argument that opiates may have been used secondarily for sedation and portended unfavorable endpoints. It may therefore be prudent to incorporate an analgesia-first approach using validated pain assessment tools to guide the administration of analgesics targeted to treat pain and pain alone (5) and using a multimodal pain management technique (pharmacological and nonpharmacological) to reduce opiate use (1). Once pain is addressed if sedation is required because of agitation and inability to redirect patients, one can then use either propofol or dexmedetomidine—both agents with similar risks for delirium yet with a superior profile over benzodiazepines (9–11). Although the study by Duprey and colleagues does not prove causation or compare head to head an analgosedation and an analgesia-first approach, it provides clinicians with a clearer understanding of the risks associated with opiates and sets the stage for a comparative trial of these two approaches in critically ill patients to determine the best strategies to address pain in this era of light sedation. ■

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References

1. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, *et al.* Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018;46:e825–e873.
2. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, *et al.*; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators; ANZICS Clinical Trials Group. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med* 2012;186:724–731.
3. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, *et al.* Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;104: 21–26.
4. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, *et al.* Caring for critically ill patients with the ABCDEF bundle: results of the ICU Liberation Collaborative in over 15,000 adults. *Crit Care Med* 2019;47: 3–14.
5. Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, *et al.* Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* 2003;58: 76–81.
6. Duprey MS, Dijkstra-Kersten SMA, Zaal IJ, Briesacher BA, Saczynski JS, Griffith JL, *et al.* Opioid use increases the risk of delirium in critically ill adults independently of pain. *Am J Respir Crit Care Med* 2021;204:566–572.
7. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, *et al.* Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma* 2008;65:34–41.
8. Agarwal V, O'Neill PJ, Cotton BA, Pun BT, Haney S, Thompson J, *et al.* Prevalence and risk factors for development of delirium in burn intensive care unit patients. *J Burn Care Res* 2010;31:706–715.
9. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, *et al.*; Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012;307: 1151–1160.
10. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared with Midazolam) Study Group. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med* 2010;38:2311–2318.
11. Hughes CG, Mailloux PT, Devlin JW, Swan JT, Sanders RD, Anzueto A, *et al.*; MENDS2 Study Investigators. Dexmedetomidine or propofol for sedation in mechanically ventilated adults with sepsis. *N Engl J Med* 2021;384:1424–1436.

Atrial Fibrillation, Obstructive Sleep Apnea, and Continuous Positive Airway Pressure: No Easy Fix

Sleep apnea (SA) and atrial fibrillation (AF) are common conditions that frequently coexist; the relationship between the two is complex and probably bidirectional (1, 2). However, whether treating patients with SA with continuous positive airway pressure (CPAP) influences the amount or duration of AF is unknown. In this issue of the *Journal*, Traaen and colleagues (pp. 573–582) report the first randomized controlled trial (RCT) to determine the effects of CPAP on AF in patients with paroxysmal AF. They convincingly demonstrate that CPAP treatment does not affect the burden of AF after 5 months of therapy (3).

This is an important area of research. Both AF and SA are not only related to debilitating symptoms in some but are also associated with embolic stroke risk. Risk management is key to stroke prevention. The trial was well designed; patients with AF were recruited from secondary care, either from cardiology clinics or patients referred for catheter ablation. All patients were screened for SA with two nights of respiratory polygraphy at home. Patients were enrolled with a mean AHI of >15 events/hour conventionally used to categorize moderate and severe SA;

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SA was common in this population, 42% of patients screened fulfilled these criteria. The majority of respiratory events were obstructive. An ESS >15 was an exclusion for the trial. Overall, 18 patients were excluded because they were too sleepy; of these, 12 also met other exclusion criteria. All patients had a CPAP run in period and, after a week off CPAP, an implantable loop recorder inserted. Patients were then randomized to receive either supportive care only ($n = 54$) or supportive care together with CPAP ($n = 55$) for 5 months. The primary endpoint was time in AF over the last 3 months of the trial compared with the month before randomization.

The mean time in AF (i.e., the AF burden) decreased from 5.6% at baseline to 4.1% during the last 3 months of CPAP intervention and from 5.0 to 4.3% in the control group. The adjusted between-group difference at follow up was −0.63 (95% confidence interval, −2.55 to 1.30) percentage points. There was no significant difference between the two groups.

The headline is interesting, but is it surprising? It is certainly biologically plausible that effective intervention to prevent hypoxemia and airway occlusion might be expected to reduce the arrhythmia burden. Preclinical models demonstrate autonomic dysfunction caused by intrathoracic pressure swings, hypoxia, hypercapnia, and intermittent airway occlusion result in electrical changes within the atria that predispose to AF (1, 2). In addition, observational studies reported that CPAP treatment of OSA was associated with a reduction in AF (4); however, a small RCT in mild (AHI > 5) nonsleepy patients with SA after cardioversion showed no benefit of CPAP in preventing recurrence of AF (5). Although the trigger to initiate AF, particularly from the pulmonary veins, plays a role in paroxysmal AF, the underlying substrate that promotes and maintains the irregular rhythm becomes increasingly important as the arrhythmia progresses. The alteration of electrical properties when persistent can lead to structural remodeling of atrial tissue to promote AF. The concept of "AF begets AF" has been well established for more than 25 years (6). Effective lifestyle modifications have been shown to be able to reverse this vicious circle. Abstaining from alcohol (7) and weight loss (8) have both been shown to reduce AF burden in RCTs. So why did this well-designed RCT fail to show an effect for CPAP in this patient group?

It is possible of course that that treatment of SA with CPAP has no effect on AF. This seems unlikely given the persuasive preclinical and observational data; however, following SERVE-HF (9), unexpected RCT findings regarding the use of respiratory support in cardiac patients should not be dismissed. It seems more likely that the trial was underpowered; the authors noted the AF burden in the study was lower than anticipated, and therefore the power to detect a 25% difference between the two groups diminished. There must also be questions about the optimal nightly adherence of CPAP, which, in the prevention of AF, might be far in excess of the 4-hour threshold shown to change sleepiness or general cardiovascular risk. If the possible benefits of therapy require cardiac structural remodeling, then perhaps 5 months of using CPAP is insufficient to see an effect. The exclusion of patients most likely to benefit from CPAP (i.e., those who are most sleepy) introduces a bias more difficult to address. The inclusion and randomization of sleepy patients raises ethical concerns. It is probably not correct to withhold a treatment known to reduce both individual morbidity and dangers posed by sleepy individuals to themselves and wider society.

This trial sits within the wider context of other recent disappointing results from RCTs in patients with SA in which CPAP treatment has failed to meet primary cardiovascular endpoints (10–12). A call for better phenotyping, innovative study design using observational studies with propensity matching (13), or an adaptive RCT design in which nonadherent patents might be rerandomized to improve trial efficacy (14) have been suggested to address these issues.

The authors should be congratulated for delivery of an RCT that includes a CPAP run-in period and uses implantable loop recorders to obtain robust arrhythmia data as a primary endpoint in this study, akin to contemporary AF studies (15), over and above the requirements of the AF consensus statement (16). For the moment, there remains no high-quality evidence that CPAP treatment influences the burden of AF in SA. We shall wait with interest for phase II of this study (2) to shine light on whether CPAP will influence the arrhythmia outcome after catheter ablation in this group of patients. ■

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References

1. Linz D, McEvoy RD, Cowie MR, Somers VK, Nattel S, Lévy P, *et al.* Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review. *JAMA Cardiol* 2018;3:532–540.
2. May AM, Van Wagoner DR, Mehra R. OSA and cardiac arrhythmogenesis: mechanistic insights. *Chest* 2017;151:225–241.
3. Traaen GM, Aakerøy L, Hunt TE, Øverland B, Bendz C, Sande LØ, *et al.* Effect of continuous positive airway pressure on arrhythmia in atrial fibrillation and sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2021;204:573–582.
4. Abe H, Takahashi M, Yaegashi H, Eda S, Tsunemoto H, Kamikozawa M, *et al.* Efficacy of continuous positive airway pressure on arrhythmias in obstructive sleep apnea patients. *Heart Vessels* 2010;25:63–69.
5. Caples SM, Mansukhani MP, Friedman PA, Somers VK. The impact of continuous positive airway pressure treatment on the recurrence of atrial fibrillation post cardioversion: a randomized controlled trial. *Int J Cardiol* 2019;278:133–136.
6. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation* 1995;92:1954–1968.
7. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, *et al.* Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;382:20–28.
8. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, *et al.* Effect of weight reduction and cardiometabolic risk

factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;310:2050–2060.
9. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, *et al.* Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;373:1095–1105.
10. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, *et al.*; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;375:919–931.
11. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, *et al.*; Spanish Sleep Network. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med* 2020;8:359–367.
12. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016;194:613–620.
13. Pack AI, Magalang UJ, Singh B, Kuna ST, Keenan BT, Maislin G. Randomized clinical trials of cardiovascular disease in obstructive sleep apnea: understanding and overcoming bias. *Sleep (Basel)* 2021;44: zsaa229.
14. McEvoy RD, Sánchez-de-la-Torre M, Peker Y, Anderson CS, Redline S, Barbe F. Randomized clinical trials of cardiovascular disease in obstructive sleep apnea: understanding and overcoming bias. *Sleep (Basel)* 2021;44:zsab019.
15. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, *et al.*; Document Reviewers. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;20:e1–e160.
16. Haldar S, Khan HR, Boyalla V, Kralj-Hans I, Jones S, Lord J, *et al.* Catheter ablation vs. thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: CASA-AF randomized controlled trial. *Eur Heart J* 2020; 41:4471–4480.

A Ginger Root or Plum Model for the Tuberculosis "Granuloma"?

Many tuberculosis (TB) researchers tend to view lung lesions as largely spherical "granulomas" and cavities as granulomas that have become necrotic, expand, and erode into bronchi. Clinical TB pathologists and radiologists, on the other hand, are aware that this image is an oversimplification, partially induced by the shift from human autopsies to animal models for immunopathology studies. Pioneering clinical histopathology studies from the preantibiotic era showed that postprimary disease begins as infection of lipid-laden foamy alveolar macrophages and bronchiolar obstruction progressing to caseating cavitary disease. Dissemination primarily happens via bronchogenic rather than lymphatic and hematogenous spread (1–6). Radiologically, bronchiole and alveolus obstruction correspond to the tree-in-bud patterns commonly seen in computed tomography (CT) scans of adult TB, as shown in postmortem thin section CT (7). Over the past decade, the CT component of positron emission tomography (PET)-CT has revealed wide networks of connected lesions with complex morphology and bronchial thickening (8, 9), consistent with early studies.

In this issue of the *Journal*, Wells and colleagues (pp. 583–595) combine micro-CT (μCT) imaging, histology, and immunohistochemistry to confirm, refine, and extend these underappreciated immunopathology concepts (10). μCT merges high resolution in the single digit micron scale with the power of three-dimensional (3D) imaging to overcome the caveat of two-dimensional (2D) histology staining, which both underestimates the connection between lesions and overestimates the distance between key pulmonary structures such as blood vessels, airways, and diseased tissue. The authors first establish a correspondence between the cellular structures seen in 2D histology images and the appearance of lesion areas in μCT 3D reconstructions. Coregistering these two imaging modalities reveals complex ginger root–shaped lesion networks, oriented along airways and the vasculature, nicely illustrated in multiple supplemental videos. The 3D rendering of lesions connected and shaped by the bronchial tree suggests that airways are progressively replaced by lesions. To support this theory, the authors resort to immunohistochemistry and histology staining, showing obstructed bronchi with necrotic material, infected neutrophils and macrophages, and extracellular bacteria, spilling from granulomas into airways, indicating bronchogenic spread of both *Mycobacterium tuberculosis* bacilli and TB disease. Small nodules are mostly spherical, wheras larger ones adopt ginger root–like shapes, and epithelial cell remnants line the outside of granulomas, consistent with nodules expanding along and destroying the bronchial architecture (Figure 1). This expansion cooccurs with vascular pruning and hemorrhage in the close vicinity of lesions, compromising access to nutrients, anti-TB drugs, and oxygen.

A limitation of the study is the reliance on resected lungs from patients with TB who had long-term and severe drug-refractory disease. However, bronchial wall necrosis has also been observed in old and more recent postmortem studies (11). Complementing μCT with lower-resolution PET-CT (6) could overcome this potential limitation because PET-CT is noninvasive, can be pursued longitudinally starting before therapy initiation, and is not limited to individuals undergoing lung resection. Through systematic observational studies, the two methodologies could inform each other to determine how much the present findings can be generalized to less severe TB disease.

The prevailing viewpoint that plum-shaped granulomas are the key lesions of both primary and post-primary TB is an oversimplification. In animal models, TB granulomas often present as spherical or ovoid structures within the parenchyma, whereas caseous pneumonia is seldom observed, although this view could partially result from biases introduced by 2D histopathology studies and the short-term nature of most models. Bronchogenic spread is not rare in rabbits and nonhuman primates (12, 13), suggesting that mammalian models present characteristics of both primary and post-primary TB but may fail to

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