

Therapeutic Angiogenesis for Ischemic Heart Disease

Michio Kawasuji, MD, PhD

Currently available approaches for treating patients with ischemic heart disease include medical therapy or coronary revascularization by percutaneous coronary angioplasty (PCA) or coronary artery bypass grafting (CABG). However, a significant number of these patients are not candidates for coronary revascularization procedures or achieve incomplete revascularization with these procedures. Consequently, many of these patients have persistent symptoms of myocardial ischemia despite intensive medical therapy. The discovery of candidate molecules able to stimulate myocardial angiogenesis has stirred a growing interest in using these molecules for therapeutic application.¹⁾ Preliminary clinical experiences suggest that therapeutic angiogenesis may provide additional blood flow to incompletely revascularized areas.²⁻⁴⁾ More recently, several studies suggest that implanted bone marrow cells may induce angiogenesis in ischemic myocardium.⁵⁾ This article reviews recent advance in therapeutic angiogenesis in the management of these patients with advanced ischemic heart disease.

It is crucial to understand the basic pathophysiological mechanisms of blood vessel formation in adult tissues. Three different processes may contribute to the growth of new blood vessels: vasculogenesis, arteriogenesis and angiogenesis.⁶⁻⁸⁾ Vasculogenesis is the primary process responsible for the growth of new vasculature during embryonic development. It is characterized by the differentiation of pluripotent endothelial cell precursors into endothelial cells that go on to form primitive vascular plexus, and is followed by recruitment of other vascular cell types to complete the process of vessel formation. Preliminary evidence suggests that vasculogenesis may play a role in mature adult tissues.⁸⁾ Arteriogenesis refers to the development of new arteries possessing fully developed tunica media.⁷⁾ The process

may involve maturation of preexisting collaterals or may reflect de novo formation of mature vessels. All vascular cell types including smooth muscle cells and pericytes are involved. Examples of arteriogenesis include formation of angiographically visible collaterals in patients with advanced coronary arterial disease. Angiogenesis is the process responsible for formation of new blood vessels lacking developed media.^{6,7)} Several steps of angiogenesis have been determined; matured endothelial cells break from their basement membrane and migrate as well as proliferate to form sprouts from parental vessels. Angiogenesis is one mechanism of blood vessel formation in adults. Examples of angiogenesis include capillary proliferation in the healing wound or along the border of myocardial infarction.

Arteriogenesis and angiogenesis may be differently regulated. Arteriogenesis generally occurs proximal from the ischemic territory where hemodynamic changes, for example, sheer stress or hematologic changes dominate, whereas angiogenesis is primarily driven by hypoxia or tissue ischemia. Candidates for pharmacological stimulation of therapeutic angiogenesis in cardiac ischemia include angiogenic cytokines such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor, growth factors involved in maturation of the vascular tree such as angiopoietins and platelet derived growth factor, CXC chemokines such as interleukin 8 and monocyte chemoattractant protein-1, and transcriptional factors that stimulate expression of angiogenic cytokines and their receptors such as hypoxia inducible factor (HIF) .

Among the major angiogenic growth factors, basic FGF (bFGF) and VEGF have been the most extensively studied. The ability of bFGF to induce angiogenesis was suggested by studies that documented significantly higher vessel counts following intracoronary or intramyocardial injection of bFGF in the setting of acute coronary occlusion in dogs.^{1,9)} In animal models of chronic myocardial ischemia, perivascular or intracoronary administration of VEGF improved collateral flow.¹⁰⁾ Clinically applicable catheter-based methods (intravenous, intracoronary,

From the First Department of Surgery, Kumamoto University School of Medicine, Kumamoto, Japan

Address reprint requests to Michio Kawasuji, MD, PhD: First Department of Surgery, Kumamoto University School of Medicine, 1-1-1 Honjo, Kumamoto 860-8556, Japan.

intramyocardial and transendocardial intramyocardial delivery) and surgical methods (transepical intramyocardial and slow-release epicardial delivery) are being evaluated.^{11,12} Therapeutic angiogenesis is not free from potential harmful effects. Animal studies and clinical trials suggested hypotension is associated with both bFGF and especially VEGF administration due to nitric oxide release and arteriolar vasodilatation.⁶ Concerns associated with angiogenic growth factors include plaque angiogenesis, proliferative retinopathy and occult malignancies.¹² Since potent angiogenic growth factors may have grave side effects, a high drug target level and low systemic exposure should be the ultimate goal. It is suggested that intramyocardial delivery of growth factors would be preferred since this would include the potential to target specific areas of the heart, likely higher efficacy of delivery, and prolonged tissue retention.¹¹

Limited efficacy data were derived from ongoing and completed phase I/II trials. A double-blind randomized trial of epicardially implanted bFGF protein in sustained release beads has been performed.³ Twenty-four patients undergoing CABG in whom one of the major arteries was not visible but ischemic myocardium was considered not bypassable, were randomized to receive ten heparin-alginate beads with bFGF. At the time of the 90-day evaluation, all seven remaining patients in the 100 μ g bFGF group were symptom-free and nuclear perfusion imaging demonstrated a significant reduction in the size of the target zone. In a 337-patient double-blind phase II trial, three different intracoronary dosages of bFGF versus placebo control were examined (FIRST trial).¹³ Ninety-day follow-up demonstrated a non-significant exercise improvement in bFGF-treated patients and a significant improvement in angina scales. Nuclear imaging did not demonstrate any overall improvement in the size of ischemic territories. There was no excess mortality or sudden death among bFGF-treated patients. A randomized, double-blind, placebo-controlled Phase II trial (VIVA trial) varying two different dosages of VEGF was completely negative with regard to exercise time, symptom improvement and nuclear imaging.¹⁴

Theoretically, angiogenesis can be achieved either by the use of growth factor proteins or by the introduction of genes encoding these proteins. The major limitation of protein therapy is the limited tissue half-time of angiogenic proteins. Sustained local production and release of growth factors through gene therapy can overcome the inherent instability of angiogenic proteins. There have been four reported trials of therapeutic an-

giogenesis involving a surgical delivery approach: protein-based delivery of acidic FGF,² and protein-based delivery of bFGF in a sustained-release heparin alginate formulation,³ plasmid-mediated delivery of VEGF 165,¹⁵ and adenovirus-mediated delivery of VEGF121.⁴ All of these trials have involved the direct intramyocardial delivery of an angiogenic mediator and have adopted the strategy of delivering growth factor to areas of reversible ischemia not amenable to conventional therapies such as PCA or coronary artery bypass surgery. Positive outcomes have been reported in terms of angina class and antianginal medications, exercise treadmill duration, angiographic scores, and myocardial perfusion. Growth factor proteins or genes encoding these substances can be administered to patients in conjunction with coronary artery bypass surgery (on-pump or off-pump) or as sole therapy. Regarding gene therapy approach to therapeutic angiogenesis, prolonged local production of potent growth factors may cause increased vascular permeability and edema or unwanted hemangioma formation. Regulatable vectors with short duration of expression are highly desirable but not yet available. Gene therapy approaches have additional concerns regarding the introduction of foreign genetic material and exposure to viral vectors. Recently, a patient died after administration of large amounts of adenoviral vector into the hepatic artery.¹⁶ After this experience, safety issues are of great concern. At the moment, protein therapy is considered to be closer to practical use than gene therapy.

More recently, animal studies have suggested that cell transplantation has great potential for inducing angiogenesis and improving regional perfusion and cardiac function. An animal study showed that use of cytokine-mobilized bone-marrow-derived angioblasts induced new blood vessel formation in infarcted myocardium. Preliminary clinical experience suggests that skeletal muscle implantation improved perfusion and function of the infarcted region. Furthermore, recent studies suggest that locally delivered bone marrow cells can generate *de novo* myocardium and ameliorate ventricular remodeling and improve cardiac function, but the mechanism of benefit is not completely understood. Cell therapy is developing as an important new modality for restoring function in patients who have few viable surviving myocytes in the infarcted region. Candidates for cell transplantation for postinfarction ventricular dysfunction include skeletal myoblasts (satellite cells),¹⁷ heart cells,¹⁸ smooth muscle cells, and bone marrow stem cells.⁵

In conclusion, the development of angiogenic growth

factor therapy offers new therapeutic alternatives for patients with advanced ischemic heart disease. Issues to establish therapeutic angiogenesis include effective delivery, proper selection of angiogenic growth factor protein, and outcome measurements. In contrast to the drawbacks of gene therapy, cell implantation appears to have great potential as a new therapy for patients with an extensive myocardial infarction.

References

1. Yanagisawa-Miwa A, Uchida Y, Nakamura F, et al. Salvage of infarcted myocardium by angiogenic action of basic fibroblast growth factor. *Science* 1992; **257**: 1401–3.
2. Schumacher B, Pecher P, von Specht BU, Stegmann T. Induction of neoangiogenesis in ischemic myocardium by human growth factors: first clinical results of a new treatment of coronary heart disease. *Circulation* 1998; **97**: 645–50.
3. Laham RJ, Sellke FW, Edelman ER, et al. Local perivascular delivery of basic fibroblast growth factor in patients undergoing coronary bypass surgery: results of a phase I randomized, double-blind, placebo-controlled trial. *Circulation* 1999; **100**: 1865–71.
4. Rosengart TK, Lee LY, Patel SR, et al. Six-month assessment of a phase I trial of angiogenic gene therapy for the treatment of coronary artery disease using direct intramyocardial administration of an adenovirus vector expressing the VEGF121 cDNA. *Ann Surg* 1999; **230**: 466–70.
5. Tomita S, Li RK, Weisel RD, et al. Autologous transplantation of bone marrow cells improves damaged heart function. *Circulation* 1999; **100** (Suppl): II 247–56.
6. Ware JA, Simons M. Angiogenesis in ischemic heart disease. *Nat Med* 1997; **3**: 158–64.
7. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. *Nat Med* 2000; **6**: 389–95.
8. Isner JM, Asahara T. Angiogenesis and vasculogenesis as therapeutic strategies for postnatal neovascularization. *J Clin Invest* 1999; **103**: 1231–6.
9. Kawasuji M, Nagamine H, Ikeda M, et al. Therapeutic angiogenesis with intramyocardial administration of basic fibroblast growth factor. *Ann Thorac Surg* 2000; **69**: 1155–61.
10. Banai S, Jaklisch MT, Shou M, et al. Angiogenic-induced enhancement of collateral blood flow to ischemic myocardium by vascular endothelial growth factors in dogs. *Circulation* 1994; **89**: 2183–9.
11. Post MJ, Laham R, Sellke FW, Simons M. Therapeutic angiogenesis in cardiology using protein formulations. *Cardiovasc Res* 2001; **49**: 522–31.
12. Simons M, Bonnow RO, Chronos NA, et al. Clinical trials in coronary angiogenesis: issues, problems, consensus: an expert panel summary. *Circulation* 2000; **102**: e73–86.
13. Simons M, Annex BH, Laham RJ, et al. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2: double blind, randomized, controlled clinical trial. *Circulation* 2002; **105**: 788–93.
14. Henry T, Annex B, Azrin M, et al. Final results of the VIVA trial of rhVEGF human therapeutic angiogenesis. *Circulation* 1999; **100**: I-476.
15. Losordo DW, Vale PR, Symes JF, et al. Gene therapy for myocardial angiogenesis: initial clinical results with direct myocardial injection of phVEGF165 as sole therapy for myocardial ischemia. *Circulation* 1998; **98**: 2800–4.
16. Hollan T. Researcher and regulators reflect on first gene therapy death. *Nat Med* 2000; **6**: 6.
17. Menasche P, Hagege AA, Scorsin M, et al. Myoblast transplantation for heart failure. *Lancet* 2001; **357**: 279–80.
18. Li RK, Weisel RD, Mickle DAG, et al. Autologous porcine heart cell transplantation improved heart function after myocardial infarction. *J Thorac Cardiovasc Surg* 2000; **119**: 62–8.