Therapeutic Angiogenesis
The New Electrophysiology?
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pproximately 15 million patients suffer from coronary and peripheral atherosclerotic diseases in the United States alone.1 The evolving development of medical and surgical therapies has significantly improved the physician’s ability to manage these patients, yet many continue to suffer debilitating symptoms from their disease and remain at risk for myocardial infarction, limb loss, and death. This clinical imperative, coupled with rapid advances in molecular biology, has led to the exploration of a plethora of therapeutic angiogenesis strategies. A method described in this issue of Circulation2 offers yet another means by which angiogenesis may be achieved and thus potentially opens a new chapter in the ongoing search for novel approaches for the treatment of ischemia.

Angiogenic and Antiangiogenic Therapy
In placing the novelty of the approach by Kanno et al into perspective, it is worth considering the important advances made during the last decade in the field of therapeutic angiogenesis. The investigators at the forefront of this field have not used a traditional pharmaceutical approach to search for potential angiogenic agents effective against vascular disease. Instead, they have chosen to arm themselves with the fruits of the molecular biology revolution by harnessing the power of endogenous human angiogenic factors. Vascular endothelial growth factor (VEGF) is the most potent and specific endogenous angiogenic factor yet identified, so it makes sense that it would have drawn the attention of cardiologists interested in angiogenic therapies. The demonstration that intra-arterial injection of recombinant VEGF could induce collateral formation in ischemic rabbit hindlimbs3 suggested that VEGF would be a useful angiogenic agent, and this has subsequently been confirmed by an impressive corpus of preclinical data.

Phase I and II clinical trials are now under way to test the effects of VEGF in patients with ischemic vascular disease, and preliminary results from some of these trials have now been published.4,5 Two methods are being used to deliver VEGF: intra-arterial injection of recombinant VEGF protein into an artery supplying ischemic tissue, or delivery of the VEGF cDNA into ischemic zones by plasmid-based or viral vectors. Preliminary data have been quite promising and promote the general concept that VEGF therapy may be beneficial in humans with vascular disease. However, practical and potential obstacles exist when VEGF is delivered either as a protein or through gene-therapy approaches, which may, to a certain extent, temper the enthusiasm generated by these preliminary studies. Intra-arterial injection of VEGF (for instance, into the coronary circulation) is invasive (and thus costly). Intravascular administration is also sure to result in some systemic delivery of VEGF, which raises at least the theoretical possibility of remote effects such as enhancement of tumor growth, diabetic retinopathy, and other diseases with prominent angiogenic components. Gene-therapy approaches also have the disadvantage of requiring systemic delivery. In addition, the short- and long-term consequences of administering genetic vectors in humans are largely unexplored and need to be addressed before their large-scale use can be recommended.

If only it were so simple. As more has been learned about angiogenesis, it is increasingly apparent that distinct genes regulate different aspects of the process. It has been known for several years that both VEGF and basic fibroblast growth factor are potent angiogenic factors deployed by tumors. This has been part of the rationale for the development of the angiotatin-potent antiangiogenic factors that inhibit tumor-stimulated angiogenesis.6 However, numerous investigators have now demonstrated that simply initiating (or inhibiting) vascular endothelial cell migration may be insufficient to modulate new vessel formation, and other factors have been identified that are necessary for the complete assembly of new blood vessels. The receptor tyrosine kinases Tie-1 and Tie-2 and their ligands and inhibitors (the angiopoietins) fall into this class.7 Yet another key component in this molecular cascade are the recently reported Eph receptors, a large family of receptor tyrosine kinases that are distinct from the receptors for VEGF, Tie-1 and Tie-2. The Eph receptors appear to be critical in early determination of whether a developing vessel will become an artery or a vein.8

Electrical Stimulation of Angiogenesis
Because of this complexity at the molecular level, the study described by Kanno et al2 is of particular interest. They demonstrate a novel method whereby VEGF production and angiogenesis can be stimulated: low-intensity (below contraction threshold) electrical stimulation of skeletal muscle. Knowing that stimulated contraction of skeletal muscle induces angiogenesis and VEGF production,9,10 the authors
speculated that this effect might be due, at least in part, to electrical stimulation per se rather than to contraction. This is not an unreasonable assumption, because low-intensity electrical stimulation can have significant cellular effects on noncontractile cells.11

Some will probably believe such an approach to be hopelessly simple and unlikely to succeed. To be certain, the hypothesis of Kanno et al is far from proven for the reasons discussed below. However, imagine the present status of percutaneous coronary revascularization had Andreas Gruentzig investigated a pharmacological or molecular approach to lessening symptomatic coronary artery stenoses. For this reason alone, it is worth considering the observations of Kanno et al in some detail.

To test their hypothesis, the authors first examined the effect of subcontractile electrical stimulation on skeletal muscle–like cells in culture and found that VEGF production was induced by electrical stimulation in a frequency-dependent manner. Having shown this effect in vitro, the authors used the rabbit ischemic hindlimb model to examine whether low-intensity electrical stimulation might also increase VEGF expression and capillary density in vivo. Electrodes were implanted into ischemic tibialis anterior muscles 1 week after femoral artery ligation, and low-intensity, low-frequency electrical stimulation was applied for another week. The authors detected increased amounts of VEGF protein after this treatment, as measured by immunohistochemistry. This increase in VEGF was accompanied by increases in blood flow and capillary density in the ipsilateral, electrically stimulated limb but not in the contralateral limb, suggesting that angiogenesis was indeed enhanced by this treatment.

In this study, the authors have examined the effect of electrical stimulation on VEGF expression and angiogenesis only in the ischemic muscle bed itself and not in tissues at a distance from the ischemic capillary bed or in nonischemic tissues. This is unfortunate because the goal of angiogenic therapy for ischemic vascular disease might be not only to increase capillary density in ischemic muscle but also to increase collateral formation around stenosed or occluded arteries. Collateral formation in response to ischemia occurs at a distance from the ischemic zone and differs from capillary sprouting histologically, arises more rapidly and by different mechanisms than does capillary sprouting, and is not hypoxia driven.12 Because induction of collateral formation might be a more efficient goal in angiogenic therapy (by increasing blood supply to an entire target organ rather than to a single ischemic bed), it will be interesting to determine whether electrical stimulation can also induce collateral formation or whether its effects will be limited to induction of capillary sprouting in ischemic tissues.

Because one of the concerns of angiogenic therapies for vascular disease is that systemic effects of these therapies distant from the ischemic zone may adversely affect the patient, it is unfortunate that measurements of VEGF in the venous circulation of treated rabbits were not performed in the present report. This concern is not entirely without basis: plasmid-based delivery of VEGF in humans causes measurable increases in venous VEGF protein levels and has resulted in contralateral limb edema in some patients, indicating that systemic delivery and at least some systemic sequelae do occur.4 What is the ideal radius for the effects of VEGF? If the effect of electrical stimulation on VEGF expression is strictly local, then there are at least theoretical reasons to believe that its safety profile might be more favorable than angiogenic therapies that result in systemic delivery of VEGF.

A broader, unresolved issue raised by the present study is whether differences exist when angiogenesis is elicited by exogenously administered growth factors rather than by
therapies designed to stimulate endogenous angiogenic pathways. It must be recognized that at this point in time, the favorable results from human angiogenic gene-therapy trials have been disclosed primarily as series of case reports. Furthermore, whereas most of the animal studies using VEGF in the setting of ischemic vascular disease have demonstrated favorable effects, some have demonstrated no effects of VEGF on parameters such as reendothelialization. In addition, some data suggest that VEGF may play a role in the microvascular complications of diabetes, and VEGF was shown to worsen neointimal lesion size without affecting collateral formation in a canine model of ischemic coronary disease. A better understanding of endogenous pathways regulating VEGF activity may help to explain why VEGF may exert both salutary and deleterious vascular effects, which ultimately could lead to more efficacious angiogenic therapies.

Moreover, the potential importance of the other molecular guardians of angiogenesis described above remains largely untested in animal models or humans. Clearly, the potential therapeutic impact of these additional pathways is not addressed in ongoing VEGF-based clinical studies. Because it is unknown whether these pathways are also affected by electrical stimulation, addressing this issue may provide intriguing insight into the most effective approaches toward achieving therapeutic angiogenesis. To revisit the angioplasty paradigm, a multitude of pathways are activated by balloon injury, and only in the past few years have the molecular puzzles begun to be solved.

Modern electrical-stimulation therapies are used to treat chronic pain syndromes and may facilitate the healing of fractures and soft-tissue wounds. On the basis of the present report, it is tempting to speculate that induction of VEGF may contribute to the salutary effects of electrical stimulation in these settings. Regardless of whether this is the case, there is considerable accumulated experience in the use of electrical stimulation in the clinical arena. It can be applied transcutaneously and is thus remarkably safe, relatively inexpensive, and easy to administer. In contrast with intravascular injection of VEGF, induction of endogenous VEGF by electrical stimulation could be performed noninvasively and repeatedly. Unlike gene therapy, electrical stimulation has been used successfully for decades, and untoward effects are unlikely if this technique is used to stimulate VEGF expression for the treatment of ischemic vascular disease.

Although angiogenic therapy holds promise for the treatment of ischemic vascular disease, we are still in the earliest stages of testing its effectiveness and of determining the best way to enhance collateral formation and new capillary growth in ischemic tissues. It will not be surprising if molecular and nonmolecular strategies become alternative or even complementary therapies to induce angiogenesis. Indeed, electrical stimulation may be yet another method for augmenting angiogenesis, and studies to examine its effectiveness in humans with ischemic vascular disease will be eagerly awaited.

References


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