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Advancement in Revascularization and Stem Cell Therapy

Synergistic use of an established technique with an adjunctive therapeutic.

Cardiovascular disease is a growing health concern in the US and developed societies. Coronary artery disease is a leading cause of death and disability, and the incidence is growing each year. There seems to be a gender gap, with an increase in the prevalence of disease in women. Coupled with the increase in obesity and lack of exercise in the majority of today's society, there is much to drive the cycle of coronary disease.

With this in mind, Cardiogenesis (Irvine, CA) sponsored an educational symposium at the recent Transcatheter Therapeutics (TCT) meeting, featuring guest speakers Warren Sherman, MD, (Columbia University); Emerson C. Perin, MD, PhD, (Texas Heart Institute); Marvin J. Slepian, MD, (University of Arizona); and Keith B. Allen, MD, (Mid America Heart Institute), to highlight exciting recent developments regarding cell therapy in cardiac applications, including transmyocardial revascularization (TMR) and its use in conjunction with autologous stem cell therapy.

Dr. Sherman emphasized that although currently there are tiered, staged, and guideline-recommended therapies for treating coronary disease, at the end of the day it comes down to "flow and vascularization." As disease progresses, it is necessary to have more flow for the myocardium to balance supply and demand. In the last 5 to 10 years, it has been shown that as disease advances, there is a tendency to do better with more invasive types of therapy rather than with medical therapy alone. Also, as has been demonstrated in the comparison of minimally invasive and PCI therapies versus bypass surgery, both therapies can be equivalent, although patients treated

with PCI show a greater incidence of a need for additional revascularization.

The BARI trial showed that there are certain subsets of patients who will do better with bypass as opposed to angioplasty, specifically in the diabetic and microvasculature substrate. The results of PCI are coming closer to those seen with bypass, especially resulting from improvements in drug-eluting stents. A comparison of PCI to bypass shows that it is not enough to partially revascularize patients; if patients are not completely revascularized, although the target lesion may be treated, patients will continue to have more events (Figure 1). The message is that more needs to be done to increase flow for patients, especially in the context of diffuse disease, small-vessel disease, and chronic total occlusions. "We have been at our wit's end trying to successfully treat these patients for the better part of 20 years. We

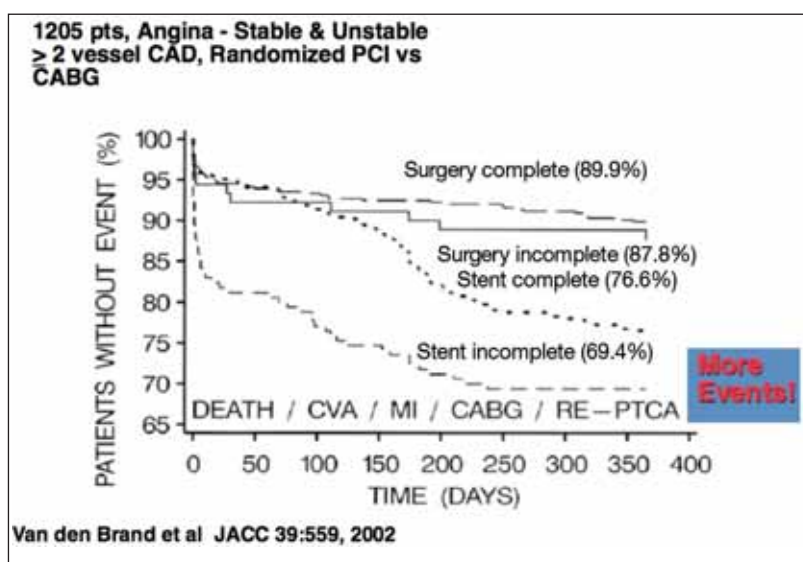


Figure 1. The effect of completeness of revascularization on event-free survival at 1 year in the ARTS trial.

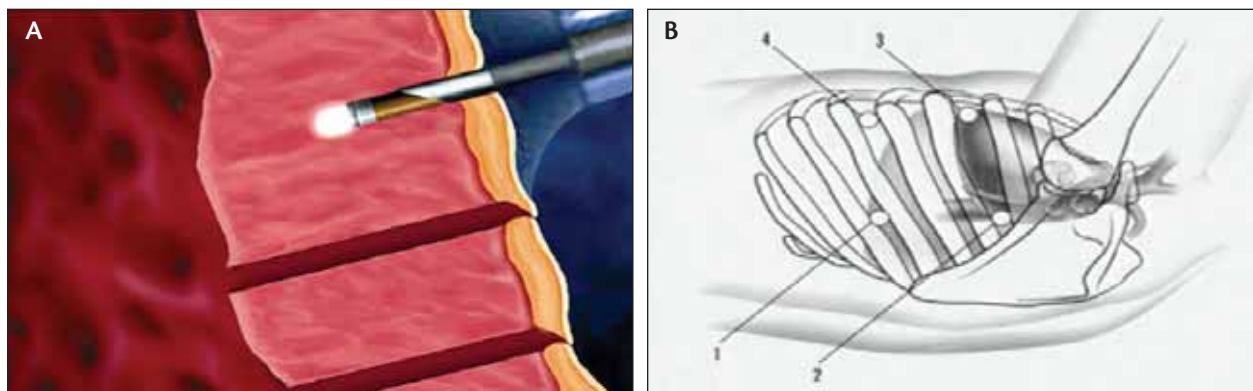


Figure 2. TMR channels are transmural through the myocardium (A). The procedure can be performed endoscopically through ports (B).

have been ignoring an approved therapy, and that is transmyocardial revascularization (TMR)," said Dr. Sherman.

The patients with the greatest need are those with diffuse disease, small-vessel disease, chronic total occlusions. According to Dr. Slepian, "We are talking about Canadian class III and IV angina patients with refractory angina, constant symptoms, and who are not improving with use of conventional therapies."

The Cleveland Clinic reported 500 consecutive patients undergoing cardiac angiography for symptomatic obstructive coronary artery disease with ischemia, and found that approximately 12% were not suitable for PCI or CABG. Furthermore, they determined that up to 5% of patients were eligible for other revascularization modalities including TMR.

TMR

TMR is a technique in which Holmium:YAG laser energy is delivered through a flexible fiberoptic to create channels in the myocardium (Figure 2). "We know from studies that this technology actually reduces angina and can provide a survival benefit compared to medical management," said Dr. Slepian.

Five randomized, controlled studies comparing TMR stand alone to maximum medical therapy in refractory angina patients (Canadian class IV) demonstrate significant angina improvement at 1 year. The angina benefit is evident in all studies individually and in meta-analyses. In addition, a significant decrease in rehospitalization is demonstrated in the year following the TMR procedure (Figure 3). Studies following patients for 3 to 5 years have reported sustained, superior angina improvement in patients treated with TMR compared to best medical therapy.

Additionally, a 5-year study of TMR stand-alone treatment demonstrated an increased survival rate compared with optimal medical therapy (Figure 4). The cumulative hazard curve shows an 8% annual mortality rate in TMR-

treated patients compared to 13% in medically managed patients after 12 months.

TMR as a stand-alone surgical procedure is performed via a limited left anterior thoracotomy, with a 3- to 4-inch incision in the fifth intercostal space. Advanced tools from Cardiogenesis enable the TMR procedure to be performed less invasively through small ports using a thoracoscopic hand piece. The system is compatible with the DaVinci™ robotic system. TMR is indicated for treatment of areas of myocardium that cannot be treated with angioplasty or bypass surgery, and has been applied adjunctively in patients who could not be completely revascularized with bypass surgery. Studies have demonstrated that these patients, when treated with TMR adjunctive to CABG, have improved outcomes.

Dr. Allen emphasized to the cardiologists in attendance the general lack of awareness of the effectiveness of TMR due to a failed percutaneous technology that attempted to replicate the surgical TMR results. He explained, "The failed direct myocardial revascularization (DMR) system did not penetrate the myocardium and delivered less than 5% of the energy delivered with the FDA-approved surgical TMR. The AHA/ACC, in its Practice Guidelines for Treatment of Chronic Stable Angina (2002) recommended TMR (Class IIA, level of evidence A), and both the STS in 2004 and the ISMICS in 2006, in consensus workforce-based analysis, gave TMR therapy a class 1 recommendation with grade A evidence."

STEM CELL THERAPY

Dr. Perin explained that the promise of stem cell therapy in treating cardiovascular disease lies in the potential of stem cells to self renew: they are eternal and never die. What was once thought to be a process that occurs only in the embryonic phase has recently been discovered to occur everyday in adults. We know now that in bone marrow cells there is repair of tissue, creation of new vessels, and an exchange of cells that happens on an ongoing basis.

Author	Patients	Centers	Laser	Perioperative Mortality (%)	F/U (y)	Channels	Significant Angina Decrease	Significant Hospitalization Decrease	Increase Perfusion	Increase Survival
Allen et al 1999 [45]	275	18	H-YAG	5	1	39	Y	Y	N	N
Frazier et al 1999 [47]	192	12	CO ₂	3	1	36	Y	Y	Y	N
Burkhardt et al 1999 [46]	182	16	H-YAG	2	1	18	Y	Y	N	N
Schofield et al 1999 [35]	188	1	CO ₂	5	1	30	Y	Y	...	N
Aalberg et al 2002 [44]	100	1	CO ₂	4	3-5	48	Y	Y	...	N

CO₂ = carbon dioxide; F/U = follow-up; H-YAG = holmium:yttrium-aluminum-garnet.

Figure 3. TMR as sole therapy: randomized trial results.

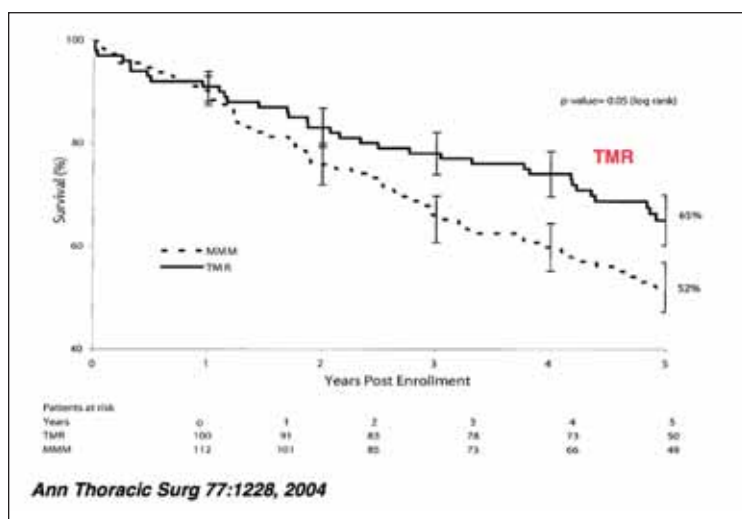


Figure 4. TMR 5-year follow-up: survival.

Cell Types

The organ most identified with stem cell therapy is bone marrow. It is in bone marrow where some of the cells that have been used to pioneer the field of regenerative medicine can be found: those are the endothelial precursor cells that help to form blood vessels. Frequently, autologous bone marrow is used, obtained via aspiration with filtering of the mononuclear components for a therapy. Many of the clinical trials that have been performed to date have utilized autologous bone marrow. A clear advantage of this strategy is the lack of concern regarding immunologic issues that can be associated with allogeneic cell transplantation. Other cells, stromal or mesenchymal cells, are also very powerful. Mesenchymal cells are very plastic and can turn into any type of tissue in the body, given the right circumstances (ie, cartilage, neurologic tissue, heart muscle, skeletal muscle).

Delivery Modalities

There are several strategies that can be used to deliver stem cells to the heart muscle. The options include intracoronary, transvenous or retrograde, intrapericardial, and intramyocardial. To date, most of the trials in clinical stem cell therapy have utilized intracoronary infusion because in the catheterization lab it is very simple to place a catheter down a coronary artery and administer the cells to a targeted vascular bed.

It has been shown that inflammation attracts stem cells in burn victims, as well as in CABG and myocardial infarction patients. These patients show a spike in VEGF and VEGF factors, which attracts circulating stem cells. This is one of the mechanisms that the human body uses to recruit stem cells to repair an area. Within this context, TMR emerges as a potentially efficient combination delivery system.

COMBINING TMR + STEM CELL THERAPY

Biointerventional therapy represents the “Holy Grail” for affecting myocardial remodeling. Rather than treat macroscopic disease with a stent or bypass graft, the ability to alter cellular physiology could result in a fundamental shift in how cardiovascular disease is managed. “When we talk about utilizing stem cells as an adjunct therapy, it is a very elegant way to think about, for example, using a laser that generates local inflammation, and having that as a location

where the cells can develop,” said Dr. Perin. “It is a very synergistic approach to be able to create inflammation and deliver a therapy, such as stem cells, at the same spot.”

The Cardiogenesis PHOENIX advanced delivery system (Figure 5) combines the creation of transmural laser channels with a needle injection system. This provides the ability to precisely deliver a therapeutic material in the tissue surrounding the laser channel. The PHOENIX system is designed to enhance the clinical efficacy achieved using TMR with adjunct therapeutic material to increase the overall patient benefit. The PHOENIX system represents “TMRplus,” in which the “Plus” can be an adjunctive therapeutic, such as autologous stem cells.

A key to successful cell therapy may revolve around retaining cells long enough to deliver growth factors or proteins supporting the angiogenic process, or even

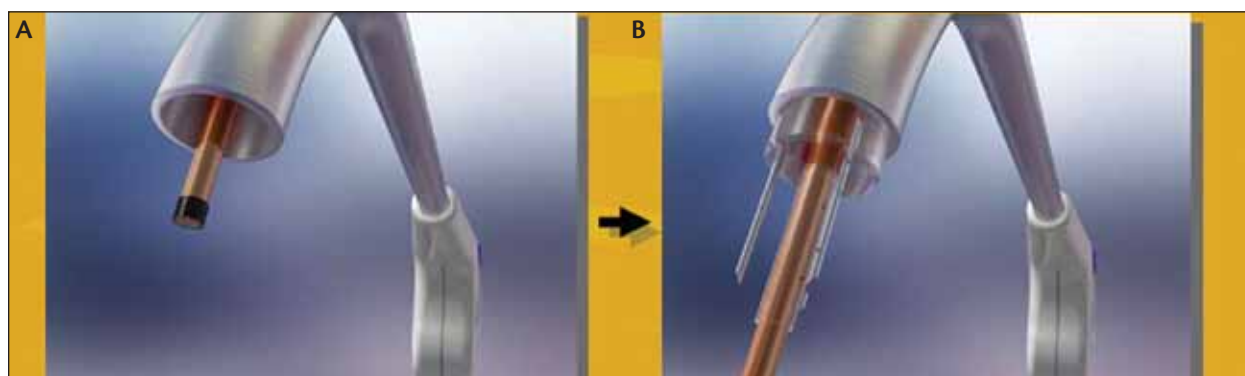


Figure 5. The PHOENIX delivery system utilizing TMR + stem cells. Creation of the thermoacoustic field or border zone with a 1-mm Holmium:YAG fiber optic laser (A). Needles (3) deploy with the fiber optic to release the biologic component throughout the thickness of the myocardium (B).

inducing them to differentiate. The important variables include: the cell product to use, the status of the tissue, where the cells are delivered, and the delivery method. Although embryonic stem cells and umbilical cord blood are excellent sources for the types of cells that would be required, they are not currently practical and are not available off the shelf. Fortunately, there is an alternative readily available: the patient's own autologous bone marrow offers an excellent source of autologous-derived bone marrow cells.

Tissue Status

The microenvironment is critical to the repair or remodeling process. Ischemic myocardium at the border zones of infarcts can be rescued with angiogenesis or myogenesis using stem cells because it is at these border zones that the inflammation cascade is initiated.

TMR combined with a therapeutic material, in addition to upgrading the myocardial repair process, serves as a biomechanical trigger that creates a border zone where remodeling or regenerative activity is achieved. At the local level, there is up-regulation of injured myocytes, the inflammation cascade is turned on, and messenger RNA is expressed. This results in platelet activation, which is critical to initiating and fueling the angiogenic process. Additionally, there is recruitment of intrinsic myocardial stem cells. These stem cells home to the area of injury, which also augments angiogenesis. At a systemic level, TMR also has an effect: the systemic inflammatory response, whether it is from a naturally occurring MI or a stimulated tissue zone created with TMR, results in cytokine release (ie, platelet activation). All of this serves as a homing signal for circulating endothelial progenitor cells, leading to angiogenesis. According to Dr. Allen, "Data have been published demonstrating that TMR combined with growth factors takes advantage of their synergistic angiogenic effect

and that TMR, in addition to initiating the myocardial repair process, serves as a biomechanical trigger to create a border zone in which enhanced stem cell activity may be achieved."

Case Report

The patient was a 74-year-old woman who had a history of two previous CABGs and a patent left internal mammary artery, with no viable bypass targets. The patient was taken to the OR, where she underwent standard bone marrow aspiration. The bone marrow aspirate was then placed in a double-density centrifuge in the OR. Every 60 mL of unconcentrated marrow yields 10 mL of concentrated mononuclear cells. The mononuclear cell layer was then used as the source for the working product.

The PHOENIX device was used to create TMR channels and the associated stimulated tissue zone, providing a fertile microenvironment within the ischemic myocardium for the precise implantation of the stem cells. Bone marrow concentrate was injected around each laser channel in increments of up to 1.0 mL. At 18 months postprocedure, the patient reported complete amelioration of angina symptoms and improved heart failure status.

CONCLUSION

"These are provocative data that we have heard today," commented Dr. Sherman. "It raises a potentially critical pathway to helping patients with refractory angina." TMR-Plus has been performed in 45 patients to date, with positive preliminary results presented at the International Cell Therapy Meeting, the Asian International Society for Minimally Invasive Cardiothoracic Surgery, and two papers presented at the Transcatheter Therapeutics (TCT) meeting. "We think that this is a novel and interesting way to proceed with cardiac stem cell therapy, potentially enhancing the efficacy of a procedure that is currently available," summarized Dr. Allen. ■

Disclaimer: Studies referenced in this paper were conducted in Europe using the CE marked Cardiogenesis PHOENIX delivery system. The PHOENIX delivery system is not approved in the United States. Contributors to this paper were provided an honorarium by Cardiogenesis. There are no significant safety risks known regarding the use of autologous bone marrow aspirate with TMR, however clinical trials are needed to establish efficacy.