective observational study of 53 patients who were admitted to our PAH clinic for routine control visits. We determined the presence of bendopnea and analyzed hemodynamic parameters, World Heart Organization (WHO) functional class, transcutaneous oxygen saturation, 6-minute walking distance (6-MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP) and right ventricular (RV) function indicators in patients with and without bendopnea.

Results: Bendopnea was present 33.9% of the PAH patients. The mean age was higher in the patients with bendopnea than in those without bendopnea, but the difference was not significant ($p = 0.201$). The patients with bendopnea had a lower 6-MWD and higher NT-proBNP level ($p < 0.001$), and worse WHO functional class symptoms ($p = 0.010$). Mean right atrial pressure, pulmonary artery pressure, and pulmonary vascular resistance were higher in the patients with bendopnea. The patients with bendopnea had a more dilated RV end-diastolic diameter and lower tricuspid annular plane systolic excursion value ($p < 0.001$ and $p = 0.001$, respectively).

Conclusions: Bendopnea was associated with worse functional capacity status, hemodynamic characteristics and RV function in our outpatient PAH patients.

Key Words: Bendopnea • Functional capacity • Pulmonary arterial hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease which is characterized by an increased pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) leading to right heart failure (HF) with high morbidity and mortality.[1,2] The initial and main symptom of PAH is almost always shortness of breath with exercise.[3] Other symptoms and clinical signs of PAH such as pretibial edema, ascites, hepatomegaly, elevated jugular venous pressure, cyanosis and syncope are usually related to a prominently impaired in right ventricular (RV) function and indicate disease severity.[4,5] A new respiratory symptom termed bendopnea has recently been described in patients with HF.[6] Bendopnea occurs while bending forward when putting on shoes or tying them.[6] This novel symptom has been associated with an increase in cardiac filling pressure, especially in the presence of a low cardiac index.[6] Recent studies have reported that bendopnea is associated with advanced

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symptoms and adverse clinical outcomes in HF patients, and the existence of bendopnea has been associated with the disease severity of HF.[7,8] However, no previous study has assessed the relationship between bendopnea and PAH. Thus, we conducted this prospective observational study to evaluate the presence of bendopnea and the relationships between bendopnea and echocardiographic characteristics, hemodynamic findings and functional status indicators in outpatient PAH patients with and without bendopnea.

METHODS

We conducted this single-center prospective observational study between December 2016 and August 2017 at the Cardiology Department of Kocaeli University Hospital. A total of 53 consecutive outpatient PAH patients who were admitted to our special PAH clinic for periodic control visits were enrolled into this study. PAH was defined as a mean PAP $\geq$ 25 mmHg in the presence of a pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg and PVR $\geq$ 3 wood units. The exclusion criteria were an age younger than 18 years, presence of an active infection, acute decompensated right HF requiring hospitalization, malignant diseases and any end-stage disease with a life expectancy less than one year. Additionally, patients who were unable to bend forward due to non-PAH causes such as musculoskeletal problems, and those with a headache, light-headedness or syncope earlier during such actions were also excluded.

Data including demographic information and medical history such as age, gender, chronic obstructive pulmonary disease (COPD), hypertension and diabetes mellitus were recorded during the periodic clinic control visits through physical examinations and interviews with patient and family members. The presence of orthopnea, pretibial edema, jugular venous distention, blood pressure, body mass index (BMI), World Heart Organization (WHO) functional class, finger transcutaneous oxygen saturation at rest (%), and 6-minute walking distance (6-MWD) were recorded from physical examination findings. Information including left ventricular ejection fraction (LVEF), RV end-diastolic diameter (RVEDD), pulmonary artery systolic pressure (PASP), and tricuspid annular plane systolic excursion (TAPSE) were obtained from transthoracic echocardiography evaluations. Hemodynamic data including mean right atrial pressure (RAP), mean PAP and PVR were recorded from the patients' last right heart catheterization study. Baseline routine biochemical analysis including blood urea nitrogen, creatinine, serum sodium, N-terminal pro-brain natriuretic peptide (NT-proBNP), hemoglobin and hematocrit levels were recorded in all patients. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Medical therapy including calcium channel blockers (CCBs), endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE-5is), prostacyclin analogues and prostacyclin receptor agonists were recorded as being positive if the patients were taking these medications.

For the bendopnea test, after instructing each patient to not hold their breath while bending and to inform the investigator if they felt short of breath, each patient was seated and prompted to lean forward at the waist as if they were wearing socks or shoes. Meanwhile, an investigator determined the time to the onset of shortness of breath according to the patient's statements. The patient was defined as having bendopnea if they reported shortness of breath within 30 seconds of bending.

The study protocol was approved by the local institutional investigation committees.

Statistical analysis

Normally distributed continuous variables were expressed as mean $\pm$ standard deviation, nonnormally distributed variables were expressed as median with an interquartile range (25th-75th percentiles), and categorical variables were expressed as counts (percentages). Comparisons of normally distributed continuous variables between groups were performed using the Student's t-test, and comparisons of nonnormally distributed continuous variables between groups were performed using the Mann Whitney U Test. Comparisons of categorical variables between groups were performed using Fisher's chi-square test and Monte Carlo chi-square test. The functional capacity indicators were considered to be a potential candidate predictor of bendopnea, and were included as covariates in a multivariate logistic regression model. The p-values for all tests were two-

sided, and statistical significance was considered at $p < 0.05$. All statistical analyses were performed using IBM SPSS for Windows® version 20.0 (SPSS, Chicago, IL, USA).

RESULTS

Patients' characteristics

A total of 53 patients with PAH were included in this study, of whom 18 (33.9%) had bendopnea. The mean time to the onset of bendopnea was 9.5 ± 2.7 seconds. The study population included patients with idiopathic PAH (n = 40, 75.5%), PAH associated with connective tissue disease (n = 3, 5.6%), and PAH associated with congenital heart disease (n = 10, 18.9%). There was no statistical difference in the relationship between the presence of bendopnea and the etiology of PAH. The mean age in the bendopnea group was higher than that in the without bendopnea group (54.9 ± 10.4 vs. 51.8 ± 10.3), although the difference was not significant (p = 0.201). In the bendopnea group, 14 patients (77.7%) were female compared to 28 patients (80.0%) in the without bendopnea group. The median BMI was 29.28 ± 7.47 kg/m^2 in the bendopnea group compared to 27.02 ± 1.99 kg/m^2 in the without bendopnea group. There were no statistical differences between the two groups in terms of gender and BMI (p = 0.851 and p = 0.493, respectively). The mean eGFR in the bendopnea group was lower than that in the without bendopnea group (75.8 ± 14.9 ml/min vs. 77.9 ± 12.6 ml/min), however the difference was not significant (p = 0.392). Concomitant symptoms of orthopnea were significantly higher in the bendopnea group than in the without bendopnea group (p = 0.009), and more patients in the bendopnea group had pretibial edema and jugular venous distention compared to those without bendopnea (p = 0.049 and p = 0.040, respectively). There were no significant differences in using medical therapy, comorbidities, blood pressure, or hemoglobin levels between the two groups. The baseline clinical characteristics of the patients with and without bendopnea are summarized in Table 1.

Table 1. Baseline clinical characteristics of the study patients with and without bendopnea

Characteristic	With bendopnea (n = 18)	Without bendopnea (n = 35)	p-value
Age (years)	54.9 ± 10.4	51.8 ± 10.3	0.201
Female, n (%)	14 (77.7%)	28 (80.0%)	0.851
Body mass index, kg/m^2	29.28 ± 7.47	27.02 ± 1.99	0.493
Systolic blood pressure, mmHg	109.7 ± 10.7	108.1 ± 8.5	0.355
Diastolic blood pressure, mmHg	59.9 ± 6.6	62.8 ± 7.1	0.125
Comorbidities, n (%)			
Hypertension	2 (11.1%)	2 (5.7%)	0.481
Diabetes mellitus	2 (11.1%)	1 (2.9%)	0.218
Hyperlipidemia	0 (0%)	2 (5.7%)	0.301
Laboratory findings			
eGFR, mL/min/1.73 m^2	75.8 ± 14.9	77.9 ± 12.6	0.392
Haemoglobin, gr/dl	11.1 ± 0.9	11.7 ± 1.3	0.128
Sodium, mEq/L	134.4 ± 3.6	136.3 ± 4.1	0.107
Concomitant symptoms, n (%)			
Orthopnea	9 (50.0%)	5 (14.3%)	0.009
Pretibial edema	8 (44.4%)	6 (17.1%)	0.049
Jugular venous distention	10 (55.6%)	9 (25.7%)	0.040
Specific medical therapy, n (%)			
Endothelin receptor antagonists	13 (72.2%)	27 (77.1%)	0.693
Phosphodiesterase type 5 inhibitors	6 (33.3%)	5 (14.3%)	0.105
Prostacyclin analogues and receptor agonists	7 (38.9%)	10 (28.6%)	0.446
Calcium channel blockers	7 (38.9%)	8 (22.9%)	0.220
Etiology of PAH, n (%)			1.000
IPAH	14 (35.0%)	26 (65.0%)	
CTD-related PAH	1 (33.3%)	2 (66.7%)	
CHD-related PAH	3 (30.0%)	7 (70.0%)	

CHD-related PAH, pulmonary arterial hypertension related to congenital heart disease; CTD-related PAH, pulmonary arterial hypertension related to connective tissue disease; eGFR, estimated glomerular filtration rate; IPAH, Idiopathic pulmonary arterial hypertension.

Assessment of functional status, echocardiographic and hemodynamic parameters

Twenty-eight of the 53 patients had a WHO functional class of III-IV, of whom 15 (83.3%) had bendopnea and 13 (37.1%) did not, and the difference was statistically significant (p = 0.010). The mean 6-MWD in the bendopnea group was lower than that in the without bendopnea group (175.6 ± 67.4 vs. 251.5 ± 66.3) and this difference was statistically very significant (p ≤ 0.001). The transcutaneous oxygen saturation in the bendopnea group was lower than that in the without bendopnea group (89.1 ± 4.9 vs. 91.7 ± 2.5), and it was nearly statistically significant (p = 0.083). In the multivariate analysis with logistic regression, WHO III-IV functional class was an independent predictor of bendopnea [p = 0.008, odds ratio (OR) 8.843, 95% confidence interval (CI) 1.779-43.963]. In addition, a lower 6-MWD and transcutaneous digital oxygen saturation were nearly significantly associated with the presence of bendopnea (p = 0.053 and p = 0.067, respectively). The median NT-proBNP level in the bendopnea group was prominently higher than that in the without bendopnea group (2862.6 ± 1935.1 vs. 1180.1 ± 1104.2), and the difference was statistically very significant between the two groups (p ≤ 0.001). The characteristics of functional status indicators and NT-proBNP levels in the patients with and without bendopnea are shown in Table 2. The echocardiographic examinations showed that the RVEDD was more dilated in the bendopnea group than in the without bendopnea group (36.1 ± 3.3 mm vs. 30.7 ± 4.8 mm), and this difference was statistically very significant (p ≤ 0.001). Additionally, there were significant differences in PASP and TAPSE between the two groups (p = 0.002 and p ≤ 0.001, respectively), but not in LVEF (p = 0.361). The echocardiographic parameters of the patients with and without bendopnea are shown in Table 2. Mean RAP and mean PAP were markedly higher in the patients with bendopnea than in those without bendopnea (p < 0.001 and p < 0.001, respectively). PVR was also found to be nearly statistically significantly higher in the patients with bendopnea compared to those without bendopnea (p = 0.05). The hemodynamic data of the patients with and without bendopnea are shown in Table 2.

DISCUSSION

Bendopnea is a type of dyspnea in patients with HF recently described by Thibodeau et al.[6] Bendopnea has been associated with adverse clinical outcomes such as more serious symptoms, rehospitalization and advanced disease stage in HF patients.[7,8] In this study, we aimed to assess the presence of bendopnea and its impact on functional status and echocardiographic characteristics

Table 2. Assessment of functional status, echocardiographic and hemodynamic features in patients with and without bendopnea

Characteristic	With bendopnea (n = 18)	Without bendopnea (n = 35)	p-value
Functional capacity indicators			
WHO III-IV functional class, n (%)	15 (83.3%)	13 (37.1%)	0.010
6-minute walking distance, m	175.6 ± 67.4	251.5 ± 66.3	< 0.001
NT-proBNP, ng/L	2862.6 ± 1935.1	1180.1 ± 1104.2	< 0.001
Transcutaneous oxygen saturation, (%)	89.1 ± 4.9	91.7 ± 2.5	0.083
Echocardiographic parameters			
RVEDD, mm	36.1 ± 3.3	30.7 ± 4.8	< 0.001
PASP, mmHg	89.1 ± 20.4	64.9 ± 24.9	0.002
TAPSE, mm	12.8 ± 2.3	15.8 ± 2.8	< 0.001
LVEF, (%)	61.9 ± 2.9	62.7 ± 2.6	0.361
Right heart catheterization findings			
Mean PAP, mmHg, median (IQR)	41.5 (36.5-45.2)	31.1 (27.1-35.1)	< 0.001
Mean RAP, mmHg, median (IQR)	9.0 (6.7-15.0)	6.0 (5.0-7.0)	< 0.001
PVR, woods units, median (IQR)	5.2 (3.5-8.5)	3.4 (2.9-4.1)	0.05

IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEDD, right ventricular end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; WHO, World Heart Organization.

in outpatient PAH patients. Patients with PAH often have symptoms and clinical signs including dyspnea, pretibial edema, abdominal swelling or ascites, jugular venous distention, cyanosis and syncope.[4,5] As these are associated with a worse clinical status and RV function, they are used to evaluate the severity of disease and risk stratification of PAH patients.[4,5] To date, bendopnea has only been demonstrated in patients with HF. To the best of our knowledge, this is the first study to report the presence of bendopnea in patients with PAH. In addition, we also observed a relationship between bendopnea and its clinical importance in these patients. The frequency of bendopnea was 18% in the study of Thibodeau et al., which included ambulatory patients with systolic HF, and 48.8% in the study of Baeza-Trinidad et al. which included patients with acute decompensated HF.[7,8] In our study population, 18 of the 53 patients (33.9%) had bendopnea.

Bendopnea has been associated with increased RV and left ventricular filling pressures in patients whose baseline filling pressures are already increased.[6] In this study, we observed that hemodynamic parameters were worse in the bendopnea group. Among them, mean RAP, mean PAP and PVR were markedly higher in the patients with bendopnea than in those without bendopnea (Table 2). In the systolic HF study of Thibodeau, hemodynamic findings such as mean RAP, mean PAP, PASP and PVR were higher in the patients with bendopnea, which is similar to our study.[6] However, worse hemodynamic parameters are strong predictors of mortality and morbidity in patients with HF or PAH.[9,10] In addition, higher mean RAP, PVR and mean PAP values have been associated with advanced disease in patients with PAH.[10] In this context, it is not surprising that higher mean RAP, mean PAP and PVR are observed in patients with bendopnea, and it indicates the presence of advanced disease in these patients. Similar to previous HF studies, we found an association between bendopnea and PASP in PAH patients.[8] The patients with bendopnea also had higher PASP values (Table 2), and this increase in PASP was associated with advanced NYHA class symptoms and short-term mortality.[8] Also, the patients with bendopnea had lower TAPSE values than those without bendopnea in our study (Table 2). TAPSE values of < 18 mm have been associated with reduced 2-year survival rates in PAH.[11] Moreover, the patients with bendopnea had a more dilated RVEDD (Table 2). It is known that all of these findings indicate the presence of advanced RV dysfunction in these patients.[12,13] Furthermore, a prominently impaired RV function reflects increased RV filling pressure, and this may explain the mechanism of bendopnea in patients with PAH. It has been demonstrated that HF patients with bendopnea have clinical signs of right HF as well as left HF.[7,8] These data suggest that that presence of bendopnea is associated with disease severity in HF.[7,8] Despite these data, the relationship between bendopnea and natriuretic peptides in patients with HF is unclear. While Thibodeau et al.[7] and Baeza-Trinidad et al.[8] did not observe an association between bendopnea and NT-proBNP in HF patients, Niu et al. found a significant relationship between bendopnea and NT-proBNP in a similar patient group.[14] In our study, the patients with bendopnea had very high NT-proBNP levels, and the difference was statistically very significant (Table 2). The explanation of this powerful relationship may be that increased NT-proBNP levels reflect worse RV function, which is characterized by the existence of RV failure with elevated RV filling pressure. Absolute levels of NT-proBNP have been correlated with hemodynamic data and clinical outcomes in patients with PAH,[15] and decreased levels of NT-proBNP have been associated with improved long-term survival rates.[16,17]

In our study, traditional symptoms including orthopnea, pretibial edema and jugular venous distention were higher in the patients with bendopnea (Table 1). The presence of orthopnea is a known predictor of mortality and morbidity in patients with HF.[18] Also, orthopnea reflects worse hemodynamics such as elevated PCWP or jugular venous pressure, and low cardiac index in these patients,[19] all of which indicate disease progression.[19] However, orthopnea is an indicator of an advanced stage of PAH and HF.[20] On the other hand, the presence of pretibial edema and jugular venous distention show the development of right HF in patients with PAH, and this reflects disease progression. Thus, in the study of Thibodeau, classical symptoms such as orthopnea, weight gain, paroxysmal nocturnal dyspnea, abdominal fullness and early satiety were more commonly observed in the patients with bendopnea.[6] Also, these patients had worse hemodynamic findings and disease characteristics.[6] Therefore, the appearance of these symptoms demonstrated the worse disease characteris-

tics in the patients with bendopnea and PAH.

We also observed a relationship between bendopnea and measures of the patients' functional capacity. The patients with bendopnea had more WHO III-IV functional class symptoms and lower 6-MWD than those without bendopnea (Table 2). Additionally, WHO III-IV functional class was a significant predictor of bendopnea, and a lower 6-MWD was nearly a statistically significant predictor of bendopnea in logistic regression analysis. Patients with a high 6-MWD have been reported to have improved mortality at 3 years compared to patients presenting with a lower 6-MWD in PAH.[21] In another study, 6-MWD values were significantly lower in the patients with bendopnea group and chronic HF with reduced ejection fraction.[14] WHO functional class is a strong predictor of the prognosis, and studies have shown that poorer WHO functional class is associated with worse 5-year survival.[22,23] Furthermore, changes in these functional classes at follow-up have been associated with increases and decreases in survival rates.[24,25] Thibodeau et al. demonstrated that HF patients with bendopnea had significantly worse NYHA functional class ($p < 0.001$).[7] Niu et al. reported that the frequency of patients with NYHA functional class IV was significantly higher in the bendopnea group than in the non-bendopnea group.[14] In addition, an association has ben reported between the time of onset of bendopnea and advanced NYHA III-IV class symptoms.[8] In this context, PAH patients with bendopnea have poor functional status, and this reflects disease severity. Transcutaneous digital oxygen saturation was lower in the bendopnea group and the difference was statistically nearly significant ($p = 0.083$). This result indicates advanced symptoms and WHO functional class and 6-MWD. Also, in our study population, we found that lower transcutaneous digital oxygen saturation level was nearly a significant predictor of bendopnea in logistic regression analysis. It has been shown that such poor functional status findings are predictors of long-term outcomes.[26]

Bendopnea can also be observed in elderly and obese people regardless of HF.[8] The mechanism of bendopnea in people with a higher BMI is not clear.[6,27] However, there are conflicting data about the relationship between bendopnea and BMI in the literature. Dominguez-Rodriguez et al. reported that there was no relationship between bendopnea and BMI in contrast to other studies.[28] In our analysis, there was no difference in BMI between the patients with and without bendopnea ($p = 0.493$). In the REVEAL registry, older male patients (aged > 60 years) also showed an increased risk of mortality.[29] However, there were no statistically significant differences in terms of age, gender, blood pressure and eGFR between the two groups. Therefore, our study population may be considered to be an age-sex matched group. Of note, there were no significant differences in several indicators of disease severity such as age, serum sodium, eGFR and hemoglobin level between the two groups.

To the best of our knowledge, this novel symptom has never been reported in PAH patients before. We first showed the existence of bendopnea in PAH patients and we also demonstrated its clinical importance as evaluated by functional capacity indicators, echocardiographic and hemodynamic characteristics. All of these results may reflect advanced symptoms and disease severity in patients with bendopnea and PAH as well as HF.

Limitations

There are some limitations to this study. First, as this study is a single-center analysis, our results may not be generalizable to other settings. In addition, the number of patients in this study is smaller than in previous HF studies. However, this is a PAH study. Also, the mean age of the study population was relatively old. The small number of patients and older age may impact the results of study. Nevertheless, the results of this study do not depend only on an older age or BMI, and the data will contribute to the literature. Additionally, bendopnea is a somewhat subjective symptom, and this may alter the results of all studies as well as the present study. The relationship between bendopnea and primary clinical outcomes such as rehospitalization and prognosis should be investigated in prospective-multicenter matched patient populations.

CONCLUSIONS

We showed the presence of bendopnea in patients with PAH and its relationship with echocardiographic, hemodynamic and clinical features. The patients with bendopnea had poor functional status including WHO III-IV class symptoms and decreased 6-MWD. These pa-

tients had prominently impaired RV function as characterized by a more dilated RVEDD, higher PASP and lower TAPSE parameters. Also, worse hemodynamic parameters including higher mean RAP, PVR and mean PAP were observed in the patients with bendopnea. In addition, in contrast to other studies, NT-proBNP levels were very high in the patients with bendopnea, and this may have reflected worse right heart function. Taken together, our results suggest that the presence of bendopnea is associated with the severity of disease in patients with PAH. Therefore, bendopnea may be used as a predictor to assess the prognosis and risk stratification in further prospective randomized studies.

CONFLICT OF INTEREST

None to declare.

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