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# Positive airway pressure therapy in heart failure patients: Long-term effects on lung function

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ABSTRACT

*Purpose:* The prevalence of sleep-disordered breathing (SDB) in patients with heart failure (HF) is high. Positive airway pressure (PAP) is first-choice therapy, but recent data indicates that PAP therapy may increase mortality in HF patients with reduced ejection fraction (HF-REF) and predominant central sleep apnea (CSA). This study investigated long-term effects of PAP therapy on pulmonary function, including respiratory muscle strength. All patients underwent multichannel cardiorespiratory polysomnography (PSG) and comprehensive lung function testing at baseline and follow-up (mean 588 ± 43 days).
*Results:* 350 patients (mean age 68 ± 10.7 years, 88% male) were included, inspiratory vital capacity, 3.3 ± 0.9 vs 3.2 ± 0.8 L; forced expiratory volume in 1 s, 2.5 ± 0.7 vs 2.4 ± 0.7 L; lung diffusion capacity, 6.2 ± 1.9 vs 5.9 ± 1.8 mmol/min/kPa; correction for hemoglobin, 1.1 ± 0.02 vs 1.1 ± 0.3 mmol/min/kPa/L; and mouth occlusion pressure, 0.42 ± 0.11 vs 0.4 ± 0.12 kPa.
*Conclusions:* PAP therapy had no negative nor positive impact on lung function, including respiratory muscle strength, in stable HF-REF patients with SDB, and is therefore safe from a respiratory perspective.


## 1. Introduction

Interest in sleep-disordered breathing (SDB) in patients with heart failure (HF) is growing, as strong epidemiological data link SDB and HF (Bitter et al., 2009; Linz et al., 2015; Oldenburg et al., 2007b; Woehrle et al., 2014). In addition, SDB is associated with increased morbidity and mortality in patients with HF (Javaheri, 2005; Javaheri et al., 2007; Jilek et al., 2011; Khayat et al., 2015; Oldenburg et al., 2016; Wang et al., 2007), and with impairment of cardiac function and HF severity. SDB is therefore an important, but still frequently under-recognized, risk factor for poor prognosis in chronic HF patients (Linz et al., 2015; Oldenburg et al., 2007a; Woehrle et al., 2014). There are two major types of SDB, and the occurrence and distribution of sleep apnea type may be dependent on factors such as HF severity and heart rhythm (Fox et al., 2016).

SDB can be treated using positive airway pressure (PAP) therapies (Becker et al., 2003; Linz et al., 2015; Teschler et al., 2001) or implantable devices (Abraham et al., 2015; Fox et al., 2014a,b), which have been shown to provide good suppression of respiratory events (Becker et al., 2003; Linz et al., 2015; Teschler et al., 2001). PAP therapy is considered the standard of care in SDB treatment. In obstructive SDB, continuous PAP therapy is used to keep the upper airways open. In central SDB, adaptive servo-ventilation (ASV) was developed to overcome cessation in breathing occurring as a result of a loss of central respiratory drive. Recently the Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo-Ventilation in Patients with Heart Failure (SERVE-HF) study showed increased mortality in patients treated with ASV therapy, despite effective suppression of respiratory events (Cowie et al., 2015). The reason behind this increased mortality is not yet known. As a result, the influence of PAP therapy on lung function is a topic of lively debate, particularly because literature on this subject is scarce, and conclusive or mechanistic studies are missing, and many unanswered questions remain (Cowie et al., 2015). The hypothesis that PAP therapy might have a negative influence on lung function and diffusion has not yet been thoroughly investigated.

This study determined lung function parameters in HF-REF patients before any treatment of SDB and after long-term PAP therapy and compared the findings with values obtained in a matched control group who did not receive PAP therapy.

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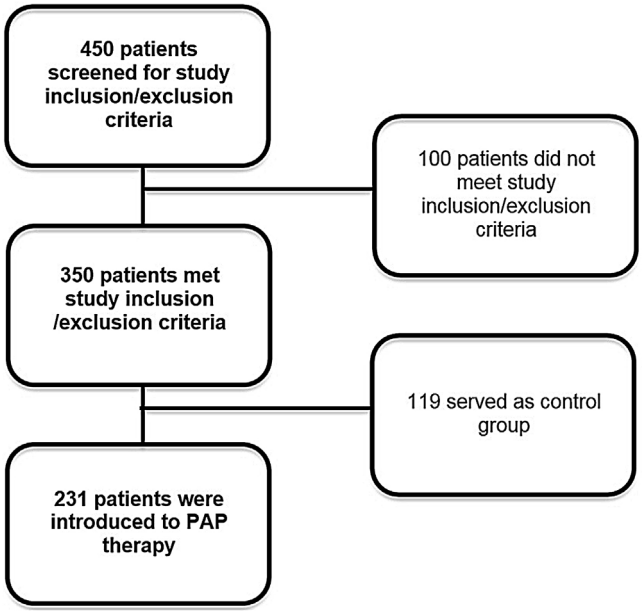


**Fig. 1.** Flow of patients through the study (CONSORT diagram).

## 2. Patients and methods

### 2.1. Study design

This retrospective analysis of prospectively collected data between July 2009 and March 2016, as well as the study protocol, were approved by the institutional ethics committee. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided informed consent prior to inclusion in the study.

### 2.2. Participants

All eligible HF-REF patients presenting with HF to our Academic Medical Center were eligible for inclusion. All study patients underwent SDB screening with polygraphy, and those with an apnea-hypopnea index (AHI) of ≥15/h then underwent full multichannel cardiorespiratory polysomnography (PSG). Inclusion criteria were stable HF-REF with left ventricular ejection fraction (LVEF) ≤45% and medically stable treatment, including indicated device therapy, according to current European Society of Cardiology guidelines (Ponikowski et al., 2016).

Exclusion criteria were acute cardiac decompensation, oxygen therapy, ongoing infections, acute coronary syndrome within 3 months prior to enrollment, active myocarditis, complex congenital heart disease, constrictive pericarditis, chronic hypoxemia (sustained oxygen saturation ≤85%) to exclude severely underlying lung disease or oxygenation dysfunction, including chronic obstructive pulmonary disease [COPD] GOLD stage >II), transient ischemic attack (TIA) or stroke within 3 months prior to enrollment, status post-heart transplant or left ventricular assist device (LVAD) implantation, prescribed inotrope therapy, primary hemodynamically significant uncorrected valvular heart disease, pregnancy, and participation in a pharmaceutical or treatment-related clinical trial within 6 months of study enrollment (Fig. 1).

### 2.3. Assessments

During PSG, nasal airflow (measured by nasal pressure, chest and abdominal effort), pulse oximetry, snoring and body position were continuously recorded. PSG recordings were analyzed by a physician specially trained in SDB and standard definitions were used to describe and score SDB as follows: an apnea was scored if the breathing signal had a reduction in flow of ≥90% for ≥10 s (without any abdominal or thoracic breathing efforts for central sleep apnea [CSA], and with visible ribcage and abdominal respiratory impedance signals for obstructive sleep apnea [OSA]) (Berry et al., 2012). Hypopnea was defined as a ≥30% reduction in flow, lasting ≥10 s and accompanied by a ≥3% drop in oxygen saturation. Patients were classified as having either predominately CSA or OSA. Obstructive hypopnea events were scored if there was snoring during the event, "flattening" of nasal pressure during inspiration and/or paradoxical thoracoabdominal excursions during the event. Hypopneas were scored as central if none of the above criteria were met. The AHI is an established maker of SDB severity and describes the number of episodes of apneas and hypopneas per hour of sleep. SDB severity was graded according to guideline recommendations (Berry et al., 2012) and our clinical routine as mild (AHI ≥5 to <15/h), moderate (≥15 to <30/h) or severe (AHI ≥30/h). Patients with an AHI <5/h were considered to have no relevant SDB and were excluded. The decision on what PAP therapy to use was based on established society recommendations.

All recordings were performed using SomnoMedics PSG equipment (SomnoMedics, Randersacker, Germany). The American Academy of Sleep Medicine (AASM) definition was used in this study; oxygen desaturation index (ODI) referred to the number of ≥3% arterial oxygen desaturations per hour (Berry et al., 2012).

### 2.4. Lung function testing

All enrolled patients underwent full lung function testing using body plethysmography at baseline and follow-up. This included assessment of static and dynamic lung function (including forced vital capacity [FVC], inspiratory vital capacity [IVC], forced expiratory volume in one second [$FEV_1$], ratio of $FEV_1$ to FVC, peak expiratory flow [PEF], mid expiratory flow at 25, 50 and 75% of FVC [MEF25, 50, 75], total airway resistance [RAW] and total lung capacity [TLC], as well lung diffusion capacity [TLCO; transfer factor of the lung for carbon monoxide] and KCO [correction for hemoglobin, based on the method of Cotes (Cotes, 1963) as recommended by the American Thoracic Society, facilitated corrections for altitude, hemoglobin, and carboxyhemoglobin], and mouth occlusion pressure determined 0.1 s [P0.1] after the start of inspiration).

Baseline testing was performed before initiation of SDB therapy in the PAP therapy group. All lung function tests were conducted with the use of KoKo® Px (nSpire Health, Inc., Longmont, CO, USA). Calibration was checked daily and all lung function testing data were reviewed and graded for quality. Acceptability and reproducibility were assessed according to the American Thoracic Society (ATS)/European Respiratory Soceity (ERS) criteria (American Thoracic Society/European Respiratory, 2002; Miller et al., 2005) and only tests that had high quality scores were included in the final analysis. Respiratory muscle strength was assessed by using the manufacturers flanged mouthpiece attached to the tube and system valve including a little leakage to prevent glottis closure and recruitment of buccal muscles. Patients needed to hold inspiratory and expiratory pressure ideally for 1.5 s to enable recording of a maximum pressure level sustained for one second. Mouth occlusion pressure determined 0.1 s (P0.1) after the start of inspiration was measured 8–15 times during spontaneous breathing. For these measurements, several recordings were performed to ensure that at least 3 tracings with reproducible values were obtained. Results are expressed as percentage of the predicted values for gender and age. Measurements were obtained in all patients on the same day as PSG recording. All assessments were performed according to ATS/ERS guidelines and recommen-