



RESPONSE TO COMMENT ON GRIMALDI ET AL.

Association of Obstructive Sleep Apnea in Rapid Eye Movement Sleep With Reduced Glycemic Control in Type 2 Diabetes: Therapeutic Implications. *Diabetes Care* 2014;37:355–363

Diabetes Care 2014;37:e60–e61 | DOI: 10.2337/dc13-2662

Babak Mokhlesi,^{1,2}
Daniela Grimaldi,^{1,2} and
Eve Van Cauter^{1,3}

We are grateful to Drs. Scarlata and Antonelli-Incalzi (1) for their interest in our recent publication in *Diabetes Care* (2). We respectfully have to disagree with their statement that our study focused on “how rapid eye movement (REM) sleep deprivation due to obstructive sleep apnea [OSA] affects glycemic control in type 2 diabetes.” Indeed, our study was a cross-sectional analysis and did not include an experimental paradigm of REM sleep deprivation. In fact, the median duration of REM sleep in our cohort was 20.3% of the total sleep time—well within the normal range (Supplementary Table 1 in ref. 2). The primary aim of our study was to estimate the impact of OSA in REM sleep and in non-REM sleep on glycemic control (as assessed by HbA_{1c}) in patients with type 2 diabetes. In addition, we simulated the impact of different durations of nocturnal CPAP therapy on HbA_{1c} and observed that longer durations of CPAP use treat more apneas and hypopneas during REM sleep and lead to better glycemic control. We explicitly specified that our simulations were based on the assumption of “optimally titrated CPAP use.” Scarlata and Antonelli-Incalzi point out that this assumption may not be met under real-life conditions.

Suboptimal CPAP adherence is common and is indeed a likely reason for the negative findings of the only randomized controlled trial of CPAP in type 2 diabetic patients with OSA (3). We also agree with Scarlata and Antonelli-Incalzi that in some instances CPAP may not effectively treat OSA despite adequate adherence. This may be due to an inadequate pressure setting, excessive mask leak, ventilatory instability, and/or emergence of central apneas due to CPAP. However, as reported by Mulgrew et al. (4), most of the residual respiratory events observed during a full-night polysomnogram on effective CPAP settings are hypopneas and central apneas that occur predominantly during non-REM sleep. Our study demonstrated that in contrast to respiratory events in REM sleep, events during non-REM sleep (i.e., apneas, hypopneas, microarousals, and oxygen desaturations) are not associated with glycemic control in patients with type 2 diabetes. Therefore, simulations that would take into account residual events occurring mostly in non-REM sleep would most likely lead to conclusions similar to those reached in our analysis.

Our model was constructed on the assumption that CPAP is initiated at the beginning of the sleep period. Scarlata and Antonelli-Incalzi share their

anecdotal experience that some of their patients start using CPAP in the middle of the night after an awakening. They incorrectly quote the official statement of the American Thoracic Society on CPAP adherence tracking systems as a reference to support this anecdotal evidence (5). Currently, we are not aware of published empirical data documenting the proportion of OSA patients who start the night on CPAP and then discontinue it after a few hours of treatment as compared with those who initiate CPAP in the middle of the night after an awakening. For what it is worth, our own anecdotal experience suggests that the vast majority of patients with OSA start the night on CPAP and then remove it after a few hours. This constructive comment by Scarlata and Antonelli-Incalzi (1) illuminates the need for a quantitative study of the modalities of CPAP use under real-life conditions and for intervention studies comparing cognitive and cardiometabolic outcomes following early versus late use of CPAP during the night.

Funding. B.M. has received funding from the National Institutes of Health (NIH). E.V.C. has received investigator-initiated grants from NIH and ResMed Foundation.

¹Department of Medicine, Sleep, Metabolism and Health Center, University of Chicago, Chicago, IL

²Department of Medicine, Section of Pulmonary and Critical Care, Sleep Disorders Center, University of Chicago, Chicago, IL

³Department of Medicine, Section of Endocrinology, Diabetes and Metabolism University of Chicago, Chicago, IL

Corresponding author: Babak Mokhlesi, bmokhles@medicine.bsd.uchicago.edu.

© 2014 by the American Diabetes Association. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

Duality of Interest. B.M. has served as a consultant to Philips/Respironics and is involved in a study sponsored by Philips/Respironics. E.V.C. has received investigator-initiated grants from the Philips/Respironics. No other potential conflicts of interest relevant to this article were reported.

References

1. Scarlata S, Antonelli-Incalzi R. Comment on Grimaldi et al. Association of obstructive sleep apnea in rapid eye movement sleep with reduced glycemic control in type 2 diabetes: therapeutic implications. *Diabetes Care* 2014;37:355–363 (Letter). *Diabetes Care* 2014;37:e59. DOI: 10.2337/dc13-2429
2. Grimaldi D, Beccuti G, Touma C, Van Cauter E, Mokhlesi B. Association of obstructive sleep apnea in rapid eye movement sleep with reduced glycemic control in type 2 diabetes: therapeutic implications. *Diabetes Care* 2014;37:355–363
3. West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax* 2007;62:969–974
4. Mulgrew AT, Lawati NA, Ayas NT, et al. Residual sleep apnea on polysomnography after 3 months of CPAP therapy: clinical implications, predictors and patterns. *Sleep Med* 2010;11:119–125
5. Schwab RJ, Badr SM, EpsteinLJ, et al.; ATS Subcommittee on CPAP Adherence Tracking Systems. An official American Thoracic Society statement: continuous positive airway pressure adherence tracking systems. The optimal monitoring strategies and outcome measures in adults. *Am J Respir Crit Care Med* 2013;188:613–620