Measurement of Myocardial Blood Flow With Positron Emission Tomography Before and After Transmyocardial Laser Revascularization

Ornella Rimoldi, MD; Sharon M. Burns, MRCP; Stuart D. Rosen, MA, MD, MRCP, FESC; Trevor E. Wistow, MD; Peter M. Schofield, FRCP; Gordon Taylor, PhD; Paolo G. Camici, MD, FESC, FRCP

Background—Transmyocardial laser revascularization (TMLR) has been proposed for treatment of refractory angina. It has been hypothesized that transmural left ventricular channels created by laser improve myocardial blood flow (MBF) in the treated zones. We aimed to assess the effect of TMLR on MBF and coronary vasodilator reserve (CVR).

Methods and Results—We measured MBF by means of PET with 15O-labeled water in 7 patients with refractory angina, Canadian Cardiovascular Society (CCS) class 3.6±0.5, on 3 occasions: before and at 7.5±2.8 weeks (FU-1) and 34.6±4.7 weeks (FU-2) after TMLR performed with a synchronized, high-powered CO2 laser. In each study, MBF was measured at rest and during maximal intravenous dobutamine. CVR was computed as dobutamine divided by resting MBF. After TMLR, CCS class was 2.2±1.7 at FU-1 and 2.4±1 at FU-2 (P=0.04 versus pre-TMLR). Resting MBF in both lasered and nonlasered regions was unchanged after TMLR. Dobutamine MBF at baseline was 1.45±0.52 and 1.55±0.52 mL·min⁻¹·g⁻¹ in lasered and nonlasered regions, respectively (P=NS). At FU-1, dobutamine MBF in nonlasered regions had increased significantly to 1.89±0.82 mL·min⁻¹·g⁻¹ (P<0.05) and was higher than in lasered regions (1.51±0.61 mL·min⁻¹·g⁻¹; P<0.05 versus nonlasered). At FU-2, dobutamine MBF in nonlasered regions was still higher than in lasered regions (1.56±0.54 versus 1.21±0.44 mL·min⁻¹·g⁻¹; P<0.01). CVR was comparable in nonlasered and lasered regions at baseline and FU-1, whereas it was higher in nonlasered regions at FU-2 (1.86±0.67 versus 1.53±0.72 mL·min⁻¹·g⁻¹; P<0.05).

Conclusions—TMLR has been shown to reduce angina in severely diseased patients. The results of our study do not support the hypothesis that the symptomatic benefit of TMLR can be ascribed to improved myocardial perfusion or CVR in lasered areas. (Circulation. 1999;100[Suppl II]:II-134–II-138.)

Key Words: coronary disease ■ revascularization ■ laser ■ myocardium ■ blood flow ■ imaging

Transmyocardial laser revascularization (TMLR) is a new technology that is being increasingly used to treat patients with severe, limiting angina who are not amenable to conventional revascularization by CABG or PTCA. Mirhosseini and Cayton1 pioneered this procedure in 1981, and the first clinical case report was published in 1983.2 Despite recent reports of symptomatic improvement,3–6 the exact mechanism of action of TMLR still remains unclear. Three hypotheses have been put forward to explain the mechanism of action of TMLR: (1) the channels produced by the laser remain patent and blood flows up them from the endocardial surface during systole;7 (2) through neovascularization, production of laser channels stimulates angiogenesis and therefore new blood vessel formation8–10; and (3) through denervation, the laser treatment affects cardiac visceral afferent nerve fibers, causing a decreased perception of chest pain.11 In the third case, an effect on myocardial blood flow (MBF) would not necessarily be required.

To ascertain whether TMLR improves the blood supply to the myocardium, in the present study, we have measured absolute MBF at rest and during dobutamine infusion before and 2 and 8 months after TMLR using PET with 15O-labeled water (H215O).12

Methods

Study Population

Seven male patients (mean age, 60±10 years) were recruited from among the MRC-TMLR trial participants13,14 between November 1996 and January 1998. Inclusion criteria were refractory angina, coronary artery disease not amenable to conventional revascularization, and reversible ischemia demonstrable by 99mTc-MIBI perfusion scanning. Exclusion criteria were unstable angina, inability to perform a treadmill exercise test, left ventricular (LV) ejection fraction, and reversible ischemia demonstrable by 99mTc-MIBI perfusion scanning.
fraction (EF) <30%, and life expectancy of <12 months owing to a nondiagnostic cause, eg, malignancy. All patients had previously undergone CABG, 4 patients on 1 occasion and 3 patients on 2 occasions, and 2 patients had had previous PTCA. Patients 2, 3, 5, and 6 had evidence of >1 previous myocardial infarction (Table 1).

**Study Design**

Regional MBF was measured noninvasively by PET under resting conditions and during peak dobutamine stress on 3 occasions: at baseline (pre-TMLR), follow-up 1 (7.5±2.8 weeks after TMLR), and follow-up 2 (34.6±4.7 weeks after TMLR). Patient 2 declined to undergo the third PET scan. Angina class (Canadian Cardiovascular Society, CCS) was scored, and exercise tolerance was evaluated by a standard treadmill test with the use of the modified Bruce protocol. A 12-minute walk distance was also measured, and LVEF was measured by radionuclide ventriculography (RNV) at baseline and 1 year after TMLR.

**Positron Emission Tomography**

Scanning was performed with an ECAT 931–08/12, 15-slice tomograph giving a 10.5-cm field of view. MBF was measured with H$_{2}$O (700 to 900 MBq) injected intravenously over 20 seconds at an infusion rate of 10 mL/min as previously described.$^{12}$ MBF was measured at rest and during peak dobutamine stress. Dobutamine was infused intravenously with a pump starting at 5 µg·kg$^{-1}$·min$^{-1}$ and increasing by 5-µg·kg$^{-1}$·min$^{-1}$ increments every 3 minutes up to a maximum of 40 µg·kg$^{-1}$·min$^{-1}$ or until chest pain, ischemic ECG changes, or a fall in systolic pressure >20 mm Hg occurred. PET acquisition was timed to start when a steady state was achieved at the maximal dobutamine dose. Patients were asked to rate chest pain on a scale from 0 (no pain) to 10 (unbearable pain). Lead II of the ECG was continuously monitored. Arterial pressure (cuff sphygmomanometer) and a 12-lead ECG were recorded every minute throughout the dobutamine stress. Maximal cardiac work was estimated as heart rate times systolic arterial pressure product (RPP) at baseline and peak stress.

**PET Data Analysis**

Analysis was performed by an operator blinded to the myocardial areas that were lasered. Dynamic H$_{2}$O images were processed with filtered back projection with a Hanning filter (cutoff frequency, 0.5), resulting in an axial resolution of 6.6 mm and a transaxial image resolution of 8.5-mm full width at half-maximum (FWHM). The images were iteratively reconstructed and resliced along the short axis.$^{12}$ Regions of interest were defined on these images. They corresponded to anteroseptal, anterior, lateral, inferior, posterior, and posteroseptal walls of the LV in the apical, middle, and basal planes. The septal regions were delimited by the junction between the right and left ventricles, and the free wall was divided according to the 16-segment model recommended by the American Society of Echo-cardiography.$^{15}$ A separate set of regions of interest was defined for the right ventricular cavity and left atrium. Subsequently, time-activity curves were generated from the dynamic image and fitted to a single tissue compartment tracer kinetic model to give values of MBF as reported previously.$^{16}$ Coronary vasodilator reserve (CVR) was calculated as the ratio of peak dobutamine MBF to baseline MBF. Regions with documented previous myocardial infarct (scar) were excluded from analysis.

**Transmyocardial Laser Revascularization**

TMLR was performed as previously described$^{6}$ via a limited left lateral thoracotomy under general anesthesia. Transmural channels were created in LV segments with evidence of reversible ischemia on the baseline $^{99}$Tc-MIBI scan. A high-powered CO$_{2}$ laser (PLC Medical Systems Inc.) was placed directly on the myocardium and fired (39±4 J) in synchrony with diastole. The epicardial holes produced were ~1 mm in diameter and ~1 cm apart. Transmural full-thickness channels were confirmed by detection of turbulent flow with carotid Doppler. A mean of 35±10 laser channels per patient was created. The LV regions treated in each patient are summarized in Table 2. Hemostasis was achieved by epicardial digital pressure or purse-string suture, and the thoracotomy was closed in routine fashion.

The study protocol was approved by the ethical committees of Papworth and Hammersmith hospitals and by the UK Administration of Radioactive Substances Advisory Committee. Written informed consent was obtained for all patients.

**Statistical Analysis**

Data are reported as mean±SD. Within-subject comparisons were performed for MBF at rest, MBF during dobutamine, and CVR between both lasered and nonlasered regions for each of the 3 scans. Group analysis was performed to assess changes in MBF and CVR between lasered and nonlasered regions and with lasered and nonlasered regions for the 3 scans. This was done by repeated-measures ANOVA with the RPP as a covariate. Angina score, exercise tolerance, 12-minute walk, and LVEF data were assessed by Wilcoxon’s signed rank test.

**Results**

**Clinical Outcome**

At baseline, the angina score was 3.6±0.5 and LVEF was 44±7% (Table 2). Patients 2, 5, and 7 had resting ECG abnormalities. Exercise tolerance was 467±194 seconds (4.45±1.36 metabolic equivalents [METs]; RPP, 16 526±5869), and the 12-minute walk distance was 606±147 m. The angina score decreased to 2.2±1.7 at follow-up 1 and 2.4±1.0 at follow-up 2 (P=0.04) (Table 2).

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**TABLE 1. Baseline Demographics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initials No.</th>
<th>Age, y</th>
<th>Previous Revascularization</th>
<th>Concomitant Disease</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.R. 1</td>
<td>60</td>
<td>CABG 2 times, PTCA</td>
<td>...</td>
<td>Aspirin, atenolol, diltiazem, nicorandil, nitrates</td>
<td></td>
</tr>
<tr>
<td>R.F. 2</td>
<td>64</td>
<td>CABG</td>
<td>...</td>
<td>Aspirin, diltiazem, nicorandil, nitrates, omeprazole</td>
<td></td>
</tr>
<tr>
<td>B.O. 3</td>
<td>56</td>
<td>CABG 2 times, PTCA</td>
<td>Diabetes</td>
<td>Aspirin, amiodarone, diltiazem, captopril, furosemide, nicorandil, nitrates, simvastatin, ranitidine, digoxin, methadone, insulin</td>
<td></td>
</tr>
<tr>
<td>P.G. 4</td>
<td>40</td>
<td>CABG</td>
<td>Hypertension</td>
<td>Aspirin, atenolol, diltiazem, nicorandil, nitrates, simvastatin, omeprazole</td>
<td></td>
</tr>
<tr>
<td>R.W. 5</td>
<td>63</td>
<td>CABG</td>
<td>Diabetes</td>
<td>Aspirin, atenolol, diltiazem, captopril, nitrates, glibenclamide</td>
<td></td>
</tr>
<tr>
<td>J.S. 6</td>
<td>69</td>
<td>CABG</td>
<td>Hypertension, cerebrovascular disease</td>
<td>Aspirin, metoprolol, diltiazem, enalapril, furosemide, nicorandil, nitrates, simvastatin</td>
<td></td>
</tr>
<tr>
<td>E.T. 7</td>
<td>67</td>
<td>CABG 2 times</td>
<td>...</td>
<td>Aspirin, furosemide, nifedipine, simvastatin, amiloride, nitrates, captopril, omeprazole</td>
<td></td>
</tr>
</tbody>
</table>
At follow-up 2, there was no significant change from baseline in exercise tolerance (458 ± 6 145 seconds, 3.47 ± 0.103 METs; RPP, 14 787 ± 4045; P < 0.05 versus baseline) or in the 12-minute walk distance at 569 ± 238 m (P = NS versus baseline). LVEF at 1 year after TMLR was unchanged in 1 patient, decreased in 4 patients, and increased in 2 patients (Table 2).

PET Scanning

The symptomatic and hemodynamic responses to dobutamine and MBF measurements are summarized in Table 2. At baseline, the maximal tolerated dobutamine dose was 27.1 ± 9.5 μg · kg⁻¹ · min⁻¹ and did not change significantly at follow-ups 1 and 2 (P = NS versus baseline). The angina score during dobutamine infusion was slightly but not significantly reduced at follow-ups 1 and 2 compared with baseline. The rest and stress RPPs were comparable in the 3 studies. Individual flow data for each patient are illustrated in Figure 1, together with the CCS class at follow-up 2. No correlation existed between stress MBF in the lasered region and CCS class at follow-up 2. The mean values of MBF and CVR in lasered and nonlasered regions before and after TMLR are reported in Figure 2. At follow-up 1, dobutamine MBF in nonlasered regions (1.89 ± 0.82 mL · min⁻¹ · g⁻¹) was significantly higher compared with baseline (1.51 ± 0.61 mL · min⁻¹ · g⁻¹; P < 0.05). MBF in lasered regions was significantly lower compared with nonlasered regions at both follow-ups 1 and 2 (P < 0.05), and CVR was lower in lasered (1.53 ± 0.72) compared with nonlasered regions (1.86 ± 0.67) at follow-up 2.

Discussion

To the best of our knowledge, the present study is the first to provide quantitative measurements of MBF before and twice after TMLR in the same patients. Our results show that there

<table>
<thead>
<tr>
<th>Patient</th>
<th>LVEF at Baseline, %</th>
<th>LVEF at 1 y, %</th>
<th>LV Lasered Region</th>
<th>CCS Class</th>
<th>Maximum Tolerated Dobutamine Dose, μg · kg⁻¹ · min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>LVEF at 1 y, %</td>
<td>LVEF at 2 y, %</td>
<td></td>
<td>CCS Class</td>
<td></td>
</tr>
<tr>
<td>W.R.</td>
<td>50</td>
<td>42</td>
<td>Anterior, inferior lateral</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>R.F.</td>
<td>34</td>
<td>32</td>
<td>Apex</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>B.O.</td>
<td>41</td>
<td>53</td>
<td>Anterior, apex, lateral</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>P.G.</td>
<td>55</td>
<td>43</td>
<td>Apex, inferior lateral</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>R.W.</td>
<td>47</td>
<td>40</td>
<td>Anterior, apex</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>J.S.</td>
<td>38</td>
<td>46</td>
<td>Anterior, inferior</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>E.T.</td>
<td>46</td>
<td>26</td>
<td>Anterior, lateral</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>44 ± 7</td>
<td>40 ± 9</td>
<td></td>
<td>3.6 ± 0.5</td>
<td>2.2 ± 1.7</td>
</tr>
</tbody>
</table>

*Significantly different from baseline.
is no significant change in resting and dobutamine MBF or CVR in the myocardial regions that have been lasered. In addition, we found increased perfusion during dobutamine in remote nonlased myocardium. Therefore, the subjective improvement in angina score reported by patients cannot be ascribed to improved myocardial perfusion by either increased flow through patent channels or neovascularization.

To date, reports of improved myocardial perfusion have been based on semiquantitative evaluation by PET or \textsuperscript{99m}Tc-MIBI SPECT.\textsuperscript{3,5,6} Measurement of absolute MBF by PET with \textsuperscript{15}O is now recognized as the gold standard for noninvasive assessment of nutritive tissue perfusion, an integrated quantity that reflects flow through both large conductance vessels and the microcirculation, as well as diffusion to and from myocardial tissue.\textsuperscript{17} This technique permits noninvasive measurement of flow per unit mass and is highly reproducible.\textsuperscript{18} The low level of radiation involved permits noninvasive measurement of flow per unit mass and is highly reproducible.\textsuperscript{18} The low level of radiation involved and the noninvasive nature of the method have also permitted acquisition of normal data from healthy volunteers of different ages for comparison with data from patients.\textsuperscript{19}

In the context of the results of the present study, the most significant previous report is that by Frazier et al.\textsuperscript{3} In a wide-ranging assessment, including PET, RNV, SPECT, and stress echocardiographic investigation of their TMLR patients, Frazier and coworkers described an improvement in anginal status, relative endocardial perfusion, and cardiac function. PET with \textsuperscript{13}N-labeled ammonia was used to semiquantitatively assess MBF distribution at rest and during dipyridamole stress. The authors reported a 14% improvement over baseline in the ratio of resting subendocardial to subepicardial perfusion in laser treated regions 3 months after TMLR. At a 6-month follow-up, that ratio in lasered regions was improved over baseline by 21% at rest and by 37% during stress. However, it is worth noting that assessment of the transmural distribution of MBF in ventricles of normal thickness currently is not accurate.\textsuperscript{20} This is due mainly to the limited spatial resolution of most PET scanners,\textsuperscript{21} including the one used in the present study that had a much better spatial resolution (ie, 8.5-mm FWHM) than that used by Frazier et al (ie, 14-mm FWHM).\textsuperscript{3} This limitation is exacerbated by the absence of correction for heart movement (ie, gated acquisition). Therefore, we did not attempt to measure subendocardial and subepicardial MBF in our patients, and our results are therefore not comparable with those of Frazier et al.\textsuperscript{3} More recently, in agreement with the results of the present study, Krabatsch et al\textsuperscript{22} failed to detect any improvement in myocardial perfusion or LV contractility despite a significant relief of anginal symptoms.

In line with our results, the histological features of lasered human myocardium clearly demonstrate that the channels produced by the laser are no longer patent at the time of autopsy.\textsuperscript{23,24} Different stages of wound healing have been observed, and there is good evidence of scar tissue formation, together with new capillaries and venules. It can be objected that morphological studies were performed in human myocardium that did not respond to treatment. However, similar findings have been reported in canine models in which myocardial channels were not patent 2 months after treatment with TMLR.\textsuperscript{10,25,26} In animal models of acute infarction, TMLR-treated regions showed increased neovascularization around the channels.\textsuperscript{9,18} However, these findings could be the result of the combined effect of ischemia and laser providing a powerful stimulus for angiogenesis in an otherwise healthy myocardium.

Experimental evidence of denervation of the myocardium with holmium:YAG laser treatment suggested that interruption of the epicardial anatomic pathway for cardiac pain could be a possible mechanism for the angina relief\textsuperscript{31} reported in patients treated with TMLR.\textsuperscript{3–6} Although the holmium:YAG laser has a higher power density than the CO\textsubscript{2} laser, the general histological morphology of the myocardium is indistinguishable.\textsuperscript{27} We hypothesize that denervation of the LV, which has been shown to elicit denervation supersensitivity to catecholamines,\textsuperscript{28} could provide an explanation for our findings of different MBFs between nonlasered and lasered regions. In addition, the direct effects of dobutamine on \(\alpha\)-receptors of the vasculature can be unmasked and can lead to regional vasoconstriction. This could contribute to a “horizontal” steal of blood from lasered to nonlasered regions as previously reported in patients with coronary heart disease.\textsuperscript{29,30} Moreover, experimental evidence of a reduction in flow distribution to the endocardium during exercise in a denervated area of the LV subtended by a stenotic artery\textsuperscript{31} also needs to be considered. These mechanisms could be responsible for the worsening of the wall motion score index during dobutamine infusion after TMLR described by Frazier and coworkers.\textsuperscript{3}

<table>
<thead>
<tr>
<th>TABLE 2. Continued</th>
</tr>
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<tbody>
<tr>
<td>Maximum RPP, bpm · mm Hg(^{-1})</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>7722</td>
</tr>
<tr>
<td>16 328</td>
</tr>
<tr>
<td>18 860</td>
</tr>
<tr>
<td>13 530</td>
</tr>
<tr>
<td>11 400</td>
</tr>
<tr>
<td>8176</td>
</tr>
<tr>
<td>12 210</td>
</tr>
<tr>
<td>12 604±3776</td>
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</tbody>
</table>
II-138 Circulation November 9, 1999

Study Limitations
Several important limitations hamper the conclusions that can be derived from the present study. First, the number of patients studied is very limited. However, this limitation is partially overcome by the fact that each patient has been studied at 3 different time points before and after TMLR; therefore, each patient serves as his own control. A second limitation might derive from the nonexact anatomic matching between the areas treated by TMLR and the regions of interest of the PET images from which MBF was computed. In this regard, however, it is worth noting that the lasered regions were large, corresponded to the territory of distribution of ≥1 of the 3 major coronary arteries, and therefore were easily identifiable on the PET image. Finally, it was beyond the scope of this study to test the antianginal efficacy of TMLR, which has been assessed in other specifically designed studies.6,14,22

References
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