Vascular Endothelial Growth Factor Inhibitors and Hypertension
A Central Role for the Kidney and Endothelial Factors?

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Vascular endothelial growth factor (VEGF or VEGF-A) has numerous physiological actions, including inducing endothelial cell permeability, proliferation, angiogenesis, lymphogenesis, and vasodilation. VEGF belongs to a family of secreted glycoproteins, including VEGF-B, -C, -D and placenta growth factor. VEGF signaling is mediated via 2 receptors, VEGFR1/Flt1 and VEGFR2/Flik.

First described as a tumor-derived factor, VEGF plays a central role in the pathogenic angiogenesis that occurs in cancerous tumors. Thus, an array of VEGF-pathway inhibitors has been developed to block the formation of tumor vessels and cause regression of tumors. Although many of these agents have shown promise in clinical trials, a number of adverse effects, including hypertension, proteinuria, arterial thromboembolia, and gastrointestinal perforation, have been reported. These multiple and diverse adverse effects support the growing evidence that VEGF may have important physiological roles in the adult human. Indeed, previous studies indicate that VEGF is expressed in virtually every tissue in the adult. The highest density of VEGF-expressing cells is found in tissues with fenestrated vasculature, such as in the kidney. Moreover, VEGF neutralization studies in animals and studies demonstrating that the endogenous soluble VEGF receptor antagonist, sFlt-1, causes significant endothelial dysfunction, proteinuria, and hypertension support the notion that VEGF may have an important effect on endothelial and vascular functions and on blood pressure regulation in the adult animal.

Although hypertension appears to be one of the most common adverse effects of VEGF inhibitors, the pathophysiological mechanisms underlying the increase in blood pressure in response to VEGF pathway inhibitors have yet to be fully elucidated. Because the endothelium is a major target organ for the actions of VEGF, it is likely that decreases in the production of endothelium-derived relaxing factors, such as NO and prostaglandin, or enhanced production of vasoconstricting factors, such as thromboxane and endothelin (ET), play a role in the hypertensive response to drugs that block the VEGF pathway. However, the relative importance of these vasoactive factors in mediating the increase in blood pressure in response to VEGF pathway inhibitors has yet to be fully elucidated. To address this important unanswered question, Facemire et al report in this issue of Hypertension that administration of a specific antibody against the major VEGF receptor, VEGFR2, to normal mice caused a rapid and sustained increase in BP of ~10 mm Hg. The hypertension in response to the anti-VEGFR2 antibody was associated with significant reductions in the expression of endothelial and neuronal NO synthases in the kidney. This effect on NO synthases is consistent with previous studies that have reported that human endothelial cells exposed to VEGF cause a release of NO and upregulate both endothelial NO synthase mRNA and protein levels in a dose-dependent manner. Whether VEGF pathway inhibition affects the expression of endothelial and/or neuronal NO synthases in extrarenal tissues was not determined in this study and remains another important unanswered question.

To further establish a role for reduced NO synthesis in the hypertension caused by blocking VEGFR2, Facemire et al treated mice with N-nitro-l-arginine methyl ester, an inhibitor of NO production. They report that N-nitro-l-arginine methyl ester administration abolished the difference in blood pressure between the vehicle- and anti-VEGFR2–treated groups. These findings suggest that VEGF, acting via VEGFR2, plays a critical role in influencing basal levels of blood pressure control by enhancing NO synthase expression and NO activity. Moreover, the results suggest that reducing nitric production and/or availability may be one mechanism underlying hypertension caused by antiangiogenic agents targeting VEGF.

Facemire et al also examined the effects of VEGFR2 blockade on the prostanoid and on the renin-angiotensin-aldosterone systems. Urinary excretion of 6-keto-PGF1α, the major metabolite of prostaglandin I2, and urinary levels of prostaglandin E2 metabolite were not affected by anti-VEGFR2 antibody. In addition, excretion of thromboxane B2, the major metabolite of the vasoconstrictor eicosanoid thromboxane A2, was not affected by VEGFR2 blockade. The hypertension in response to VEGFR2 blockade was also associated with reductions in renin expression and urinary aldosterone excretion. Collectively, these data indicate that stimulation of the renin-angiotensin-aldosterone system or alterations in the balance of vasodilator and vasoconstrictor prostanoids do not play a role in causing hypertension in response to VEGFR2 blockade. However, whether metabolite excretion of prostanoids accurately reflects the changes in vascular production is unclear. Thus, a potential role for...
alterations in prostanoids in causing hypertension in response to inhibition of VEGF signaling should still be considered.

Another important endothelial-derived factor that may play a role in mediating the hypertension produced by VEGF inhibition but was not examined in the study by Facemire et al.\textsuperscript{9} is the vasoconstrictor ET-1.\textsuperscript{7} Although most studies have reported no significant changes in circulating levels of ET-1 during various forms of hypertension, a role for ET-1 as a paracrine or autocrine factor in hypertension has been reported.\textsuperscript{7} In addition, a recent study has suggested an important role for ET-1 in mediating the hypertension in a model of preeclampsia that has elevated levels of the soluble VEGF receptor antagonist, sFlt-1.\textsuperscript{4} Thus, another potential mechanism whereby VEGF blockade could increase blood pressure is by enhancing ET-1 synthesis. However, the relative importance of the ET system in mediating increases in blood pressure in response to VEGF pathway inhibitors remains to be determined.

Although the exact physiological mechanisms whereby VEGF inhibition leads to hypertension are unknown, experimental and theoretical evidence strongly support a central role for the kidneys in the pathogenesis of hypertension.\textsuperscript{13} According to the renal-body fluid feedback concept for blood pressure control, chronic increases in arterial pressure occur as the result of abnormalities in the relationship between renal perfusion pressure and sodium excretion.\textsuperscript{13} That is, for long-term increases in arterial pressure to occur, a reduction in the capability of the kidney to excrete sodium and water must be present. Indeed, a common defect that has been found in all forms of hypertension examined to date, including genetic and experimental models and human essential hypertension, is a hypertensive shift in the pressure-natriuresis relationship.\textsuperscript{13} Interestingly, in the study by Facemire et al.,\textsuperscript{9} the anti-VEGFR2 antibody caused a rightward and parallel shift in the chronic pressure-natriuresis relationship (see Figure 1). The parallel shift in the chronic pressure-natriuresis relationship suggests that abnormalities in vascular rather than tubular function may be involved in hypertension.

The altered pressure-natriuresis relationship in response to blockade of VEGF receptors may be the result of endothelial dysfunction leading to decreases in the production of endothelium-derived relaxing factor, such as NO (see Figure 2). Supporting this contention is the fact that the hypertension in response to the anti-VEGFR2 antibody was associated with significant reductions in the expression of endothelial and neuronal NO synthases in the kidney. The net result of these changes would reduce renal hemodynamics and the kidney’s ability to excrete sodium and water. Unfortunately, the effect of the anti-VEGFR2 antibody on renal hemodynamics was not established in the study by Facemire et al.\textsuperscript{9}

Another potential mechanism for the alteration in the chronic pressure-natriuresis relationship in response to VEGF inhibitors is the alteration in glomerular structure and function (see Figure 2). VEGF and VEGFRs are highly expressed in the kidney. VEGF is expressed in podocytes in the glomerulus, and VEGFRs are present on endothelial, mesangial, and peritubular capillary cells.\textsuperscript{14} Signaling between endothelial cells and podocytes is thought to be important for maintenance of the filtration function of the glomerulus, and inhibitors of VEGF signaling have been shown to result in alterations in glomerular structure and function.\textsuperscript{14,15}

Although it is thought that blockade of the VEGF-A signaling pathway plays a critical role in the hypertension produced by VEGF inhibitors, a recent study by Machnik et al.\textsuperscript{16} suggests a role for VEGF-C. The authors propose that macrophages regulate salt-dependent volume and blood pressure by a VEGF-C–dependent buffering mechanism. They suggest that VEGF-C, which is produced by macrophages, stimulates lymphatic vessel growth, creating a third fluid compartment that buffers the increased total body sodium and

\textbf{Figure 1.} Effect of anti-VEGFR2 antibody on the chronic pressure-natriuresis relationship in control and antibody-treated mice. Notice that anti-VEGFR2 antibody caused a rightward and parallel shift in the chronic pressure-natriuresis relationship. Redrawn from data in Reference 9.

\textbf{Figure 2.} Potential mechanism whereby inhibitors of VEGFR signaling lead to hypertension. Blockade of VEGF receptors results in endothelial dysfunction leading to decreases in the production of endothelium-derived relaxing, such as NO and prostaglandin, or enhanced production of vasoconstrictor factors, such as thromboxane and ET. Inhibitors of VEGF signaling may also result in alterations in glomerular structure and function. The net result of these changes causes elevations in blood pressure by increasing total peripheral resistance and by reducing renal hemodynamics and the kidney’s ability to excrete sodium and water (depicted by a decrease in the pressure-natriuresis relationship).
volume and buffers the high blood pressure in response to increases sodium intake. They reported that macrophage depletion or inhibition of VEGF-C signaling increased blood pressure in response to a high-sodium diet. The authors suggested that the increase in blood pressure was attributed to a decrease in lymphatic vessel growth and a reduction in the fluid compartment. However, the fact that macrophage depletion or inhibition of VEGF-C signaling caused a chronic increase in blood pressure indicates that inhibition of VEGF-C signaling also reduces the kidney’s ability to excrete sodium and water. Future studies will be necessary to discern the renal mechanisms whereby macrophage depletion or inhibition of VEGF-C signaling alters the pressure-natriuresis relationship.

In summary, there is growing amount of evidence suggesting that VEGF may have important physiological roles in the adult human. Results from VEGF neutralization studies in animals and clinical trials in humans demonstrating significant endothelial dysfunction and hypertension implicate VEGF as having an important role in maintaining normal endothelial function and blood pressure regulation in the adult animal. Additional elucidation of the mechanisms whereby VEGF achieves this important physiological function could provide new drug targets to minimize the risk of significant hypertension and proteinuria in patients treated with VEGF pathway inhibitors.

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