LETTERS TO THE EDITOR

Percutaneous Laser Revascularization in Patients With Chronic Total Occlusions

As clinical investigators of the percutaneous myocardial revascularization (PMR) device, we read with interest “A Prospective, Multicenter, Randomized Trial of Percutaneous Transmyocardial Laser Revascularization in Patients With Nonrevascularizable Chronic Total Occlusions” (PMR-CTO trial) by Stone and colleagues (1). Based upon the lack of available follow-up data and objective evidence, we do not agree with their negative conclusions regarding this study or with their generalizations regarding different laser systems.

There was approximately 50% available follow-up data for both primary study end points at six months: namely total exercise duration and angina improvement. The limited six-month follow-up data favors PMR-treated patients and may have achieved significance with complete follow-up at 6 and 12 months. Importantly, the review of major adverse events through six months supports the reasonable safety of the procedure.

The discussion regarding laser technology, along with the conclusion of the need for further study of PMR, leaves the impression that the laser systems used in the various studies are similar and presumes that the difference in trial outcomes is explained by protocol design. Despite being HO:YAG systems, the lasers used in the various studies discussed are not similar regarding energy delivery and tissue interaction. The (DMR) laser system used in the DIRECT study transmitted a single energy pulse to the endocardial surface and did not advance into the endocardium to create a channel. The DMR system was designed for triggering an endogenous tissue response, not for channel formation (2). The CardioGenesis PMR laser systems fiberoptics deliver multiple energy pulses while penetrating into the myocardium to create deep, non-transmural channels. Based on the negative outcome for the DIRECT trial utilizing the DMR system, it is clear that fiberoptic penetration into the myocardium and significant channel formation, as with PMR, are essential to achieving clinical benefit.

For PMR, the placebo question has been effectively addressed by the independently conducted, randomized, double blind, true-sham BELIEF trial, which was performed to assess the potential of placebo as a principal mechanism for angina improvement with the CardioGenesis Axcis PMR system. The investigators concluded that the significant 12-month clinical benefit for PMR-treated patients, compared to sham control, was not attributable to placebo (3). During the BELIEF trial, patients, investigators, and assessors were blinded, and cardiac medications were held constant. In the PMR-CTO trial, physicians were not blinded, and patient blinding (i.e., heavy sedation, PMR simulation, eye cover) may not have been consistently achieved. Whereas Stone and colleagues challenge the lack of increased exercise tolerance or reduction in ischemia in BELIEF, the study was not designed or intended to show a change in those measures. Studies performed with the CardioGenesis PMR system, examining perfusion with positron emission tomography (PET), have shown significant perfusion improvement (4,5).

Three randomized, multi-center trials [PACIFIC (6), PMR010 (7), and the independent BELIEF] encompassing nearly 650 patients have been completed with the CardioGenesis PMR systems. All have consistently demonstrated a significant clinical benefit favoring the PMR-treated patients in all primary end points, with significantly improved functional capacity at 12 months. PMR is not DMR.

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REPLY

We agree with Perin et al. that a pressing clinical need exists for an effective therapeutic approach for the large number of patients with advanced coronary artery disease and no revascularization options (1). However, given the potential risks and resource utilization of laser myocardial revascularization, it is mandatory that its clinical utility be definitively demonstrated in appropriately designed randomized trials, especially as most studies have not shown a reduction in inducible ischemia with this technique. In this regard, few would question that blinding and placebo effect issues have clouded the promising new field of laser myocardial revascularization and have delayed the regulatory approval of this potentially useful modality.

We attempted to address these issues with a multicenter, randomized prospective trial of percutaneous myocardial revascularization (PMR) incorporating blinding. Our trial revealed sig-
significant periprocedural complications associated with the laser technique (including pericardial tamponade or effusions in 7.0% of patients, and ventricular arrhythmias necessitating cardioversion in 5.6%), without enduring improvement in symptoms or exercise tolerance (2). Perin and Colleagues bemoan the lack of 12-month follow-up in our study. Unfortunately, such data was requested and not supplied by the sponsor. Moreover, the weak trend in our study toward less angina in PMR-treated patients at 3 months was diminishing at 6 months, making it doubtful that 12-month follow-up would have revealed significant symptomatic improvement. Their second comment reiterates our acknowledged limitation that the rate of paired exercise testing was lower than anticipated. However, as statistically discussed in the report (2), given the observed mean difference in exercise tolerance of only 17 s between groups, it is highly unlikely that a greater number of patients would have altered our conclusions.

Third, Perin et al. question the fact that our study was adequately blinded, which may have contributed to the negative findings. This is counterintuitive; lack of blinding would have favored the active treatment group, making the trial more positive. Moreover, it is unclear how blinded the BELIEF study was; the laser in the sham group was connected to a “lead box,” which likely precluded the characteristic visual and acoustic signals when the laser was fired. This small (only 82 randomized patients) though well-designed study also showed no difference in exercise tolerance between PMR and placebo groups, and incremental improvement in angina by ≥1 class at 12 months in only 24% of treated patients (n = 10), which may have been due to chance given the small sample size (3). We therefore cannot agree with their statement that BELIEF has “effectively addressed” the placebo question, given the results of the much larger, blinded DIRECT trial (4).

Finally, although we agree with Perin and Co-workers that the three holmium yttrium-aluminium-garnet (YAG) laser systems subjected to clinical trials are different, and stated so in the last paragraph of our report (2), we strongly disagree with their statement that “Based on the negative outcome for the DIRECT trial utilizing the DMR system, it is clear that fiberoptic penetration into the myocardium and significant channel formation, as with PMR, are essential to achieving clinical benefit.” Evaluating whether the different modes of energy delivery or myocardial penetration has anything to do with clinical efficacy would require a comparative study between the two systems, or absent this, at least a positive adequately sized multicenter blinded study of PMR using the CardioGenesis system.

We suggest that rather than arguing the merits of the currently completed trials, all of which are flawed to some degree, Perin et al. focus on lobbying for an adequately powered, appropriately blinded clinical trial to once and for all either prove the safety and efficacy of PMR, or, alternatively, demonstrate its futility. Otherwise, it is doubtful that this once promising approach will ever become widely accepted by the clinical community.

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Stented Angioplasty or Coronary Artery Bypass Graft Surgery for Multivessel Disease?

The recent report from the ARTS trial focuses on the effect of completeness of revascularization on the outcome within each cohort (1). In the previous report from the trial, on the basis of a small difference in the cost of treatment during the first year in favor of stented angioplasty, but in the absence of difference in the rate of major complications and with a repeat revascularization rate more than five times greater among the stented patients, the investigators concluded that there is no advantage to surgery over angioplasty in patients with multivessel disease (2). Now we learn that when the interventional cardiologists estimated that, using stented angioplasty, they could achieve a degree of revascularization equal to surgical revascularization, they were, in fact, able to provide this degree of completeness to a substantially lower number of patients (70.5% vs. 84.1%). The significantly better revascularization in the surgical group was accomplished without increased incidence of stroke, myocardial infarction, or death. Patients in this trial, who were randomized to stented angioplasty and received incomplete revascularization (30%), could have much better freedom from death and other major complications, reducing the need for subsequent bypass surgery from 10% to only 0.2% to 1.1%, with only minimal effect of completeness of revascularization. However, the investigators elected to emphasize the effect of complete revascularization; the fact that even with complete revascularization, the stented patients had a one-year event-free survival much inferior to their surgical counterparts does not appear, as it should, in the conclusions of their report.

Another unanswered question is what happened to the left ventricle (LV) using an approach that resulted in the need for repeat revascularization in every fifth patient. Were all the ischemic episodes indicating the need for further revascularization procedures free of irreversible myocardial damage? And was the subsequent procedure, carrying a 5% to 6% infarction rate in the index procedure, free of damage the second time? Has LV function remained unchanged in both groups?

The researchers conclude that the effectiveness and cost-effectiveness of angioplasty can be further enhanced by careful selection of patients. The cohort assigned to this study consisted of lesser proportion of patients with totally obstructed vessels, small or multileision vessels, and at least two lesions in arteries >2.75 mm, leading to two different territories. Such patients are almost ideal candidates for angioplasty. Careful selection of candidates from among these patients will further limit the application of the study results to the entire population of patients with multivessel disease.