Reply to Lalonde *et al*.

From the Authors:

We read with interest the response to our recent paper, "Effect of Continuous Positive Airway Pressure on Arrhythmia in Atrial Fibrillation and Sleep Apnea" (1), in which we conclude that continuous positive airway pressure (CPAP) did not result in a significant reduction in atrial fibrillation (AF) burden. We agree with Lalonde and colleagues that the study limitations include a relatively small sample size, a relatively short follow-up period of 5 months, and a "lower than anticipated" observed percentage of time in AF that decreased the power of the study. Thus, we cannot as such exclude a type II error. These are also discussed as limitations of the study in the original paper. However, we observed no trend toward a positive effect of CPAP treatment in the percentage of time in AF or in the number and duration of AF episodes measured by advanced measurement techniques, namely the gold standard implantable loop recorder.

Obstructive sleep apnea (OSA) has been associated with multiple cardiovascular conditions, including AF (2). Physiologically, it is easy to recognize that OSA might lead to AF and that CPAP could reduce AF burden. In reality, it remains unclear whether OSA is causally connected to AF or if the association just reflects a shared risk factor profile.

As noted by Lalonde and colleagues, several nonrandomized controlled trials and observational studies have suggested a favorable relationship between reduction in sleep-disordered breathing and lower recurrence of AF after cardioversion or pulmonary vein ablation (3). It is important to recognize that none of these observational trials used continuous monitoring of AF burden by loop recorders and that the positive results from these studies failed on first contact with a randomized controlled trial (RCT) (1, 4, 5). Also, results yet to be published from phase 2 of our trial (AF Recurrence Post Ablation) showed no difference between CPAP and usual care in AF recurrence (6).

Since the mid-1980s, CPAP therapy has been the first-line therapy for OSA, based on the fact that the CPAP device is a highly effective treatment modality in terms of reducing obstructive respiratory events (7). However, low adherence to CPAP is a problem, and the rate of CPAP adherence has remained persistently low for the past 20 years (8).

Although very effective in reducing respiratory events, CPAP therapy is not yet a proven adjunct to manage cardiovascular disease. Recent RCTs have demonstrated that CPAP treatment has a neutral effect on secondary cardiovascular prevention (9, 10).

The large SAVE (CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea) RCT showed that CPAP did not decrease cardiovascular events, including AF (11). However, use of CPAP resulted in significant beneficial effects on daytime sleepiness, quality of life, mood, and work productivity, with a fairly low mean adherence of 3.3 hours per night (11). In contrast, the mean adherence to CPAP therapy in our study was above the recommended limit of 4 hours per night, and the apnea–hypopnea index decreased significantly from 27.6 events per hour at baseline to 2.3 events per hour during treatment, demonstrating good sleep apnea control. Potential bias from the subjective nature of a questionnaire remains.

Unanticipated harm from seemingly beneficial interventions cannot be ignored in the treatment of cardiovascular diseases. In our study, a total of nine serious adverse events occurred in eight patients: seven events in the CPAP group and two in the control group. Although the numbers are small, this CPAP story should sound familiar.

Despite the promise of multiple observational studies and short-term RCTs, treatment of central sleep apnea by adaptive servo-ventilation in patients with heart failure resulted in an increased risk of cardiovascular deaths (SERVE-HF [Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure] trial) (12). Taking this into account, it would be irresponsible to discount any possibility of harm related to CPAP therapy in patients with AF.

Kiely and colleagues demonstrated that cardiac output was reduced when positive airway pressure was delivered in patients with AF compared with those in sinus rhythm (13). Thus, we cannot assume benefit, or even lack of harm, when treating patients with AF with CPAP.

The prevalence of OSA in the general population is high, but most have minimal symptoms (14, 15). The threshold for diagnosing sleep apnea is so low that the majority of the adult male population will qualify as having the disease. Not everyone diagnosed with a sleep disorder will benefit from CPAP. Among patients with AF, more than 80% and more than 40% have apnea–hypopnea indexes above 5 and 15 events per hour, respectively (16), but we still lack the data to prove they will benefit from CPAP.

Meanwhile, CPAP continues to underperform in RCTs, and there is no evidence that treating OSA in these patients prevents AF burden or recurrence.

Current European Society of Cardiology 2020 guidelines for the diagnosis and management of AF state, "Optimal management of OSA may be considered, to reduce AF incidence, AF progression, AF recurrences, and symptoms. However, it remains unclear how and when to test for OSA and implement OSA management in the standard work-up of AF patients" (class of recommendation and level of evidence: IIb, C) (17). At this time, it would be unjustified to recommend universal screening for OSA in patients with AF. ■

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