Recently, using the expensive and time-consuming ELISA method, HERESI *et al.* [10] have shown that plasma IL-6 concentrations >4.7 pg·mL^{-1} provide incremental prognostic information in PAH, with valid concentrations above the theoretical sensitivity (LLOD 0.7 pg·mL^{-1}). Similarly, using MSD multiplex technology, SOON *et al.* [2] showed that serum IL-6 was also associated with survival in PAH patients, with concentrations (19.87±7.45 pg·mL^{-1}) above the sensitivity (LLOQ 1.58 pg·mL^{-1}), making such a cytokine very promising for the prognosis of PAH.

In conclusion, multiplex analysis provides much information from a single biological sample, and is therefore popular and more frequently used in PAH studies. However, cytokine concentrations are low and often close to the sensitivity of the assay, depending on the multiplex assays. This currently prevents the routine clinical use of such biomarkers, and should encourage clinicians to take advantage of the biochemists' analytic experience.

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Sensitivity must be considered for cytokines when using multiplex technology in PAH-related clinical studies http://ow.ly/tAT9l

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Is auto-servoventilation unnecessary in patients with heart failure and apnoea?

To the Editor:

We read with great interest the recent report by ARZT *et al.* [1]. They investigated the potential benefit of auto-servoventilation (ASV) in addition to an optimal medical management (OMM) on cardiac function and quality of life in patients with congestive heart failure (CHF) coexisting with central and obstructive sleep apnoea (COSA). As the interest of ASV remains debated in patients with CHF and "pure" central sleep apnoea [2], there is no clear evidence of the superiority of ASV over constant positive airway pressure (CPAP) in patients with CHF and COSA [3–5]. In our opinion, some aspects of the report by ARZT *et al.* [1]

need to be underlined and discussed because of their potential daily clinical implications as well as the design of future studies.

First, depending on the study and the inclusion criteria, patients with CHF and COSA constitute heterogeneous populations with significant differences in the proportion of central sleep disordered breathing. In the study by ARZT *et al.* [1], central events represented <50% of the total events and there were no inclusion criteria based on the type of event. In other studies, such criteria on the proportion between central and obstructive events were used. For example, in a study by RANDERATH *et al.* [3], the central events needed to represent <80% of the total events, and the obstructive events need to represent between 20% and 50% of total events. As a consequence, without a consensus definition of ''COSA'', comparative analysis of the published studies is difficult and limited.

Second, the authors report the results of their study in an intention-to-treat (ITT) analysis and fail to demonstrate any statistical additional effect of ASV on the primary outcome (left ventricular ejection fraction (LVEF)). ITT is a very challenging analysis in studies comparing medical devices with strong adherence issues compared with drug trials. Of course, ITT analysis is the most rigorous and appropriate fashion to present the results, but the conclusions of the ITT analysis need to be relativised considering that 13 out of 32 of the patients allocated to ASV were excluded from analysis because of cardiovascular medication change (11 out of 31 patients in the OMM-alone group). In addition, three patients withdrew from the ASV group and two from the OMM-alone group, and one patient did not receive the allocated intervention. Unfortunately, the sample size for the primary outcome (improvement in LVEF of 4%) was calculated assuming a dropout rate of 15%. In our opinion, the great proportion of patients excluded because of cardiovascular medication changes stresses the need of a longer run-in period in future studies and/or a sample size calculated assuming a greater dropout rate. Alternatively, an evaluated outcome could be the number of cardiovascular medication changes during the study and/or cardiac worsening. In this regard, 8% of the patients in the ASV group presented a cardiac worsening *versus* 14% in the OMM-alone group.

Third, despite randomisation, important differences could influence the results. Levels of N-terminal brain natriuretic protein (NT-proBNP) were higher in the OMM-alone group (1611 ± 2102 *versus* 1039 ± 1034 $ng \cdot mL^{-1}$) and may be a potential cause of bias from regression to the mean. Treatments are also more important in this group (resynchronisation therapy, 17% *versus* 8%; loop diuretics, 91% *versus* 65%; β-blockers, 91% *versus* 78%). This suggests different haemodynamic statuses between the two groups not reflected by LVEF alone and New York Heart Association functional class. Other parameters of myocardial relaxation and contractility [6] or effort adaptation [7] are important parts of heart failure mechanisms. A simple functional evaluation such as the 6-min walking test is of great interest in these cases and is easily feasible in daily practice.

Fourth, the authors perform a very interesting pre-specified subanalysis with ASV compliance as the variable of interest ($\geqslant$4 h *versus* <4 h per night, *versus* OMM alone). Unfortunately, the results of the primary outcome (LVEF) were not reported in this pre-specified subanalysis, but the authors report statistically significant improvements in secondary outcomes including NT-proBNP levels and the physical component score of the SF-36 questionnaire in the group using ASV $\geqslant$4 h *versus* OMM alone. Future studies should include this type of subanalysis, which provides important additional information and hints to understand better the conflicting results from previous recent studies, as demonstrated recently [8, 9]. However, considering the number of patients included in this pre-specified subanalysis, it would be interesting to know if the results are still significant after a correction for multiple tests.

Fifth, a subanalysis with the level of ASV pressure as the variable may be of interest [3–5, 10]. Despite a study initially not powered to investigate this question, RANDERATH and TREML [5] have reported a reduction of the apnoea–hypopnoea index associated with a statistically significantly lower level of pressure treatment irrespective of the ventilator mode (ASV or CPAP). We have recently reported a pressure-dependent haemodynamic effect of CPAP in severe CHF [10]. To our knowledge, there are no evidence-based data on the superiority of one mode of ventilation over the other at an equal mean pressure. As a consequence, in patients with CHF and COSA, a control group with CPAP is an alternative option to the OMM-alone group or constitutes a potential third group of study.

In conclusion, patients with CHF and COSA are a heterogeneous population and studies are still needed to determine the predictive factors of failure or success of pressure support in these patients. In this regard, the results of the ADVENT-HF trial (Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure) [11] will be determinant. Furthermore, the SERVE-HF study should give us additional data [12]. In contrast to the ADVENT-HF study, patients included in the SERVE-HF study require $\geqslant$50% central events and correspond to a different phenotype of patients with CHF and apnoea.

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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%