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## Sleep Apnea and the Risk of Atrial Fibrillation Recurrence: Structural or Functional Effects?

Daniel J. Gottlieb, MD, MPH

A strong association between obstructive sleep apnea (OSA) and atrial fibrillation has been consistently observed in both epidemiological and clinical cohorts, and multiple studies demonstrate that OSA is associated with an increased risk of atrial fibrillation recurrence following chemical or electrical cardioversion or pulmonary vein isolation by catheter ablation. The study by Neilan et al, in this issue of the *Journal of the American Heart Association*,<sup>1</sup> adds to a growing number of studies demonstrating that not only is OSA associated with an increased risk of atrial fibrillation recurrence following pulmonary vein isolation, but also that treatment with continuous positive airway pressure (CPAP) appears to eliminate this excess risk.<sup>2-4</sup> These studies share certain important methodological limitations. The presence of OSA was systematically assessed in only one study<sup>4</sup>; in the others it was based on a prior diagnosis of OSA at the time of pulmonary vein isolation. The “non-OSA” groups therefore almost certainly include many patients with OSA, likely resulting in underestimation of the association of OSA with atrial fibrillation recurrence compared with non-OSA controls, while overestimating the benefits of OSA treatment. Adherence to CPAP was generally based on self-report, and thus likely overestimated, which would lead to an underestimate of the benefits of CPAP. Most importantly, none of these studies was a randomized clinical trial. As CPAP non-adherence may be a marker of poorer adherence to other recommended medical therapies that could affect the recurrence of atrial fibrillation, this could lead to an overestimate of the benefits of CPAP therapy. Notwithstanding these limitations, the

consistency of the observations in these clinical cohorts contributes to a body of evidence that strongly implicates OSA as a cause, and not merely a correlate, of atrial fibrillation.

Obstructive sleep apnea is characterized by repeated episodes of partial or complete pharyngeal collapse during sleep, resulting in large negative swings in intrathoracic pressure during attempts to ventilate through the obstructed airway (Mueller maneuver), intermittent hypercapnic hypoxia, and arousal at the termination of the obstructive events. The negative intrathoracic pressure results in large changes in transmural pressure and atrial volume, while both hypercapnic hypoxia and arousal increase sympathetic nervous system activation and result in large surges in blood pressure. These consequences of OSA are likely responsible for well-documented cardiac structural changes, including increases in left ventricular mass index<sup>5</sup> and left atrial volume.<sup>6</sup> In a sample of patients with severe OSA, normal left ventricular ejection fraction, and no history of atrial fibrillation studied with cardiac magnetic resonance imaging before and 6 and 12 months after initiation of CPAP, it was shown that CPAP treatment was associated with a marked decrease in left ventricular mass index and both left and right atrial volume indices.<sup>7</sup> As left atrial diameter is a known predictor of recurrence of atrial fibrillation, cardiac structural changes are plausibly responsible for the elevated rates of recurrence observed in patients with OSA. Neilan and colleagues sought to explore this possibility by determining whether treatment of OSA leads to beneficial cardiac remodeling in a population with atrial fibrillation, and whether such beneficial remodeling mediated a reduction in the risk of recurrent atrial fibrillation following pulmonary vein isolation.<sup>1</sup> In addressing this question they take advantage of cardiac magnetic resonance imaging performed as a routine component of the pre-ablation evaluation, presenting the largest sample of OSA patients to date evaluated with this state-of-the-art measure of cardiac structure and function. Consistent with prior echocardiographic studies, they find that the strongest structural correlates of OSA are higher left ventricular mass index and larger left atrial diameter. Moreover, these differences are accounted for almost entirely by CPAP-non-adherent patients, while patients reporting CPAP use >4 hours per night have

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From the VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA.

**Correspondence to:** Daniel J. Gottlieb, MD, MPH, VA Boston Healthcare System (111PI), 1400 VFW Parkway, West Roxbury, MA 02132. E-mail: djgottlieb@partners.org

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left ventricular mass index and left atrial diameter that are virtually identical to those in the “non-OSA” group. As CPAP treatment had been initiated in advance of magnetic resonance imaging, the authors conclude that treatment with CPAP led to beneficial cardiac remodeling. While the data are consistent with this interpretation, the availability of cardiac imaging at only a single time point markedly limits the strength of inferences that can be drawn regarding structural remodeling.

Unfortunately, the authors did not take full advantage of the available data to address the important question they pose: whether the lower incidence of recurrent atrial fibrillation in treated OSA is a result of the posited beneficial effect of treatment on cardiac structure (and conversely, whether cardiac structural abnormalities explain the increased risk of recurrence in untreated OSA). No formal mediation analysis is presented. The multivariable proportional hazards regression that the authors present, however, suggests that structural changes may not underlie the increased recurrence risk in untreated OSA, at least so far as left atrial dimension is concerned. In this model, although left atrial dimension is significantly associated with increased risk of recurrence, the adjusted hazard ratio for recurrent atrial fibrillation in untreated OSA (compared with no OSA) is 2.8 (95% confidence interval, 2.0 to 3.9), similar to the crude difference in recurrence between these groups. This is consistent with the similar findings in studies of like design,<sup>2,3</sup> although as cardiac imaging was not repeated following the baseline evaluation, one could speculate that remodeling occurring during the period of follow-up might have reduced the risk of recurrence. (No inference can be made with regard to left ventricular mass index, which was not included in this model.) Given the high prevalence of OSA in patients with atrial fibrillation, and the apparent large effects of CPAP treatment on rates of recurrence following pulmonary vein isolation, it would not be difficult to design an adequately powered randomized clinical trial to conclusively determine whether CPAP therapy in fact reduces the risk of late recurrence of atrial fibrillation, a finding that would have major implications for clinical practice. By embedding a repeat measure of cardiac structure at an appropriate interval after the initiation of CPAP therapy, it would be possible to clarify the true effect of OSA treatment on cardiac remodeling, and provide an opportunity to formally test the extent to which such remodeling mediates the observed reduction in risk of recurrent atrial fibrillation.

There is good reason to expect, however, that the mechanisms whereby CPAP therapy protects against recurrent atrial fibrillation are not operating through cardiac structural remodeling. It has been shown that the risk of paroxysmal atrial fibrillation is markedly increased in the immediate post-apnea period,<sup>8</sup> suggesting that acute effects

of the obstructed breathing events may be important triggers for induction of atrial fibrillation. This may reflect the effects of acute gas exchange abnormalities, changes in autonomic activity, or the mechanical effects of large intrathoracic pressure swings. Hypoxemia following obstructed breathing events is commonly cited as a potential mediator of atrial fibrillation in OSA, although more recently an important role has been suggested for hypercapnia, which acutely reduces vulnerability to atrial fibrillation by increasing atrial effective refractory period, but increases vulnerability to atrial fibrillation through increased atrial conduction time, which persisted following return to eucapnia in an animal model.<sup>9</sup> Increases in cardiac sympathetic and parasympathetic activity have been demonstrated to precede the onset of fibrillation in pacing-induced models of atrial fibrillation.<sup>10</sup> More recent studies have suggested the importance of both autonomic systems in rendering the atria at increased risk of fibrillation following induced apneas.<sup>11,12</sup> Linz has emphasized the particular importance of negative intrathoracic pressure in promoting atrial fibrillation through vagal activation, which results in a marked shortening of the atrial effective refractory period.<sup>12</sup> In these animal models, combined beta-blockade plus atropine,<sup>11</sup> anterior right ganglionic plexus ablation,<sup>11</sup> or renal sympathetic denervation,<sup>12</sup> but not beta-blockade alone, prevented the induction of atrial fibrillation. The large changes in atrial dimension that have been demonstrated during the Mueller maneuver in humans<sup>13</sup> might also acutely alter atrial electrophysiology.

Whether it is the acute effects of apneic events or the chronic structural changes resulting from OSA that predispose to recurrent atrial fibrillation may have important therapeutic implications. If it is the former, specific treatment of OSA with CPAP, or an alternative therapy that controls OSA, may be needed to reduce risk of recurrence. This will likely be a considerable clinical challenge, as only half of patients with diagnosed OSA in the study by Neilan<sup>1</sup> were adherent to CPAP; this figure would likely be even lower if OSA was identified by routine screening of patients with atrial fibrillation, because most OSA cases so identified do not report excessive sleepiness.<sup>4</sup> On the other hand, if it is the autonomic effects of acute apneic events that trigger recurrent atrial fibrillation, there may be effective alternatives to prevent OSA-related recurrence for the many patients with comorbid atrial fibrillation and OSA who are intolerant of CPAP. These may include pharmacologic modalities, renal sympathetic denervation, or modification of the ablation procedure to include superior vena cava, as well as pulmonary vein, isolation, as has been suggested elsewhere for patients with OSA.<sup>14</sup>

## Disclosures

None.

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