A link between A-fib and sleep apnea is no surprise, but why?

Patients with atrial fibrillation (A-fib) are often also diagnosed with sleep apnea, as noted and discussed by Ayache et al (page 709) in this issue of the *Journal*. It is well recognized that A-fib is more prevalent in older patients and is associated with many comorbidities, including hypertension, diabetes mellitus, coronary artery disease, heavy alcohol use, obesity, and some valvular disorders, in addition to the association with sleep apnea. While causation (as distinct from association) is virtually impossible to prove from observational and epidemiologic studies alone, many of the above comorbidities are recognized before the onset of the A-fib. Sleep apnea shares many of these comorbidities, and thus it is no surprise that a significant proportion of patients with A-fib are diagnosed with it. But sleep apnea, with its associated intermittent hypoxia, seems to promote the onset or worsen the course of A-fib in some patients.

Is the relationship between A-fib and sleep apnea more than a coincidence stemming from the number of shared associated comorbidities? Significantly, the treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) has been shown to decrease the recurrence of A-fib after pharmacologic or electrical conversion and after interventional pulmonary vein interruption.[1] This suggests that at least in some cases, sleep apnea plays an active role in initiating and possibly also maintaining A-fib. The immediate culprit mediators that come to mind are hypoxia and hypercapnea; both are at least partially ameliorated by the successful use of CPAP, and both are reasonable physiologic candidates for induction of A-fib. Hypoxia is supported by clinical observation, and hypercapnea by experimental modeling.[2]

It is easy for clinicians to conceptualize the organ effects of hypoxia and hypercapnea. We are accustomed to seeing clinical ramifications of these in the emergency department and intensive care unit, particularly those affecting the brain and heart, organs critically dependent on transmembrane ion flow. We may recall from biochemistry classes the effects of hypoxia on intracellular metabolism and the implications on energy stores, mitochondrial function, and ion translocation. Recent work on the cellular effects of hypoxia, including research that resulted in a Nobel prize, has drawn major attention to patterned cellular responses to intermittent and persistent hypoxia. This includes recognition of epigenetic changes resulting in localized cardiac remodeling and fibrosis,[3] factors that clearly affect the expression of arrhythmias, including A-fib.

But the interrelationship between A-fib and sleep apnea may be even more convoluted and intriguing. It now seems that most things cardiac are associated with inflammation in some guise, and the A-fib connection with sleep apnea may not be an exception. Almost 20 years ago, it was recognized that A-fib is associated with an elevation in circulating C-reactive protein (CRP),[4] a biomarker of "inflammation," although not necessarily an active participant. Recent reviews of this connection have been published,[5] and successful anti-inflammatory approaches to preventing A-fib us-

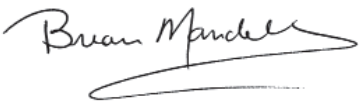
doi:10.3949/ccjm.86b.11019

ing colchicine have been described.[6] So how does this tie in with sleep apnea?

A number of papers have now demonstrated that sleep apnea is also associated with an elevation in CRP,[7] perhaps due to increases in tumor necrosis factor (TNF)-alpha in response to the intermittent hypoxia of sleep apnea. TNF can drive the inflammatory response through increased expression of genes regulated by nuclear factor kappa-B.[8] While it certainly warrants consideration that the elevated biomarkers of inflammation in patients with sleep apnea actually reflect the presence of the frequent comorbidities, including visceral obesity, treating sleep apnea with CPAP (comparable to what I noted above in patients with A-fib) has been shown to reduce circulating CRP levels.[9]

As our understanding of the biologic underpinnings of A-fib and sleep apnea continue to grow, the practical clinical implications of the relationship between them, as described by Ayache et al, may achieve greater clarity. The two conditions commonly coexist, and treating the sleep apnea results in better rhythm-directed outcomes in the A-fib.

Stay tuned, there is certainly more to learn about this.



BRIAN F. MANDELL, MD, PhD
Editor in Chief

1. **Shukla A, Aizer A, Holmes D, et al**. Effect of sleep apnea treatment on atrial fibrillation recurrence: a meta-analysis. JACC Clin Electropysiol 2015; 1(1–2):41–51. doi:10.1016/j.jacep.2015.02.014
2. **Stevenson IH, Roberts-Thomson KC, Kistler PM, et al**. Atrial electrophysiology is altered by acute hypercapnea but not hypoxemia: implications for promotion of atrial fibrillation in pulmonary disease and sleep apnea. Heart Rhythm 2010; 7(9):1263–1270. doi:10.1016/j.hrthm.2010.03.020
3. **Zhang W, Song M, Qu J, Liu G**. Epigenetic modifications in cardiovascular aging and diseases. Circ Res 2018; 123(7):773–786. doi:10.1161/CIRCRESAHA.118.312497
4. **Chung MK, Martin DO, Sprecher D, et al**. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001; 104(24):2886–2891. doi:10.1161/hc4901.101760
5. **Guo Y, Lip GY, Apostolakis S**. Inflammation in atrial fibrillation. J Am Coll Cardiol 2012; 60(22):2263–2270. doi:10.1016/j.jacc.2012.04.063
6. **Lee JZ, Singh N, Howe CL, et al**. Colchicine for prevention of post-operative atrial fibrillation: a meta-analysis. JACC Clin Electrophysiol 2016; 2(1):78–85. doi:10.1016/j.jacep.2015.09.016
7. **Van der Touw T, Andronicos NM, Smart N**. Is C-reactive protein elevated in obstructive sleep apnea? A systematic review and meta-analysis. Biomarkers 2019; 24(5):429–435. doi:10.1080/1354750X.2019.1600025
8. **Ryan S, Taylor CT, McNicholas WT**. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnea syndrome? Thorax 2009; 64(7):631–636. doi:10.1136/thx.2008.105577
9. **Ishida K, Kato M, Kato Y, et al**. Appropriate use of nasal continuous positive airway pressure decreases elevated C-reactive protein in patients with obstructive sleep apnea. Chest 2009; 136(1):125–129. doi:10.1378/chest.08-1431