

PEER-REVIEW REPORT

Name of journal: World Journal of Respiriology

Manuscript NO: 41741

Title: Treatment of central sleep apnea in patients with heart failure: now and future

Reviewer's code: 02493519

Reviewer's country: Japan

Science editor: Ya-Juan Ma

Date sent for review: 2018-08-30

Date reviewed: 2018-09-03

Review time: 4 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

General and major comments The authors addressed a very important clinical issue with regard to the propriety of whether CSA associated with chronic heart failure should be actively treated applying the positive airway pressure (PAP). The authors summarized the clinical trials, including the short-term trial, the small-scale RCT, and

the large-scale, long-term RCT (CANPAP, SERVE-HF, and so on). The authors also introduced the large-scale RCT that is ongoing at present (ADVENT-HF). The most appealing finding in this field was harvested from the study of SERVE-HF (n= 1,325, observation period= 5 years) published in NEJM in 2015. The study showed no difference in the primary endpoint and a negative impact of PAP treatment (in this trail, ASV was applied) on the secondary endpoints such as all-cause mortality and cardiovascular mortality, though the AHI, ESS, and 6-min walking distance were indeed improved. Thus, these findings led the authors of SERVE-HF to recall the important role of the classical hypothesis that CSA has a variety of beneficial effects on cardiac function, including CSA-elicited inhibition of sympathetic nerve activity but augmentation of parasympathetic nerve activity, reduction in respiratory muscle work, increasing cardiac output due to inhibiting the swinging of thoracic pressure, and so on. Although the article is well written, the reviewer would require the authors to add the following matters, as well. 1) As at present, the SERVE-HF trial demonstrated the most valuable findings in the field of CSA in association with heart failure, the beneficial effects of CSA on maintaining or even improving the cardiac function should be argued more extensively quoting not only the paper published by the current author but also the appropriate historical literatures. 2) Although the reviewer knows that this may not be the focus in this editorial, the readers in WJR will also have much interest in the issue of whether OSA should be actively treated by the PAP therapy (CPAP) in patients concurrently having OSA and heart failure. The large-scale, long-term SAVE trial published in NEJM in 2016 addressed this issue. They concluded no benefit of CPAP treatment on the primary endpoints of cardiovascular mortality and frequency of hospital admission. The results obtained from the SAVE trail (for OSA) are qualitatively the same as those reported by the SERVE-HF (for CSA), indicating that irrespective of the type of sleep apnea (either CSA or OSA), the expensive, active PAP therapy has no

clinical benefit at all on the most important endpoint of improving the survival rate in patients with sleep apnea (CSA and/or OSA) and heart failure. These points should be discussed and included in the text. 3) The study design introduced by the ADVENT-HF trial is of great interest for the reviewer, because this design is essentially different from and unique in comparison with the designs employed by many other studies performed in the past, i.e., the ADVENT-HF trial targets both the heart-failure patients with CSA-predominant SAS and those with OSA-predominant SAS, resulting in that the ADVENT-HF does not separate the patients having heart failure and CSA from those having heart failure and OSA. The reviewer is quite convinced that the basic consideration adopted by the ADVENT-HF is essentially valid, because the subjects with significant CSA forcibly express OSA, as well. This is because the depression of respiratory center neurons during emergence of CSA concurrently inhibits the pharyngeal muscles opening the upper airway, leading to the upper airway collapse (i.e., occurrence of OSA). Therefore, the reviewer thinks that it is indispensable for estimating the treatment effect of sleep apnea without separating CSA and OSA in patients with heart failure. Based on these facts, the reviewer would require the authors to explain the unique design taken by the ADVENT-HF not superficially but more deeply. 4) The abbreviation of “ADHD” seems to be not explained in the text (p. 10)

INITIAL REVIEW OF THE MANUSCRIPT

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