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Beneficial effects of adaptive servo-ventilation on natriuretic peptides and diastolic function in acute heart failure patients with preserved ejection fraction and sleep-disordered breathing

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Abstract

Purpose Adaptive servo-ventilation (ASV) is a ventilator algorithm able to correct breathing through anticyclic support of breathing in patients with central sleep apnea (CSA). So far, very few data exist regarding the role of ASV on acute heart failure with preserved ejection fraction (HFpEF).

Methods We performed a single-center prospective, randomized, case-control study in consecutive acute HFpEF (left ventricle ejection fraction, LVEF ≥ 45%) patients with sleep-disordered breathing (SDB, apnea–hypopnea index, AHI > 15/h) and prevalence of CSA.

Results We included ten consecutive patients randomized for ASV on top of standard therapy for acute heart failure (group 1) versus standard care alone (group 2). ASV therapy significantly reduced AHI and CSA. An improvement in cardiac diastolic function was seen in group 1 compared to group 2 (E/E' 17.5 to 9.6, $p < 0.02$ vs 18.5 to 14.5, $p = 0.4$). Brain natriuretic peptide (BNP) markedly decreased in cases, but not in controls (298 to 84 pg/ml, $p < 0.02$ vs 280 to 120 pg/ml, $p = 0.06$). Right ventricle (RV) function significantly improved in group 1, differently from group 2.

Conclusions An acute use of ASV seems effective in reducing BNP and improving diastolic and RV function in acute HFpEF patients with SDB and CSA, compared to standard treatment.

Keywords Heart failure with preserved ejection fraction · Central sleep apnea · Diastolic function · Right ventricle · Adaptive servo-ventilation

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome characterized by diastolic cardiac dysfunction and preserved left ventricle (LV) ejection fraction (LVEF), in a clinical setting of heart failure (HF) [1, 2]. Sleep-disordered breathing (SDB) represents one of the main comorbidities affecting clinical outcome and quality of life of HFpEF patients [3, 4]. Adaptive servo-ventilation (ASV) is a sophisticated device able to normalize breathing in patients with SDB and prevalence of central sleep apnea (CSA) [5–7].

In literature, only two randomized studies concerning the role of ASV in HFpEF exist [8, 9]. The aim of this research is to define the effect of ASV on brain natriuretic peptide (BNP) and on diastolic and right ventricle (RV) function in acute HFpEF patients with SDB and CSA.

Methods

Study population

All consecutive HFpEF patients with history of SDB admitted to the cardiology ward for decompensated HF were considered for inclusion in a single-center case-control study, approved by the ethical committee of Papa Giovanni XXIII Hospital (Bergamo). Inclusion criteria were as follows: (i) > 18 years old, (ii) presence of acute HF with New York Heart Association (NHYA) Class ≥ III within 48 h from hospital admission, (iii) LVEF ≥ 45%, (iv) brain natriuretic peptide

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(BNP) > 200 pg/ml, and (v) history of SDB with an apnea–hypopnea index (AHI) > 15/h and prevalence (> 50%) of CSA. Exclusion criteria were as follows: (i) acute coronary syndrome at the time of admission, (ii) implanted pacemaker, and (iii) presence of mitral valve mechanical prosthesis. Enrolled patients were matched according to age and body mass index (BMI) and randomly assigned to either 7-day ASV treatment on top of the standard care for acute HF (group 1) or standard treatment for acute HF only (group 2). All patients provided their written informed consent.

Enhanced adaptive servo-ventilation

ASV (ResMed AutoSet™ CS-A) is a ventilator device designed to normalize breathing in patients with SDB and CSA. The new feature of expiratory positive airway pressure (EPAP) permits to change the air pressure following patient's ventilation breath by breath. The ventilator algorithm was applied using a well-fitting nasal mask in the default settings (EPAP 5 cmH_2O, inspiratory positive airway pressure, IPAP, 3–10 cmH_2O).

Echocardiographic and BNP assessment

All patients underwent a trans-thoracic echocardiography (TTE) at randomization and after 7 days of treatment, according to the American Society of Echocardiography guidelines [10]. TTE was performed using a specific echocardiographic system (Vivid 9, GE Healthcare, Horten, Norway) with a 3.5-MHz transducer. Every patient was also screened with a blood test analysis for BNP at hospital admission and 7 days after treatment.

Statistical analysis

Data are displayed as mean and standard deviation (SD) for continuous variables and as percentage for categorical variables. PRISM 4 Software (GRAPHPAD PRISM 4.0; GraphPad Software, La Jolla, CA, USA) was used for statistical analyses. All the variables were compared between group 1 and group 2 using non-parametric Wilcoxon tests (for continuous variables) or Fisher's exact tests (for categorical variables). p values < 0.05 were considered significant.

Results

Ten consecutive patients with decompensated HFpEF and SDB were enrolled. Table 1 shows baseline clinical features of patients.

Effects of enhanced ASV on echocardiographic parameters and BNP

ASV therapy (group 1) markedly reduced AHI and CSA (39.6 ± 3.2 to 3 ± 1, $p < 0.001$, and 31.2 ± 1.6 to 1 ± 0.6, $p < 0.0001$). An improvement in cardiac diastolic function was seen in group 1 compared to group 2: E/E' significantly reduced from 17.5 ± 1.5 to 9.6 ± 1.2 ($p < 0.02$) in group 1, versus a non-significant reduction from 18.5 ± 1.9 to 14.5 ($p = 0.4$) in controls. Pulmonary artery pressures (PAPs) showed a consistent reduction in group 1 versus group 2 (36 ± 1.6 to 23 ± 1.8 mmHg, $p < 0.05$ vs 35 ± 1.6 to 29 ± 2.3 mmHg, $p = 0.07$). Furthermore, RV function improved in group 1 with respect to group 2 (tricuspid annular plane systolic excursion, TAPSE 16 ± 1.4 to 17 ± 1.3 mm, $p = 0.05$ vs 15 ± 1.6 to 16 ± 1.4 mm, $p = 0.06$; fractional area change, FAC 39 ± 2.0 to 43 ± 1.7%, $p = 0.03$ vs 36 ± 1.8 to 38 ± 2.2%, $p = 0.5$), and BNP significantly reduced (298 ± 30.0 to 84 ± 26.3 pg/ml, $p = 0.04$ vs 280 ± 57.3 to 120 ± 43.6 pg/ml, $p = 0.06$). Diuretic dosage during the 7 days of treatment did not change between the two groups (564 ± 127 mg vs 622 ± 174 mg, $p = 0.56$). Of note, in group 1, no patients reported any adverse event after ASV treatment, and ASV was well tolerated by every patient. The length of stay was similar (9.4 ± 2 vs 9.6 ± 1.5 days, $p = 0.86$); no patient was hospitalized at 30 days after discharge, while only one patient in group 2 reported a new hospitalization for HF within 90 days. The effects of ASV treatment in group 1 are displayed in Table 2.

Discussion

Our pilot study showed a favorable effect of ASV on improvement of echocardiographic parameters of cardiac diastolic function and on reduction of BNP in acute HFpEF patients. Furthermore, we also observed a positive trend in RV function, probably related to a reduction of cardiac pre- and afterload.

SDB causes orthosympathetic activation, endothelial inflammation, myocardial stiffness, and finally LV hypertrophy [11, 12]. Moreover, SDB is linked to adipose tissue deposition, arterial hypertension, atrial fibrillation, and kidney disease, which are typical HFpEF comorbidities. Bitter and colleagues reported that the prevalence of CSA is unexpectedly high in HFpEF, and it is related to the worsening of diastolic dysfunction [13, 14]. Nonetheless, very limited data are available regarding the role of ASV in HFpEF [8, 9]. Some experts highlighted that the negative results of the SERVE-HF trial [15] cannot be extended to HFpEF population, since a different impact of ASV on patients with a preserved LVEF is presumably expected [16, 17]. The CAT HF trial [9] enrolled both HFrEF (n =

Table 1 Baseline characteristics of patients enrolled

	ASV group ($n = 5$)	Non-ASV group ($n = 5$)	p value
Age (n)	69 ± 4	70.8 ± 5	0.54
Male, n (%)	5 (100)	5 (100)	–
BMI	27.0 ± 1	26.3 ± 1.5	0.56
NHYA III (%)	40	60	–
NHYA IV (%)	60	40	–
LVEF (%)	49.0 ± 3.8	52.6 ± 5.5	0.26
Hypertension (%)	80	80	–
AF (%)	60	40	–
CKD (%)	20	40	–
COPD (%)	0	0	–
BB, n (%)	4 (80)	4 (80)	–
ACE-I, n (%)	4 (80)	5 (100)	–
MRA, n (%)	4 (80)	3 (60)	–
Diuretics (mg)	564 ± 127	622 ± 174	0.56
AHI	39.6 ± 3.2	34.2 ± 5.1	0.08
CSA	31.2 ± 1.6	24.8 ± 4.7	0.02
E/E' (average between lateral and septal E')	17.5 ± 1.5	18.5 ± 1.9	0.48
PAPs (mmHg)	36 ± 1.6	35 ± 1.8	0.52
TAPSE (mm)	16 ± 1.4	15 ± 1.6	0.63
FAC (%)	39 ± 2.0	36 ± 1.8	0.54
BNP (pg/ml)	298 ± 30.0	280 ± 57.3	0.57
Length of hospitalization (days)	9.4 ± 2	9.6 ± 1.5	0.86

ASV, adaptive servo-ventilation; *BMI*, body mass index; *NHYA*, New York Heart Association; *LVEF*, left ventricle ejection fraction; *AF*, atrial fibrillation; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *BB*, beta-blockers; *ACE-I*, ACE inhibitors; *MRA*, mineral receptor antagonists; *AHI*, apnea–hypopnea index; *CSA*, central sleep apnea; *PAPs*, pulmonary artery pressures; *TAPSE*, tricuspidal annular plane systolic excursion; *FAC*, fractional area change; *BNP*, brain natriuretic peptide

101) and HFpEF ($n = 24$) patients, randomized to ASV versus optimal medical therapy (OMT) alone. Due to the negative results of SERVE-HF, it was stopped earlier, showing that ASV did not ameliorate 6-month cardiac prognosis compared to OMT alone. Nevertheless, a pre-specified analysis suggested that the response to ASV might be better in patients with a preserved LVEF.

Several possible mechanisms by which ASV may favor diastolic and RV function in acute HFpEF could be suggested: improvement of nocturnal oxygenation, decrease of diastolic stiffness, attenuation of orthosympathetic tone with modulation of neuro-hormonal balance, and reduction of inflammation [18, 19]. All of these conditions could have beneficial effects also on the global management of HFpEF patients,

Table 2 Effect of ASV on echocardiographic and biohumoral parameters in group 1

	Basal ($n = 5$)	After ASV treatment ($n = 5$)	p value
AHI (event/h)	39.6 ± 3.2	3 ± 1	*< 0.001*
CSA (event/h)	31.2 ± 1.6	1 ± 0.6	*< 0.0001*
E/E' (average between lateral and septal E')	17.5 ± 1.5	9.6 ± 1.2	*< 0.02*
PAPs (mmHg)	36 ± 1.6	23 ± 1.8	*< 0.05*
TAPSE (mm)	16 ± 1.4	17 ± 1.3	*0.05*
FAC (%)	39 ± 2.0	43 ± 1.7	*0.03*
BNP (pg/ml)	298 ± 30.0	84 ± 26.3	*0.04*

Significant values are shown in italic

ASV, adaptive servo-ventilation; *AHI*, apnea hypopnea index; *h*, hour; *CSA*, central sleep apnea; *PAPs*, pulmonary artery pressures; *TAPSE*, tricuspidal annular plane systolic excursion; *FAC*, fractional area change; *BNP*, brain natriuretic peptide

whose phenotyping is essential to its diagnosis and treatment [20]. In this setting, identification and treatment of SDB as a peculiar comorbidity affecting HFpEF phenotype could be important steps forward for a more accurate and appropriate therapeutic approach of these patients.

Study limitation

Some limitations have to be addressed. Firstly, the very small sample size from a single-center study does not allow obtaining substantial conclusions, although the randomized design of study strengthens the results. Secondly, we could not assess long-term prognosis, since ASV was tested only during hospitalization. However, a numeric difference between group 1 and group 2 was observed for HF rehospitalization within 90 days.

Conclusion

ASV may have beneficial effects in reducing BNP and improving diastolic and RV function in acute HFpEF subjects with SDB and CSA. These preliminary findings suggest that a long-term use of ASV in HFpEF patients with SDB should be considered for bigger randomized prospective studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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