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EDITORIAL COMMENT

A Tunnel at the End of the Light?*

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Despite the great strides made in coronary revascularization (or possibly because of these), there remains a patient population experiencing anginal symptoms who are not considered candidates for either coronary artery bypass graft surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Most have had one or more attempts at traditional revascularization, although some have diffusely diseased distal vessels precluding these forms of therapy. Although one would have at first thought that the number of such "nonrevascularizable" patients to be small, this does not appear to be the case. Furthermore, the frustration associated with the management of such patients serves to underscore the magnitude of this condition. The clinical spectrum of these patients varies markedly. Most have

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chronic angina that is relatively stable, but may be incapacitating. Others are unstable and may experience difficulty in being weaned from parenteral medication. Some have triple-vessel disease and a large amount of myocardium at risk; others have only a small region served by a single vessel. Some have poor left ventricular function, while others have no contractile impairment. Some are taking many medications; others have difficulty tolerating even small amounts of antianginal drugs. The need for alternative approaches to the care of these patients is clear. The goals of such therapy would be to enhance the quality of life and reduce the morbidity and perhaps mortality associated with coronary disease. The paradigm for achieving these outcomes is to reduce ischemia by favorably influencing coronary perfusion or myocardial demand. A number of novel techniques, presently in various stages of development, have been suggested to address this need. One of the most intriguing is transmyocardial laser revascularization (TMR).

Transmyocardial revascularization. It is ironic that the left ventricle, which is literally bathed in oxygenated blood, has as its most common affliction, ischemia. Not surprisingly, efforts have been extended to more directly perfuse myocardium from blood within the left ventricle when the coronary artery supply is compromised. Initial enthusiasm to employ a laser probe to create transmural tunnels was based on the presumption that the tunnels would remain patent and, in a fashion, mimic the ventricular sinusoids of the reptilian heart. Despite the early controversy surrounding the long-term patency of these laser tracts (1), most investigators now agree that the channels occlude soon after their creation and there is no direct camerosinusoidal blood flow long term (2–4).

The lack of substantive anatomic or angiographic evidence of "revascularization" would have doomed TMR long ago had it not been for a surprisingly high rate of clinical success. A worldwide registry of over 3,000 patients reported a decrease in anginal class in 80%, with 30% having no angina at one-year follow-up (5). These results are quite remarkable in that the typical patient undergoing TMR has Canadian Cardiovascular Society (CCS) class III or IV angina, has had one or more bypass surgeries or angioplasties, or both, is taking multiple medications for ischemic heart disease and is not considered a candidate for traditional revascularization. True, angina is a subjective complaint and it is difficult to exclude a powerful placebo effect when "laser" and "surgery" are combined. Although patients often have a modest increase in exercise tolerance after treatment, there have not been the dramatic improvements in perfusion scanning that accompany traditional revascularization. Yet pain relief is sustained in many, and there is a suggestion of an improvement in ischemic threshold by dobutamine stress echocardiography (6) as well as some reports of increased perfusion on radionuclide (7) and positron emission tomographic scanning (8).

Pathophysiology of TMR. Accepting the fact that the channels produced by the laser probe do not remain patent, alternative mechanisms to explain the clinical efficacy achieved by TMR have been explored. Animal studies lend support to two not mutually incompatible hypotheses—angiogenesis and sympathetic denervation. The injury produced by the laser energy results in the elaboration of vascular growth factors that stimulate angiogenesis (9). Histologic confirmation of neovascularity in ischemic myocardium after TMR is impressive (10). It appears, however, that this response is not specific for laser injury in that a power drill (11), needle (12) and radiofrequency ablation system (13) have all produced similar results. Some investigators suggest, however, that laser energy per se may be an important factor in the neovascularization process (14).

Allowing for the moment that there is an advantage to laser-induced TMR, is there a difference between the types of laser employed? Although there appears to be some variation in the histopathology produced, the primary distinguishing characteristic between lasers is the inability of the carbon dioxide system to transmit energy through

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optical fibers. This limits the use of this device to direct application to the heart by thoracotomy. Other laser types (e.g., holmium, excimer) employ fiberoptic catheters that are capable of being delivered to the epicardium through an endoscope (15) or intravascularly, through a guide catheter to the endocardium (16).

The dark side of TMR. The clinical efficacy of TMR is achieved at some cost. Initial reports cited an operative mortality of about 10%, with an incidence of death at 1 year being ~20% (17,18). Overall morbidity of the operative procedure is also high, with an incidence of myocardial infarction of 19%, cardiac ischemia of 52% and noncardiac morbidity of 35% (19,20). Patients with acute coronary syndromes and those with poor ventricular function appear to be at greatest risk. Support of the latter using intraaortic balloon counterpulsation may be beneficial (21); however, it should be noted that unlike CABG or PTCA, there is no immediate revascularization afforded by TMR. Any increase in perfusion probably takes weeks to occur as the process of angiogenesis evolves.

It is likely that much of the mortality and morbidity associated with TMR is related to a learning curve during which both technical expertise and case selection are refined. Procedural mortality rates <5% are now commonly being reported (22–24). Although the process of lasing channels through the heart appears to produce little acute or chronic myocardial damage, the risk of thoracotomy alone is significant in this patient group.

Controlled trials of TMR. In view of the discrepancy between symptomatic improvement and objective evidence of increased perfusion to ischemic regions, controversy surrounds the risk-benefit ratio of TMR. It has been assumed that randomized, controlled trials would establish the clinical utility of this form of therapy. March (23) reported the results of a study in which 198 patients were randomized to TMR or continued medical management. This multicenter investigation demonstrated an improved anginal class, a decrease in reversible perfusion defects on dipyridamole stress thallium SPECT study and a marked decrease in the occurrence of unstable angina over 12 months of follow-up. Sixty percent of patients randomized to medical therapy crossed over to TMR. In contradistinction to this study, Schofield et al. (24) reported a less satisfying experience. Although anginal class was significantly improved by TMR as compared with medical therapy at 12 months, differences in objective exercise performance were not impressive. There was no benefit to TMR on fixed or reversible ischemic sites revealed by sestamibi study. The operative mortality rate was 5%, and the survival rate at one year was 89% in the TMR group versus 96% in the medically treated patients. The authors conclude that adoption of TMR cannot be advocated. In an accompanying commentary to this paper, Pretre and Turina (25) emphasize a conservative view toward the use of the laser, characterizing it as "an expensive analgesic device."

Percutaneous myocardial revascularization. Although TMR might lend itself to combined procedures in which traditional bypass (26), minimally invasive bypass (27) and/or valve surgery (28) is performed, the morbidity and mortality accompanying it as a stand-alone procedure are major obstacles to its use. Much of this risk appears related to thoracotomy, however, and may be obviated by a percutaneous approach. Kim et al. (29) demonstrated the feasibility of creating myocardial channels from the endocardial surface of the left ventricle using a catheter system introduced through the femoral artery. The methodology allowed for all segments of the left ventricle to be accessed by the laser under fluoroscopic guidance. Care was taken in catheter design and employment to avoid "through and through" perforation of the myocardium, as thought necessary with the epicardial approach.

In addition to reducing the morbidity and mortality associated with thoracotomy, percutaneous transmyocardial revascularization (also called direct myocardial revascularization [DMR]) theoretically provides access to portions of the left ventricle (i.e., septum) not easily approached from the epicardium. A limitation of the percutaneous approach, however, is the difficulty of reproducing the carefully spaced matrix of entry sites in the ischemic region with the precision afforded by direct observation. The introduction of a nonfluoroscopic catheter navigation system may improve the operator's ability to reach a target region and more precisely locate and then tag the sites that are lased (30).

The present study. Lauer et al. (31), in this issue of *JACC*, presents procedural and follow-up data of 34 patients undergoing percutaneous laser TMR. A mean of 10.4 laser channels per ischemic region was created; all but seven patients had only one region treated. There was no periprocedural mortality and surprisingly little morbidity. Six patients developed small pericardial effusions within 24 h of the procedure, none required drainage and all spontaneously resolved. Over a six-month follow-up period the CCS anginal class decreased from a mean of 3.1 to 1.3, and bicycle exercise duration increased from a mean of 384 to 514 s. There was, however, no improvement in perfusion detected by radionuclide scanning. Since the submission of this report, a great deal of clinical experience with DMR has accumulated. Shawl et al. (32), using a slightly different holmium DMR system, demonstrated similar safety and antianginal efficacy in a small group of patients. Preliminary results of a trial in which 221 patients were randomized to DMR versus medical therapy were recently presented (33). Those randomized to DMR experienced a marked improvement in anginal class, which was sustained over the six-month follow-up period. There was no procedural mortality, pericardial tamponade or ventricular fibrillation, emphasizing the relative safety of this form of therapy.

Although the efficacy of the percutaneous procedure seems roughly comparable to that of TMR, it is of interest to note that the number of channels made with the former

is typically about one-half of that reported with the latter. One might assume that the channel "density" per ischemic region would have some influence on the ultimate results achieved, and further research is necessary to clarify this point.

Laser revascularization today. Transmyocardial laser revascularization has been approved by the Food and Drug Administration for treatment of chronic stable angina in patients with class III and IV symptomatology in whom conventional revascularization cannot be performed. A variety of percutaneous systems are in various stages of the regulatory evaluation. Combining the laser procedures with more traditional forms of revascularization (CABG and PTCA) is being studied. Despite the rather remarkable and sustained nature of the symptomatic improvement encountered with TMR and DMR, objective confirmation of improved myocardial perfusion has been inconsistent, and objectively assessed increases in exercise tolerance have been modest. Although randomized studies appear to confirm the results of the pilot and registry experience, the potential of a dramatic placebo effect cannot be discarded. Skeptics will remind us of other experiences with expensive cardiovascular procedures that have not stood the test of time.

We must learn more about the pathophysiology of TMR. If denervation is the primary effect, do we need to be concerned about asymptomatic ischemia? Is there an effect of the procedure that might promote atherosclerotic progression? Assuming that the safety and efficacy of DMR is confirmed, it seems likely that this will be the favored approach to patients with ischemic territories that cannot be revascularized by conventional means. So TMR will be reserved for patients undergoing other procedures requiring thoracotomy.

Both procedures will be extended far beyond the current indication for TMR. For instance, patients undergoing conventional CABG or PTCA might have TMR or DMR performed in the same zone to protect against recurrent ischemia should the bypass fail or angioplasty site restenose. Interventional cardiologists may wish to extend the role of percutaneous intervention by using DMR for regions served by "nonangioplastiable" vessels, even if such vessels were suitable for bypass. For example, a patient might have angioplasty and stenting of an ideal lesion in the left anterior descending coronary artery and DMR to the region served by a chronically occluded right coronary artery instead of double-vessel bypass surgery. It will be important to study such applications carefully before assuming their safety and effectiveness.

Expectations for the future. It is natural that other mechanisms capable of creating myocardial channels (mechanical drill, radiofrequency energy, ultrasound) be vigorously pursued. Assuming the mechanism of laser myocardial revascularization is the induction of nonspecific tissue injury, one or more of these devices may be less expensive alternatives to the laser treatment. If angiogenesis is the mechanism of pain relief, exploration of approaches to maximize neovascularization is needed. There is currently great enthusiasm for gene therapy as a stimulus for angiogenesis. Direct intramyocardial gene transfer has been shown to stimulate angiogenesis (34). Sayeed-Shah et al. (35) have suggested that transfection efficiency of plasmid vascular endothelial growth factor is increased with the concomitant use of TMR. Percutaneous intramyocardial delivery of replication-deficient adenovirus has been demonstrated (36). Clinical trials combining a percutaneous myocardial "channel-making" technology and the insertion of a cytokine or genetic material will begin soon.

Conclusions. Although the mechanism of the symptomatic relief afforded by TMR remains uncertain, it would appear to be a reasonable approach to the patient with refractory symptoms who is not considered a candidate for conventional revascularization. At best, the procedure relieves symptoms by inducing neovascularization that is capable of reducing but not eliminating ischemia caused by disease of the epicardial arteries. At worst, the procedure denervates angina-producing regions of the heart and may or may not have a beneficial physiologic effect accompanying the analgesia. In assessing the ultimate role of TMR and DMR, the value of alternative "nonrevascularizing" nonpharmacologic therapies such as spinal cord stimulation (37), transcutaneous electrical nerve stimulation (38) and external counterpulsation (39) must also be considered. There may, in fact, be a light at the end of the tunnel for patients with nonrevascularizable angina.

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