

Research article

Effect of home non-invasive ventilation on left ventricular function and quality of life in patients with heart failure and central sleep apnea syndrome

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Abstract: Central Sleep Apnea Syndrome (CSAS) and Cheyne-Stokes breathing are prevalent in patients with heart failure with reduced ejection fraction (HFrEF). Positive respiratory pressure therapy (PAP) associated with drug therapy for heart failure can improve quality of life, although tolerance to PAP therapy can be difficult to achieve.

Materials and method: Patients for this prospective, mono-center, cohort study were selected from patients with chronic heart failure who present at the Sleep Laboratory of the Medical Clinic of Pneumology, Oradea who underwent polysomnography. 38 HFrEF and CSAS patients were included between January 2019 to December 2021 in the study, with an apnea-hypopnea index (AHI) ≥ 15 /hour of sleep. Echocardiographic hemodynamic parameters (left ventricular ejection fraction-LVEF, mitral regurgitation score), PAP compliance, and quality of life using the severe respiratory failure questionnaire (SRI) at the initiation of PAP and after 3 months were included.

Results: After 3 months of PAP therapy LVEF increased significantly (from 31.4% \pm 12.2 to 38.0% \pm 10.9, $p=0.0181$), AHI decreased (from 40.1 \pm 18.7 to 6.8 \pm 6.1 events/h, $p<0.0001$) and all the categories of SRI showed improvement with significant general score increase (from 57.0 \pm 15.1 to 66.6 \pm 16.9, $p<0.0001$).

Conclusion: The association of PAP therapy with drug therapy in patients with HFrEF and CSAS improves hemodynamic parameters and quality of life.

Keywords: Chronic heart failure, positive airway pressure therapy, central sleep apnea syndrome

1. Introduction

Central Sleep Apnea Syndrome (CSAS) with Cheyne-Stokes respiration occurs frequently among patients with heart failure. Up to 45% of patients with left ventricular ejection fraction (LVEF) $\leq 40\%$ may suffer from this respiratory disorder during sleep [1,2].

Modern pathophysiological concepts suggest that CSAS is caused by increased sensitivity of chemoreceptors for carbon dioxide, a delayed transfer of variations in blood gas

pressures to chemoreceptors, and the influence of adjacent brain centers (circadian rhythms, wake/sleep center) on respiratory center [3]. Cheyne-Stokes respiration is characterized by periodic changes in tidal volumes, resulting in 30-60 cycles of hyperventilation alternating with periods of hypoventilation or even apnea with a crescendo-descending pattern. Respiration after apnea is associated with awakenings and episodes of sympathetic activation. These episodes can occur several hundred times during the night in a patient with severe CSAS [4]. Repeated awakenings prevent entering the deep sleep phase, which causes daytime sleepiness and fatigue. The activation of the sympathetic nervous system coincides with low blood and tissue oxygenation levels. Heart rate, blood pressure, and calculated heart load increase periodically during sleep. As a result, stress on an already affected heart multiplies [5]. Sympathetic activation is a proven, independent risk factor for worsening heart dysfunction and sudden cardiac death [6].

Epidemiological studies have demonstrated negative progression and decreased survival for patients with left heart failure and CSAS [7,8]. Andreas et al. [9] concluded that sleep-related Cheyne-Stokes respiration or insomnia is associated with increased mortality and increased need for heart transplant within a few months. Thus, treatment of CSAS in combination with optimal drug therapy can influence the course of chronic heart failure, quality of life, and survival [10].

Quality of life assessment in patients with home ventilation is a well-known problem in patients with chronic respiratory failure of pulmonary and dystrophic causes [11,12], but little was studied in patients with heart failure and CSAS. The effect of positive airway pressure therapy (PAP) at home on the quality of life itself is difficult to assess given the inconvenience caused by the procedure, the limitation of movements, or the mask itself [13]. These inconveniences are detrimental to the improvement in the quality of life given by the possible improvement in the diastolic and systolic function of the left ventricle.

The positive effects of PAP at home for chronic cardiac patients with CSAS are undeniable, but the hemodynamic effect, in this case, is also multifactorial. Is it just a stop to the evolution of myocardial dysfunction by preventing these episodes of awakening, hypoxemia, and sympathetic activation, or can it be an improvement given by the positive effect of positive chest pressure on an afterload-dependent heart? It remains an open question.

Another question is whether initiating home ventilation also brings an improvement in quality of life or just in hemodynamics. To follow the evolution of quality of life in these patients we used a questionnaire specific to patients ventilated at home with chronic respiratory failure: the SRI (Severe Respiratory Insufficiency) [14] questionnaire containing 7 subchapters evaluating the categories of disease-related and associated symptoms (SRI-RC: Respiratory complaints, SRI-PF: Physical functioning, SRI-AS: Associated symptoms and sleep, SRI-SR: Social relations, SRI-AX: Anxiety, SRI-WB: well-being and SRI-SF: Social functioning). The questionnaire can be used for research purposes without any fee (<https://www.atemwegsliga.de/en-sri.html>).

Clinical trials involving PAP at the patient's home are hampered by the difficult selection of patients (especially in Romania, where ventilation in cardiac patients is not a service settled by the National Health Insurance) and the doubtful compliance of patients to this treatment, sometimes considered unpleasant at night.

Our study aims to follow patients with CSAS who initiate PAP therapy at home, on a stable drug regimen. The evolution of the non-invasively measured hemodynamic values (echocardiographic Simpson method) will indicate the extent to which PAP therapy has intervened in the evolution of chronic heart failure, and the follow-up of the SRI questionnaire scores will give us information on the overall effect of ventilation on the quality of life.

2. Materials and Methods

For this prospective, monocentric, cohort study patients who presented to the Sleep Laboratory of the Medical Clinic of Pneumology, Oradea who were diagnosed with chronic heart failure were selected to undergo polysomnography, between January 2019 to December 2021. After checking the inclusion and exclusion criteria, informed consent was obtained from all subjects involved in the study.

Inclusion criteria: NYHA II, III, or IV heart failure diagnosed for more than 1 year ($FEVS \leq 45\%$); central sleep disorders with the indication of PAP therapy with an apnea-hypopnea index (AHI) ≥ 15 events/hour; stable, ambulatory patient with optimal drug treatment; no changes in the cardiac failure treatment regimen over the past 3 months (possible dose adjustment of diuretics).

Exclusion criteria: Pure right ventricular failure with pulmonary hypertension; stenotic valvular disease; constrictive pericarditis or pericardial effusion; intracardiac shunt; pulmonary or neurological diseases that may affect ventilation (central alveolar hypoventilation, COPD, pulmonary fibrosis, ischemic stroke sequels, neuropathies, brain tumors); acute myocardial infarction within the last 6 months; ventricular arrhythmias; OSAS (obstructive sleep apnea syndrome); consumer of any substance that may affect breathing control: alcohol, sedatives, hypnotics, theophylline; renal failure with the need for dialysis.

Apart from the usual demographic criteria followed were noted: etiology of heart failure, current medication, and laboratory parameters (hematocrit, glomerular filtration rate, natriuretic peptide). The monitored echocardiographic parameters were: LVEF (%) – Simpson method, mitral regurgitation score (grade) – appreciation of the color flow regurgitation jet (CW) at initiation and after 3 months. The following polysomnographic criteria were: AHI, desaturation index (ODI – 4% decrease in capillary blood saturation), and treatment compliance (hours/night). All patients used the same type of nasal mask, but different ventilator models in auto-CPAP or BIPAP modes (depending on the recommendation of the attending physician). The centralization of SRI questionnaires will give us the 7 underscores and a total score that were recorded at the initiation of ventilation and 3 months.

The individual treatment regimen will be established by the attending physician, the investigators having no influence on the therapeutic decisions.

Statistical analysis: Each continuous variable will be checked for the distribution of values compared to the normal population using the Kolmogorov-Smirnov test. Depending on the result of this test, continuous variables with normal distribution will be represented by the mean and standard deviation in brackets, and those with asymmetric distribution by median and interquartile range. Also depending on the character of the variable will be used parametric (Student test for dependent and independent samples) or non-parametric (Mann-Whitney and Wilcoxon test) tests using MedCalc® medical statistics software version 12.5.0.0 (MedCalc® Software, Mariakerke, Belgium). The categorical variables will be described by their absolute values and percentages in brackets and will be studied using the chi-square and chi-square trend tests. The limit of statistical significance was considered 0.05.

The possible limitations and errors identified that may occur in this study are as follows:

- The costs borne by patients for the rental of PAP equipment, low compliance with such treatment, and the need for periodic reassessments may result in a small number of participants in this study.
- Errors due to differences in echocardiographic assessments will be excluded by the fact that only one cardiologist will make the examinations for all patients included in the study.
- Using specific questionnaires with targeted questions, the intellectual capacity of patients can influence the accurate assessment of their quality of life.

3. Results

Among the patients with heart failure diagnosed with CSAS by polysomnography at the Clinic, 38 accepted the PAP treatment at home between January 2019 and December 2021. 1 patient unfortunately died during follow-up and one did not show up for reassessment. Thus, 36 patients finished the demographical, clinical, paraclinical, echocardiographic, and quality of life evaluation.

The initial demographical, clinical, and paraclinical characteristics are found in Table 1:

Table 1: Baseline demographical, clinical, and paraclinical characteristics:

| Characteristics | Study sample (n=36) | Statistical significance (p) |
|---|---------------------|------------------------------|
| Gender – M/F | 31/5 | <0.0001 |
| Age (years) – mean (SD) | 65.7 (10.8) | - |
| Provenience – U/R | 20/16 | 0.6171 |
| BMI (kg/m ²) – mean (SD) | 25.4 (4.1) | - |
| Etiology (percentage): | | <0.0001 |
| • hypertrophic | 1 (2.8%) | |
| • ischemic | 9 (25%) | |
| • dilated | 24 (66.7%) | |
| • valvular | 2 (5.5%) | |
| Treatment regimen (percentage): | | - |
| • beta-blocker | 32 (88.9%) | |
| • ACEIs / ARBs | 31 (86.1%) | |
| • aldosterone antagonist | 28 (77.8%) | |
| • diuretics | 33 (91.7%) | |
| • antiarrhythmic | 5 (13.9%) | |
| Haematocrit (percentage) – mean (SD) | 39.6 (8.4) | - |
| eGFR (ml/min/1.73m ²) – mean (SD) | 58.9 (11.8) | - |

M = male, F = female, SD = standard deviation, U = urban, R = rural, BMI = body mass index, ACEIs = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, eGFR = estimated glomerular filtration rate.

The evolution of polysomnographic parameters is characterized by significant improvement in both AHIs (from 40.1±18.7 to 6.8±6.1 events/h, p<0.0001) and ODI (from 33.1±18.7 to 3.9±3.1 events/h, p<0.0001). The average use of the device was 4.1±1.1 hours/night.

From a hemodynamic point of view, the evolution of patients during the 3 months of treatment can be seen in Table 2:

Table 2: Haemodynamic evolution of patients during follow-up

| Criteria | At initiation (n=36) | 3 months reassessment (n=36) | Statistical significance (p) |
|--|----------------------|------------------------------|------------------------------|
| NYHA class: I/II/III/IV | 0/24/11/1 | 7/13/6/0 | 0.0158 |
| NT-proBNP (pg/ml) – median (IQR) | 497 (510) | 236 (351) | 0.0118 |
| LVEF (percentage) – mean (SD) | 31.4 (12.2) | 38.0 (10.9) | 0.0181 |
| Mitral regurgitation score – mean (SD) | 1.7 (0.9) | 1.1 (0.7) | 0.0023 |

NYHA = New York Heart Association, SD = standard deviation, NT-proBNP = N-terminal-pro-brain natriuretic peptide, IQR = interquartile range.

Quality of life questionnaires gave more satisfactory results at 3 months in all subcategories and overall scores (Figure 1).

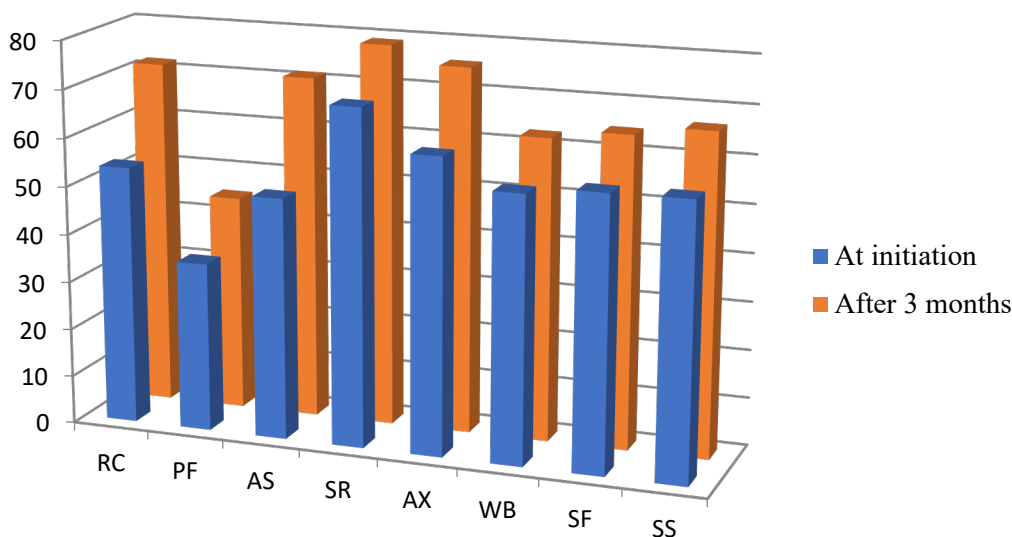


Figure 1: Subcategories of SRI (severe respiratory insufficiency) questionnaire and total score at treatment initiation and after 3 months – mean values (CR: respiratory complaints, PF: physical functioning, AS: Associated symptoms and sleep, SR: social relations, AX: anxiety, WB: well-being and SF: social functioning, SS: total score)

4. Discussion

There are multiple mechanisms by which PAP therapy can relieve heart failure in patients with CSAS: reduction of preload and afterload [15], reduction of upper airway obstruction, assisting of the inspiratory muscles [16], an increase of end-expiratory volumes and alveolar pressure, reduction of the volume of the left ventricle [17], attenuation of the activity of the sympathetic nervous system with reduced frequency of ventricular arrhythmias and anti-inflammatory effect [18]. These patients usually have low carbon dioxide partial pressure due to hyperventilation caused by irritation of the vagal receptors by pulmonary congestion and increased sensitivity of chemoreceptors for carbon dioxide [19]. PAP can maintain a more constant level of carbon dioxide by increasing diurnal levels due to reduced pulmonary congestion [20].

The progression to worsening of these patients without the treatment of sleep disorders is well documented [21], and recent studies have demonstrated the positive effect of PAP by increasing LVEF, and stroke volume and reducing the severity of mitral insufficiency [22,23]. Our study demonstrates in accordance with these studies the improvement of left ventricular systolic function but brings a novelty by assessing the quality of life before and after applying PAP treatment at home. Quality of life questionnaires have been widely used for patients with chronic respiratory failure ventilated at home and have demonstrated their positive evolution, especially in more serious cases at baseline [24,25], but have not been used to our knowledge in patients with heart failure and CSAS. Our results on the evolution of the subcategories in the SRI questionnaire are comparable to those seen in other patients with chronic respiratory failure, which confirms the importance of home PAP therapy in this category of patients.

5. Conclusions

The benefits of home PAP therapy in patients with chronic heart failure and CSAS are multiple; preventing hypoxemia periods and assisting periodically the contractile function of LV by decreasing afterload can stop the progression of this disease or even improve hemodynamically in some cases. The introduction of PAP therapy is also associated with significant improvement in quality of life.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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