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ASV for 4 h per day improves NT-proBNP levels and the SF-36 physical component in heart failure with apnoea http://ow.ly/u4ryl

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From the authors:

D. Jaffuel and colleagues raised several important aspects with respect to our previously published randomised controlled trial of auto-servoventilation (ASV) in heart failure patients with sleep disordered breathing (SDB) [1]. We appreciate the opportunity to comment.

Their first point addresses the type of SDB we studied. Our aim was to include heart failure patients with an at least moderate degree of SDB. Therefore, the inclusion criterion was as clear and simple as an apnoea–hypopnoea index $\geqslant$20 events per hour of sleep, assessed by in-laboratory polysomnography. As a consequence, our sample encompassed the full spectrum of SDB types, from ''pure'' central sleep apnoea (CSA) to ''pure'' obstructive sleep apnoea (OSA), with some patients with coexisting CSA and OSA in the middle. Randomisation was stratified according to the predominant type of SDB, there being 36 patients with predominant OSA and 32 patients with predominant CSA in the trial. This design aspect allowed us to analyse the outcomes separately for CSA and OSA: both the changes in left ventricular ejection fraction (LVEF) and N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline to 12 weeks were similar in the ASV and control groups in both the OSA and the CSA patients (LVEF: OSA, 3.6$\pm$3.5%

versus 4.6±6.9%; CSA, 3.7±6.3 *versus* 3.4±7.0%; NT-proBNP: OSA, -243±483 ng·mL^{-1} *versus* 47±219 ng·mL^{-1}; CSA, -488±659 ng·mL^{-1} *versus* 246±912 ng·mL^{-1}). In summary, the subanalyses of CSA and OSA patients confirmed the analysis of the entire sample showing a similar increase of LVEF in the ASV and control groups as well as a greater reduction of NT-proBNP in the ASV compared with the control group. Our data did not support that ASV would be more effective in OSA than CSA or *vice versa*.

Secondly, D. Jaffuel and colleagues stress the important point that we observed cardiac worsening in 8% of the patients from the ASV group and 14% in the control group. As a consequence, the medical interventions (*e.g.* dose of diuretics) appeared to be higher in the control arm. One may speculate whether such mechanisms may contribute to a false-negative cardiac outcome in such studies. In the analysis of the present trial, we considered this mechanism and made an effort to alleviate this potential bias by providing the per protocol analyses without the patients with changes in cardiac medication within the trial period. For future trials, the suggested design aspects of a longer run-in period including the assurance of stable cardiac medication and the inclusion of cardiac worsening as an outcome in larger trials may contribute to rule out this potential bias.

The third point raises the question that, despite randomisation, important differences could influence the results as levels of NT-proBNP were higher in the control group compared with the ASV group. We statistically accounted for the higher NT-proBNP level in the control group and found a robust reduction of NT-proBNP in the ASV compared with the control group, respectively (-372±581 ng·mL^{-1} *versus* 142±640 ng·mL^{-1}, p=0.010) [1].

Fourthly, in the pre-specified subanalysis according to the time of ASV use, we did not find an increasing effect on LVEF associated with longer daily use of ASV. Similar to the majority of randomised controlled trials of ASV in heart failure patients with SDB, we did not find an effect of ASV on LVEF and confirmed a significant reduction of NT-proBNP by ASV [2–6]. The subanalyses of positive airway pressure (PAP) users (*e.g.* >4 h) are generally valuable, however, such analyses are only explanatory and can never provide the highest level of evidence. In our opinion, the better alternative would be adequately powered studies or a run-in period identifying potential participants who do not tolerate PAP therapy.

D. Jaffuel and colleagues' final point raises the question of ventilator mode and continuous PAP therapy as an alternative control group. So far, there is no clear evidence that PAP therapy improves cardiac outcome in heart failure patients on contemporary medical and device therapy. Therefore, the first step would be to provide such evidence before comparing different modes of PAP therapy.

In summary, it is important to note that, to date, PAP therapy is indicated in a large proportion of heart failure patients having SDB with SDB-related symptoms. In addition to symptom relief, in the clinical setting, the use of continuous PAP and ASV in heart failure patients with severe SDB is associated with improved survival [7, 8]. Therefore, at present, ASV is indicated and needed in a large number of heart failure patients with SDB and should be applied in specialised centres.

The present study [1] and the ongoing large long-term trials ADVENT-HF (www.clinicaltrials.gov identifier NCT01128816) and SERVE-HF (www.controlled-trials.com identifier ISRCTN19572887) aim to complement our knowledge by evaluating the question of whether the indication of ASV treatment can be extended to heart failure patients with moderate-to-severe SDB without related symptoms or to other subgroups of heart failure patients with SDB.

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Auto-servoventilation is indicated and needed in a large number of heart failure patients with SDB
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Sex matters in pulmonary arterial hypertension

To the Editor:

It has been known for a while that female sex is a risk factor for pulmonary arterial hypertension (PAH), but that women with the condition survive better than men [1–3]. Further light has been shed on this paradox by the excellent meta-analysis recently reported by VENTETUOLO *et al.* [4] in the *European Respiratory Journal*. The authors showed that female patients with idiopathic or connective tissue-associated PAH have higher cardiac output and lower pulmonary vascular resistance. The average differences in male patients were small, but sufficient to translate into a 5–8% difference in mortality. What could be the explanation of this?

Population studies have shown that female lungs differ from those of men. Women have smaller lungs, decreased maximal expiratory flow rates and lower lung diffusing capacities [5]. These sex-related differences in the respiratory system persist after adjustment for body dimensions, which has been referred to as a ''dysanapsis'', or unequal growth of the lung parenchyma and bronchial tree with respect to body size. However, smaller lungs at any given body size do not affect gas exchange [6] and, if anything, would increase rather than decrease pulmonary vascular resistance. The control of breathing is also different in women, with progesterone-dependent, increased peripheral chemosensitivity [7], which results in in slightly but significantly lower arterial partial pressure of carbon dioxide [8]. However, hypocapnia has been shown to be a predictor or poor survival in PAH [9]. As the prognostic impact of sex on PAH was lost after the age of 45 years, VENTETUOLO *et al.* [4] understandably thought of possible anti-remodelling effects of oestrogens or pro-remodelling effects of testosterone.

We previously reported exercise stress echocardiographic measurements of higher resistive vessel distensibility in healthy women compared with men, which limits the increase in pulmonary artery pressures as flow increases [10]. The difference smoothened out after the age of 45 years, very much like in the study by VENTETUOLO *et al.* [4]. This adds argument in favour of oestrogen.

The fascinating aspect of the study by VENTUOLO *et al.* [4] is that beneficial effects of oestrogen seem to persist in the extensively remodelled pulmonary resistive vessels of PAH patients. Whether this is mechanically similar can be tested by exercise stress measurements of the pulmonary circulation and recalculation of resistive vessel distensibility from a curvilinear fit of four or five pressure–flow coordinates [11]. This can be performed noninvasively.

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Pre-menopausal women with pulmonary arterial hypertension survive better than men
http://ow.ly/vGL7M

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