Ischemic preconditioning seems to occur more readily with sustained hypoxemia than with intermittent hypoxemia.[3] Patients with OHS are exposed to both types of hypoxemia; therefore, it is likely that there is an additive effect. In fact in our study, the prevalence of cardiovascular morbidity was lowest in patients with OHS who also had the most severe form of OSA. This finding supports the notion that sustained and intermittent hypoxemia may result in a more powerful angiogenic stimulation than either one alone. Clearly these findings are hypothesis generating, and further research is necessary. In summary, we do not think sustained hypoxemia is the only reason for the protective cardiovascular effect we observed in our patients with OHS and the most severe form of OSA, but rather it is a combination of cumulative exposure to significant hypoxemia during wakefulness due to hypoventilation plus intermittent hypoxemia during sleep due to very severe OSA. It remains unclear whether hypercapnia modulates the effect of hypoxemia, since experiments involving hypoxic preconditioning did not include exposure to hypercapnia.

Juan F. Masa, MD, PhD
Jaime Corral, MD
Javier Gómez-de-Terreros, MD, PhD
María-Ángeles Sánchez-Quiroga, MD
Cáceres, Spain
Babak Mokhlesi, MD, FCCP
Chicago, IL

AFFILIATIONS: From the Pulmonary Section (Drs Masa, Corral, and Gómez-de-Terreros), San Pedro de Alcántara Hospital; Pulmonary Section (Dr Sánchez-Quiroga), Virgen del Puerto Hospital, Plasencia; Department of Medicine (Dr Mokhlesi), Section of Pulmonary and Critical Care, University of Chicago; CIBER de enfermedades respiratorias (CIBERES) (Drs Masa, Corral, and Gómez-de-Terreros), Madrid, Spain.

FINANCIAL/NONFINANCIAL DISCLOSURES: See earlier cited article for author conflicts of interest.

CORRESPONDENCE TO: Juan F. Masa, MD, PhD, Pulmonary Section, San Pedro de Alcántara Hospital, Avda. Pablo Naranjo S/N, 10003 Cáceres, Spain; e-mail: fmasa@separ.es

DOI: http://dx.doi.org/10.1016/j.chest.2016.09.036

References

1. Masa JF, Corral J, Romero A, et al. Protective cardiovascular effect of sleep apnea severity in obesity hypoventilation syndrome. *Chest*. 2016;150(1):68-79.
2. Shizukuda Y, Mallet RT, Lee SC, Downey HF. Hypoxic preconditioning of ischaemic canine myocardium. *Cardiovasc Res*. 1992;26(5):534-542.
3. Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation*. 2005;112(17):2660-2667.

Does Nocturnal Hypoventilation Have a Protective Effect on Cardiovascular Comorbidity in Obesity Hypoventilation Syndrome?

To the Editor:

We recently read with great interest the article by Masa et al,[1] published in *CHEST* (July 2016), in which the authors examined the association between OSA severity and cardiovascular morbidity in patients with obesity hypoventilation syndrome (OHS). Surprisingly, their results showed an inverse relationship between cardiovascular morbidity and severity of OSA, except for ischemic heart disease. As hypothesized by Lavie and Lavie,[2] the cycles of apneic/hypopneic events in OSA that resemble cycles of ischemia/reperfusion could exert a protective effect from more severe ischemic and cardiovascular events, similar to ischemic preconditioning. There is the possibility that these factors may be a particular characteristic of OHS. Moreover, Cadby et al[3] reported an independent association between the presence and severity of OSA and incident atrial fibrillation in a large clinic-based cohort group over a median 12-year follow-up period. What is the role of nocturnal hypoventilation and of tonic desaturation in the etiopathogenesis of cardiologic comorbidity?

It is known that patients with OHS often exhibit cycles of intermittent hypoxia and reoxygenation due to apneic/hypopneic events. Moreover, tonic desaturation caused by hypoventilation often co-exists. We previously demonstrated that nocturnal hypoventilation, defined as a period of persistent ($\geq$ 2 min) reduction (two-thirds) of abdominal and rib cage excursion, associated with persistent sustained oxygen desaturation of 10% and a mean increase of transcutaneous $CO_2 > 7$ mm Hg for at least 15% of the total sleep time, is present in approximately 50% of severely obese patients.[4] These patients also have a high respiratory disturbance index score.

Ryan et al[5] showed that intermittent hypoxia/reoxygenation in OSA may produce a selective and dose-dependent activation of the inflammatory pathway, whereas sustained hypoxia may lead to an adaptive effect with reduced expression of proatherogenic and proinflammatory factors such as tumor necrosis factor-α. The investigators hypothesized that these mechanisms may be an important underlying factor in

the cardiovascular pathophysiology of OSA. Could these conclusions be extended to OHS?

To this extent, it would be interesting to examine the role of nocturnal hypoventilation in these patients with OHS described by Masa et al,[1] particularly in those with severe OSA and high BMI who may remain mildly or severely hypoxemic between apneic events, resulting in a mild or severe degree of sustained hypoxia in addition to intermittent hypoxia.

Giorgio Castellana, MD
Pierluigi Carratù, MD, PhD
Silvano Dragonieri, MD, PhD
Lorenzo Marra, MD
Onofrio Resta, MD, FCCP
Bari, Italy

AFFILIATIONS: From the Institute of Respiratory Disease, University of Bari "Aldo Moro."

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Giorgio Castellana, MD, Institute of Respiratory Disease, University of Bari "Aldo Moro," Piazza Giulio Cesare, 11, 70124 Bari, Italy; e-mail: giorgiocastellana@virgilio.it

DOI: http://dx.doi.org/10.1016/j.chest.2016.08.1469

References

1. Masa JF, Corral J, Romero A, et al. Protective cardiovascular effect of sleep apnea severity in obesity hypoventilation syndrome. *Chest*. 2016;150(1):68-79.
2. Lavie L, Lavie P. Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. *Med Hypotheses*. 2006;66(6):1069-1073.
3. Cadby G, McArdle N, Briffa T, et al. Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort. *Chest*. 2015;148(4):945-952.
4. Resta O, Foschino-Barbaro MP, Legari G, et al. Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. *Int J Obes Relat Metab Disord*. 2001;25(5):669-675.
5. Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation*. 2005;112(17):2660-2667.

Response

To the Editor:

We are grateful to Dr Castellana and colleagues for their interest in our article recently published in *CHEST*.[1] In their letter, they question the role of nocturnal hypoventilation and of tonic oxygen desaturation in the pathogenesis of cardiovascular comorbidity.

In our dataset, the severity of OSA and intermittent hypoxemia measured according to the oxygen desaturation index was the only factor associated with reduced cardiovascular morbidity. Sustained hypoxemia assessed by using daytime Pa_{O_2} and percentage of total sleep time with oxygen saturation $< 90\%$ was not associated with reduced cardiovascular morbidity. We cannot rule out with certainty whether there was an additive effect of sustained hypoxemia on top of intermittent hypoxemia in leading to reduced cardiovascular morbidity. However, if one assumes that sustained hypoxemia has a greater role in cardiovascular protection, we would have expected the hypoxemic patients with obesity hypoventilation syndrome and the lowest severity of OSA, based on the apnea-hypopnea index or oxygen desaturation index, to have the lowest prevalence of cardiovascular comorbidities.

Juan F. Masa, MD, PhD
Jaime Corral, MD
Javier Gómez-de-Terreros, MD, PhD
María-Ángeles Sánchez-Quiroga, MD
Cáceres, Spain
Babak Mokhlesi, MD, FCCP
Chicago, IL

AFFILIATIONS: From the Pulmonary Section (Drs Masa, Corral, and Gómez-de-Terreros), San Pedro de Alcántara Hospital; Pulmonary Section (Dr Sánchez-Quiroga), Virgen del Puerto Hospital, Plasencia; Department of Medicine (Dr Mokhlesi), Section of Pulmonary and Critical Care, University of Chicago; CIBER de enfermedades respiratorias (CIBERES) (Drs Masa, Corral, and Gómez-de-Terreros), Madrid, Spain.

FINANCIAL/NONFINANCIAL DISCLOSURES: See earlier cited article for author conflicts of interest.

CORRESPONDENCE TO: Juan F. Masa, MD, PhD, Pulmonary Section, San Pedro de Alcántara Hospital, Avda. Pablo Naranjo S/N, 10003 Cáceres, Spain; e-mail: fmasa@separ.es

DOI: http://dx.doi.org/10.1016/j.chest.2016.08.1470

Reference

1. Masa JF, Corral J, Romero A, et al. Protective cardiovascular effect of sleep apnea severity in obesity hypoventilation syndrome. *Chest*. 2016;150(1):68-79.

Introducing High-Sensitivity Cardiac Troponin T as a Biomarker of OSA-Related Cardiovascular Morbidity in Obesity Hypoventilation Syndrome

To the Editor:

We read with interest the recent article published by Masa et al[1] in *CHEST* (July 2016) reporting that the