GENERAL THORACIC SURGERY

TRANSMYOCARDIAL LASER REVASCULARIZATION: CLINICAL EXPERIENCE WITH TWELVE-MONTH FOLLOW-UP

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We are investigating a new technique for myocardial revascularization in which an 800 W carbon dioxide laser is used to drill 1 mm diameter channels into a beating heart after left thoracotomy. Clotting occludes the channels on the subepicardium, and in the long-term setting, blood from the left ventricular cavity flows through these channels to perfuse the ischemic subendocardium. To test the efficacy of this technique in a preliminary clinical trial, we used it as sole therapy for 21 consecutive patients. All patients had hibernating myocardium, reduced coronary flow reserve, or both, had distal diffuse coronary artery disease, and had angina refractory to normal therapy. Eight patients were excluded from follow-up because of death ($n = 5$), revascularization ($n = 2$), or diaphragmatic paralysis resulting in postoperative respiratory incapacity ($n = 1$). In the remaining 13 patients available for follow-up, the mean angina class (Canadian Cardiovascular Society) was 3.7 ± 0.4 before operation and 1.8 ± 0.6 12 months after operation ($p < 0.01$). Mean resting left ventricular ejection fraction was $48\% \pm 10\%$ before operation and $50\% \pm 8\%$ at 12-month follow-up. At 12 months, resting mean subendocardial/subepicardial perfusion ratio had increased by $20\% \pm 9\%$ in septal regions treated by laser but decreased by $2\% \pm 5\%$ in untreated regions ($n = 11, p < .001$). These results suggest that revascularization by this laser technique positively affects subregional myocardial perfusion and may result in clinical benefits for patients with reversible myocardial ischemia. Studies to date have not demonstrated significant changes in global and regional ventricular contractile function. (J THORAC CARDIOVASC SURG 1996;111:791-9)

After the description of the Beck¹ and Vineberg² procedures, Massimo and Boffi³ reported in 1957 the experimental results of implanting a T-shaped

plastic tube into the myocardial wall to bring oxygenated blood from the left ventricular cavity into the ischemic myocardium. Needle acupuncture to salvage the ischemic myocardium was proposed by Sen and coworkers⁴ in 1965. On the basis of Sen and coworkers' report and after experimentation in their own laboratory, White and Hershey⁵ reported the successful restoration of normal ventricular rhythm in a 61-year-old man with myocardial ischemia and resultant refractory ventricular fibrillation. Revascularization was accomplished with prolonged intermittent cardiac compression and transmural acupuncture with a 2.5 mm knobbed cannula. The cannula was used to create 85 channels on the left ventricular free wall and 15 channels on the right ventricular free wall before double internal mammary arterial implantation and omentopexy. Their patient was free of symptoms at the tenth postoperative month. In 1968, Sen and associates⁶ reported the results of early clinical trials with four patients.

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Table I. Preoperative patient characteristics

Characteristics	Patients (n = 21)	
	No.	%
Previous MI		
Anterior	3	14
Inferior	8	38
Anterior + inferior	1	5
Previous revascularization (CABG or PTCA)		
None	2	10
1	8	38
≥ 2	12	57
Concurrent illnesses		
Congestive heart failure	11	52
Arrhythmias	10	48
Diabetes mellitus	3	14

CABG, Coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

In 1969, Sen⁷ suggested that multiple myocardial acupuncture result in improved contractility or rapid electrical defibrillation in acute pump failure after prolonged cardiopulmonary bypass. He also speculated that the technique would be useful for the surgical treatment of acute and chronic coronary occlusion and the intermediate coronary syndrome. In 1981, Mirhoseini and Cayton⁸ first proposed using a laser to create transmyocardial channels. Mirhoseini, Fisher, and Cayton⁹ were the first to use this technique in a patient whose heart was not beating.

Okada and colleagues¹⁰ first used an 85 W carbon dioxide laser to create six holes in the contracting anterior left ventricular wall of a 55-year-old man with constrictive pericarditis and severe angina. They reported improved clinical outcome 9 months after the operation. Since 1990, a high-powered carbon dioxide laser (800 W) has been used to perform transmyocardial laser revascularization (TMLR) on the beating hearts of human beings.^{11, 12}

More recently, we reported 6-month follow-up results of TMLR with the 800 W carbon dioxide laser. The technique was used as sole therapy in patients who had distal diffuse coronary artery disease; hibernating myocardium, reduced coronary blood reserve, or both; and angina refractory to normal therapy.¹³ We report here the 12-month postoperative results of these patients. We believe that it is important to document our experience across a longer interval because this new treatment modality, if substantiated by time and by other investigators, could have an important implication for the surgical treatment of coronary artery disease.

Methods

Patients. Patients were enrolled in the study after signing a consent form approved by the Institutional Review Board of St. Luke's Episcopal Hospital. Twenty-one consecutive patients (mean age 63 ± 10 years, 14% female) were treated with the laser as sole therapy after documentation by positron emission tomography (PET) of perfusion defects in the left ventricular free wall. Of these patients, four (19%) had unstable angina when enrolled in the study and seven (33%) had a left ventricular ejection fraction (LVEF) of $35\% \pm 5\%$. Other relevant preoperative characteristics of patients are given in Table I.

Patient evaluation and data analysis. Patients were evaluated before operation and 12 months after operation with PET for myocardial ischemia and viability,¹⁴ and with dobutamine echocardiography for regional wall motion analysis and LVEF at rest and during stress.¹⁵ Thallium 201 single-photon emission computed tomography (²⁰¹Tl-SPECT) was used to determine myocardial perfusion at rest and during stress, and multigated acquisition radio-nuclide ventriculography was used to determine LVEF at rest. Stress was induced in patients with stable angina on a treadmill with a modified Bruce protocol before the ²⁰¹Tl-SPECT test.¹³ Time on the treadmill was recorded for each patient and averaged for baseline and for the follow-up period. Patients who could not exercise for reasons unrelated to heart disease did not undergo a treadmill test.

Data from PET, dobutamine echocardiography, and ²⁰¹Tl-SPECT tests were analyzed in short-axis projections of the myocardium at basal, middle, and distal levels. Regions of interest at each level were identified as septal, anterior, lateral, and inferior. The septum was further subdivided into inferoseptal and antero-septal segments at the basal and middle levels; the apex was considered an independent segment.

For PET analysis, the relative perfusion was measured for transmural regions and for subendocardial and sub-epicardial subregions. Perfusion values from the PET measurements were used to calculate subendocardial/sub-epicardial perfusion ratio (SEn/SEp).

Regional myocardial wall motions observed during dobutamine echocardiography were assigned subjective scores of 1 (normokinetic), 2 (hypokinetic), 3 (akinetic), or 4 (dyskinetic). The wall motion score index (WMSI) was calculated by separately averaging the scores of lased (anterior, lateral, and inferior) and nonlased (septal and, in some cases, basal inferior) segments.

Regional myocardial viabilities assessed from ²⁰¹Tl-SPECT were assigned scores of 4 (normal), 2 (ischemic), 1 (ischemia around scar), and 0 (scar) on the basis of subjective assessment of perfusion at peak stress and redistribution. Individual scores were averaged separately among lased and nonlased regions.

Statistical analysis. The statistical significance of the differences between the lased and nonlased regions at 12 months, or of differences between the same regions at baseline and 12 months, were analyzed with a paired, two-tailed Student's *t* test.

Surgical procedure. Patients were intubated with a double-lumen Carlson tube. A left anterolateral thoracot-

Table II. Clinical characteristics of 13 patients before operation (baseline) and 12 months after operation

	Baseline	12 mo
Angina class*	3.7 ± 0.4	1.8 ± 0.6†
Time on treadmill (min)	4.3 ± 2.1	10.0 ± 3.8†

*Canadian Cardiovascular Society classification.

† $p < 0.001$.

omy was performed at the fourth intercostal space. The left lung was deflated. If intrapericardiac adhesions were present as a result of previous coronary artery bypass operations, they were dissected. The heart was placed in a pericardial cradle. A sterile focusing end-piece coupled to the articulating arm of the 800 W carbon dioxide Heart Laser (PLC Medical Systems, Inc., Milford, Mass.) was brought into the surgical field draped in a sterile cover. An end-piece with a mirror mounted at the tip to deflect the output laser beam by 90 degrees was used to create channels in the proximal diaphragmatic aspect of the left ventricular free wall. Detection of intraventricular microbubbles by transesophageal echocardiography was interpreted as confirmation of the transmural penetration of each pulse. Multiple full-thickness laser perforations of the contracting myocardium were induced and confirmed, predominantly in the regions determined before operation to exhibit ischemia in viable myocardium. Because the infrared wavelength at which the carbon dioxide laser emits radiation ($\lambda = 10,660$ nm) is highly absorbed by fatty tissue as well as by water, the output pulse energy of the laser was increased from an initial value of 15 J to a maximum of 60 J when excessive epicardial fat precluded full penetration at the lower power. Hemostasis was ensured with external digital pressure or, rarely, epicardial purse-string sutures. The incision was closed routinely.

Results

Perioperative. An average of 36 ± 5 pulses were delivered per patient, with 76% confirmation by transesophageal echocardiography. The perioperative mortality and morbidity associated with the procedure have been reported in detail elsewhere.¹³ Briefly, a 64-year-old man had right-sided hemidiaphragmatic paralysis immediately after operation; a 47-year-old man had a brief episode of atrial tachyarrhythmia 3 days after operation (the arrhythmia was successfully managed medically); a 72-year-old woman died of ventricular tachyarrhythmia 5 days after operation, possibly caused by a perioperative infarct observed during cardiac autopsy; and an 80-year-old man with preoperative chronic obstructive pulmonary disease and angina decubitus died of aspiration pneumonia 8 days after operation. With the exception of this last man, no patient required inotropic support in the perioperative phase.

Table III. Mean LVEF before operation (baseline) and 12 months after operation

Analytic method	LVEF (%)	
	Baseline	12 mo
MUGA (resting $n = 12$)	48 ± 10	50 ± 8
Dobutamine echocardiography ($n = 10$)		
Rest	41 ± 10	41 ± 12
Stress	45 ± 11	48 ± 17

MUGA, Multigated acquisition radionuclide ventriculography.

Twelve-month follow-up. A 56-year-old man died of an inferior myocardial infarct 94 days after operation, a 77-year-old man died of renal insufficiency 97 days after operation, and a 72-year-old woman died of a refractory ventricular fibrillation 287 days after operation. Two patients were rerevascularized 87 and 91 days after laser operation with bypass grafting and coronary angioplasty, respectively, to treat new lesions.

The eight patients excluded from follow-up at 12 months were the 5 who died, the two who had rerevascularization, and the one whose 12-month rerevascularization was postponed until after the placement of a diaphragmatic pacemaker. This report therefore describes the clinical and functional results of the 13 patients who were reevaluated at the completion of the study. At 12 months after operation, no patients had unstable angina. Eleven patients reported significant relief from their preoperative angina (reduction by at least two classes in the Canadian Cardiovascular Society angina classification) and had either returned to work or been free from symptoms for the past 6 months. The average angina class at follow-up was 1.8 ± 0.6 , significantly lower than the average baseline angina class of 3.7 ± 0.4 ($p < 0.001$, Table II). The average time on the treadmill increased significantly at 12 months ($p < 0.001$, Table II). The mean LVEFs at rest and during stress did not change significantly during the 12 months (Table III).

Two patients did not have adequate acoustic windows for optimal echocardiographic study. Baseline and 12-month echocardiographic WMSIs at rest and with low-dose and high-dose dobutamine stress are depicted in Fig. 1. Although the resting WMSI in the laser regions decreased from 1.91 ± 0.65 at baseline to 1.82 ± 0.79 (that is, wall motion improved) and the WMSI in the nonlaser regions increased from 1.82 ± 0.79 at baseline to 1.98 ± 0.61 during the 12-month follow-up period, the changes,

Fig. 1. WMSI by echocardiographic analysis of 15 cardiac segments per patient at rest and during low-dose ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and high-dose ($40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) dobutamine infusion. 1, Normokinetic; 2, hypokinetic; 3, akinetic; 4, dyskinetic; *p* not significant for lased versus nonlased and baseline versus 12 months.

Fig. 2. Myocardial perfusion and viability status as a percentage of normal by ^{201}Tl -SPECT analysis of 15 cardiac segments per patient; *p* not significant for lased versus nonlased and baseline versus 12 months.

unlike those seen at 6-month follow-up,¹³ did not reach a level of statistical significance. WMSIs at low-dose and high-dose dobutamine stress deteriorated for both the lased and the nonlased segments during the 12-month follow-up period (Fig. 1).

Follow-up with ^{201}Tl -SPECT of 12 patients (one patient did not undergo ^{201}Tl -SPECT follow-up)

Table IV. Transmural 15-segment analysis by PET of myocardial perfusion and viability status with respect to baseline in 11 patients 12 months after TMLR

	Lased segments (free wall)		Nonlased segments (septum)	
	No.	%	No.	%
Improved	33	30	20	36
Same	33	30	24	45
Worse	44	40	10	18
Total segments	110		55	

indicated that the average perfusion of the lased regions increased from $45\% \pm 21\%$ of normal at baseline to $51\% \pm 23\%$ of normal at 12 months; the perfusion of the nonlased segments decreased from $73\% \pm 22\%$ of normal at baseline to $70\% \pm 21\%$ of normal at 12 months (Fig. 2). The increase in perfusion in the treated segments represented an improvement of 13% from baseline values but was not statistically significant compared with the change in perfusion of the nonlased segments.

Regional myocardial perfusion and viability status in transmural sections were monitored with conventional PET during the first year after operation. One patient did not have a PET study before the opera-

Fig. 3. Subregional analysis of myocardial SEn/SEp by PET at rest ($n = 11$ patients) and during dipyridamole stress ($n = 9$ patients). Change in SEn/SEp with respect to baseline was significantly different in lased segments compared with nonlased segments both at rest ($p < 0.0001$) and under stress ($p < 0.01$).

tion, however, and another patient could not be studied at 12 months because of technical problems. In the 11 patients for whom preoperative and 12-month follow-up PET data were available, 30% of the lased regions showed marked improvement at 12 months, but 40% were worse compared with baseline (Table IV). Among the nonlased segments, the perfusion of 15% remained unchanged.

Additionally, the relative perfusion across the subregions of the myocardium (SEn/SEp) was measured with subregional PET analysis. At 12 months after operation, perfusion was measured in 11 patients at rest and in nine patients during stress. The average resting SEn/SEp increased from 0.96 ± 0.07 at baseline to 1.10 ± 0.04 at 12 months in the lased segments. SEn/SEp decreased from 1.07 ± 0.07 at baseline to 1.00 ± 0.02 at 12 months in the nonlased control segments of the septum ($p < 0.0001$, Fig. 3). During stress, SEn/SEp increased from 0.87 ± 0.10 at baseline to 1.17 ± 0.04 at 12 months in the lased segments and from 0.96 ± 0.05 at baseline to 1.01 ± 0.01 at 12 months in the control segments ($p < 0.01$, Fig. 3).

Discussion

First reported by Mirhoseini, Fisher, and Cayton⁹ in 1983, TMLR is a relatively new therapeutic modality for patients with coronary artery disease. In this study we wished to measure objective im-

Table V. A 2×2 table for evaluating accuracy and sensitivity of subregional 15-segment myocardial perfusion analysis by PET in accordance with clinical status after TMLR ($n = 11$)

Analysis by PET	Clinical status	
	Better	Same
Better	8	1
Worse	1	1

Accuracy = (True positives + True negatives)/All cases = $(8 + 1)/11 = 82\%$.

Sensitivity = True positives/(True positives + False negatives) = $8/(8 + 1) = 89\%$.

provement in myocardial perfusion when the laser was used as the sole treatment for such patients. Our access to and long experience with PET in the assessment of myocardial viability and perfusion prompted our use of this modality in the hope of obtaining the most accurate available assessment of the laser technology. In this preliminary study of limited size, patients with documented coronary artery disease and reversible myocardial ischemia had a significantly improved clinical status and a markedly increased treadmill tolerance 12 months after TMLR was used as a sole therapy. The echocardiographic WMSIs and LVEFs at rest and during stress, however, remained unchanged by dobut-

amine. Regional myocardial perfusion by ^{201}Tl -SPECT showed positive, although not significant, trends toward improvement. In contrast, studies by PET did indicate a significant change in relative subendocardial perfusion.

The myocardial perfusion and viability status were assessed by PET on short-axis projections within transmural regions as well as within subendocardial and subepicardial subregions. Transmural analysis of the 110 laser segments in the left ventricular free wall of 11 patients revealed that the perfusional and metabolic status in 33 segments (30%) was better at 12 months than at baseline and that the status in the remaining 70% of the segments was either unchanged or worse at 12 months (Table IV). Because nine of the 11 patients (82%) reported significantly improved anginal symptoms, the results of transmural PET analysis were in poor agreement with the clinical condition of the patients. Subregional PET analysis, however, revealed that SEN/SEP had increased by at least 15% over baseline in eight of the nine patients with improved clinical status and decreased by 1% in one of the two patients whose anginal symptoms were unchanged after operation (Table V). Overall, the 12-month subregional PET analysis represented the clinical status of the patients with an accuracy of 82% and a sensitivity of 89%; by similar calculations, the transmural PET analysis had an accuracy of 55% and a sensitivity of 44%.

Subregional PET analysis involves the differentiation of the subendocardial perfusion (which is expected to increase if the laser channels connect with myocardial sinusoids and remain functional) from the subepicardial perfusion (where no change is expected because the peripheral portion of the channel is sealed immediately by clot formation). In transmural analysis, however, tracer concentration is averaged by the computer across the myocardial thickness, sacrificing in part the sensitivity of the calculations to changes in perfusion in the radial direction. In that regard, our results support the use of subregional PET analysis in patient selection and follow-up for TMLR.

The reversal of SEN/SEP at 12 months in favor of subendocardial perfusion indirectly suggests the patency of the laser channels. The finding of endothelialized laser tracts connecting with native myocardial vessels has been reported in an isolated case¹²; however, such direct evidence of channel patency and functionality is currently scarce. It is therefore not clear whether the majority of laser-induced channels indeed remain open for prolonged times or

whether the observed clinical and perfusional effects of the procedure are mediated through other mechanisms. For example, the thermal, mechanical, or oxidative stresses associated with the insult may elicit adaptive responses and mediate angiogenesis in the laser-treated zones.^{16, 17} These possibilities should be assessed in experimental models that (1) correctly represent the collateral-dependent anatomy of the hibernating human myocardium and (2) use the relevant laser parameters. In contrast with such alternative modalities as the low-power carbon dioxide laser¹⁸ or the Ho:YAG laser,¹⁹ which have been proposed and used experimentally in TMLR, current carbon dioxide laser technology can achieve high pulse energies to cross the contracting myocardium in a fraction of a single cardiac cycle. This minimizes the incidence of arrhythmias and allows the creation of straight laser tracts with smooth edges. The high absorption/scattering ratio of the photons at this wavelength, on the other hand, keeps the collateral damage to cardiovascular tissue at a minimum.²⁰

Because this preliminary study lacked a control group, the results in no way validate TMLR as sole treatment for obstructive coronary artery disease refractory to conventional treatment. The results do demonstrate, in an extensive longitudinal follow-up with 50 PET scans at scheduled intervals, statistically significant improvement in relative subendocardial perfusion consistent with the clinical improvement observed in most (9/11) patients. We therefore believe that further evaluation of the efficacy of TMLR in the clinical setting is warranted. Larger clinical trials with appropriate control groups would be useful in evaluating the clinical value and potential of this promising technology.

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Discussion

Dr. Lawrence H. Cohn (*Boston, Mass.*). We have used this same high-energy heart laser at the Brigham since March of 1993, after about a year's work in our laboratory before that done by my colleague, Dr. Keith Horvath. We have used similar indications. We have only used this laser in the isolated situation, without any concurrent operation. A refereed group of physicians at our hospital proved that these patients were not candidates for cardiologic intervention or operation. They definitely had to have reversible ischemia. We believe that this therapy is not good for ischemic cardiomyopathy; therefore, the ejection fraction should be at least 30%.

Similar to the group presented here, these are patients, mostly men, with very advanced coronary disease. Seventeen of our 19 patients in whom only this therapy was used had a previous operation, very severe angina class, and a mean ejection fraction of 45%.

To evaluate any changes in myocardial perfusion, we

have used a computerized polar map by the use of sestamibi thallium scans. We have results for 11, 10, and 7 patients at 3, 6, and 12 months after operation, respectively. The septal flow, which is not lased, shows virtually no change in myocardial perfusion. Conversely, in the free wall, correlating with areas in which we did perform laser drilling, there are significant increases in perfusion both at rest and with stress at 3, 6, and 12 months after operation, suggesting to us that this modality did increase myocardial perfusion.

Finally, we have been performing the technique lately in the laboratory with the help of Dr. DeGuzman. We have used this technique through a thoracoscope in a 35 kg porcine model where obviously there was no previous operation. Through a thoracoscope, this procedure could be done in anyone with a free pericardium. The cutting of the pericardium and finally use of the laser probe to make appropriate channels can be seen through the thoracoscope. This procedure has been done in five animals, all of which have survived.

I have two questions. Do the results in the PET scans that you have done correlate with the drilled areas; in other words, does increased nutrition correlate with where you actually drilled? Finally, how can you, if at all possible, evaluate the laser treatment in those patients in whom you did a concomitant coronary bypass?

Dr. Frazier. I think the laser has shown its value, particularly in these PET scan studies. Moreover, Dr. Gould, who has had extensive experience with PET scanning and who was originally very skeptical of TMLR, has confirmed that TMLR generally results in improvement in these patients, especially in the endocardial area. Of course, when TMLR is combined with other procedures, it is very difficult to assess the laser's effect; therefore, I do not believe that combined procedures are going to help establish the value of TMLR. I have the clinical impression, however, that acutely ill patients whose status is decompensated—such as the two patients in our series who underwent TMLR after sustaining a myocardial infarction—are better suited to demonstrating the true worth of this technique. For the technique to gain approval and widespread use, we will have to depend on scientific data, such as is being accumulated in cases in which TMLR is the sole means of therapy.

Dr. M. Mirhoseini (*Milwaukee, Wis.*). TMLR has had a long journey. Since 1969, after Sen's operation with the needle, we developed the concept of using a carbon dioxide laser to drill these channels. This is based on the following technical criteria: a laser powerful enough to penetrate the thickness of the left ventricular myocardium; short pulse duration to prevent lateral thermal injury, which is very important; the carbon dioxide laser, when it reaches the water, stops at 10.6 μ m of energy; and laser energy triggered by electrocardiography in the non-vulnerable phase of the R wave of PR intervals prevents arrhythmia and arrives at the ventricular cavity during diastole, when the heart is filled.

Initially we did extensive research on this. Publications are available, and the results of the research were published in the *Journal of Microsurgery* and also published after presentation to the World Congress of Cardiac Surgery in Detroit. We had trouble bringing this to the

clinical standard in the operating room, however, because such a large laser required very big modifications. The next step for us was therefore to use a smaller, lower-powered laser and use the laser in the arrested heart during cardiopulmonary bypass, for which we received clinical permission from the Institutional Review Board of St. Luke's Medical Center. The research was mostly done at the Medical College of Wisconsin. Some of these cases were initially presented at the Society of Thoracic Surgery meeting in Toronto and were published in the *Annals of Thoracic Surgery*. In some of these patients who underwent combined operation, 3 or 4 years after operation we could demonstrate some of these laser channels with angiography by a special technique of cineangiography with high resolution.

The series of operations that we performed on 30 patients between 1985 and 1987 involved combined procedures. Then a new high-energy laser was developed by PLC Systems here in Boston, so we could use this 800 W laser for the procedure to make these channels.

I would like to bring to your attention the last series of procedures. There were 42 in this study. Three of them were eliminated because they were done on transplanted hearts. Thirty-nine patients had been under study. I congratulate Drs. Frazier Cooley on their excellent results. Our results are very similar to their results with respect to clinical follow-up, selection of patients, and criteria for using the laser. Most of these patients are in an older age group and are sick patients with previous multiple coronary artery bypass grafts and angioplasties. Angina subsides or disappears in most patients, but there is a rate of attrition in 2 years after operation. Now a few of them are coming back with angina. Although regional wall motion improves, the overall ejection fraction does not seem to change.

You demonstrated that the subendocardium perfused better in your paper that I reviewed. To what do you attribute that better perfusion in the endocardium? Which is the higher pressure level of the myocardium?

Dr. Frazier. Anatomically, most of the sinusoids are concentrated in the endocardium, so if TMLR is going to result in improved perfusion, that is where most improvement will be seen. In using PET scanning to assess the results of TMLR, we were not so impressed with this method until we analyzed the endocardial and epicardial regions separately, which is not normally done. By analyzing each region separately, we found a statistically significant degree of improved endocardial perfusion in these patients.

We are all indebted to Dr. Mirhoseini for this early experimental work. Obviously, continued studies are necessary to define the role of TMLR in the care of these challenging patients.

Dr. Craig R. Smith (*New York, N.Y.*). We have had a remarkable relief of angina in a very small series of patients treated at Columbia Presbyterian recently with the carbon dioxide laser. We have a much longer experience trying to develop a percutaneous alternative with a holmium laser. Based on this experience, I will make two brief comments and ask one question.

Experimentally, we have looked at an isolated heart model that completely separates coronary perfusion from

ventricular blood and have been unable to show any quantitatively significant flow through these channels. This is at odds with our own experimental findings and those of Horvath, Cohn, and others, which have shown reversal of acute ischemia in laser regions. Second, after a fairly exhaustive look at many specimens with the carbon dioxide and the holmium lasers, we have been unable to find what we would describe as patent channels. I think what we do see is interesting. We see irregular endothelium-lined spaces occupying columns of intense neovascularity at the sites of channel formation, and I suggest that this may turn out to be a more accurate description of what was shown today. This is consistent with perhaps a more chronic mechanism and is also consistent with a more delayed improvement in scan findings, for example, but it is not consistent with the prompt relief of angina that is so often reported. That is another unresolved paradox.

In your autopsied specimens, how many out of the number of channels you know you have created have you identified and sectioned, and are the results consistent? I add my plea that the question of efficacy be answered in patients where this is used as sole therapy before we advocate widespread use as adjunctive therapy, because I think we still have a lot to learn.

Dr. Frazier. I think that your first allusion was to a different type of laser, using a different method; it therefore can be related only to the experimental animal in which it was used. I do not believe that you can draw any clinical conclusions about it one way or the other. It was a research experiment in which you were not able to show any perfusion. In that experiment, the laser approach was from the inside out, which is different from that of the TMLR. In our method, the use of a high-energy carbon dioxide laser is important to create effective channels. Although the energy is quite high, it causes little lateral damage. I believe that the character of the high-energy carbon dioxide laser delivered externally has clinical potential.

I think that neovascularization does occur and may play an important role in the improved perfusion we have demonstrated. I also think that the laser channels remain open. In fact, other experiments have shown them to be open, even in the dog, which is a poor model. I also believe that there are patients in whom these channels do not stay open. The channels were open in our patient who died at 3 months, however, and another patient of Dr. Mirhoseini's, who died at 3 years and in whom open channels were demonstrated. Nevertheless, their precise contribution to blood flow is unknown and is a fitting subject for future research. Clearly, patients with severe coronary artery disease will have a proliferation of sinusoidal lakes and may therefore be more likely to benefit from TMLR. Our goal now is to define the patient group that will benefit most from this procedure.

Dr. Hassan Najafi (*Chicago, Ill.*). With a measurable degree of skepticism, about a year ago I consented to have our institution, Rush-Presbyterian-St. Luke's, become involved in this project. Dr. Robert March, one of my younger associates, pursued this and during the ensuing many months performed the procedure in 22 patients.

I confine my brief remarks to the 15 patients who

underwent this procedure as their sole modality of treatment. These patients had had an average of two previous coronary bypass operations and some five or six percutaneous transluminal coronary angioplasties. They were in class IV, were not candidates for cardiac transplantation, and were mostly homebound. This operation was performed with no mortality, no complications, and a length of stay of 7 days. With the exception of one patient, who remains in class IV, the patients have had significant subjective improvement, which has been supported by conventional noninvasive studies showing improvement of perfusion to ischemic segments of the myocardium. I am no longer skeptical about this procedure. For a patient in class IV for whom there is no other operation or treatment and who wishes to have this operation performed, because it is a rather safe procedure, I think that it is a reasonable adjunct to our armamentarium for treatment of patients with coronary artery disease.

Dr. Rodney J. Landreneau (*Pittsburgh, Pa.*). I would like to state that I do not believe that this procedure should be considered as a primary means of achieving acute myocardial revascularization. We have evaluated the effect of TMLR on regional myocardial perfusion and regional wall motion function in the acute canine ischemic model. Radioactive microsphere distribution, myocardial pH, and local high-energy phosphate moiety concentrations were assessed in the left anterior descending distribution before and after control occlusion and after occlusion and TMLR. Sonomicrometric assessment of regional wall motion was also performed. Blood flow, tissue pH, high-energy phosphate concentrations, and ventricular wall motion were predictably disturbed after left anterior descending occlusion. TMLR resulted in no acute improvement in any of these parameters.

The physiologic data presented here support the idea that the benefit of TMLR results from augmenting regional collateral flow to the ischemic myocardium at risk by augmenting endocardial-myocardial sinusoidal connections and possibly by creating bridges across watershed regions within the myocardium. The effect obviously takes time to develop, as documented by the late improvement seen in this group. I wonder whether this group has looked at the possibility of further enhancement in collateral development in these regions in their laboratory, perhaps along the same line of delivery that Dr. Wayne Isom's group is looking at with angiogenic factors being locally instilled. We have a debt of gratitude to Drs. Sen, Beck, Vineberg, and Mirhoseini for their pioneering efforts in these areas of direct myocardial revascularization.

Dr. Frazier. We performed an animal experiment similar to that described by Dr. Landreneau, and we were unable to show short-term improvement in an exact canine model, but our long-term studies did show statistically significant improvement. Our results will be appearing in an upcoming issue of *Lasers in Medicine*, and I believe that they show the importance of similar animal studies. In the long run, however, I am not sure how seriously such studies can be taken, because the animals do not model the condition that we will be addressing clinically.

I appreciate Dr. Najafi's comments. The patient group in question is an extremely challenging one, and it demonstrates the feasibility of performing TMLR in very sick patients. Nevertheless, the degree of benefit must be clearly defined and studied, along with such fundamental issues as the number of laser channels that should be made in a given patient, the optimal energy level of the laser, and other important mechanical factors.

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