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Obstructive Sleep Apnea and Major Depressive Disorder in Cardiovascular Disease

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In a recent editorial, Ehrmann et al. (1) proposed that comorbid obstructive sleep apnea (OSA) may help to explain the association between major depressive disorder (MDD) and cardiovascular disease (CVD). MDD and OSA are highly comorbid, both are risk factors for incident CVD and for cardiac events in established heart disease, and they share many of the same cardiac risk factors (2, 3).

As Ehrmann et al note, intermittent hypoxia secondary to sleep apnea leads to an increase in inflammatory cytokines, nitric oxide synthase inhibition, sympathetic predominance, and endothelial dysfunction, all of which are thought to contribute to the development and progression of CVD. MDD is also associated with these risk markers (2), and it is possible that MDD and OSA may have additive or even synergistic effects on the risks of incident CVD and recurrent cardiac events. We propose two additional ways in which these conditions may interact to further increase CVD risk. First, patients with MDD may have a blunted ventilatory response to hypercapnia. Findings from our study of depression and OSA are consistent with this possibility. Second, the vasodilatory response to rising levels of CO₂ may also be blunted in patients with MDD. Other studies support this possibility.

We recruited 53 medically stable CVD patients with MDD, 43 nondepressed patients (ND), and 36 patients with subclinical depressive symptoms, to undergo two nights of polysomnography in order to estimate the prevalence of undetected OSA (4). All participants had preserved left ventricular function and no known or suspected sleep disorders at the time of the study. Polysomnography showed that nearly all of the patients had at least a few apneic episodes per hour of sleep. However, only 10% of the MDD and 8% of the ND patients had OSA that was severe enough to warrant initiation of continuous positive airway pressure (CPAP) therapy. The mean number of apneic events per hour did not differ between patients with MDD (6.1 ± 0.8) and those who were not depressed (4.4 ± 0.9 ; $p > 0.05$). However, the mean duration of obstructive apneic episodes was longer in patients with MDD (23.30 ± 1.1 seconds) than in the ND patients (20.3 ± 1.3), even after

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adjusting for age, gender, body mass index, history of heart failure, hypertension, diabetes, and current smoking (4). Mixed apneic events, that is, those with both central and obstructive features, were also significantly longer in patients with MDD (27.8 ± 1.5 sec) than in ND patients (22.8 ± 1.0 sec; $p=0.01$), as were purely central apneic events (MDD, 21.8 ± 1.0 sec; ND, 16.9 ± 1.1 sec; $p=0.03$). Although most of the patients in this study had no more than mild-to-moderate OSA, the prolonged apneic episodes in patients with MDD cumulatively exposes them to substantially more hypoxia than ND patients experience. In patients with clinically significant OSA, this could lead to a greater risk for cardiac events.

Why should patients with MDD have longer episodes of sleep apnea than medically comparable ND patients? Obstructive events terminate when chemoreceptors detect rising arterial CO_2 (hypercapnia) and signal respiratory centers in the brain to clear the airway and resume inspiration. There is evidence that depression in medically well psychiatric patients may blunt the respiratory response and delay the cortical arousal response to hypercapnia (5–8). A recent fMRI study of depressed patients with documented OSA found more lesions in the frontal cortex, insula, cingulate, and areas proximal to the amygdala and hippocampus in depressed compared to ND patients (9). The insula, cingulate, hippocampus, and deep cerebellar nuclei respond to hypercapnia in humans (10), which suggests that chemoreceptive modulatory functions could be dysregulated in these patients.

There is also evidence that hypoxia due to OSA may be more harmful in patients with MDD than in ND patients. When CO_2 levels rise in healthy individuals, there is a compensatory dilation of cerebral arterioles in the downstream vascular beds which increases cerebral blood flow. This helps to mitigate the negative effects of hypoxia on neuronal functioning during cessation of breathing (11). This compensatory response declines with age, but adults with MDD show an even greater decline in vasomotor reactivity to CO_2 inhalation than do ND adults of the same age, even after controlling for ischemic white matter hyperintensities (11). Thus, hypoxia secondary to sleep apnea may be more damaging to patients with MDD than to ND patients.

Our results require replication in patients with clinically significant OSA and MDD. Future studies will then be needed to elucidate the specific mechanisms underlying the prolongation of apneic events in MDD; to determine whether the extended duration of these events is associated with increased inflammatory, coagulant, and cardiovascular responses; and to investigate whether event durations can be shortened by treating depression. This may be especially important in patients with MDD whose sleep apnea is not thought to warrant CPAP yet who still may be at high risk for cardiac events. In the meantime, we agree with Ehrmann and colleagues that the combination of OSA and MDD may greatly increase the risk for cardiovascular events in these patients.

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References

1. Ehrmann DE, Deldin F, Pitt B. Is sleep apnea a potential link between major depressive disorder and cardiovascular disease? *Int J Cardiol.* 2011; 147:1–23. [PubMed: 21131071]
2. Carney RM, Freedland KE. Depression in patients with coronary heart disease. *Am J Med.* 2008; 121:20–27.

3. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol.* 2008; 52:686–717. [PubMed: 18702977]
4. Carney RM, Howells WB, Freedland KE, et al. Depression and obstructive sleep apnea in patients with coronary heart disease. *Psychosom Med.* 2006; 68:443–448. [PubMed: 16738077]
5. Damas-Mora J, Jenner FA, Sneddon J, Addis WD. Ventilatory responses to carbon dioxide in syndromes of depression. *J Psychosom Res.* 1978; 22:473–476. [PubMed: 750657]
6. Damas-Mora J, Souster L, Jenner FA. Diminished hypercapnic drive in endogenous or severe depression. *J Psychosom Res.* 1982; 26:237–245. [PubMed: 6804626]
7. Damas-Mora J, Grant L, Kenyon P, Patel MK, Jenner FA. Respiratory ventilation and carbon dioxide levels in syndromes of depression. *Br J Psychiatry.* 1976; 129:457–464. [PubMed: 990660]
8. Shershow JC, Kanarek DJ, Kazemi H. Ventilatory response to carbon dioxide inhalation in depression. *Psychosom Med.* 1976; 38:282–287. [PubMed: 940908]
9. Cross RL, Kumar R, Macey PM, et al. Neural alterations and depressive symptoms in obstructive sleep apnea patients. *Sleep.* 2008; 31:1103–1109. [PubMed: 18714782]
10. Harper RM, Macey PM, Woo MA, et al. Hypercapnic exposure in congenital central hypoventilation syndrome reveals CNS respiratory control mechanisms. *J Neurophysiol.* 2005; 93:1647–1658. [PubMed: 15525806]
11. Matsuo K, Onodera Y, Hamamoto T, Muraki K, Kato N, Kato T. Hypofrontality and microvascular dysregulation in remitted late-onset depression assessed by functional near-infrared spectroscopy. *Neuroimage.* 2005; 26:234–242. [PubMed: 15862223]