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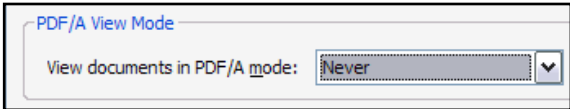
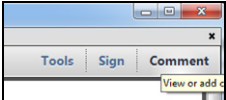
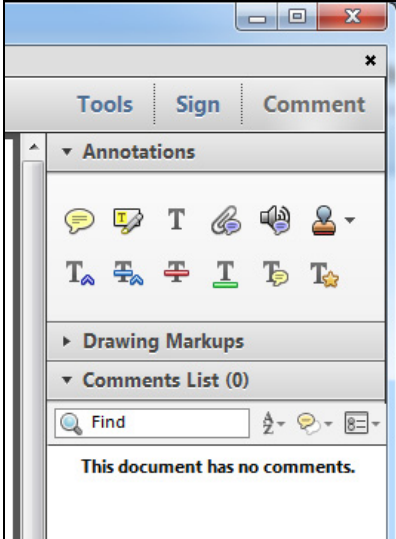
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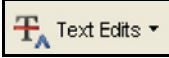


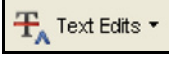

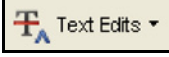







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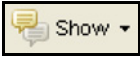
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EDITORIAL COMMENT

Obstructive Sleep Apnea and Atrial Fibrillation: Is the Link Real?*

Q6 Q1 Atul Malhotra, MD,† Sanjiv M. Narayan, MD,† Tomas G. Neilan, MD,§ Kathleen Sarmiento, MD, MPH†

Increasingly compelling data link obstructive sleep apnea (OSA) to cardiovascular impact, independent of known comorbidities (1). OSA is estimated to affect ~10% of individuals (2), a figure that has been increasing due to the obesity pandemic and an aging population, both of which contribute to OSA risk (3). In addition, diagnostic technology has become more sensitive over time such that the earlier prevalence of OSA was likely underestimated, and the prevalence in patients with cardiovascular disease is likely to be considerably higher than 10% (estimated 50% to 80%), although rigorous epidemiological data are still evolving (4,5). OSA is defined by repetitive collapse of the pharyngeal airway during sleep, resulting in fluctuations in intrathoracic pressure, hypoxemia, hypercapnia, and catecholamine surges (6). Hypoxemia and hypercapnia generate pulmonary artery vasoconstriction, leading to right heart strain. In addition to autonomic abnormalities, inflammatory pathways have been implicated in OSA, perhaps as a result of hypoxemia plus obesity (7).

Although OSA has been associated with atrial fibrillation (AF) (8), definitive causal data are still

lacking (9). Several theoretical possibilities may explain an interaction between OSA and AF:

- 1) Given that both OSA and AF are reaching epidemic proportions, their association may be based on chance alone, perhaps resulting from common risk factors such as obesity and aging. However, epidemiological data suggest that OSA independent of obesity is associated with AF; that obesity independent of OSA is associated with AF, particularly in younger individuals (10); and that weight loss in obese individuals (11) or primary treatment of OSA (8,12) can reduce the burden of AF. Thus, the link between OSA and AF seems more than an association due to chance.
- 2) OSA may predispose to AF via some combination of intrathoracic pressure swings yielding atrial chamber stretch, surges in catecholamines leading to elevated left ventricular end-diastolic pressure, and, perhaps, increased systemic inflammation in OSA leading to AF risk. OSA has been associated with ventricular remodeling/fibrosis and atrial chamber dilation, both of which are contributors to AF (13).
- 3) AF could theoretically worsen OSA. Reduced forward flow can destabilize ventilatory control, and elevated left atrial pressure may cause ventilatory control instability (6,14). Whether restoration of normal sinus rhythm leads to improvement in OSA severity is unclear.
- 4) The primary mechanisms for AF could be caused by OSA (15). Indeed, unless OSA is addressed, pulmonary vein ablation to eliminate triggers has shown high AF recurrence rates in patients with OSA. Mechanistically, OSA may create particular difficulty in achieving durable pulmonary vein isolation, contribute to trigger formation outside the pulmonary veins, or promote AF-maintaining substrates by swings in intrathoracic pressure and atrial stretch. For instance, localized electrical circuits (rotors) in diverse bi-atrial locations may

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the †Pulmonary, Critical Care and Sleep Medicine Division, University of California San Diego and UCSD Veteran Affairs Medical System, La Jolla, California; ‡Cardiology Division, Stanford University, Palo Alto, California; and the §Division of Cardiology, Department of Medicine, Cardiac MR PET CT Program, Division of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. Dr. Malhotra has received research funding from the National Institutes of Health and the American Heart Association. Dr. Narayan is the inventor on intellectual property owned by the University of California Regents relating to atrial fibrillation, and licensed to Topera, Inc., and owns equity in Topera, Inc.; he also reports financial relationships with Medtronic and Biotronik. Dr. Narayan has also received research funding from the National Institutes of Health and the American College of Cardiology. Dr. Neilan is funded by the American Heart Association (12FTF12060588), and Dr. Sarmiento is funded by the American Sleep Medicine Foundation.

sustain human AF (16), and ablating such sources in patients with OSA can improve success over pulmonary vein isolation alone.

In this issue of the *Journal*, important light is shed on the link between AF and OSA via a sophisticated, newly developed animal model. Iwasaki et al. (20) provide evidence that repetitive induction of apnea promotes AF in a mechanically ventilated rat model. Compared with 2 groups of control animals, with open respiration (no ventilator) or sham ventilation (no obstruction), those with induced apnea displayed substantially enhanced AF inducibility on invasive electrophysiological testing, slowing of atrial conduction velocity on optical mapping, down-regulation of connexin 43 (important for electrical wave propagation), and increased atrial fibrosis. The authors also observed marked changes in left ventricular structure, with hypertrophy, dilation, and diastolic dysfunction. The authors concluded that induced obstruction caused atrial conduction to slow and promoted AF inducibility. These mechanistic data are likely to provide reassurance of the clinical importance of the observed associations.

Despite the novel findings, a number of questions remain for both clinicians and scientists. First, does the model of Iwasaki et al. (20) mirror clinical OSA? Other than the animals' obvious lack of metabolic

abnormalities and obesity, the technical aspects of induced obstruction seem appropriate. Electrophysiologically, there has been recent doubt that refractory period shortening contributes to human AF (18), despite earlier studies (19). Indeed, Iwasaki et al. did not observe shortened refractoriness, whereas their results implicating conduction slowing from fibrosis and connexin down-regulation in causing AF are compelling. Second, do these results support ongoing clinical studies testing whether patients with AF should routinely be screened for OSA? Third, these data suggest that AF related to OSA is substrate based rather than trigger based, explaining the limitations of pulmonary vein isolation and further motivating approaches to define AF-maintaining substrates. Fourth, does AF promote OSA, and if so, does treatment of AF improve OSA? Given the recent emphasis on the multifactorial nature of OSA pathogenesis, perhaps OSA patients with unstable ventilatory control would be particularly amenable to addressing issues regarding AF and cardiac function (6). We applaud Iwasaki et al. (20) for these new insights.

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KEY WORDS atrial pressure, connexin 43, lung, models, animal, pulmonary veins, rats, ventricular remodeling