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Original Article

Treatment of sleep apnea in chronic heart failure patients with auto-servo ventilation improves sleep fragmentation: a randomized controlled trial

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ABSTRACT

Background: Impaired sleep efficiency is independently associated with worse prognosis in patients with chronic heart failure (CHF). Therefore, a test was conducted on whether auto-servo ventilation (ASV, biphasic positive airway pressure [BiPAP]–ASV, Philips Respironics) reduces sleep fragmentation and improves sleep efficiency in CHF patients with central sleep apnea (CSA) or obstructive sleep apnea (OSA).
Methods: In this multicenter, randomized, parallel group trial, a study was conducted on 63 CHF patients (age 64 ± 10 years; left ventricular ejection fraction 29 ± 7%) with CSA or OSA (apnea–hypopnea Index, AHI 47 ± 18/h; 46% CSA) referred to sleep laboratories of the four participating centers. Participants were randomized to either ASV ($n = 32$) or optimal medical treatment alone (control, $n = 31$).
Results: Polysomnography (PSG) and actigraphy at home (home) with centralized blinded scoring were obtained at baseline and 12 weeks. ASV significantly reduced sleep fragmentation (total arousal index$_{PSG}$: −16.4 ± 20.6 vs. −0.6 ± 13.2/h, $p = 0.001$; sleep fragmentation index$_{home}$: −7.6 ± 15.6 versus 4.3 ± 13.9/h, $p = 0.003$, respectively) and significantly increased sleep efficiency assessed by actigraphy (SE$_{home}$) compared to controls (2.3 ± 10.1 vs. −2.1 ± 6.9%, $p = 0.002$). Effects of ASV on sleep fragmentation and efficiency were similar in patients suffering from OSA and CSA.
Conclusions: At home, ASV treatment modestly improves sleep fragmentation as well as sleep efficiency in CHF patients having either CSA or OSA.

1. Introduction

Chronic heart failure (CHF) affects 1–2% of the adult population and prevalence increases up to 4–16% in patients over 55 years [1–4]. Central sleep apnea (CSA) and obstructive sleep apnea (OSA) are reported in 25–40% and 49–72% of CHF patients, respectively [5–8]. Patients with CHF have a significantly shorter sleep duration and reduced sleep efficiency (SE) assessed by polysomnography (PSG) when compared with individuals from a community sample whether or not they have OSA [9]. Two reasons justify the use of sleep fragmentation and sleep as treatment targets in CHF patients with sleep-disordered breathing (SDB): (1) patients with CHF have poor SE, and SE assessed by PSG is a strong predictor for mortality in CHF patients, independent of other known risk factors for mortality [10]. (2) High SE early after initiation of continuous positive airway pressure (CPAP) in patients with OSA without known heart disease is an important factor in determining their subsequent use of this treatment modality [11,12].

In patients with CHF, it is often difficult to manage concomitant sleep disorders such as insomnia, periodic limb movement disorder, sleep disturbances either as a consequence of depression or due to the presence of CHF per se in patients with CHF [13,14]. Therefore, CSA or OSA, which can be treated with positive

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airway pressure (PAP), are promising targets for improving sleep fragmentation and sleep quality in CHF [15].

It remains unclear if treatment of CSA with PAP in patients with CHF can improve sleep fragmentation and sleep quality. In patients with OSA having normal cardiac function, PAP therapy leads to a significant reduction of sleep fragmentation and an increase of the time in sleep stage N3 as well as rapid eye movement (REM) sleep [16]. The effects of PAP therapy on sleep structure in CHF patients having sleep apnea, especially with CSA, are rather unclear. Only a few randomized studies address this issue in patients with CHF and CSA and/or OSA. In the largest trial, a subanalysis of the CANPAP study with 205 HF patients, the effects of CPAP on CSA were determined. Apnea–hypopnea index (AHI) was significantly reduced, but neither arousal frequency nor sleep structure changed significantly [17]. On PSG assessment, studies of autoservo ventilation (ASV) in CHF patients with CSA and/or OSA report conflicting effects on sleep fragmentation and sleep quality. While two studies reported a reduction of arousal frequency and restoration of sleep structure within the first night of ASV treatment in CHF patients with CSA [9,18], another study showed that treatment of CSA with ASV in CHF patients significantly improved CSA and OSA, but had no effect on arousal frequency [19]. In these studies, sleep quality was assessed by PSG in a sleep laboratory when CPAP or ASV were used throughout a single night. This does not reflect the time of use of the PAP device and effects on sleep fragmentation and SE at home over a longer period of time.

A test was conducted to see if ASV (biphasic positive airway pressure (BiPAP)–ASV, Philips Respironics) reduces sleep fragmentation and improves SE as assessed by in-laboratory PSG and also home actigraphy in patients with severe CSA or OSA.

2. Methods

2.1. Design and participants

An analysis was conducted in a multicenter, randomized, rater-blinded, open label, parallel group trial (ISRCTN04353156) on the effects of ASV on arousals, sleep efficiency, and sleep stages (assessed by PSG) and sleep fragmentation and sleep efficiency (assessed by actigraphy). Such analyses were not prespecified. The prespecified primary and secondary outcomes of the trial (ISRCTN04353156) were previously published [20]. Patients with CHF and SDB were found to have reduced NT-proBNP levels on ASV, but an improvement in left ventricular ejection fraction (LVEF) or quality of life was not greater than in the control group [20].

The study complies with the Declaration of Helsinki. The protocol was approved by the local ethics committees, and all patients provided written informed consent. Inclusion criteria were a medical history of CHF due to ischemic, nonischemic, or hypertensive cardiomyopathy, age 18–80 years, impaired exercise capacity (New York Heart Association, NYHA, class II or III), impaired LVEF ≤40%, stable clinical status, and stable optimal medical therapy according to the guidelines of the European Society of Cardiology [21] for at least four weeks and an AHI ≥20/h of sleep assessed by in-laboratory PSG [22,23].

Exclusion criteria were unstable angina, myocardial infarction, cardiac surgery, or hospital admissions within the previous three months, New York Heart Association (NYHA) class I or IV, pregnancy, contraindications for BiPAP AutoSV, patients receiving oxygen therapy, severe restrictive and obstructive airways disease, CHF due to primary valve disease, patients awaiting heart transplant, inability or unwillingness to provide written informed consent, and diurnal symptoms of OSA requiring immediate treatment, for example, falling asleep while driving.

2.2. Randomization and intervention

Eligible patients were randomized 1:1, to receive either optimal medical management or optimal medical management plus ASV therapy (BiPAP–ASV, Philips Respironics). Randomization was performed by a computerized schedule in random blocks of four and was stratified by the type of sleep apnea (eg, OSA and CSA) [20]. Details of the initiation of ASV have been described previously [20].

2.3. Outcome measures

2.3.1. Polysomnography

PSG was performed at a screening visit, at ASV initiation, to ensure abolition of the AHI and after a 12-week follow-up. At follow-up, patients in the control group received diagnostic PSG, whereas patients in the ASV group received PSG during ASV treatment [20]. Airflow and thoracoabdominal effort were recorded quantitatively by nasal pressure cannula and respiratory inductance plethysmography [9]. According to standard diagnostic criteria, sleep stages, apneas, hypopneas, and arousals were measured, defined, and scored by two experienced sleep technicians who were blinded to group status. Apneas were defined as absence of airflow ≥10 s (measured reduction of airflow to less than 10% peak 'nominal' airflow). Hypopneas were defined as a ≥50% reduction in airflow from baseline for ≥10 s or with a discernible reduction in airflow, if it was in association with a 4% oxygen desaturation or an arousal. Apneas and hypopneas had to be classified obstructive if out-of-phase thoracoabdominal motion or airflow limitations were present. This study classified mixed apneas as central. AHI was defined as the number of apneas and hypopneas per hour of sleep. Patients with ≥50% of all apneas and hypopneas being central in nature were classified as having CSA. Patients with a proportion <50% of central apneas and hypopneas were classified as having OSA. Arousals were defined as a cortical response to stimulus characterized by at least a 3-s increase in electroencephalogram (EEG) frequency: the appearance of alpha or beta rhythm, an obvious change to an ascending sleep stage, in REM sleep as an increase in submental EMG, or the appearance of a K-complex, regardless of sleep stage. The arousal was classified as a respiratory arousal, when it occurred during or 1 s after an apnea or hypopnea. When the arousal occurred 1 s before or after the leg movement, it was classified as a movement arousal. Total arousals contained respiratory arousals, movement arousals, and spontaneous arousals [24]. For subanalyses of arousals, data from one study site were available ($n = 18$). SE assessed by PSG (SE_{PSG}) was defined as the ratio of total sleep time to time in bed. To ensure quality control, a blinded analysis of each sleep study was centralized and performed by two experienced sleep technicians at the University of Pennsylvania.

2.3.2. Actigraphy

Compared with the "gold standard" PSG in sleep laboratory, wrist actigraphy was shown to be a reliable method to evaluate sleep fragmentation and sleep quality in the patients' natural environment at home [25]. A total of 5 days before therapy titration and during the last seven days of their 12 weeks of therapy, the participants were asked to wear an Actiwatch® (Model AW64; Cambridge Neurotechnology Ltd, Cambridge, UK) on their nondominant wrist . Participants also used the event marker of their Actiwatch® to mark sleep times.

The Actiwatch® measured activity with a piezo-electric accelerometer that recorded intensity, amount, and duration of movement in all directions. All movements over 0.05 g were recorded with a sampling frequency of 32 Hz. Actigraph data from 1-min epochs were collected, and automatic scoring of sleep was performed using a validated algorithm. According to the level of activity in the surrounding 2 min (±2 min), this algorithm analyzed recorded activity counts in