Direct laser myocardial revascularization

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Direct laser myocardial revascularization is a new therapy for patients with refractory angina and ischemia who are not candidates for conventional revascularization techniques. Almost all patients with refractory angina have triple-vessel coronary artery disease and more than 70% have undergone coronary artery bypass grafting (CABG). Repeat conventional revascularization procedures may not be feasible in some of these patients because of diffuse coronary atherosclerosis, multiple prior unsuccessful interventions, lack of graft material, excessive comorbidity or other factors.

Laser revascularization involves the use of laser energy to create multiple channels (~1.5 mm diameter) in areas of critically ischemic tissue. Multiple sources of laser energy including CO_2, Ho:YAG, and XeCl excimer lasers, in addition to radiofrequency energy, have been used to create channels. Channels may be created in an epicardial-to-endocardial orientation with a transthoracic approach (transthoracic myocardial revascularization-TMR) or endocardial-to-epicardial orientation with a percutaneous technique (percutaneous myocardial revascularization-PMR). TMR is performed as an open heart procedure while PMR can be performed by an interventional cardiologist in the cath lab. A specifically designed guiding catheter is used to introduce the laser catheter into the left ventricle. The laser catheter is then directed towards the target region and placed in contact with the ischemic myocardium. Laser energy is transmitted through the laser catheter to create a series of channels on the endocardial surface. In PMR the channels extend from the endocardial surface roughly halfway to two-thirds through the myocardial wall. Two TMR systems (PLC Medical Systems and Eclipse) have been approved by the Food and Drug Administration for clinical use and several PMR systems have recently completed clinical evaluation (CardioGenesis, Eclipse, Biosense and others).

All trials to date have the palliation of angina as their main goal. Clinical end points include improvement in exercise tolerance, quality of life, and myocardial perfusion. The first clinical studies of TMR investigated its use as an adjunctive therapy (in combination with CABG) in areas of the myocardium that could not be revascularized by CABG. Subsequent trials evaluated TMR as the sole therapy in patients with refractory angina and showed progressive improvement of clinical symptoms during a 6-month follow-up period lasting at least 12 months in the majority of cases. A phase II multicenter trial of TMR enrolled 201 patients with class III or IV angina and follow-up to 12 months showed that 79% had reduction in angina to class 0, I, or II with 30% of the patients in class 0. In this study the perioperative mortality rate was reduced from 11% in the first 97 patients to 4% in the following 104 patients by identifying age and low left ventricular function as potential perioperative risk factors.

A phase III trial randomized 200 patients with class III or IV angina to TMR or medical management. Event-free survival (absence of death, acute myocardial infarction, or unstable angina) at 12 months was significantly higher in the TMR group than in the control group (71 vs 20%). No effect on mortality was seen even though the TMR group underwent an invasive procedure. Marked reduction in angina was noted in the TMR group with 80% of the patients in class II or less at 12 months with no significant change in the control group. Nu-

clear SPECT imaging studies were also performed in this study and compared with pre-TMR scans, the number of ischemic, or reversible, perfusion defects were reduced by more than 40% at 1 year post-TMR. Need for hospitalization as treatment for unstable angina was also dramatically reduced, from a baseline of 67% of all patients enrolled having been admitted to the hospital at least once with unstable angina during the 12 months preceding the entry into the study, to only 13% of the TMR group admitted to the hospital with unstable angina symptoms in the 12 months following the TMR procedure. Based on the results from this randomized trial the Food and Drug Administration approved TMR for clinical use with the PLC Medical Systems laser.

Recently two other TMR protocols sponsored by CardioGenesis and Eclipse were completed. The CardioGenesis ATLANTIC study randomized 182 patients with class III (38%) or IV (62%) angina to TMR and continued medical therapy (n = 92) or continued medical therapy alone (n = 90). At 12 months 47.8% of the TMR group patients compared to 14.3% in the medication group were in class II or lower ($p < 0.001$). Total exercise duration increased by a median of 65 s in the TMR group compared to a 46 s decrease in the medication group ($p < 0.0001$). One patient died perioperatively (1.1%). Total 1-year mortality was 5.4% in the TMR group compared to 10% in the medication group ($p = 0.66$).

A randomized study of TMR using the PLC Medical Systems CO_2 laser conducted at several European centers has recently been published in *The Lancet*. Patients treated with TMR in this trial showed considerably less benefit than reported in previous studies. The study randomized 188 patients with class III or IV angina to TMR plus normal antianginal therapy or medical management with antianginal therapy alone. One-year mortality was 11% (11 patients) for the TMR group and 4% (4 patients) for the medical management group ($p = 0.14$). Perioperative mortality in the TMR group accounted for 5 of the 11 deaths and was attributed to 3 acute myocardial infarctions, 1 pulmonary embolism, and 1 pulmonary edema. Canadian Cardiovascular Society score for angina had decreased by at least two classes in 25% of TMR and 4% of medical management patients at 12 months ($p < 0.001$). Mean treadmill exercise time was 40 s longer and mean 12-min walking distance was 33 m further in the TMR group than in the medical management group but these differences were not statistically significant or thought clinically important. The number of left ventricular segments with reversible myocardial ischemia fell in both treatment groups, with no significant differences.

In reality, TMR therapy is limited in clinical utility because of the morbidity and even mortality associated with a transthoracic approach that requires general anesthesia and a several-day hospitalization. Due to these issues, the percutaneous approach to laser revascularization seems more attractive, assuming that similar clinical outcomes can be achieved with less morbidity and mortality. Enrollment in two randomized clinical trials of PMR in combination with continued medical therapy vs medical therapy alone for patients with refractory angina not amenable to coronary angioplasty or CABG has recently been completed. In the CardioGenesis study in which we participated, 221 patients with class III (61%) or IV (39%) angina were randomized to PMR and medication (n = 110) or medication alone (n = 111). All treated patients completed the procedure successfully. There were no procedural deaths. One incident of procedural ventricular tachycardia required cardioversion. There was one incident of myocardial perforation requiring intervention. There was one periprocedural death at 28 days. These acute results indicate that PMR has an acceptable safety profile and is associated with negligible morbidity. Although clinical follow-up of these patients is continuing, preliminary data show that PMR appears to improve the functional status and quality of life of patients with coronary artery disease. At 6 months, 46% of PMR-treated patients have at least a two angina class improvement compared to 6% of non-PMR patients. At 12 months, the primary end point of total exercise tolerance increased by a median of 89.0 s in the PMR-treated group compared to a 12.5 s median increase in the non-PMR patients ($p = 0.008$). Blinded assessment of Canadian Angina Class was II or lower in 34.1% of PMR patients compared to 13% in the non-PMR patients ($p = 0.0017$). Total 1-year mortality was 7.3% in the PMR group compared to 2.7% in the non-PMR group ($p = 0.21$, two-sided Fisher s exact test). The most recent follow-up data from the other randomized trials will be presented during this conference. Clinical improvement following PMR is at least comparable to that seen with TMR as nearly 70% of PMR-treated patients have a reduction in angina at 6 months by one or two angina classes compared to just 10% of the medically treated group.

The precise mechanism for the improvement in angina is still controversial. Two of the most compelling possible mechanisms include some forms of limited local denervation and angiogenesis. The original hypothesis was that the channels remained patent and directly supplied with oxygenated blood from the left ventricular chamber to the myocardium. This theory was based on observations from reptilian hearts in which a dense network of arborizing channels extends from the ventricular cavity to the myocardium. Consequently, all but a thin shell of the subepicardial myocardium is supplied directly from the ventricular chamber. The fact that this hypothesis is not operational in humans is supported by observations showing that the channels are thrombosed within 24 to 48 hours of the procedure and

soon thereafter are obliterated by fibrosis. Another possible mechanism invokes the destruction of afferent nerves by the laser channeling causing interference in the recognition of symptomatic ischemia.

Recent studies suggest that the healing response to injury induced by the channel creation may be associated with angiogenesis and increased myocardial vascularity. The local expression of angiogenic growth factors such as vascular endothelial growth factor, basic fibroblast growth factor, and macrophage chemoattractant protein-1 has been shown to be increased following PMR in animal models and is associated with increased capillary density. *Postmortem* histologic studies demonstrate an increased density of microvessels in the revascularized region as many as 4 years after the operation. Regional myocardial perfusion assessed by positron emission tomography is increased at 6 months after TMR compared to baseline. Multiple studies using animal models also demonstrate improved perfusion in regions treated with laser revascularization compared to control regions. Burkhoff et al. studied an ischemic canine model with an amaroid constrictor on the left anterior descending coronary artery. Eight weeks after the creation of TMR channels there was evidence of improved myocardial perfusion in the TMR group during adenosine stress and increased vascular proliferation as assessed by bromodeoxyuridine uptake and histologic evidence of increased vascular density (1.4× greater) in the myocardium surrounding the TMR channel. Thus, TMR in the setting of chronic ischemia stimulated angiogenesis and the new vessels persist for at least 2 months and are capable of mediating an improvement in myocardial blood flow. This is likely a nonspecific response to tissue injury and introduces the possibility that concomitant administration of genes encoding angiogenic growth factors may further enhance angiogenesis. Thermal injury associated with TMR/PMR has been shown to enhance the efficiency and degree of myocardial transgene expression.

The eventual utility of laser revascularization in the treatment of end-stage coronary artery disease is still uncertain. Certainly some patients improve symptomatically following TMR and PMR. Whether this is due to a placebo effect or true enhancement of myocardial perfusion remains to be seen. Because of the operative risks associated with TMR as the sole therapy, it is likely that TMR will be used only as an adjunct to CABG for patients who are unable to be completely revascularized by CABG alone. PMR may have broader clinical applicability if long-term benefit in patients can be demonstrated. If treatment with angiogenic growth factors, either by direct intracoronary administration or by intramyocardial injection proves efficacious, laser revascularization may be yet another use of laser energy in interventional cardiology that fails to live up to initial expectations.

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