Physiology, Histology, and 2-Week Morphology of Acute Transmyocardial Channels Made With a CO₂ Laser

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Background. Transmyocardial revascularization with a CO₂ laser appears to improve symptoms in patients with refractory angina. However, it remains controversial as to whether blood flow through the channels is the mechanism of benefit, especially in the acute setting.

Methods and Results. Three protocols were used to test whether blood flows through transmyocardial CO₂ laser revascularization channels. First, channels were made in excised, cross-perfused dog hearts (n = 5) using a CO₂ laser (The Heart Laser; PLC Systems Inc, Milford, MA; 40 J/pulse) followed by ligation of the proximal left anterior descending coronary artery. Colored microspheres injected into the left ventricular chamber failed to detect any significant transmyocardial blood flow. In the second protocol (n = 4), laser channels were created in the left anterior descending artery territory, the left anterior descending artery was ligated, and the hearts were excised after 24 hours. Triphenyltetrazolium chloride staining revealed that no viable myocardium was detected around the laser channels in the ischemic myocardium. Finally, channels examined 2 weeks after creation in normal (n = 6) or ischemic (n = 4) myocardium did not maintain their original caliber but were invaded by granulation tissue, which included a large amount of smaller vascular spaces and vessels of various sizes.

Conclusions. Transmyocardial laser revascularization channels made with this CO₂ laser did not provide acute myocardial perfusion or preserve myocardial viability in the face of acute ischemia. Channel morphology changes dramatically within the first 2 weeks. To the degree that these findings pertain to human myocardium, the results suggest that transmyocardial blood flow may not be the mechanism of benefit of this procedure, particularly in the acute setting.

myocardium was examined. The results show that in canine myocardium, there is no detectable myocardial perfusion through acute CO2 TMLR channels and that the fate of these channels is to be invaded by granulation tissue within 2 weeks of creation in either normal or infarcting myocardium. The limitations and potential clinical implications of these findings are discussed.

Material and Methods
All animals were cared for by a veterinarian in accordance with the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research and the “Guide for the Care and Use of Laboratory Animals” prepared by the National Academy of Sciences (NIH publication 85-23, revised 1985).

Acute Isolated Heart Study
Laser channels were created in hearts of 5 mongrel dogs (24 to 28 kg) and then studied after being isolated and cross-perfused by blood circulating from a second support dog [10]. The support dog (ie, the animal not subjected to TMLR) was anesthetized (pentobarbital sodium, 30 mg/kg intravenously), heparinized (5,000 U intravenous bolus), intubated, and mechanically ventilated. The carotid artery was cannulated to monitor arterial blood pressure. Both femoral arteries and veins were cannulated and connected to a perfusion system used to supply oxygenated blood to the isolated heart (Fig 1). Total flow to the isolated heart was regulated by a peristaltic pump. An in-line flow probe (Transonic Systems Inc, Ithaca, NY) was used to measure total coronary flow (discussed further below).

The heart donor dog was also anesthetized (pentobarbital sodium, 30 mg/kg intravenously) and mechanically ventilated, and a left thoracotomy was performed. Transmyocardial laser revascularization channels were created over the anteroapical region of the heart (-1/cm², 11 to 13 channels/heart) using the CO2 laser that is currently being tested in clinical studies (The Heart Laser). The system was set to deliver 40 J/pulse (the average energy being used in clinical trials). Confirmation of channel creation was obtained by noting the occurrence of bright red (oxygenated) blood pumping vigorously during systole from the ventricular chamber, which was observed in 93% of the laser pulses, a criterion that was validated by directly visualizing endocardial penetration at the end of the experiment. A shallow epicardial stitch (5-0 polypropylene) was used if a channel did not stop bleeding spontaneously within 2 minutes.

After TMLR, and with the heart still in situ, the LAD was dissected just distal to the first diagonal branch and a piece of 3-0 silk was passed around the vessel. All visible epicardial collaterals were ligated with a 5-0 stitch to minimize collateral flow to the distal LAD territory. Thirty minutes after creation of the channels, a median sternotomy was performed, the dog was anticoagulated with heparin (5,000 U bolus, intravenously), the proximal aorta was cannulated and the heart was arrested by infusion of cardioplegia (University of Wisconsin solution; 4°C) in the standard manner. The pulmonary hila were ligated and the heart was explanted and submerged in University of Wisconsin solution while the coronary arteries (right, circumflex, and left anterior descending) were individually cannulated with 8F pediatric arterial cannulas. The aortic valve cusps were sutured closed using a running stitch (6-0 polypropylene suture). The coronary artery cannulas were connected to the arterial line of the perfusion apparatus, and coronary perfusion with normothermic blood was begun. The total ischemic time averaged 30 minutes. Hearts subsequently beat spontaneously at rates that ranged between 90 and 118 beats per minute and averaged (± standard deviation) 102 ± 11 beats per minute.

To control the LV volume and pressure, we introduced a large-bore cannula (28F) connected to a reservoir into the LV chamber via the left atrial appendage (see Fig 1). In addition, a thin cannula (3 to 4 mm outer diameter) with side holes was placed through the LV apex; this was used to drain blood from the LV when desired (discussed below). We then ligated the LAD by tying the previously placed 3-0 silk and allowed the heart to stabilize for 20 minutes.

Separation of the normal coronary circulation and transmyocardial blood flow was possible in this prepara-
tion because the coronary arteries were perfused directly and the aortic valve was sutured closed. Coronary perfusion pressure was therefore controllable independent of LV pressure generation through regulation of blood flow from the support dog by adjusting the speed of the peristaltic pump of the perfusion system (see Fig 1). Coronary perfusion pressure was set at a mean value of 80 to 100 mm Hg. Left ventricular pressure generation was regulated by varying the amount of blood within the ventricular chamber and the height of the reservoir connected to the large-bore cannula within the LV chamber (discussed further below).

Colored microspheres (15 μm diameter; \( \sim 3 \times 10^6 \) microspheres/mL in a saline suspension with 0.01% Tween 80 and thimerosal; Dye-Trak; Triton Technology, Inc, San Diego, CA) were used to estimate regional coronary artery flow and to detect blood flow through the channels. In each experiment, injections of four different colored microspheres (white, yellow, red, and blue) were used to measure regional blood flows under four different conditions; the colors were chosen in random order in each experiment. Regional blood flow from the normal coronary vasculature was determined at the start of the protocol by injecting 0.2 mL of the first colored microspheres into the coronary arterial perfusion line. The microsphere solution was mixed thoroughly using a vortex before being drawn into a 1-mL syringe and was injected rapidly into the perfusion line approximately 25 cm from the heart. Next, microspheres were injected into blood placed within the LV chamber under two different loading conditions. One condition was a low loading condition in which peak LV pressure generation was approximately 20 mm Hg, and the other was a high loading condition in which peak LV pressure generation ranging between 100 and 120 mm Hg. For each condition, 0.5 mL of the mixed microspheres were injected every 2 minutes for 10 minutes (total of 2.5 mL with an approximate total microsphere dose of 7.5 \( \times 10^8 \)). If appreciable myocardial perfusion can be achieved via CO\(_2\) TMLR channels then, as suggested by some investigators [1, 2], perfusion should be greater at the high load as compared with the low load. At the end of each 2-minute period, a 1-mL sample of LV blood was obtained (for determination of microsphere concentration), the LV was quickly drained through the apical vent and then refilled with the same amount of blood, and the next injection was performed. After performance of the intraventricular injections at both loading conditions, a final set of microspheres (0.2 mL) was injected into the coronary artery to measure the collateral blood flow.

The period of cross perfusion lasted about 1 hour: 30 minutes for surgical preparation and about 30 minutes for the experimental protocol. At the end of the experiment, the heart was removed from the perfusion system and cut into small (~1 g) samples from the LAD/laser channel region and from the left circumflex region.

**Microspheres Analysis**

Retrieval and quantitative analysis of the microspheres were performed as described previously [9, 11]. In brief, tissue samples were digested and the spheres were retrieved by filtration of the digestate. The dye on the microspheres was then itself digested into solution using dimethylformamide, and the photometric absorption of the resulting sample was measured by a diode array spectrophotometer (model 8452A; Hewlett-Packard Co, Palo Alto, CA). The composite spectrum of each dye solution was resolved at the peak frequencies into the contributions from the individual colored spheres using a matrix inversion technique [11]. The number of spheres in each sample was calculated according to the absorbance of each dye color using standardization curves generated from known quantities of spheres from the same batch.

Regional blood flow (RBF) from the coronary circulation was calculated by a standard technique modified for the direct coronary injection of the microspheres [12]:

\[
\text{RBF} = \frac{\text{CBF}_{\text{total}} \cdot N}{N_{\text{total}}}
\]

where \( \text{CBF}_{\text{total}} \) is the total coronary blood flow measured from the in-line flow probe, \( N \) is the number of microspheres per gram of tissue detected in the sample, and \( N_{\text{total}} \) is the total number of microspheres injected into the coronary perfusion line. Regional myocardial perfusion directly from the LV chamber through the laser channels was indexed by the number of appropriately colored microspheres per gram of tissue detected in the laser-treated region as compared with the number of spheres of the same color in the non-laser-treated region. No attempt was made in the present study to quantify the absolute amount of flow through the channels (for reasons that will become clear).

**Assessment of Myocardial Viability Surrounding CO\(_2\) TMLR Channels 24 Hours After LAD Ligation**

The goal of the protocol described above was to obtain direct evidence of myocardial perfusion through CO\(_2\) TMLR channels. Because, as will be discussed below, there are potential limitations of using the isolated heart preparation for this purpose, we sought corroborating evidence of blood flow through TMLR channels. Thus, the second protocol was designed to address the same question using a completely different experimental paradigm. The rationale behind this protocol is that if CO\(_2\) TMLR channels provide any physiologically meaningful amount of myocardial perfusion, then they should be able to preserve myocardial viability in the face of a sudden decrease in coronary blood flow, at least in the immediate vicinity of the laser channels.

Four dogs were sedated with midazolam (0.1 mg/kg) and anesthesia induced with an intravenous bolus injection of thiopental (7 to 10 mg/kg). Anesthesia was maintained by 1.0% to 2.0% inhaled isoflurane. A left thoracotomy was performed and the pericardium was opened. Carbon dioxide TMLR channels were made with a density of 1/cm\(^2\) (an average of 10 channels/heart) in the territory supplied by the LAD after the takeoff of the first diagonal branch. Three additional TMLR channels were created in the circumflex territory to obtain histologic samples of channels made in normal myocardium. As described above, penetration of the channel through the entire myocardial wall was confirmed by vigorous pump-
ing of blood, which was observed in 93% of the laser bursts; 92% of these channels required a shallow epicardial stitch. The LAD and all visible epicardial collaterals to this territory were ligated. The thoracotomy was closed and the animal recovered from anesthesia. Twenty-four hours after the operation, the animal was euthanized with a lethal injection of pentobarbital and the heart was excised.

The portions of the LV containing the laser channels were identified. The ischemic-channel region and the control-channel region were separated and the myocardium was sliced into three layers (ie, epicardial outer third, endocardial inner third, and middle third). The middle layers were stained with triphenyltetrazolium chloride to identify viable myocardium. The epicardial and the endocardial layers were fixed overnight in 10% neutral-buffered formalin before dehydration and paraffin embedding. Four-micrometer sections were stained with hematoxylin and eosin and with trichrome and examined microscopically.

**Histologic Appearance of CO₂ TMLR Channels 2 Weeks After Creation in Normal and Infarcting Myocardium**

To test the long-term morphology of the CO₂ channels, we treated a total of 10 dogs with the CO₂ laser using surgical and laser procedures identical to those described above for the 24-hour study. An average of 17 channels (~1/cm²) were made over the distal LAD distribution as described above. In 4 of the animals, the LAD was dissected and ligated (3-0 silk) just distal to the first diagonal branch; no LAD ligation was performed in the remaining 6 animals. The chest was closed and the dogs were allowed to recover. Two weeks after the operation the animals were anesthetized and the hearts explanted as described above; all animals survived until the time of sacrifice. Channel locations could be identified easily in noninfarcted animals from small epicardial scars at the original point of entry of the laser energy into the myocardium. Identification of channels in the infarcted animals was difficult due to infarct contraction and scar formation. Transmural blocks of tissue were cut from the ventricular wall with each block containing, when possible, a single channel region. These samples were prepared for microscopic examination as detailed above.

**Statistical Analysis**

All data are presented as mean ± standard deviation. The statistical significance between multiple groups was determined by analysis of variance. In all cases, a p value less than 0.05 was considered significant.

**Results**

**TMLR Channels Made With the CO₂ Laser Do Not Provide Significant Myocardial Perfusion in the Acute Setting as Assessed by Microspheres**

The microscopic appearance of a typical acute channel made with the CO₂ laser in normal canine myocardium, shown in Figure 2 (hematoxylin and eosin stained), reveals an elliptical channel lumen measuring approximately 850 × 1100 µm in diameter with an elliptical zone of thermal damage with thickness measuring approximately 250 µm in the cross-fiber direction and 1,150 µm in the fiber direction.

Photometric absorbance spectra of samples retrieved from myocardium in the circumflex region (Fig 2A) and the LAD laser-treated region (Fig 3B) of the same heart studied in the isolated heart protocol are shown in Figure 3 (note the change in y-axis scale between the two panels). The spectrum from the circumflex sample shows two prominent peaks, which correspond to the wavelengths of the yellow and blue spheres that were injected into the coronary arteries; no discernible peaks were detected in this sample at the wavelengths corresponding to the white and red spheres applied within the LV, indicating that there is no significant nonspecific penetration of blood into the myocardium in non-laser-treated regions. In the spectrum obtained from myocardium of the LAD territory, reduced peak heights at the yellow and blue wavelengths demonstrated that residual coronary flow into the region was markedly reduced to less than 10% of that in the normal region. However, this spectrum also did not show any peaks at wavelengths that would have corresponded to the white or red microspheres injected into the LV chamber. This suggests that in this example there was no significant blood flow from the LV chamber into the myocardium through the laser channels.

The results from all 5 acute hearts studied in this protocol are presented in Table 1 (which summarizes coronary flow) and Table 2 (which summarizes findings pertaining to flow through the channels). Regional blood flow in the circumflex region averaged 1.68 ± 0.80 mL/min at the beginning and 1.64 ± 0.95 mL/min at the end of the experiment. In the laser-treated LAD territory, total regional coronary blood flow, presumably due to collateral blood flow, was reduced to an average of ~7% of normal, which confirmed that the amount of blood
A. LCx Territory

B. LAD/Channel Territory

Fig 3. Typical spectra from an acute isolated heart study in which yellow and blue spheres were injected into coronary arteries and white and red spheres were injected into the left ventricular cavity. (A) Spectrum from circumflex (LCx) territory revealing no detectable flow from the chamber. (B) Spectrum from the left anterior descending artery (LAD) territory, which was rendered ischemic and in which channels were created. This spectrum reveals a marked reduction in direct coronary flow (by comparison of yellow and blue peaks with those in panel A) but no extra spikes corresponding to red and white spheres, suggesting no perfusion from the chamber.

supplied to these regions from the normal coronary circulation was markedly reduced. Furthermore, the magnitude of this collateral blood flow was similar in the epicardial and endocardial regions of the ventricular wall. Also, the amount of collateral blood flow into this region did not vary significantly from the beginning to the end of the experiment (see Table 1), suggesting that on average the preparations were stable throughout the experimental period.

Table 1. Coronary Collateral Blood Flow (mL • g⁻¹ • min⁻¹)

<table>
<thead>
<tr>
<th>Region</th>
<th>Time of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD with channels (epicardium)</td>
<td></td>
</tr>
<tr>
<td>Start of Experiment</td>
<td>0.10 ± 0.09</td>
</tr>
<tr>
<td>End of Experiment</td>
<td>0.11 ± 0.08</td>
</tr>
<tr>
<td>LAD with channels (endocardium)</td>
<td></td>
</tr>
<tr>
<td>Start of Experiment</td>
<td>0.10 ± 0.05</td>
</tr>
<tr>
<td>End of Experiment</td>
<td>0.13 ± 0.05</td>
</tr>
<tr>
<td>LCx without channels</td>
<td></td>
</tr>
<tr>
<td>Start of Experiment</td>
<td>1.68 ± 0.80</td>
</tr>
<tr>
<td>End of Experiment</td>
<td>1.64 ± 0.95</td>
</tr>
</tbody>
</table>

Table 2. Myocardial Perfusion Through Transmyocardial Laser Revascularization Channels (no. of microspheres per gram of tissue)

<table>
<thead>
<tr>
<th>Region</th>
<th>LV Loading Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD with channels (epicardium)</td>
<td></td>
</tr>
<tr>
<td>Low (20 mm Hg)</td>
<td>182.6 ± 145.7</td>
</tr>
<tr>
<td>High (120 mm Hg)</td>
<td>443.3 ± 286.4</td>
</tr>
<tr>
<td>LAD with channels (endocardium)</td>
<td></td>
</tr>
<tr>
<td>Low (20 mm Hg)</td>
<td>308.3 ± 281.1</td>
</tr>
<tr>
<td>High (120 mm Hg)</td>
<td>513.8 ± 290.1</td>
</tr>
<tr>
<td>LCx without channels</td>
<td></td>
</tr>
<tr>
<td>Low (20 mm Hg)</td>
<td>272.2 ± 162.3</td>
</tr>
<tr>
<td>High (120 mm Hg)</td>
<td>346.6 ± 298.8</td>
</tr>
</tbody>
</table>

There was a trend for the number of micropheres per gram of myocardium derived from blood within the LV chamber to be greater in the endocardial than epicardial region of the laser-treated area and to be less in the circumflex area; however, there was no statistically significant difference in sphere densities among these three regions and the absolute value of these differences was small. There was also a trend for sphere density to be greater when intraventricular pressure was high (120 mm Hg) as compared with when it was low (20 mm Hg), although this did not reach statistical significance either. These findings indicate that on average there was no significant myocardial perfusion through the TMLR channels from the LV chamber into the myocardium.

Myocardial Viability Was Not Preserved Around CO₂ TMLR Channels 24 Hours After LAD Ligation

A total of 40 channels were made within the distal LAD territory of the hearts of the 4 dogs that were sacrificed 24 hours after the initial operation. Of these channels, 30 were identified as being within the ischemic zone, whereas the remaining 10 were in border zone areas between normal and infarcted tissue. All of these 30 channels were identified macroscopically and were examined after triphenyltetrazolium chloride staining. These channels were also examined histologically. The channels were all patent and maintained connection with the LV chamber as was evident upon gross inspection of the endocardium.

Triphenyltetrazolium chloride staining of channels made in normal myocardium (Fig 4A) revealed a thin layer of necrosis immediately around each channel (due to the initial thermal damage). However, the myocardium surrounding this thin layer of necrosis stained normally (ie, it was viable myocardium). This thin layer of thermal necrosis was confirmed by the blue staining surrounding the channel observed with trichrome stains (Fig 5A) (note the normally staining red myocytes beyond the thin layer of necrosis surrounding the channel). In contrast, triphenyltetrazolium chloride staining of tissue surrounding channels in the ischemic zone was totally white (Fig 4B), indicating the lack of any viable myocardium around channels in this region. This was again
confirmed on microscopic sections stained with tri-chrome, which failed to show any viable myocytes within the region (Fig 5B).

CO₂ TMLR Channels Undergo Significant Morphologic Changes After 2 Weeks

Epicardial scars were identified at the original laser entry sites in hearts of the 6 animals that underwent TMLR but in which the LAD was not ligated. In addition, as noted in the Material and Methods section, most of the channels had shallow epicardial stitches, which reliably identified their location. When the LV chamber was opened, small elliptical endocardial scars were identified, which likely represented the original entry point of the laser channel into the cavity. There were no channel entry points that appeared macroscopically to represent an opening of a channel into the myocardium. A typical example, shown in Figure 6A, reveals that the original channel region is invaded with granulation tissue containing lacunar spaces filled with fibrin; these spaces are endothelialized in most cases and contained red blood cells. The largest of these lacunar spaces measured approximately 50 μm in diameter. These regions also typically contained many capillaries in their centers.

In tissue examined 2 weeks after laser treatment with simultaneous LAD ligation, many channels were obscured by the massive healing response incited by the infarction. For this reason, no definitive channels were identified within the actively healing myocardium of these infarcting regions. Furthermore, as would be ex-
Fig 6. (A) Microscopic appearance (trichrome stain) of a chronic (2-week) transmyocardial CO_2 laser revascularization channel made in normal myocardium. The original channel region is replaced by an evolving scar with fibrosis surrounding lacunar spaces and well-formed capillaries. Surrounding myocardium appears normal. (B) Similarly stained tissue from the infarct zone at 2 weeks showing a channel remnant (center) surrounded by totally necrotic myocardium (blue).

expected from the results obtained after only 24 hours, there was no viable myocardium identified around areas in which channels were identified. An example, taken from infarcting myocardium not yet overwhelmed by the granulation tissue response to the infarct, is shown in Figure 6B. Here, a channel remnant is seen surrounded by totally necrotic myocardium. No organization of this channel, which is in a central portion of the infarct, distant from the advancing front of granulation tissue, is yet seen.

Comment
The results of this study demonstrate that in normal canine myocardium, there is no detectable acute blood flow through TMLR channels made with a CO_2 laser. This conclusion is derived from two independent experimental preparations. First was an isolated cross-perfused heart in which the aortic valve remained shut so that blood flow through channels could be detected using colored microspheres placed within the ventricular chamber. These microspheres failed to appear in the myocardium with a greater density than in the non-laser-treated circumflex region, even when ventricular pressure was allowed to reach 120 mm Hg. Second, we examined, on both macroscopic and microscopic scales, myocyte viability around the channels in a region deprived of normal coronary blood flow for 24 hours. On a macroscopic scale, the finding of no viable myocardium around the channels despite widely patent channels at this time point suggests that net myocardial perfusion is less than 20% of normal, because this is approximately the lower limit of blood flow required to maintain cell viability. However, the microscopic finding of no viable myocardium (not even a single cell layer) suggests that there is no blood flow through the channels, because any steady supply of oxygenated blood would be expected to provide sufficient nutrients for a few layers of myocytes. Finally, it was observed that these CO_2 myocardial channels undergo a significant morphologic change within 2 weeks, as they are invaded with granulation tissue, which often contains endothelial-lined lacunar spaces (often as large as 50 μm in diameter) and capillaries.

The results of the present study are consistent with those of some previous studies, which concluded that no significant blood flows through TMLR channels [7-9, 13]. In one study, TMLR channels made with a holmium:yttrium-aluminum garnet laser failed to preserve myocardial viability around the channels after a 6-hour LAD ligation [13]. Two other studies, which employed different types of CO_2 lasers, failed to demonstrate any acute increase in myocardial perfusion due to TMLR channels [7, 8]. A previous study from our laboratory, using a similar isolated heart preparation, showed that although blood flow through holmium:yttrium-aluminum garnet channels was detectable by colored microsphere analysis, its magnitude was so small that it could not have contributed in a physiologically meaningful way to myocardial perfusion. Finally, one group of investigators reasoned from studies of the physiology of blood flow within the myocardium that blood flow through transmyocardial channels (made with needles in this case) is a physical impossibility; the same arguments would apply to transmyocardial channels made by any means [14]. However, because the clinically used CO_2 laser was not used in these previous studies, their relevance to the clinical setting has been questioned.

In contrast, results of several studies suggest that the presence of TMLR channels confers a physiologic benefit in the setting of acute and chronic ischemia [15-17]. The most recent of these, a study by Horvath and colleagues [17] conducted in sheep, showed that contractile function was better preserved in ischemic areas treated with the CO_2 laser than in nontreated regions, or even myocardium reperfused after 60 minutes of ischemia; however, this study did not examine whether this myocardium would remain alive 24 hours after the LAD occlusion. Histologic results presented in that same study were interpreted as providing evidence of channel patency 30
days after creation. The reason for the discrepancy between these findings and those of the present study is uncertain. Differences in experimental models employed (dog versus sheep) may be one factor. However, because the physical factors governing the dynamics of myocardial perfusion through TMLR channels should be the same across species (including human myocardium) this may not be the only explanation.

Recently Whittaker and associates [18] created TMLR channels in rat myocardium and demonstrated that these channels were patent (although with a caliber significantly decreased from the acute setting) 2 months after creation. They ligated the LAD to make the laser-treated region ischemic and injected particulate pigment into the femoral vein. The pigments were histologically found in the laser channels but at a very low frequency (1 particle per slide); in contrast, the nonischemic region was heavily stained by the pigment. Therefore, if regional perfusion in other species without extensive collaterals. Finally, normal coronary flow, which is similar to collateral flow in other species (including human myocardium) this may not be the only explanation.

Additionally, we have examined flow potential and histology only in acute (within 24 hours) and subacute (up to 2 weeks) settings. Although clinical experience is related more to the setting of chronic ischemia and long-term relief of angina, understanding gleaned from the current studies provides information that is potentially vital to clinical understanding of the procedure in several respects. First, angina relief follows quickly after the operation, with patients typically leaving the hospital with much less or no angina [5, 19]. Second, preliminary (unpublished) clinical experience reveals relatively high perioperative mortality and morbidity in patients with unstable angina. Third, this perioperative morbidity is mostly related to myocardial infarction. These and other factors render it imperative, at least as a first step, to understand the acute blood flow potential through TMLR channels. Results of recent studies in rats suggest that over longer time periods (3 months), TMLR channels confer a statistically significant (though physiologically small) benefit in terms of myocardial protection in the face of acute LAD ligation [18], which is not apparent in the acute setting. It is not established whether this benefit is mediated by increased blood flow, whether the source of blood flow is via collateral flow or via direct perfusion from the chamber, or whether this benefit could be observed in hearts of larger animals. Nevertheless, these important recent findings suggest that the physiology of acute and chronic channels may differ, a notion that needs to be investigated thoroughly.

Results of initial clinical studies indicate that in patients with medically refractory angina who cannot be treated with either coronary artery bypass grafting or percutaneous transluminal coronary angioplasty there is an average two-class reduction in angina 3 months after TMLR treatment [5, 6, 19]. Furthermore, this benefit is sustained and has not shown any trend to diminish over time periods up to a year. Results of positron emission tomography [5] and sestamibi [6] scanning studies have indicated that myocardial perfusion is improved in treated areas 3 to 6 months after the operation. On a quantitative basis, the positron emission tomographic studies have indicated a statistically significant increase in the ratio between endocardial and epicardial myocardial perfusion (14% at 3 months and 21% at 6 months).

However, the methods employed did not permit assessment of whether the increased perfusion is due to blood flow through patent channels or whether a different mechanism, such as stimulation of angiogenesis, is responsible. Furthermore, the degree to which channels remain patent is controversial from histologic examinations of autopsy specimens obtained at different time points [1, 3, 20].

Experimental studies, such as described in the present report, address issues of mechanism of action and do not address issues of clinical effectiveness. Therefore, the negative findings of lack of acute channel blood flow and morphologic change at 2 weeks do not in any way suggest lack of clinical efficacy to treat angina; the results of the clinical studies stand on their own merit independent of the mechanism(s) of action. Furthermore, as reviewed above, there is always the question of whether experimental conditions adequately mimic clinical conditions, a situation that raises questions about the relevance of the experimental results. However, it is important that the mechanism of clinical benefit of TMLR be elucidated. Such information may be useful for devising means of identifying patients most likely to benefit from the procedure. Furthermore, questions related to optimizing laser firing parameters, choosing the best laser,
and whether other energy sources (eg, radiofrequency or ultrasound devices or simpler needle systems) will provide equal clinical benefit can only be addressed once the mechanism of benefit is defined. This will likely require further studies in both the clinical and basic science arenas. To the degree that the present studies pertain to the clinical setting, the results suggest that mechanisms other than blood flow through TMLR channels should be considered in future studies.

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References