



NCR: Catalyst for Discovery

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A grayscale MR microscopy image showing a complex network of branching vessels, likely the pulmonary vasculature, against a dark background. The vessels are bright and contrast sharply with the surrounding tissue.

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Growth Factors: An Alternative to Bypass Surgery

Naturally occurring proteins known as angiogenic factors, which promote blood vessel growth, show promise in treating patients with blocked coronary arteries who are not good candidates for bypass surgery. The experimental therapy, developed by scientists at the Angiogenesis Research Center at Beth Israel Deaconess Medical Center at Harvard Medical School in Boston and evaluated at the NCCR-supported General Clinical Research Center (GCRC) there, significantly improved blood flow in the heart and apparently prevented episodes of chest pain, or angina.

When the coronary vessels become blocked, blood flow to heart tissue becomes impeded, depleting it of oxygen. If too much tissue becomes oxygen-starved, or ischemic, heart failure occurs. Bypass surgery, which involves grafting vessels from other parts of the body next to blocked coronary vessels, generally improves blood flow, although sometimes the surgery cannot restore adequate circulation. Some patients require one or more repeat procedures and still have difficulty with the simplest physical tasks. It is these patients who are most likely to benefit from the experimental treatments,

says Dr. Michael Simons, director of the Angiogenesis Research Center and associate professor of medicine at Harvard Medical School. Together with Dr. Roger Laham, assistant professor of medicine at Harvard and director of clinical research at the Angiogenesis Research Center, Dr. Simons' team has already evaluated the angiogenic factor known as basic fibroblast growth factor (bFGF) in Phase II clinical trials, and the results of another trial involving more than 300 patients will be available shortly.

The researchers first made the connection between growth factors and coronary circulation in 1992, when they noted that some patients had completely obstructed coronary vessels yet exhibited no clinical symptoms of coronary disease. "When we looked closely at these patients' hearts, we saw that they had an extensive network of collateral vessels," explains Dr. Laham. "This created a kind of biologic bypass that provided adequate blood flow to the heart despite almost completely blocked coronary vessels."

A subsequent study of cardiac tissue from humans and animals revealed an increased expression of two vascular growth factors and their receptors in the ischemic myocardial tissues—bFGF and vascular endothelial growth factor (VEGF). Although these factors are found naturally in everyone, people who produce more growth factors when the heart's circulation is challenged apparently develop enough collateral circulation to restore blood flow to the starved cardiac tissue.

"The next logical step was to find a way to provide the growth factors when they were not naturally increased," Dr. Laham recalls. In 1994 the researchers conducted preclinical studies on pigs with blocked coronary arteries and found that administration of growth factors improved cardiac function and restored circulation to ischemic areas of the heart.

The investigators then needed a strategy for administering the proteins close to the heart over an extended period of time. In collaboration with Dr. Elazer R. Edelman, Massachusetts Institute of Technology in Boston, the scientists developed capsules made of a polymer called heparin alginate. These capsules could contain the growth factors and gradually release them in the fatty tissues near the



Drs. Roger Laham (left) and Michael Simons administer vascular growth factors to the hearts of patients with blocked coronary arteries. The growth factors promote development of new blood vessels to the heart. (Photos courtesy of Beth Israel Deaconess Medical Center, Harvard University)

coronary vessels over periods of three to four weeks after implantation.

Tests of the new capsules in pigs showed that the treatment was safe as well as effective in improving coronary blood flow. Following approval by the Food and Drug Administration, clinical trials began.

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The researchers enrolled 24 patients scheduled for bypass surgery in a double-blinded placebo-controlled study that was carried out in the NCCR-supported GCRC at Beth Israel. The patients were randomly assigned to receive either high-dose or low-dose bFGF capsules, or a placebo. Within three months, patients who had received the high-dose capsules had significantly improved blood flow to their hearts. Subsequent examination using magnetic resonance imaging showed that these patients also had significantly smaller ischemic regions in their hearts, and after 16 months, none of them experienced chest pain. No adverse effects were noted in any of the patients who had received the capsules.

With the efficacy of bFGF established in the first trial, the researchers went on to study other less invasive delivery protocols, such as intracoronary (IC), intravenous (IV), and intramyocardial administration. For IC delivery, a catheter is inserted in the femoral vein near the groin and then threaded through the aorta to the heart. Once the catheter is in place, the doctors can infuse the growth factors into the coronary vessels.

This approach, while less invasive than surgery, is not without its problems. "The reason that the IC approach might not work is because there is so much blood flowing through the heart, and then into the systemic circulation, that only a small portion of the growth factors given by infusion actually stays in the heart," says Dr. Laham. Less than 1 percent of the growth factors remained in the heart after one hour, the remainder went into the systemic circulation. Because bFGF is relatively safe, this recirculation didn't cause problems, but similar trials with VEGF showed an important complication. "VEGF seriously reduced blood pressure. It's not possible to administer enough VEGF without reaching the toxic level using the IC approach," explains Dr. Laham.

Yet another promising technique under consideration is intramyocardial delivery. Traditionally, this procedure required opening the chest and injecting the material directly into the heart muscle, a major surgical procedure that the doctors tried to avoid. Instead, the team developed intramyocardial catheters that used either fluoroscopy or electromagnetic energy to localize the catheter inside the heart. The catheter contains a needle that is directed into the myocardial tissue; once in place, the growth factors are injected. Compared with IC delivery, intramyocardially injected growth factors have better tissue retention; at one hour after administration, 20 percent of radiolabeled factors remained in the heart.

Dr. Simons and his colleagues recently completed a multicenter double-blinded placebo-controlled study of IC delivery of bFGF in more than 300 patients, the results of which will be presented at cardiology meetings this spring. The study was conducted in part at the GCRC at Beth Israel.

Although treatments with angiogenic growth factors may not eliminate the need for bypass surgery, the entire field of cardiovascular medicine is evolving so rapidly with improved catheter-based procedures that bypass surgery may become a niche procedure, performed only in certain cases, predicts Dr. Laham.

Meanwhile, he finds the excitement surrounding the development of the latest treatments to be exhilarating. "It's almost like the excitement that started after angioplasty, when it was being done in just a few patients and no one knew what would happen," he says. "That's what may happen with these growth factors, and I've been very fortunate to be part of it."

—Linda Berris

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For more information about NCCR's Clinical Research area, see <http://www.nccr.nih.gov/clinical.htm>.

Additional Reading

1. Laham, R. J., Rezaee, M., Post, M., et al., Intrapericardial delivery of fibroblast growth factor-2 induces neovascularization in a porcine model of chronic myocardial ischemia. *Journal of Pharmacology and Experimental Therapeutics* 292:795-802, 2000.
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