

Histologic Analysis of Transmyocardial Channels: Comparison of CO₂ and Holmium:YAG Lasers

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Background. Transmyocardial laser revascularization using different lasers is being tested in the treatment of refractory angina. We conducted comparative analysis of the acute and chronic myocardial effects of these different lasers.

Methods. Transmyocardial channels were made in normal dog hearts with either a holmium:yttrium-aluminum garnet or a CO₂ laser. Channels were examined histologically 6 to 24 hours, 2 to 3 weeks, and 6 weeks after creation.

Results. Regardless of the laser source, the channels were occluded by thrombus within 6 to 24 hours. Subsequently, organization and neovascularization of the channel region occurred. Thermoacoustic damage was initially greater with the holmium:yttrium-aluminum

garnet laser, but the channel appearances were indistinguishable from those made with the CO₂ laser by 6 weeks.

Conclusions. Histologically, the myocardial effects of the CO₂ and holmium:yttrium-aluminum garnet lasers are similar and differ predominantly in the amount of acute thermoacoustic injury. Channels are rapidly occluded by thrombus and are replaced by neovascularized collagen. This suggests that the physiologic effects of these two lasers may be similar and that mechanisms other than blood flow through chronic patent channels should be considered as contributing to the clinical benefits observed with this procedure.

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Angina pectoris results from diminished myocardial perfusion relative to demand. Coronary artery-derived perfusion can be increased by both medical and operative interventions, including vasodilator therapy, angioplasty, and coronary artery bypass grafting. Frequently, however, medical interventions are inadequate to cope with the severity of the perfusion deficit and operative intervention is not feasible. In these situations, various alternative methods to increase blood flow to the heart or to reduce the patient's perception of pain have been explored, some of which have shown limited success. These techniques include endocardial incisions [1], cardiac acupuncture [2], fistula creation [3], pedicle grafting [4], omental implantation [5], vessel implantation [6], and sympathectomy [7].

More recently, transmyocardial laser revascularization (TMLR) was devised as a method of bypassing the coronary circulation altogether [8, 9], instead perfusing the myocardium with oxygenated blood derived directly from the left ventricular chamber, thus attempting to replicate the embryonic and reptilian cardiac circulations [10]. The TMLR procedure involves the use of a laser to create a channel through the free wall of the left ventricle into the ventricular chamber. The creation of multiple transmyocardial channels would, in theory, permit oxygenated blood in the left ventricular chamber to reach and perfuse the myocardium directly. Currently, CO₂ and holmium:yttrium-aluminum garnet (YAG) lasers are

being evaluated in ongoing international clinical trials for the relief of otherwise untreatable angina. These studies have shown promising initial results for the immediate and long-term symptomatic relief of angina [11, 12].

Lasers that emit light of different wavelengths may differ in some respects with regard to their acute effects on myocardial tissue. Whether differences in acute tissue effects translate into differences in more chronic settings, however, has not been studied adequately. To provide a foundation for better understanding of the physiology and clinical effects of TMLR with different lasers, we conducted a comprehensive histologic evaluation and comparison of transmyocardial laser channels in dogs using the CO₂ and holmium:YAG lasers, which are currently undergoing human clinical trials. We examined the natural history of laser channel morphology over a 6-week period. The results of these studies indicate that the laser channels created with both the CO₂ and holmium:YAG lasers are rapidly occluded by thrombus and that over the ensuing weeks, they are replaced by a proliferation of vessels and fibrous scar. The potential implications of these findings in the clinical setting 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

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and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences (NIH publication 85-23, revised 1985). This study was approved by the Institutional Animal Care and Use Committee of Columbia University.

Acute studies were performed under general anesthesia with pentobarbital (30 to 60 mg intravenously) and with the dogs mechanically ventilated. In chronic studies, general anesthesia was established with pentothal (2.5%, 15 mL intravenously), and the animals were then intubated and maintained on inhaled isoflurane (1% to 2%) in addition to pancuronium bromide (1 mg intravenously). Peripheral intravenous catheters were placed for administration of fluids. A left lateral thoracotomy was performed, and the heart was exposed and suspended in a pericardial cradle.

Transmyocardial laser channels were created using either a CO₂ laser (The Heart Laser; PLC Systems Inc, Milford, MA) or a holmium:YAG laser (The CardioGenesis ITMR System, Sunnyvale, CA) in the left ventricular free wall. Approximately ten transmyocardial channels were created in each animal in the territory supplied by the distal left anterior descending coronary artery after the first diagonal branch, with a density of approximately 1/cm². Transmyocardial CO₂ laser channels were created using a single 40-J pulse. Transmyocardial holmium:YAG laser channels were created using bursts of 2-J pulses (total energy approximately 20 to 30 J/channel) delivered through a fiber optic cable with a quartz focusing lens. Creation of a transmural channel was confirmed by the presence of vigorous pulsatile bleeding during systole through the epicardial laser entry point for the CO₂ laser and by bleeding and passage of the fiber tip into the ventricular chamber for the holmium:YAG laser. Hemostasis occurred either spontaneously, after manual compression, or with a shallow epicardial U stitch (5-0 Prolene, Ethicon, Somerville, NJ).

All animals survived to their respective sacrifice times. No obvious detrimental sequelae were observed after the TMLR procedure. The animals were sacrificed by lethal injection of pentobarbital. For the acute studies, the animals were sacrificed at either 6 to 8 hours (n = 12) or 24 hours (n = 4). Animals used for chronic studies were sacrificed at either 2 to 3 weeks (n = 14) or 6 weeks (n = 6). After explanting the heart, we identified the channels by gross examination and created a transmural block of tissue containing, when possible, a single channel. The samples were labeled with unique identifiers and fixed in 10% neutral buffered formalin for 16 hours. The myocardium was then sectioned transversely, in an axis perpendicular to the channel axis, at 1.5- to 2-mm intervals extending from the epicardial to the endocardial surfaces (Fig 1a). In this way, channels were analyzed throughout their entire transmural course extending from the epicardium to the endocardium. In cases in which channels were not readily apparent, the entire ventricular free wall was submitted for analysis. The tissue was then dehydrated and embedded in paraffin. Four-micrometer sections were cut and stained with hematoxylin and eosin and with Masson's trichrome stain for microscopic analysis.

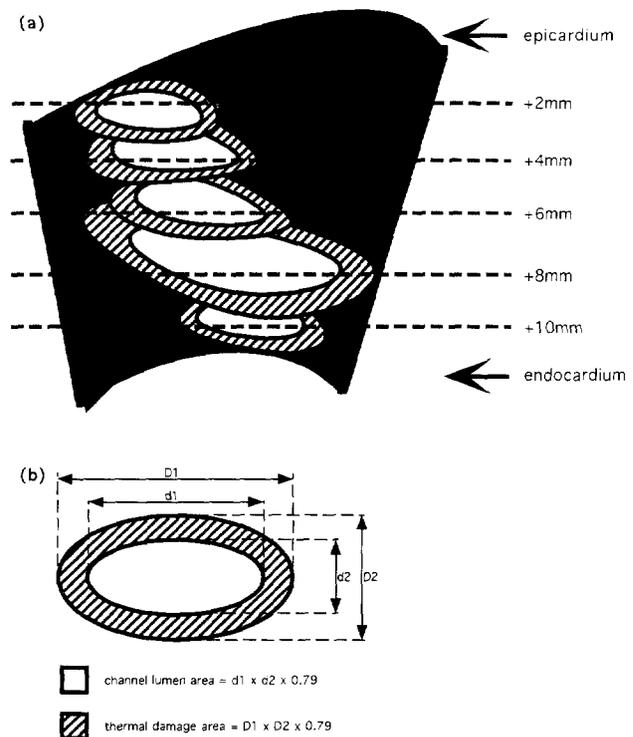


Fig 1. (a) Transverse sections were taken through the myocardial wall extending from the epicardium to the endocardium. (b) Calculated channel lumen area and total area of thermoacoustic laser damage (including the channel lumen).

The laser channel lumen area and the total area of thermal damage were quantified by measuring the long and short axes of the respective areas, as illustrated in Figure 1b. The area contained within the channel perimeter was estimated according to the formula for the area of an ellipse (channel area = $d1 \cdot d2 \cdot 0.79$); similarly, the total area of thermal damage was calculated assuming an elliptical geometry (total thermal area = $D1 \cdot D2 \cdot 0.79$). These measurements were then collated as a function of depth from the epicardial surface. All measurements were made using a standard microscope eyepiece scale micrometer. All results are presented as mean \pm 1 standard error of the mean. The results obtained with the CO₂ and holmium:YAG channels were compared by Student's unpaired *t* test, with *p* less than 0.05 considered significant.

Results

Evaluation of Acute Laser Channels at 6 to 8 and at 24 Hours

A total of 16 dogs were analyzed: 12 at 6 to 8 hours and 4 at 24 hours. Ten of the dogs were treated with the CO₂ laser and 6 were treated with the holmium:YAG laser. A combined total of 102 laser channels (41 CO₂, 61 holmium:YAG) were analyzed histologically; 327 cross-sections of these channels (average of three per channel) were evaluated at all levels throughout the ventricular wall. No

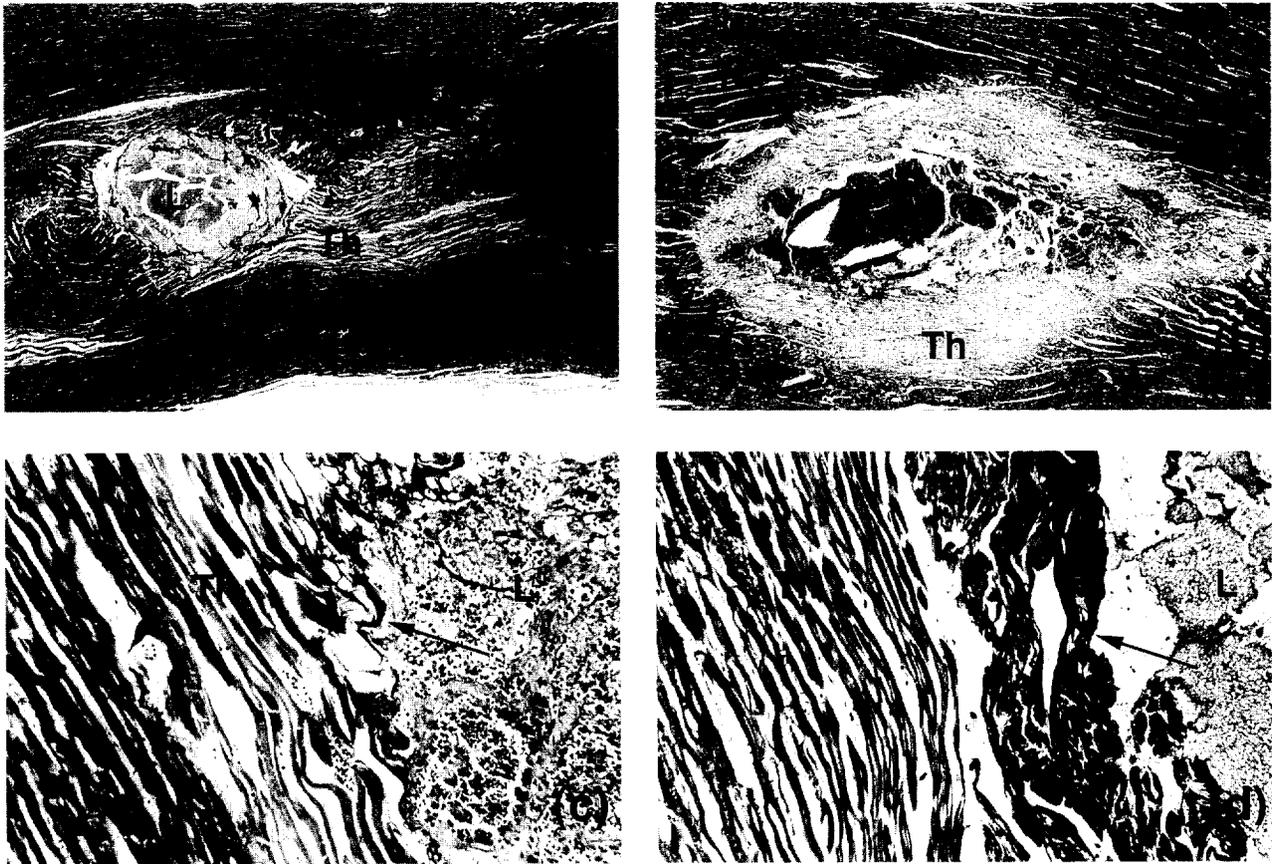


Fig 2. Acute CO₂ (a, c) and holmium:YAG (b, d) laser channels showing the channel lumen (L), rim of lacunar change (arrows), zone of thermo-coagulated myocardium (Th), normal myocardium (N), and rim of hypercontracted darkly staining myocytes (arrowheads). (Masson's trichrome stain; a, b: $\times 20$; c, d: $\times 200$; all before 33% reduction.)

differences in channel characteristics were seen between the animals sacrificed at 6 to 8 hours versus 24 hours, and these results therefore were not separated.

All acute laser channels were readily identifiable throughout their course. In transverse section, these generally had an elliptic configuration, with their long axis running parallel to the axis of adjacent myocytes (Fig 2). The channels showed features characteristic of myocardial laser injury identified in previous studies [13, 14]. These included a centrally ablated channel lumen and a thin rim of lacunar change surrounded by a zone of thermal necrosis, which was sharply demarcated from adjacent normal-appearing myocardium by a prominent zone of contraction band necrosis. These features are highlighted in the typical CO₂ and holmium:YAG channels shown in Figures 2a and 2b, respectively. We noted varying degrees of fascicular separation and widening of the perivascular interstitium, consistent with peripheral thermoacoustic laser damage. The majority of channel lumens contained red blood cells enmeshed in a fibrillar fibrin network, consistent with fresh thrombus. The finding of thrombus suggests that there is no substantial flow through these acute channels. Rare sections showed dramatic interstitial blood in an arborizing pattern extending from the channel site. The thrombus within the channel lumen, the zone of lacunar change, and the

region of thermal necrosis were readily apparent in the magnified views of the edge of the channel lumen (Figs 2c, 2d). These morphologic characteristics were present in both CO₂ and holmium:YAG laser channels.

Differences between CO₂ and holmium:YAG laser channels were evident when measuring the channel lumen and the area of thermal damage (Figs 3A, 3B). The CO₂ channel lumens were approximately two thirds of the size of holmium:YAG lumens, and the area of CO₂-induced thermal damage averaged approximately one third of that of holmium:YAG thermal damage. The channel lumen size and the area of thermal damage did not vary significantly as a function of depth from 4 to 10 mm from the epicardium (see Figs 3A, 3B). Channel dimensions at 2 mm from the epicardial surface tended to be smaller, probably because of their proximity to sites of epicardial closure.

Evaluation of Chronic Laser Channels at 2 to 3 and at 6 Weeks

Channels from a total of 20 dogs were analyzed: 14 at 2 to 3 weeks and 6 at 6 weeks. Ten dogs were treated with the CO₂ laser and 10 with the holmium:YAG laser. Gross identification of channels was increasingly difficult with the passage of time. When recognized, these were seen as areas of elliptical fibrous scar, which extended in a

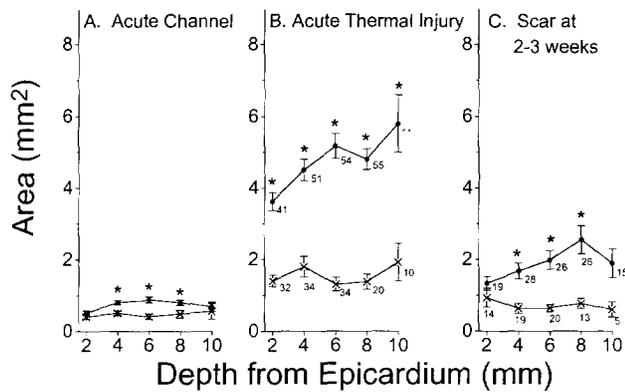


Fig 3. Summary of channel lumen and thermoacoustic damage cross-sectional areas for CO₂ (crosses) and holmium:YAG lasers (filled circles) in acute studies (A, B), and of thermoacoustic scar in 2- to 3-week chronic studies (C). Measurements are shown at different depths from the epicardial surface through the left ventricular wall. The number by each point indicates the number of individual channels measured at each particular depth; note that these are the same for A and B. The number of channels measured varies at each depth because of the varying thickness of the left ventricular wall and the incomplete identification of some channels through their entire mural course. (**p* < 0.05 compared with corresponding measurement in CO₂ channels by unpaired Student's *t* test.)

simple linear fashion from the epicardium to the endocardium, similar to the configuration of the acute laser channels. Because of the inconspicuous presence of laser channels, the entire laser-treated ventricular free wall was submitted for histologic evaluation in an attempt to identify as many channels as possible. A combined total of 75 laser channels (32 CO₂, 43 holmium:YAG) were analyzed histologically; 197 cross-sections of these channels (average of 2.5 per channel) were evaluated at all levels throughout the ventricular wall.

At 2 weeks, channels rarely had the recognizable architecture of acute laser channels, with organizing fibrin thrombus in the central lumen (Fig 4a) surrounded by a rim of fibrous scar replacing the zone of thermal damage. In the majority, however, the central channel area was entirely replaced by fibrous tissue and contained a scattering of chronic inflammatory cells, including lymphocytes and histiocytes (Fig 4b). Not a single patent channel with a diameter comparable with that of the original channel was ever identified. Abundant neovascularization was present within the scar at 2 to 3 weeks, including capillaries and arterioles (Figs 4c, 4d). The scar size and vascularity were reduced at 6 weeks (Figs 4e, 4f). The degree of vascularization within this scar tissue replacing the channel lumen was highly variable, including capillaries and arterioles. As in the acute studies, the dimensions of the chronic laser channel remnant did not vary significantly through the left ventricular wall with either laser (Fig 3C), with the exception of the holmium:YAG scar at 2 mm depth, which was smaller than that measured at 8 mm. The area of channel remnant was dramatically reduced at 2 to 3 weeks as compared with the original area of thermal damage (53% reduced with CO₂, 59% with holmium:YAG; see Fig 3C,

Fig 5). As shown in Figure 3C, the area of involvement was generally larger for the holmium:YAG than for the CO₂ laser. As exemplified in Figures 4e and 4f, the channel remnant area was reduced even further at 6 weeks (86% reduced with CO₂, 93% with holmium:YAG; see Fig 5) so that the majority of laser channels were entirely replaced with vascular fibrous tissue consistent with completed scar. The area of acute thermal damage, 2- to 3-week scars, and 6-week scars (pooled data from all measurements made, regardless of depth from the epicardium), shown in Figure 5, summarizes the time course of scar contraction as well as the finding that over time, the area of involvement became the same for the two lasers. The appearances of laser channels at these time points were therefore consistent with an evolving, richly vascular cicatricial process.

Elliptic scars were identified on the endocardial surface, representing the scarred channel entry points. These entry sites were not patent macroscopically in any of the chronic studies. In contrast, thebesian veins and arterioluminal vessel orifices were identified microscopically, as expected, on normal endocardial surfaces. These are readily distinguished from artificially created channels by their lack of prominent fibrous walls, their irregular course through the myocardium, and their lack of a transmural vertical course. An example (Fig 6) of a normally occurring intramyocardial sinusoid cut longitudinally, which is surrounded by a thin layer of subendocardial collagen, is shown alongside an acute laser channel cut in cross-section to reveal the similarity in cross-sectional dimension and to highlight the potential problem of identifying such a structure as a chronic, patent channel rather than a naturally occurring vascular structure.

Comment

Acute transmural laser channels created with either CO₂ or holmium:YAG lasers exhibit an elliptic morphology, which includes a centrally ablated core rimmed by a zone of lacunar change and thermal myocyte necrosis. This characteristic appearance has been described previously in several animal models, including the rat [15], dog [14], sheep [16], and pig [17], and is also seen in humans treated with TMLR [18]. The size of the channel core and the area of thermally damaged tissue are larger with the holmium:YAG laser than with the CO₂ laser, as is predicted by the differing energy characteristics of these two laser beams. Regardless of the laser type used, the channel cores are occluded by fibrin thrombus in the acute setting, a histologic finding that suggests that there is no substantial acute blood flow through these channels. This observation is consistent with our previous measurements of flow using microspheres, which showed little or no blood flow through acute channels [19, 20]. Additional functional evidence supporting the lack of acute ventricular-derived blood flow through these channels is their inability to prevent myocardial infarction in the face of an acute ligation of the left anterior descending artery, even in the zone immediately adjacent to a laser channel [20, 21].

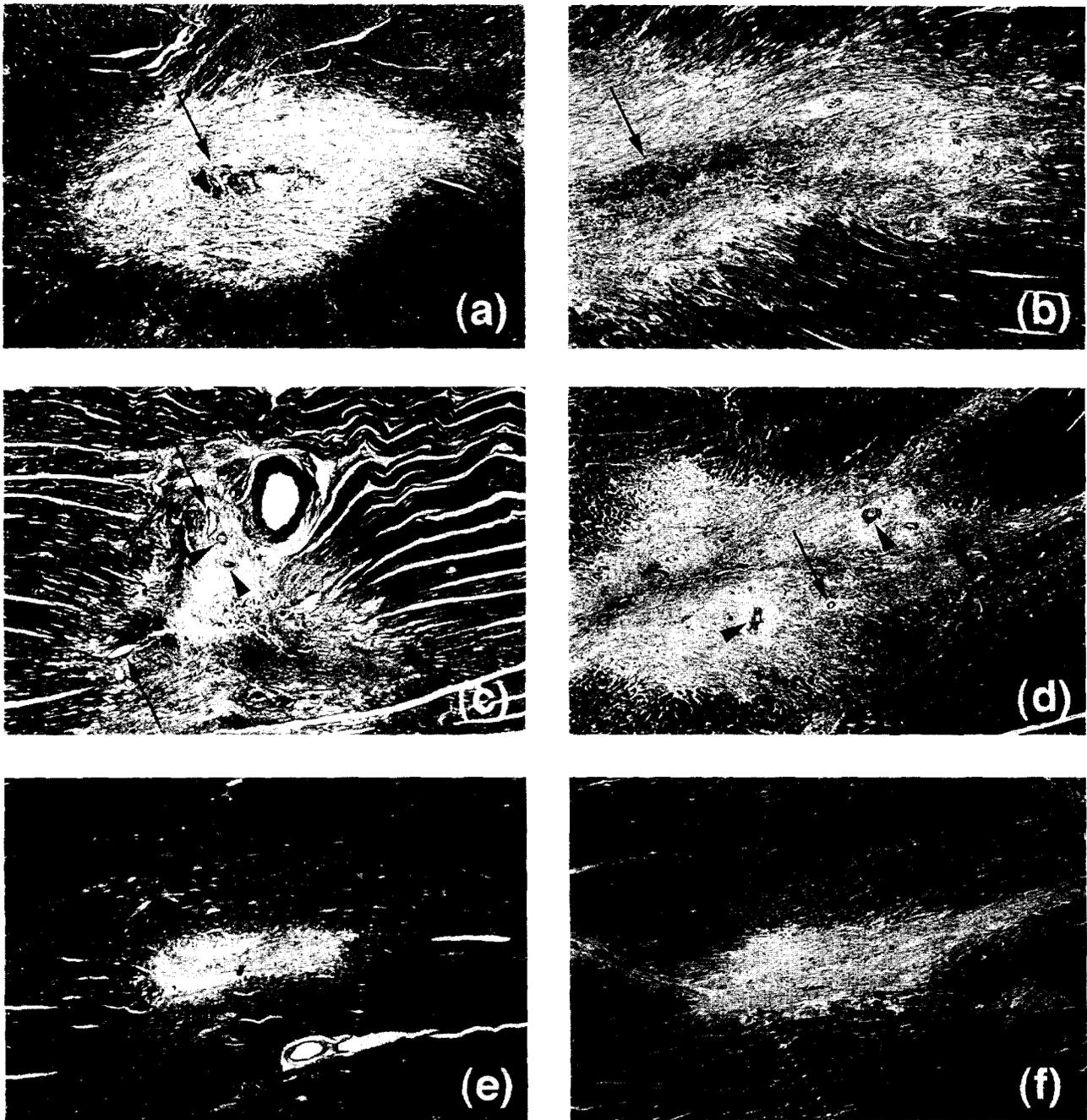


Fig 4. Channel area scars at 2 to 3 weeks (a, b, c, d) and at 6 weeks (e, f) after CO₂ (c, e) and holmium:YAG (a, b, d, f) laser treatment. Central fibrin plugs are shown by arrow (a); lymphocytes and histiocytes are shown by arrow (b); capillaries are shown by arrows and arterioles by arrowheads (c, d). (Masson's trichrome stain; a, e, f: $\times 32$; b, c, d: $\times 80$; all before 8% reduction.)

Examination of the laser channels over the ensuing weeks reveals that the thrombosed channels are organized by the ingrowth of new vessels and fibroblasts, similar to the generalized healing response typical of other organs. These newly formed vessels include a proliferation of capillaries, characteristic of granulation tissue, but also include muscular arterioles within the channel remnant, vessels that are not commonly found in healing wounds. Indeed, endothelial and smooth muscle cells show evidence of active proliferation (not observed

commonly in vessels of normal myocardium) when studied with nuclear markers of cell proliferation in vessels removed (up to 2 to 3 mm) from the laser channels [22]. In addition to the vascular response, fibroblasts lay down collagen, resulting in occlusion of the laser channel by fibrosis, eventually producing marked cicatricial contraction of the channel area by 6 weeks. These processes are histologically similar for the CO₂ and holmium:YAG laser channels, and by 6 weeks the two channels are indistinguishable.

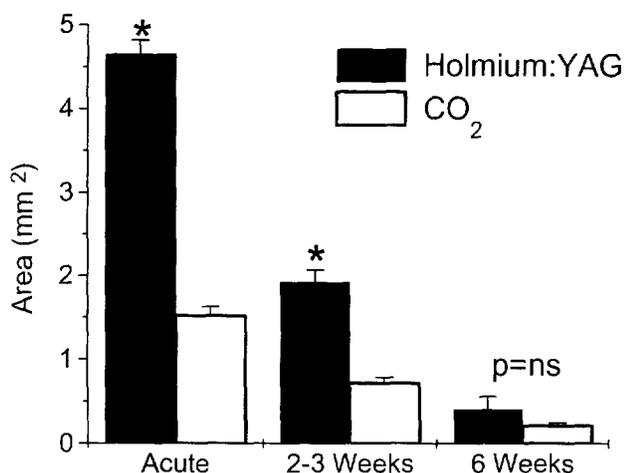


Fig 5. Comparison of the total area of thermoacoustic damage with the CO₂ and holmium:YAG lasers at the different study time points. See text for further details. (ns = not significant; *p < 0.05 compared with the corresponding measurement in CO₂-treated tissue by unpaired Student's t test.)

The present histologic study was performed in normal dog hearts with the main goal of comparing the tissue effects of two lasers currently undergoing clinical evaluations. Studies were done in the absence of infarction or ischemia to avoid any potentially confounding factors that could complicate the comparison of effects of the two lasers. The dog heart offers the advantage of having transverse mural dimensions and tissue characteristics that are similar to those in the human heart. The present study not only confirms the expectation of increased acute thermal injury with the holmium:YAG laser, but also provides quantitative information concerning the extent of this difference and reveals the important observation that over a relatively short time, these differences disappear.

In addition to providing this comparison, our analysis describes the morphologic evolution of the channel over 6 weeks. The histologic findings, which suggest little, if any, acute blood flow capacity of laser channels, and invasion and subsequent occlusion of the channels by granulation tissue, have been dismissed by some investigators on the basis that the findings do not apply to human tissue under the "chronically ischemic" conditions in which the technique is applied clinically. However, we [23] and others [18] have examined autopsy specimens of patients who died at various times after successful TMLR operations that show essentially the same histologic findings as we document here in canine myocardium. For findings in the canine myocardium to be dramatically different from those in human tissue, a fundamental difference in the myocardial response to laser injury must be postulated in different species or in the setting of "chronic ischemia." Although material properties may vary between the normal state and chronic ischemia, no such fundamental difference in the healing response has been noted previously in this setting or in different species. Although a single case report has claimed long-term channel patency in a patient after

TMRL [24], the diameter of the "patent channels" ranged between 20 and 75 μ m with perichannel fibrosis of 150 to 400 μ m, in striking contrast to the original laser channel diameters of almost 1 mm. These dimensions are in fact almost identical to the vascular structures within the scarred channel region seen in our animal TMLR model and also in our own human TMLR autopsy experience [23]. The observations may therefore be better interpreted as scarred "channel remnants" revascularized with capillary-sized vessels, rather than as truly endothelialized laser channels. Thus, the discrepancy between our study and this previous report may be related more to terminology than to a fundamental difference in observations. Nevertheless, further evidence from human tissue is required before definitive conclusions can be made regarding the long-term patency of TMLR channels using different lasers in human subjects.

It is also important to recognize that careful examination of all normal, untreated hearts will reveal endothelium-lined vessels with patent endocardial orifices connected directly to the intramural circulation. These anatomically normal structures, which include myocardial sinusoids, arterioluminal vessels, and thebesian veins, communicate directly with the left ventricular chamber (see Fig 6) and yet are not thought to exhibit substantial reverse flow or to conduct ventricular blood into the myocardium, either in health or in ischemic heart disease. Accordingly, investigators should consider establishing procedures for ensuring that structures examined in autopsy specimens represent TMLR channels or their remnants, and not these normally occurring myocardial structures.

Clinical reports have indicated that symptomatic relief of angina using TMLR is observed in the postoperative period, with patients leaving the hospital with substantially less angina [11, 12]. If applicable to the clinical setting, the results of this histologic study provide further support for the proposition that factors other than direct perfusion through laser channels should be considered as mechanisms underlying this acute clinical effect. Possible alternative explanations include induction of local "anesthesia" through destruction of myocardial efferent

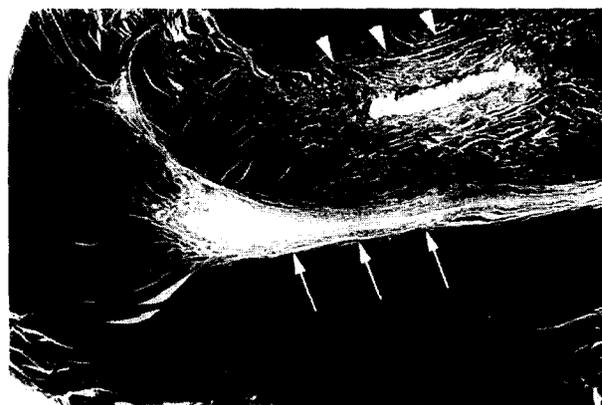


Fig 6. Normal myocardial sinusoid (arrows) adjacent to an acute (holmium:YAG) laser channel (arrowheads). See text for further details. (Masson's trichrome stain; $\times 20$.)

neural pathways and stimulation of vasodilatation and collateralization of regional blood flow by thermoacoustic effects or by the elaboration of locally acting vasoactive agents.

Data concerning angina relief in the chronic setting (available for the CO₂ laser) suggest that the effect is sustained and may be associated with improved regional blood flow [11, 12]. Neovascularization within channel areas and the apparent angiogenic stimulation seen in surrounding myocardium may contribute to the observed long-term clinical benefits of TMLR in the relief of angina. The intrachannel fibrin thrombus and the thermally infarcted myocardium may both contribute substantially to the angiogenic stimulus, possibly mediated through factors such as fibroblast growth factor, transforming growth factor- β , and vascular endothelial growth factor. Fibrin thrombus is a potent stimulator of neovascularization, and infarcted myocardium elicits a tremendous local angiogenic stimulus [25]. However, whether these new vessels contribute to myocardial perfusion and whether they connect with and conduct blood from the ventricular chamber in humans [15] or from surrounding myocardium will require further studies.

In conclusion, the histologic appearances of transmural channels made with CO₂ and holmium:YAG lasers have similar qualitative characteristics and differ only quantitatively in the sizes of the channel lumens and the area of surrounding thermal damage. Over time, tissue reaction to the laser injury appears identical for both lasers tested and exemplifies the granulation tissue response followed by cicatricial fibrosis and scar contraction. One intriguing finding not normally associated with wound healing was the discovery of muscular arterioles within channel remnants, in addition to the proliferating capillaries characteristic of granulation tissue. It is currently unclear whether and how these vessels contribute to the chronic clinical benefits of TMLR. Independent of the importance of these vessels, the results of this study suggest that mechanisms other than blood flow through large-diameter channels should be considered as contributing to both the acute and chronic clinical benefits of TMLR.

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