

The impact of positive airway pressure on cardiac status and clinical outcomes in patients with advanced heart failure and sleep-disordered breathing: a preliminary report

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Received: 4 July 2010 / Revised: 3 September 2010 / Accepted: 22 September 2010 / Published online: 2 October 2010
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Abstract

Introduction Heart failure (HF) is a major public health problem associated with high rates of morbidity and mortality. Patients with HF exhibit a high prevalence of sleep-disordered breathing (SDB). We have investigated the long-term impact of positive airway pressure (PAP) therapy on heart function and clinical outcomes in patients with advanced HF and concomitant SDB.

Materials and methods We assessed 18 patients with advanced HF (New York Heart Association (NYHA) functional classification III–IV) and concomitant SDB (diagnosed with polysomnography) either of obstructive or central type. Eleven patients who received PAP therapy (auto-titrating PAP or adaptive servo-ventilation) for 12 months were compared with seven patients who refused this therapy. All participants were assessed at both baseline and end of follow-up for NYHA functional status, left and right ventricular function, neurohormonal activation, and exercise tolerance. The rates of hospitalization, deaths, and the combination of both were also recorded.

Results Patients treated with PAP achieved better functional status, higher left ventricular ejection fraction, improved longitudinal right ventricular contractile function, lower

levels of b-type natriuretic peptide, and greater exercise performance compared to those who remained untreated. PAP-treated group had a significantly lower incidence of the prespecified combined end-point (i.e., hospital admissions and death) than the control group (87.5 vs. 18.2%, $p=0.013$). Interestingly, the mortality rate was 28% (two out of seven patients) in the control group, while no deaths were recorded in the PAP-treated group.

Discussion In this preliminary study, we found that treatment of SDB, irrespective of type, in stable patients with advanced HF receiving optimal medical therapy was associated with improvement in cardiac functional status, ventricular contraction, physical performance, and neurohormonal status, leading to better clinical outcomes.

Keywords Heart failure · Sleep-disordered breathing · Positive airway pressure therapy · Cardiac status · Clinical outcome

Introduction

Heart failure (HF) is a common clinical entity with increasing prevalence and high rates of morbidity and mortality [1, 2]. Repeated admissions and excessive use of health care resources are major concerns linked to HF since advances in medical therapy have only partially improved the clinical outcomes in HF patients [3].

It has been recognized that sleep-disordered breathing (SDB) presenting either as obstructive sleep apnea (OSA) or central sleep apnea (CSA) with or without Cheyne–Stokes respiration (CSR) is common in patients with HF with the former described in 11–40% and the latter in 25–40% of chronic HF patients [4–7]. Both types of SDB have been related to poor prognosis in HF syndrome and may

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lead to progression of the disease through several pathophysiological pathways, such as intermittent hypoxia, increased sympathetic activity, endothelial dysfunction, oxidative and inflammatory stress, or coagulopathy [8–10].

Treatment of SDB has recently emerged as a novel treatment modality in patients with end-stage HF [11]. Several studies have shown short-term improvement of heart function after treatment with various forms of positive airway pressure (PAP), such as continuous positive airway pressure (CPAP), bi-level pressure or adaptive servo-ventilation (ASV), in both types of SDB [11, 12]. Especially in the presence of CSR, the use of ASV has been shown to be the most effective mode of treatment of CSA in HF patients [13]. Auto-titrating positive airway pressure (APAP) is a mode of PAP therapy of OSA with similar efficacy to fixed pressure CPAP and associated with better compliance of patients to therapy [14, 15]. However, it has not been extensively investigated in HF patients [16, 17]. Moreover, there is not enough evidence currently available concerning the long-term effects of SDB treatment on cardiac status and the quality of life in HF patients, thus preventing the routine referral of these patients to sleep centers for the evaluation and treatment of SDB [12].

In this study, we investigated the long-term impact of positive airway pressure therapy (APAP or ASV) on heart function and clinical outcomes in patients with advanced HF irrespective of the type of SDB.

Materials and methods

Patients and study design

This is a prospective, non-randomized investigation in a tertiary hospital setting. Eligible patients were those with chronic HF aged between 18 and 80 years, with ejection fraction (EF) below 40% and functional class III or IV according to the New York Heart Association (NYHA) criteria. All patients were clinically stable for at least 3 months and were receiving maximal medical therapy according to the current chronic HF guidelines [18]. Exclusion criteria included HF from other cause than ischemic or dilated heart disease, unstable angina, myocardial infarction in the previous 6 months, severe valvular heart disease, neurological disorders, lung diseases requiring supplemental oxygen therapy, hospitalization in the last 3 months for HF decompensation, and known uncontrolled malignancy. All eligible patients were recruited for evaluation of concomitant SDB in the sleep laboratory irrespective of clinical symptoms related to sleep apnea. Patients who were diagnosed as having SDB (with either predominant obstructive or central respiratory events) were assigned to treatment with APAP in the case of predomi-

nant OSA, or with ASV in the case of predominant CSA either with or without CSR. Patients who refused to receive PAP therapy after detailed explanation of the method were shifted into the control group (Fig. 1), whereas subjects who were non-compliant with therapy were excluded from the final analysis.

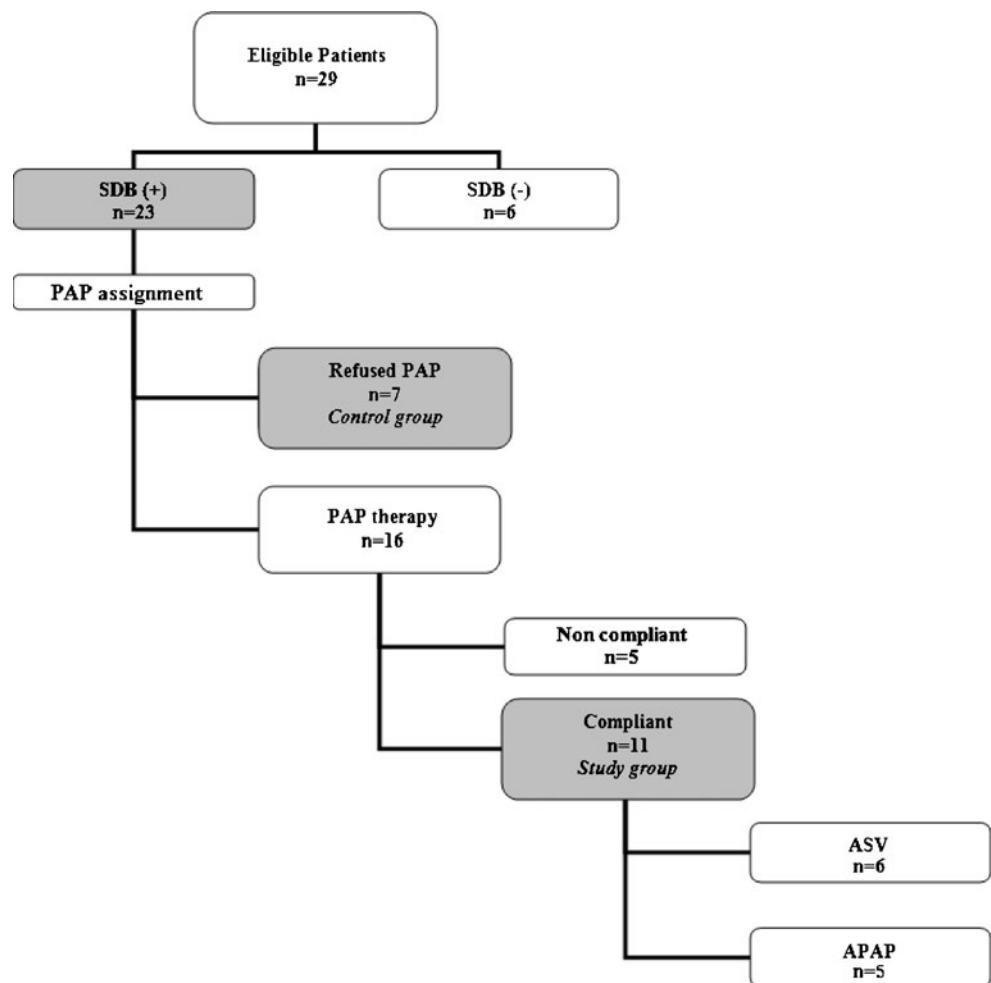
Between February 2006 and December 2008, 29 patients were eligible according to inclusion criteria. Among them, six did not have any kind of SDB while 23 patients were diagnosed as having predominant OSA or predominant CSA/CSR. Seven patients who refused PAP therapy after a 2-week trial of therapy were treated only with optimal medical therapy and classified as the control group. Reasons of refusing therapy were the development of mask claustrophobia, discomfort and no subjective perception of improvement. Among patients who agreed to receive PAP therapy (i.e., 16), two were lost from follow-up and, hence, were excluded from analysis along with three patients who did not have good compliance to therapy. Finally, our study population consisted of 18 patients (13 men, aged 68.9 ± 10.19 years) with 11 of them receiving PAP therapy (six patients on ASV and five on APAP) along with optimal medical therapy, and the remaining seven patients (control group) receiving optimal medical therapy only (Fig. 1).

At baseline all patients enrolled, underwent thorough clinical evaluation and laboratory tests including conventional echocardiography and Doppler tissue imaging (DTI) study, comprehensive full night polysomnography (PSG), 6-min walking test (6-MWT), b-type natriuretic peptide (BNP) measurement, and standard blood tests. Follow-up was repeated every 2 months over a period of 12 months. Bimonthly follow-up included cardiological clinical examination and clinical evaluation of HF symptoms, adjustment of medical therapy as needed and assessment of compliance to PAP treatment by using data downloaded from APAP or ASV devices. Adequate compliance was defined as use of the device more than 4 h per night on at least 70% of nights of the follow-up period. Deaths and hospitalizations due to decompensation of HF during the observation period were also recorded. Patients admitted and discharged alive were categorized as a hospitalization, whereas those that died in the hospital as a death. After 12 months all baseline laboratory tests were repeated.

The study was approved by the ethics committee of our institution and patients signed a written informed consent before inclusion in the study.

PSG and PAP therapy

Full overnight PSG according to standard techniques included monitoring of central and occipital channels of electroencephalogram (C4-A1, C3-A2, O1-A2, and O2-A1), electrooculogram, and submental and anterior electromyograms.

Fig. 1 Patient recruitment flow diagram

Electrocardiogram and heart rate were monitored using the standard limb leads. Airflow was detected by monitoring airflow through a thermistor and a nasal pressure transducer. Respiratory efforts were monitored with piezoelectric transducers placed around the chest and abdomen. Arterial oxygen saturation (SaO₂) was measured continuously by pulse oximetry using a finger probe. Body position was assessed with a body position sensor. All variables were recorded on a computerized system (Alice 5; Healthdyne; Marietta, GA).

PSG recordings were manually scored over 30-s periods, according to the current (2007) guidelines of the American Academy of Sleep Medicine [19, 20]. Apnea was defined as the reduction in airflow of $\geq 90\%$ of baseline, lasting for at least 10 s. It was classified as an obstructive apnea when associated with the presence of an inspiratory effort, as central apnea in the absence of an inspiratory effort, or, as mixed apnea if inspiratory effort was absent in the initial part of the event and present at the final part. Hypopnea was defined as the reduction in baseline airflow of $\geq 30\%$ with a $\geq 4\%$ desaturation, lasting for at least 10 s. The apnea/

hypopnea index (AHI) was calculated as the number of apnea and hypopnea events per hour of sleep. Clinically significant OSA was defined as an AHI > 10 events per hour. CSA/CSR was diagnosed when the AHI was > 10 and central apneas represented more than 70% of the respiratory events with the presence of CSR (characteristic pattern of periodic crescendo–decrescendo in airflow amplitude). PSG scoring was made by the same sleep technician under the supervision of an experienced physician in sleep medicine who was responsible for the interpretation of the sleep studies.

Patients diagnosed with SDB underwent a second night of full PSG for application of PAP therapy using an APAP or ASV device. Patients with predominant OSA were offered an APAP device which automatically adjusts the therapeutic pressure based on a titration algorithm. The monitoring of the efficacy of treatment was supervised by a sleep technician in order to avoid excess pressure delivery, and thus, preventing the appearance of PAP-induced central events which would be undesirable in HF patients. The settings of APAP were between 5 and 8 cmH₂O for minimum pressure and 10–14 cmH₂O for maximum

pressure. Patients with predominant CSA/CSR were offered ASV after manually titration of therapeutic pressures. On ASV, the end-expiratory pressure was set at 4–8 cmH₂O in order to eliminate obstructive events, minimum support was set at 4 cm H₂O and maximum support at 10 cm H₂O using a device that automatically tracks the respiratory rate of patient under monitoring of heart rate and blood pressure. The target was to reduce the AHI < 10 and eliminate CSR.

All patients assigned to PAP therapy underwent an initial daytime education on PAP treatment before the second PSG and offered a 2-week trial period before inclusion in the study. They were instructed to use their PAP device at least 6 h per night and support was provided by the sleep laboratory personnel in case of any problems throughout the study period. Compliance with PAP therapy was evaluated by downloading usage data from the PAP devices.

Echocardiographic methods

1. Standard transthoracic examination

Conventional echocardiographic examination was performed early in the morning with a commercially available imaging system (SSA-380A Toshiba Powervision-Japan) using a 2.5-MHz phased array transducer employing second harmonic imaging. All studies were performed and interpreted by the same experienced physician who had Level 3 echocardiographic training as defined by the American College of Cardiology/American Heart Association [21], and was unaware of the patients' subgroup. Left ventricular ejection fraction (LVEF) was assessed with the biplane Simpson's method using conventional apical 4- and 2-chamber views. Using conventional pulse wave Doppler, the peak early velocity (E) of the transmitral flow was measured. The two-dimensional echocardiographic study of the RV was performed from the four-chamber view, and the following parameters were measured at end-diastole: Tricuspid annular diameter was measured between the hinge points of the leaflets with the lateral wall and the septum (RVD₁). Mid-cavity diameter was also measured at the 4-chamber view (RVD₂). Pulmonary artery systolic pressure (PASP) was determined using the modified Bernoulli equation ($P = 4 \times V^2 + \text{right atrial pressure}$). The use of the inferior vena cava size and dynamics was applied for estimation of the right atrial pressure [22].

2. Pulse wave DTI study

After establishing the resting baseline measurements, a pulse wave DTI study was accomplished, as previously described [23, 24]. From the apical four-chamber view a 5 mm pulsed Doppler sample volume for DTI was positioned just apical to the RV free wall at the level of the tricuspid valve. Every effort was made to obtain a Doppler angle of incidence close to 0-

degrees between the interrogating Doppler beam and the longitudinal motion of the RV, to adjust the sample volume size proportionally to annular motion and to obtain recordings at end-expiratory apnea. The peak systolic myocardial velocity at the tricuspid level (SmRV) was measured. Moreover, the average peak early diastolic velocity (E') from the septal and lateral mitral annulus was recorded. The value assigned to each parameter was the average of five cycles. In addition, the ratio E/E' was also calculated.

B-type natriuretic peptide

Venous blood for BNP measurement was drawn and was immediately analyzed using Triage[®] System for BNP (Biosite diagnostics, La Jolla, CA, USA), a test based on fluorescence immunoassay. This test has a range of 5–5,000 pg/mL, with an average 95% analytical sensitivity of 0.2–4.8 pg/mL. Coefficients of variation are 10.1%, 12.4%, and 16.2% for mean values 28.8, 584.4, and 1,080.4 pg/mL. The median value of three consecutive readings of the same test device was used for the final analysis.

Six-minute walking test

The 6-MWT was performed to evaluate clinically the functional status of HF patients according to a standardized test procedure [25]. In brief, patients were asked to walk around a walking track for 6 min and the distance covered was measured. The test was self-paced, and the patient was allowed to rest if needed.

Statistical analysis

Continuous variables are expressed as the mean \pm SD or medians (interquartile range) for skewed data and categorical variables as percentages. Comparisons of the continuous variables between groups were made using the *t* test or Mann–Whitney *U* statistical test, as appropriate. Associations between two categorical variables were tested by the chi-square test. All tests were two-tailed, and $p < 0.05$ was considered significant. Statistical analysis was performed with Statistical Package for Social Sciences software (release 15.0, SPSS, Inc., Chicago, Illinois).

Results

Patients' characteristics-PSG study

The demographic characteristics and PSG findings of the patients enrolled are shown in Table 1. As shown in the

Table 1 Demographic characteristics and baseline polysomnographic features in PAP-treated and control patients

Variable	PAP (n=11)	No PAP (n=7)	p value
Age (years)	67.6±12	71.3±6	0.49
Weight (kg)	80.6±26	64.8±10	0.24
Height(m)	1.65±0.08	1.68±0.05	0.42
Ischemic CM (n)	6	4	0.91
Dilated CM (n)	5	3	0.91
BMI (kg/m ²)	29.5±9	22.7±3	0.15
Central apneas ^a	42 (0–111)	27 (8–73)	0.91
Obstructive apneas ^a	29 (5–40)	8.5 (0–11)	0.056
Mixed apneas ^a	3 (0–17)	6 (1–13)	0.72
Hypopneas ^a	55 (6–74)	49 (13–98)	0.80
AHI (events/h)	30.3±14	20.8±13	0.19
Mean SaO ₂ (%)	90.9±2.5	92.5±1.7	0.19
TST<90% ^a (%)	2.3 (0.2–15.1)	0.9 (0.2–2.8)	0.22

BMI body mass index, AHI apnea/hypopnea index, SaO₂ oxygen saturation, TST<90% the percentage of total sleep time with SaO₂<90%, CM cardiomyopathy

^a Median value of total respiratory events per night and of TST<90%

latter table no statistically significant differences were detected between treatment and control group regarding age, weight, height, and body mass index. Comparison of PSG findings between the two groups showed that PAP-treated group had a marginally greater number of obstructive respiratory events than the control group ($p=0.056$). No significant differences between groups were found for the rest of the variables assessed.

The mean nightly usage of PAP therapy was 4.5 ± 1.3 h per night at the end of follow-up period (i.e., 12 months) without a significant difference between those who used APAP and ASV. Eight out of 11 patients (i.e.73%) were compliant with treatment as defined by use of PAP more than 4 h during more than 70% of nights. Patients with mean usage of less than 2 h or use in less than 50% of nights were excluded from the final analysis.

Evaluation of cardiac status

1. Baseline data

As shown in Table 2 baseline evaluation showed no significant differences between the two groups in the NYHA class ($p=0.59$), LVEF ($p=0.26$), and echocardiographic findings. Similarly, BNP values as well as the distance covered in the setting of 6-MWT did not differ between groups.

2. Twelve-month data

In contrast to the baseline data at the end of the follow-up period (i.e., at 12 months), a statistically significant difference in NYHA functional class was

observed in PAP-treated vs. non-treated patients ($p<0.001$, Table 2) along with a better performance in the 6-MWT (<0.001) in comparison to control subjects. In addition, the PAP-treated patients had a significant increase in LVEF when compared with untreated patients ($p=0.033$). Interestingly, longitudinal RV contractile function, as detected with DTI and expressed by SmRV was significantly improved ($p<0.001$). This is probably attributed to the significant reduction of the RV afterload (as reflected by PASP estimation). No significant differences regarding RV dimensions were observed between the two groups. Moreover, myocardial wall stress and LV filling pressures were both decreased, as assessed by BNP the former ($p=0<001$) and E/E' ratio the latter, which was decreased though marginally ($p=0.046$).

3. Impact of PAP therapy on cardiac clinical status

When data of PAP-treated patients were separately analysed significant improvements were detected in almost all parameters measured at the end of the study as compared with the baseline measurements. Left ventricular EF increased by approximately 16% ($p<0.001$), the distance covered in 6-MWT increased by 10% ($p<0.001$) and NYHA class was substantially improved (2.0 ± 0.1 post-PAP vs. 3.4 ± 0.5 pre-PAP, $p<0.001$). Myocardial wall stress and LV filling pressures (LVFP) decreased

Table 2 Baseline and 12-month values of the parameters assessed in PAP-treated and control patients

Variable	PAP (n=11)	No PAP (n=7)	p value
NYHA class pre	3.4±0.5	3.6±0.7	0.59
NYHA class post ^a	2.0±0.1	3.6±0.7	<0.001
LVEF pre (%)	29.5±6	26.5±4	0.26
LVEF post (%)	34.7±	26±4	0.033
E/E' ratio pre	10.2±3	11.4±3	0.54
E/E' ratio post	7.0±0.9	10.9±3.1	0.046
RVD ₁ pre (mm)	31.8±3	34.8±3	0.15
RVD ₁ post (mm)	33.4±3	35.2±2	0.21
RVD ₂ pre (mm)	33.7±4	37.6±2	0.10
RVD ₂ post (mm)	35.4±2.5	38±2.3	0.08
PASP pre (mmHg)	43±10	43±7	0.99
PASP post (mmHg)	36±6	48±10	0.009
SmRV pre (cm/s)	10±1.5	8.7±1.2	0.11
SmRV post (cm/s)	11.1±0.8	7.1±0.5	<0.001
6-MWT pre (m)	447.5±37	419.5±22	0.14
6-MWT post (m)	488±20	408±20	<0.001
BNP pre (pg/ml)	504±72	568±57	0.11
BNP post (pg/ml)	446±76	595±43	<0.001

Pre baseline measurements, post 12-month data. See “Materials and methods” section for abbreviations and definitions of the parameters assessed

both, as it was estimated by BNP values and E/E' ratio reductions ($p=0.001$ and 0.009 , respectively). Regarding the right ventricle (RV), a significant improvement ($p=0.012$) was noticed in the longitudinal contractile function as measured by SmRV ($p=0.012$), along with a decrease ($p=0.004$) in PASP. It is of note that a trend for both RV diameters reduction was seen ($p=0.063$ for RVD_1 and $p=0.056$ for RVD_2).

4. Hospitalizations and mortality

Two patients (18.2%) in the PAP-treated group in comparison with four (57.1%) in the control group were hospitalized due to HF decompensation over the study period ($p=0.101$, see Table 3). Regarding mortality, two cardiac deaths were recorded in the control group (~28%) and none in the PAP group ($p=0.137$). Both deaths were in-hospital 4 and 8 months, respectively, after patients' inclusion in the study, and were attributed to intractable pump failure. When hospitalizations and deaths were combined as a composite end-point, PAP-treated group showed a significantly lower incidence of unfavorable outcomes (18.2% vs. 85.7%, $p=0.013$).

Discussion

In this investigation we showed that PAP therapy for SDB of any type (obstructive, central or both) in stable patients with advanced HF resulted in a significant and sustained improvement of cardiac and functional status, less neuro-hormonal activation and fewer hospital admissions and deaths over a 12-month period.

SDB in HF might be manifested as either OSA or CSA with or without CSR. The predominant type of SDB in each patient depends on the degree of obesity and the severity of HF. The prevalence of OSA may be higher in obese patients or in those with less severe HF, whereas CSA is more common in those with more severe HF and worse functional status [26, 27]. Our findings confirm the high prevalence of SDB in advanced HF as ~80% (i.e., 23 out of 29) of patients had SDB.

There is evidence supporting that SDB is associated with increased mortality and morbidity in HF patients although this finding has not been confirmed in all relevant studies.

Untreated OSA (AHI>15) in patients with HF has been associated with increased death rates independently of confounding factors and an approximately 2-fold higher risk for death and hospitalizations over 2 years [28, 29]. However, it seems that increased risk is confined in patients with ischemic and not in HF of other etiologies [30]. Regarding the prognostic role of CSA/CSR in HF there is also evidence that central apnea may increase mortality independently of other risk factors although, even in this case, the findings are disparate [31, 32]. CSA/CSR has been associated with increased morbidity, death, and rates of cardiac transplantation whereas CSR, when present, tends to imply a worse prognosis [33–36].

The relative lack of consistency in studies investigating the impact of SDB in clinical outcomes of HF might be due to differences in methodology and duration of follow-up, definitions and severity of SDB, and differences in the etiology, severity or medical treatment of HF. To our knowledge this is the first study to evaluate in patients with advanced HF and concomitant SDB of either type, the long-term impact of PAP therapy on cardiac status and clinical outcome. Despite the small number of participants (as this is a preliminary report) a significantly lower incidence of hospital admissions and mortality ($p=0.013$) was detected at the end of the 12-month follow-up period in the group of PAP-treated patients.

In patients with HF and OSA, CPAP has been regarded as an effective therapy not only for OSA but also for the underlying HF in short-term investigations that showed improvement of LVEF, NYHA class, and quality of life [37–40]. APAP which is an alternative mode of PAP application in OSA patients, has been found to be equally effective to CPAP and has been linked with enhanced compliance to treatment [15]. However, the effects of APAP in HF patients have not been thoroughly investigated. A recent study, in patients with HF and OSA, found that APAP improved subjective sleepiness after 6 weeks but had no effect on cardiac functional status during this short-term period [16]. Thus, there is lack of studies evaluating the long-term effects of CPAP or APAP therapy on heart function. Concerning treatment of CSA (with or without CSR) in HF patients, several forms of PAP therapy including CPAP, bi-level pressure support and the novel ASV have been used [13, 41, 42]. In short-term randomized studies it has been shown that CPAP improves LVEF in patients with CSA especially in the presence of CSR but, according to other trials, this is true for only a minority of patients [35, 43–46]. Thus, the use of CPAP is not widely recommended since there is no evidence of improving long-term mortality and there are cautions for possible adverse effects in non-responders [41, 45, 47]. Concerning ASV, it has been found to be superior to CPAP in eliminating CSA/CSR in HF patients, improving LVEF, functional status,

Table 3 Mortality and hospitalization rates in the groups studied

Variable	PAP ($n=11$)	No PAP ($n=7$)	p value
Deaths	0	2 (28.6%)	0.137
Hospitalizations	2 (18.2%)	4 (57.1%)	0.101
Combined events	2 (18.2%)	6 (85.7%)	0.013

quality of life, exercise tolerance, and enhancing compliance [13, 44, 48–50]. ASV treatment had a favorable impact on cardiac function, functional status, exercise tolerance and quality of life after 6 months [49, 51]. However, long-term benefit on mortality has not yet been proven.

In the present study, the choice of the most appropriate mode of ventilation for each patient was based on the prominent type of SDB. Thus, we offered APAP for patients with OSA, and ASV for those with CSA/CSR. In this specific population of stable patients with advanced HF and SDB of any type, we found that PAP therapy improved cardiac and functional status. We wish to emphasize that improvement of heart function was sustained for 12 months. Good compliance to PAP therapy seems to be the most important key of effective therapy and sustained benefit from PAP in HF. We adopted a close follow-up schedule (bimonthly) with aim to evaluate and enhance compliance in all patients providing adequate education and support by authorized and trained personnel.

In this investigation, we also sought to assess the impact of PAP therapy in less investigated parameters, such as E/E' ratio, a simple non invasive measurement that predicts LVFP [52, 53]. Previous studies have shown that $E/E' < 8$ accurately predicts normal LVFP, whereas $E/E' > 15$ identifies increased LVFP [53]. We found that E/E' ratio was significantly decreased over 12 months ($p=0.009$) to a value suggestive of low LVFP (7.0 ± 0.9), demonstrating an important mechanism of beneficial effect of PAP on LV function. In line with this finding and with previously published data, treatment with PAP was associated with significantly lower BNP values at the end of the study [54]. BNP reflects neurohormonal activation which constitutes an important pathophysiologic mechanism leading to HF syndrome and has been introduced as a tool for the diagnosis and management of HF, in terms of effectiveness of therapy [24]. The modification of neurochemical profile in HF patients by PAP may explain improvement of clinical outcomes. We wish to stress that neither E/E' ratio nor BNP changed throughout the study in the control group. Another remarkable finding of this study is related to RV systolic function which has not been evaluated in detail in HF patients receiving PAP therapy. Although successful treatment of OSA has been shown in a study to improve RV function no data are available for HF patients with SDB [55]. Hence, our finding of longitudinal RV contractile function improvement (as detected with DTI and expressed by SmRV) earns particular importance. Furthermore, along with RV systolic function improvement a significant decrease of the PASP with PAP therapy was found. This may be due to a better LV performance as reflected by LVEF improvement, decreased LVFP and less neurohormonal activation. PAP application has been also shown to reduce pulmonary arterial systolic

pressure levels by restoring the normal levels of vasoactive mediators, thus aborting vasoconstriction and endothelial cell proliferation [56]. Nevertheless, further investigations of RV function in patients with HF and SDB are certainly needed.

Finally, in our study population, a statistically significant improvement in the 6-MWT covered distance (by ~40 m) was noticed in the PAP-treated group. As it has been shown in previous studies, 6-MWT is an integral element of the functional capacity assessment and prognosis in patients with chronic cardiopulmonary disease [57].

The effect of PAP therapy on functional capacity along with its favorable effects on several other parameters above reported contributed in a dissociation of the subgroups assessed regarding clinical status, cardiac function and, most importantly, clinical outcomes. Indeed, no deaths and fewer hospital admissions were recorded in the PAP-treated patients as compared to the control group. The difference was significant ($p=0.013$) when deaths and hospitalization rates were examined in combination.

Study limitations

Some study limitations should be considered in the interpretation of our results. The most important is related to the small number of participants. However, the limited sample size did not prevent us from reaching statistically significant results. Certainly, randomized multicenter studies are needed to confirm our findings.

Secondly, this is a non-randomized study with the control group including patients who refused PAP therapy. Although someone could consider that the latter patients were less compliant to medical advice, we made every possible effort to control their adherence to medical treatment through a close follow-up.

Conclusion

This prospective study demonstrated that treatment of SDB with PAP therapy in patients with advanced HF, irrespective of SDB type, leads to a sustained (12 months) improvement in cardiac function, physical performance, neurohormonal activation, and decreased morbidity and mortality. Physicians should closely evaluate patients' compliance which might be a crucial factor for the accomplishment of the best possible results. Our preliminary data firmly support the routine investigation and treatment of SDB in patients with advanced HF.

Conflicts of interest The authors declare they have no conflicts of interest

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