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Research Article

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Low Integrated Area of Desaturation Index after Adaptive Servo-Ventilation Therapy is a Strong Indicator to Predict Fatal Cardiovascular Events in Heart Failure Patients

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Abstract

Background: Adaptive servo-ventilation (ASV) has been used to treat heart failure (HF) with sleep-disordered breathing. However, there are no polysomnographic data correlated with HF prognosis. Therefore, the present study aimed to establish whether integrated area of desaturation (IAD) index, immediately after ASV therapy, was effective in predicting the incidence of fatal cardiovascular events in patients with HF, over a five-year follow-up period.

Methods: Fifty-seven patients with HF were enrolled for ASV treatment. Patients were categorised into 4 groups based on IAD index before (pre-IAD index) and after (post-IAD index) ASV therapy: Group A, pre-IAD index ≥ 50% sec/min and post-IAD index < 15% sec/min (n = 5); Group B, pre-IAD index ≥ 50% sec/min and post-IAD index ≥ 15% sec/min (n = 22); Group C, pre-IAD index < 50% sec/min, post-IAD index < 15% sec/min (n = 15) and Group D, pre-IAD index < 50% sec/min, post-IAD index ≥ 15% sec/min (n = 15). We observed patients over a five-year follow-up period, and noted fatal cardiovascular events (death from progressive HF, cardioembolic stroke or fatal cardiac arrhythmias).

Results: Incidence of fatal cardiovascular events significantly decreased in low post-IAD index groups compared with high post-IAD index groups (Group A and C versus Group B and D; P = 0.034).

Conclusions: Results of the present study suggest that low IAD index after ASV therapy may be a useful parameter to assess the efficacy of ASV therapy in HF patients.

Keywords: *Adaptive servo-ventilation; Integrated area of desaturation index; Sleep-disordered breathing; Heart failure*

Abbreviations: AHI: Apnea–Hypopnea Index; ASV: Adaptive Servo-Ventilation; CT90%: Cumulative Percentage Time at Oxygen Saturation below 90%; HF: Heart Failure; HFrEF: Heart Failure with Reduced Ejection Fraction; IAD: Integrated Area of Desaturation; LVEF: Left Ventricular Ejection Fraction; ODI: Oxygen Desaturation Index; PSG: Polysomnography; SDB: Sleep-Disordered Breathing

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Introduction

Adaptive servo-ventilation (ASV) has been originally used to treat sleep-disordered breathing (SDB), including central sleep apnoea, Cheyne–Stokes respiration [1-3] and obstructive sleep apnoea [4]. Furthermore, ASV has been recently shown to be effective for heart failure (HF) treatment in patients with SDB [1, 5-13]. However, Cowie., *et al*. [14] reported that ASV therapy has adverse effects in patients with HF with reduced ejection fraction (HFrEF) and predominant central sleep apnoea (SERVE-HF study). Despite these conflicting results, several studies have reported that ASV was an effective device for HF treatment [1, 5-13]. Based on these results, we deemed it necessary to examine which HF patients can be effectively treated with ASV.

It is common to evaluate the severity and prognosis of SDB using apnoea-hypopnoea index (AHI), cumulative percentage time at oxygen saturation below 90% (CT90%), or 3% oxygen desaturation index (3%ODI). However, little is known about the relationship between these polysomnographic data and fatal cardiovascular events in patients with HF undergoing ASV therapy [10,11,15,16]. Therefore, the objective of the present study was to establish whether integrated area of desaturation (IAD) index was effective in predicting the incidence of a fatal cardiovascular event in patients with HF, over a five-year follow-up period. IAD index, devised by the Tokyo Medical University, is calculated by dividing the total area of desaturation by the total sleep time using polysomnography (PSG) [15]. Therefore, in comparison to other PSG data, the IAD index can more accurately measure SDB severity, as it takes into account the duration and degree of hypoxia.

Materials and Methods

Study design and ethical considerations

The present study was a two-centre, prospective cohort study. We enrolled 57 patients with HF, classified into New York Heart Association classes II–IV and used ASV for HF treatment. All the patients were treated at Gunma University Hospital and Isesaki Municipal Hospital between February 2009 and April 2011. The research protocol was approved by the Institutional Review Board for Human Research of both the hospitals, and written informed consent was obtained from each patient before the study.

After medical therapy was optimised, all the patients were examined overnight by PSG, and IAD index was calculated to assess the severity of SDB before ASV therapy. Successive ASV treatment was administered for three months. Immediately thereafter, patients were re-examined overnight by PSG, and IAD index was calculated. Patients were classified into 4 groups based on their IAD index before (pre-IAD index) and after (post-IAD index) ASV therapy. Patients with pre-IAD index ≥ 50% sec/min and post-IAD index <15% sec/min were designated as Group A (n = 5), those with pre-IAD index ≥ 50% sec/min and post-IAD index ≥ 15% sec/min were designated as Group B (n = 22), those with pre-IAD index < 50% sec/min and post-IAD index < 15% sec/min were designated as Group C (n = 15), and those with pre-IAD index < 50% sec/min and post-IAD index ≥ 15% sec/min were designated as Group D (n = 15) (Figure 1). We observed the patients over a 5 year follow-up period and noted any fatal cardiovascular events (e.g., death from progressive HF, cardio-embolic stroke or fatal cardiac arrhythmias) to establish long-term prognosis. Non-cardiovascular related deaths were excluded from the present study.

Sleep evaluation and treatment devices

To assess the severity of SDB, all the patients underwent overnight PSG using digital polygraph (E-Series Plus; Compumedics, Abbotsville, Australia). We measured chest and abdominal movement using two bands (Inductive Respiratory Bands). Airflow was measured using a thermistor and arterial oxygen saturation was measured using pulse oximetry with a finger probe (Nonin 8000J Adult Flex Sensor). Electroencephalography, electrooculography and chin electromyography were also conducted. We scored sleep stage and arousal according to standard criteria [17,18]. We defined apnoea as the absence of airflow for > 10 sec and defined hypopnoea as > 50%

decrease in airflow accompanied by >3% desaturation. We investigated PSG data, AHI, central apnoea index, obstructive apnoea index, 3% ODI, CT90%, minimum oxygen saturation level and baseline oxygen saturation level. IAD index was calculated by dividing the total area of desaturation by total sleep time, measured in minutes. Baseline oxygen saturation level was determined using the average of 10 min in the sleeping position, before the patients fell asleep (Figure 2).

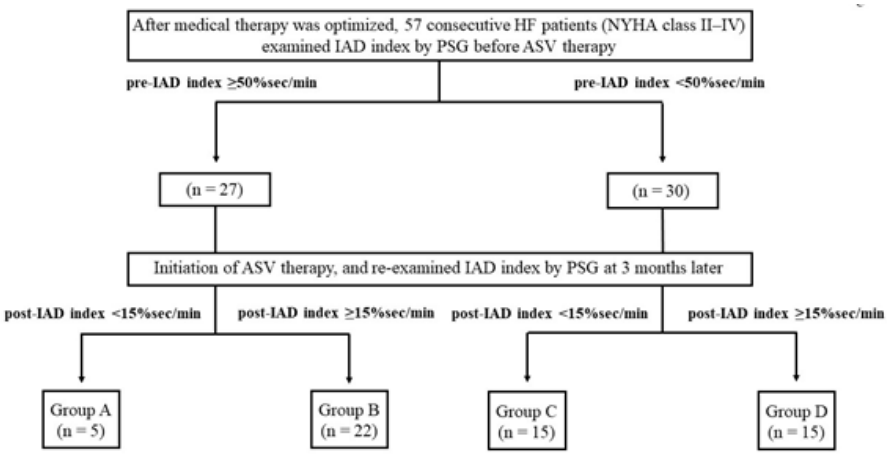

Figure 1: *The present study protocol. HF, heart failure; NYHA, New York Heart Association IAD, integrated area of desaturation; ASV, adaptive servo-ventilation.*

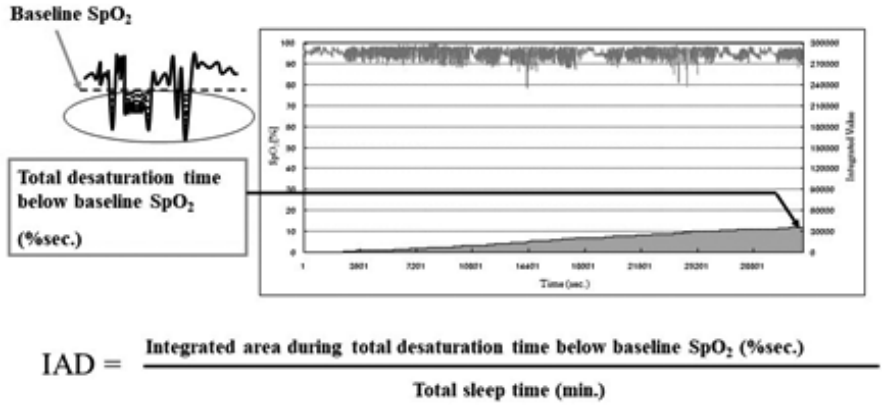

Figure 2: *Equation for how to calculate the IAD index. IAD, integrated area of desaturation.*

For HF treatment, we used the ASV device (AutoSet-CS; ResMed, Sydney, Australia) with a full facemask (ResMed). Expiratory positive airway pressure was set to 4 cm H_2O, and optimum inspiratory support pressure was set to a minimum of 3-8 cm H_2O. The backup respiratory rate for SDB was 15 breaths/min. We performed ASV titration for reduced SBD when required.

Data collection

We assessed physical examination, medical history, oral agents, venous and arterial blood samples, and transthoracic echocardiography data as baseline data, prior to ASV therapy. Venous blood samples were examined after overnight fasting. Arterial blood samples were examined with patients in the supine position ensuring sufficient room air at rest. Hypertension was defined as blood pressure ≥ 140/90 mmHg or the use of antihypertensive drugs. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dL,

triglycerides ≥ 150 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL or the use of cholesterol-lowering drugs. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL, HbA1c ≥ 6.5% or the use of insulin or oral antihyperglycemic drugs. Left ventricular ejection fraction (LVEF) was examined by transthoracic echocardiography using Simpson's method.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) or median (25%–75% range). Categorical data were expressed as a percentage. To analyse the incidence of fatal cardiovascular events between 4 groups, we used Kaplan–Meier analysis and log-rank test. In all analyses, $P < 0.05$ was considered to be statistically significant.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). EZR is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) and modified version of R designed to add statistical functions frequently used in biostatistics.

Results

We enrolled 57 patients with HF New York Heart Association classes II–IV in the present study. Table 1 shows the clinical characteristics of the patients. The mean age was 70 ± 11 years, and 72% of the patients were male. The average body mass index was 24.6 ± 5.8 kg/m^2, average LVEF was 40.7 ± 17.4% and median brain natriuretic peptide level was 339 (217–654) pg/ml. Table 2 shows PSG data before and after three months of ASV therapy. The average AHI was 42.4 ± 24.7 /h, 3% ODI was 27.8 ± 17.1 /h and CT90% was 7.6 ± 14.9%. The average pre-IAD index was 71.1 ± 58.2% sec/min, the mean post-IAD index was 36.6 ± 30.1% sec/min.

Figure 3 shows a scatter plot depicting the patients who incurred a fatal cardiovascular event. Data points uniformly distributed in the vertical axis represent the pre-IAD index, whereas those inclined to the right in the horizontal axis represent the post-IAD index. Groups with lower than average post-IAD index experienced fewer fatal cardiovascular events than those with high post-IAD index, regardless of the severity of pre-IAD index (Group A; 0.0%, Group B; 40.9%, Group C; 13.3%, Group D; 40.0%). Figure 4 shows the Kaplan–Meier analysis for the incidence of fatal cardiovascular events between the four groups. The incidence of fatal cardiovascular events was significantly different between the low post-IAD index groups (Group A and C) and the high post-IAD index groups (Group B and D) (Group A and C versus Group B and D; log-rank test: $P = 0.034$).

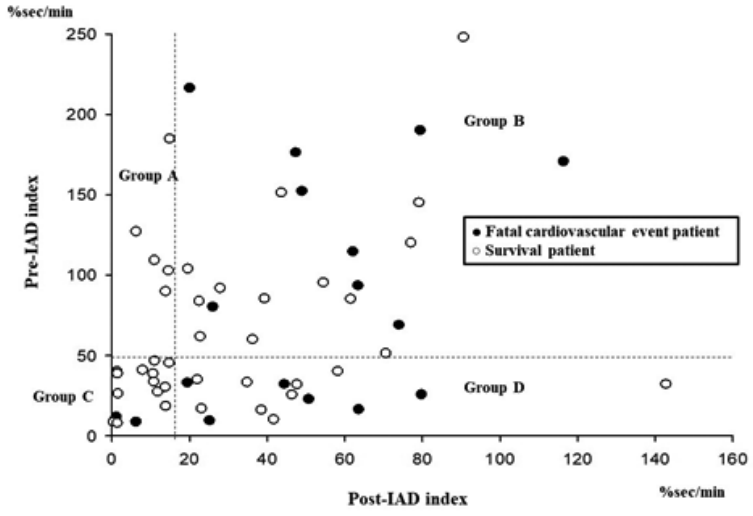

Figure 3: *Scatter plot for the fatal cardiovascular events about all patients. IAD, integrated area of desaturation.*

Variables	n = 57
Age, years	70 ± 11
Males, n (%)	41 (72)
Body mass index, kg/m^2	24.6 ± 5.8
Underlying heart disease, n (%)	
Ischemic cardiomyopathy	24 (42)
Valvular heart disease	8 (14)
Cardiomyopathy (DCM or HCM)	18 (32)
Arrhythmia	4 (7)
others	3 (5)
Coronary risk factors, n (%)	
Hypertension	40 (70)
Dyslipidemia	22 (39)
Diabetes mellitus	15 (26)
Current smoking	14 (25)
Blood pressure, mmHg	
Systolic	123 ± 19
Diastolic	68 ± 9.6
Left ventricular ejection fraction (%)	40.7 ± 17.4
Brain natriuretic peptide , pg/ml	339 (217-654)
Estimated GFR, ml/min/1.73m^2	51.3 ± 21.4
Low-density Lipoprotein cholesterol, mg/dl	112.4 ± 34.9
High-density Lipoprotein cholesterol, mg/dl	49.7 ± 13.8
Triglyceride, mg/dl	103.3 ± 61.3
Fasting blood sugar, mg/dl	113.7 ± 49.4
Hemoglobin A1c, %	6.4 ± 0.88
Arterial O_2 tension, mmHg	88.6 ± 21.4
Arterial CO2 tension, mmHg	36.6 ± 4.7
Medication, n (%)	
Beta-blocker / ACE inhibitor or ARB	50 (88)
Aldosterone antagonist	16 (28)
Diuretics	16 (28)

Data are presented as the mean value ± SD or median, or number (%).
DCM, dilated cardiomyopathy ; HCM, hypertrophic cardiomyopathy
GFR, glomerular filtration rate ; ACE, angiotensin I-converting enzyme
ARB, angiotensin II receptor blocker

Table 1: *Clinical characteristics.*

Variables	n = 57
before ASV therapy	
Total sleeping time, min	288 ± 142
AHI, /h	42.4 ± 24.7
CAI, /h	8.4 ± 12.1
OAI, /h	8.1 ± 15.0
Baseline oxygen saturation level, %	95.9 ± 1.9
Minimum oxygen saturation level, %	84.0 ± 12.1
ODI at the 3% level, /h	27.8 ± 17.1
CT 90%, %	7.6 ± 14.9
pre-IAD index, %sec/min	71.1 ± 58.2
3 months after ASV therapy	
post-IAD index, %sec/min	36.6 ± 30.1
Data are presented as the mean value ± SD, or number (%).	
AHI, Apnea hypopnea index ; CSA, Central apnea index	
OAI, Obstructive apnea index ; ODI, oxygen desaturation index	
CT 90%, cumulative percentage time at oxygen saturation <90%	
IAD, integrated area of desaturation	

Table 2: *Polysomnography.*

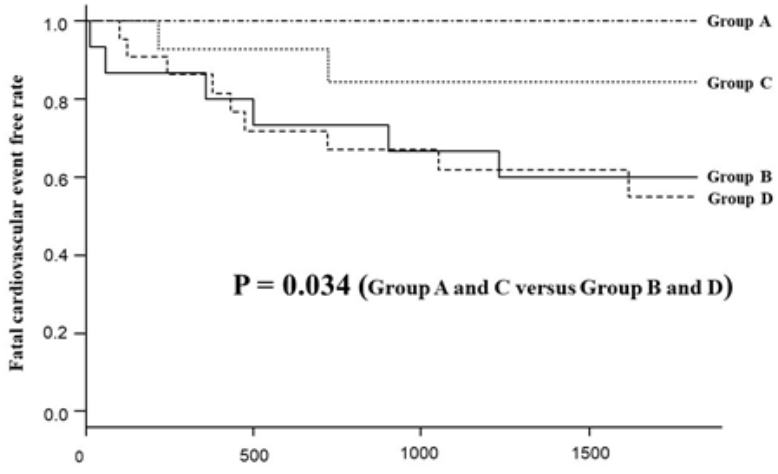

Figure 4: *Kaplan-Meier analysis for the fatal cardiovascular event-free rate between the four groups.*

Discussion

In the present study, 57 patients with HF were enrolled for ASV treatment. These patients were classified into 4 groups based on IAD index before and after ASV therapy. We observed patients over a 5 year follow-up period and noted any fatal cardiovascular events (e.g., death from progressive HF, cardio-embolic stroke or fatal cardiac arrhythmias). The results showed that low IAD index after ASV therapy was correlated with a decrease in fatal cardiovascular events in HF patients, regardless of severity of SDB as indicated by the IAD index before ASV therapy. ASV therapy could also be performed safely regardless of the severity of IAD index before ASV therapy.

A previous report compared IAD indexes between patients with cardiovascular events and non-cardiovascular events retrospectively, and focussed only on SDB patients with obstructive sleep apnoea [15]. Another report targeted only patients with acute or old myocardial infarction [19]. In contrast, the present study investigated the long-term prognosis of patients with various types and stages of HF after ASV therapy. Furthermore, the present study targeted patients with any SDB related conditions associated with HF. To our knowledge, the present study is the first to investigate the prognosis of HF after ASV therapy, according to IAD index prospectively.

It is well known that SBD increases cardiovascular and all-cause mortality [20-23]. However, conventional indexes of SDB, including AHI, 3%ODI, CT90%, are only measured as a frequency or ratio, and these indexes may not accurately assess the severity of SDB. Conversely, IAD index considers the duration and degree of hypoxia, thereby measuring the severity of SDB quite accurately. It is our opinion that this is the reason that the patients with high IAD index after ASV therapy experienced fatal cardiovascular events more often.

Until now, ASV has been commonly used for HF treatment, and studies have shown that ASV is an effective treatment for HF. However, recently, the SERVE-HF study reported that ASV therapy had adverse effects in patients with HFrEF. Based on this result, it is particularly important to consider how ASV therapy affects HFrEF patients. The present study showed good prognosis if the IAD index after ASV therapy was low, regardless of the severity of the IAD index before ASV therapy.

The present study has limitations; most importantly, it included only a small number of patients from only two centres. These limitations may have biased the results, and it is necessary to conduct a larger, multicenter study in the future.

Conclusion

In conclusion, the present study showed that low IAD index after ASV therapy in HF patients could reduce fatal cardiovascular events despite IAD index prior to ASV treatment being severe. Furthermore, our results suggest that low IAD index after ASV therapy may be a useful parameter to assess the long-term efficacy of ASV therapy in HF patients.

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