IJC Metabolic & Endocrine 1 (2013) 20–26

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

Adaptive servo-ventilation improves exercise oscillatory ventilation and ventilatory inefficiency in patients with heart failure and central sleep apnea☆,☆☆

Shuji Joho *[,1], Ryuichi Ushijima, Takashi Akabane, Yoshitaka Oda, Hiroshi Inoue

From the Second Department of Internal Medicine, University of Toyama, Toyama, Japan

ARTICLE INFO

Article history:
Received 30 October 2013
Accepted 1 November 2013
Available online 8 November 2013

Keywords:
Heart failure
Sleep apnea
Ventilation
Sympathetic nerve activity

ABSTRACT

Background: Adaptive servo-ventilation (ASV) can improve ventilatory inefficiency and exercise oscillatory ventilation (EOV) in patients with heart failure (HF) and central sleep apnea (CSA). Although these improvements might originate from both increase in cardiac function and decrease in sympathetic nerve activity, mechanisms underlying the interrelationship remain unknown.

Methods: We compared cardiopulmonary exercise test, muscle sympathetic nerve activity (MSNA) and echocardiography findings at baseline and 3.5 ± 0.8 months (mean ± SD) of follow-up in 28 patients with both HF (New York Heart Association functional class II and III; left ventricular ejection fraction (LVEF) <45%) and CSA (apnea–hypopnea index (AHI) ≥15/h). Of these, 17 patients consented (ASV group) and 11 patients declined (non-ASV group) to undergo ASV treatment. Compliance with ASV and changes in AHI were determined from data collected by integral counters.

Results: VE/VCO_2-slope and EOV amplitude at baseline were positively correlated with MSNA, but not with LVEF. ASV therapy reduced VE/VCO_2-slope and EOV amplitude (both $p < 0.01$) in association with decrease in MSNA ($p < 0.01$) and increase in LVEF ($p < 0.001$). In non-ASV group, however, these parameters remained unchanged. Change in VE/VCO_2-slope was correlated with both change in AHI and average use of ASV. By contrast, change in EOV amplitude was correlated with change in AHI. Changes in VE/VCO_2-slope and EOV amplitude were correlated with changes of MSNA ($p < 0.05$), but not with those in LVEF.

Conclusions: ASV improves ventilatory inefficiency and EOV probably via suppression of CSA and its sympathoinhibitory effect.

1. Introduction

Patients with heart failure (HF) frequently have both central sleep apnea (CSA) and obstructive sleep apnea during asleep [1,2]. Sleep apnea causes repetitive episodes of hypoxia and arousal from sleep, thereby activating the sympathetic nervous system to result in a predisposition to arrhythmias; thus sleep apnea might comprise an independent risk factor for major cardiac events [3–5].

In patients with CSA, several respiratory abnormalities during cardiopulmonary exercise test have been identified. Ventilatory efficiency during exercise is impaired in HF patients with CSA compared with those without CSA [6]. Nocturnal continuous positive airway pressure alleviated CSA and improved ventilatory inefficiency [7]. Exercise oscillatory ventilation (EOV) is known as a slowly and consistently fluctuating ventilation throughout the entire period of exercise test, or disappearing during early exercise, or only disappearing at peak exercise [8,9]. Similar to CSA, ventilatory inefficiency or EOV is also an independent predictor of poor outcome in patients with HF [10,11].

Adaptive servo-ventilation (ASV), which can almost eliminate CSA and normalize breathing, has recently become applicable to patients with HF accompanied by CSA [12]. ASV can improve cardiac function, EOV, ventilatory inefficiency and hypercapnic chemosensitivity in patients with HF and CSA [13–16]. However, mechanisms underlying these improvements remain unknown. It has been shown that sympathoexcitation relates to increased chemosensitivity and ventilatory inefficiency in patients with HF [17–19]. We also showed that ASV decreased sympathetic nerve activity measured directly as muscle sympathetic nerve activity (MSNA) in association with suppression of CSA in patients with HF [20]. Therefore, the present study aimed to investigate whether ASV improved EOV and ventilatory efficiency and, if so, to elucidate the underlying mechanisms. We hypothesized that treating CSA with ASV would improve EOV and ventilatory inefficiency through effects on cardiac function and sympathetic nerve activity.

☆ Conflict of interest: none declared.
☆☆ Disclosures: None.

* Corresponding author at: Second Department of Internal Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. Tel.: +81 76 434 7297; fax: +81 76 434 5026.
E-mail address: sjoho@med.u-toyama.ac.jp (S. Joho).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

2214-7624
http://dx.doi.org/10.1016/j.ijcme.2013.11.001

2. Methods

2.1. Study protocol

The present study included 40 patients with stable HF (New York Heart Association functional classes II and III, left ventricular ejection fraction (LVEF) <45%, a first HF diagnosed at least six months before enrolment), treatment according to current guidelines for ≥3 months and sleep-disordered breathing (apnea–hypopnea index (AHI) ≥15/h) with dominant central apnea and hypopnea (Fig. 1). The etiology of heart disease was ischemic ($n = 12$) and non-ischemic ($n = 28$). Patients with pacemakers, defibrillators, or resynchronization devices were included if the device had been implanted for more than six months. Patients with primary valvular heart diseases were excluded. Patients with stroke, respiratory failure or pulmonary disease, severe anemia and end-stage renal disease treated by hemodialysis were also excluded from the study.

Cardiopulmonary exercise test and MSNA including measurements of neurohumoral factors were analyzed at baseline. However, seven of 40 patients disagreed to participate in the follow-up study. Therefore, the remaining 33 patients underwent an ASV test. Twenty of them agreed to continue with ASV, but the remaining 13 declined during mask fitting or daytime ASV testing. Repeated cardiopulmonary exercise test was refused by 1 of 20 patients who accepted ASV treatment and 1 of 13 patients who declined ASV treatment. Microneurography results were not of sufficient quality for 2 of 20 patients who accepted ASV treatment and 1 of 13 patients who declined ASV treatment during the follow-up (Fig. 1). All patients were followed up monthly in our outpatient clinic. Measurements of cardiorespiratory polygraphy, cardiopulmonary exercise test, humoral factors, and 2-dimensional echocardiography and microneurography were also performed at 3.5 ± 0.8 months (mean ± SD) of follow-up in 28 patients who consented ($n = 17$; ASV group) or declined ($n = 11$; non-ASV group) to undergo ASV treatment. The Institutional Ethics Board of Toyama University Hospital approved the study protocol, which complied with the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2. Sleep study

The patients were monitored using a cardiorespiratory monitoring device (Somté, Compumedics, Abbotsford, Australia) to determine proportion of CSA and obstructive sleep apnea during sleep [21]. Electrocardiographic recordings, nasal airflow (nasal pressure), thoracic and abdominal effort, arterial oxygen saturation, pulse rate and body position were analyzed. Thoracoabdominal movements were recorded by respiratory inductance plethysmography, and oxyhemoglobin saturation was monitored using finger pulse oximetry.

Respiratory events (CSA, obstructive sleep apnea, and mixed apnea and hypopnea) were detected and oximetry findings were visually evaluated. The oxygen desaturation index was defined as number of instances per hour of total recording in which oxyhemoglobin saturation fell by ≥4%. Apnea was defined as complete cessation of air flow for >10 s, and hypopnea as >50% attenuation of air flow accompanied by a reduction in SpO_2 of ≥4%. AHI was calculated for each patient as the mean number of apneic and hypopneic events per hour of the recording. The central and obstructive apnea indices were calculated as the mean number of central and obstructive apneic events, respectively.

2.3. Cardiopulmonary exercise test

Each subject was evaluated at least 2 h after a meal [18]. Patients were asked to perform progressive maximal symptom-limited exercise while seated upright on an electronically braked cycle ergometer (Aerobike 75XL, Combi, Tokyo, Japan). Initially, patients performed unloaded cycling for 3 min. Then, the work rate was increased progressively by 5 to 10 watts every minute. The work rate increment was individualized on the basis of the subject's exercise capacity. Every subject terminated the exercise because of leg fatigue or dyspnea. Heart rate was monitored together with blood pressure, which was measured by the cuff method at 1-min intervals throughout the test. Oxygen uptake (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), tidal volume, and respiratory rate were continuously measured on breath by breath basis using a metabolic measurement cart equipped with an oxygen and carbon dioxide analyzer (Minato AE-300, Osaka,

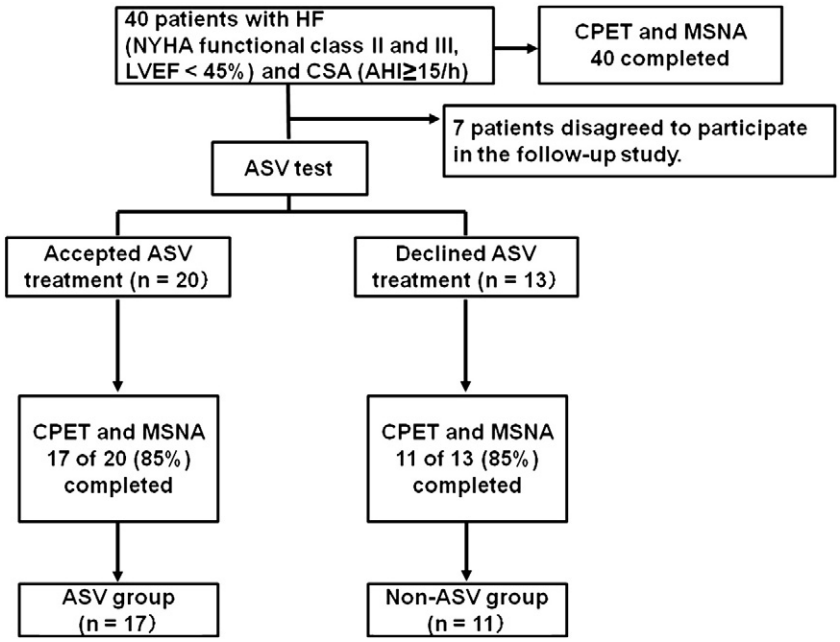

Fig. 1. Flow chart of study population. ASV, adaptive servo-ventilation; CPET, cardiopulmonary exercise test, CSA, central sleep apnea; HF, heart failure; MSNA, muscle sympathetic nerve activity; NYHA, New York Heart Association.