Blowing Away Fatty Liver: Mission Impossible?

Nonalcoholic fatty liver disease (NAFLD) describes a group of conditions in which there is accumulation of excess fat in the liver. The most common and mild form of NAFLD, fatty liver, affects up to 25–30% of the general population. Each year, 0.1% of patients with fatty liver progress to nonalcoholic steatohepatitis, in which fat accumulation is associated with liver cell inflammation, which can lead to severe liver scarring and cirrhosis. Almost 50% of those with NAFLD meet criteria for metabolic syndrome (1).

There is growing cross-sectional data that implicates obstructive sleep apnea (OSA) in the development and progression of NAFLD, as assessed by liver biopsies or validated noninvasive screening tools for liver fibrosis (2, 3).

Intermittent hypoxia is thought to be a plausible mechanism through which OSA might drive abnormal lipid metabolism and fatty liver (4). However, there is significant interaction between the risk factors for NAFLD and OSA, such that it is proving difficult to clarify cause and effect and therefore what treatment approaches are likely to be effective (5).

To date, randomized controlled trials (RCTs) have failed to demonstrate a clinical effect of continuous positive airway pressure (CPAP) on noninvasive markers of NAFLD severity (Table 1) (6–9). More broadly, RCTs of CPAP versus sham CPAP have failed to demonstrate efficacy in improving any components of metabolic syndrome (10). However, it is still argued that failure to demonstrate the positive effect of CPAP on metabolic syndrome is not so much related to a flawed intervention as it is to flawed methodology (11). Criticisms of previous studies have included investigation of populations without significant metabolic pathology at baseline, failure to examine markers of metabolic syndrome as the primary outcome and insufficient power to enable effective secondary analysis, intention-to-treat analysis impacted by poor compliance, short treatment periods (<3 mo), and prevalence of significant obesity masking treatment effect on metabolic outcomes.

In this issue of the *Journal*, Ng and colleagues (pp. 493–501) go a long way to putting this argument to bed, at least for NAFLD (12). They performed a large RCT ($n = 120$) of CPAP versus subtherapeutic CPAP on a population with confirmed NAFLD for a treatment period of 6 months (the longest RCT to date). Furthermore, their primary end point was intrahepatic triglyceride (IHTG) percentage—a sensitive and reproducible marker of liver fat content measured with proton-magnetic resonance spectroscopy (13).

In this study, the intimate association of NAFLD and OSA was again demonstrated with a staggering 98% of patients recruited from a hepatology clinic diagnosed with OSA on screening sleep study. Furthermore, there were significant correlations between OSA severity and liver steatosis. However, Ng and colleagues found no significant difference between therapeutic and subtherapeutic CPAP on either IHTG or other secondary markers of liver fat, steatosis, and fibrosis. This remained the case in both the intention-to-treat and per-protocol analyses. Comprehensive subgroup analyses of older and more obese patients as well as in those with milder degrees of liver steatosis and fibrosis also failed to demonstrate any between-group differences.

Importantly, in their study, CPAP compliance at 6 months was satisfactory (mean use, 4.4 h in the therapeutic group) and likely reflects real-life use and previous large RCTs (14). Furthermore, subgroup analysis comparing CPAP use over 4 hours with lower use did not show any significant difference in effect. Previous studies have deliberately recruited patients with moderate to severe OSA. Ng and colleagues randomized all patients with a diagnosis of OSA syndrome (respiratory event index [REI] > 5 units + OSA symptoms), and as a result, the mean REI was significantly lower in this study compared with previous study groups. However, subgroup analysis did not show any change in effect with increasing OSA severity.

The most significant limitation of this study was the use of subtherapeutic CPAP, which was actually fixed at 4 cm H_2O as the control arm, whereas previous studies have used sham CPAP at levels between 0.5 and 1 cm H_2O (8–10). As a result, a significant treatment effect was observed in the control arm, with REI reducing from 28 to 11 (Δ, −17) compared with 23 to 4 (Δ, −19) in the treatment group. It is therefore difficult to conclude that failure to demonstrate a significant difference between CPAP and sham CPAP is due to lack of effect of CPAP versus a significant effect of subtherapeutic CPAP.

Previous studies have demonstrated the beneficial effects of lifestyle modification and weight loss in the treatment of both OSA and NAFLD (15, 16). In an RCT of CPAP + lifestyle intervention versus CPAP or weight loss alone, Chirinos and colleagues (17) showed greater reductions in insulin resistance and triglycerides in the combined group versus CPAP alone. Furthermore, in the per-protocol analysis of patients meeting adherence criteria, combined treatment resulted in a larger reduction in systolic blood pressure and mean arterial pressure than did either CPAP or weight loss alone. In this study, Ng and colleagues also demonstrated that a change in IHTG and controlled attenuation parameter, both markers of liver fat, was associated with degree of weight loss.

In their comprehensive review, Gaines and colleagues conclude that the complex bidirectional relationship between OSA and metabolic syndrome, with visceral obesity a key driver of both, means that CPAP and other mechanical treatments of OSA (surgery) are unlikely to ever be successful at treating metabolic syndrome unless combined with weight loss (5). In this large RCT, Ng and colleagues come close to definitively demonstrating that CPAP alone is not effective in the management of NAFLD and suggest, in concordance with Gaines, that we should perhaps turn our attention to the role of CPAP as an adjunct to weight loss and lifestyle modifications in the treatment of metabolic syndrome in those with OSA.

In conclusion, Ng and colleagues provide further weight to the increasingly strong argument that despite the clear association between intermittent hypoxia and NAFLD, the

Originally Published in Press as DOI: 10.1164/rccm.202009-3578ED on October 15, 2020

Table 1. Randomized Sham-controlled Studies Examining the Effect of CPAP on Fatty Liver

	Year	Population (*n*)	Duration (*mo*)	AHI (*Events/h*)	BMI (kg/m^2)	Outcome Measure of Fatty Liver	Study Outcome
Sivam *et al.* (6)	2012	27	2	50	33	Intrahepatic adiposity (MRI)	Negative
Kritkou *et al.* (7)	2013	42	2	32 (F), 42 (M)	27 (F), 30 (M)	Intrahepatic adiposity (CT)	Negative
Hoyos *et al*. (8)	2012	65	3	40	31	Intrahepatic adiposity (MRI)	Negative
Jullian-Desayes *et al.* (9)	2016	103	3	43	28	Blood biomarkers	Negative
Ng *et al.* (12)	2020	120	6	23	27.5	Intrahepatic adiposity (MRI)	Negative

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; CT = computed tomography; MRI = magnetic resonance imaging.

management of OSA with CPAP alone does not improve hepatic steatosis and fibrosis. By conducting a large 6-month RCT in patients already diagnosed with NAFLD, and measuring specific noninvasive markers of intrahepatic lipid content, Ng and colleagues address many of the concerns held about the methodology of previous RCTs. Although the use of subtherapeutic CPAP rather than true sham CPAP leaves some room for doubt, this study provides clear direction that future studies should focus on the promising role of combination treatments and multidisciplinary teams to focus on weight reduction in concert with CPAP for the management of metabolic syndrome and concomitant OSA. ■

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

Anna E. B. McLean, M.B. B.S.
Department of Respiratory and Sleep Medicine
Royal Prince Alfred Hospital
Sydney, New South Wales, Australia

Frédéric Gagnadoux, M.D., Ph.D.
Department of Respiratory and Sleep Medicine
University Hospital of Angers
Angers, France
and
INSERM UMR 1063
University of Angers
Angers, France

Brendon J. Yee, M.B. Ch.B., F.R.A.C.P., Ph.D.
Department of Respiratory and Sleep Medicine
Royal Prince Alfred Hospital
Sydney, New South Wales, Australia
and
Sydney Medical School
The University of Sydney
Sydney, New South Wales, Australia

References

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73–84.
2. Tanné F, Gagnadoux F, Chazouillères O, Fleury B, Wendum D, Lasnier E, *et al*. Chronic liver injury during obstructive sleep apnea. *Hepatology* 2005;41:1290–1296.
3. Trzepizur W, Boursier J, Le Vaillant M, Ducluzeau PH, Dubois S, Henni S, *et al*.; on the behalf of the METABOL group. Increased liver stiffness in patients with severe sleep apnoea and metabolic comorbidities. *Eur Respir J* 2018;51:1800601.
4. Mesarwi OA, Loomba R, Malhotra A. Obstructive sleep apnea, hypoxia, and nonalcoholic fatty liver disease. *Am J Respir Crit Care Med* 2019; 199:830–841.
5. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Bixler EO. Obstructive sleep apnea and the metabolic syndrome: the road to clinically-meaningful phenotyping, improved prognosis, and personalized treatment. *Sleep Med Rev* 2018;42:211–219.
6. Sivam S, Phillips CL, Trenell MI, Yee BJ, Liu PY, Wong KK, *et al*. Effects of 8 weeks of continuous positive airway pressure on abdominal adiposity in obstructive sleep apnoea. *Eur Respir J* 2012;40:913–918.
7. Kritikou I, Basta M, Tappouni R, Pejovic S, Fernandez-Mendoza J, Nazir R, *et al*. Sleep apnoea and visceral adiposity in middle-aged male and female subjects. *Eur Respir J* 2013;41:601–609.
8. Hoyos CM, Killick R, Yee BJ, Phillips CL, Grunstein RR, Liu PY. Cardiometabolic changes after continuous positive airway pressure for obstructive sleep apnoea: a randomised sham-controlled study. *Thorax* 2012;67:1081–1089.
9. Jullian-Desayes I, Tamisier R, Zarski JP, Aron-Wisnewsky J, Launois-Rollinat SH, Trocme C, *et al*. Impact of effective versus sham continuous positive airway pressure on liver injury in obstructive sleep apnoea: data from randomized trials. *Respirology* 2016;21:378–385.
10. Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Launois S, Borel AL, Levy P, *et al*. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. *Sleep Med Rev* 2015;21:23–38.
11. Phillips CL, Hoyos CM, Yee BJ, Grunstein RR. CrossTalk opposing view: sleep apnoea causes metabolic syndrome. *J Physiol* 2016;594: 4691–4694.
12. Ng SSS, Wong VWS, Wong GLH, Chu WCW, Chan T-O, To K-W, *et al*. Continuous positive airway pressure does not improve nonalcoholic fatty liver disease in patients with obstructive sleep apnea: a randomized clinical trial. *Am J Respir Crit Care Med* 2021;203:493–501.
13. Noureddin M, Lam J, Peterson MR, Middleton M, Hamilton G, Le TA, *et al*. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. *Hepatology* 2013;58:1930–1940.
14. 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.
15. Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, *et al*. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. *J Hepatol* 2013;59:536–542.
16. Ng SSS, Chan RSM, Woo J, Chan TO, Cheung BHK, Sea MMM, *et al*. A randomized controlled study to examine the effect of a lifestyle modification program in OSA. *Chest* 2015;148:1193–1203.
17. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, *et al*. CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014;370:2265–2275.