Clinical Research in Cardiology (2022) 111:663–672
https://doi.org/10.1007/s00392-021-01969-x

ORIGINAL PAPER

Prognostic effect of sleep-disordered breathing on hospitalized patients following acute heart failure

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Received: 17 May 2021 / Accepted: 2 November 2021 / Published online: 11 November 2021

Abstract

Background Identifying patients at risk for poor clinical outcomes following acute heart failure (AHF) is essential. However, data regarding the prognostic effect of sleep-disordered breathing (SDB) and treatment with positive airway pressure (PAP) on clinical outcomes of hospitalized patients following AHF is lacking.

Objectives This study investigated the prognostic effect of SDB, PAP treatment, and compliance with PAP treatment on patient clinical outcomes. Polysomnography was performed in hospitalized patients whose left ventricular ejection fraction was < 50%. Patients were divided into groups based on whether SDB was defined as an apnea–hypopnea index ≥ 15 and if they had received PAP treatment. Furthermore, patients with SDB and PAP were subdivided into more and less compliant groups. We assessed the incidences of deaths and rehospitalizations due to heart failure.

Results Overall, 241 patients were enrolled; 73% had SDB and 29% were initiated on PAP treatment. At a median follow-up of 1.7 years, 74 clinical events (32 deaths, 42 rehospitalizations) occurred. In the multivariable analysis, compared with the non-SDB group, SDB without PAP treatment was associated with an increased risk of clinical outcomes (hazard ratio [HR] 1.79, $P = 0.049$), whereas SDB with PAP treatment was not (HR 0.78, $P = 0.582$). Among patients with PAP treatment, a more compliant group was also inversely associated with clinical events (HR 0.11, $P = 0.012$).

Conclusions In hospitalized patients with AHF, untreated SDB was associated with worse clinical outcomes that might be reversible by PAP treatment. However, this potential may be suppressed in less compliant patients.

Keywords Acute heart failure · Sleep-disordered breathing · Positive airway pressure

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Introduction

Acute heart failure (AHF) is a major cause of mortality and readmission, despite improvements in treatment options [1]. Identification of high-risk AHF patients and mitigation of risk factors are crucial to improve clinical outcomes [2].

In recent studies, sleep-disordered breathing (SDB) was often observed in patients with AHF (about 75% cases), who develop either obstructive sleep apnea (OSA) or central sleep apnea (CSA) [3]. OSA is a risk factor for hypertension [4], coronary artery disease [5], and atrial fibrillation (AF) [6], all of which contribute to AHF pathogenesis. In contrast, CSA in patients hospitalized with AHF might be a consequence of increased left ventricular (LV) filling pressure and/or fluid retention [7]. The relationship between the presence of SDB and long-term clinical outcomes has been reported in patients with AHF

[8, 9]. Positive airway pressure (PAP) treatment is one of the most effective options to suppress SDB in patients with heart failure (HF) [10]. Effective treatment of SDB by adherence to PAP has been reported to improve long-term outcomes [11]. Khayat et al. reported that PAP treatment of AHF-associated SDB patients might improve long-term clinical outcomes, as determined by cardiorespiratory monitoring, which measures respiratory effort, oxygen saturation, nasal flow, and pulse rate [9]. Conversely, overnight polysomnography (which is equipped with an electrocardiogram, electroencephalogram, electrooculogram, and electromyogram in addition to sensors for respiratory effort, oxygen saturation, air flow, and pulse rate) is generally regarded as a standard technique for detecting SDB, especially in patients with HF [14]. However, to the best of the knowledge, no studies have analyzed the relationship between SDB as determined by polysomnography and clinical outcomes of patients with AHF. Thus, we investigated whether the presence of SDB determined by polysomnography is associated with poor prognosis in patients with AHF and in-hospital initiation of PAP therapy for such SDB can reverse it, and whether PAP adherence may contribute to improved clinical outcomes.

Methods

Subjects

In this observational study, patients diagnosed with AHF who were hospitalized at our institution (Juntendo University Hospital, Tokyo, Japan) between May 2012 and April 2018 were enrolled in the study. Patients with heart failure who met the modified Framingham criteria (which only included variables in the Framingham criteria estimated at admission) were eligible for the study [12, 13]. After the initial improvement of AHF, overnight polysomnography was performed to check their eligibility for the inclusion and exclusion criteria. The inclusion criteria were as follows: (1) men or women aged ≥ 20 years and (2) left ventricular ejection factor (LVEF) < 50% measured by echocardiography. The exclusion criteria were as follows: (1) requirement of oxygen therapy, acute coronary syndrome, and/or cardiac surgery during the previous 4 weeks; (2) end-stage renal disease requiring dialysis; (3) cerebrovascular disease with neurological deficits; (4) life-threatening malignancy; (5) apparent obstructive lung disease; and (6) known SDB. The Institutional Review Board of the Juntendo University Hospital approved the study protocol (871), and the study complied with the Declaration of Helsinki. Informed consent was obtained from all patients.

Sleep study and PAP

All the patients underwent overnight polysomnography using Alice PDX (Philips Respironics, Murrysville, PA, USA) for a few days during the first hospitalization for AHF and after initial improvement of AHF acute signs and symptoms. Electrocardiograms, electroencephalograms, electrooculograms, and electromyograms were performed, and thoracoabdominal motion was monitored using respiratory inductance plethysmography. Air flow was measured using an oronasal thermal airflow sensor and nasal pressure cannula, and oxyhemoglobin saturation was monitored using oximetry. Definitions and scoring methods were based on the American Academy of Sleep Medicine manual version 2.2 [14]. Apneas were classified as OSA or CSA according to the presence or absence of thoracoabdominal motion, respectively. Hypopneas were classified as central if none of the following criteria were met: snoring during the event, increased inspiratory flattening of the nasal pressure compared to baseline breathing, and associated thoracoabdominal paradox during but not before the event [14]. Apneas and hypopneas were quantified, and SDB severity was assessed using the frequency of apneas and hypopneas per hour of sleep (i.e., apnea–hypopnea index [AHI]). In this study, SDB was defined as an AHI ≥ 15 (non-SDB group, AHI < 15 events per hour; SDB group, AHI ≥ 15 events per hour). Obstructive and central AHI were computed separately. In addition, patients with SDB were classified into an obstructive-dominant group (i.e., ≥ 50% obstructive events) and a central-dominant group (i.e., ≥ 50% central events).

PAP treatment was initiated, with either continuous PAP (CPAP) or adaptive servo ventilation (ASV) based on the patient's own or attending physicians' decisions. In this study, patients with SDB were classified as those with or without PAP treatment (the former included those who could optimally use PAP ≥ 1 month). Furthermore, compliance with PAP treatment was defined by the status of PAP usage. A more compliant group had an average nightly usage of PAP more than the median level, whereas that of a less compliant group was less than the median level during the entire period.

Other data collection

Baseline data were collected prospectively at the time of the sleep study. In addition, a clinical chart review was performed to obtain medical history. The New York Heart Association (NYHA) functional class was assessed at the time of sleep study. Renal function was presented as estimated glomerular filtration rate (eGFR), which was

calculated by the Modification of Diet in Renal Disease equation with Japanese coefficient from baseline serum creatinine levels [15]. Echocardiography was performed at the time of sleep study, and LVEF was obtained using the modified Simpson method. We followed all patients from the date of sleep study during the initial hospitalization until April 2019. All patients were followed up in our clinic, and the outcome data were obtained by reviewing the medical records of our hospital. The endpoints of interest were the composite of mortality and readmission due to HF exacerbation until April 2019.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation for normally distributed variables or as medians with interquartile ranges for non-normally distributed variables. Categorical variables are presented as numbers and percentages. To compare the baseline characteristics between the two groups, the χ^2 test or Fisher's exact test was used for categorical variables and a *t* test for normally distributed variables or the Mann–Whitney *U* test for non-normally distributed variables was used for continuous variables. The event-free survival curves were drawn using the Kaplan–Meier method and compared between groups using a log-rank test. First, we assessed the relationship between SDB status (non-SDB, SDB with and without PAP treatment) and clinical outcomes in all subjects. Univariate Cox proportional hazards regression analysis was used to identify the association between clinical outcomes and variables including age, female sex, medical history (i.e., etiology of HF, history of HF, diabetes mellitus, and AF), systolic blood pressure, heart rate, LVEF, laboratory tests (i.e., b-type natriuretic peptide [BNP], hemoglobin, eGFR, sodium, and potassium), medications (i.e., loop diuretics, angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker, β-blockers, and aldosterone blockers), and SDB status. The assumption of proportional hazards was assessed using a log-minus-log survival graph. Variables with *p* values < 0.1 in each univariable analysis, were included in the multivariable Cox proportional hazards regression analysis with backward elimination. The first-order interactions in the multivariable Cox proportional hazards models were examined by entering interaction terms between the SDB status and predominant type (i.e., obstructive or central). Second, the PAP groups were further analyzed as PAP compliance status (more or less) was included instead of the SDB status. In this analysis, although the assumption was verified, a time-dependent Cox model including nightly PAP usage per month, instead of the compliance status, was constructed, since the compliance status changed during the study period. In this model, the average nightly PAP usage per month was considered instead of the compliance status of PAP treatment. The first-order interactions in the multivariable Cox proportional hazards models were examined by entering interaction terms between compliance status and predominant type (i.e., obstructive or central). All analyses were performed using the statistical software package R software version 3.4.3 (R Core Team, Vienna, Austria).

Results

Patients with and without SDB

Data from 241 patients were analyzed. Among them, 177 patients (73.4%) had SDB (Fig. 1) and 52 patients (29.4%) were initiated on PAP (ASV, 27 [51.9%] and CPAP, 25 [40.1%]) based on their personal decision or the attending physicians' decisions. The baseline characteristics according to SDB status are shown in Table 1. Because the NYHA class was assessed at the time of polysomnography after the initial improvement of acute signs of HF, NYHA class II was observed in a greater proportion of all patients. The results of the sleep study are shown in Table 2. The median duration between initial improvement of AHF and polysomnography was 3.0 (interquartile range, 2.8) days.

At a median follow-up of 1.7 years (interquartile range, 2.3 years), 74 patients (31%) had clinical events (32 deaths and 42 rehospitalizations, respectively). Among the 74 patients, 16 (22%) in the non-SDB group, 8 (11%) in the SDB with PAP group, and 50 (68%) in the SDB without PAP group reported clinical events. The Kaplan–Meier survival curves according to SDB status are shown in Fig. 2. The cumulative event-free survival was worse in SDB patients without PAP and better in SDB patients with PAP than in those without SDB (log-rank test, $p < 0.001$). Variables with *p* values < 0.1 in each univariable analysis, are summarized in Table 3. In the multivariable analysis, compared with non-SDB patients, SDB patients without PAP had a significantly higher risk of poor clinical outcome (hazard ratio [HR] 1.79, 95% confidence interval [CI] 1.00–3.37, $P = 0.049$), whereas SDB patients with PAP showed similar (rather better) risk (HR 0.78, 95%CI 0.31–1.84, $P = 0582$). The interaction between the predominant type and SDB status/clinical outcome relationship was not significant ($p = 0.822$), indicating that SDB status/clinical outcome relationship did not differ according to the predominant type of respiratory events.

Compliance with PAP treatments in PAP-treated patients

Of the 52 PAP-treated patients, compliance data of 8 patients were not available, and data from 44 patients were analyzed. The median value of nightly PAP usage among these 44 patients was 4.2 h (interquartile range, 2.7 h): 22

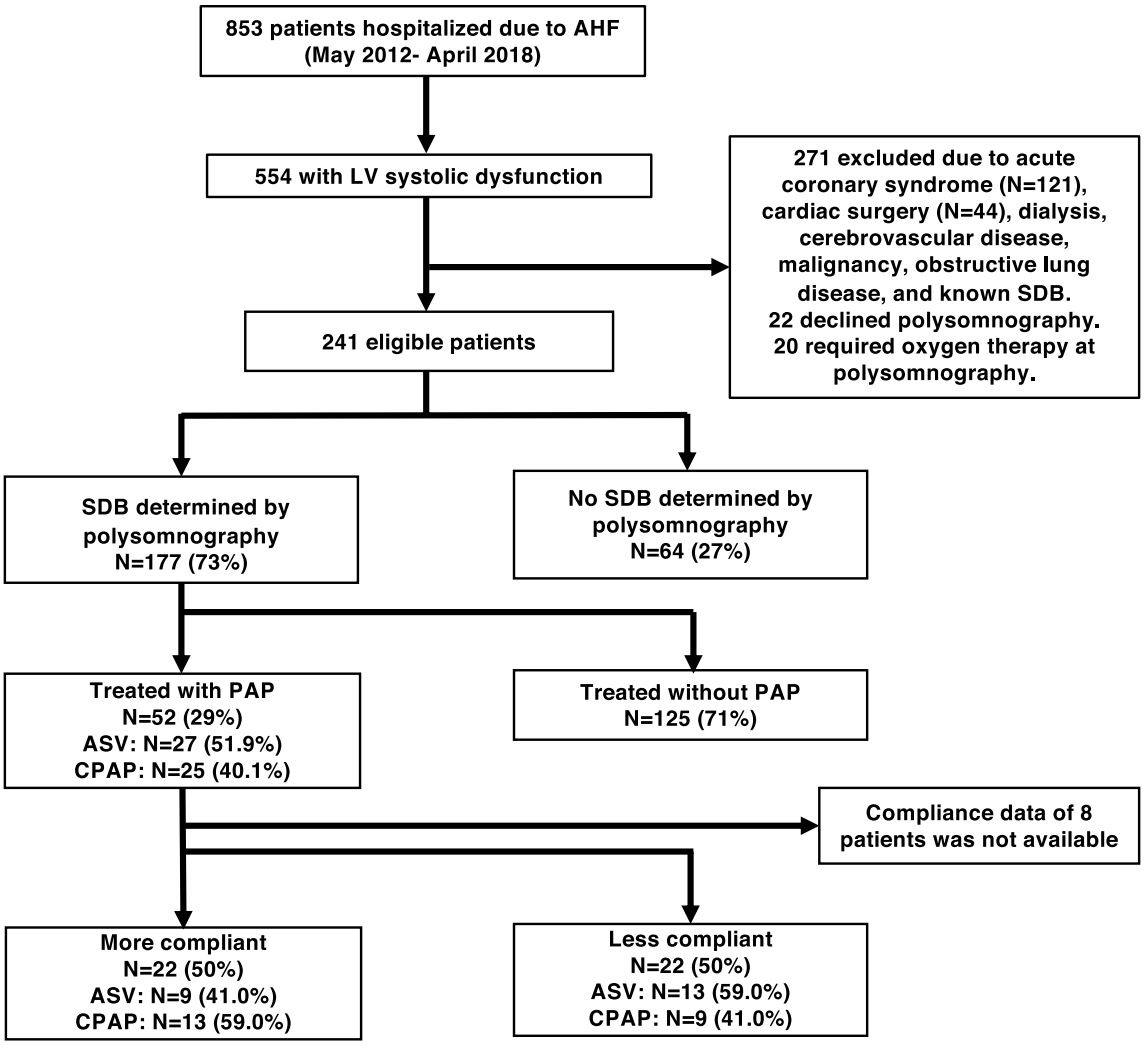

Fig. 1 Flow diagram of the study population. From May 2012 to April 2018, 853 patients with AHF were hospitalized at Juntendo University Hospital. Among them, 554 had LV systolic dysfunction (defined as LVEF < 50% via echocardiography). A total of 271 patients were excluded for the following reasons: requirement of oxygen therapy, acute coronary syndrome ($n = 121$) and/or cardiac surgery ($n = 44$) during the previous 4 weeks, end-stage renal disease requiring dialysis, cerebrovascular disease with neurological deficits, life-threatening malignancy, apparent obstructive lung disease, and known SDB. Twenty-two patients refused to undergo polysomnography for personal reasons. Twenty patients required oxygen therapy at polysomnography. Thus, 241 eligible patients were enrolled for the study. Furthermore, eight patients treated with PAP were excluded, because compliance data of them were not available. Abbreviations *AHF* acute heart failure, *ASV* adaptive servo ventilation, *CPAP* continuous positive airway pressure, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *PAP* positive airway pressure; SDB, sleep-disordered breathing

patients were classified as more compliant (average usage, 6.1±1.0 h) and 22 were classified as less compliant (average usage, 3.0±0.9 h). The baseline characteristics and results of the sleep study of patients with more and less compliance to PAP treatment were comparable (Tables 4 and 5, respectively).

During the follow-up period, one event (one rehospitalization) occurred in the more compliant group and eight events (five deaths and three rehospitalizations) occurred in the less compliant group. Variables with p values < 0.1 in each univariable analysis, are summarized in Table 6. More compliance to PAP treatment was significantly associated with a lower risk of clinical outcome (HR 0.13, 95%CI 0.02–1.83, $p = 0.021$) in the multivariable analysis. The interaction between the predominant type and compliance status/clinical outcome relationship was not significant ($P = 0.914$), indicating that the compliance status/clinical outcome relationship did not differ according to the predominant type of respiratory events. In addition, the interaction between the PAP type and compliance status/clinical outcome relationship was not significant ($p = 0.546$), indicating that the compliance status/clinical

Table 1 Baseline characteristics of patients in accordance with the presence of SDB/ status as PAP treated or untreated

	Non-SDB $N=64$	SDB with PAP $N=125$	SDB without PAP $N=52$	*p* value
Age, year	60.5 ± 13.1	63.9 ± 14.1	60.4 ± 12.3	0.146
Female sex, *n* (%)	24 (37.5)	28 (22.4)	5 (9.6)	0.002
BMI kg/m^2	22.3 ± 4.2	24.6 ± 4.9	26.0 ± 5.8	0.002
NYHA class at polysomnography				
III, IV, *n* (%)	15 (23.4)	42 (33.6)	11 (21.2)	0.157
Ischemic etiology, *n* (%)	14 (21.9)	43 (34.4)	15 (28.9)	0.204
History of HF, *n* (%)	31 (48.4)	60 (48.0)	25 (48.1)	0.998
AF, *n* (%)	22 (34.4)	49 (39.2)	14 (26.9)	0.296
Diabetes, *n* (%)	13 (20.3)	40 (32.0)	18 (34.6)	0.164
Systolic BP, mmHg	102.7 ± 16.4	106.0 ± 15.9	112.0 ± 16.3	0.008
Diastolic BP, mmHg	58.7 ± 9.9	60.2 ± 9.8	64.4 ± 11.5	0.009
Heart rate, /min	69.8 ± 10.6	71.6 ± 12.1	71.2 ± 14.8	0.620
LVEF, %	33.9 ± 10.6	33.9 ± 10.7	33.7 ± 10.8	0.991
Hemoglobin, g/dl	13.5 ± 2.6	13.7 ± 2.3	14.9 ± 2.4	0.004
eGFR, ml/min/1.73 m^2	58.3 ± 24.4	54.1 ± 22.4	63.8 ± 23.1	0.038
Sodium, mmol/l	138.8 ± 3.4	139.7 ± 3.3	139.9 ± 2.5	0.072
Potassium, mmol/l	4.4 ± 0.4	4.7 ± 0.3	4.3 ± 0.4	0.589
BNP, pg/ml	240.1 [377.4]	309.0 [355.8]	209.2 [431.9]	0.250
ICD, n (%)	6 (11.1)	8 (6.4)	5 (10.0)	0.674
CRT, n (%)	5 (7.8)	9 (7.2)	2 (3.9)	0.619
Beta blockers, *n* (%)	59 (92.2)	118 (94.4)	47 (90.4)	0.616
ACE-Is/ARBs, *n* (%)	52 (81.3)	97 (77.6)	47 (90.4)	0.140
Aldosterone blockers, *n* (%)	45 (70.3)	74 (59.2)	34 (65.4)	0.310
Loop diuretics, *n* (%)	51 (79.7)	102 (81.6)	42 (80.8)	0.951

Variables are expressed as mean ± standard deviation, median [interquartile range], or *n* (%). *ACE-I* angiotensin-converting enzyme inhibitor, *AF* atrial fibrillation, *ARB* angiotensin II receptor blocker, *BMI* body mass index, *BNP* B-type natriuretic peptide, *BP* blood pressure, *CRT* cardiac resynchronization therapy, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *ICD* implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association

Table 2 Sleep study findings of patients with and without SDB

	Non-SDB $N=64$	SDB with PAP $N=125$	SDB without PAP $N=52$	*p* value
Total sleep time, min	349.7 ± 74.9	353.0 ± 97.3	371.1 ± 74.0	0.178
Sleep efficiency, %	65.3 ± 3.9	68.1 ± 2.8	70.8 ± 4.4	0.858
% of slow wave sleep, % of TST	8.8 [12.1]	5.2 [9.1]	6.2 [8.5]	< 0.001
% of REM sleep, % of TST	16.9 ± 6.3	14.0 ± 6.9	16.7 ± 6.7	0.004
Arousal index, event/h of sleep	17.3 [10.4]	35.3 [22.6]	34.7 [21.1]	< 0.001
AHI, events/h of sleep	8.9 [5.5]	37.8 [26.1]	40.5 [23.7]	< 0.001
Obstructive, events/h of sleep	3.5 [5.7]	15.5 [18.1]	18.9 [25.3]	< 0.001
Central, events/h of sleep	4.1 [5.6]	21.7 [23.2]	18.3 [28.1]	< 0.001
Mean SO_2, %	96.6 ± 1.4	95.1 ± 2.0	94.7 ± 2.4	< 0.001
Minimum SO_2, %	89.5 ± 4.7	82.2 ± 7.1	78.5 ± 10.5	< 0.001
% of time SO_2 < 90%, %	0 [0.2]	1.4 [6.3]	4.7 [15.0]	< 0.001
Obstructive-dominant, *n* (%)	26 (40.6)	38 (30.4)	22 (42.3)	0.204

AHI apnea–hypopnea index, *REM* rapid eye movement, *SO_2* arterial oxyhemoglobin saturation, *TST* total sleep time

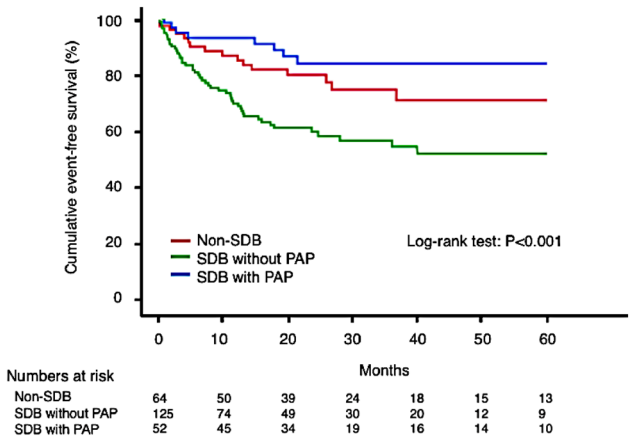

Fig. 2 Kaplan–Meier event-free survival curves of patients in accordance with the presence of SDB status as PAP treated or untreated. The cumulative event-free survival for the composite of mortality and readmission due to HF exacerbation was worse in SDB patients without PAP and better in SDB patients with PAP than in those without SDB (log-rank test, $p < 0.001$). Abbreviations: *PAP* positive airway pressure, *SDB* sleep-disordered breathing

outcome relationship did not differ according to the PAP type. Furthermore, the results of additional analysis using the time-dependent model including average nightly PAP usage per month instead of the compliance status showed that longer average nightly usage was also associated with a decrease in the risk of clinical outcome (HR 0.48, 95%CI 0.29–0.86, $P = 0.012$).

Discussion

The findings of this study, which analyzed a single-center observational cohort of 241 hospitalized patients with AHF and LV systolic dysfunction, provided several novel insights into the relationship between SDB and clinical outcome in patients with AHF. First, we found that the presence of SDB in patients with AHF was associated with an increased risk of mortality or readmission due to HF exacerbation. Second, such an association between SDB and mortality was not persistent in PAP-treated patients. Third, the possible effects of PAP treatment on clinical outcome may differ according to the compliance status: the shorter the nightly usage of PAP, the worse the clinical outcome. Finally, these relationships did not differ according to the predominant type of respiratory events and the PAP type.

SDB, either OSA or CSA, has been reported as a predictor of poor clinical outcome in patients with stable systolic HF [16, 17]. However, SDB remains undiagnosed in the majority of patients with HF [18]. In association with LV systolic dysfunction, some data suggest a relationship between the SDB presence and clinical outcome in hospitalized patients with AHF [9, 19]. In all these studies, SDB was determined

Table 3 Univariable and multivariable Cox regression analyses in all patients for the composite of mortality and readmission due to HF exacerbation

	Univariable		Multivariable	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (1-year increase)	1.02 (1.01–1.04)	0.006	–	–
Ischemic etiology—yes	2.07 (1.04–2.70)	0.001	–	–
History of HF—yes	1.99 (1.62–2.35)	0.002	–	–
NYHA class III, IV—yes	2.54 (1.82–4.90)	< 0.001	2.39 (1.42–3.97)	< 0.001
Use of diuretics—yes	2.04 (1.21–5.38)	0.027	2.11 (1.06–4.79)	0.048
LVEF (1% increase)	0.98 (0.96–1.00)	0.080	–	–
Hemoglobin (1 g/dl increase)	0.8 (0.73–0.88)	< 0.001	–	–
Serum sodium (1 mmol/l increase)	0.90 (0.85–0.97)	< 0.001	0.93 (0.87–1.00)	0.053
Log-transformed BNP (1 increase)	1.90 (1.50–2.49)	< 0.001	1.52 (1.16–2.04)	0.004
eGFR (1 ml/min/1.73 m^2 increase)	0.97 (0.96–0.98)	< 0.001	0.98 (0.97–0.99)	0.003
Total sleep time (1-min increase)	0.99 (0.99–1.00)	0.035	–	–
% of REM sleep (1% increase)	0.94 (0.91–0.97)	< 0.001	0.96 (0.93–1.00)	0.051
% of Time $SO_2 < 90\%$ (1% increase)	1.01 (0.99–1.02)	0.008	–	–
SDB—no	Reference		Reference	
SDB—yes, PAP user—yes	0.57 (0.23–1.31)	0.194	0.78 (0.31–1.84)	0.582
SDB—yes, PAP user—no	2.06 (1.20–3.74)	0.008	1.79 (1.00–3.37)	0.049

Variables with *p* values < 0.1 in each univariable analysis were included in the multivariable Cox proportional hazards regression analysis with backward elimination

BNP B-type natriuretic peptide, *CRP* C-reactive protein, *CRT* cardiac resynchronization therapy, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *ICD* implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *NYHA* new york heart association, *REM* rapid eye movement

Table 4 Baseline characteristics of PAP-treated patients with more and less compliance to the treatments

	More compliant $N=22$	Less compliant $N=22$	p value
Age, years	61.7 ± 13.1	59.1 ± 12.8	0.502
Female sex, *n* (%)	1 (5.3)	3 (12)	0.622
BMI kg/m^2	26.1 ± 6.1	25.7 ± 6.4	0.806
NYHA class at polysomnography			0.999
III, IV, *n* (%)	3 (13.6)	3 (13.6)	
Ischemic etiology, *n* (%)	7 (31.8)	5 (22.7)	0.736
History of HF, *n* (%)	12 (54.6)	8 (36.7)	0.364
AF, *n* (%)	4 (19.9)	6 (27.3)	0.721
Diabetes, *n* (%)	7 (31.8)	9 (40.9)	0.755
Systolic BP, mmHg	112.5 ± 17.3	113.7 ± 15.5	0.812
Diastolic BP, mmHg	63.1 ± 9.8	67.5 ± 12.1	0.197
Heart rate, /min	71.7 ± 15.3	70.5 ± 11.9	0.769
LVEF, %	33.7 ± 11.9	33.1 ± 9.6	0.858
Hemoglobin, g/dl	15.4 ± 2.4	15.1 ± 2.2	0.636
eGFR, ml/min/1.73 m^2	62.3 ± 25.7	63.1 ± 20.8	0.915
Sodium, mmol/l	140.1 ± 2.4	139.2 ± 2.4	0.658
Potassium, mmol/l	4.3 ± 0.3	4.4 ± 0.4	0.322
BNP, pg/ml	167.6 [466.3]	263.3 [387.9]	0.727
ICD, *n* (%)	1 (5.3)	4 (16)	0.370
CRT, *n* (%)	1 (5.3)	1 (4.0)	0.842
Beta blockers, *n* (%)	20 (90.9)	22 (100.0)	0.488
ACE-Is/ARBs, *n* (%)	20 (90.9)	19 (86.4)	0.999
Aldosterone blockers, *n* (%)	12 (54.6)	15 (68.2)	0.537
Diuretics, *n* (%)	18 (81.8)	20 (90.9)	0.664

Variables are expressed as mean ± standard deviation, median [interquartile range], or *n* (%). *ACE-I* angiotensin-converting enzyme inhibitor, *AF* atrial fibrillation, *ARB* angiotensin II receptor blocker, *BMI* body mass index, *BNP* B-type natriuretic peptide, *BP* blood pressure, *CRP* C-reactive protein, *CRT* cardiac resynchronization therapy, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *ICD* implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *NYHA* new york heart association

Table 5 Sleep study findings of PAP-treated patients with more and less compliance to the treatments

	More compliant $N=22$	Less compliant $N=22$	p value
Total sleep time, min	383.3 ± 68.8	371.4 ± 72.2	0.581
Sleep efficiency, %	73.1 ± 2.6	69.6 ± 2.6	0.337
% of slow wave sleep, % of TST	7.1 [8.0]	4.4 [7.9]	0.201
% of REM sleep, % of TST	16.7 ± 6.9	16.8 ± 5.9	0.952
Arousal index, event/h of sleep	32.7 [26.8]	34.9 [23.8]	0.932
AHI, events/h of sleep	41.4 [19.4]	38.9 [32.1]	0.443
Obstructive, events/h of sleep	21.9 [21.9]	16.0 [22.8]	0.760
Central, events/h of sleep	18.4 [30.7]	21.1 [31.5]	0.294
Mean SO_2, %	93.9 ± 2.7	95.3 ± 2.1	0.061
Minimum SO_2, %	76.7 ± 9.5	78.0 ± 12.3	0.838
% of time $SO_2 < 90\%$, %	9.4 [19.2]	3.3 [12.0]	0.456
Obstructive-dominant, *n* (%)	10 (45.6)	10 (45.6)	0.999

AHI apnea–hypopnea index, *ODI* oxygen desaturation index, *REM* rapid eye movement, SO_2 arterial oxyhemoglobin saturation, *TST* total sleep time

Table 6 Univariable and multivariable Cox regression analyses in PAP-treated patients for the composite of mortality and readmission due to HF exacerbation

	Univariable		Multivariable			
	HR (95% CI)	*p*	proportional hazard model		Time-dependent model	
			HR (95% CI)	*p*	HR (95% CI)	*p*
eGFR (1 ml/min/1.73 m^2 increase)	0.97 (0.93–1.00)	0.036	0.93 (0.87–0.98)	0.007	0.95 (0.90–0.99)	0.017
Use of diuretics—yes	2.11 (1.22–5.37)	0.048	–	–	–	–
More compliant—yes	0.13 (0.01–0.83)	0.028	0.11 (0.01–1.10)	0.012		
Nightly PAP usage (1-h increase)	0.55 (0.26–0.77)	0.026			0.48 (0.29–0.86)	0.012

Variables with p values < 0.1 in each univariable analysis were included in the multivariable Cox proportional hazards regression analysis with backward elimination

eGFR estimated glomerular filtration rate

by cardiorespiratory polygraphy [8, 9]. We agree that the use of cardiorespiratory polygraphy for the detection and classification of SDB in patients hospitalized with AHF is practical and generalizable. However, the detection of SDB by cardiorespiratory polygraphy has not yet been established in patients with HF [20]. In addition, in patients with AHF, OSA is prevalent in a study, where SDB was identified by cardiorespiratory polygraphy, whereas CSA is prevalent in studies, where SDB was identified by full polysomnography [3]. Indeed, in the present study, predominant OSA was less frequent in other studies, where SDB was identified by cardiorespiratory polygraphy [10, 11]. Thus, the prognostic significance of SDB determined by cardiorespiratory polygraphy may not be the same as that determined by polysomnography, and the prognostic effect of SDB determined by polysomnography in hospitalized patients following AHF should be elucidated. However, no studies have analyzed the relationship between SDB determined by polysomnography and clinical outcomes of patients. To the best of our knowledge, the present study is the first to show the influence of SDB determined by polysomnography on clinical outcome and to confirm that the prognostic effect of SDB was consistent even if SDB was determined by polysomnography.

SDB is potentially treatable and expected to provide beneficial effects on the cardiovascular system of patients with HF. However, SDB treatment is not included in the standard care of HF. In patients with stable HF, many studies have investigated the beneficial effects of SDB (either OSA or CSA), treatments with PAP on the functional capacity, plasma levels of BNP, and LV systolic function [21–23]. In addition, observational studies have suggested that in patients with stable HF, SDB with PAP treatment reduces the risk of mortality and/or hospitalization due to HF [11, 17]. However, to the best of our knowledge, there are no adequately powered randomized controlled studies on the beneficial effects of SDB treatment with CPAP on mortality and/or rehospitalization [24]. Furthermore, treatment of predominant CSA by ASV in stable HF patients with reduced ejection fraction failed to show beneficial effects on composite clinical outcomes but showed an increased risk of all-cause and cardiovascular mortality [25]. In patients with AHF, Khayat et al. suggested the potential mortality benefit of PAP treatment for SDB, either OSA or CSA, which were determined by cardiorespiratory polygraphy [9]. The present study further confirms that PAP treatment may have beneficial effects on clinical outcome in patients with SDB, regardless of OSA or CSA, but SDB was determined by polysomnography. Two short-term prospective studies have suggested the potential benefits of PAP treatment in hospitalized patients following AHF. The first study analyzed 46 hospitalized patients following AHF with regard to LV systolic dysfunction and found that treatment for OSA during hospitalization by bi-level PAP was associated with improvement of LV systolic function [26]. The second study was a randomized controlled trial, but was prematurely terminated because of the failure to show better clinical outcomes using the same PAP treatment in patients with stable HF [25]. In that study, ASV for SDB did not show beneficial effects on the primary endpoint of global rank score at 6 months in 126 patients hospitalized with AHF, including both HF with reduced and preserved ejection fraction [27]. In addition, a positive effect of ASV was suggested in a subgroup of patients with preserved ejection fraction, but no clinical benefits were observed in a subgroup of patients with reduced ejection fraction [27]. Considering the positive associations between PAP treatment and clinical outcome in observational studies and that a randomized controlled trial using PAP treatment causes no potential harm in patients with AHF [27], it is worth reconsidering another randomized controlled trial using PAP treatment in patients with AHF.

At this point, our assessment of the relationship between compliance status and clinical outcome in PAP-treated patients should be taken into account. This is basically consistent with the results of an observational study of 65 patients with stable HF undergoing CPAP treatment for OSA; that is, patients who were more compliant with CPAP

treatment were significantly associated with better clinical outcomes the composite of death and hospitalization [11]. On one hand, these findings suggest that the confounding effects associated with the type of patients who seek SDB treatment could explain the positive results of PAP treatment in observational studies, including the present study. On the other hand, it reminds attending physicians of the importance of better treatment compliance. In this regard, hospitalized patients with AHF can be good candidates, because they can acclimatize to PAP treatment during hospitalization, and the medical staff can support the initial use of PAP a few days following the start of PAP treatment [28]. In the present study, we adopted the median value of the average nightly usage during the entire period as the cutoff for CPAP compliance. In most studies of patients without HF measuring compliance with PAP treatment, the average nightly usage of PAP is approximately 4 h, which is comparable with that of other studies. The result of the time-dependent model in the multivariable analysis considering the alternation in PAP usage during the entire period showed that longer nightly usage of PAP was associated with better clinical outcomes. Thus, an association between compliance status and prognosis among AHF-associated patients with SDB should be emphasized.

This study had some limitations. First, this was an observational study, and unknown confounders might have affected the prognosis even after multivariable analysis; thus, the findings need to be formally tested to confirm the causal relationship. Second, because the application of PAP treatment was non-randomized, it is difficult to rule out selection bias; therefore, motivation to receive PAP treatment may have biased the results. In addition, selection of PAP type, CPAP, or ASV, which was based on the patient's personal decision or attending physicians' decisions, might have influenced the results. Third, because we excluded HF patients with preserved ejection fraction, the results of our study are not applicable in HF patients with preserved ejection fraction. Fourth, the small number of clinical events, which was related to the small number of subjects, resulted in limited statistical power for the detection of differences in outcomes between the two groups. In particular, the low event rate in the analysis regarding the relationship between compliance status and clinical outcome should be interpreted with caution.

Conclusions

In hospitalized patients following AHF in association with LV systolic dysfunction, the presence of untreated SDB was associated with an increased risk of mortality or readmission due to HF exacerbation. This increased risk may be reversible with PAP treatment, and the prognosis is better among patients with more compliance to PAP.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00392-021-01969-x.

Acknowledgements We are indebted to Nanako Shiroshita, Mitsue Kato and Fusae Kawana for scientific advice.

Author contribution SI contributed to this manuscript. Study design: SI and TK. Data collection: authors. Data analysis and statistical analysis: SI and TK. Manuscript draft: SI and TK. Critical revision, editing, and approval of the final manuscript: all authors. SI, TK, HD, and TM are responsible for the overall content as guarantors.

Funding This study is partly supported by a Grant-in-Aid for Scientific Research (Grant Number, 26507010); JSPS KAKENHI (Grant Number, JP17K09527); JSPS KAKENHI (Grant Number, JP18K15904); a grant to The Intractable Respiratory Diseases and Pulmonary Hypertension Research Group from the Ministry of Health, Labor and Welfare (20FC1027); a grant from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) Program for the Strategic Research Foundation at Private Universities, 2014–2018, Japanese Center for Research on Women in Sport, Juntendo University, Project for Fostering, Survey Research for the Strategic Strengthening of Female Athletes 2017–2018 by the Japan Sports Agency. These funding sources did not play any other role in this study.

Declarations

Conflict of interest Dr. S. Ishiwata, Dr. T. Kasai, Dr. A. Sato, Dr. Y. Matsue, and Dr. R. Naito are affiliated with a department endowed by Philips, ResMed, and Fukuda Denshi. Dr. T. Kasai is affiliated with an endowed department by Paramount Bed. Dr. Y. Matsue received an honorarium from Otsuka Pharmaceutical Co. and Novartis Japan, and received research funds from Otsuka Pharmaceutical Co. and Pfizer Japan Inc. Dr. H. Daida reports research grants from CANON MEDICAL SYSTEMS CORPORATION, Philips Japan, Ltd., TOHO HOLDINGS CO., LTD., ASAHI KASEI CORPORATION, Inter Reha Co., Ltd., scholarship grants from Nippon Boehringer Ingelheim Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K., MSD K.K., Daiichi-Sankyo Company, Limited, Pfizer Co., Ltd., Mitsubishi Tanabe Pharma Corp., Astellas Pharma Inc., Takeda Pharmaceutical Co. Ltd., TEIJIN PHARMA LTD., Shionogi & Co. Ltd., Actelion Pharmaceuticals Ltd., Actelion Ltd., KOWA Pharmaceutical Company Ltd., Bayer Yakuhin, Ltd, lecture fees from Amgen Inc., Daiichi-Sankyo Company, Ltd., KOWA Pharmaceutical LTD., MSD K.K.

Ethics approval The Institutional Review Board of the Juntendo University Hospital approved the study protocol (871).

Informed consent The study complied with the Declaration of Helsinki. Informed consent was obtained from all patients.

Consent to publish Consent to publish was obtained.

Consent to participate All study participants provided informed consent.

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