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Rudolf M. Verdaasdonck, "Transmyocardial revascularization: the magic of drilling holes in the heart," Proc. SPIE 10297, Matching the Energy Source to the Clinical Need: A Critical Review, 102970B (24 January 2000); doi: 10.1117/12.375212

SPIE.

Event: Digital Optical Computing, 1990, Los Angeles, United States

Transmyocardial revascularization: the magic of drilling holes in the heart

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ABSTRACT

Drilling holes in myocardial tissue using high-power lasers has shown to be effective in relieving angina in patients in an end-stage coronary heart disease who do not respond to medication and are unsuitable for standard revascularization techniques. An overview is presented of the interaction of various laser systems with myocardial tissue and the many experimental and clinical studies that have been conducted to elucidate the mechanism of the therapeutic effect of transmyocardial (laser) revascularization (TMR or TMLR).

An angina relief of 2 classes with an acceptable mortality (5 – 10 %) and morbidity (20 - 30 %) rate is achieved in the majority of patients. Adverse effects can be minimized by critical patient selection and by a percutaneous approach (PMR). There is no significant difference in the results between the treatment modalities. The acute beneficial effect of TMLR might be attributed to sympathetic denervation. The combined thermal and mechanical injury has shown to provoke an angiogenic response that may be enhanced by adding growth factors. Consequent improvement of the myocardial reperfusion and functionality has been observed but needs further verification with, e.g., high-resolution scintigraphic techniques. Based on the experience in over 7000 patients, TMLR shows to be an effective and safe procedure resulting in a significant improvement in the quality of life for a carefully selected patient group suffering from end-stage coronary disease.

Keywords: Transmyocardial Revascularization, Coronary Disease, Literature Review, Laser Surgery, Laser-Tissue Interaction, Holmium, Excimer, CO₂ laser, Angina, Heart.

1. INTRODUCTION

Over the last few years several thousands of patients suffering from an end-stage coronary heart disease have been treated by transmyocardial laser revascularization (TMR or TMLR). High power laser systems are used to drill channels through the myocardium assuming that blood from the left ventricle provides reperfusion of ischemic regions resulting in a reduction of angina. The majority of patients seem to benefit from the procedure, however the therapeutic effect of the treatment is not well understood. Since there are no randomized trials yet with large numbers and objective measurements confirming the benefit, there is a large skepticism within the societies of cardiologists and cardiac surgeons on the procedure.

In this paper an update will be given on the status of TMLR. First the pathology and the anatomy of normal and diseased myocardium will be discussed followed by a short historical overview of the development of TMR. Next the laser systems available for treatment will be reviewed and the mechanism of action during exposure of the myocardium will be discussed in detail. Depending on the laser system, various strategies have been developed for the treatment. Several animal studies have been conducted or are in progress to prove the working mechanism of TMLR. In the

Matching the Energy Source to the Clinical Need: A Critical Review, edited by Thomas P. Ryan,
Proc. of SPIE Vol. 10297 (Vol. CR75), 102970B · © (2000) 2017 SPIE
CCC code: 0277-786X/17/\$18 · doi: 10.1117/12.375212

meantime companies are pushing TMLR on the market all over the world with various laser systems. With data from initial studies, they applied for approval of the FDA, to get the techniques accepted. A summary will be given of the clinical results. Following, various hypotheses will be discussed for the mechanisms of TMLR.

The status of TMLR and related subjects was reviewed excellently in a book edited by Klein et al.¹ in 1997. In two more recent papers experimental and clinical results of TMLR are being reviewed till the beginning of 1999^{2,3}. This overview provides additional information of the present state of TMR (October 1999). Hopefully, it will contribute to the discussion to elucidate the working mechanism of TMLR and which randomized studies are needed to show if TMLR is just magic or a useful tool to treat patients who suffer from end-stage coronary artery disease without further therapeutic alternatives.

2. PATHOLOGY

Coronary arterial sclerosis is the main reason for chronic myocardial ischemia. The progression of the sclerosis takes place over many years and might already start at young adult age. The patient is not aware of his disease till the occlusions exceed 70 % of the original volume due to various compensation mechanisms. Besides an active regulatory system which influences the luminal width of an artery, the capacity of blood flow in side branches can increase or even new ones can be formed compensating for the original flow. Sometimes, natural anastomoses are formed from the major arteries surrounding the heart.

At some moment, symptoms will expose the presence of myocardial ischemia. This can occur abruptly by a (near) heart attack due to arterial spasm or an occluding thrombus. Immediate medical care is necessary to prevent partial myocardial destruction or arrhythmia resulting in instant death. The symptoms can also show up gradually by increasing angina, 'chest pain', especially during activity and stress. Medication is the first treatment of choice. If the symptoms sustain, diagnosed stenoses can be dilated by percutaneous transluminal balloon angioplasty (PTCA) or more invasively, coronary artery bypass surgery (CABG) can be performed. However, some patients do only benefit temporarily from these treatments or are poor candidates for either treatment due to the presence of diffuse small arterial disease or too small coronary arteries to receive a bypass. Relying on medication only, these patients are severely handicapped with a poor quality of life. Therefore, new therapeutic alternatives like transmyocardial revascularization need to be considered although they seem extraordinary at first instance.

The original idea of TMR is inspired by the reptilian heart where blood from the left ventricle directly perfuses the myocardium through a network of channels. Also in humans indications were found for the existence of alternative routes that could contribute to the perfusion of the myocardium. As early as the beginning of the 17th century, it was discovered that channels existed draining the venous blood in the ventricles called the Thebesian veins. Much later in 1933 the arteriosinusoidal vessels were discovered on the arterial side by Wearn et al.⁴ The number of coronary ventricular anastomoses as well as their contribution to the blood supply to the myocardium is not well known.

Comparison of this human 'perfusion' network with the reptilian heart is based on a strong simplification or an exaggeration. Reptiles have a 'normal' coronary system. However, their very spongy, filigree like inner part of the ventricular myocardium is

nourished by convection of the surrounding blood (figure 1). Due to the spongy character of the ventricular inner wall, the total surface area exposed to the ventricular blood is immense. Compared to this, the surface of the 'perfusion' network above or the channels created by TMLR is minimal and can not be seriously considered to provide the same mechanism of nourishment in human hearts.

figure 1 :
Drawing from reptile heart showing the spongy structure
(from 19th century anatomy textbook).

3. HISTORY

Based on pathologic findings of connections between the ventricles and the myocardium, it was postulated that direct perfusion of the myocardium should have a beneficial effect. One of the procedures developed and sometimes even used today is the Vineberg procedure where the internal mammary artery is implanted in a mechanically created hole in the myocardium⁵. Massimo and Boffi implanted plastic tubes with side holes to supply blood to the sinusoids in the myocardium⁶ while Goldman used perforated graft for a similar procedure⁷. Channels created by mechanical punctures from the left ventricle into the myocardium were reported by Sen^{8,9}, Khazei¹⁰ and Walter¹¹. However, Pifarre reported that the channels closed due to fibrosis within 6 weeks postoperatively¹². With the development and success of direct coronary artery grafting the puncture methods become outmoded. Only a few investigators continued the evaluation of alternative techniques of revascularization in conjunction with bypass grafting.

The initial experiments to use a laser to drill the channels in the myocardium were performed by Mirhoseini in 1971^{13,14}. He used a 400 W CO₂ laser to drill holes in a canine model. He used one pulse of 400 J triggered by the ECG in the diastolic phase to create the channels which showed to preserve the myocardium after ligation of the left anterior descending coronary artery. These results were reproduced by Eliseenko¹⁵ who claimed to have evidence of flow through the channels to the capillary and venous network using scintigraphy. Okada in Japan also showed reduction in the infarction site in lased hearts after coronary ligation and improvement in the electrocardiogram (ECG) in the months following surgery¹⁶.

The first patient was treated in 1983 by Mirhoseini in Milwaukee¹⁷. Followed by another 20 patients during the next 6 years. In 1987 Fisher and Crew joined forces to start TMLR procedures in Daly City, Ca., and contacted the company Laser Engineering

in Milford, Mass., to develop a clinical CO₂ system to deliver 50 J in 100 ms. Since 1989 tens of patients have been treated with the first prototype of the present Heart laser. In 1992, PLC Systems was founded from Laser Engineering, marketing the 800 W Heart laser capable to create a 40 mm deep hole in the myocardium in a single shot of 80 J in 100 ms. Based on the successful initial results and 'magic' of transmyocardial laser revascularization, PLC was followed by other companies. Each developed their own laser systems and strategies to perform TMLR as discussed in more detail in the following paragraphs.

4. TMR LASER TISSUE INTERACTION

4.1 Laser systems for TMLR

Although a high power (>400 W) CO₂ laser has proven to be effective to create a channel in the myocardium, a similar result can be achieved with other laser systems. The goal would be to create of a channel for 'reperfusion' of typically 20 to 40 mm long and ~1 mm diameter preferably on a beating heart within the ~100 ms duration during the diastolic phase in one or multiple shots. In first instance, the channel should stay open, which might be associated with minimal thermal damage. From the early research by Mirosheini¹⁴, it was already shown that continuous wave lasers induced too much thermal damage and that the channels occluded immediately. To minimize thermal injury, pulsed lasers are the preferred choice. The lasers should have a 'strong' interaction with myocardial tissue and be able to ablate tissue efficiently in a short time. The laser systems available that primarily meet these conditions are high power or pulsed CO₂ lasers, the Holmium:YAG laser, the XeCl excimer laser and the Erbium:YAG laser. Their characteristics are presented in table 1 together with some other pulsed lasers of interest. The interaction of pulsed lasers is discussed in the next part followed by detailed description of the lasers currently used for TMLR.

table 1: Characteristics of laser systems for TMR

laser system	XeCl Excimer	Dye	Nd:YAG pulsed	Ho:YAG	Er:YAG	CO ₂ pulsed
wavelength [nm]	308	400-800	1064	2100	2940	10600
pulse domain [μ s]	0.01 - 0.15	1 - 10	~300	~300	~300	10 - 2000
max pulse energy [mJ]	300	1000	1000	4000	1000	5000
max rep rate [Hz]	200	10	10 - 40	10 - 40	10 - 40	1000
max power [W]	10	10	100	80	20	100
penetration depth [μ m]	40	250	1400	300	1	20
effect. pen. depth [mm]	1	3	3	6	3	30
delivery device	fiber	fiber	fiber	fiber	art.arm (fiber)	art.arm
absorbing component	proteins water	blood pigments	pigments	water	water	water

4.2 Pulsed laser-tissue interaction

Pulsed laser systems generate laser pulses with lengths in the range of sub milliseconds down to picoseconds. In this short time, a considerable amount of energy is delivered to the tissue, sufficient to increase the temperature far over 100 degrees centigrade. In such a short time, the water contents in a tissue volume, determined by spot size and penetration depth, is instantly turned into vapor. This vapor is created at high pressure and starts expanding to a 1600-fold of its original liquid volume in tens to hundreds of microseconds. This way explosive vapor bubbles are formed with a potentially large mechanical force (figure 2).

figure 2: Sequence of an expanding and imploding vapor bubble induced by a holmium laser pulse in water. The frames are 50 μ s apart totally covering $\sim 600 \mu$ s.

At a tissue surface in an air environment, the vapor will escape from the surface into the air environment with some momentum towards the tissue. This might induce mechanical damage in the tissue. If the vapor is formed inside a small channel deeper inside the tissue, the vapor will push the wall of the channel aside and leave mechanical damage behind while escaping to the surface (figure 3). After the laser pulse, the channel will collapse to a diameter about the size of the original beam. If the energy is delivered by an optical fiber, the fiber will block the way to the surface and the vapor will penetrate deeper into the tissue, creating fissures in the tissue structure. While expanding, the vapor will cool down and turn back into liquid releasing the latent heat of vaporization, which is diffused to the environment.

If the explosive vapor formation takes place in a water or blood environment (e.g., in the left ventricle during a percutaneous approach), the pressure from the surrounding tissue is equal to the liquid on top of the tissue surface. Consequently, the vapor bubble will expand symmetrically in all directions. It will expand along the path of lowest mechanical resistance creating fissures between tissue layers. Considerable mechanical damage can be induced into the tissue far from the position of the irradiation. The typical size of these vapor bubbles is in the range of 1 mm up to 10 mm depending on the energy of the laser pulse. For lasers with a larger penetration depth in tissue, more energy is needed in one laser pulse to exceed the vaporization threshold. However, at the moment the threshold is reached, a large volume of tissue water is vaporized resulting in a big vapor bubble and potentially more mechanical damage. The mechanical effects inflicted on soft tissue by explosive vapor bubbles can be considered as collateral damage. Vapor formation is, however, fundamental to the ablation mechanism of pulsed

laser systems¹⁸. The forceful explosions can be applied effectively to break hard tissues like stones that are abnormal in the human body (lithotripsy).

figure 3: High speed image sequence of a deep channel formed during tissue irradiation with a 300 μ s focussed erbium laser beam.

During expansion, the vapor will cool down and eventually turn back into water releasing its latent heat of vaporization. In contrast to vapor expanding in an air environment, the vapor generated in liquid or tissue is still confined near the site of irradiation and will heat the tissue in contact with the vapor. At a water/tissue interface there will be a forceful turbulence providing effective cooling of the tissue surface. Within tissue, the energy released after the collapse of the vapor bubble will heat up the surrounding tissue (figure 4). This thermal energy is rapidly conducted to the environment and, in less than one second, ambient temperatures are restored. If, however, a next laser pulse follows within 0.5 seconds, the cooling process has not ended and the temperature rise will result in further temperature increase. At higher pulse repetition rates, there will be substantial heat conduction to the surrounding tissue resulting in thermal damage (figure 4). Special imaging techniques can be applied to study the thermal dynamical effects during tissue irradiation¹⁹ as presented in figure 4.

figure 4: left, vapor bubble in a water environment partly penetrating the surface of a transparent tissue model. Right, thermal image showing the thermal effects inside tissue when vaporization energy is release, while the surface is cooled by turbulent water

4.3 Effective penetration depth

The definition of penetration depth (table 1, row 7) has to be reconsidered during tissue ablation when the length of the laser pulse is in the microsecond region. Laser light, which is highly absorbed by tissue, has a very shallow penetration depth. E.g., the CO₂ and erbium laser have a penetration depth in the order of micrometers. Based on this information, a surgeon would consider these lasers not suitable to create deep channels. However, the energy absorbed during the first microseconds of the laser pulse can be sufficient to vaporize the top layer of the tissue creating a hole into the tissue. The beam enters the hole continuing to vaporize the tissue at the bottom of the crater as long as the pulse lasts. This way the beam can penetrate up to centimeters into the tissue. This phenomenon is visualized in figure 3 using high speed photography during exposure of a transparent tissue model with a focussed CO₂ or Erbium laser beam. During a 300 μ s long pulse, a 15 mm long vapor channel is formed in the gel. For obvious reasons, this phenomenon has been called 'the Moses effect'¹⁸. Although this effect is perfectly for TMLR, it is potentially hazardous for superficial ablation as applied in e.g. laparoscopic procedures.

The 'effective' penetration depth of lasers is a resultant of the volume of tissue that can be ablated with the energy in one laser pulse. It can vary strongly depending on the fiber diameter or the spot size at the tissue surface. For a small diameter fiber or spot, the volume will expand into the depth penetrating deeper compared to a large spot. Additionally, the expanding vapor can create fissures extending even deeper into the tissue.

4.4 Shock waves

In literature there is confusion in terminology between acoustic effects, shock waves and explosive vapor bubbles. At the very moment pulsed laser light is absorbed in the tissue, the instant thermal expansion of the tissue can induce a stress wave in the medium traveling near sonic velocities. In physics this phenomenon is called a shock wave. The shock wave is perfectly spherical and dissipates within 1 μ s. In the center of the spherical shock wave, a kernel of vapor at very high pressure is formed and starts

expanding at high velocity (figure 5, left). In many papers the explosive bubble itself is incorrectly referred to as shock wave. Due to the sound associated with expansion and implosion the bubble is also regarded as acoustic effect.

figure 5: Left: shock waves induced by cavitation bubbles, notice the kernel at the center of each spherical wave. Right: shock wave induced at the implosion of a holmium vapor bubble.

If the spherical shape of a vapor bubble is preserved during the implosion, the collision at the center is such forceful that another stress wave is formed in the medium (liquid or tissue, figure 5, right). This is again considered to be a 'real' shock wave. The damage due to shock waves is controversial. There is no clear evidence that shock waves induce damage. Ultrasonic respirators used for tumor resection in the brain generate shock waves continuously at 20 kHz but adverse effects in the delicate brain tissue have never been reported²⁰. The mechanical damage observed in the tissue exposed to pulsed lasers must be ascribed to the explosive and imploding vapor.

4.5 CO₂ laser characteristics for TMLR

4.5.1 Laser delivery system

The wavelength of the CO₂ laser can not be transported through optical fibers. The beam is transported through an articulated arm constructed from a set of hollow tubes with reflecting surfaces such as mirrors positioned in the joints. Choosing the proper materials, the reflectors can withstand the high peak powers. An articulated arm usually consists of six to eight mirrors mounted on rotating holders to provide steering in any direction. The holders are connected to each other by a set of rigid tubes. If properly aligned, the beam will exit the arm at the same position and angle independent from the position of the freely movable tubes. The alignment of the arm is very critical. In principle, the original beam characteristics do not change during transportation through an articulated arm. Only the beam diameter will increase depending on the beam divergence and length of the articulated arm. So the beam coming out of the articulated arm has a diameter of several millimeters and usually has a Gaussian distribution.

To obtain ablation effects in tissue and to have precision and control, an optical system is present at the end of the articulated arm to focus the beam at the target tissue. The optical components must be compatible with the wavelength of the beam. In case of the CO₂ laser lenses of fluorozirconate glass are used. The focal length of the lens is chosen depending on the distance and desired spot size on the target tissue. Due to the Gaussian energy distribution in the spot, the tissue is most efficiently vaporized in the center of the beam. At the rim of the spot more thermal damage can be observed. For application, the

focussing optics is incorporated in hand pieces with spacers to ensure the beam is focussed at the surface with the desired spot size. Instead of focussing, a telescopic system can be used to obtain a parallel beam with a small diameter, e.g., 1 mm. The spot size on the tissue is now independent of the distance between the hand piece and the tissue.

4.5.2 Fiber delivery for CO₂

Recently, fibers have become available for the delivery of high power CO₂ laser pulses²¹. The fibers with diameters of 500 to 1000 μm consist of hollow silica tubes with a special reflection coating on the inner wall. It has been demonstrated that several Joules of energy can be transported²². However, some problems have to be solved before the system can be applied clinically. E.g. the end of the hollow fiber is open so it can not be used in a wet environment like blood or tissue.

4.5.3 Pulsed CO₂ laser-tissue interaction

The formation of the channel in the myocardium by a high power CO₂ laser is similar to the sequence in figure 3. A rapidly growing vapor channel is formed during the laser pulse of several milliseconds. The vapor pressures creates an opening of a few millimeter in the tissue enabling the beam to reach deeper layers (figure 6, left) until the left ventricle chamber is reached and blood is vaporized. If the laser pulse is continuing at the moment of penetration of the left ventricle, the channel is prolonged in the blood. Eventually, the beam could hit the other wall. The lateral expanding vapor can induce small tears along the wall of the myocardium. Most of the vapor and ablation products escape through the surface of the epicardium. However, when the vapor condenses after the laser pulse, the channel collapses to the diameter of the original laser beam (figure 6, middle) and gas formed by ablation products mixes with the blood in the left ventricle. These bubbles can be observed using ultrasound. During the laser pulse, the wall of the channel is heated by direct absorption of laser beam and by heat transfer from the superheated water vapor (figure 6, right). After the laser pulse, part of the condensation heat finds its way into the channel wall. The total thermal effect can be substantial, resulting in a zone of coagulation and necrosis along the channel wall.

figure 6: CO₂ laser-tissue interaction. left: expanded channel during ablation, middle: collapsed channel with small cracks alongside, right: thermal effects along channel wall directly after the laser pulse.

4.6 Holmium:YAG laser characteristics for TMLR

4.6.1 Delivery system

The laser pulses from the Holmium:YAG laser can easily be coupled into an optical fiber with a diameter as small as 300 μm . To reduce transmission losses, the fibers have to be from a special grade with a minimum of water impurities: low OH^- fibers. The fibers are very flexible and can be advanced through catheter based systems for a percutaneous approach. To obtain a relative large diameter channel, the fiber end is modified to enlarge the spot size resulting in a tip of about 1 millimeter. During a series of laser pulses, the tip is advanced into the ablation channel.

4.6.2 Tissue interaction

Comparable with the CO_2 laser, a channel is formed during a laser pulse penetrating into the tissue. Much more energy is needed to initiate tissue vaporization due to the lower absorption of the holmium laser light. This results in a larger volume of tissue that is transformed into vapor and consequently a larger vapor bubble. This vapor bubble can only partly escape to the tissue surface due to the presence of the fiber tip and expands into the tissue creating an opening in front of the fiber (figure 7, left). This way the beam is able to ablate deeper tissue layers until the end of the laser pulse at about 300 μs . Due to pressure and momentum, the vapor bubble will expand further creating fissures and cracks along the channel wall. These defects may extend up to several millimeters into the tissue structure (figure 7, middle). Consequently, the vapor bubble will collapse releasing the latent heat of vaporization along the surface of the channel. The thermal energy is diffused and conducted into the tissue. Since the energy contents of one laser pulse is relatively large, the residual heat is substantial (figure 7, right). The vapor was not able to escape to the surface so all the energy remains in the tissue, resulting in a relatively large volume of coagulated tissue. After each pulse the fiber tip can be advanced several millimeters through the channel formed in the myocardium. The process is repeated each additional pulse. However, when penetrating deeper into the tissue, the escape route of vapor to the surface is totally blocked. If consequent pulses follow within 0.5 seconds, the thermal energy temperature will build up resulting in even more thermal damage.

figure 7: Holmium laser-tissue interaction. Left: bubble during ablation in transparent tissue model, middle: collapsed channel with large cracks alongside, right: extensive thermal effects along channel wall during tissue penetration with fiber

4.7 XeCl Excimer laser characteristics for TMLR

4.7.1 Delivery system

The excimer laser is also fiber delivered. The coupling of the energy into the fiber is more complicated. Due to the very short pulse time of tens of nanoseconds, the power densities of the focussed beam at the fiber entrance easily exceed the damage threshold of the fiber material and will damage the fiber. Therefore the pulse length has to be stretched to 100 ns and the energy has to be coupled to a large diameter fiber ($> 600 \mu\text{m}$) or be a divided over a bundle of smaller fibers. The transmission of UV wavelength of the excimer laser also requires very high purity of the fiber core material (fused-silica). The transmission will drop during intensive use of the fiber. Catheter systems with flexible fiber bundles enable a percutaneous approach similar to excimer based laser angioplasty catheters.

4.7.2 Tissue interaction

The UV light from the excimer laser is effectively absorbed by the tissue proteins. Tissue ablation of excimer lasers is ascribed to the breaking of the molecular bounds of tissue. Although this mechanism might be appropriate for the 193 nm ArF excimer laser as used in cornea shaping, the ablation mechanism of the 308 nm XeCl excimer has to be considered thermal. The energy absorbed by the cell membranes and compounds, is effectively transferred into thermal energy that heats the cellular water. Similar to the other lasers, water vapor is formed instantly at high pressure. Due to the short penetration depth, a relatively small amount of energy is necessary to exceed ablation threshold. Pulses of tens of mJ create vapor bubbles twice the size of the laser catheter (figure 8, left). The laser pulse has already ended during the 100 μs expansion time of the vapor bubble followed by a similar time for the collapse. During expansion and implosion the bubble is almost spherical. After each pulse only about 1 millimeter tissue is vaporized. The vapor creates small fissures in the channel wall but most of the surrounding tissue is pliable for the deformation by the bubble (figure 8, middle). Due to the small energy contents of the pulse, the residual latent heat of vaporization only affects the tissue in direct contact with the ablation channel. To create a long channel in a short time, the fiber is advanced with little force into the tissue with a high pulse frequency, typically 20 to 40 Hz. At this pulse frequency, there is some heat accumulation and conduction to the surrounding tissue (figure 8, right).

figure 8: Excimer laser-tissue interaction. Left: bubble during ablation in transparent tissue model, middle: collapsed channel with small fissures alongside, right: thermal effects along channel wall during tissue penetration with fiber

4.8 Other laser systems

The lasers described above are the systems available and attractive to perform TMLR due to the stage of technical development of the laser system itself and the energy delivery system. On a scientific basis, also erbium and pulsed dye lasers are candidates as well.

The erbium laser has a similar interaction with the myocardium as the CO₂ laser with the advantage that erbium fiber delivery systems are available, although not fully developed. The pulse energy is, however, lower compared to the CO₂ laser so one would need more than one pulse if applied without fiber delivery system. In combination with a fiber delivery system, the interaction of the erbium laser can be compared with the excimer laser. The fiber delivery system is fragile, expensive and less practical compared to systems for the excimer laser. With the development of erbium laser systems in the near future, higher pulse energies and repetition rates could be achieved. With a more practical fiber delivery system, the erbium laser would have advantages over the other laser systems as to practical size and presumably lower cost.

The interaction of the pulsed dye laser with myocardial tissue is comparable with the holmium laser. However, dye lasers are less attractive for their complex technology and higher exploitation costs.

4.9 Comparison laser systems

The interaction of different laser systems with myocardium can be compared at various criteria.

4.9.1 Efficiency of channel formation

It can be of practical use to know how efficient a laser system can drill a hole in the myocardium in relation to speed and energy used. For this purpose the author and co-workers conducted an experiment measuring fiber penetration using the holmium and excimer laser in relation to exerted force during exposure of bovine myocardium²³. For fiber penetration speeds up to 5 mm/pulse were observed. However, the highest penetration speed and penetration per pulse was obtained with a focussed beam of a pulsed CO₂ laser (up to 30 mm/pulse). The excimer laser showed to be more efficient in penetration per unit of energy resulting in less thermal side effects as compared to holmium and CO₂. The results are summarized in figure 9 presenting the penetration efficiency of the laser systems. Only the CO₂ laser is capable of creating the channel in one pulse. The holmium laser uses typically 10-20 pulses while the excimer uses 40-60 pulses to achieve a 30 mm transmural hole. Depending on the pulse repetition rate and optional ECG synchronization it takes 5 – 10 seconds to make the channel.

table 2: quantitative data from literature²⁸ of TMLR channels created with either 1 mm CO₂ beam or delivered through a by 600 μ m fiber

	CO ₂	Ho:YAG	XeCl excimer
Channel diameter [mm]	1.0	0.6	0.6
Unilateral damage [mm]	0.5 $\pm$ 0.2	1.8 $\pm$ 0.7	0.7 $\pm$ 0.2
Volumetric damage [cm ³]	1.5 $\pm$ 1.0	8.5 $\pm$ 5.3	1.9 $\pm$ 0.7

figure 9: Comparison of the penetration efficiency of laser systems typically used for TMLR.
 Laser settings for Holmium: 350 mJ and 750 mJ at 3 Hz, 1 mm fiber tip.
 Laser settings for Excimer: 30 mJ at 20 and 40 Hz, 1 mm fiber tip.
 Laser settings for CO₂: 350 mJ focussed to 0.5 and 1.0 mm spot at 3 Hz.

4.9.2 Channel characteristics

Several studies have been published describing the properties of the channels created with common laser systems for TMLR in vitro and, in vivo acutely and with a follow-up to several months^{23,24,25,26,27}. The findings are summarized below.

figure 10: general features of the channels created with three laser modalities showing the extent of thermal damage and mechanical fissures in the wall.

The general features of the laser channels are depicted in figure 10 and figure 11. There is always a rim of thermal damage and fissures along the channel wall. During penetration of the fiber into the myocardium randomly during the heart cycle, a channel is formed through the various moving muscle layers. Therefore the channel is not expected to be straight and will be closed most of the time during the cycle of the heartbeat. The channel is expected to be straighter when the fiber is advanced

synchronized with the heartbeat. The channel created with one shot of the CO₂ laser is expected to be straight and open²⁵ during the diastolic phase (figure 11).

figure 11:
schematic comparison between channel
created with fiber delivery and channel
created in one shot by a focussed beam.

The extent of coagulated and necrotic tissue along the channel wall and the size of fissures into the wall differ with the laser system and laser settings. table 2 shows the degree determined from histologic examination as published by Kadipasaolu et al.²⁸. This data shows, in contrast with the conclusion of the authors themselves, that there is only a significant difference in tissue damage between the CO₂ and the holmium laser. The tissue injury by the excimer laser is similar to the CO₂ laser. However, the relatively lesser thermal damage is counteracted by the larger mechanical damage. This observation is consistent with the results of other published data^{23,24,25,26,27}.

5. TREATMENT STRATEGIES

5.1 Open chest approach

The straightforward approach is applying laser energy to the heart during an open chest procedure. The patient is connected to a heart-long machine and the heart is arrested during the procedure. The laser energy is delivered by a hand piece, which is positioned on the epicardium of a hybernating location of the left ventricle (figure 12). The hand piece either contains optics to focus the CO₂ beam on the surface or an optical fiber, which is advanced into the myocardium during pulsing of the laser. During arrest the left ventricle can only be partly filled with blood so the surgeon has to be careful not to damage structures the moment he perforates the wall entering the left ventricle. At locations that have been identified as reversible ischemic areas, on average a one-millimeter diameter transmural channel is created per square centimeter.

TMLR can also be performed on a beating heart. By applying some pressure, the hand piece is positioned on the epicardium and lightly moved along with the heart motion. For the CO₂ laser only one shot is sufficient to create a hole within 20 to 40 ms. The laser pulse is triggered on the R-wave of the ECG so the pulse is fired during the diastolic phase. During this time, the left ventricle is totally filled with blood and the wall is temporally motionless and insensible for stimulation.

The fiber-delivered devices are used either with or without triggering. Without triggering, arrhythmia can occur due to mechanical stimulation by the explosive bubbles²⁸. Normally, the arrhythmia disappear immediately after the laser exposure. The ventricular arrhythmias can be suppressed by applying lidocaine on the epicardium. When the fiber is advanced during laser activation synchronized with the heart beat, the arrhythmia are minimized²⁹. A short train of 6 pulses within 100 ms was given shortly after the R-wave preventing stimulation of the heart. Most transmural channels were achieved within 8 heart cycles without causing arrhythmia.

figure 12: Schematic view of channel formation with the Heart laser hand piece (source PLC)

Due to the presence of the fiber in the myocardium arrhythmia might still occur. The transmural channels will bleed for one to two minutes and can easily be controlled by digital compression before a coagulum closes the channel at the epicardial side. In the rare cases the channel keeps bleeding an epicardial suture is placed to seal the channel. On average 30 to 40 channels are created.

During most procedures transesophageal echocardiography is used to evaluate the channel formation and to confirm the transmural penetration of the laser. At the moment, the beam enters the left ventricle the vapor bubbles are clearly visible on the echograph. The echograph also helps to rule out accidental mitral valve injury. For the fiber delivered procedures, echocardiography is not essential. The tactile feedback from the fiber and change in the pitch of the acoustic signal of the ablating laser pulse clearly verify the entering of the ventricular chamber. A doppler probe can be employed on the carotid artery in the neck to watch gas bubbles going to the brain. The small bubbles are assumed be harmless³⁰.

The procedure might be improved by locally immobilizing the position where the hole is drilled using one of the fixation techniques that are commercially available nowadays. One of those systems is the 'Octopus' which was developed at the University Hospital Utrecht, The Netherlands³¹. Two small arms with a row of suction cups enable immobilization of the epicardium at locations that might be difficult to approach otherwise. In vivo experiments showed that the surgeon has a better control advancing the fiber into the myocardium during lasing²⁹. One might even consider an applicator that advances the fiber with a constant force or speed.

*figure 13:
Fiber penetration into the myocardium
at a position immobilized using the
'Octopus' during an in vivo experiment
in a pig.*

5.2 Open chest in combination with bypass procedure

Although the indication for performing a TMR procedure is treating patients without other treatment options, it can be combined with bypass surgery (CABG). If some regions of the hibernating myocardium still have arteries with a suitable anastomosis site, bypassing is the preferred method of treatment. However, if other regions can not be bypassed, TMLR is performed in that region. Only during the open chest procedure, the surgeon can make the final decision if he will perform bypass surgery, TMLR or a combined therapy³². To prove the safety of TMLR, the first clinical studies investigated its use in combination with CABG in areas of the myocardium that could not be surgically revascularized. The combined procedure makes the evaluation of the efficacy of the TMLR procedure difficult since it is not clear how the TMLR contributed to the improvement of the patient³³. Potentially, scintigraphic studies can show an improved perfusion in the CABG area as well as the TMLR areas. Only randomized trials including thousands of patients in various treatment groups, may prove a significant difference between the treatment modalities. However, surgeons performing either CABG or TMLR procedures feel they should not withhold the patient the most appropriate treatment due to the randomization in a study. In one of the first large randomized trials there was a crossover of 60 % to TMLR treatment group from the group originally selected for medication management³⁴. The condition of these patients worsened that far compared to the TMLR group that the investigators found it not ethical to deny them the TMLR treatment. Due to the large crossover in this study, the FDA refused the first request for approval of TMLR.

5.3 Minimal invasive opening

The heart can be approached from the left side of the patient by a left anterolateral thoracotomy and entering through the fourth, fifth or sixth intercostal space (figure

14,left). The pericardium is opened and elongated hand pieces are positioned on the target areas on the epicardium. This approach is common for most Heart laser CO₂ procedures³⁵. The laser beam comes in parallel to the epicardial surface and is directed sideward just above the target side by a mirror in the hand piece. In case of a fiber delivery the fiber is steered through a ninety degree curve at the end of the hand piece (figure 14,right).

figure 14: Left: approach of the heart for a TMLR procedure through a left anterolateral thoracotomy. Right: fiber delivery hand piece for the holmium laser (source Eclipse).

5.4 Thoracoscopic procedure

The TMLR procedure can be performed using thoracoscopy. Using two or three holes between the ribs, video guidance is used to position the tube for delivering the laser energy on the epicardium. This method can be applied for both fiber delivered and focussed laser beams^{36,37}. For the fiber delivered laser pulses, it is helpful to immobilize the target location using, e.g., the octopus technique. The arms can be entered through different slots in the chest. This method has successfully been applied in animal studies²⁹. The thoracoscopic approach is normally not used in patients who have had cardiac surgery before due to adhesions.

5.5 Percutaneous procedure

Percutaneous myocardial revascularization PMR is a totally different approach by creating the channels from the inside of the ventricle. Using the 'standard' catheterization techniques, fibers can be positioned perpendicular to the ventricular wall. The fiber is positioned using fluoroscopy or electrophysiology mapping techniques like the biosense system³⁸ for the location of the hibernating myocardium. During laser exposure, the fiber tip is advanced up 6 – 8 mm into the myocardium.

figure 15: Artist's impression of PMR with a holmium delivery device (source Eclipse).

This approach has been fully developed for the holmium laser. After animal studies^{39,40} percutaneous transmyocardial laser revascularization (PMLR) has already successfully been applied in patients^{41,42}. It is expected that an excimer laser system will follow soon.

Although in first instance the CO₂ light can not be delivered through fibers, new fiber technologies may be available in the near future. It has already been shown that high energy CO₂ laser pulses can be delivered thoracoscopically through hollow wave guides^{21,43}.

6. TMLR COMPANIES

Since PLC started the marketing of the TMR technology using lasers, several laser companies have followed with their own laser system. PLC is however far ahead of the competitors as to numbers of patients treated and they were the first of the two companies until October 1999, which have FDA approval. In table 3 an overview is presented of companies on the market with the TMR technology they are developing or marketing. Most 'laser' companies have strategic alliances with big companies in the cardiovascular or cardiac surgery field for their superior marketing organization. When the technology of a small start-up company gets interesting, one of the leading companies in the field will take a major interest in that company. This market is rather dynamic so the data presented in table 3 (updated Sept '99) could already have changed.

table 3: overview companies marketing TMR laser technology

Company	Laser Type	Corporate Partner	# pts treated (estim. sept '99)
Acculase	XeCl excimer	Baxter	> 20
CardioDyne (Trimeddyne)	Ho:YAG		
CardioGenesis	Ho:YAG	Boston Scientific	> 500 (50 PMR)
CircuLase	Pulsed CO ₂		
Eclipse Surgical	Ho:YAG	Sorin Biomedica	> 500 (50 PMR)
Medolas	XeCl excimer	AutoSuture	> 500
Optimedix	CO ₂		
PLC Systems	CO ₂		> 5000
Spectranetics	XeCl excimer	U.S. Surgical	

Cardiogenesis was probably the second company actively working on the TMR technology using the Holmium:YAG laser. Eclipse Surgical Technologies also developed a Holmium:YAG laser based TMLR system and is the second company with FDA approval. Both holmium companies have also developed a percutaneous approach for TMLR. CardioDyne is a subdivision from Trimeddyne which has been selling Holmium:YAG lasers for many years in the field of angioplasty and orthopedic surgery. Spectranetics and Medolas are already on the market for many years with their excimer systems for laser angioplasty. Spectranetics has also developed a successful procedure for the removal of pacemaker leads. For all companies the approval of their TMLR technology by the FDA is the major obstacle. Now that TMLR using the Heart laser has obtained approval, PLC has cleared the way for the other companies. However, the FDA has not approved the use of TMLR in conjunction with angioplasty or bypass grafting.

7. CLINICAL DATA

7.1 Indications, inclusions and protocols

Transmyocardial revascularization has originally been developed as the last option of treatment for patients with angina class III or IV who do not benefit from the highest dose of the standard medication. Further, the ischemic and hibernating areas of the myocardium are not suitable for bypass surgery. Other indications that might be considered for treatment are vasculopathies after heart transplantation and cardiomyopathies related to microangiopathy⁴⁴.

For most studies the following guidelines are used for considering a patient for TMLR treatment

- Disabling angina pectoris Class III or IV (Canadian Cardiovascular Society Angina Score: CCSAS)
- In first instance not suitable for conventional bypass surgery or PTCA.
- In combination with bypass surgery when some hibernating areas are not suitable for grafting
- Angina persisting on maximal tolerated doses of two different cardiac medications (nitrates, β -blockers, calcium-channel blockers, and trimetazidine).
- Evidence of viable ischemic myocardium (e.g. DTST).
- Evidence of adequate perfusion in one the regions supplied by one of the major coronary arteries from recent coronary angiogram.
- Reproducible Exercise Tolerance Test by modified Bruce protocol resulting in angina.
- No recent hospitalization due to acute ischemic syndrome (< 1 month).
- No recent interventions or myocardial infarction (< 3 months).
- No cardiac transplant recipient
- Ejection fraction of 30 percent or greater.
- No congestive heart failure or severe chronic obstructive pulmonary disease

7.2 Pre- and post operative evaluation

Various studies are going on with slightly different protocols depending of the goal. To obtain quantitative data before the procedure and for the follow-up after the procedure most studies include the following examinations

7.2.1 Myocardial perfusion

Coronary arteriography can be applied to visualize the anatomy of coronary arteries down to a diameter of about 1-mm. This technique, however, does not provide quantitative data on the regional perfusion of the myocardium.

Myocardial scintigraphy, however, provides information on the myocardial perfusion on a cellular level. Different techniques are applied with various radioactive tracers. Each tracer shows a specific part of the metabolism during uptake in the cell. This way information can be obtained on the 'health' of a cell. The resolution of the imaging techniques showing the distribution of the tracers in the myocardium is in the order of cm^3 .

Single-positron emission computer tomography (SPECT) is performed in most patients to assess the extent and reversibility of the myocardial ischemia using dipyridamole stress thallium-201. Dipyridamole and thallium are injected at stages before, during and after stress exercise. SPECT imaging at those stages show the distribution of these

agents in the myocardium revealing the locations that are normal, have a reversible or a permanent perfusion defect ³⁴.

Positron Emission Tomography (PET) is used to demonstrate 'hibernating myocardium': lack of perfusion with still existing metabolism present. Rest-stress myocardial perfusion can be studied using ¹³N-ammonia or ^{99m}Tc-MIBI as agent while for resting glucose metabolism ¹⁸F-deoxyglucose is used.

7.2.2 Motion and function of the myocardium

X-ray cardiocinematography is applied to study the dynamics of the ventricular cavities. The contours of the cavities are projected in two perpendicular planes during the heart cycle. It is difficult to obtain accurate volumetric data from this imaging technique. The techniques can only be applied while the patient is at rest stage.

Echocardiography is applied to visualize regional wall motion and quantify the left ventricular ejection fraction (LVEF). This method can be applied during physical and pharmacological stress (e.g. dobutamine). It might even be possible to visualize the created TMR channels using 2-D echocardiography ⁴⁵.

Scintigraphy can also be applied for visualization of intracardiac radio-activated blood reflecting the inner ventricle contour (GBP = gated blood pool). The images are acquired gated on the ECG to obtain contours at the various stages of the heart cycle (multiple gated scintigraphic angiography: MUGA). This provides quantitative data of regional and overall filing of the ventricular chamber.

One of the latest developments in scintigraphy is ECG gated SPECT and PET registration. From the acquired data, a computer animation of the beating heart is reconstructed showing the correlation between the regional perfusion/metabolism and regional wall motion. It is possible to determine regional amplitudes of wall and regional ejection fractions.

The validity of MRI and CT imaging of the myocardial wall dynamics are under investigation. After TMLR myocardial signal alteration and perfusion differences have been observed. Using T₁-weighted ECG-gated spin echo sequences the myocardium was studied before and after injection of gadolinium. The clinical value of the change observed need to be defined. Visualization of individual channels was not possible ⁴⁶.

7.2.3 Exercise tolerance

Depending on the pre-operative condition of the patient, a treadmill tolerance test is conducted according to specific protocols (e.g. Bruce protocol⁴⁷). During testing, the exercise intensity is increased every 3 minutes until symptoms occurred. Maximum exercise time and symptoms at stopping are recorded. The maximum distance covered during a 12-min walk also provides information on the condition of the patient.

7.2.4 Patient perception

Qualitative data are obtained from protocolled interviews to assess the quality of life e.g. Short Form-36 or the Seattle Angina Questionnaire (SAQ). The angina class is determined according the Canadian Cardiovascular Society Angina Score: CCSAS.

7.2.5 Addition post operative evaluation

Most clinical studies report on short term mortality (peri-operative or 1 – 7 days) and long term death rate (6 months to total length of follow-up) as well as morbidity. Hospital admission for angina and use of medication is also recorded during follow-up.

7.3 Clinical results

7.3.1 Overall summary

The clinical results of major, recent and interesting studies published are summarized in table 4. The estimated number of patients treated worldwide with TMLR is near 7000. In table 3 the estimated numbers per laser modality are presented.

Most striking is the improvement of two angina classes in 70 to 80% of the patients. There is an instant improvement directly after the procedure and it persists over a year. Some studies report a slight improvement (10-20 %) of the LVE and perfusion. The short-term mortality was in the initial studies 10 - 15 %. More recent studies show lower mortality percentages below 5% due to more appropriate patient selection ⁴⁸. The mortality of 1 year follow-up is an additional 10 %. The average hospital stay is 5 to 10 days. Compared to medical treated groups there is no change in life expectancy, however the quality of life is greatly improved. Number of hospitalization due to angina related complaints dropped from 5 to 1 in the period of six months before and after the procedure. Exercise tolerance improved about 40 % for TMLR patients while it decreased 15 % for patients in medication therapy. The angina relief increases during the first year and seems to decrease gradually afterwards as reported by some studies ⁴⁹

7.4 Complications

7.4.1 Mortality

The perioperative deaths are mostly due to acute myocardial infarctions and pulmonary problems. March et al. ³⁴ found a relation between the time interval from an episode of unstable angina and perioperative deaths. If angina occurred within 7 day before TMLR, the perioperative mortality was 27%. Using aggressive medication the stabilization necessary for the TMLR procedure could be achieved. In this same study the crossover group from medication to TMLR had a 15% perioperative mortality rate and survival of 73% at one year. The crossover group was a notable 60%. The perioperative mortality decreased significantly due to the learning curve and patient selection. Most studies report that early deaths during the hospital stay and late deaths were related to sudden arrhythmia and pump failure due to myocardial infarctions. Indicators for late death showed to be age and LVEF.

7.4.2 Morbidity

The most common postoperative complications are summarized below with an estimated percentage for occurrence based on the studies presented in table 4 : congestive heart (left-ventricular) failure ~15 %; arrhythmias ^{28,34} ~20 %; myocardial infarction directly after TMR ~ 7 %; bleeding ~15 %; wound or respiration infection ~ 30 %. Other adverse effects reported are respiration failure, pneumo thorax and embolizations ⁶⁸. Injury to chordae or valves caused by the CO₂ beam were rarely reported and did not have major consequences ³⁴.

From the experience in the first studies and a larger group of patients treated risk factors could be determined: previous CABG, gender female, age > 55, creatine kinase > 1600 IU, absence intercoronary collaterals, pulmonary arterial pressure > 21 mm Hg, LVEF < 40% and occurrence of unstable angina within 15 days before procedure. Most of them are similar to the risk factors related to coronary bypass surgery ⁶⁹. Depending on the treatment inclusions, which may differ between studies, patients with higher risk factors can be rejected for TMLR. However, these are also the patients who need the procedure most.

table 4: Summary clinical results of published studies.

study	year start	year end	# reference	laser system or medication	# patient	2 angina class improv at 1 yr	exercise test improvement	% early death	% late death	LVEF improvement	perfusion improv. (SPECT / PET)	ave. hosp stay days	# hospitalization 1 yr
initial studies													
Frazier		95	50	CO ₂	21	yes		7	10	yes	20%		
Horvath	93	95	51	CO ₂	20	yes		10	15		improv		
sole TMLR													
Krabatsch	94	97	48	CO ₂	171	yes		7		no	no		
Horvath		97	35	CO ₂	200	75%		9	8		improv		decr
Agarwal	95	97	52	CO ₂	102	yes	yes	15		no	no	9	
Nagele	95	97	49	CO ₂	60	yes		12	11		worse		
Burns		98	53	CO ₂	967	34%	yes	10					
Milano	95	96	54	Holm	22	yes	yes	0	8		no	7	
Allen		97	55	Holm	42	yes		12	0		yes	6	
Al-Sheikh		98	56	Holm	8	100%		0			yes		
comb CABG/TMLR													
Moosdorf		97	57	CO ₂	134	yes					40%		
Vincent	94	97	33	CO ₂	268	yes	yes	10					
Trehan	95	97	58	CO ₂	77	yes	yes	2	0		yes		
Lutter		97	59	CO ₂	67	yes	yes	13		no	no		
Morgan	95	97	60	Exc	30	>80%		0	0		yes		
Diegeler		97	61	Holm	28	yes	yes	0	2	no	no	8	
comparison TMLR versus medication													
Schofield	93	97	62	CO ₂	94	25%	no	5	6	no	no	10	0.5
Schofield	93	97	62	medic	94	4%	no	n.a.	4	no	no		0.8
March		98	34	CO ₂	97	72%		3	12		20%		
March		98	34	medic	101	13%		n.a.	21		-27%		
Frazier		98	63	CO ₂	91	72%	yes	3	12		20%		2
Frazier		98	63	medic	101	13%		n.a.	21		-27%		69
Jones	96	97	64	Holm	43	yes	yes	2	10			3.2	
Jones	96	97	64	medic	43	yes	no	n.a.	12				
Allen		98	65	Holm	132	76%	yes	9	7		no		
Allen		98	65	medic	143	32%			11				
Burkhoff		98	66	Holm	92	48%	yes						
Burkhoff		98	66	medic	90	14%	decr						
percutaneous (PMR)													
Galli	98	98	42	Holm	15	yes		0	0				
Kaul	98	98	67	Holm	55	yes		0	0				

7.5 Controversial results

TMLR has been controversial from the beginning because up till now there is no proven anatomical, physiological, histological, diagnostic, and clinical rationale for the efficacy of the treatment ⁷⁰. In general the various clinical studies can only show significant improvement of qualitative data while only few studies present significant improvement of quantitative data ^{34,63} which is contradicted by other studies.

The randomized trials reported by the 'first-generation' investigators are in general enthusiastic and positive ^{34,35}. However, these studies could be biased by the earlier results from prospective non-controlled trials and the close corporation and support by the manufacturers ⁷⁰. The sceptical conclusions from more recent trials ^{49,62} dispute the benefit of the procedure which according to investigators only has a temporarily relief for the patient at the cost of a high mortality and morbidity rate. Other studies, however, show clearly that with the appropriate patient selection the mortality of the TMLR group is similar or less compared to medication management groups while the condition of the later gets worse. It is unquestionably that the quality of life greatly improves for the TMLR patients. At this moment, it is too early to determine for how long these effects last. The sceptical paper by Schofield et al. ⁶² and the associated commentary ⁷⁰ provoked an interesting discussion in the *Lancet* with the 'positive' investigators ^{71,72,73,74,75} defending their results and pointing out misinterpretation of data and difference in patient selection. There also exists discussion on the treatment strategy either treating the reversible areas identified by nuclear studies or treating the entire ventricle ⁷³. All discussants conclude that more clinical and experimental studies are necessary and hasty judgements should be avoided.

If coronary bypass surgery and coronary angioplasty would have been approached with the same skepticism as is happening with TMLR, the acceptance of both these procedures would have been doubtful. Both revascularization techniques do not significantly prolong the life expectancy but greatly improve the quality of life. The symptom relief can, however, also be achieved by medication therapy ⁷⁶.

It has also been implied that improvements can be obtained by fine adjustments of the medical therapy. In one study, the patients already selected for TMLR, were reevaluated after an intensified antianginal therapy ⁴⁹. In most cases the therapeutic modification was an addition of molsidomin to nitrates. About 50% of the patients had a good clinical response to the medication and were therefore treated further medically.

8. HYPOTHESIS WORKING MECHANISM OF TMLR

8.1 Direct perfusion

As discussed in the pathology section, the original hypothesis that the oxygen rich blood from the left ventricular chamber would allow direct myocardial perfusion through the newly formed channels similar to a reptilian heart is improbable ⁷⁷. Results from studies using labeled microspheres were negative ^{78,79}. In another independent study it was shown that the TMR channels failed to preserve viability of even a single layer of myocytes around the patent channels in an infarction inflicted area ⁸⁰. There is also no evidence to support the notion that TMR channels could allow intraventricular blood to reach the myocardium by connecting with intramyocardial sinusoids. Furthermore, the existence of myocardial sinusoids has become controversial⁸¹. Klaus et al. obtained a remarkable result studying the dynamics of flow through TMLR channels in patients 15 day after the procedure using contrast echocardiography ⁸². The channels were perfused

during systole and the small area of myocardium showed contrast during the next heart cycles till the material was washed away through the coronary venous system.

Experimental studies and data obtained from postmortem examinations^{83,84,85,86,87} show that several weeks after the TMR almost all channels are occluded independent of the laser source used. Only UV lasers seem to have a higher incidence of patent channels²⁷.

*figure 16:
patent TMLR channels with connections
into the myocardium (source PLC)*

In some animal studies, it was shown that the myocardium could be protected against functional deterioration after acute ischemic events⁸⁸. This result is opposite to the finding in other animal studies showing no protection at all^{89,90}. Nevertheless, it could reduce ischemia-related arrhythmia and increase coronary flow transiently⁹¹.

The reason for the reduction in angina directly after the procedure must be found in one of the other hypotheses.

8.2 Angiogenesis

The improvement of the angina class and exercise tolerance of TMLR treated patients could be a secondary effect of neovascularization through angiogenesis^{92,93}. The myocardial injury inflicted by the laser during the channel formation could promote the upregulation of local growth factors resulting in the migration of endothelial cells to the laser-treated segment. As discussed in the previous paragraph most channel thrombose within a few days after treatment. The channel remnants after several weeks, however, show the presence of endothelial cells and prominent neovascular response in the surrounding tissues^{94,95,96,97,98}. Somehow laser light is essential to provoke this tissue response. Several studies have shown that only the laser created channels resulted in channel derivatives in association with neovascular response. In channels where the fiber was passed through the myocardium without activation of the laser this response was lacking^{96,99}. A recent study, however, reports increased angiogenic factor expression and concomitant neovascularization at up to 4 weeks in channels created with an 18-gauge needle^{100,101} which would be similar to laser created channels.

The relation of the neovascular response to the magnitude of thermal and mechanical damage induced by the different laser systems is unclear. As described in the laser-tissue interaction section, there is an essential difference in thermal and mechanical effects of each laser type. Animal and clinical studies, however, show similar clinical results. It was shown, however, that too much thermal damage as induced by low power continuous wave lasers was ineffective¹⁴.

Angiogenesis is induced by growth factors that belong to the class of mediators referred to as angiogens. Two important groups of angiogens that play a major role in the neovascularization process are the vascular endothelial growth factor (VEGF) and the fibroblast growth factor (FGF). The role of these growth factors in the neovascularization process is described in more detail by Lee et al.⁹². The angiogens stimulate budding and growth of small vessels from preexistent blood vessels and increase the lumen of preexistent vessels by endothelial and smooth muscle cell proliferation. Even new blood vessels may be formed by vasculogenesis which was until recently believed only to be confined to the embryo phase¹⁰².

It has been proven that the delivery of this growth factors in ischemic regions of the heart stimulate the growth of collateral blood vessels⁹². The presence of higher concentration of growth factors in laser created TMR channels has been proven^{93,103}. In various animal studies the effect of angiogenesis in TMLR-treated areas of hibernating myocardium was shown^{77,104,105,106,107}. The evidence presented strongly indicates that angiogenesis has a major role in the mechanism of action of TMLR.

It is apparent that TMLR could be combined with therapeutic angiogenesis to provide a synergistic effect. On one hand, the gene therapy could be useful in augmenting the angiogenic response to TMLR. TMLR, on the other hand, could provide a source of blood inflow for the collateral vessels developed as a result of the angiogenic therapy (figure 17). The results of the initial studies combining the two therapies look promising^{94,108,109}.

figure 17: TMLR channels providing blood to the neovascularized myocardium (source PLC)

8.3 Sympathetic denervation

Patients treated with TMLR show an immediate relief in angina that can not be attributed to improved perfusion of the myocardium. Only after a few weeks angiogenesis might contribute to an improved perfusion and relieve of angina as described in the paragraph above. The potential mechanism to explain the acute improvement in angina class could be denervation of the myocardium¹¹⁰. During TMLR nerve fibers in the myocardium are destroyed disabling pain sensation. The patients feel

better and are not restricted by pain sensation. It can even be hypothesized that due to more exercise the hibernating myocardium might be stimulated resulting in angiogenesis.

Sundt and Kwong have shown the effect of denervation of the myocardium in a canine model ^{110,111}. Myocardial regions of which the nerves were destroyed chemically and regions where TMLR channels were formed using a holmium laser, did not show any response during stimulation. Also immunoblots with an antibody against tyrosine hydroxylase, a sympathetic nerve-specific enzyme, showed the loss of nerves in chemical and laser treated areas.

In contrast, Hirsch et al. found the opposite result ¹¹². Stimulation of sympathetic and parasympathetic efferent neurons by electrical or chemical means did not change the local ventricular contractile responses before and after TMLR using the holmium laser. Therefore, the efficacy of TMLR could not be ascribed to local denervation.

Assuming that sympathetic denervation is one of the mechanisms behind the benefits from TMLR, some caution might be considered. If pain can be interpreted as a warning mechanism, the deactivation might result in debilitation of the hibernating myocardium. Consequently, irreversible damage might occur resulting in death due to arrhythmia and LVEF failure. However, an increased incidence of myocardial infarction and sudden death has not been reported in relation to TMLR patients yet. In the follow-up, TMLR patients should be alert on other symptoms of ischemic diastolic dysfunction of the heart like dyspnoea and fatigue.

8.4 Improved synchronization

The creation of the laser channels could influence the electrical conductivity of the hibernating myocardium, which would contribute to synchronous contraction of the myocardium resulting in an improved LVEF ¹¹³. The region of hibernating myocardium consists of islands with vital muscle cells surrounded by scar tissue. The pathway of the electric stimuli from the AV node has changed compared to healthy tissue. This signal might be delayed or even 'captured' in the hibernating myocardium resulting in an unorganized contraction with a decrease of the LVEF. The increased perfusion due to the TMLR channels could revive the hibernating myocardium and improve the synchronization of wall contraction as observed in some studies ¹⁰⁵.

8.5 Wall contraction due to scarring

In a recent animal study by Mueller et al. ²⁶ it is suggested that scars resulting from the TMLR channels might be responsible for the clinical improvement of the patient. The healing response was followed in time comparing TMLR channels formed in healthy myocardium and in an area with an infarction. All channels were occluded after one week and whitish scar tissue was formed after two weeks. In the scar tissue from the infarction, the former channels could no longer be distinguished due to a similar healing response. However, the TMLR scars exhibited an increased vascular density in comparison with scar tissue of myocardial infarction, which did not extend into their immediate vicinity ¹¹⁴. Due to cicatricial contraction the initial lesion size in the myocardium reduced up to 100 %. By applying Laplace law, this contraction effect could reduce the cavity diameter and therefore the wall stress and the oxygen consumption. This mechanism might explain the angina relief and improved regional wall motion. This would also imply that larger lesions as produced with the holmium laser in comparison to the CO₂ and Excimer laser, would be more effective. However, one would expect to achieve similar clinical results just by sticking hot needles in the

myocardium. If cicatricial contraction is the mechanism of action for TMLR, low cost thermal devices could replace the expensive and complex laser systems.

8.6 Placebo

A thoracotomy has a placebo effect and a psychological effect. However, this effect only lasts for two months at most and appears in about 30 % of the patients. TMLR has proven to have a far better result. On average 70-80% of the patients benefit from the procedure. Most of the patients treated were physically disabled before the procedure and could resume an almost normal lifestyle after the procedure. A double blind study including a control group for the placebo effect would not be ethical.

8.7 Combination of mechanisms

The effects observed in patients after a TMLR treatment can not be attributed to just one of the mechanisms described above. Most probable, it will be a combination of several mechanisms since some of them are strongly related. There tends to be conformity in the cardiovascular field to the following scenario: The acute beneficial effect of TMLR results from sympathetic denervation and maybe partly a placebo effect. The channels occlude by a thrombus within a few days. In the following weeks the healing response induces angiogenesis improving the perfusion and consequently the (synchronized) contraction of the myocardium. The neovascularization remains for over a year.

9. FUTURE OF MYOCARDIAL REVASCULARIZATION

9.1 Costs effectiveness of TMLR

The costs related to TMLR will play a role in the acceptance of the technology. Since the reimbursement policy by insurance companies and public health care differs from country to country, TMLR may be more accessible through private practitioners. Although, the TMLR procedure is expensive it might be cost effective in the long term. If patients can reduce largely in antianginal medication and hospitalization frequency is reduced the invested cost will be compensated. In addition, due to the improved quality of life, the patients can partially return to their professional life. For the time being, TMLR should be concentrated in a few expert centers in each country, which have obtained adequate experience to minimize mortality and morbidity. They may be able to prove the cost effectiveness and act as training institutes for new centers to follow in the future when TMLR has become more accepted.

9.2 Laser systems and strategies

After the approval of TMLR by the FDA for the CO₂ Heart laser, other companies with different laser systems are following soon. Only large studies might show variation in clinical outcome, which show to be rather similar up till now.

By fine-tuning the parameters of the different lasers, the local tissue injury can be controlled. The degree of injury will induce local inflammation, which plays a critical role in the stimulation of both capillary and larger vessel growth. The combination of TMLR and simultaneous delivery of VEGF or genes, that promote angiogenesis and endothelial cell motility, may be synergistic.

Recently, more studies are being published on percutaneous myocardial revascularization PMR^{41,67,115,116}. The results suggest a slightly greater functional improvement, similar changes in angina score, no deaths during hospital stay and low morbidity. Although PMR is not expected to improve the results of TMLR, the lower

risk involved may gain more acceptance for the improvements obtained with this less invasive approach. The percutaneous approach is technically only feasible using fiber delivered holmium or excimer laser systems. A fiber delivery system for high power CO₂ lasers has been developed but is not suitable for intraventricular use.

Heart transplants recipients with cardiac allograft diffuse vasculopathy¹¹⁷ are being considered for TMLR treatment. A small group of patients has already been treated and were asymptomatic after three months of follow-up¹¹⁸.

9.3 TMR using other energy sources

It is unclear which characteristics of the channels in the myocardium are critical for the clinical improvement. As shown in the laser–tissue interaction section (paragraph 4.9.2) the channels measure around 1 mm and are associated with thermal and mechanical injury in the surrounding myocardium. Other modalities are also capable to create similar channels in the myocardium. The use of hot needles would be straightforward, however, the channels would probable collapse directly. The therapy should include actual tissue ablation and thermal effects.

9.3.1 Radio frequency ablation

Radio frequency ablation is already being used for the epicardial and percutaneous endocardial treatment of arrhythmia^{119,120,121}. An electrical current can be induced locally in the tissue, resulting in an instant heating and vaporization of tissue similar to a laser. It is difficult to transport high currents through small catheters with sufficient energy to ablate tissue in a short time due to impedance losses. For arrhythmia surgery large tissue areas are coagulated with exposure time during tens of seconds. However, it has been shown that myocardial tissue can be ablated instantly using a catheter based spark erosion device¹²². A similar device can be used to drill holes.

9.3.2 Microwave

In a similar setting as described above for radio frequency, microwave energy can be used for the local heating of myocardium^{123,124,125}. Due to its nature, it will be difficult to concentrate the microwaves in a small area to induce sufficient heating for tissue vaporization. However, if local thermal damage could already induce angiogenesis, microwaves could still have potential for TMR.

9.3.3 Ultrasound

Ultrasound is an alternative energy delivery technique that can elevate tissue temperature quickly. Ultrasound has already been applied for the coagulation of tissue noninvasively deep in the body using either external sources or by means of intracavitary applicators. Arrhythmia have been treated using ultrasound systems^{123,126}. Extracorporeal lithotripsy devices based on focussed ultrasound have been proven to effectively break down stone, e.g., in the kidney, with minimal collateral damage. Short high-energy bursts of ultrasonic waves that are focussed inside the body induce local stresses that result in cavitation effects in soft tissues. Smith et al. have shown the feasibility of this technique by drilling holes during *in vivo* tests using canine myocardium¹²⁷. The great advantage of ultrasound compared to laser is that TMR could be performed in a completely noninvasive image-guided procedure from an external ultrasound source. The channels could be made of practically any desired shape with a device significantly less expensive than current laser systems.

Other modalities combine laser with ultrasound¹²⁸. Ultrasonic waves are generated by a transducer attached to a silica fiber that also transports the laser energy. The tip of the

fiber vibrates at high velocity creating cavitation bubbles in a liquid. The imploding cavitation bubbles effectively remove soft tissue. This technique is being developed for percutaneous TMR application.

9.4 Improved diagnostics

One of the major objective criteria to prove the efficacy of TMLR is the perfusion and the wall motion, which can be studied with scintigraphic techniques. The results from various clinical studies are not consistent due to the difference in resolution of the scanners. Only the-state-of-the-art PET scanners are capable showing high resolution images of regional myocardial perfusion. Frazier et al.^{129,130} have shown evidence of improved sub endocardial perfusion after TMLR treatment of patients.

Also 3-D echocardiography and new imaging MRT techniques can provide additional evidence of improved wall motion, functionality and metabolism.

9.5 Need for international registry

To overcome all the skepticism regarding transmyocardial revascularization, the researchers, clinical investigators and manufacturers should join forces in an international registry to acquire as much patient data within a reasonable time as possible. Also protocols should be established which make the comparison of data from different centers and laser modalities possible. Hopefully, this international database can provide answers to the many questions regarding the mechanism of TMLR.

10. CONCLUSIONS

TransMyocardial Laser Revascularization shows to be an effective and relatively safe procedure to reduce anginal symptoms of patients in an end-stage coronary heart disease who do not respond to medication and are unsuitable for standard revascularization techniques. The associated mortality and morbidity is acceptable and can be further improved using the appropriate patient selection and using a percutaneous approach.

There is no significant difference in the results between the treatment modalities. The acute beneficial effect of TMLR might be attributed to sympathetic denervation. The combined thermal and mechanical injury provokes an angiogenic response that might be enhanced by external growth factors. The consequent improvement of the myocardial reperfusion and functionality needs further verification with, e.g., high-resolution scintigraphic techniques.

Laser drilling in the heart is not based on magic but on clear physics. However, the therapeutic mechanism of action is complex and needs further investigation.

ACKNOWLEDGEMENTS

The author likes to acknowledge the contribution and support of his co-workers Christiaan van Swol and Matthijs Grimbergen. He also likes to thank TMLR investigators and representatives from TMLR companies for the fruitful discussions and providing the latest patient data.

REFERENCES

1. "TMLR Management of coronary artery diseases," Klein,M., Schulte,H.D., Gams,E. eds., Springer-Verlag, Berlin, 1998.
2. Abramov,D., Bhatnagar,G., Tamariz,M., Guru,V., and Goldman,B.S., Current status of transmyocardial laser revascularization: review of the literature. *Can.J Cardiol.* **15**, 303-310, 1999.
3. Hughes,G.C., Abdel-aleem,S., Biswas,S.S., Landolfo,K.P., and Lowe,J.E., Transmyocardial laser revascularization: experimental and clinical results. *Can.J Cardiol.* **15**, 797-806, 1999.
4. Wearn,J., Klump,T.C., and Zschiesche,A.B., The nature of vascular communications between the coronary arteries and the chambers of the heart. *Am Heart J* **9**, 143-170, 1933.
5. Vineberg,A., Evidence that revascularization by ventricular-internal mammary artery implants increases longevity. Twenty-four year, nine months follow-up. *J Thorac.Cardiovasc.Surg.* **70**, 381-397, 1975.
6. Massimo,C. and Boffi,L., Myocardial revascularization by a new method of carrying blood directly from the left ventricle cavity into the coronary circulation. *J Thorac Surg* **34**, 257-264, 1957.
7. Goldman,A., Greenstone,S.M., and Preuss,F.S., Experimental methods for producing a collateral circulation to the heart directly from the left ventricle. *J Thorac Surg* **6**, 373, 1956.
8. Sen,P.K., Udawadia,T.E., and Kinare,S.G., Transmyocardial acupuncture: a new approach to myocardial revascularization. *J Thorac.Cardiovasc.Surg.* **50**, 189, 1965.
9. Sen,P.K., Daulatram,J., Kinare,S.G., Udawadia,T.E., and Parulkar,G.B., Further studies in multiple transmyocardial acupuncture as a method of myocardial revascularization. *Surgery* **64**, 861-870, 1968.
10. Khazei,A.H., Kime,W.P., Papadopoulos,C., and Cowley,R.A., Myocardial canalization: a new method of myocardial revascularization. *Ann Thorac Surg* **6**, 163-171, 1968.
11. Walter,P., Hundeschagen,H., and Borst,H.G., Treatment of acute myocardial infarction by transmural blood supply from the ventricular cavity. *Eur Surg Res* **3**, 130-138, 1971.
12. Pifarre,R., Jasuja,M.L., Lynch,R.D., and Neville,W.E., Myocardial revascularization by transmyocardial acupuncture. A physiologic impossibility. *J.Thorac.Cardiovasc.Surg.* **58**, 424-431, 1969.
13. Mirhoseini,M. and Cayton,M.M., Revascularization of the heart by laser. *J Microsurg* **2**, 253-260, 1981.
14. Mirhoseini,M. and Cayton,M.M., Transmyocardial laser revascularization: historical background and future directions. *J.Clin.Laser.Med.Surg.* **15**, 245-253, 1997.
15. Eliseenko,V.I., Skobelkin,O.K., Brekhov,E.I., and Zdravovskii,S.R., [Morphological bases of myocardial revascularization by laser irradiation]. *Biull Eksp Biol Med* **98**, 737-739, 1984.
16. Okada,M., Transmyocardial laser revascularization (TMLR): a long way to the first successful clinical application in the world. *Ann.Thorac.Cardiovasc.Surg.* **4**, 119-124, 1998.
17. Mirhoseini,M., Fisher,J.C., and Cayton,M.M., Myocardial revascularization by laser: a clinical report. *Laser Surg Med* **3**, 241-245, 1983.
18. Leeuwen,A.G.J.M.v., Veen,M.J.v.d., Verdaasdonk,R.M., and Borst,C., Non-contact tissue ablation by holmium:YSGG laser pulses in blood. *Lasers Surg Med* **11**, 26-34, 1991.
19. Verdaasdonk,R.M., Imaging laser induced thermal fields and effects. In "Laser-Tissue interaction VI" (S.L.Jacques, Ed.), pp. 165-175, SPIE, Bellingham, 1995.
20. Verdaasdonk,R.M., Swol,C.F.P.v., and Grimbergen,M.C.M., High-speed and thermal imaging of the mechanism of action of the Cavitation Ultrasonic Surgical Aspirator (CUSA). *SPIE proceedings* **3249**, 72-84, 1998.

21. Matsuura, Y., Abel, T., and Harrington, J.A., Optical properties of small-bore hollow glass waveguides. *Applied Optics* **34**, 6842-6847, 1995.
22. Snaijer, A.d., Verdaasdonk, R.M., Grimbergen, M.C.M., and Swol, C.F.P.v., Design and realization of a fiber delivery system for the continuous wave and pulsed CO₂ laser. *SPIE proceedings* **3262**, 108-118, 1998.
23. Sachinopoulou, A., Verdaasdonk, R.M., and Beek, J.F., Comparison of ablation channels created by the ultrapulsed CO₂ laser, the Holmium laser and 308 nm Excimer laser in view of Trans-Myocardial Revascularization (TMR). *SPIE proceedings* **2671**, 42-48, 1996.
24. Fisher, P.E., Khomoto, T., DeRosa, C.M., Spotnitz, H.M., Smith, C.R., and Burkhoff, D., Histologic analysis of transmyocardial channels: comparison of CO₂ and holmium:YAG lasers. *Ann.Thorac.Surg.* **64**, 466-472, 1997.
25. Jansen, E.D., Frenz, M., Kadipasaoglu, K.A., Pfefer, T.J., Altermatt, H.J., Motamedi, M., and Welch, A.J., Laser-tissue interaction during transmyocardial laser revascularization. *Ann.Thorac.Surg.* **63**, 640-647, 1997.
26. Mueller, X.M., Tevacaari, H.T., Genton, C.Y., and von Segesser, L.K., Myocardial scarring after transmyocardial laser revascularization: A potential mechanism of clinical improvement? *Lasers Surg Med* **25**, 79-87, 1999.
27. Whittaker, P., Spariosu, K., and Ho, Z.Z., Success of transmyocardial laser revascularization is determined by the amount and organization of scar tissue produced in response to initial injury: results of ultraviolet laser treatment. *Lasers.Surg.Med.* **24**, 253-260, 1999.
28. Kadipasaoglu, K.A., Sartori, M., Masai, T., Cihan, H.B., Clubb, F.J.J., Conger, J.L., and Frazier, O.H., Intraoperative arrhythmias and tissue damage during transmyocardial laser revascularization. *Ann.Thorac.Surg.* **67**, 423-431, 1999.
29. Grundeman, P.F., Leeuwen, A.G.J.M.v., Verdaasdonk, R.M., Jansen, E.W.L., Mansvelt Beck, H.J., and Borst, C., Thoracoscopic creation of transmural laser channels in the beating porcine heart using conventional lasers: closed chest application of the 'Octopus' cardiac immobilization method. *Eur Heart J* 1996.
30. von Knobelsdorff, G., Brauer, P., Tonner, P.H., Hanel, F., Naegle, H., Stubbe, H.M., and Esch, J.S., Transmyocardial laser revascularization induces cerebral microembolization. *Anesthesiology* **87**, 58-62, 1997.
31. Borst, C., Jansen, E.W.L., Tulleken, C.A.F., Grundeman, P.F., Mansvelt Beck, H.J., van Dongen, J.W., Hodde, K.C., and Bredee, J.J., Coronar artery bypass grafting without cardiopulmonary bypass and without interruption of the native coronary flow using a novel anastomosis site restraining device ("Octopus"). *J Am Coll Card* **27**, 1356-1364, 1996.
32. Trehan, N., Mishra, Y., Mehta, Y., and Jangid, D.R., Transmyocardial laser as an adjunct to minimally invasive CABG for complete myocardial revascularization. *Ann.Thorac.Surg.* **66**, 1113-1118, 1998.
33. Vincent, J.G., Bardos, P., Kruse, J., and Maass, D., End stage coronary disease treated with the transmyocardial CO₂ laser revascularization: a chance for the 'inoperable' patient. *Eur.J.Cardi thorac.Surg.* **11**, 888-894, 1997.
34. March, R.J., Transmyocardial laser revascularization with the CO₂ laser: one year results of a randomized, controlled trial. *Semin.Thorac.Cardiovasc.Surg.* **11**, 12-18, 1999.
35. Horvath, K.A., Cohn, L.H., Cooley, D.A., Crew, J.R., Frazier, O.H., Griffith, B.P., Kadipasaoglu, K., Lansing, A., Mannting, F., March, R., Mirhoseini, M.R., and Smith, C., Transmyocardial laser revascularization: results of a multicenter trial with transmyocardial laser revascularization used as sole therapy for end-stage coronary artery disease. *J.Thorac.Cardiovasc.Surg.* **113**, 645-653, 1997.
36. Horvath, K.A., Thoracoscopic transmyocardial laser revascularization. *Ann.Thorac.Surg.* **65**, 1439-1441, 1998.

37. Milano,A., Pietrabissa,A., and Bortolotti,U., Transmyocardial laser revascularization using a thoracoscopic approach. *Am.J.Cardiol.* **80**, 538-539, 1997.
38. Kornowski,R., Hong,M.K., Haudenschild,C.C., and Leon,M.B., Feasibility and safety of percutaneous laser revascularization using the Biosense system in porcine hearts. *Coron.Artery.Dis.* **9**, 535-540, 1998.
39. Kim,C.B., Kesten,R., Javier,M., Hayase,M., Walton,A.S., Billingham,M.E., Kernoff,R., and Oesterle,S.N., Percutaneous method of laser transmyocardial revascularization. *Cathet.Cardiovasc.Diagn.* **40**, 223-228, 1997.
40. Weber,H.P., Heinze,A., Richter,U., Ruprecht,L., Zhuang,S., and Unsold,E., Transcatheter endomyocardial laser revascularization: a feasibility test. *Thorac.Cardiovasc.Surg.* **46**, 74-76, 1998.
41. Kornowski,R., Bhargava,B., and Leon,M.B., Percutaneous transmyocardial laser revascularization: An overview [In Process Citation]. *Catheter.Cardiovasc.Interv.* **47**, 354-359, 1999.
42. Galli,M., Zerboni,S., Politi,A., Llambro,M., Bonatti,R., Molteni,S., and Ferrari,G., Percutaneous transmyocardial revascularization with holmium laser in patients with refractory angina: a pilot feasibility study. *G.Ital.Cardiol.* **29**, 1020-1026, 1999.
43. Snaijer,A.d., Verdaasdonk,R.M., Grimbergen,M.C.M., and Swol,C.F.P.v., Design and realization of a fiber delivery system for the continuous wave and pulsed CO2 laser. *SPIE proceedings* **3262**, 108-118, 1998.
44. Maisch,B., Funck,R., Schonian,U., and Moosdorf,R., [Indications for transmyocardial laser therapy]. *Z.Kardiol.* **85 Suppl 6:269-79**, 269-279, 1996.
45. van der Wouw,P.A., van der Sloot,J.A., van der Meulen,J., Tukkie,R., and Beek,J.F., Transmyocardial laser channels [In Process Citation]. *J.Am.Soc.Echocardiogr.* **11**, 986-988, 1998.
46. Weber,C., Maas,R., Steiner,P., Beese,M., Hvalic,M., Stubbe,M., and Bucheler,E., [Transmyocardial laser revascularization--the initial experiences of imaging in MRT]. *Rofo.Fortschr.Geb.Rontgenstr.Neuern.Bildgeb.Verfahr.* **169**, 260-266, 1998.
47. Bruce,R.A. and McDonough,J.R., Stress testing in screening for cardiovascular disease. *Bull N Y Acad Med* **45**, 1288, 1969.
48. Krabatsch,T., Tambeur,L., Lieback,E., Shaper,F., and Hetzer,R., Transmyocardial laser revascularization in the treatment of end-stage coronary artery disease. *Ann.Thorac.Cardiovasc.Surg.* **4**, 64-71, 1998.
49. Nagele,H., Stubbe,H.M., Nienaber,C., and Rodiger,W., Results of transmyocardial laser revascularization in non- revascularizable coronary artery disease after 3 years follow-up [In Process Citation]. *Eur.Heart J.* **19**, 1525-1530, 1998.
50. Frazier,O.H., Cooley,D.A., Kadipasaoglu,K.A., Pehlivanoglu,S., Lindenmeir,M., Barasch,E., Conger,J.L., Wilansky,S., and Moore,W.H., Myocardial revascularization with laser. Preliminary findings. *Circulation* **92**, II58-II65, 1995.
51. Horvath,K.A., Mannting,F., Cummings,N., Shernan,S.K., and Cohn,L.H., Transmyocardial laser revascularization: operative techniques and clinical results at two years. *J.Thorac.Cardiovasc.Surg.* **111**, 1047-1053, 1996.
52. Agarwal,R., Ajit,M., Kurian,V.M., Rajan,S., Arumugam,S.B., and Cherian,K.M., Transmyocardial laser revascularization: early results and 1-year follow-up. *Ann.Thorac.Surg.* **67**, 432-436, 1999.
53. Burns,S.M., Sharples,L.D., Tait,S., Caine,N., Wallwork,J., and Schofield,P.M., The transmyocardial laser revascularization international registry report. *Eur.Heart J* **20**, 31-37, 1999.

54. Milano, A., Pratali, S., De Carlo, M., Pietrabissa, A., and Bortolotti, U., Transmyocardial holmium laser revascularization: feasibility of a thoracoscopic approach [In Process Citation]. *Eur.J.Cardiothorac.Surg.* **14 Suppl 1:S105-10**, S105-S110, 1998.
55. Mack, C.A., Patel, S.R., and Rosengart, T.K., Myocardial angiogenesis as a possible mechanism for TMLR efficacy. *J.Clin.Laser.Med.Surg.* **15**, 275-279, 1997.
56. Al-Sheikh, T., Allen, K.B., Straka, S.P., Heimansohn, D.A., Fain, R.L., Hutchins, G.D., Sawada, S.G., Zipes, D.P., and Engelstein, E.D., Cardiac Sympathetic Denervation After Transmyocardial Laser Revascularization. *Circulation* **100**, 135-140, 1999.
57. Moosdorf, R., Rybinski, L., Hoffken, H., Funck, R.C., and Maisch, B., [Transmyocardial laser revascularization in stable and unstable angina pectoris]. *Herz.* **22**, 198-204, 1997.
58. Trehan, N., Mishra, M., Kohli, V.M., Mishra, A., Jangid, D.R., and Bapna, R., Transmyocardial laser revascularisation as an adjunct to CABG. *Indian Heart J.* **48**, 381-388, 1996.
59. Lutter, G., Frey, M., Saurbier, B., Nitzsche, E., Hoegerle, S., Brunner, M., Martin, J., Lutz, C., Spillner, G., and Beyersdorf, F., [Treatment strategies in therapy refractory angina pectoris: transmyocardial laser revascularization] Behandlungsstrategien bei therapierefraktärer Angina pectoris: Transmyokardiale Laserrevaskularisation. *Z.Kardiol.* **87 Suppl 2**, 199-202, 1998.
60. Morgan, I. and Campanella, C., Transmyocardial laser revascularisation in Edinburgh. *Br.J.Theatre.Nurs.* **7**, 4-9, 1998.
61. Diegeler, A., Schneider, J., Lauer, B., Mohr, F.W., and Kluge, R., Transmyocardial laser revascularization using the Holium-YAG laser for treatment of end stage coronary artery disease. *Eur.J.Cardiothorac.Surg.* **13**, 392-397, 1998.
62. Schofield, P.M., Sharples, L.D., Caine, N., Burns, S., Tait, S., Wistow, T., Buxton, M., and Wallwork, J., Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial [see comments]. *Lancet* **353**, 519-524, 1999.
63. Frazier, O.H., March, R.J., and Horvath, K.A., Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease [see comments]. *N Engl.J Med* **341**, 1021-1028, 1999.
64. Jones, J.W., Schmidt, S.E., Richman, B.W., Miller, C.C., Sapire, K.J., Burkhoff, D., and Baldwin, J.C., Holmium:YAG laser transmyocardial revascularization relieves angina and improves functional status [In Process Citation]. *Ann.Thorac.Surg.* **67**, 1596-1601, 1999.
65. Allen, K.B., Dowling, R.D., Fudge, T.L., Schoettle, G.P., Selinger, S.L., Gangahar, D.M., Angell, W.W., Petracek, M.R., Shaar, C.J., and O'Neill, W.W., Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina [see comments]. *N Engl.J Med* **341**, 1029-1036, 1999.
66. Burkhoff, D., Schmidt, S., Schulman, S.P., Myers, J., Resar, J., Becker, L.C., Weiss, J., and Jones, J.W., Transmyocardial laser revascularisation compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomised trial. ATLANTIC Investigators. Angina Treatments-Lasers and Normal Therapies in Comparison. *Lancet* **354**, 885-890, 1999.
67. Kaul, U., Shawl, F., Singh, B., Sudan, D., Sapra, R., Ghose, T., and Dixit, N.S., Percutaneous transluminal myocardial revascularization with a holmium laser system: procedural results and early clinical outcome [see comments]. *Catheter.Cardiovasc.Interv.* **47**, 287-291, 1999.
68. Grocott, H.P., Amory, D.W., Lowry, E., Newman, M.F., Lowe, J.E., and Clements, F.M., Cerebral embolization during transmyocardial laser revascularization. *J.Thorac.Cardiovasc.Surg.* **114**, 856-858, 1997.
69. Higgins, T.L., Fawzy, E.G., and Loop, F.D.e.al., Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. *JAMA* **267**, 2344-2348, 1992.

70. Pretre,R. and Turina,M.I., Laser to the heart: magic but costly, or only costly? [comment] [see comments]. *Lancet* **353**, 512-513, 1999.
71. Hetzer,R. and Krabatsch,T., Transmyocardial laser revascularisation [letter; comment]. *Lancet* **353**, 1706-1707, 1999.
72. Horvath,K.A. and Kadipasaoglu,K.A., Transmyocardial laser revascularisation [letter; comment]. *Lancet* **353**, 1704-1705, 1999.
73. Lansing,A.M., Transmyocardial laser revascularisation [letter; comment]. *Lancet* **353**, 1705-1707, 1999.
74. McMurray,J., Transmyocardial laser revascularisation [letter; comment]. *Lancet* **353**, 1704-1707, 1999.
75. Moosdorf,R., Transmyocardial laser revascularisation [letter; comment]. *Lancet* **353**, 1705-1706, 1999.
76. RITA-2 trail participants, Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. *Lancet* **350** , 461-468, 1997.
77. Roethy,W., Yamamoto,N., and Burkhoff,D., An examination of potential mechanisms underlying transmyocardial laser revascularization induced increases in myocardial blood flow. *Semin.Thorac.Cardiovasc.Surg.* **11**, 24-28, 1999.
78. Kohmoto,T., Fisher,P.E., Gu,A., Zhu,S.M., Yano,O.J., Spotnitz,H.M., Smith,C.R., and Burkhoff,D., Does blood flow through holmium:YAG transmyocardial laser channels? *Ann.Thorac.Surg.* **61**, 861-868, 1996.
79. Kohmoto,T., Uzun,G., Gu,A., Zhu,S.M., Smith,C.R., and Burkhoff,D., Blood flow capacity via direct acute myocardial revascularization. *Basic.Res.Cardiol.* **92**, 45-51, 1997.
80. Kohmoto,T., Fisher,P.E., Gu,A., Zhu,S.M., DeRosa,C.M., Smith,C.R., and Burkhoff,D., Physiology, histology, and 2-week morphology of acute transmyocardial channels made with a CO2 laser. *Ann.Thorac.Surg.* **63**, 1275-1283, 1997.
81. Tsang,J.C.C. and Chiu,R.C.J., The phantom of "myocardial sinusoids": A historical reappraisal. *Ann Thorac Surg* **60**, 1831-1835, 1995.
82. Klaus, B. Blood flow characteristics through transmyocardial laser created channels. *J Am Coll Cardiol.* 1997. (Abstract)
83. Burkhoff,D., Fisher,P.E., Apfelbaum,M., Kohmoto,T., DeRosa,C.M., and Smith,C.R., Histologic appearance of transmyocardial laser channels after 4 1/2 weeks. *Ann.Thorac.Surg.* **61**, 1532-1534, 1996.
84. Gassler,N., Wintzer,H.O., Stubbe,H.M., Wullbrand,A., and Helmchen,U., Transmyocardial laser revascularization. Histological features in human nonresponder myocardium. *Circulation* **95**, 371-375, 1997.
85. Krabatsch,T., Schaper,F., Leder,C., Tulsner,J., Thalmann,U., and Hetzer,R., Histological findings after transmyocardial laser revascularization. *J Card Surg.* **11**, 326-331, 1996.
86. Schweitzer,W., Schneider,J., Maass,D., and Hardmeier,T., [Transmyocardial laser revascularization. Histopathology of laser channels in 10 postoperatively deceased patients 1 to 18 days after treatment with a CO2 laser]. *Pathologe.* **18**, 374-384, 1997.
87. Sigel,J.E., Abramovich,C.M., Lytle,B.W., and Ratliff,N.B., Transmyocardial laser revascularization: three sequential autopsy cases. *J.Thorac.Cardiovasc.Surg.* **115**, 1381-1385, 1998.
88. Yano,O.J., Bielefield,M.R., and Jeevanandam,V.e.al., Prevention of acute regional ischemia with endocardial laser channels. *Ann Thorac Surg* **56**, 46-53, 1993.

89. Malekan,R., Kelley,S.T., Suzuki,Y., Reynolds,C., Plappert,T., Sutton,M.S., Edmunds,L.H.J., and Bridges,C.R., Transmyocardial laser revascularization fails to prevent left ventricular functional deterioration and aneurysm formation after acute myocardial infarction in sheep. *J.Thorac.Cardiovasc.Surg.* **116**, 752-762, 1998.
90. Misfeld,M., Szabo,K., Kraatz,E.G., Grossherr,M., Schmidtke,C., Pilgrim,M., Kuhnel,W., and Sievers,H.H., Electron-microscopic findings after transmyocardial laser revascularization in an acute ischemic pig model. *Eur.J.Cardiothorac.Surg.* **13**, 398-403, 1998.
91. Tjomsland,O., Grund,F., Kanellopoulos,G.K., Kvernebo,K., and Ilebekk,A., Transmyocardial laser induces coronary hyperemia and reduces ischemia- related arrhythmias, but fails to delay development of myocardial necrosis after coronary artery occlusion in pigs. *J Cardiovasc.Surg (Torino)* **40**, 325-331, 1999.
92. Lee,L.Y. and Rosengart,T.K., Transmyocardial laser revascularization and angiogenesis: the potential for therapeutic benefit. *Semin.Thorac. Cardiovasc.Surg.* **11**, 29-35, 1999.
93. Spanier,T., Smith,C.R., and Burkhoff,D., Angiogenesis: a possible mechanism underlying the clinical benefits of transmyocardial laser revascularization. *J.Clin.Laser.Med.Surg.* **15**, 269-273, 1997.
94. Fleischer,K.J., Goldschmidt-Clermont,P.J., Fonger,J.D., Hutchins,G.M., Hruban,R.H., and Baumgartner,W.A., One-month histologic response of transmyocardial laser channels with molecular intervention. *Ann.Thorac.Surg.* **62**, 1051-1058, 1996.
95. Kadipasaoglu,K.A., Pehlivanoglu,S., Conger,J.L., Sasaki,E., de Villalobos,D.H., Cloy,M., Piliuko,V., Clubb,F.J.J., Cooley,D.A., and Frazier,O.H., Long- and short-term effects of transmyocardial laser revascularization in acute myocardial ischemia. *Lasers.Surg.Med.* **20**, 6-14, 1997.
96. Mack,C.A., Magovern,C.J., Hahn,R.T., Sanborn,T., Lanning,L., Ko,W., Isom,O.W., and Rosengart,T.K., Channel patency and neovascularization after transmyocardial revascularization using an excimer laser: results and comparisons to nonlased channels. *Circulation* **96**, II-9, 1997.
97. Malekan,R., Reynolds,C., Narula,N., Kelley,S.T., Suzuki,Y., and Bridges,C.R., Angiogenesis in transmyocardial laser revascularization. A nonspecific response to injury. *Circulation* **98**, II62-II65, 1998.
98. Horvath,K.A., Chiu,E., Maun,D.C., Lomasney,J.W., Greene,R., Pearce,W.H., and Fullerton,D.A., Up-regulation of vascular endothelial growth factor mRNA and angiogenesis after transmyocardial laser revascularization. *Ann Thorac Surg* **68**, 825-829, 1999.
99. Whittaker,P., Rakusan,K., and Kloner,R.A., Transmural channels can protect ischemic tissue: Assessment of long-term myocardial response to laser- and needle-made channels. *Circulation* **93**, 1-10, 1996.
100. Chu,V., Kuang,J., McGinn,A., Giaid,A., Korkola,S., and Chiu,R.C., Angiogenic response induced by mechanical transmyocardial revascularization. *J Thorac Cardiovasc.Surg* **118**, 849-856, 1999.
101. Chu,V.F., Giaid,A., Kuang,J.Q., McGinn,A.N., Li,C.M., Pelletier,M.P., and Chiu,R.C., Thoracic Surgery Directors Association Award. Angiogenesis in transmyocardial revascularization: comparison of laser versus mechanical punctures. *Ann Thorac Surg* **68**, 301-307, 1999.
102. Schaper,W. and Ito,W.D., Molecular mechanisms of coronary collateral vessel growth. *Circ Res* **79**, 911-919, 1996.
103. Pelletier,M.P., Giaid,A., Sivaraman,S., Dorfman,J., Li,C.M., Philip,A., and Chiu,R.C., Angiogenesis and growth factor expression in a model of transmyocardial revascularization. *Ann.Thorac.Surg.* **66**, 12-18, 1998.

104. Hughes,G.C., Lowe,J.E., Kypson,A.P., St, Phippen,A.M., Peters,K.G., Coleman,R.E., DeGrado,T.R., Donovan,C.L., Annex,B.H., and Landolfo,K.P., Neovascularization after transmyocardial laser revascularization in a model of chronic ischemia. *Ann.Thorac.Surg.* **66**, 2029-2036, 1998.
105. Hughes,G.C., Kypson,A.P., St, Annex,B.H., Coleman,R.E., DeGrado,T.R., Donovan,C.L., Lowe,J.E., and Landolfo,K.P., Improved perfusion and contractile reserve after transmyocardial laser revascularization in a model of hibernating myocardium [In Process Citation]. *Ann.Thorac.Surg.* **67**, 1714-1720, 1999.
106. Yamamoto,N., Kohmoto,T., Gu,A., DeRosa,C., Smith,C.R., and Burkhoff,D., Angiogenesis is enhanced in ischemic canine myocardium by transmyocardial laser revascularization. *J.Am.Coll.Cardiol.* **31**, 1426-1433, 1998.
107. Kohmoto,T., DeRosa,C.M., Yamamoto,N., Fisher,P.E., Failey,P., Smith,C.R., and Burkhoff,D., Evidence of vascular growth associated with laser treatment of normal canine myocardium. *Ann.Thorac.Surg.* **65**, 1360-1367, 1998.
108. Brilla,C.G., Rybinski,L., Gehrke,D., and Rupp,H., [Transmyocardial laser revascularization-an innovative pathophysiologic concept]. *Herz.* **22**, 183-189, 1997.
109. Sayeed-Shah,U., Mann,M.J., Martin,J., Grachev,S., Reimold,S., Laurence,R., Dzau,V., and Cohn,L.H., Complete reversal of ischemic wall motion abnormalities by combined use of gene therapy with transmyocardial laser revascularization. *J.Thorac.Cardiovasc.Surg.* **116**, 763-769, 1998.
110. Sundt,T.M. and Kwong,K.F., Clinical experience with the holmium:YAG laser for transmyocardial laser revascularization and myocardial denervation as a mechanism. *Semin.Thorac.Cardiovasc.Surg.* **11**, 19-23, 1999.
111. Kwong,K.F., Kanellopoulos,G.K., Nickols,J.C., Pogwizd,S.M., Saffitz,J.E., Schuessler,R.B., and Sundt,T.M., Transmyocardial laser treatment denervates canine myocardium [see comments]. *J.Thorac.Cardiovasc.Surg.* **114**, 883-889, 1997.
112. Hirsch,G.M., Thompson,G.W., Arora,R.C., Hirsch,K.J., Sullivan,J.A., and Armour,J.A., Transmyocardial laser revascularization does not denervate the canine heart. *Ann Thorac Surg* **68**, 460-468, 1999.
113. Dorschler,K. and Muller,G., The role of laser in cardiac surgery [In Process Citation]. *Thorac Cardiovasc.Surg* **47 Suppl 3**, 385-387, 1999.
114. Mueller,X.M., Tevaearai,H.T., Genton,C.Y., Chaubert,P., and von Segesser,L.K., Are there vascular density gradients along myocardial laser channels? *Ann Thorac Surg* **68**, 125-129, 1999.
115. Oesterle,S.N., Reifart,N.J., Meier,B., Lauer,B., and Schuler,G.C., Initial results of laser-based percutaneous myocardial revascularization for angina pectoris. *Am J Cardiol.* **82**, 659-62, A6, 1998.
116. Oesterle,S.N., Yeung,A., and Ali,N.e.al., The CardioGenesis percutaneous myocardial revascularisation randomized trial: initial clinical results. *J Am Coll Cardiol* **33 (suppl A)**, 380A, 1999.
117. Weis,M. and von Scheidt,W., Cardiac allograft vasculopathy: a review. *Circulation* **96**, 2069-2077, 1997.
118. Malik,F.S., Mehra,M.R., Ventura,H.O., Smart,F.W., Stapleton,D.D., and Ochsner,J.L., Management of cardiac allograft vasculopathy by transmyocardial laser revascularization. *Am.J.Cardiol.* **80**, 224-225, 1997.
119. Grubman,E., Pavri,B.B., Lyle,S., Reynolds,C., Denofrio,D., and Kocovic,D.Z., Histopathologic effects of radiofrequency catheter ablation in previously infarcted human myocardium. *J Cardiovasc.Electrophysiol.* **10**, 336-342, 1999.

120. Petersen,H.H., Chen,X., Pietersen,A., Svendsen,J.H., and Haunso,S., Temperature-controlled irrigated tip radiofrequency catheter ablation: comparison of in vivo and in vitro lesion dimensions for standard catheter and irrigated tip catheter with minimal infusion rate. *J Cardiovasc.Electrophysiol.* **9**, 409-414, 1998.
121. Watanabe,G., Misaki,T., Nakajima,K., Ueda,T., and Yamashita,A., Thoracoscopic radiofrequency ablation of the myocardium. *Pacing Clin.Electrophysiol.* **21**, 553-558, 1998.
122. Maat,L.P., Slager,C.J., van Herwerden,L.A., Schuurbiers,J.C., van Suylen,R.J., Kofflard,M.J., ten Cate,F.J., and Bos,E., Spark erosion myectomy in hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg* **58**, 536-540, 1994.
123. He,D.S., Zimmer,J.E., Hynynen,K., Marcus,F.I., Caruso,A.C., Lampe,L.F., and Aguirre,M.L., Preliminary results using ultrasound energy for ablation of the ventricular myocardium in dogs. *Am J Cardiol.* **73**, 1029-1031, 1994.
124. Thomas,S.P., Clout,R., Deery,C., Mohan,A.S., and Ross,D.L., Microwave ablation of myocardial tissue: the effect of element design, tissue coupling, blood flow, power, and duration of exposure on lesion size. *J Cardiovasc.Electrophysiol.* **10**, 72-78, 1999.
125. Watanabe,H., Hayashi,J., Sugawara,M., Hiratsuka,M., and Eguchi,S., Experimental application of microwave tissue coagulation to ventricular myocardium. *Ann Thorac Surg* **67**, 666-671, 1999.
126. Strickberger,S.A., Tokano,T., Kluiwstra,J.U., Morady,F., and Cain,C., Extracardiac ablation of the canine atrioventricular junction by use of high-intensity focused ultrasound. *Circulation* **100**, 203-208, 1999.
127. Smith,N.B. and Hynynen,K., The feasibility of using focused ultrasound for transmyocardial revascularization [In Process Citation]. *Ultrasound.Med.Biol.* **24**, 1045-1054, 1998.
128. Desinger,K., Stein,Th., Tschepe,J., and Muller,G., Laser ultrasound surgical therapy (LUST). *Minimal Invasive Medizin* **7**, 123-127, 1996.
129. Frazier,O.H., Kadipasaoglu,K.A., and Cooley,D.A., Transmyocardial laser revascularization. Does it have a role in the treatment of ischemic heart disease? *Tex.Heart Inst.J.* **25**, 24-29, 1998.
130. Kadipasaoglu,K.A. and Frazier,O.H., Transmyocardial laser revascularization: effect of laser parameters on tissue ablation and cardiac perfusion. *Semin.Thorac.Cardiovasc.Surg.* **11**, 4-11, 1999.

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