

To the editor:

Blood levels of vascular endothelial growth factor in obstructive sleep apnea–hypopnea syndrome

To better understand how humans adapt to hypoxia, Imagawa and colleagues measured serum levels of vascular endothelial growth factor in patients with sleep apnea–hypopnea syndrome. They found substantially elevated serum levels of vascular endothelial growth factor (VEGF) in those patients.¹ However, what conclusions can be drawn from this finding regarding the purpose of their study? VEGF at higher levels in blood causes mobilization of endothelial progenitor cells from the bone marrow and promotes angiogenesis *in vivo*.² VEGF is not only a potent inducer of angiogenesis but also a very potent mediator of capillary leakage. Thus, if free-circulating VEGF in the reported amounts has been present in the studied patients, one would assume clinical effects caused by vessel leakage such as edema, weight gain, or cardiopulmonary problems.

A simple explanation for the finding of elevated serum levels of VEGF in hypoxic patients with sleep apnea–hypopnea might be thrombocytosis. Hypoxia causes thrombocytosis,³ and virtually all of the VEGF that is measurable in serum samples is released from platelets during the clotting process *in vitro*.^{4,5} Unfortunately, no blood platelet counts were reported by Imagawa and colleagues. When plasma samples are analyzed instead of serum samples, negligible amounts of circulating VEGF can be found.⁶

Response:

Elevation of vascular endothelial growth factor in patients with obstructive sleep apnea–hypopnea syndrome is not due to increased platelet counts

Gunsilius et al raise the possibility that the elevated vascular endothelial growth factor (VEGF) levels that we saw in our patients with obstructive sleep apnea–hypopnea syndrome (OSAHS) may be due to increased platelet counts that in turn lead to higher production of VEGF during clotting. Because we did not report platelet counts of our patients, this was a reasonable supposition. However, we can report additional data that argue against this hypothesis (Table 1). First, the platelet counts in our patients were normal, and second, there was no correlation between platelet count and apnea–hypopnea index (AHI). On the other hand, as reported in our paper,¹ VEGF levels increased significantly with increasing AHI.

Gunsilius et al wondered whether we observed edema, weight gain, or cardiopulmonary problems in our patients, which would be

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expected to result from chronic elevated VEGF levels. We did see edema, weight gain, and systemic hypertension in some of the patients with severe OSAHS, but there was no clear relationship between the levels of VEGF and these symptoms. However OSAHS is a temporary problem that occurs during only a portion of the day,² and half-lives of VEGF and erythropoietin (Epo) are less than 6 hours. Therefore, a lack of correlation between VEGF levels and these symptoms is not surprising. Still, cardiac arrhythmia and conduction disturbances³ and pulmonary hypertension⁴ have been reported in patients with sleep apnea, but in both cases these conditions were not chronic but occurred on a daily cycle.

The simple explanation for the elevated VEGF levels in patients with OSAHS is that it is induced by hypoxia. However, induction of VEGF may be a complex process that may involve other factors such as interleukin-6 and tumor necrosis factor α .⁵ Further studies of these latter factors are needed to clarify the response of VEGF.

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Table 1. Levels of VEGF and platelet counts with severe OSAHS and controls

AHI	Serum VEGF (pg/mL)	Platelet count ($\times 10^4/\mu\text{L}$)	n
Less than 5 (control)	150 \pm 111	24.8 \pm 5.0	45
30-49	250 \pm 202*	25.3 \pm 7.2	41
50-69	582 \pm 415*	24.4 \pm 6.1	37
70-89	547 \pm 517*	24.0 \pm 4.3	22
90-109	450 \pm 250*	25.9 \pm 10.1	6
Greater than 110	755 \pm 182*	28.0 \pm 5.7	4

* $P < .005$ compared to AHI < 5.

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To the editor:

Oxygen saturation in the bone marrow of healthy volunteers

In recent years there has been a great deal of progress in understanding the homeostasis of different tissue microenvironments, and this has been particularly true of the hematopoietic system. Insights into the interaction of the microenvironmental stromal cells of the bone marrow with the blood-forming stem cells and their progeny have been substantial and have led to clinical applications. An example of this is the use of hematopoietic growth factors for the treatment of peripheral blood cytopenias and other hematologic disorders. Understanding the basic biology of the bone marrow has led to such therapies. The hemopoietics, including recombinant granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and interleukin-11, have been cloned from the stromal cells and introduced into clinical use.¹ Recently, our laboratory and others have been examining the response of the bone marrow to hypoxia, which is an experimental model of hemorrhagic shock.² In addition, it has been demonstrated that hematopoietic growth factors signal, in part, through the formation of reactive oxygen species.³ However, to date, there have been no reports in the scientific literature regarding the partial pressure of oxygen (pO₂) and the oxygen saturation in the normal marrow microenvironment. Such information is important for interpreting the current literature.

In order to establish a baseline for comparison in experimental conditions and to design the appropriate research models, we performed gas analysis in a series of 5 healthy volunteer bone marrow donors. All subjects underwent posterior superior iliac crest bone marrow aspiration using an Illinois aspiration needle, after obtaining informed consent in accordance with a clinical protocol approved by the institutional review board of the University of Medicine and Dentistry of New Jersey. Donors were aged 24 to 46, and were all in excellent health. Specimens were obtained using aseptic technique, and marrow was aspirated into a blood gas syringe. Specimens were brought on ice to the laboratory and analyzed using a CIBA-Corning Corporation Model 278 blood gas

analyzer (East Walpole, MA). The mean pO₂ of the marrow aspirates was 54.9 mm Hg ± 0.98, with mean O₂ saturation of 87.5% ± 1.1%. Peripheral blood mean O₂ saturation was obtained by pulse oximeter at the same time, with a mean O₂ saturation of 99%. The marrow cavity is sinusoidal, and anatomically the fluid flowing through the marrow cavity is a mixture of arterial and venous blood. A search of the National Library of Medicine database (Medline) yielded a single prior report of marrow gas analysis; however, this was a study of 82 men, all with chronic pulmonary disease, and no healthy subjects were included as controls. In this group, the mean pO₂ in the marrow was 48 mm Hg (range 33.5 to 64.1 mm Hg).⁴ The pO₂ and oxygen saturation of the marrow in the normal state is a critical reference point for determining the effects of hypoxemia upon the bone marrow microenvironment both in experiment conditions and in clinical situations. We are continuing to investigate the effects of hypoxemia in experimental and clinical settings, but identifying and reporting the normal oxygen content of the marrow microenvironment here provides documentation of the baseline for comparison in future laboratory and clinical studies.

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