Inflammatory Ideas about Sleep Apnea

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In this issue of *Respiration*, Imagawa et al. [1] continue their studies of the augmented levels of vascular endothelial growth factor (VEGF) in 110 sleep apnea patients, reporting that they are not explained by increases in the proinflammatory cytokines tumor necrosis factor (TNF)-alpha or interleukin (IL)-6.

In a previous study, the same authors found in the same group of patients that erythropoietin (EPO) levels were slightly increased and VEGF levels were increased by a greater amount [2]. The patients studied had an apnea-hypopnea index (AHI) that ranged between 30 and more than 110, although only 10 patients had AHIs of 90 or more. It is of interest that EPO levels were significantly elevated in all patients with AHI levels less than 90 but not in the more severely affected group, perhaps because of the small numbers involved. VEGF levels were significantly elevated even in the small group with the greatest AHI.

Intermittent hypoxia as occurs in sleep apnea has multiple physiological consequences, including increases in EPO and VEGF. Hypoxia has been shown to decrease the breakdown of a transcription factor, hypoxia-inducible factor-1, which triggers the induction of many genes like EPO and VEGF and which compensates for the reduction in blood oxygen levels by increasing red cell mass (EPO) or inducing the formation of new blood vessels (VEGF) [3]. It also induces genes responsible for endothelin and multiple enzymes involved in anaerobic metabolism [4].

Some cytokines, such as IL-8, IL-6, and IL-1, have been reported to increase VEGF levels, but in any case even if elevated cytokine levels were found, the methods used in this paper [1] would not have demonstrated a causal relationship but only an association. What is somewhat surprising is that no elevation in either TNF-alpha or IL-6 was found. However, only a single measurement of the cytokines was made in each patient in the morning upon awakening, and both IL-6 and TNF-alpha have circadian rhythms [5, 6].

The transcription factor NF-kappaB can also be induced by hypoxia, and it can increase production of both TNF-alpha and IL-6 [3]. TNF-alpha also acts in a positive feedback manner to increase NF-kappaB. In addition, TNF-alpha and IL-6 levels have been reported by others to be increased in patients with obstructive sleep apnea, although a complicating issue is that increasing body mass index correlates positively with both cytokine levels and AHI.

There is increasing evidence indicating that cytokine levels can significantly affect sleep both positively and negatively. The cytokines IL-1, IL-6 and TNF-alpha, in particular, promote sleep when injected into animals [7, 8].

In addition, obstructive sleep apnea is sometimes associated with airway inflammation [9]. TNF-alpha and IL-6 are critical elements in inflammatory responses. Imagawa et al. [1] point out that inflammation also increases

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VEGF. Experimentally produced resistive breathing, which occurs spontaneously in obstructive sleep apnea, is reported to increase both IL-6 and TNF- α [10, 11].

It is easy to understand how sleep apnea, by producing intermittent systemic hypoxia, increases VEGF. Even local hypoxia gives rise to increases in VEGF. VEGF is

the major mediator of angiogenesis. Angiogenesis is an important factor in many diseases, including cancer, and it promotes tumor spread, retinopathies and rheumatoid arthritis. It would be interesting to see whether the incidence of these diseases is greater in patients with obstructive sleep apnea.

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