

ATS Core Curriculum 2021

Adult Sleep Medicine: Sleep Apnea

Shazia M. Jamil^{1,2}, Shirin Shafazand^{3*}, Katherine A. Dudley⁴, Melissa C. Lipford⁵, Chenjuan Gu⁶, Jonathan C. Jun⁶, Isadore Budnick⁷, Eric M. Davis⁷, David Kent⁸, Jeffrey J. Stanley⁹, Rachel Quaney¹⁰, Nancy H. Stewart¹¹, Kirsten Young¹², Shannon Sullivan¹³, Jakob I. McSparron¹⁴, Tisha Wang¹⁵, Elizabeth Guzman¹⁶, Başak Çoruh¹⁷, and Margaret M. Hayes¹⁸

¹ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Scripps Clinic, La Jolla, California; ² Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, School of Medicine, University of California San Diego, La Jolla, California; ³ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Miami, Miami, Florida; ⁴ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Mount Auburn Hospital and Harvard Medical School, Boston, Massachusetts; ⁵ Department of Neurology and Center for Sleep Medicine, Mayo Clinic, Rochester, Minnesota; ⁶ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Johns Hopkins University, Baltimore, Maryland; ⁷ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Virginia, Charlottesville, Virginia; ⁸ Department of Otolaryngology–Head and Neck Surgery, Vanderbilt University, Nashville, Tennessee; ⁹ Department of Otolaryngology–Head and Neck Surgery, University of Michigan, Ann Arbor, Michigan; ¹⁰ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, The Ohio State University, Columbus, Ohio; ¹¹ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Kansas, Lawrence, Kansas; ¹² Division of Pulmonary, Critical Care Medicine, Department of Medicine, Baystate Health and University of Massachusetts Medical School, University of Massachusetts, Worcester, Massachusetts; ¹³ Division of Pulmonary Medicine, Department of Pediatrics, Stanford University, Stanford, California; ¹⁴ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Michigan, Ann Arbor, Michigan; ¹⁵ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of California Los Angeles, Los Angeles, California; ¹⁶ American Thoracic Society, New York, New York; ¹⁷ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Washington, Seattle, Washington; and ¹⁸ Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Harvard University, Boston, Massachusetts

ORCID IDs: 0000-0001-7627-7346 (S.M.J.); 0000-0001-5788-3535 (J.C.J.); 0000-0001-8183-5269 (D.K.).

ABSTRACT

The American Thoracic Society Sleep Core Curriculum updates clinicians on important sleep topics, presented during the annual meeting, and appearing in summary here. This year's sleep core theme is sleep-disordered breathing and its management. Topics range from pathophysiological mechanisms for the association of obstructive sleep apnea (OSA) and metabolic syndrome, surgical modalities of OSA treatment, comorbid insomnia and OSA, central sleep apnea, and sleep practices during a pandemic. OSA has been associated with metabolic syndrome, independent of the role of obesity, and the

(Received in original form February 27, 2021; accepted in final form May 19, 2021)

This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern.

*S. Shafazand is Associate Editor of *ATS Scholar*. Her participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

ATS Scholar Vol 2, Iss 3, pp 484–496, 2021
Copyright © 2021 by the American Thoracic Society
DOI: 10.34197/ats-scholar.2021-0027RE

pathophysiology suggests a role for sleep fragmentation and intermittent hypoxia in observed metabolic outcomes. In specific patient populations, surgical treatment modalities for OSA have demonstrated large reductions in objective disease severity compared with no treatment and may facilitate adherence to positive airway pressure treatment. Patient-centered approaches to comorbid insomnia and sleep apnea include evaluating for both OSA and insomnia simultaneously and using shared-decision making to determine the order and timing of positive airway pressure therapy and cognitive behavioral therapy for insomnia. The pathophysiology of central sleep apnea is complex and may be due to the loss of drive to breathe or instability in the regulatory pathways that control ventilation. Pandemic-era sleep practices have evolved rapidly to balance safety and sustainability of care for patients with sleep-disordered breathing.

Keywords:

obstructive sleep apnea; central sleep apnea; insomnia; upper airway surgery; metabolic syndrome

METABOLIC CONSEQUENCES OF UNTREATED OBSTRUCTIVE SLEEP APNEA

Chenjuan Gu and Jonathan C. Jun

Obstructive sleep apnea (OSA) is a highly prevalent disorder. It is well established that obesity predisposes individuals to developing OSA and that untreated OSA may exacerbate metabolic dysfunction and obesity (1).

Laboratory OSA Models

Intermittent hypoxia and sleep fragmentation are two hallmarks of OSA, and potential mediators of changes in metabolism. In laboratory experiments, intermittent hypoxia exposure induced insulin resistance in mice and healthy humans, whereas sleep

fragmentation impaired both insulin-dependent and insulin-independent glucose disposal (1). A leading hypothesis contends that intermittent hypoxia leads to tissue oxidative stress, inflammation, and the dysregulation of adipokines. In addition, sleep fragmentation and intermittent hypoxia (via stimulation of arterial chemoreceptors) activate the sympathetic nervous system and the hypothalamus–pituitary–adrenal axis (1). In turn, autonomic activation can lead to insulin resistance and cardiometabolic dysfunction (Figure 1). Autonomic activation stimulates the release of counterregulatory hormones (e.g., cortisol, catecholamines, and glucagon) and mobilizes fatty acids from adipose tissues, which in turn inhibit insulin action in tissues.

Author Contributions: The following authors conceived of and provided a first draft of the following sections: METABOLIC CONSEQUENCES OF UNTREATED OBSTRUCTIVE SLEEP APNEA (C.G., J.C.J.), SURGICAL TREATMENT OF OSA (D.K., J.J.S.), COMORBID INSOMNIA AND SLEEP APNEA (R.Q., N.H.S.), PATHOPHYSIOLOGY AND TREATMENT OF CENTRAL SLEEP APNEA (I.B., E.M.D.), and SLEEP CENTER MANAGEMENT IN THE ERA OF CORONAVIRUS DISEASE (K.Y., S. Sullivan). S.M.J., S.S., K.A.D., M.C.L., and E.G. coordinated the team; S.M.J., S.S., K.A.D., and M.C.L. prepared the manuscript draft, with critical editing and review being performed by J.I.M., T.W., B.C., and M.M.H. All authors contributed to editing the final version to be published.

Correspondence and requests for reprints should be addressed to Shazia M. Jamil, M.D., Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Scripps Clinic and University of California San Diego School of Medicine, 10666 North Torrey Pines Road, Mail Drop 207W, La Jolla, CA 92037. E-mail: jamil.shazia@scrippshealth.org.

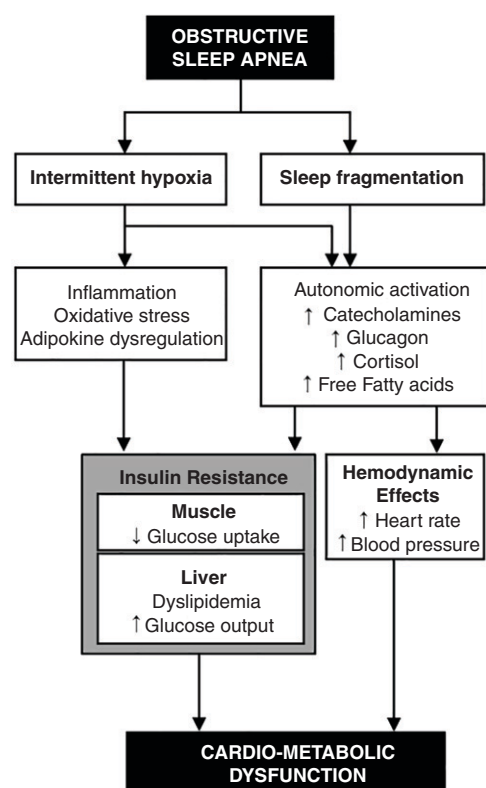


Figure 1. Mechanisms underlying metabolic impacts of obstructive sleep apnea. ↑ = increase; ↓ = decrease; HPA = hypothalamus–pituitary–adrenal; SNS = sympathetic nervous system.

Observational Studies of OSA and Metabolic Dysfunction

Several observational studies have revealed a close relationship between OSA and metabolic dysfunction, independent of obesity. OSA increased the odds of metabolic syndrome, a clustering of clinical features made up of abdominal obesity, hyperglycemia, hypertension, and atherogenic dyslipidemia (2). Patients with OSA exhibited a greater prevalence and incident risk of type 2 diabetes mellitus and worse glycemic control than OSA-free populations (3). Some studies also reported a more atherogenic lipid profile in patients with OSA (1). Most of these studies only adjusted for obesity in terms of the body

mass index (BMI), although visceral obesity results in a greater predisposition to developing OSA and metabolic dysfunction (1). Thus, these studies clearly identify OSA as a marker of metabolic dysfunction but cannot establish causation.

Treatment Effects on Metabolic Outcomes

Meta-analyses of studies in patients with type 2 diabetes mellitus revealed no overall effect of continuous positive airway pressure (CPAP) on glycemic control (4). However, CPAP improved insulin sensitivity in certain groups, such as patients with prediabetes and those with insulin resistance (5, 6). Regarding dyslipidemia, a meta-analysis revealed decreased total cholesterol after CPAP but revealed no effect on other lipid levels (7). It is important to note that CPAP adherence in most of these studies was relatively low (~2.4 to 6.2 h/night), perhaps explaining the limited *effectiveness* of CPAP in altering metabolic outcomes. However, CPAP improved glucose metabolism in settings of directly observed adherence (6, 8). Similarly, CPAP withdrawal for 3 nights increased plasma free fatty acids, glucose, and cortisol in CPAP-compliant patients with severe OSA (9). These short-term CPAP *efficacy* data indicate that OSA has the potential to induce harmful metabolic changes. However, the applicability of these studies to the long-term health of the general population with OSA remains unclear. Although OSA treatment might be expected to improve daytime energy and activity, leading to weight loss, it was actually observed that CPAP promoted modest weight gain (10). Further research is needed to clarify the effects of CPAP on the metabolic outcomes of OSA.

REFERENCES

1. Younas H, Gu C, Rathore A, Jun JC, Polotsky VY. Metabolic syndrome and sleep apnea: a bidirectional relationship. In: Richard A, Johnston BTS, editors. *Mechanisms and manifestations of obesity in lung disease*. Cambridge, MA: Academic Press; 2019. pp. 169–200.
2. Xu S, Wan Y, Xu M, Ming J, Xing Y, An F, *et al*. The association between obstructive sleep apnea and metabolic syndrome: a systematic review and meta-analysis. *BMC Pulm Med* 2015;15:105.
3. Pamidi S, Tasali E. Obstructive sleep apnea and type 2 diabetes: is there a link? *Front Neurol* 2012;3:126.
4. Zhu B, Ma C, Chaiard J, Shi C. Effect of continuous positive airway pressure on glucose metabolism in adults with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Sleep Breath* 2018;22:287–295.
5. Abud R, Salgueiro M, Drake L, Reyes T, Jorquera J, Labarca G. Efficacy of continuous positive airway pressure (CPAP) preventing type 2 diabetes mellitus in patients with obstructive sleep apnea hypopnea syndrome (OSAHS) and insulin resistance: a systematic review and meta-analysis. *Sleep Med* 2019;62:14–21.
6. Pamidi S, Wroblewski K, Stepien M, Sharif-Sidi K, Kilkus J, Whitmore H, *et al*. Eight hours of nightly continuous positive airway pressure treatment of obstructive sleep apnea improves glucose metabolism in patients with prediabetes: a randomized controlled trial. *Am J Respir Crit Care Med* 2015;192:96–105.
7. Xu H, Yi H, Guan J, Yin S. Effect of continuous positive airway pressure on lipid profile in patients with obstructive sleep apnea syndrome: a meta-analysis of randomized controlled trials. *Atherosclerosis* 2014;234:446–453.
8. Mokhlesi B, Grimaldi D, Beccuti G, Abraham V, Whitmore H, Delebecque F, *et al*. Effect of one week of 8-hour nightly continuous positive airway pressure treatment of obstructive sleep apnea on glycemic control in type 2 diabetes: a proof-of-concept study. *Am J Respir Crit Care Med* 2016;194:516–519.
9. Chopra S, Rathore A, Younas H, Pham LV, Gu C, Beselman A, *et al*. Obstructive sleep apnea dynamically increases nocturnal plasma free fatty acids, glucose, and cortisol during sleep. *J Clin Endocrinol Metab* 2017;102:3172–3181.
10. Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Benseñor IM, Lotufo PA. Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax* 2015;70:258–264.

SURGICAL TREATMENT OF OSA

David Kent and Jeffrey J. Stanley

Although positive airway pressure (PAP) therapy is a highly efficacious treatment for OSA, some patients are unable to tolerate it, limiting the potential subjective and objective benefits to be gained from PAP. A variety of alternatives for PAP-intolerant patients have been developed over the past several decades, including use of an oral appliance and surgical interventions. Improved surgical techniques introduced during the past 15 years have led

to more effective and less morbid procedures tailored to the individual patient (1–4).

Structural surgeries, such as nasal surgery, palatal modification, tongue base advancement or resection, multilevel surgery, and maxillomandibular advancement, are designed to reduce upper airway collapsibility. These surgeries have demonstrated substantial improvements in patient-centered outcomes in PAP-intolerant patients, including excessive daytime sleepiness (measured by a decrease in the Epworth Sleepiness Scale score by up to 6 points), sleep-specific quality

of life (measured by an increase in the Functional Outcome of Sleep Questionnaire score by up to 4 points), and snoring (measured by a decrease in the visual analog scale score by 4–5 points) (1–3). Improvements in objective measures of disease severity in PAP-intolerant patients include a reduction in the apnea–hypopnea index (AHI) and oxygen desaturation index by 50–60% and a reduction in systolic and diastolic blood pressure by 6 mm Hg and 2–3 mm Hg, respectively. Permanent serious morbidity, including dysphagia, is rare, as is perioperative mortality (5). All patients undergoing surgical treatment should undergo postoperative polysomnography and follow up in the sleep disorders center because residual symptomatic sleep apnea is not uncommon and may require additional intervention including PAP therapy.

Upper airway stimulation via implantation of a hypoglossal nerve stimulator has been shown to achieve similar improvements to structural surgeries in daytime sleepiness, quality of life, and disease severity as measured by the AHI in PAP-intolerant patients (4). Eligibility requirements include PAP intolerance, an AHI ≥ 15 and ≤ 65 events/h with $< 25\%$ central or mixed events, a BMI $< 32 \text{ kg/m}^2$, and drug-induced sleep endoscopy demonstrating a lack of complete concentric collapse at the velum. Importantly, this newer treatment modality has been

shown to normalize the AHI in approximately 40% of patients, while avoiding the morbidity often associated with soft tissue and craniofacial surgical options. Drug-induced sleep endoscopy has shown utility as a tool for refining surgical procedural selection, including hypoglossal nerve stimulation, in patients considering surgery (6).

Upper airway surgery has also been used as an adjunctive treatment to facilitate the use of PAP. Surgeries targeting the nose, tonsils, and soft palate have demonstrated clinically significant reductions in therapeutic PAP requirements, with the mean decrease in pressure being 2–3 cm H₂O. Soft tissue surgeries have additionally demonstrated significant increases in PAP adherence of $> 2 \text{ h/night}$ (7, 8). Tables 1 and 2 summarize subjective and objective outcomes after various surgical treatments for OSA.

Bariatric surgery for patients with OSA and obesity can reduce the disease burden (9, 10). After bariatric surgery, the Epworth Sleepiness Scale score has been shown to decrease by up to 6 points. For patients with a presurgical BMI $> 31 \text{ kg/m}^2$, systolic and diastolic blood pressure decreased by 9 and 6–7 mm Hg, respectively. For patients with a presurgical BMI $> 35 \text{ kg/m}^2$, the AHI and oxygen desaturation index were found to decrease by 60–70%. However, this observed improvement in disease severity may not be

Table 1. Subjective outcomes after surgical treatments of OSA

	Upper Airway Surgery	Upper Airway Stimulation	Bariatric Surgery
Sleepiness decrease (ESS)	↓↓	↓	↓↓
Snoring decrease (VAS)	↓↓	↓↓	NA
Quality of life increase (FOSQ)	↑	↑	NA

Definition of abbreviations: ↑ = increase on the assessment scale; ↓ = decrease on the assessment scale; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; NA = not applicable; OSA = obstructive sleep apnea; VAS = visual analog scale.

This table is a schematic representation of the literature on subjective outcomes of various surgical treatments for OSA. The strength of the response is denoted by the number of arrows.

Table 2. Objective outcomes after surgical treatments of OSA

	Upper Airway Surgery	Upper Airway Stimulation	Bariatric Surgery
PAP therapy adherence increase, h/night	2	NA	NA
PAP requirement decrease, cm H ₂ O	2–3	NA	3
AHI decrease, %	50–60	70	66
4% ODI decrease, %	50–60	70	66
24-h blood pressure decrease (SBP, DBP), mm Hg	6, 2–3	NA	9, 7

Definition of abbreviations: AHI=apnea–hypopnea index; DBP=diastolic blood pressure; NA=not applicable; ODI=oxygen desaturation index; PAP=positive airway pressure; SBP=systolic blood pressure.

sustained in patients whose weight loss is not maintained. Therapeutic PAP pressure requirements were also found to decrease by an average of 3 cm H₂O after bariatric

surgery. Low incidences of iron malabsorption, vitamin deficiency, reflux, and gastric ulceration have been reported after this type of surgery.

REFERENCES

1. Browalddh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. *Thorax* 2013;68:846–853.
2. Browalddh N, Bring J, Friberg D. SKUP(3) RCT; continuous study: changes in sleepiness and quality of life after modified UPPP. *Laryngoscope* 2016;126:1484–1491.
3. Woodson BT, Strohl KP, Soose RJ, Gillespie MB, Maurer JT, de Vries N, *et al.* Upper airway stimulation for obstructive sleep apnea: 5-year outcomes. *Otolaryngol Head Neck Surg* 2018;159:194–202.
4. Boon M, Huntley C, Steffen A, Maurer JT, Sommer JU, Schwab R, *et al.*; ADHERE Registry Investigators. Upper airway stimulation for obstructive sleep apnea: results from the ADHERE registry. *Otolaryngol Head Neck Surg* 2018;159:379–385.
5. Friedman JJ, Salapatias AM, Bonzelaar LB, Hwang MS, Friedman M. Changing rates of morbidity and mortality in obstructive sleep apnea surgery. *Otolaryngol Head Neck Surg* 2017;157:123–127.
6. Van de Heyning PH, Badr MS, Baskin JZ, Cramer Bornemann MA, De Backer WA, Dotan Y, *et al.* Implanted upper airway stimulation device for obstructive sleep apnea. *Laryngoscope* 2012;122:1626–1633.
7. Azbay S, Bostanci A, Aysun Y, Turhan M. The influence of multilevel upper airway surgery on CPAP tolerance in non-responders to obstructive sleep apnea surgery. *Eur Arch Otorhinolaryngol* 2016;273:2813–2818.
8. Friedman M, Soans R, Joseph N, Kakodkar S, Friedman J. The effect of multilevel upper airway surgery on continuous positive airway pressure therapy in obstructive sleep apnea/hypopnea syndrome. *Laryngoscope* 2009;119:193–196.

9. Feigel-Guiller B, Drui D, Dimet J, Zair Y, Le Bras M, Fuertes-Zamorano N, *et al.* Laparoscopic gastric banding in obese patients with sleep apnea: a 3-year controlled study and follow-up after 10 years. *Obes Surg* 2015;25:1886–1892.
10. Dixon JB, Schachter LM, O'Brien PE, Jones K, Grima M, Lambert G, *et al.* Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *JAMA* 2012;308:1142–1149.

COMORBID INSOMNIA AND SLEEP APNEA

Rachel Quaney and Nancy H. Stewart

Insomnia and sleep apnea are common sleep disorders, and their cooccurrence is frequent and wrought with challenges (1). First identified in 1973, the combination is found in up to 40% of adults worldwide and is found in up to 58% of patients who present for sleep disorder treatment (2, 3). This cooccurrence has been associated with increased psychiatric and medical morbidity as well as decreased quality of life compared with either sleep apnea or insomnia alone (3).

The diagnosis of comorbid insomnia and sleep apnea can be complicated, in part because of limitations in validated assessments for both disorders simultaneously. Therefore, in clinical practice, isolated evaluation of either suspected sleep apnea or insomnia may

occur, as questionnaires and diagnostics for these two entities remain separate (Figure 2), leading to distinct treatment pathways (4).

Moreover, OSA is often considered the primary problem, and insomnia is often considered the secondary problem by default, with OSA being treated before insomnia is addressed (1).

This sequential approach to comorbid insomnia and sleep apnea has its limitations. The presence of insomnia symptoms is associated with low adherence to PAP therapy, contributing to both inadequate treatment and failure to fulfill the reimbursement requirements (1). On the other hand, cognitive behavioral therapy for insomnia (CBT-I) is well accepted as the mainstay of treatment for insomnia but has traditionally not been used in patients with untreated sleep apnea for fear of exacerbating daytime sleepiness.

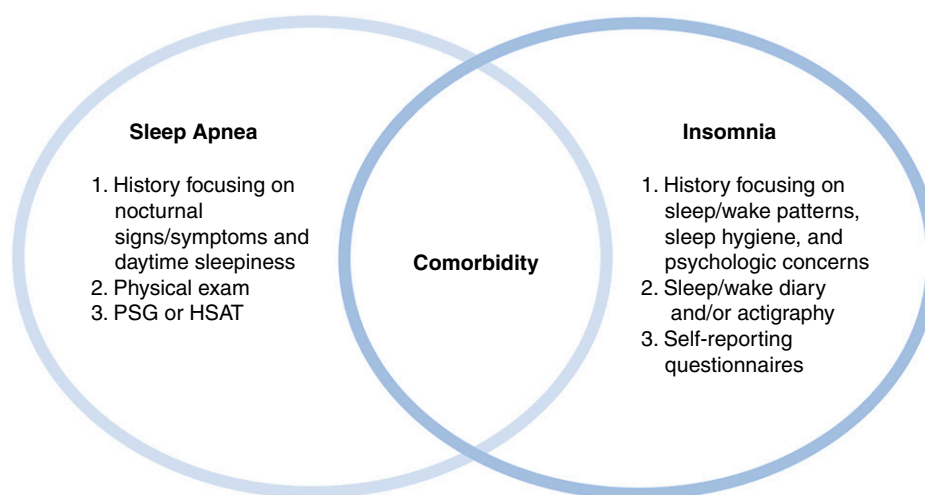


Figure 2. The diagnostic dilemma of comorbid insomnia and sleep apnea. HSAT = home sleep apnea test; PSG = polysomnography.

Concomitant treatments for both insomnia and OSA are gaining evidence for patients with both disorders, although the timing of CBT-I treatment and PAP treatment is still being evaluated (1, 5–8). In one study, patients with comorbid insomnia and sleep apnea who received CBT-I before PAP treatments showed higher PAP treatment acceptance, greater average nightly adherence to PAP, improved insomnia severity, and a greater reduction in the AHI than the control group (6, 7). Another study found that the addition of CBT-I, either before or in conjunction with PAP therapy, led to improvement in insomnia severity compared with PAP alone. However, no difference was demonstrated in PAP adherence for those receiving CBT-I (5). Further highlighting the complexity of this topic, another study showed a similar reduction in insomnia severity for patients with comorbid insomnia and sleep apnea using both PAP and either CBT-I via a self-help book (9) or sleep hygiene as the control arm.

This improvement in insomnia severity was therefore attributed to PAP therapy (9).

Although the timing of multimodal therapy for comorbid insomnia and sleep apnea needs to be further elucidated, it is clear that therapist-delivered CBT-I is safe and effective in patients with both disorders, even with the transient increase in daytime sleepiness that occurs with initiation of CBT-I and sleep restriction (8). Further research and guidelines are needed to define characteristics of comorbid insomnia and sleep apnea. This is to identify patients who are most likely to benefit from a limited resource such as CBT-I-capable therapists and to identify the optimal timing of treatment interventions. Currently, patient-centered approaches to comorbid insomnia and sleep apnea should include evaluating for both OSA and insomnia simultaneously and using shared-decision making to determine the order and timing of PAP therapy and CBT-I.

REFERENCES

1. Ong JC, Crawford MR, Wallace DM. Sleep apnea and insomnia: emerging evidence for effective clinical management. *Chest* 2021;159:2020–2028.
2. Zhang Y, Ren R, Lei F, Zhou J, Zhang J, Wing YK, *et al.* Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev* 2019;45:1–17.
3. Sweetman A, Lack L, Bastien C. Co-morbid insomnia and sleep apnea (COMISA): prevalence, consequences, methodological considerations, and recent randomized controlled trials. *Brain Sci* 2019;9:371.
4. Ong JC, Crawford MR, Kong A, Park M, Cvengros JA, Crisostomo MI, *et al.* Management of obstructive sleep apnea and comorbid insomnia: a mixed-methods evaluation. *Behav Sleep Med* 2017;15:180–197.
5. Sweetman A, Lack L, Catchside PG, Antic NA, Smith S, Chai-Coetzer CL, *et al.* Cognitive and behavioral therapy for insomnia increases the use of continuous positive airway pressure therapy in obstructive sleep apnea participants with comorbid insomnia: a randomized clinical trial. *Sleep (Basel)* 2019;42:zsz178.
6. Sweetman A, McEvoy RD, Smith S, Catchside PG, Antic NA, Chai-Coetzer CL, *et al.* The effect of cognitive and behavioral therapy for insomnia on week-to-week changes in sleepiness and sleep parameters in patients with comorbid insomnia and sleep apnea: a randomized controlled trial. *Sleep (Basel)* 2020;43:zsaa002.
7. Bjrovatn B. Bedre søvn: en håndbok til deg som sover dårlig. Bergen, Norway: Fagbokforlaget; 2013.

8. Sweetman A, Lack L, McEvoy RD, Antic NA, Smith S, Chai-Coetzer CL, *et al.* Cognitive behavioural therapy for insomnia reduces sleep apnoea severity: a randomised controlled trial. *ERJ Open Res* 2020;6:00161-2020.
9. Bjorvatn B, Berge T, Lehmann S, Pallesen S, Saxvig IW. No effect of a self-help book for insomnia in patients with obstructive sleep apnea and comorbid chronic insomnia: a randomized controlled trial. *Front Psychol* 2018;9:2413.

PATHOPHYSIOLOGY AND TREATMENT OF CENTRAL SLEEP APNEA

Isadore Budnick and Eric M. Davis

Central sleep apnea (CSA) is defined by lack of ventilatory effort and complete airflow cessation on polysomnography (1). CSA can be classified into two main groups: hypercapnic and nonhypercapnic (eucapnic/hypocapnic) (2). Nonhypercapnic CSA is more common and occurs in patients with heart failure, acute ischemic stroke, and high-altitude periodic breathing (2). Hypercapnic CSA is seen in patients with, neuromuscular disease, thoracic abnormalities, or opioid intoxication (2). Common symptoms of CSA, which are also present in other forms of sleep-disordered breathing, include excessive daytime sleepiness, poor subjective sleep, and morning headaches.

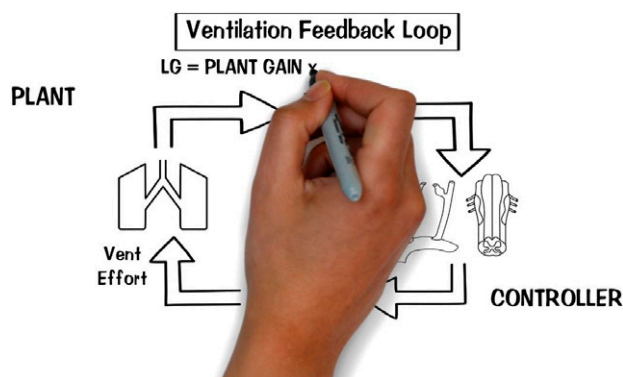
Hypercapnic CSA occurs from a loss of the drive to breathe in combination with either a blunted central respiratory controller response or reduced tidal volumes from neuromuscular weakness (2). In contrast, nonhypercapnic CSA is caused by instability in the regulatory pathways that control ventilation (3).

Disturbances such as hypoxemia or transitions from wakefulness to sleep are associated with periods of hyperpnea, which lead to increased minute ventilation and subsequent decreases in the partial arterial carbon dioxide pressure (PaCO_2) (2). When the PaCO_2 falls below the apneic threshold as determined by the central chemoreceptors, a central apnea ensues (4). Ventilation resumes when the PaCO_2 rises above the apneic threshold (1). Increased loop

gain, in part, accounts for the ventilatory instability and periodic breathing as described through the animated video we provide (Video 1) and as described in detail in the literature (3, 5).

The mainstay of treatment for hypercapnic and nonhypercapnic CSA is management of the underlying cause. For the purposes of this brief review, we will focus the discussion on CSA associated with cardiac disease. In heart failure, optimization of the volume status and/or improvement in the left ventricular ejection fraction (LVEF) has been found to improve CSA (6). Guidelines recommend a trial of CPAP for nonhypercapnic CSA (1, 7), which improves CSA by preventing upper airway occlusion, decreasing circulatory delay, and minimizing plant gain (*see* Video 1 for an explanation) by increasing lung volumes (8). CPAP improves the AHI in CSA; however, a broad mortality benefit was not identified in the original trial (9). A subsequent *post hoc* analysis determined that there is a transplant-free survival benefit (as well as a reduction in the LVEF) in those patients treated with CPAP who had a reduction in the AHI to fewer than 15 events/h on treatment (10).

New treatment modalities for CSA have been explored, including adaptive servo-ventilation (ASV), acetazolamide, and transvenous phrenic nerve stimulators. ASV, a form of PAP that augments ventilatory effort in a manner proportional to the patient's effort, has been shown to improve the central AHI and LVEF in CSA (7). However, in the largest trial of CSA in heart failure, ASV was associated with increased all-cause mortality in



Video 1. Conceptualizing loop gain and central sleep apnea.

patients with an LVEF $\leq 45\%$ (11). ASV is therefore not recommended for the treatment of CSA in this group. There are a limited number of trials examining the use of ASV in other conditions associated with CSA. Data on the long-term mortality benefit in conditions such as CSA associated with high-altitude periodic breathing and hypercapnic CSA related to opioid medication are lacking (1). Acetazolamide is an alternative approach for reducing the central apnea index. In response to metabolic acidosis, which occurs after acetazolamide administration, there is

are increases in the PaCO_2 reserve (difference between eupnea PaCO_2 and apnea threshold) and alterations in loop gain that are associated with a reduction in the central apnea index (12, 13). Lastly, transvenous phrenic nerve stimulators ensure stable ventilation, and prospective studies in CSA have demonstrated improved physical performance and hypoxemia (14). Future directions include enhancing the understanding of loop gain, determining the impact of PAP in select subpopulations, and researching alternative treatments for CSA.

REFERENCES

1. Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, *et al.* Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. *Eur Respir J* 2017;49:600959.
2. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. *Chest* 2007;131:595–607.
3. White DP. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med* 2005;172:1363–1370.
4. Dempsey JA, Skatrud JB. A sleep-induced apneic threshold and its consequences. *Am Rev Respir Dis* 1986;133:1163–1170.
5. Dempsey JA, Smith CA. Pathophysiology of human ventilatory control. *Eur Respir J* 2014;44:495–512.
6. Cowie MR, Gallagher AM. Sleep disordered breathing and heart failure: what does the future hold? *JACC Heart Fail* 2017;5:715–723.
7. Aurora RN, Chowdhuri S, Ramar K, Bista SR, Casey KR, Lamm CI, *et al.* The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. *Sleep (Basel)* 2012;35:17–40.
8. Orr JE, Malhotra A, Sands SA. Pathogenesis of central and complex sleep apnoea. *Respirology* 2017;22:43–52.

9. Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, *et al.*; CANPAP Investigators. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005;353:2025–2033.
10. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, *et al.*; CANPAP Investigators. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation* 2007;115:3173–3180.
11. 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.
12. Schmickl CN, Landry SA, Orr JE, Chin K, Murase K, Verbraecken J, *et al.* Acetazolamide for OSA and central sleep apnea: a comprehensive systematic review and meta-analysis. *Chest* 2020;158:2632–2645.
13. Ginter G, Sankari A, Eshraghi M, Obiakor H, Yarandi H, Chowdhuri S, *et al.* Effect of acetazolamide on susceptibility to central sleep apnea in chronic spinal cord injury. *J Appl Physiol (1985)* 2020;128:960–966.
14. Potratz M, Sohns C, Dumitrescu D, Sommer P, Fox H. Phrenic nerve stimulation improves physical performance and hypoxemia in heart failure patients with central sleep apnea. *J Clin Med* 2021;10:202.

SLEEP CENTER MANAGEMENT IN THE ERA OF CORONAVIRUS DISEASE

Kirsten Young and Shannon Sullivan

The coronavirus disease (COVID-19) pandemic generated rapid changes for the practice of sleep medicine. Documents from professional societies such as the American Academy of Sleep Medicine (1) and the American Thoracic Society (2) as well as a “perspective document” from European sleep experts (3) are available to help guide practices with facility reopening and management. Such guidance addresses critical strategies for screening and COVID-19 testing; clinical modifications, including telemedicine, staff protections, and discontinuation of some services (e.g., mask fitting); and laboratory considerations, including diagnostic testing, PAP titration, and issues specific to pediatric patients. These documents also recognize the need to adapt to national and regional factors. Recommendations are predicated on limited evidence and thus require ongoing reevaluation.

Clinical practices have quickly ramped up telemedicine offerings. Payer changes now

widely support telehealth (covering phone as well as video visit types). Government payers may allow postponement and waivers for recertifications and loosening of restrictions on durable medical equipment ordering as well as of replacement requirements.

Regarding laboratory services, home sleep apnea testing is preferred over in-laboratory testing whenever possible, although this approach has limitations in pediatric populations and other subpopulations (4). Patients requiring in-person studies should undergo screening and testing for COVID-19 before and at the time of an in-person visit (Figure 3). Appropriate personal protective equipment and use of disposables whenever possible are advised (1–3, 5). For nondisposables, allowing 72 hours of rest between uses is recommended (1).

A primary concern for laboratories is the risk of aerosolized COVID-19 due to PAP ventilation (5). Circuit filters have been proposed, and proper ventilation and engineering controls are recommended. Whenever possible, minimizing exposure risk through use of autotitration and remote monitoring of data is

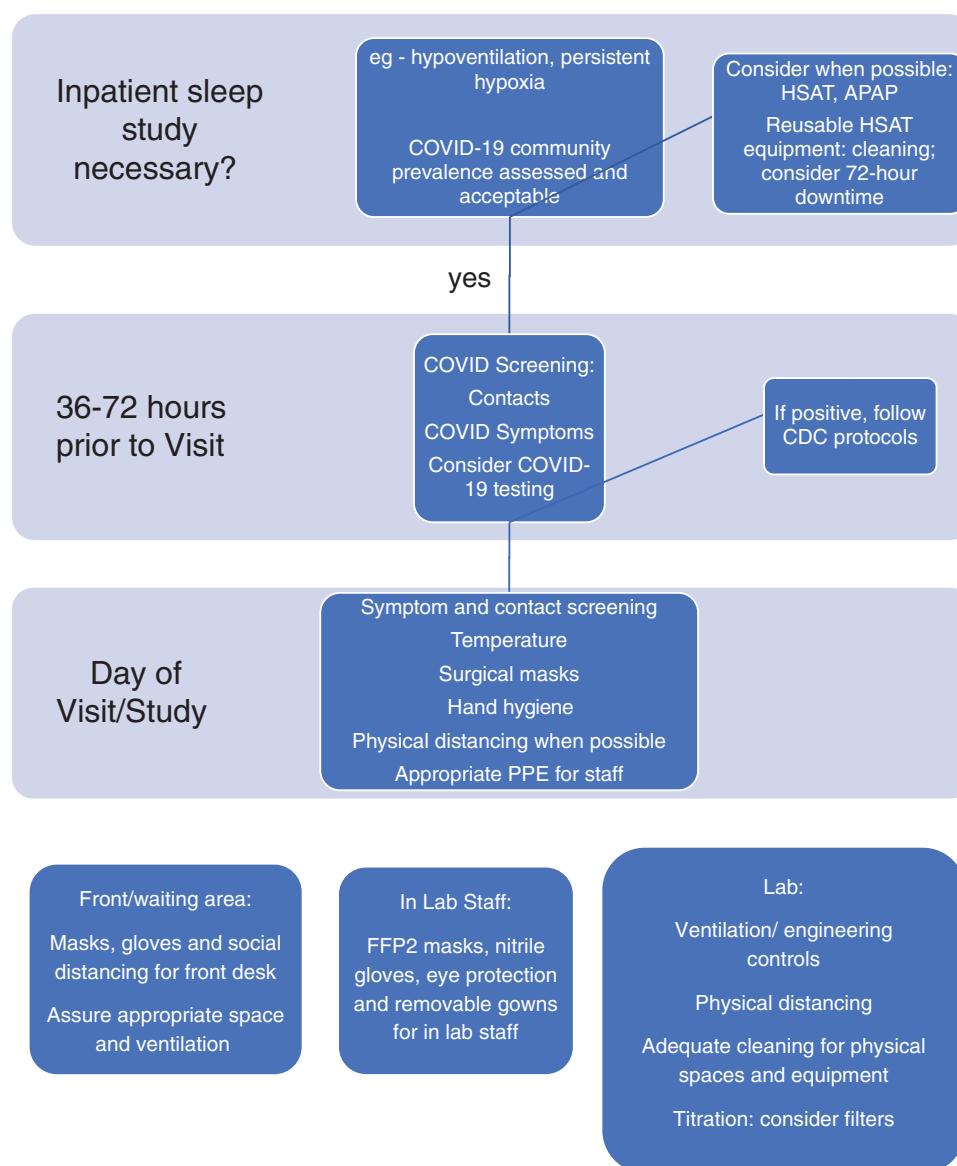


Figure 3. Process flow for coronavirus disease (COVID-19) screening and testing for sleep testing laboratories. APAP = auto-positive airway pressure device; CDC = Centers for Disease Control and Prevention; FFP2 = filtering face piece class 2; HSAT = home sleep apnea test; PPE = personal protective equipment.

recommended. Overall, the pandemic has increased discussion around best practices for laboratory versus home-based PAP management (6, 7).

There is limited guidance available regarding use of PAP in the home setting for patients who become infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Disease risks and benefits, the status of other inhabitants, and the ability to self-isolate according to Centers for Disease

Control and Prevention guidance are considerations (6). Equally important is that sleep apnea has been linked to the risk of worse COVID-19 outcomes, including mortality (8, 9).

If PAP is continued, data are lacking on the best mitigation strategies. Use of antiviral filters have been proposed, although these require a nonvented, full-face mask. Such measures have unknown real-world impact and may be associated with patient

intolerance and be difficult to use. Replacing filters, tubing, and masks and careful device cleaning after infection has been resolved are recommended.

Unresolved issues include how to best manage special circumstances (e.g., pediatric patients), widening disparities in sleep center access, and a strained provider workforce.

Workforce fatigue, burnout, and financial pressures have been reported, with 36% of 551 sleep providers surveyed applying for

financial assistance to maintain their practices (10).

Not without challenges, pandemic-era sleep practices have nonetheless evolved rapidly to balance safety, sustainability, and novel methods of care. Such innovations born of necessity will hopefully outlast the pandemic and continue to serve patient care into the future.

Author disclosures are available with the text of this article at www.atsjournals.org.

REFERENCES

1. Considerations for the practice of sleep medicine during COVID-19. Darien, IL: American Academy of Sleep Medicine; 2021 [updated 2021 Jan 18; accessed 2021 Feb 22]. Available from: <https://aasm.org/covid-19-resources/considerations-practice-sleep-medicine>.
2. Wilson KC, Kaminsky DA, Michaud G, Sharma S, Nici L, Folz RJ, *et al*. Restoring pulmonary and sleep services as the COVID-19 pandemic lessens: from an association of pulmonary, critical care, and sleep division directors and American Thoracic Society-coordinated task force. *Ann Am Thorac Soc* 2020;17:1343–1351.
3. Schiza S, Simonds A, Randerath W, Fanfulla F, Testelmans D, Grote L, *et al*. Sleep laboratories reopening and COVID-19: a European perspective. *Eur Respir J* 2021;57:2002722.
4. Sullivan S, Anastasi M, Beam E, Berneking M, Cheung J, Epstein IJ, *et al*. Opportunities and unknowns in adapting pediatric sleep practices to a pandemic world. *J Clin Sleep Med* 2021;17:361–362.
5. Sullivan SS, Gurubhagavatula I; Public Safety Committee of the American Academy of Sleep Medicine. Exhaled air dispersion and use of oronasal masks with continuous positive airway pressure during COVID-19. *Eur Respir Rev* 2020;29:200144.
6. National forum on COVID-19 vaccine. Bethesda, MD: Centers for Disease Control and Prevention; 2021 [accessed 2021 Jan 18]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/index.html>.
7. Patel SR, Donovan LM. The COVID-19 pandemic presents an opportunity to reassess the value of polysomnography. *Am J Respir Crit Care Med* 2020;202:309–310.
8. Miller MA, Cappuccio FP. A systematic review of COVID-19 and obstructive sleep apnoea. *Sleep Med Rev* 2021;55:101382.
9. Strausz S, Kiiskinen T, Broberg M, Ruotsalainen S, Koskela J, Bachour A, *et al*; FinnGen. Sleep apnoea is a risk factor for severe COVID-19. *BMJ Open Respir Res* 2021;8:e000845.
10. Ramar K. AASM takes the pulse of the sleep field and responds to COVID-19. *J Clin Sleep Med* 2020;16:1939–1942.