Is servoventilation in central sleep apnoea syndrom still working?

Este servoventilația în sindromul de apnee de tip central încă funcțională?

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Abstract

Last black box on adaptive servoventilation in central apnoea syndrome generate many connective problems concerning the alternative therapies.The authors are starting from two recent french articles on this same subject and are trying to see what is missing and what we have to do .

Keywords: ***adaptive servoventilation, central sleep apnoea syndrome, alternative therapies***

Rezumat

Ultima „cutie neagră" pe servoventilația adaptativă în sindromul de apnee centrală a generat multe probleme conexe privind terapiile alternative. Autorii, pornind de la două articole franceze recente privind acest subiect încearcă să vadă ce lipsește și ce este de făcut.

Cuvinte-cheie: ***servoventilație adaptativă, sindromul de apnee în somn formă centrală, terapii alternative***

Introduction

On May 2015 it was one study who revolutionized the habits and indications of adaptive servoventilation (ASV) in central sleep apnoea syndrome and generated many other articles, echoes and editorials like the last one of the French Society of Pneumology experts[1,2]. The early results of SERVE –HF study[3,4] have shown that adaptive servoventilation may be harmful in patients with heart failure (HF) and low ejection fraction (LVEF less than 45%) and with central sleep apnoea.

This results coming from the major sponsor ResMed brought finally a safety notice on 13 May 2015 after analyzing the results indicating a 10% annual risk of cardiovascular death in ASV patients versus 7.5% in the control group. The design of the study started from some facts: central sleep apnoea is associated with poor prognosis and death in patients with heart failure and adaptive servoventilation is a therapy that uses a non-invasive ventilator to treat central sleep apnoea by delivering servo-controlled inspiratory pressure support on top of expiratory positive airway pressure. The authors tried to investigate the effects of adaptive servo-ventilation in patients who had heart failure with reduced ejection fraction and predominantly central sleep apnoea[3,4].

They randomly assigned patients with a left ventricular ejection fraction of 45% or less, an apnoea–hypopnea index (AHI) of 15 or more events (occurrences of apnoea or hypopnea) per hour, and a predominance of central events all receiving guideline-based medical treatment with adaptive servo-ventilation or guideline-based medical treatment alone (control)[3]. The primary end point in the time-to-event analysis was the first event of death from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock), or unplanned hospitalization for worsening heart failure[3]. The incidence of the primary end point did not differ significantly between the adaptive servo-ventilation group and the control group (54.1% and 50.8%, respectively; hazard ratio, 1.13; 95% confidence interval [CI], 0.97 to 1.31; P=0.10) but concerning all-cause mortality and cardiovascular mortality they found a significantly higher prevalence in the adaptive servo-ventilation group than in the control group (hazard ratio for death from any cause, 1.28; 95% CI, 1.06 to 1.55; P=0.01; and hazard ratio for cardiovascular death, 1.34; 95% CI, 1.09 to 1.65; P=0.006) [3]. They elaborate two conclusions:

- on one part adaptive servo-ventilation had no significant effect on the primary end point in patients who had heart failure with reduced ejection fraction and predominantly central sleep apnoea,
- all-cause and cardiovascular mortality were both increased with this therapy.

Even if the results do not regard patients with less severe or without heart failure and patients with other indications for treatment with ASV the American Academy of Sleep Medicine (AASM) has released a special safety notice on 15 May 2015[6], including recommendations for the approach to patients with heart failure and predominant central breathing disturbances, who are newly diagnosed or under treatment with ASV underlining some limits of ASV like:

- to stop prescribing ASV to treat CSA in patients with symptomatic heart failure and LVEF <45%
- to assess the presence of heart failure before starting treatment with ASV
- to contact patients with symptomatic heart failure who have been treated with ASV since 2005, advise them of the risk and strongly consider recommending to stop ASV treatment.

Also the The French National Authority for Health (HAS) has published its assessment report of ASV medical devices and associated services for the management of central SAS(sleep apnoea syndrome) and Cheyne-Stokes respiration, validated by the CNED-iMTS (National Commission for the evaluation of medical devices and

health technologies), on June 2,2015[7]. They emphasized: "Based on the available data, ASV devices should be specifically monitored. Under these conditions, the CNED-iMTS considers the inscription of these devices exclusively by brand name. The Commission will decide on the benefit of ASV based on the body of evidence which may be developed by the manufacturers in their possible registration applications to the LRPS (liste des produits et prestations remboursables).

This reports finally brought after a large debate, in different societies trying to avoid that the patients remain alone in confronting his disease, or in order to give a response to all our concerns and questions, faced with the need to take a decision to discontinue ventilation in patients we had seen evolve favourably on treatment[1].One example is the position paper-like article whose text is contained in this issue of the "*Revue des maladies respiratoires"* (Priou et al. Adaptive servo-ventilation: How does it fit into the treatment of central sleep apnoea syndrome?)[2]. Why they have done this? Because despite some clear progress in the treatment of HF (therapeutic, resynchronisation), the prevalence of central sleep apnoea syndrome (SAS) remains still high(20-30% of HF), and its presence is an independent factor of poor prognosis[8]. They defined some chapters for this category of patients:

1. for avoiding ***the risk of HF worsening with sudden discontinuation*** of ASV, since ASV decreases the left ventricular pre- and post-load they recommend being vigilant regarding the hemodynamic status and to monitor the respiratory disorder during sleep in order to propose a possible alternative[9,2].

2. *the alternative to be offered* is :

- the ***CPAP*** for patients responding to CPAP (residual AHI<15/h)(10) who had a prolonged survival has been considered a reasonable alternative by the AASM but without evidence of long-term efficacy. In addition, automatic CPAP should not be used in this clinicalsituation[2].
- ***Oxygen therapy*** has also been proposed at mean flow rates of 3 L/min (on some meta-analysis +5% on the ejection fraction (95%CI 0.3 to 9.8), and -15/h (95% CI -7 to -23 on the apnoea-hypopnea index-AHI)[11]. It is considered a reasonable alternative by the AASM but without evidence of long-term efficacy[2]
- ***medications:***

✔ like *theophylline* because it's increasing respiratory drive in patients with already an increased drive and this with some adverse effects it's not used in HF patients[2]

✔ *acetazolamide*[2] is not a realistic indication because in clinical routine leading to metabolic acidosis, modifies the ventilatory response to CO_2 and increases the apnoeic threshold

- *the addition of a dead space allows increasing* $PaCO_2$(of 100-150 mL)would allow increasing by 1-2 mmHg end-tidal PCO_2, allowing $PaCO_2$to distance itselffrom the apnoeic threshold but it's not a realistic indication inclinical routine[2]
- *addition of* CO_2 *and transvenous phrenic stimulation* remain experimental[2]

3. what we have to do with ***the other indications of adaptive servo-ventilation?!***

A. For ***HF with preserved LVEF*** (left ventricular ejection fraction) (29,5% of the French patients)[2,12] ASV has allowed improving the NYHA class, systolic BP, BNP level, associated with a significantly higher event-free survival rate in the arm treated with ASV[13].

B. For ***"complex SAS"*** (an obstructive SAS on diagnostic examination, and whose central persistent AHI or *de novo* AHI on CPAP remains high) (central apnea index ≥5/h or AHI≥15/h) (with prevalence of 5-15%[2,14] ASV was effective on the correction of nocturnal respiratory events.

C. For ***opioid-induced central SAS*** (a prevalence of 30% with a dose-dependent relationship between the daily doses of morphine and the prevalence of respiratory disorders, in particular with the central apnoea index)[2,15] adding ASV was effective to decrease AHI, sleep fragmentation and toreduce nocturnal desaturations[16].

D.For ***idiopathic central SAS*** there are low evidence-based publications for interventions like: addition of a dead space, CO_2, hypnotics and ASV[2].

E. For ***central SAS due to a stroke(***10% in a retrospective study)(2,17)ASV, as compared with CPAP, improved very significantly the respiratory events by decreasing the AHI from 54.4/h to 4.7/h, and enhanced alertness by decreasing the Epworth scale score from 8.6 to 5.9.

4. *What we have to do with the patients already on ASV where we have to remove the equipment?*

It's a question where the French experts are answering very honestly. The frustration of patients who perceive the subjective benefits is completed by them of the doctors who are not founding recognized therapeutic alternative. They recommend[2] to setup a register of equipment removal in these patients allowing the collection of a maximum of information at the time and after ASV discontinuation (quality of life questionnaires, cardiovascular clinical data, reassessment of the LVEF not later than 6 months, biological data such as NTProBNP(natriuretic brain protein), or the results of a new poly(somno)graphy without ASV ventilation for patients whose initial test is old.

What we have to do in the future?

Of course as the authors of the French article are pointing out there are many things to do like[2]:

- to implement randomized prospective studies on large samples to assess the benefits of ASV in each of its indications.
- to have more prospective, randomized, long term studies, with the ASV on various etiologies of central SAS
- to register all that means (the number of patients per etiology, implementation modalities (CPAP failure, first-line prescription...), therapeutic benefits (correction of abnormal respiratory events, daytime alertness, quality of life) and tolerance of ASV (compliance, pressure tolerance), safety, reimbursement.

It's still much work to be done and every case has to be judge by a group of experts because the patient remain the most important piece in this puzzle where we have in this moment more contraindications as indications if they have Central SAS. ■

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