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Stabil ayaktan pulmoner arteryel hipertansiyon hastalarında bendopne ve klinik sonlanımlar arasındaki ilişki

The relationship between bendopnea and clinical outcomes in stable pulmonary arterial hypertension outpatients

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ÖZ

GİRİŞ ve AMAÇ*: Bendopne kalp yetersizliği (KY) hastalarında öne eğilince nefes darlığı gelişmesi olarak yeni tanımlanmış solunumsal bir yakınmadır. KY hastalarında kötü klinik sonlanımlarla ilişkili olduğu gösterilmiştir. Bir önceki çalışmamızda pulmoner arteryel hipertansiyon (PAH) hastalarında bendopnenin varlığını göstermiştik. Çalışmamızın amacı; PAH hastalarında bendopne varlığının klinik sonlanımlarla olan ilişkisini araştırmaktır.*

YÖNTEM ve GEREÇLER: *Rutin periyodik kontolleri için spesifik PAH polikliniğimize başvurmuş 62 ayaktan PAH hastasından oluşan bir gözlemsel çalışma planladık. Çalışmanın sonlanımları, 3. ve 12. ayda KY nedenli hastaneye yatış ve tüm nedenli ölümler idi.*

BULGULAR: *Çalışma grubunun % 25.8'inde bendopne mevcuttu. 3. ayda KY nedenli hastaneye yatış oranları bendopnesi olan hastalarda olmayanlara göre istatistiksel olarak daha yüksekti (p=0.003). İki grup arasında 3. ay tüm nedenli ölümlerde anlamlı fark yoktu (p=0.427). 12. ayda KY nedenli hastaneye yatış oranları bendopnesi olan hastalarda olmayanlara göre istatistiksel olarak daha yüksekti (p<0.001). 12. ayda tüm nedenli ölümler bendopnesi olan hastalarda belirgin olarak daha fazlaydı (p=0.004). Çok değişkenli lojistik regresyon analizinde, bendopne 3. ve 12. ay KY nedenli hastaneye yatışlar ve 12. Ay tüm nedenli ölümlerin bağımsız öngördürücü olarak bulundu ancak 3. ay tüm nedenli ölümlerde öngördürücü olarak saptanmadı.*

TARTIŞMA ve SONUÇ: *Bendopne stabil ayaktan PAH hastalarında kötü klinik sonlanımlarla ilişkili bulundu. Bendopne, PAH hastalarında prognoz ve risk değerlendirmesinde kullanışlı olabilir.*

Anahtar Kelimeler: *Bendopne, pulmoner arteryel hipertansiyon, kalp yetersizliği, hastaneye yatış.*

ABSTRACT

INTRODUCTION: *Bendopnea is a novel respiratory symptom recently reported, which is described shortness of breath when bending forward in patients with heart failure (HF). It has been shown that bendopnea is associated with worse clinical outcomes in HF patients. We first reported that the presence of bendopnea in pulmonary arterial hypertension (PAH) patients in our previous study. The aim of this study was to evaluate the relationship between bendopnea and clinical outcomes in stable PAH outpatients with and without bendopnea.*

METHODS: *We conducted a prospective observational study of 62 patients who admitted to our special PAH clinic for routine periodic controls. Clinical outcomes of study were HF-related hospitalization and all-cause mortality at 3 and 12 months.*

RESULTS: *Bendopnea was present 25.8% in the study population. HF-related hospitalization at 3 months was statistically significant higher in patients with bendopnea than patients without bendopnea (p=0.003). There was no statistically difference between two groups in term of all-cause mortality at 3 months (p=0.427). HF-related hospitalization at 12 months was statistically significantly higher in patients with bendopnea (p<0.001). All-cause mortality at 12 months was markedly higher in with bendopnea group than the without bendopnea group (p=0.004). In multivariable logistic regression analysis, bendopnea was an independent predictor of HF-related hospitalization at 3 and 12 months, also bendopnea was a predictor of all-cause mortality at 12 months but not at 3 months.*

DISCUSSION AND CONCLUSION: *Bendopnea was associated worse clinical outcomes in stable PAH outpatients. Bendopnea may be used for prognosis and risk assessment in PAH patients.*

Keywords: *Bendopnea, pulmonary arterial hypertension heart failure, hospitalization*

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INTRODUCTION

A novel respiratory symptom which is named bendopnea, has been recently reported in patients with heart failure (HF) (1). It was described that experienced dyspnea while bending forward when putting on shoes or trying them up (1). Bendopnea reflects the higher cardiac filling pressures in HF patients (1). In recent studies reported that, bendopnea was associated with more serious symptoms and worse clinical outcomes in patients with HF (2,3). The existence of bendopnea reflects severity of disease in patients with HF (2,3). Pulmonary arterial hypertension (PAH) is a chronic, progressive disease which is characterized by an increased pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR). It eventually leads to right heart failure (RHF) and associated with high rehospitalization and mortality rates (4,5,6). The main and onset symptom of PAH is usually exertional dyspnea (7,8). Furthermore, other symptoms and clinical signs like pretibial edema, ascites, hepatosplenomegaly, increased jugular venous pressure, and cyanosis are usually related to the right heart dysfunction, which were also associated with adverse clinical outcomes in patients with PAH (9,10,11,12). The presence of each of these parameters are associated with long-term survival in patients with PAH (13). Recently, we first showed that bendopnea was an important finding in patients with PAH (14). We also demonstrated that the patients with bendopnea had more severe right heart dysfunction and haemodynamics in that study (14). However, the relationship between bendopnea and clinical outcomes in stable PAH outpatients was not previously evaluated in any study. Thus, we aimed to assess the effect of bendopnea to clinical outcomes in stable PAH outpatients.

METHODS

We conducted a single-center prospective observational study between December 2016 and January 2018 in our cardiology clinic. According to the presence of bendopnea or not, a total of 62 consecutive stable PAH outpatients who admitted to our special PAH clinic for periodic control visits were enrolled to the study. PAH were defined by a mean PAP ≥25 mmHg in the presence of a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg and PVR >3 wood units. Exclusion criteria were younger than 18 years of age, presence of an active infection, 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 orthopedic problems, and having headache, lightheadness or syncope earlier during this manoeuvre-like situations were excluded.

The data included demographic information and medical history such as age, gender, hyperlipidemia, hypertension and diabetes mellitus were recorded during the periodic clinic control visit by physical examination and interview with patient and family members. 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 obtained from physical examination findings. The information included left ventricular ejection fraction (LVEF), right ventricular end-diastolic diameter (RVEDD), and tricuspid annular plane systolic excursion (TAPSE) were obtained from the transthoracic echocardiography evaluation. Hemodynamic data including mean right atrial pressure (RAP), mean PAP and PVR were recorded from patients' last right heart catheterization examination. Baseline routine biochemical analysis including blood urea nitrogen, creatinine, serum sodium, N-terminal pro-brain natriuretic peptide (NT-proBNP), and haemoglobin 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 (CCB), Endothelin receptor antagonists (ERA), Phosphodiesterase type 5 inhibitors (PDE-5is), Prostacyclin analogues and prostacyclin receptor agonists were recorded as positive if the patients had these medications.

The study patients were followed up for 12 months after enrollment. Clinical outcomes of study were HF-related hospitalization and all-cause mortality at 3 and 12 months. Data included clinical outcomes of the patients in the study was obtained from the electronic national hospital records or from

telephone contact with the patient or family members after 12 months.

The presence of bendopnea was investigated by a simple test. The patients were seated and prompted to lean forward at the waist as if they were wearing socks or shoes. Before starting the test, each patient was instructed about not to hold their breath during bending and informed to report when they feel shortness of breath. Meanwhile, an investigator determined the time to the onset of shortness of breath according to the patient's statements. The patient was accepted as having bendopnea if shortness of breath was reported within 30 seconds of bending.

The study protocol was approved by local institutional investigation committees.

Statistical Analysis

Normally distributed continuous variables were expressed as mean±standard deviation, non-normally 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 the groups were performed using the Student's t test and nonnormally distributed continuous variables between the groups were performed using the Mann Whitney U Test. Comparisons of cathegorical variables between the groups were performed using the Fisher ChiSquare test and Monte Carlo ChiSquare test. Multivariable logistic regression analysis was used to evaluate in predicting clinical outcomes at 3 and 12 months. 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 62 stable PAH outpatients were enrolled to this study. Bendopnea was present in 16 of the study patients' (25.8%) and the mean time to the onset of bendopnea was 10.2±3.1 seconds. The study population was consisted of patients with idiopathic PAH (n=48, 77.4%), connective tissue disease related PAH (n=6, 9.7%) and congenital heart disease related PAH (n=8, 12.9%). There was no statistically difference the relationship between the presence of bendopnea and etiology of PAH (p=0.233). There was no statistically difference in term of age in patients with and without bendopnea (47.2±9.5 *vs*. 49.9±11.9, p=0.298). Of the 19 patients (56.3%) were female in the bendopnea group and 32 patients (69.6%) were female in the without bendopnea group. The mean BMI was 24.9±2.7 kg/m^2 in the with bendopnea group and was 25.5±2.4 kg/m^2 in the without bendopnea group. There was no statistically difference between the patients with bendopnea and without bendopnea in terms of gender and BMI (p=0.332 and p=0.459, respectively). The median eGFR in the with bendopnea group was lower than the patients without bendopnea, but it was no statistically significant (69 ml/min *vs*. 74 ml/min, p=0.164). Among echocardiographic characteristics, the median RVEDD was statistically significant higher in patients with bendopnea than without bendopnea (33 mm *vs.* 30 mm, p<0.001). TAPSE was found markedly lower in patients with bendopnea compared with patients without bendopnea (p<0.001). The median PVR, mean PAP and mean RAP levels were significantly higher in patients with bendopnea than without bendopnea (p<0.001, p<0.001 and p<0.001, respectively). Additionally, current medical therapy, comorbidities, blood pressure, and haemoglobin levels were not different between these two groups. The baseline clinical characteristics of the patients with and without bendopnea are summarized in Table 1.

Assessment of clinical outcomes

Clinical outcomes of the study in patients with and without bendopnea are shown in Table 2. The most of the clinical events at 3 and 12 months were HF-related hospitalization in study patients. The number of all-cause mortality at 12 months were 5 in the study. HF-related hospitalization at 3 months was statistically nearly significantly higher in patients with bendopnea than the patients without bendopnea in the *Chi-Square test* [5 events (31.3%) *vs.* 2 events (4.3%), p=0.003]. There was no statistically

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

Characteristic	All patients (n=62)	With bendopnea (n = 16)	Without bendopnea (n = 46)	*P*-value
Age (years)	49.1±11.3	47.2±9.5	49.9±11.9	.298
Female, *n (%)*	41 (66.1%)	9 (56.3%)	32 (69.6%)	.332
Body mass index, *kg/m²*	25.3±2.5	24.9±2.7	25.5±2.4	.459
Systolic blood pressure, *mmHg*	108.1±8.9	105.6±8.9	109.1±8.8	.073
Comorbidities, n (%)				
Hypertension	10 (16.1%)	2 (12.5%)	8 (17.4%)	.647
Diabetes mellitus	5 (8.1%)	3 (18.8%)	2 (4.4%)	.068
Hyperlipidemia	2 (2.9%)	1 (6.3%)	1 (2.2%)	.427
Laboratory findings				
eGFR, *mL/min/1.73m², median (IQR)*	71.0 (61.3-78.0)	69.0 (59.0-77.0)	74.0 (67.0-79.0)	.164
Haemoglobin, *gr/dl, median (IQR)*	11.0 (10.4-11.8)	11.1 (10.5-11.8)	11.0 (10.2-11.9)	.905
Sodium, *mEq/L, median (IQR)*	134 (132-135)	133 (131-136)	134 (133-135)	.178
NT-proBNP, *ng/L, median (IQR)*	1330 (622-1855)	1780 (1320-2590)	896 (609-1680)	.001
6-minute walking distance, *m, median (IQR)*	208 (124-275)	116 (78-172)	242 (189-291)	<0.001
Oxygen saturation, *(%),median (IQR)*	92 (89-94)	88 (85-91)	93 (91-94)	<0.001
Functional capacity class, n (%)				<0.001
WHO-1	6 (9.7%)	0 (0.0%)	6 (13.0%)	
WHO-2	32 (51.6%)	2 (12.5%)	30 (65.2%)	
WHO-3	19 (30.6%)	9 (56.3%)	10 (21.7%)	
WHO-4	5 (8.1%)	5 (31.3%)	0 (0.0%)	
Echocardiographic features				
RVEDD, *mm, median (IQR)*	31 (28-33)	33 (31-36)	30 (25-33)	<0.001
TAPSE, *mm, median (IQR)*	15 (13-18)	13 (12-15)	16 (14-18)	<0.001
LVEF, *(%),median (IQR)*	62 (60-64)	61 (60-62)	62 (60-64)	.165
Right heart catheterization findings				
Mean PAP, *mmHg, median (IQR)*	32 (28-39)	41 (37-45)	31 (27-35)	<0.001
Mean RAP, *mmHg, median (IQR)*	7 (5-9)	9 (8-14)	6 (5-8)	<0.001
PVR, *woods units, median (IQR)*	4.0 (3.1-6.9)	7.2 (5.2-8.5)	3.6 (3.1-4.5)	<0.001
Specific medical therapy, n (%)				
Endothelin receptor antagonists	53 (85.5%)	16 (100.0%)	37 (80.4%)	.056
Phosphodiesterase type 5 inhibitors	13 (20.1%)	5 (31.3%)	8 (17.4%)	.241
Prostacyclin analogues and receptor agonists	16 (25.8%)	7 (43.8%)	9 (19.6%)	.057
Calcium channel blockers	18 (29.0%)	4 (25.0%)	14 (30.4%)	.680
Etiology of PAH, n (%)				.233
IPAH	48 (77.4%)	11 (68.8%)	37 (80.4%)	
CTD-related PAH	6 (9.7%)	1 (6.3%)	5 (10.9%)	
CHD-related PAH	8 (12.9%)	4 (25.0%)	5 (8.7%)	

CTD-related PAH = Pulmonary arterial hypertension related to connective tissue disease; CHD-related PAH = Pulmonary arterial hypertension related to congenital heart disease; eGFR = Estimated glomerular filtration rate; IQR = Interquartile range; IPAH = Idiopathic pulmonary arterial hypertension; LVEF = Left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAP = Pulmonary artery 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.

Table 2. Short and mid-term clinical outcomes in stable PAH outpatients with and without bendopnea.

Clinical endpoint	With bendopnea (n = 16)	Without bendopnea (n = 46)	*P*-value
3-months, number of events, (%)			
HF-related hospitalization	5 (31.3%)	2 (4.3%)	.003
All-cause mortality	1 (6.3%)	1 (2.2%)	.427
12-months, number of events (%)			
HF-related hospitalization	11 (68.8%)	6 (13.0%)	<0.001
All-cause mortality	4 (25.0%)	1 (2.2%)	.004

HF = Heart failure; PAH = Pulmonary arterial hypertension.

difference between the two groups in term of all-cause mortality at 3 months [1 events (6.3%) *vs.* 1 event (2.2%), p=0.187]. HF-related hospitalization at 12 months was significantly higher in patients with bendopnea than the patients without bendopnea [11 events (68.8%) *vs.* 6 events (13.0%), p<0.001]. All-cause mortality at 12 months was observed higher in with bendopnea group than the without bendopnea group [4 events (25.0%) *vs.* 1 events (2.2%), p=0.004]. In the multivariable logistic regression analysis showed that, bendopnea was an independent predictor of HF-related hospitalization at 3 months (p=0.047, odds ratio [OR] 3.65, 95% CI 1.02-13.10), but not all-cause mortality at 3 months (p=0.172, [OR] 5.48, 95% CI 0.48-62.93). Additionally, we found that bendopnea was an independent predictor of HF-related hospitalization and all-cause mortality at 12 months (p<0.001, [OR] 5.22, 95% CI 2.08-13.14 and p=0.026 [OR] 4.63, 95% CI 1.20-17.86, respectively). Also, among other potential variables in model, NT-proBNP and mean RAP were statistically significantly associated with worse clinical outcomes in multivariable analysis. Multivariable logistic regression analysis of bendopnea for clinical outcomes in stable PAH outpatients are shown in Table 3.

Table 3. Multivariable logistic regression analysis for the relationship between bendopnea and clinical outcomes in stable PAH outpatients.

Clinical endpoint	Odds ratio (95% CI)	*P*-value
3-months		
HF-related hospitalization	3.65 (1.02-13.10)	.047
All-cause mortality	5.48 (0.48-62.93)	.172
12-months		
HF-related hospitalization	5.22 (2.08-13.14)	<0.001
All-cause mortality	4.63 (1.20-17.86)	.026

CI = Confidence interval; HF = Heart failure; PAH = Pulmonary arterial hypertension.

DISCUSSION

To the best of our knowledge, this is first study to show that bendopnea is associated with worse short and mid-term clinical outcomes in stable PAH outpatients. Bendopnea was shown as a novel type of dyspnea symptom in patients with HF by Thibodeau et al (1). They also demonstrated that bendopnea was associated with adverse clinical outcomes, advanced symptoms and disease severity (2). We have firstly reported that the presence of bendopnea was associated more severe right heart dysfunction and haemodynamic characteristics in patients with PAH (14). The aim of our present study was to evaluate the relationship between bendopnea and clinical outcomes including HF-related hospitalization and all-cause mortality at 3 and 12 months in stable PAH outpatients.

The frequency of bendopnea was 25.8% in this study population, however, it was 33.9% in our first study and this might be explained by the number of the patients. Thibodeau et al. have reported the frequency of bendopnea of 18% in ambulatory systolic HF patients and another study conducted by Baeza-Trinidad et al. have showed that the frequency of bendopnea 48.8% in the patients with acute decompensated heart failure (ADHF) (2,3). Furthermore, Dominguez-Rodriguez et al. showed that preoperative bendopnea ratio was 42% in patients with severe aortic stenosis (AS) (15).

In this study, we found that bendopnea was associated with HF-related hospitalization at 3 and 12 months, and all-cause mortality at 12 months only except all-cause mortality at 3 months. It has been demonstrated that patients with bendopnea had an increased positional right and left ventricular filling pressures during bending especially in the presence of low cardiac index (1). We showed that haemodynamic parameters including mean RAP, mean PAP and PVR were worse in stable PAH outpatients with bendopnea similar to our previous study (14). Similar to present study, Thibodeau et al. have showed that haemodynamic findings such as mean RAP, mean PAP, and PVR were higher in systolic HF patients with bendopnea (1). Another study conducted by Thibodeau et al. have demonstrated that bendopnea was associated with worse clinical outcomes in ambulatory systolic HF

patients. HF admission at 1, 3, and 6 months were significantly higher in patients with bendopnea than the patients without bendopnea (2). Additionally, they showed that death at 1 months was higher in patients with bendopnea, however, all-cause death at 3 and 6 months were not different in their study (2). They also found that composite of HF admission and death at 1, 3, and 6 months were different between the two groups (2). The possible explanation of their results was the increased congested state due to higher cardiac filling pressures. They have also suggested that increased congested state of patient causes to the sympathetic overactivation and myocardial apoptosis which eventually lead to adverse clinical outcomes (2). Similar to study of Thibodeau et al, we showed that HF-related hospitalization at 3 and 12 months and all-cause mortality at 12 months were higher in patients with bendopnea. We did not find mortality difference at 3 months, small number of deaths might be the possible reason of this finding. If the number of events or patients was high in our study, all-cause mortality at 3 months could also be different. Larina et al. have recently showed that bendopnea was associated with worse echocardiographic characteristics and clinical outcomes in elderly ambulatory patients with HF (16). Bendopnea was present 38.8% of their study patients (16). They demonstrated that bendopnea was an independent predictor of mid-term HF-related rehospitalization and mortality (16). Dominguez-Rodriguez et al. have been demonstrated that preoperative presence of bendopnea in severe AS patients was associated with higher postoperative clinical events (15). In-hospital mortality was statistically nearly significantly higher in patients with bendopnea than the patients without bendopnea in their study. Additionally, patients with bendopnea had higher 30-day postoperative mortality rates (15). They also showed that duration of the mechanical ventilation and length of stay in hospital were significantly much more in AS patients with bendopnea (15). Similar to our study,they observed that severe AS patients with bendopnea had baseline worse haemodynamic profile and functional capacity class (14). Baeza-Trinidad et al. have reported that bendopnea was associated with short-term mortality and worse functional class in ADHF patients (3). They have also found that ADHF patients with bendopnea had a higher mortality rates than the patients without bendopnea at 6 months, however they did not find any difference related with HF readmission at 6 months between groups (3). We demonstrated that stable PAH outpatients with bendopnea have worse basal right heart haemodynamics and volume status than the patients without bendopnea. These may cause to easy decompensation and/or development of de novo RHF in patients with PAH. In this context, it was not surprise that higher rates of HF-related hospitalization at 3 and 12 months and all-cause mortality at 12 months were observed in stable PAH outpatients with bendopnea.

In conclusion, we first demonstrated that bendopnea was associated short and mid-term HF-related hospitalization and mid-term all-cause mortality in stable PAH outpatients. These data suggest that bendopnea may be used as a common and easy-use physical examination marker in the prediction of adverse clinical outcomes in patients with PAH.

LIMITATIONS

There are some limitations of this study. First, as this study is a single-center observational analysis, our results may not reflect accurate data to the literature. Number of patients with bendopnea in that study is smaller than previous HF and PAH studies. Also, there are a small number of events especially for all-cause mortality at 3 months in our study. But, it should be remembered that this is a PAH study and total follow-up time is only 12 months. The basal haemodynamic status of study population were obtained from the patients' last right heart catheterization results, it did not confirm with a current right heart catheterization. Bendopnea is a somewhat subjective symptom which may influence the results of all studies as well as our study. This study should be confirmed with large-scale prospective-randomized controlled multicenter studies.

CONCLUSION

Bendopnea is a new respiratory symptom, which is experienced dyspnea while bending forward when putting on shoes or trying them up (1). Bendopnea which reflects a higher right and left ventricular filling pressures, has shown associated with worse clinical outcomes in HF patients (1,2). We demonstrated the presence of bendopnea in PAH outpatients in our previous study (13). Now, we first reported that bendopnea was a strong independent predictor of HF-related hospitalization at 3 and 12 months and all-cause mortality at 12 months in stable PAH outpatients. Therefore, bendopnea may be used as a predictor for assessment of prognosis and risk stratification in PAH patients with the results of further prospective randomized studies.

CONFLICT OF INTERES

None to declare

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