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Long- and Short-Term Effects of Transmyocardial Laser Revascularization in Acute Myocardial Ischemia

Kamuran A. Kadipasaoglu, PhD,* Seckin Pehlivanoglu, MD, Jeff L. Conger, BS, Eisaku Sasaki, MD, Diego H. de Villalobos, MD, Michael Cloy, Vitaly Piluiko, MD, Fred J. Clubb, Jr., DVM, PhD, Denton A. Cooley, MD, and O. Howard Frazier, MD

Cardiovascular Research Laboratory, Texas Heart Institute, Houston, 77030

Background and Objective: **This study examined the effect of transmyocardial laser revascularization (TMLR) on infarct size and global and regional left ventricular (LV) function.**
Study Design/Materials and Methods: **Acute ischemia was induced in 24 dogs by ligating the left anterior descending artery. TMLR was done through a left thoracotomy in 12 dogs. The 12 control dogs had ligation only. Global and regional LV function were measured before ligation, then at 6 hours or 3 months after ligation. We calculated the volumetric ratio of damaged myocardium to myocardium at risk (V_d/V_r).**
Results: **At 6 hours, global compensation despite regional dyskinesia was universal; V_d/V_r was the same in control and TMLR dogs. At 3 months, global function during stress was significantly higher in TMLR dogs than in control dogs ($P < .05$); regional contractions were synergic only in TMLR dogs; mean V_d/V_r was significantly lower in TMLR dogs.**
Conclusion: **TMLR limits infarct expansion and improves long-term global and regional function after acute ischemia. Lasers Surg Med 20:6–14, 1997.** **© 1997 Wiley-Liss, Inc.**

Key words: myocardial perfusion; CO_2 laser; left ventricular function; transmyocardial laser revascularization

INTRODUCTION

In the late 1970s and early 1980s, Mirhoseini et al. [1,2] reported the first experimental use of laser energy to create transmyocardial channels. In 1983, the same group of investigators reported the first clinical use of transmyocardial laser revascularization (TMLR) on a cardioplegically arrested heart [3]. Subsequent improvements in the technology allowed for these channels to be created in the beating heart with a single, high-energy laser pulse fired during the late diastolic period of the cardiac cycle [4]. The efficacy of TMLR, however, has been questioned, because recent experiments have failed to show improvement in myocardial perfusion or the presence of patent channels after the procedure [5–8]. The variety of experimental models and laser parameters used in these studies has made comparing results difficult.

In this study, we used an 800-watt CO_2 laser to create transmyocardial channels with a single, high-energy pulse in the contracting myocardium of dogs with acute myocardial ischemia. Specifically, we studied the effect of TMLR on the global and regional function of the left ventricle (LV) and on the viability of the LV at 6 hours and at 3 months after occlusion of the left anterior descending coronary artery (LAD).

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*Correspondence to: Kamuran A. Kadipasaoglu, Texas Heart Institute, MC 1-268, 1101 Bates Street, Houston, TX 77030.

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MATERIALS AND METHODS

All procedures used in this study were approved by the Institutional Animal Care and Use Committee at the Texas Heart Institute (Houston), and animals were maintained in accordance with guidelines of the Guide for Care and Use of Laboratory Animals (Department of Health and Human Services publication, NIH, No. 83-23, revised 1985).

Study Design

Mongrel dogs (n = 24) were randomly assigned to experimental (n = 6) or control (n = 6) acute groups (studied 6 hours after initial protocol) or to experimental (n = 6) or control (n = 6) chronic groups (studied 3 months after initial protocol). TMLR was done through a left thoracotomy in the 12 experimental group dogs. The LAD was ligated to induce acute myocardial ischemia. Control dogs (n = 12) received ligation only. Hemodynamic measurements were made before ligation and after a waiting period of 6 hours (acute groups) or 3 months (chronic groups) after ligation. After the waiting period, hemodynamic measurements were taken before and after stressing the heart with an infusion of saline.

Surgical Technique

Animals were given a single dose of cephalothin sodium (20 mg/kg, intramuscularly). Thiopental was administered intravenously (5–15 mg/kg), and anesthesia was maintained with isoflurane (1–3%) with oxygen. A 10 cm × 10 cm area over the lumbosacral junction was clipped, and morphine sulfate (0.1 mg/kg) was administered through a 20-French epidural catheter for analgesia. Nasal body temperature was maintained at 37–38°C with a warming blanket. Electrodes were used to monitor the electrocardiogram.

A polyethylene catheter was inserted into the left carotid artery for monitoring arterial pressure. A quadruple lumen thermodilution catheter was inserted into the left external jugular vein and advanced distally into the pulmonary artery for monitoring cardiac output, pulmonary artery pressure, and pulmonary capillary wedge pressure. A transducer-tipped pressure catheter (Millar Instruments, Houston, TX) was inserted into the left femoral artery and advanced retrograde in the aorta and across the aortic valve for measuring LV pressures. A left thoracotomy was performed, and the heart was isolated in a pericardial cradle. To minimize arrhythmias, we administered intravenously a fluid bolus of lidocaine (1 mg/kg). In addition, bretylium tosylate (5 mg/kg) and propranolol (0.04–0.06 mg/kg) were administered intravenously, the lidocaine was given at 50–75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in a continuous drip. After vital parameters were stabilized, we collected baseline hemodynamic data.

Next, the LAD was dissected and isolated immediately distal to the bifurcation of its first diagonal branch. We placed a snare occluder loosely around the artery. For testing purposes, we briefly occluded the snare and produced epicardial cyanosis in the region of the myocardium supplied by the occluded artery. The contours of the region were traced on cellophane paper to determine by planimetry the surface area at risk. Releasing the snare restored blood flow to the area at risk and reversed cyanosis. We ligated the distal ends of the arteries perfusing the borders of the area at risk to minimize collateral blood supply in the postoperative phase.

Experimental Laser Protocol

Transmyocardial channels were created in the beating heart with an 800-watt pulsed CO_2 laser (Laser Engineering, Milford, MA) coupled to an articulating arm. The output wavelength of the laser was 10,600 nanometers (infrared), the output energy was 30 joules, and the pulse duration was 38 milliseconds. Laser activation was synchronized with the R wave of the electrocardiogram to avoid creating arrhythmias by stimulating the heart during the electrically vulnerable ventricular repolarization period (T wave) [1]. The articulating arm of the laser was connected to a specially designed focusing probe (Laser Engineering), which was placed on the epicardial surface of the heart within the area at risk. Channels 1 mm in diameter were created ~ 1 cm apart within the affected zones (~ 1 channel/cm^2 of area at risk). After each channel was formed, we gently applied manual pressure to the epicardium to secure hemostasis. When all channels were created, the animals were assigned to the acute group or to the chronic group. Animals in the acute group were kept in the operating room for the next 6 hours.

Myocardial Stress Protocol

Animals in the acute group were subjected to the stress protocol at the end of the 6-hour waiting period; animals in the chronic group were subjected to the protocol at 3 months after the initial

procedure. To induce myocardial stress, we intravenously infused saline at a constant rate (10 cc/kg body weight/min) for 10 minutes. This protocol increased both cardiac preload and the myocardial demand for oxygen and magnified subtle hemodynamic abnormalities that may not have been detected at baseline conditions [9].

Data Collection

Data on the hemodynamic status of each animal were collected at three different time periods. Baseline data were collected in duplicate before ligation of the LAD. The second and third data sets were collected after the waiting period: one immediately before implementation of the stress protocol and one immediately after. We used these data to calculate the relevant indices of regional and global LV function.

Global left ventricular function. We used the stroke work index (SWI) and the LV rate of pressure change (dP/dt) as indicators of global LV function. The following formula was used to calculate the SWI from left and right heart catheterization data:

SWI (g-m/m^2/beat) = [(AoP-PCWP) × CO/HR] × 0.0136, where AoP is systolic arterial pressure, PCWP is the pulmonary capillary wedge pressure, CO is the cardiac output, HR is the heart rate, and 0.0136 is a unit conversion constant.

Regional left ventricular function. We used the rate of systolic wall thickening (R_t, expressed in mm/sec) as an indicator of regional function. Pairs of ultrasonic crystals were implanted in the area of the myocardium at risk and in the lateral myocardial region supplied by the obtuse marginal branches of the left circumflex coronary artery. The crystal pairs were connected to a monitor to record the systolic and diastolic wall thicknesses of the myocardium inside and outside the zone at risk. We used simultaneous tracings of LV dP/dt to identify the start (upstroke of the dP/dt curve) and end (negative peak of dP/dt curve) of systole. We calculated the duration of systole, and we used this calculation to determine the velocity of systolic contraction, which is expressed as the total change in muscle thickness (mm) divided by the duration of systole (sec). Negative systolic deflection of the sonomicrometer tracings (thickness of the muscle at systole minus thickness of the muscle at diastole <0) was interpreted as paradoxical motion (asynergic contraction).

Myocardial perfusion. The indicator of myocardial perfusion was the percentage of the myocardium with ischemic changes. Anesthetized animals were euthanized with an overdose of KCl. In the acute group, the heart was excised and placed in ice-cold saline. The left coronary ostium was cannulated with a catheter connected to a pressurized (150 mm Hg) bag containing blue ink (Toyoba, Japan). The LAD was cannulated with a 21-gauge needle immediately distal to the ligature(s). The area at risk was infused with triphenyl tetrazolium chloride (TTC), an oxidation-reduction indicator that deposits a red pigment in the presence of succinic dehydrogenase activity, indicating tissue viability [10]. After incubating for 30 minutes at 40°C, the heart was placed overnight in 10% buffered formalin. Then, 10 mm sections were cut parallel to the atrioventricular plane.

Individual sections were analyzed by computerized planimetry. We measured the area of the LV muscle that stained blue with the Toshiba ink (area not at risk) and the area from which the blue dye was excluded (area at risk). Within the area at risk, viable, or TTC-reactive, tissue appeared red, whereas the area of potential infarction, or TTC-negative tissue, maintained its original color (Fig. 1). Areas measured on individual sections were added to their respective counterpart on other sections. The volume of myocardium at risk and the volume of TTC-negative myocardium were reconstructed from the areas, assuming cylindrical geometry for individual sections. The results, expressed as a ratio, were normalized to the volume of myocardium at risk and to the total volume of the left ventricular muscle. The epicardial area at risk, traced during surgery and measured by planimetry, was divided by the volume of myocardium at risk of the respective animal, and the average unit volume corresponding to unit area of epicardial cyanosis was calculated.

After cardiectomy, cannulation of the left coronary ostium, and perfusion of the blue dye, the heart from dogs in the chronic groups was placed in cold saline. Because it was occluded in most animals in the chronic group, the LAD was not cannulated. Instead, the heart was sectioned as described, and the sections were incubated in a TTC solution at 40°C for 30 minutes.

Postoperative Care

In the chronic animals, the pericardium was left open and the incision was closed in the routine manner. The animals were given routine postoperative care after the laser procedure.

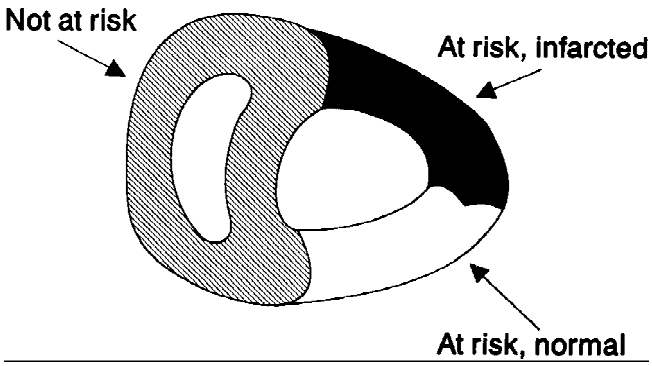


Fig. 1. Representation of a prepared 10-mm left ventricular section analyzed by computerized planimetry. The area not at risk is defined by the diagonal lines (blue stain). Within the area at risk, viable (TTC-reactive) tissue is defined by the light area, whereas the area of potential infarction (TTC-negative tissue) is defined by the dark area.

Cephalothin sodium (20 mg/kg, IM) was administered twice daily for 3 days after operation. If the animal required more pain relief than the 20 hours of analgesia provided by the epidural, buprenorphine (15 μg/kg, IM) was administered every 6–8 hours.

Histology

Fixed tissue was dehydrated in acetone and embedded in a methacrylate medium (Histo-Resin, Reichart-Jung, Heidelberg, Germany). Sections 1-μm thick, cut with an LKB Historange (Bromma, Sweden) microtome, were stained with hematoxylin and eosin and examined under a Zeiss light microscope.

Statistical Analysis

A single-tailed, unpaired Student's t-test was used to compare control and experimental animals in respective groups. A single-tailed paired Student's t-test was used to compare the cardiac indexes in individual animals at baseline vs. post-TMLR and poststress. A value of $P<0.05$ was considered significant.

RESULTS

The mean SWI of all 24 dogs at baseline was 46.6 ± 11.8 g-m/kg/beat, and the mean dP/dt was 2000.4 ± 214.0 mmHg/sec. After transient occlusion of the LAD, the mean surface area of epicardial cyanosis was 40.5 ± 7.2 cm^2. The mean rate of systolic myocardial contractions within both the normal and the risk regions was 2.8 ± 1.2 mm/sec at baseline. No statistically significant differences were noted in baseline values between any experimental group and its respective control. Approximately 40 laser channels were created within the area at risk of each experimental animal.

In the acute group, two control and two experimental animals died immediately after the start of the stress protocol. In the chronic control group, one animal died on postoperative day 34, and two dogs died immediately after the start of the stress protocol. No chronic experimental animals died during the study.

Global Left Ventricular Function

During the 6-hour waiting period in the acute groups, the hemodynamic responses of the experimental animals did not differ significantly from those of the control animals (Fig. 2). In both groups, dP/dt and SWI decreased steadily but not significantly over the 6 hours after LAD ligation. Upon infusion of saline in the stress procedure, the SWI increased whereas the dP/dt decreased in both groups; however, neither change was statistically significant.

The dP/dt in chronic experimental dogs did not change significantly during the waiting period. In the chronic control animals, the mean dP/dt decreased significantly ($P < 0.03$) over the 3-month waiting period when compared with the baseline value and with the value from the experimental group (Fig. 2). In both the chronic control and experimental groups, the SWI did not change significantly during the 3-month period. In experimental chronic animals, both the dP/dt and SWI increased in response to the increased cardiac preload associated with the saline infusion, whereas both indices remained unchanged in control animals. These differences between the two groups were statistically significant ($P < 0.02$ for dP/dt and $P < 0.05$ for SWI).

Regional Left Ventricular Function

In both experimental and control acute groups, the R_t in normal myocardial regions did not vary significantly over the 6-hour waiting period (Fig. 3, upper panel). In the same two groups of dogs, the myocardial regions a risk thickened asynergically at the end of 6 hours (Fig. 3, lower panel).

In the normal myocardial regions of the experimental and control chronic groups, the R_t did not vary significantly over the 3-month waiting period (Fig. 4, upper panel). As in the acute groups, however, the R_t of the normal myocar-

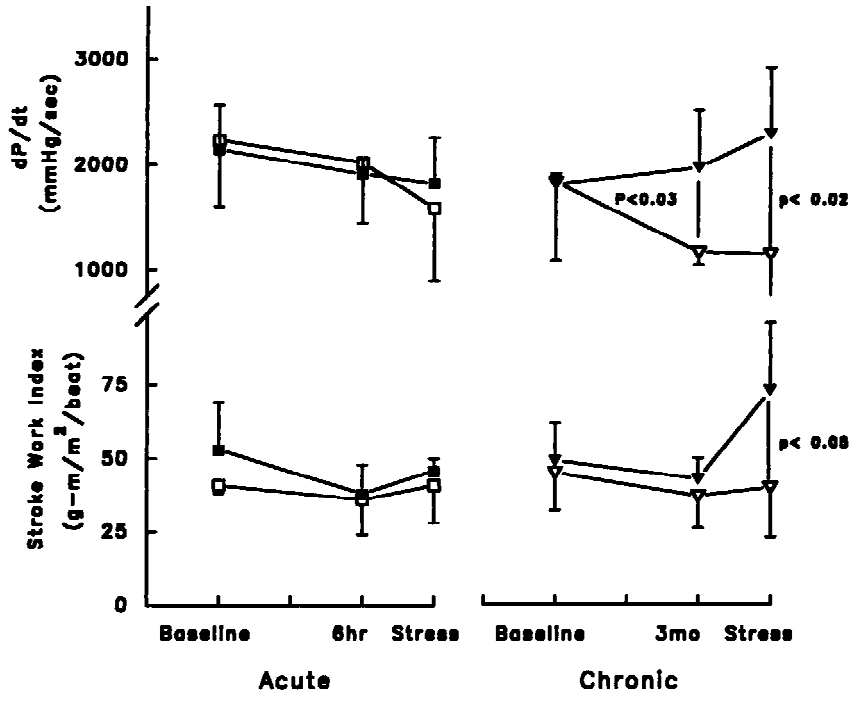


Fig. 2. Left ventricular function in acute and chronic experimental and control dogs at 6 hours and 3 months. dP/dt, rate of change in left ventricular pressure; SWI, stroke work index (g-m/m^2/beat).

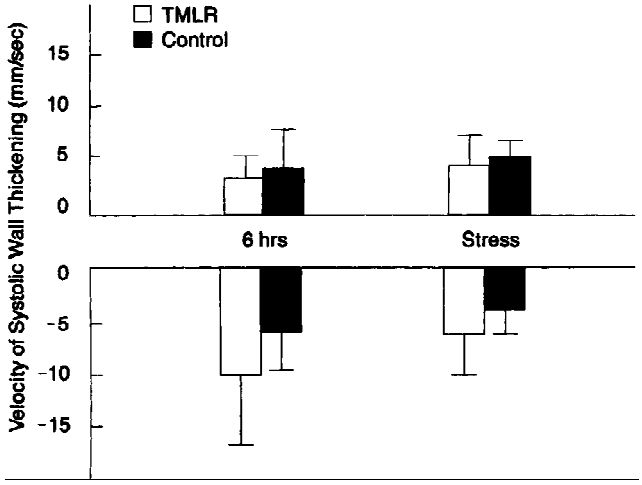


Fig. 3. Regional left ventricular function (indicated by the velocity of systolic wall thickening) after 6 hours (with and without induced myocardial stress) in normal (upper panel) and at-risk (lower panel) myocardial regions of experimental and control dogs.

dium in the chronic groups increased in response to stress (Fig. 4, upper panel). In the area at risk of chronic control animals (Fig. 4, lower panel), we observed paradoxical myocardial contraction at the end of the 3-month waiting period, both before and after stress (Fig. 4, lower panel). None of the chronic experimental animals, however, exhibited paradoxical myocardial contractions in the area at risk before or during stress at the end of the 3-month period (Fig. 4, lower panel). In the chronic experimental group, the mean R_t decreased slightly ($P = 0.13$) at 3 months before the infusion of saline (2.3 ± 1.6 mm/sec) when compared with the baseline value (2.8 ± 1.2), but the response to stress was positive ($R_t = 2.6 \pm 2.0$).

Myocardial Perfusion

In acute animals, the volume of myocardium at risk was 732.8 ± 300.0 cm^3, an average of 45.2% ± 15.2% of the total LV muscle volume. For chronic animals, the volume at risk was 689.0 ± 124.6 cm^3, an average of 49.3% ± 13.5% of the total LV muscle volume (p = NS). When the volume of myocardium at risk was normalized by the surface area at risk for all the animals, the mean ratio was 17.5 ± 6.4 cm^3 of tissue/cm^2 of discolored surface.

For the animals in the acute groups, the volume of myocardium at risk comprised 33% ± 12% TTC-negative tissue in experimental dogs and

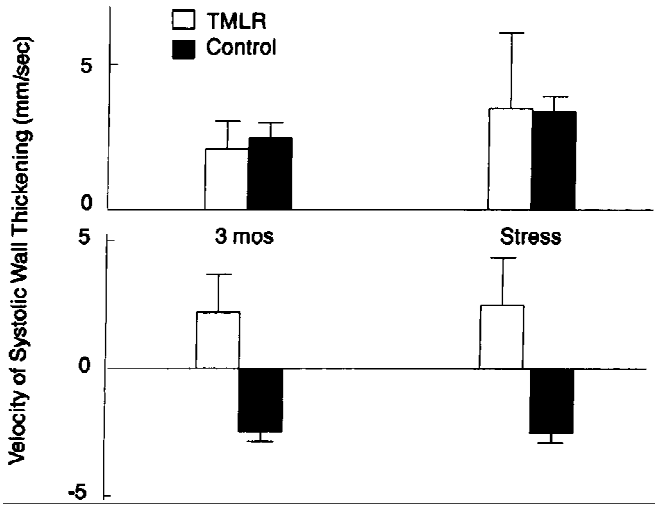


Fig. 4. Regional left ventricular function (indicated by the velocity of systolic wall thickening) after 3 months (with and without induced myocardial stress) in normal (upper panel) and at-risk (lower panel) myocardial regions of experimental and control dogs.

30.8% ± 10.5% in control dogs (P = NS). For the animals in the chronic groups, the volume at risk comprised 15.2% ± 4.5% TTC-negative tissue in the experimental animals and 27.8% ± 5.3% in control animals ($P < 0.03$).

Histology

Histologic identification of the volume of myocardium at risk was consistent with gross observations. The only access of blue dye to the perfusion bed distal to the ligatures would be via collateral circulation in the chronic setting. For this reason, the minimal penetration of blue dye in the area at risk suggested little collateral blood supply. The histologic structure of tissue outside the ischemic areas was normal, and blue dye was detected in the arteries and the interstitium of these areas.

In the myocardium at risk of acute experimental animals, laser-induced tracks measuring 0.50 mm to 0.75 mm in width were filled with fibrin, erythrocytes, and neutrophils (Fig. 5). The endocardial portion of the tracks contained mostly fibrin and some neutrophils, whereas the subepicardial segments contained a mixture of fibrin and erythrocytes. In the tissue adjacent to the tracks, dense eosinophilic, hypercontracted myocytes extended to a radius of 0.2 mm. Neutrophils were seen up to 0.55 mm away from the tracks. Diffuse, transmural edema and hemorrhage marked the outer periphery of the laser tracks.

In the chronic experimental animals, the laser channels were characterized by vascular tracks, approximately 0.5 mm in diameter (Fig. 6). Perpendicular to the epicardial surface, these thin-walled vessels extended into the myocardium and were lined with endothelial cells. The presence of multiple, small, irregular-shaped, capillarylike vessels surrounding the tracks suggested increased vascularity.

DISCUSSION

In the acute groups, mortality during the stress period was the same (2 dogs died in each group). However, in the chronic groups, all dogs in whom laser channels had been created survived the stress treatment, whereas only 50% of the unprotected control dogs survived.

Global hemodynamic parameters (dP/dt and SWI) did not deteriorate in either the experimental or control dogs in the acute groups, despite asynergic contractions of the ischemic myocardial segments. This suggested global compensation of the LV function during severe regional dysfunction. After the 3-month waiting period in the chronic groups, the hemodynamic response to preload challenge was significantly increased over baseline values only in the experimental animals in whom the zone at risk of ischemia had been treated by TMLR. In the chronic control dogs, the systolic response failed to meet the increase in myocardial oxygen demand. In addition, the mode of systolic thickening of the regions at risk returned to synergy with the rest of the heart muscle in the experimental animals, but not in the control animals. Furthermore, the amount of infarcted tissue was significantly less in chronic TMLR-treated animal than in their respective controls. These findings suggest a delayed protective effect of TMLR after acute ischemia. We conclude that in the long-term, TMLR significantly decreases mortality by improving global and regional LV function and by limiting expansion of the infarction zone after acute ischemia.

In an acute study conducted on sheep hearts, Horvath et al. [11] concluded, in agreement with our results, that TMLR improves contractility and diminishes necrosis in the area of risk. Our results differed from theirs in that beneficial regional effects of the procedure on myocardial contractility also have been observed by Horvath et al. [11] in the acute phase. The main difference



Fig. 5. Light micrographs of myocardial tissue in the at-risk myocardium of an acute experimental animal. The section of myocardial tissue shows an endocardial track (arrows) measuring 0.5 mm in width and extending 1 to 2 mm before being lost in the sectioning plane. The track is filled mostly with fibrin with a moderate infiltrate of neutrophils and scattered erythrocytes. By contrast, the subepicardial track (not shown) is an admixture of fibrin and erythrocytes (hematoxylin & eosin stain; bar = 100 μm).

between canine and ovine models of experimental ischemia consists in the collateralization potential of the canine myocardium, which is absent in the sheep heart. We attempted to account for this by ligating the epicardial vessels marginal to the area at risk. It could be argued, however, that in a controlled setting, the importance of collaterals should diminish. The agreement of the chronic results of the two experiments is consistent with this assumption. However, we have no explanation for the differences observed in the acute phase of the procedure, although the small size of either study may have been a factor.

Several investigators, however, have questioned the effectiveness of TMLR. Hardy et al. [5] reported that channels created with an 86-watt continuous wave CO_2 laser were occluded and that cardiac mechanics were similar before and after lasing. In addition, they observed no significant increase in average regional endocardial blood flow in the lased tissue when compared with that in control tissue, except when LV pressure was elevated by placing a clamp to the aorta. Landreneau et al. [6] used a continuous wave 80-watt CO_2 laser to create channels in cardioplegically arrested hearts. They reported that myocardial perfusion and oxidative metabolism did not improve and that regional contractile function decreased significantly after TMLR. In a study of the acute effects of TMLR in dogs with acute myocardial ischemia, Whittaker et al. [8] measured regional blood flow, segmental shortening, and lactate content after creating transmural channels with a pulsed Ho:YAG laser operated at 300 mJ/pulse and 3 Hz. They reported no immediate benefits associated with TMLR.

Several important differences exist between the experimental conditions in the above-mentioned studies and those in our study. Most importantly, the differences in physical parameters of the laser, such as the energy and duration of the laser pulse, may account for the disparate findings. Because lasers used in earlier studies could not deliver the high pulse energy necessary to ablate a transmyocardial channel in the contracting myocardium with a single pulse, these

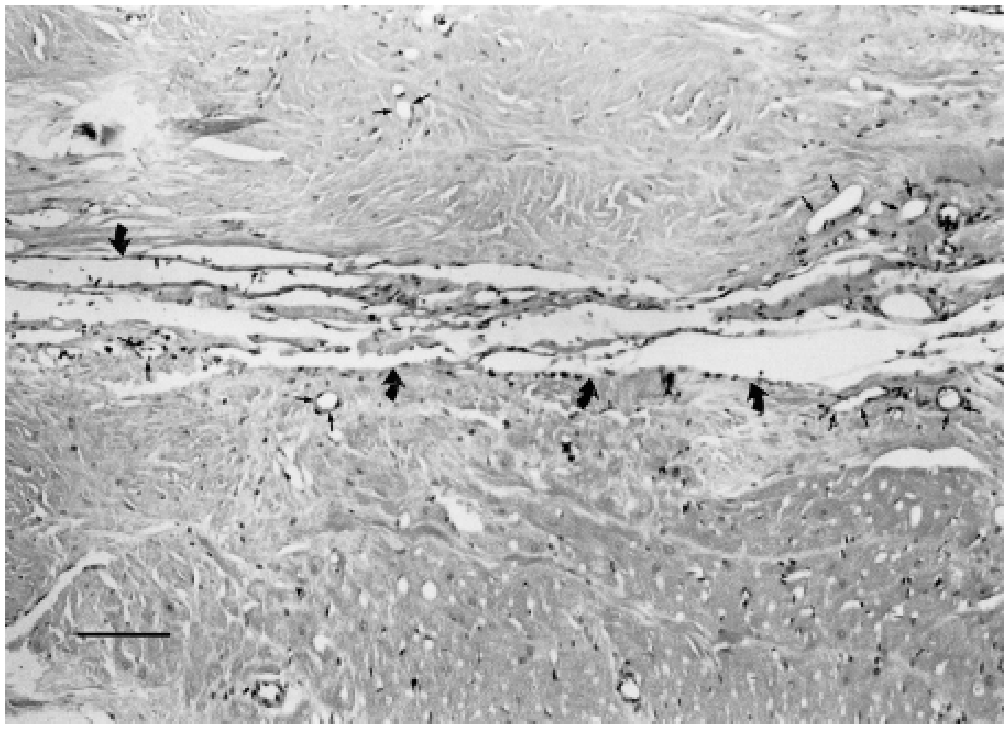


Fig. 6. Light micrographs of laser-induced tracks in the at-risk myocardium of a chronic experimental animal. A section of left ventricular myocardial tissue shows a vascular track perpendicular to the epicardial surface (arrowheads). The track is a thin-walled vessel lined with endothelial-like cells, and a thin area of fibrosis (<0.1 mm) exists around the vessel. Notice the increased vascularity around the track, possibly due to multiple capillary-like vessels on the periphery (fine arrows) (hematoxylin & eosin stain; bar = 100 μm).

experiments were performed either on beating hearts with multiple pulses per channel or on cardioplegically arrested hearts in which myocardial wall tension had been eliminated.

The effects of multiple, low-energy pulses versus a single pulse used to create a single channel may be significantly different at the histologic level. The high pulse energy of the Heart Laser (80 joules maximum) allowed us to penetrate the myocardium with a single pulse. However, even the maximum pulse energy of the Ho:YAG laser is one order of magnitude less than that used in this study and, therefore, necessitates multiple pulsation. Furthermore, the duration of its pulse is 10^4 times shorter (5×10^{-6} with the Ho:YAG vs. 50×10^{-3} with the CO_2 laser). The adverse acoustic effect of fast ablation on tissue with shorter thermal relaxation time has already been shown [12,13]. Therefore, higher levels of collateral damage are expected with low-power, very short pulse ablation modalities, due to the thermal and structural components of tissue ablation. This is in agreement with the conclusions of Deckelbaum et al. [14], who showed that, at sufficiently high levels of the average power, the collateral damage caused by infrared radiation will be optimally reduced.

Movement of the left ventricle during multiple pulsation potentially contributes to the formation of jagged channels. Also, external pressure applied to the laser fiber may cause additional mechanical trauma secondary to the dotter effect. These changes, in turn, may amplify the tissue response, resulting in excessive fibroproliferation that may reduce long-term channel patency.

In addition to the physical parameters of the laser, the physiologic conditions of our study differed from those traditionally used. In most experimental settings, ischemia has been created 30 minutes to 6 hours before the application of TMLR. Allowing that much time to elapse before treatment produces the irreversible effects of myocardial ischemia, and ongoing necrosis may impede the beneficial effects of TMLR. Moreover, even if TMLR is initiated immediately after the onset of acute ischemia by the ligation of the coronary artery, the ischemic time will be different across the area at risk since creating all the chan-

nels may require 30–45 minutes. We circumvented this problem by first performing TMLR throughout the area at risk and then creating ischemic conditions immediately afterward. Currently, we are in the process of conducting experiments in hibernating porcine hearts [15] for a better simulation of the collateral-dependent microanatomy of chronic myocardial ischemia in humans.

Functional success with TMLR should be characterized by both long-term channel patency and increased regional perfusion. Before our study, long-term channel patency had been reported in animal experiments [4] and in one clinical case [16]. The neo-endothelialization of the laser tracts, observed at 3 months in the present study, may be a positive prognosticator of the long-term patency of the channels. Yet, increased microvascularity in the tissue adjacent to the tracts may be due to angiogenetic effects of the laser [17], but more experiments are needed to support this possibility. As for regional perfusion, Frazier et al. [18] recently reported their results on the subregional analysis by Positron Emission Tomography (PET) of TMLR-treated humans. In 11 patients at 12 months after TMLR, they showed that the relative subendocardial/subepicardial tracer uptake ratio increased significantly in the lased regions of the myocardium when compared with control regions (septum) that were not lased. These PET results correlated well with the clinical status of the subjects and were supportive of the potential merit of TMLR as an alternative therapy. The clinical efficacy of TMLR in refractory coronary artery disease is currently being investigated in prospective, randomized, multicenter trials under the auspices of the Food and Drug Administration.

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