Journal of Cardiology 63 (2014) 302–307

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Safety and efficacy of adaptive servo-ventilation in patients with severe systolic heart failure

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ARTICLE INFO

Article history:
Received 5 May 2013
Received in revised form 7 September 2013
Accepted 13 September 2013
Available online 25 December 2013

Keywords:
Heart failure
Adaptive servo-ventilation
Sleep-disordered breathing

ABSTRACT

Background and purpose: It is unclear whether adaptive servo-ventilation (ASV) is safe and effective in patients with severe systolic heart failure (HF). Our aim in this study was to estimate the safety and efficacy of ASV therapy for patients with severe systolic HF.

Methods and subjects: Seventy-six HF patients (age: 69 ± 12 years; 53 men), categorized as New York Heart Association (NYHA) Class II–IV, with left ventricular ejection fraction (LVEF) of <50%, received ASV therapy after optimal medical therapy to determine the safety and efficacy of ASV. Patients were divided into 2 groups based on their LVEF: group L (LVEF < 30%; $n = 42$) and group H (LVEF ≥ 30%; $n = 34$). After 6 months of ASV therapy, we compared the changes in LVEF, brain natriuretic peptide (BNP), and incidence of fatal cardiovascular events between the groups.

Results: The groups differed significantly with respect to beta-blocker treatment before ASV therapy ($p < 0.0001$). After 6 months of ASV therapy, LVEF and BNP levels had improved in both groups. In group L, LVEF had improved from 24.1 ± 5.6% to 35.2 ± 10.6% ($p < 0.0001$) and BNP from 591 (273–993) pg/ml to 142 (39–325) pg/ml ($p = 0.002$). Moreover, 1-year follow-up data showed a tendency toward improvement of NYHA classification in group L (group L: 50%; group H: 29%; $p = 0.07$), and showed no significant difference with regard to fatal cardiovascular events between the 2 groups (group L: 11.9%; group H: 5.9%; $p = 0.36$).

Conclusions: Our study demonstrated that ASV therapy is safe and effective for use in very severe systolic HF patients as well as in relatively mild systolic HF patients.

Introduction

Adaptive servo-ventilation (ASV) was originally developed as a treatment modality for patients with central sleep apnea (CSA) and complex sleep apnea syndrome, but has also been used for obstructive sleep apnea [1–6]. Sleep disordered-breathing (SDB) is closely related to cardiovascular disease, including heart failure (HF) [7–14], and is also closely related to the incidence of fatal cardiovascular events and mortality [15,16]. For treating HF patients, continuous positive airway pressure (CPAP) has been found to be effective [17–19]. However, the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) study found that this treatment did not affect survival, and their data showed the existence of non-responders to CPAP among patients who have both CSA and HF [20].

In recent years, ASV has been used to treat patients with HF. ASV therapy has beneficial effects on abnormal ventilation; it improves sympathetic nerve activity by providing appropriate ventilatory support using expiratory positive airway pressure and a pressure support system [1,21,22]. Furthermore, ASV therapy has been shown to prevent fatal cardiovascular events and improve survival in HF patients and is beneficial even in patients who suffer not only from severe SDB, but also from mild to moderate SDB [23–25]. However, it is unclear whether ASV therapy is safe and effective for patients who suffer from severe systolic HF with low left ventricular (LV) function. For this reason, we attempted to determine the safety and efficacy of ASV therapy in severe systolic HF patients by evaluating the adverse events, including fatal cardiovascular events, and improvement in LV function in HF patients treated with ASV therapy.

Methods

Study design and ethical considerations

The present study enrolled 246 consecutive HF patients who presented at our hospital with Class II–IV symptoms, as defined by

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0914-5087/$ – see front matter © 2013 Published by Elsevier Ltd on behalf of Japanese College of Cardiology.
http://dx.doi.org/10.1016/j.jjcc.2013.09.008

the New York Heart Association (NYHA) classification for the stages of HF. All procedures were performed at our medical center. After medical therapy was optimized, full-night polysomnography was performed and 76 patients who suffered from systolic HF [left ventricular ejection fraction (LVEF) < 50%] were treated with ASV. We monitored the patients' physical status, including improvements in the LVEF, and brain natriuretic peptide (BNP). The patients were classified into 2 groups based on their LVEF. The group of patients with LVEF < 30% was designated as group L, and the other group with LVEF ≥ 30% was designated as group H. Forty-two patients were classified into group L and 34 into group H. Entry criteria in this study are shown in Fig. 1. After ASV therapy, NYHA classification and incidence of fatal cardiovascular events including death from progressive HF, cardioembolic stroke, and fatal cardiac arrhythmias were monitored for 1 year.

This study was conducted in accordance with the recommendations of the Declaration of Helsinki (1975), and the protocol was approved by the Institutional Review Board. Written informed consent was obtained from each patient at the start of the study.

Sleep study and treatment devices

For sleep evaluation, all patients who underwent full-night polysomnography were assessed by digital polygraphy (E-Series Plus; Compumedics, Abbotsville, Australia). Assessment included monitoring by electroencephalography, electrooculography, and chin electromyography. Chest and abdominal movements were monitored using 2 inductive respiratory bands. Airflow was assessed using a thermistor. Arterial oxygen saturation was measured continuously at a sampling frequency of 1 s using a pulse oximeter with a finger probe (Nonin 8000J Adult Flex Sensor; Compumedics). Sleep stages and arousals were scored according to standard methods [26,27]. Apnea was defined as the complete cessation of airflow lasting for ≥10 s. Hypopnea was defined as a decrease in airflow of ≥50% for ≥10 s accompanied by desaturation (3% decrease in arterial oxygen saturation) and/or an electroencephalographic arousal response. The apnea–hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour of sleep.

In this study, ASV (AutoSet-CS; ResMed, Sydney, Australia) was administered using a full facemask (ResMed). It consisted of 4 cm H_2O expiratory positive airway pressure and a suitable minimum to maximum inspiratory support, which was within the recommended minimum manufacturer setting range of 3–8 cm H_2O. The backup respiratory rate was 15 breaths/min.

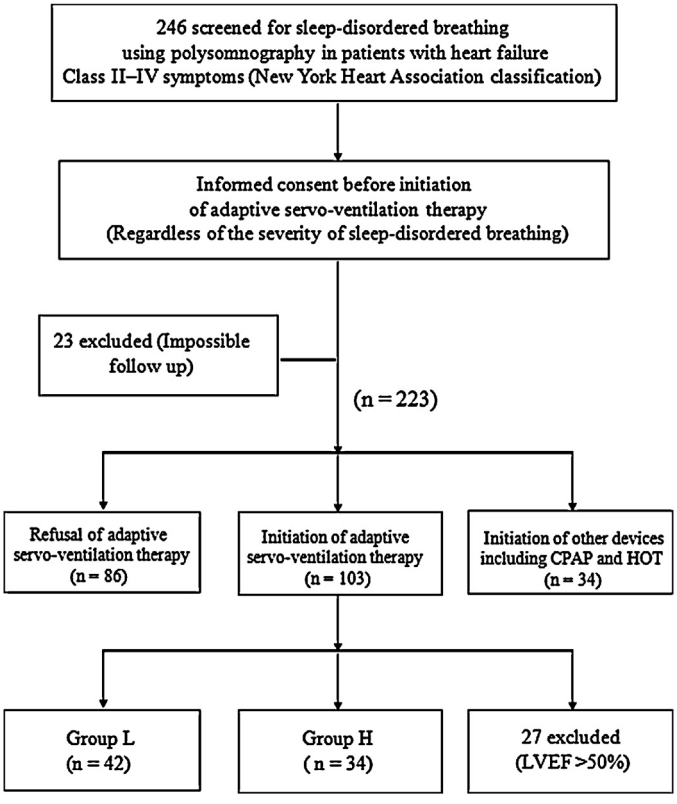

Fig. 1. Entry criteria in this study. CPAP, continuous positive airway pressure; HOT, home oxygen therapy; LVEF, left ventricular ejection fraction.

Data collection

Baseline data included medical history, physical examination, and biochemical blood examination. Before ASV therapy, venous blood samples were obtained after overnight fasting and BNP levels were recorded. Arterial blood samples were obtained for blood gas analysis with the patients in a supine position and not receiving supplemental oxygen. Furthermore, 2-dimensional transthoracic echocardiography was performed. The LV end-diastolic and end-systolic dimensions were measured by M-mode echocardiography, and LVEF was calculated by the modified Simpson's method.

Presence of dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of ≥150 mg/dL, a low-density lipoprotein cholesterol value of ≥140 mg/dL, and/or a high-density lipoprotein cholesterol value of <40 mg/dL. Presence of hypertension was defined as the recent use of antihypertensive drugs or blood pressure level of ≥130/80 mmHg, and the presence of diabetes mellitus was defined as the recent use of insulin or antidiabetic drugs, a fasting blood glucose value of ≥126 mg/dL, and/or a hemoglobin A_{1c} value of ≥6.5%.

After ASV therapy, we established the 6-month follow-up data including LVEF and BNP levels. Furthermore, we calculated NYHA classification and incidence of fatal cardiovascular events including death from progressive HF, cardioembolic stroke, and fatal cardiac arrhythmias and excluding death from other reasons.

Statistical analysis

Continuous data were expressed as mean ± standard deviation and were compared between the 2 groups using a 2-tailed *t*-test. Skewed data were presented as median and inter-quartile range and analyzed by the Wilcoxon signed-rank test. Categorical data were expressed as counts (expressed as percentage) and were compared using a chi-square test. The survival rate (fatal cardiovascular event-free rate) was calculated by Kaplan–Meier analysis, and a log-rank test was used to assess the differences between the two study groups. The significance level was set at 5%, and all analyses were performed using JMP software (JMP 10; SAS Institute Inc., Cary, NC, USA).

Results

The study group consisted of 76 HF patients. The mean age was 69 ± 12 years. After treating the underlying disease in the acute phase, these 76 patients were treated with ASV. Forty-two patients were classified into group L and 34 into group H. Patient characteristics are presented in Table 1. No significant differences were observed between the 2 groups with regard to gender and history of coronary risk factors (hypertension, dyslipidemia, diabetes mellitus, and smoking). By contrast, a significant difference was noted between the groups with regard to drug therapy (beta-blocker treatment) (group L: 64%; group H: 9%; $p < 0.0001$). Before ASV therapy, significant differences were noted between the 2