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LETTERS TO THE EDITOR

The Art and Science of Transmyocardial Laser Revascularization

If Jackson Pollack is the artist, then the recent study in *JACC* by Saririan and Eisenberg on myocardial laser revascularization is indeed state of the art. The investigators (1) are to be commended for attempting to clarify the work that has been done with this technique, but unfortunately the result is less than satisfactory. To equate Ho:YAG and CO_2 lasers as well as transmyocardial laser revascularization (TMR) and percutaneous myocardial laser revascularization (PMR) without understanding that vast differences exist in the laser-tissue interactions and in their ability to treat the full thickness of the myocardium is analogous to saying that calcium channel blockers and beta-blockers are of equal importance postmyocardial infarction because they are both "blockers." This lack of discernment is most obvious in the researchers' discussion of suggested mechanisms of action.

Throughout the discussion, the investigators list a number of different experiments without identifying what type of laser was used, what type of model was employed, and whether the model employed re-creates the clinical scenario. In addition, they ignore several studies that do clarify the mechanism. These omissions continue when describing the clinical work. Where significant differences exist in the clinical trials, the results are lumped together. In an attempt to tabulate the published series of TMR patients with 12-month follow-up, the researchers ignored over 220 patients who demonstrated a significant perfusion benefit after CO_2 TMR. The investigators are familiar with these studies, as they do reference them elsewhere in their report. This perfusion benefit has also been demonstrated using the same CO_2 laser in a randomized clinical trial. Although this is acknowledged by the investigators, it is immediately discounted and considered to be a placebo effect. They claim that a placebo effect can demonstrate an 80% improvement in exertional angina, but this has not been demonstrated at one year, and certainly it has not been demonstrated out beyond five years, as has been reported with CO_2 TMR.

Moreover, they do not explain how perfusion benefit can be achieved by placebo. They claim that the patients who crossed over from medical therapy to TMR in the aforementioned CO_2 TMR trial did so owing to a subjective end point of angina and as a result of investigator bias. In fact, crossovers occurred after patients developed unstable angina and were unweanable from intravenous heparin and nitroglycerin after three attempts to decrease this maximal medical therapy. This treatment was not controlled by the investigators and is far from subjective.

Also, comments on the perfusion data from the European CO_2 TMR trial are misleading. Although it is true that a decrease occurred in the number of myocardial segments with reversible ischemia for patients treated with medical therapy and for TMR, the decrease in the medical management group was due in part to a doubling of the fixed defects. No significant increase occurred in the fixed defects in the TMR group.

To include PMR in this discussion without noting its severe limitations is inappropriate; for example, regardless of the mechanism, a 3- to 4-mm divot created on the subendocardium cannot be considered to be as complete a treatment as a full thickness transmural channel. I do agree with the investigators that a review of the TMR literature suggests that the clinical benefits of PMR are largely due to the placebo effect. Apparently the U.S. Food and Drug Administration (FDA) agrees because the FDA recently deemed Ho:YAG PMR not to be worthy of approval.

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REPLY

We would like to thank Dr. Horvath for his insightful comments. The goal of our paper was to present an unbiased review of the topic of myocardial laser revascularization with an emphasis on randomized, controlled clinical trials. Given the word limitations imposed on our manuscript, it would have been inappropriate for us to delve into laser-tissue interactions at the expense of important clinical data. Moreover, an appropriate reference on laser-tissue interactions was made available to the reader.

At no point in our paper did we "equate" transmyocardial revascularization (TMR) and percutaneous myocardial laser revascularization (PMR). These are distinctly separate techniques. Neither do we suggest that the CO_2 and Ho:YAG lasers are of equal value. Any claim, however, that the CO_2 laser is superior to the Ho:YAG laser is speculative, and remains to be shown in a head-to-head randomized clinical trial.

The experimental studies quoted in our paper used animal models of chronic myocardial ischemia, akin to patients with chronic angina. We found no study that entirely explains the mechanism of action of TMR. There are several studies for and against each hypothesis; therein lies the controversy.

We presented the trials in tabular form to emphasize their similarities. Differences were noted in the text. As Dr. Horvath points out, a number of small, nonrandomized studies with short-term follow-up demonstrate enhanced perfusion post-TMR. This could either be related to laser-induced angiogenesis, or to the natural development of collateral vessels in patients with chronic ischemia. The latter explanation emphasizes the danger of relying on the results of uncontrolled studies because, for the most part, enhanced perfusion has not been confirmed in randomized clinical trials. Transmyocardial laser revascularization did not improve myocardial perfusion in four of five trials in which perfusion was assessed before and at various times after enrollment. In the trial by Frazier et al. (1), in which a benefit was seen, there was only a 49% follow-up in the medical arm of the study. Also, the degree of symptomatic improvement was vastly disproportionate to the degree of improvement in perfusion.

In the trial by Frazier et al. (1), 59% of patients initially assigned to maximal medical therapy crossed over to the TMR group. The investigators allowed crossover as an enticement for patients to

remain in the study if medical therapy failed and the end point of angina was reached. Angina, unfortunately, is a subjective measure. Irrespective of how "objective" the investigators were in determining the success or failure of antianginal therapy, the use of a subjective end point may have inadvertently introduced bias into the trial. It is difficult to draw proper conclusions from such a trial when large crossover rates are allowed.

With respect to the European trial by Schofield et al. (2), the number of sites with irreversible segments was adjusted for baseline, and for repeated within-patient, between-site measures. Therefore, to suggest that a "doubling" of fixed defects in the medical therapy group implies enhanced perfusion in the TMR group is inappropriate, especially because a subgroup analysis of the same TMR patients showed no improvement in myocardial perfusion with PET scanning (3).

To conclude, we believe that the reported benefits of TMR, even out to five years, may be related to the placebo effect. It is the most plausible mechanism of action, given the lack of concrete evidence to the contrary. A properly powered, blinded, sham-controlled surgical trial of TMR could certainly settle this issue. In the absence of such a trial, however, more studies using new perfusion imaging modalities must be conducted to elucidate the true value of this technique.

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Mitochondrial Dysfunction in Heart Failure

I read with interest the report in the *Journal* by Scheubel et al. (1). Although their conclusion that a deficit in the activity of respiratory chain complex I may not be due to generalized damage of mitochondrial deoxyribonucleic acid (DNA) and gene expression is most likely true, their statement in the discussion that "in an experimental model of tachypacing-induced heart failure without any drug treatment, a depression in the activities of all complexes containing mitochondrially encoded subunits, including the mitochondrial adenosine triphosphatase, was described . . . , indicating disturbed mitochondrial gene expression," is inaccurate.

Marin-Garcia et al. (2) in their study of mitochondrial function in pacing-induced cardiac failure reported that the activity levels of complexes I and IV (complexes containing mitochondrially encoded subunits) were unchanged (normal) relative to controls. Only one complex of the electron transport chain (complex III) and adenosine triphosphate synthase (complex V) were affected without changes in peptide content of specific mitochondrial proteins. The reduced levels of complex III and complex V activities did not appear to be due to generalized mitochondrial damage, necrosis, or overall decreased levels of mitochondria as gauged by unchanged levels of respiratory complex I, complex II (nuclear encoded), complex IV, and citrate synthase (also nuclear encoded). The levels of mitochondrial DNA deletions (7.4 kb) were extremely low in comparison to wild-type genomes and probably of no significance. Therefore, the investigators' conclusion that depression in the activity levels of the respiratory enzymes and complex V in the pacing-induced cardiac failure indicate disturbed mitochondrial gene expression is misguided. However, I do agree that the protective role of drug treatment against mitochondrial DNA damage remains to be proven.

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2. Marin-Garcia J, Goldenthal MJ, Moe GW. Abnormal cardiac and skeletal muscle mitochondrial function in pacing-induced cardiac failure. Cardiovasc Res 2001;52:103–10.

REPLY

We thank Dr. Marin-Garcia for the interest in our study (1). He is right in stating that our citation of his study (2) "indicating disturbed mitochondrial gene expression" is inaccurate. We regret such inaccuracies, which must have occurred during several reformulations of our text. The reasons for the reduced activities in complex III and complex V in his tachypacing-induced failure model (2) remain undetermined at present. However, we are happy that Dr. Marin-Garcia agrees to our conclusion that a depressed complex I activity in failing human myocardium may not be due to generalized damage of mitochondrial deoxyribonucleic acid.

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