Blood to Save Brain

Zvonimir Katusic, MD, Mayo Clinic, Rochester, MN, discussed recent work exploring the therapeutic potential of stimulating angiogenesis via circulating endothelial precursors and endothelial progenitor cells (EPCs).

The ability of EPCs to withstand oxidative stress as a result of a high level of manganese superoxide dismutase (MnSOD) enzymatic activity allows them to perform complex regenerative functions under the conditions of ischemia/reperfusion induced by stroke. Transplantation of early outgrowth EPCs into the lumen of injured arteries has been shown to stimulate regrowth of the endothelium in as little as 4 weeks. EPCs also have been shown to prevent dysfunction of regenerated endothelium by enhancing endothelium-dependent relaxation to acetylcholine. When injected directly into the cisterna magna in animal studies, EPCs stimulated production of the vasoprotective molecules prostacyclin and cAMP. In contrast, injected cells inhibited the production of thromboxane A2 (a molecule that favors platelet aggregation, blood clotting, and vasoconstriction) in the basilar artery. In light of all of these results, it is possible that EPCs may prevent vasospasm after subarachnoid hemorrhage, stimulate formation of collateral vessels, and inhibit thrombosis and restenosis.

S. Thomas Carmichael, MD, David Geffen School of Medicine, University of California, Los Angeles, CA, discussed the integrated responses in neurovasculogenesis after stroke. Although stroke causes cell death, it also leads to the birth and migration of new neurons within the sites of ischemic damage by inducing neurogenesis in the microvasculature adjacent to the infarct (peri-infarct cortex). Waves of newly born immature neurons (neuroblasts) migrate from their origin in the subventricular zone to the peri-infarct cortex and form a tight spatial relationship with the blood vessels. This migration is mediated, in part, by the cytokine erythropoietin.

Within this neurovascular niche, the neuroblasts sprout new connections and closely associate with the remodeling vasculature. Neurogenesis and angiogenesis are causally linked in the reorganizing of the peri-infarct cortex through vascular production of stromal-derived factor 1 (SDF1) and angiopoietin 1 (Ang1), which are trophic factors for migrating neuroblasts and improve behavioral recovery. Dr. Carmichael pointed out the challenges that lay ahead in the field, including the need to understand the environments of neural repair that may lead to novel stroke therapies and how these environments relate to cellular interactions and growth factor signaling in peri-infarct tissue. The role of post-stroke neurogenesis in neurological recovery after stroke remains undefined, and future work will need to define the behavioral effects of post-stroke neurogenesis and the interaction of behavioral or neurorehabilitative "stimulation" and neuronal regeneration, particularly in the aged brain.

In his presentation, Patrick D. Lyden, MD, University of California San Diego and Veterans Affairs Stroke Centers, San Diego, CA, suggested that angiogensis (growth of new blood vessels) may have both favorable and deleterious effects following an acute stroke. As pointed by Dr. Carmichael, angiogenesis signaling after ischemia may create a vascular niche and promote neurogenesis and functional recovery. However, an imbalance in angiogenesis contributes to the pathogenesis of numerous malignant, inflammatory, ischemic, infectious, immune, and wound-healing disorders.

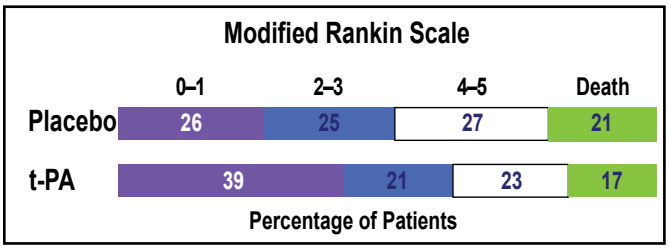
Ischemia-evoked angiogenic signals also have been associated with leaky microvessels and phagocytic macrophages. This association with an increased number of macrophages has been dubbed the "clean up" hypothesis. Following ischemia, microvessel density increases only in the ischemic margin adjacent to areas of pannecrosis, where no neuronal structure can be observed. Increased numbers of macrophages also are observed in this area, suggesting that ischemia-induced microvessels are formed to facilitate macrophage infiltration and removal of necrotic debris. Blocking macrophage infiltration reduces angiogenesis in the microvasculature niche. Dr. Lyden concluded by saying that more effective stroke interventions may be possible through a better understanding of the role of angiogenesis.

The Impact of Medical Legal Issues on Stroke Treatment

Justin Zivin, MD, PhD, University of California, San Diego, CA, presented data demonstrating how legal issues influence the treatment of stroke. Recombinant tissue plasminogen activator (rt-PA) is a well-known FDA-approved thrombolytic treatment. It is estimated that only 4%-8% of acute ischemic stroke patients receive rt-PA, when up to 40%-50% of patients could derive benefit from the drug. In Dr. Zivin's opinion, fear of malpractice lawsuits depresses the use of this drug. The literature and regulatory approvals support the idea that rt-PA is a valid

therapy for acute ischemic stroke. In a recent re-analysis of the NINDS rt-PA trial, "none of the bad outcomes was increased by rt-PA," said Dr. Zivin (Figure 1). Demaerschalk (*Stroke* 2007) estimated the likelihood of being helped to being harmed (LHH) by rt-PA to be approximately 10. In other words, rt-PA therapy would be 10 times more likely to help a patient with acute ischemic stroke than to harm them.

Figure 1. NINDS rt-PA Trial.



These findings have not always translated into clinical practice. A survey conducted by the American College of Emergency Physicians indicated that 40% of emergency room doctors were unlikely to use rt-PA under ideal conditions (Brown et al. *Ann Emerg Med* 2005). When asked why, 65% cited concerns about intracerebral hemorrhage, 23% said due to lack of efficacy, and 12% replied that both reasons contributed to their decision. Ironically, the decision not to use rt-PA has resulted in more lawsuits than lawsuits that have been filed due to harm caused by using the drug (Bambauer et al. *Ann Neurol* 2006). "Many physicians believe that 'to do no harm' is a good strategy to avoid malpractice suits. What they fail to realize under those circumstances is that to fail to treat, to decide not to do something, is a decision. Failure to treat with rt-PA is more likely to result in adverse legal decisions," said Dr. Zivin.

What can physicians do in this increasingly litigious environment? According to Michael Weintraub, MD, New York Medical College, Valhalla, NY, detailed documentation is absolutely critical. Legibly documenting time of symptom onset, time of diagnosis, time of workup completion, and rationale for using or not using rt-PA is particularly important. "Poor medical records can suggest negligence to the jury," noted Dr. Weintraub. John P. Conomy, MD, JD, Case Western Reserve University, Cleveland, OH, offered additional advice. Because patients often turn to the internet to educate themselves, physicians need to be aware of this and step up their efforts to educate patients. Physicians should also educate themselves about the legal issues they face. "Attorneys know a great deal about a great many things. Physicians as a group know very little about law, because they've been taught very little about law. I think it belongs in the curricula of medical schools, at least in an introductory way," summarized Dr. Conomy.

Clinical Approaches to Brain Repair After Stroke

Patients who suffer strokes experience residual symptoms in many areas. Reports in the literature indicate that 38% of patients reported major difficulty in hand function 1-3 months post-stroke (Duncan et al. *Stroke* 2003), and up to 65% of patients could not use their paretic hand in daily activities 6 months post-stroke (Mayo et al. 2002). "The impact of manual function on independent living is significant…this is one of the precursors of losing independent capability," said Carolee Winstein, PhD, PT, University of California, Los Angeles, CA. Different approaches are being explored to help alleviate post-stroke disability, and studies suggest that intensive, task-oriented upper limb training (TOULT) may be effective. The Stroke Arm Recovery (STAR) trial was a phase 2, unblinded, single-center study that compared TOULT, strength training (ST), and standard care (SC) on upper limb recovery. The TOULT group was significantly better than the SC group in measures of impairment ($p=0.04$) and strength ($p=0.02$). Nine months later, the less severe stroke patients outperformed the ST group in strength ($p<0.05$; Winstein et al. *Arch Phys Med Rehabil* 2004). In the phase 3 Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial, 222 stroke patients were randomized to receive either constraint-induced movement therapy (CIMT) or SC 3-9 months post-stroke. Patients who received CIMT had statistically significant, clinically relevant improvements that lasted for at least one year (Wolf et al. *JAMA* 2006). "The critical elements of constraint therapy remain unresolved. Is it the task-oriented training, is it the shaping repetition, is it the forced use?" commented Dr. Winstein. These questions are in need of additional research.

Electromagnetic brain stimulation methodology and its potential effect on motor stimulation training were reviewed by Leonardo Cohen, MD, National Institutes of Health, Bethesda, MD. "One line of evidence that has been demonstrated so far...is that when different forms of brain stimulation are applied over the primary motor cortex (M1), there is a resultant increase in motor cortical excitability," said Dr. Cohen. This led to the idea that stimulation may provide a synergistic effect on motor training in humans, and emerging technologies are in the proof-of-concept stage