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Editorial

EDITORIAL

Reversing coronary vascular sequelae of intermittent hypoxia: what is the window of opportunity?

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Patients with obstructive sleep apnea (OSA) are at increased risk for morbidity and mortality from cardiovascular disease (CAD), including myocardial infarction and sudden cardiac death [1, 2]. In observational studies, investigators have found that the risk for these cardiovascular events is reversed by continuous positive airway pressure [2]. Animal models of OSA provide further evidence that OSA plays a critical role in the pathogenesis of CAD. Chronic exposure to intermittent hypoxia (IH), a hallmark feature of OSA, induced atherosclerosis in C57BL6/J mice who were resistant to disease in the absence of IH [3]. IH also accelerated atherosclerosis in apolipoprotein E-deficient (ApoE–/–) mice [4], which are atherosclerosis-prone. Interestingly, in atherosclerosis-naïve mice, IH-induced fatty streaks, represented early-stage lesions. In ApoE–/– mice, on the other hand, IH induced fibrinous plaques, which cannot be easily reversed. These experimental findings pose the question of whether therapeutic intervention in OSA should target cardiovascular disease at early stages to be effective.

Vascular endothelium dysfunction precedes gross vascular morphological changes and clinical manifestations of atherosclerosis [5]. Impaired endothelial and endothelium-independent coronary vasoreactivity are associated with an increased incidence of cardiovascular events [6]. Moreover, the association between vasoreactivity and cardiovascular risk was strongest in lower-risk populations, suggesting that endothelial function may play an important role early in the course of CAD pathogenesis [5]. Since patients with OSA have evidence of endothelial dysfunction [7], improving endothelial function is an attractive target to prevent the onset of clinical atherosclerosis and its complications. Timing of intervention may be critical to altering disease course. Animal models enable investigators to intervene at specific time points.

Badran et al. [8] examined left anterior descending coronary artery vascular reactivity in mice exposed to IH compared to room air for 2, 6, 16, and 28 weeks. The authors measured endothelial function by inducing muscle relaxation and vasodilation in response to acetylcholine as well as blood velocity at the baseline and hyperemic conditions. They found that coronary artery relaxation was not impaired after 2 weeks of IH. The first evidence of vascular dysfunction was detected after 6 weeks of IH and further worsened and plateaued after 16 weeks. After 6 weeks of IH, coronary blood velocity in the hyperemic condition fell, in which did not occur at the baseline condition, indicating that IH adversely affected coronary artery vasodilation. To determine whether treatment of sleep apnea could reverse impairments in coronary vascular reactivity, the authors also conducted these measurements after 6 weeks of IH followed by recovery under room air. The author reported a complete reversal of coronary blood velocity abnormalities after recovery. Taken together, these findings suggest that IH causes impairments in vascular reactivity, and that these impairments are reversible early in the course of the disease. Moreover, Badran et al. [8] are the first to describe the pathological effects of IH on the coronary arteries in a mouse model, an important innovation that is relevant to human coronary artery disease, and distinguishes the present study from previous investigations.

The study by Badran et al. has several notable limitations. First, C57BL/J6 are relatively protected against atherosclerosis and even prolonged severe exposures produced only early lesions [3]. In atherosclerosis-prone models, the window for intervention may be markedly narrowed if present at all. Thus, the relevance for human OSA-associated CAD remains uncertain and could be clarified with similar experiments in atherosclerosis-prone models. Second, the mechanisms by which IH reduces vascular reactivity

at the differing time points are not known. Third, reversibility was demonstrated only after 6 weeks. As a result, it remains unknown whether reductions in coronary vascular reactivity become fixed after longer exposures. In fact, prolonged exposure to IH indices vascular inflammation with corresponding epigenetic changes, which were not reversed with the cessation of the exposure [9]. Fourth, the authors measure blood velocity rather than a flow, which may be a more biologically meaningful outcome. For instance, increases in baseline blood velocity after 28 weeks of IH may reflect arterial narrowing and paradoxical reductions in flow. Fifth, the experiments were conducted only in male mice. Given marked sex differences in susceptibility to OSA and its complications, studies in females are of importance.

It is important to note that IH-induced vascular dysfunction was first observed after 6 weeks of exposure. A crude comparison of murine and human lifetime (2 years vs. 80 years life expectancy) suggests that 4–5 years may lead to significant to coronary vascular dysfunction. This dysfunction may be reversible at this time point, before the development of fixed atherosclerotic lesions.

The findings by Badran et al. [8] provide new context for recent randomized controlled trials of CPAP treatment in patients with CAD. In these studies, SAVE [10], RICCADSA [11], and ISAAC [12], CPAP therapy did not confer significant cardiovascular benefits in patients with existing CAD. Negative outcomes in these studies have been attributed in part to low CPAP adherence and insufficient duration of follow-up. An important perspective from the study by Badran et al. is that intervention may be introduced too late in the time course of OSA and CAD. An important question raised by these studies is whether intervention with CPAP in prior clinical trials is just too little, or also too late?

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