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Muscle sympathetic nerve activity and adaptive servo-ventilation: questions remain

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Sudden cardiac death presumably due to cardiac arrhythmias is one of the hypotheses to explain the observed higher cardiovascular mortality in the adaptive servo-ventilation (ASV) group of the SERVE-HF study [1, 2]. In this regard, we congratulate TAMISIER et al. [3] for their efforts to clarify the effect of ASV on muscle sympathetic nerve activity (MSNA) in patients with central sleep apnoea (CSA) and heart failure with reduced left ventricular ejection fraction (HFrEF). Analysing data from an SERVE-HF ancillary study, they concluded that: 1) suppression of CSA with ASV did not seem to have a significant effect on chronic HFrEF-related sympathetic activation; and 2) simultaneous suppression of CSA and reduction in MSNA was associated with increased cardiovascular mortality. In our opinion, these conclusions might be different if some confounding factors were considered.

In addition to the limitation evoked by the authors (i.e. a type II error risk in the per-protocol analyses because of a lower number of patients in the ASV group (14 patients) than the calculated number of required subjects (16 patients)), we consider that the ASV efficiency on sleep disordered breathing (SDB) also needs to be questioned before acknowledging their conclusions. In the data reported in their table S3, 25% of patients adherent to ASV therapy had an apnoea-hypopnoea index (AHI) measured by polygraphy or polysomnography of at least 21.3 h⁻¹ and a sleep time with peripheral oxygen saturation (SpO₂) <90% of at least 43.5 min. It is a matter of fact that not only a residual AHI greater than 15 h⁻¹ under continuous positive airway pressure treatment [4] but also an SpO₂ time greater than 22 min [5] are associated with an excess in mortality of patients with CSA and chronic HFrEF.

Because TAMISIER et al. [3] initially hypothesised that ASV would reduce sympathetic tone by normalising breathing during sleep, the failure of ASV to address SDB for at least 25% of the population may have enhanced the risk of type II error. Reporting individual data and/or stratifying the data according to the efficacy of ASV on SDB before analysing variables such as MSNA, 24-h urinary catecholamine levels and cardiovascular mortality may help the journal readers to analyse this interesting SERVE-HF ancillary study. Stratified analyses of ongoing trials will need to take this ASV efficacy issue into account. Furthermore, these data reported by TAMISIER et al. [3] challenge the efficacy of ASV therapy in the SERVE-HF study [6]. It has been shown that the AHI reported by ASV devices is not as accurate as expected, hence the value of polysomnography monitoring under ASV treatment [7]. In the SERVE-HF study [6], ASV treated patients were considered effectively treated, but the measured AHI data were expressed as mean and minimum/maximum rather than median and quartile. This not only limits our ability to assess the true effectiveness of ASV therapy in the SERVE-HF study, but also to make a comparison with this ancillary study by TAMISIER et al. [3].

A limitation of this ancillary study pinpointed by the authors merits further detail. This ancillary study explored peripheral sympathetic vascular tone and not the cardiac sympathetic tone. In this regard, it is important to underline that peripheral sympathetic vascular tone measured using peroneal microneurography is not affected by medical treatments such as beta-blockers [8]. This is both a strength and a limitation: a strength because it is possible to isolate the impact of ASV on sympathetic tone, but a limitation because in real life, the patient's sympathetic tone is the result of multiple factors, including drug treatment.

In conclusion, more than definitive answers, this ancillary study provides insights that should determine the design of future research to limit confounding factors. Pending the result of the ADVENT-HF study, new studies are needed in the modern era taking into account the evolution of medical treatments for these patients [9] and in particular the potential impact of sacubritil/valsartan or gliflozin treatments on CSA [10].

Conflict of interest:

A. Bourdin has nothing to disclose. D. Jaffuel reports personal fees for lectures and meeting attendance from Philips Healthcare and Lowenstein, personal fees for meeting attendance from Resmed, personal fees for lectures and meeting attendance, and non-financial support for board membership from SEFAM, grants and personal fees for lectures from Novartis, personal fees for lectures from Jazz, personal fees for advisory board work from Bioproject, personal fees for lectures and non-financial support for board membership from NOMICS, outside the submitted work. F. Roubille reports grants and personal fees from Novartis, personal fees from AstraZeneca, Servier, Boehringer, Vifor, Bayer, Pfizer, Novonordisk, Air Liquide, Abott and Lilly, outside the submitted work. J.P. Mallet has nothing to disclose.

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