Vascular Endothelial Growth Factor and Sleep Apnea: Clutching at Straws in the Night

E. Paul Cherniack

Miami Veterans Affairs Medical Center and the University of Miami Miller School of Medicine, Miami, Fla., USA

Vascular endothelial growth factor (VEGF) is a vasodilator that induces the proliferation of endothelial cells, increases vascular permeability, and causes greater production of nitrous oxide and prostacyclin. It is believed to play a role in the pathogenesis of asthma, emphysema, acute respiratory distress syndrome and lung cancer [1].

There has also been interest in defining a role for VEGF in obstructive sleep apnea syndrome (OSAS). Patients with OSAS are believed to be at increased risk of cardiovascular disease [2]. Individuals with OSAS are 1–4 times more likely to develop hypertension with increasing severity of OSAS [3]. Hypoxia is believed to stimulate the production of VEGF [4]. Investigators have sought to implicate VEGF as part of the mechanism by which OSAS results in greater incidence of cardiovascular disease. Reports that VEGF levels were elevated in OSAS also led to an effort to explore if VEGF could be a serum marker for the presence of OSAS [5].

However, efforts to establish a relationship between VEGF and OSAS have yielded mixed results. Many but not all studies have found elevated VEGF levels in subjects with OSAS [6]. Some but not all investigations have observed a correlation between the severity of OSAS (as measured by the apnea/hypopnea index) and VEGF [6]. The relationship between OSAS and VEGF may be obscured by a possible correlation between VEGF and age, but reports vary as to whether this relationship exists [6].

In the current issue of *Respiration*, an investigation of 100 subjects with OSAS did not find a correlation between oxygen desaturation or the apnea/hypopnea index and VEGF level. Instead, there was a greater correlation between subject age and VEGF level [6].

That studies yield differing results as to whether a relationship exists between OSAS and VEGF level should not be viewed as surprising. There are differences in subject ages and severity of the disease in the populations studied. If one is to assume that OSAS does increase VEGF, duration of the disease, in addition to duration of hypoxia during the night, might be important, but has not been addressed in this or previous investigations. Clarification of the association between VEGF and age awaits determination of VEGF in normal subjects of different ages.

The relationship between OSAS and cardiovascular disease is quite complex. The nature of the association may be influenced by the confounding variables of obesity, exercise, and altitude [7, 8]. Catecholamines, C-reactive protein, fibrinogen, plasminogen activator inhibitors, and other cytokines such as interleukin 6, are likely to be involved [2]. The lesson to be learned from this and other studies of the role of VEGF is that a potential connection between OSAS and cardiovascular disease is not best understood by the narrow focus on this single cytokine.

References

- 1 Voelkel NF, Vandivier RW, Tuder RM: Vascular endothelial growth factor in the lung. *Am J Physiol Lung Cell Mol Physiol* 2005; 290:209–221.
- 2 Kasasbeh E, Chi DS, Krishnaswamy G: Inflammatory aspects of sleep apnea and their cardiovascular consequences. *South Med J* 2006;99:58–67.
- 3 Hedner J, Bengtsson-Boström K, Peker Y, et al: Hypertension prevalence in obstructive sleep apnoea and sex: a population-based case-control study. *Eur Respir J* 2006;27: 564–570.
- 4 Marti HH, Risau W: Systemic hypoxia changes the organ specific distribution of vascular endothelial growth factor and its receptors. *Proc Natl Acad Sci USA* 1998;95: 15809–15814.
- 5 Gozal D, Lipton AJ, Jones KL: Circulating vascular endothelial growth factor level in patients with obstructive sleep apnea. *Sleep* 2002;25:59–65.
- 6 Peled N, Shitrit D, Bendayan D, Peled E, Kramer MR: Association of elevated levels of vascular endothelial growth factor in obstructive sleep apnea syndrome with patient age rather than with obstructive sleep apnea syndrome severity. *Respiration* 2007;74:50–55.
- 7 Silha JV, Krsek M, Sucharda P, et al: Angiogenic factors are elevated in overweight and obese individuals. *Int J Obes (Lond)* 2005;29: 1308–1314.
- 8 Pavlicek V, Marti H, Grad S, et al: Effects of hypobaric hypoxia on vascular endothelial growth factor and the acute phase response in subjects who are susceptible to high-altitude pulmonary oedema. *Eur J Appl Physiol* 2000;80:497–503.