Hypothesis and development of a minimally invasive approach for percutaneous transmyocardial revascularization with Holmium laser

Mario Galli, Stefano Mameli, Elena Butti, Roberto Bonatti, Alessandro Politi, Santino Zerboni, Giovanni Ferrari

Catheterization Laboratory, Cardiology Department, S. Anna Hospital, Como, Italy

Key words:
Coronary artery disease; Laser; Myocardial revascularization.

Background. **Percutaneous transluminal myocardial revascularization (PTMR) is a new procedure to improve perfusion of the ventricular wall for patients with intractable angina and untreatable by surgery or conventional catheter-based intervention. Actually PTMR requires femoral approach to utilize 8F-9F system device. We now report the feasibility study of PTMR using a laser delivered through a novel Eclipse system and new 6F and 7F guiding catheters that allow to perform PTMR even in patients with peripheral vascular disease and particularly suitable for alternative small vascular access.**

Methods. **Percutaneous vascular access for PTMR treatment was obtained via the femoral or radial artery. A 6F or 7F mono-directional catheter carrying flexible fiber optics was used with a Holmium laser (Eclipse system) and was placed across the aortic valve into the left ventricular cavity to create channels of 5 mm in depth from the endocardial surface into the myocardial tissue. From June 1999 to September 2000, 39 patients (28 males, 11 females, mean age 72 ± 8 years, range 58-86 years) underwent PTMR with the Eclipse system. Preoperative mean Canadian Cardiovascular Society (CCS) angina class was 3.5 ± 0.5 and previous myocardial procedures had been performed in 39 patients (18 coronary artery bypass graft and 31 coronary angioplasty).**

Results. **The procedure was well tolerated and a procedural success was obtained in all patients (100%). We performed a mean of 19 ± 7 channels in a mean fluoroscopy time of 21 ± 9 min. We report only one procedural complication: one embolic stroke (2.4%). No hospital major adverse cardiac events were observed. The average length of hospital stay was 3.1 days. The mean CCS angina class at entry was 3.5 and it declined from 3.5 ± 0.5 to 1.25 ± 0.8 at discharge. At the follow-up of 8.2 ± 3.9 months the mean CCS was 1.5 ± 0.7.**

Conclusions. **This experience confirmed the safety and technical feasibility of PTMR with this mini-invasive approach with a reduction in operative and fluoroscopy time. The PTMR with the 6F or 7F guiding catheter is feasible in high risk patients even when the femoral approach is contraindicated. Immediate and short-term results confirm that a clinical improvement is obtained in most patients.**

(Ital Heart J 2001; 2 (4): 312-316)

Received May 22, 2000; revision received January 12, 2001; accepted January 18, 2001.

Address:

Dr. Mario Galli

Laboratorio di Emodinamica Ospedale S. Anna Via Napoleona, 60 22100 Como E-mail: emodin@tiscalinet.it

Introduction

Despite the widespread application of angioplasty and coronary artery bypass graft techniques, many patients continue to have diffuse coronary disease for which conventional revascularization techniques are not suitable.

Percutaneous direct myocardial revascularization (DMR) is a new technique that has contributed to the widening of the horizons of interventional cardiology and is expected to have an impact on the strategy employed in dealing with patients with refractory ischemic symptoms[1-3]. The efficacy of this method has been supported by studies comparing DMR performed with the Holmium:yttrium-garnet (Ho:YAG) laser system (by surgical approach) to treatment with maximal medical therapy in patients with angina and DMR as an adjunct to bypass surgery[4-6].

Actually, due to technological advances in the Holmium medium, percutaneous DMR can be performed using catheter-based systems[7]. Therefore, using percutaneous DMR treatment, it is possible to create channels from the endocardial surface into the myocardial tissue. Access is via the femoral artery, thus avoiding surgical thoracotomy

and general anesthesia. This technique can be performed using the standard percutaneous interventional techniques but actually requires a large sheath to utilize the 8F-9F guiding catheters.

In the currently undergoing investigative clinical trials with the Eclipse system (one of the three commercially available catheter-based systems), phases I and II, the efficacy of this technique has been demonstrated. However, some technical problems related to the suboptimal characteristics of the percutaneous device have been highlighted. Moreover these problems were related to the difficult manipulation of the guiding catheter which limited the procedure in patients with favorable groin access and without large akinetic-dyskinetic segments[8].

To improve the efficacy and safety of percutaneous DMR with the Eclipse system we designed and developed new mono-directional 6F and 7F guiding catheters to perform this technique even in patients with procedural contraindications to percutaneous DMR using the standard device, particularly in patients with severe left ventricular dysfunction or with poor groin access.

Methods

The Eclipse system (Eclipse Surgical Technologies, Sunnyvale, CA, USA) uses a pulsed Ho:YAG laser with a Slim Flex laser fiber (36 flexible fiberoptic) delivery system located in an 8.3F, 5-7 cm maneuverable tip, deflectable DMR catheter with manual advancement of the fiber into the myocardium. The energy delivered is 0.7 J and produces an output wavelength of 2.1 μm per pulse. The energy is delivered by the fiberoptic and produces intramyocardial channels 1 mm in diameter and 1-2 mm deep per pulse for three pulses. This system requires fluoroscopic imaging guidance for left ventricular orientation.

After a period of experience (described in the pilot study) with the use of this device in patients with refractory class 3-4 angina, we have developed a new device with the aim of simplifying and making the DMR procedure easier and safer. *In vitro* observations have been performed in order to determine whether it was possible to reduce the guiding catheter diameter whilst at the same time maintaining the fiberoptic laser wire dimensions presently employed in the Eclipse system. Tests have been performed in a custom-made model to check the performance of the fiber inside a series of different catheters (i.e. material-inner diameter). At the end of the tests, it was decided that the polyurethane sheathed catheters (nylon-pebax) were the best for DMR via the percutaneous approach. With the characteristics of this material, it has been possible to obtain a mono-directional catheter with a high directional control and with inner lumen diameters of 0.68 and 0.74 inches for the 6F and 7F catheters respectively. This is compatible with the dimensions of the traditional Eclipse laser fiberoptic (1 mm). A smooth stainless "cup" at the tip of the catheter has been assembled to improve the safety of the device by avoiding the possibility that the laser fiber advances for more than 3 mm out of the device. This modification reduces trauma by the distal tip and the chances of mechanical perforation of the left ventricle. The catheter tip was also designed to be used as a marker for catheter positioning in the ventricular chamber (Fig. 1). We have also developed several curves each of which with a geometry specifically designed for the segment to be treated. The curves have been elaborated and tested with a computerized graphic system.

Another step of our project concerned the handle. We modified the original Eclipse handle by making it leakage-proof. Thus, monitoring of the endocavitary pressure and injection of contrast medium during the procedure are possible (Fig. 2).

Tests have been performed on experimental models before *in vivo* utilization of this device in order to verify the dimensions and characteristics of the laser channels. The latter were similar to those obtained with the traditional Eclipse system.

To avoid the possibility of custom defects, all devices were single tested *in vitro* in a "white chamber" before utilization. The devices were then sterilized in conformity with standard procedures for endovascular equipment. This project and its development were entirely performed in agreement with Eclipse.

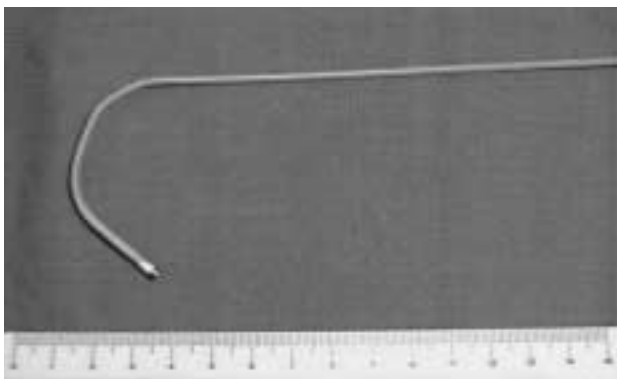

Figure 1. *Detail of the 6F guiding catheter curve and tip.*

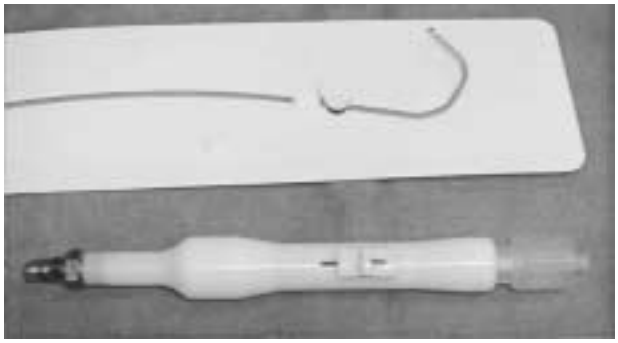

Figure 2. *Image of the handle prototype.*

Technique of percutaneous direct myocardial revascularization. A 6F or 7F, 23 cm long introducer (Arrow Corp., Reading, PA, USA) was used for the vascular access (femoral or radial artery) using the standard technique. Heparin (70 IU/kg) was administered intravenously. A pigtail catheter was then advanced into the left ventricle and ventriculograms in the 30° right anterior and 45° left anterior oblique projections were performed. The pigtail catheter was then substituted by the mono-directional 6F-7F catheter over a 0.035-J exchange guidewire (Fig. 3). The radio-opaque tip of the catheter was then positioned in the target region and placed against the endocardium. The guidewire was removed and, using the radio-opaque marker as reference, the fiberoptic was advanced into the catheter until it reached the tip. During laser energy delivery the fiberoptic was advanced for a maximum distance of 3 mm using the one-hand operated control. Thus, a channel 1 mm in diameter and with a maximum depth of 5 mm was created within the myocardium (Fig. 4). By applying a torque to the catheter whilst advancing the tip, the physician was able to treat the target region of the endocardium. The total number of channels was limited by the 1-cm spacing requirement with a mean of 20 channels for each myocardial segment.

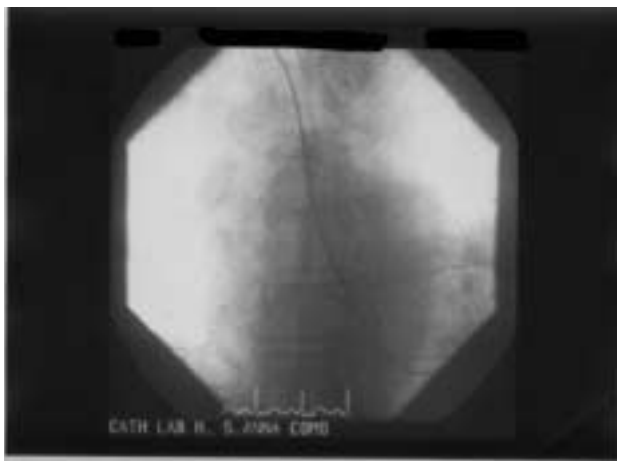

Figure 3. *Advancement of the 6F guiding catheter through the subclavian artery and the aorta into the left ventricle over a 0.035 J wire.*

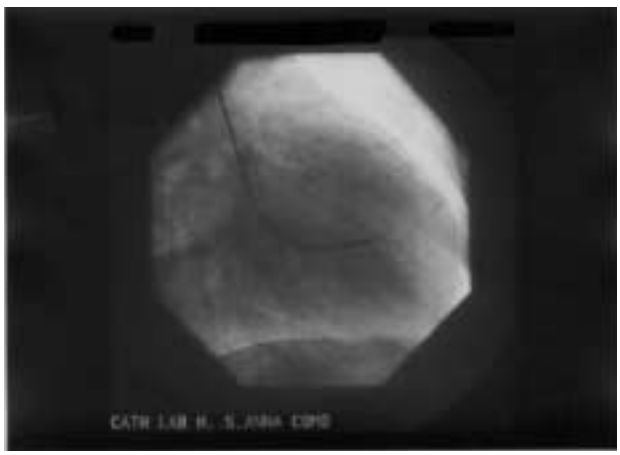

Figure 4. *Thirty degree right anterior oblique angiogram. The fiberoptic is advanced inside the catheter during energy delivery.*

Results

Between June 1999 and September 2000, 39 consecutive patients with refractory ischemic symptoms were enrolled into the study. Percutaneous DMR was performed using the prototype 6F-7F catheters. The patients were enrolled after being informed on the techniques and the goals of the study. Thirty-one out of the 39 patients were in Canadian Cardiovascular Society (CCS) class III angina and 8 in class IV angina despite maximal medical therapy. The location and extent of the ischemic regions were determined by thallium-201 scintigraphy during exercise or pharmacologically induced stress test. In patients with clinical instability, the ischemic regions were localized by estimating the coronary anatomy and the electrocardiographic modifications during anginal crises. Demographic and clinical data are shown in table I. Some of the patients had been previously excluded from percutaneous DMR treatment using the current (Eclipse) catheter because they did not meet the criteria of the original protocol (ejection fraction < 30%, wall thickness < 9 mm, femoral access not possible). A total of 46 segments were treated (1.3 ± 05 segments per patient) with an average of 19 ± 7 channels created by the laser.

Procedural data are summarized in table II. There were no major intra or postoperative adverse clinical events (deaths, myocardial infarction, myocardial perforation). The average length of hospital stay was 3.1 ± 1.3 days. The mean CCS functional class at entry was 3.5 ± 0.5 and it declined to 1.25 ± 0.8 at discharge. At the follow-up of 8.2 ± 3.9 months (range 3 to 18 months) the mean anginal class was 1.5 ± 0.7. One patient died of non-cardiac causes; 3 patients (7.5%) were re-hospitalized at 3, 5 and 8 months postoperatively due to

Table I. Demographic characteristics (39 patients).

Age (years)	72 ± 8 (58-86)
Male	28
Diabetes mellitus	28
Hypertension	30
Previous MI	29
Previous CABG	18
Previous PTCA	31
Multivessel disease	31
Angina CCS (mean)	3.5 ± 0.5
LVEF	39 ± 8 (25-60)

CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = coronary angioplasty.

Table II. Procedural characteristics and results.

Treated regions	46
Treated regions/patients	1.3
Anterior	18
Antero-lateral	12
Lateral	10
Inferior	6
PTMR channels	19 ± 7
Fluoroscopy time	21 ± 9
Total procedural time	35 ± 17
Procedural complications	
Embolic stroke	1 (2.4%)
In hospital outcome	
MACE	0

MACE = major adverse cardiac events (death, myocardial infarction, left ventricular dysfunction or perforation); PTMR = percutaneous transmyocardial revascularization.

worsening of angina symptoms. Two patients were discharged after modification of medical therapy (persistent ischemia was confirmed at scintigraphy in the regions treated with percutaneous DMR); 1 patient underwent coronary angioplasty of the left main coronary artery. Four patients (10%) did not improve whereas in 1 patient (2.5%) symptoms deteriorated from class II to IV and he was treated with neurospinal stimulation. Finally, 77.5% of patients had improvement in angina (a reduction in two or more CCS classes). Table III shows the changes in the functional class after treatment.

Table III. Canadian Cardiovascular Society (CCS) angina class at entry, discharge and follow-up.

CCS	Baseline	Discharge	Follow-up
0	0	8	6
I	0	17	14
II	0	10	12
III	30	4	5
IV	9	0	1
≤ II	0	356	30
III-IV	39	4	7
Mean CCS	3.5 ± 0.5	1.25 ± 0.8	1.5 ± 0.7

Discussion

The development of DMR was driven by the belief that, via an endoventricular approach, Ho:YAG laser energy could be used to ablate myocardial tissue and thus to create endocardial channels. The recent opportunity to perform DMR using percutaneous transcatheter operative techniques has made the procedure easier. These techniques permit treatment of high risk patients and obviate the need of thoracotomy and of open-heart surgery. During percutaneous DMR, channels are created from inside the ventricle and extend from the endocardium towards the epicardium. This is in contrast with the epicardial approach employed during open-heart surgery.

The mechanisms leading to relief of angina following such "endomyocardial treatment" are the same as those which are activated following laser DMR at open-heart surgery: stimulation of angiogenesis and/or enhanced collateral vessel formation by laser-induced myocardial injury and an anesthetic effect resulting from damage to myocardial nerve fibers. The patent channel hypothesis of blood flow to ischemic areas through continued myocardial perfusion has been refused like in surgical DMR by recent animal studies.

Current clinical studies are primarily evaluating the feasibility and safety of the percutaneous DMR procedure with three laser systems (Biosense, Johnson & Johnson, NJ, USA; Cardiogenesis, Sunnyvale, CA, USA; Eclipse, Sunnyvale, CA, USA) that apply the same type of energy (Ho:YAG laser energy) but with significantly different catheters and delivery systems in terms of characteristics and size (traditionally 8F-9F devices)[9-11]. As confirmed by experimental observations *in vitro* and by animal studies, in all systems the predominant effects of these lasers on the target tissue are photothermal and photoacoustic.

The results reported in our preliminary experience with a 9F guiding catheter confirmed the feasibility and safety of percutaneous DMR. The operative success was high (93%) and the complication rate low (6%). Our immediate and mid-term clinical results were very promising and comparable with those observed in percutaneous DMR prospective or randomized trials in which the Eclipse system was employed[12-16]. Moreover, during the procedure with the 9F Eclipse device we noted some technical problems that should be solved, particularly those related to catheter manipulation and stiffness. In fact, the non-optimal maneuverability has sometimes made treatment of the same myocardial regions such as the inferior or postero-lateral areas difficult. Moreover, operative complications (i.e. perforation) are probably due to the stiffness of the tip of the 9F guiding catheter. In fact, with the 9F guiding catheter we reported one myocardial perforation attributable to difficulties we encountered because of catheter stiffness and problematic manipulation. This complication was treated conventionally without clinical sequele.

In order to improve the safety and efficacy of this procedure we designed a minimally invasive guiding catheter. Our attention was focused on the guiding catheter and we reduced its dimensions so as to make it compatible with tools normally used for coronary procedures (6F and 7F introducers, 0.035 J guidewires). We started from the consideration that significant changes in the tissue response to laser can be obtained only by varying the laser parameters including the number of pulses, energy per pulse and laser fiber configuration. In fact, experimental observations had confirmed that the created channels differ according to the dimensions of the fiberoptic and laser parameters utilized and vary from 300 to 1000 μ in diameter and 4 to 5 mm in depth.

We hypothesized that the possibility of creating intramyocardial channels is not related to the characteristics of the guiding catheter but only to the type and amount of energy delivered by the fiberoptic laser. It was on the basis of this hypothesis that we developed our device. The feasibility of performing percutaneous DMR using a minimally invasive catheter was confirmed by "*in vitro* observations" which demonstrated that the characteristics of the channel obtained with the traditional Eclipse device were similar to those of the channel created with the minimally invasive catheter.

The performance tests of the new catheter on an experimental model confirmed the facility of tracing and of safely manipulating this device. This was due to the atraumatic tip. Moreover, the computerized design of the catheter curves and tip allowed precise and stable contact with the myocardial tissue. The results of our clinical feasibility study confirmed the efficacy of these technical modifications. The mono-directional catheter (6F or 7F) with a soft atraumatic tip allows performance of percutaneous DMR in patients with severe left ventricular dysfunction and smooth myocardial segments[17].

This catheter technology and design permit treatment of myocardial areas adjacent to the akinetic segments thus reducing the chances of mechanical perforation. The clinical results of our "minimally invasive" approach for percutaneous DMR are similar to those of other published clinical studies but with evident reduction of procedure complexity (fluoroscopy time, procedural time). Our experience shows that, using a miniaturized catheter, percutaneous DMR can be performed successfully even in high risk patients, in case of poor groin access or when the femoral approach is contraindicated. This new device may be useful when percutaneous DMR must be performed via small vessels such as the radial artery.

In conclusion, this study describes the hypothesis and development of a minimally invasive approach for percutaneous transmyocardial revascularization. The results of our procedure confirm the technical feasibility of percutaneous DMR using this approach. The safety of the method is confirmed by the absence of operative complications even in patients with severe left ventricular dysfunction and poor groin access for whom the transcutaneous procedure would not have been suitable. These data suggest that percutaneous DMR is an alternative therapeutic option for patients with intractable angina symptoms. The results using this technique are definitely encouraging. Ongoing developments in this field may render this procedure a potent tool for the mitigation of the ravishing effects of coronary artery disease.

References

1. Smith JA, Dunning JJ, Parry AJ, et al. Transmyocardial laser revascularization. J Card Surg 1995; 10: 569-72.
2. Horvath KA, Cohn LH, Cooley DA, et al. 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 1997; 113: 645-54.
3. Cooley DA, Frazier OH, Kadipasaoglu KA, et al. Transmyocardial laser revascularization: clinical experience with twelve-month follow-up. J Thorac Cardiovasc Surg 1996; 111: 791-9.
4. Donatelli F, Triggiani M, D'Ancona G, et al. Rivascolarizzazione transmiocardica con laser in pazienti con coronarosclerosi periferica. Indicazioni e risultati preliminari. G Ital Cardiol 1997; 27: 430-5.
5. Horvath KA, Mannting F, Cummings N, Shernan SK, Cohn LH. Transmyocardial laser revascularization operative techniques and clinical results at two years. J Thorac Cardiovasc Surg 1996; 111: 1047-53.
6. Allen KB, Fudge T, Shoetle GP, et al. Prospective randomized multicenter trial of transmyocardial revascularization plus coronary artery bypass grafting versus coronary artery bypass grafting alone. (abstr) Circulation 1998; 98 (Suppl I): I-476.
7. Kim CB, Kesten R, Javier M, et al. Percutaneous method of laser transmyocardial revascularization. Cathet Cardiovasc Diagn 1997; 40: 223-8.
8. Oeterle SN, Reifart NJ, Meier B, Lauer B, Shuler G. Initial results of laser based percutaneous myocardial revascularization for angina pectoris. Am J Cardiol 1998; 82: 659-62.
9. Milano A, De Carlo M, Pratali S, et al. Rivascolarizzazione transmiocardica con laser ad olmio: risultati preliminari. G Ital Cardiol 1997; 27: 1011-8.
10. Whitlow PL, Knopf WD, O'Neil WW, et al. Percutaneous transmyocardial revascularization in patient with refractory angina. (abstr) Circulation 1998; 98 (Suppl I): I-87.
11. Kornowski R, Bhargava B, Leon M. Percutaneous transmyocardial laser revascularization: an overview. Catheter Cardiovasc Interv 1999; 47: 354-9.
12. Galli M, Zerboni S, Politi A, et al. Percutaneous transmyocardial revascularization with holmium laser in patients with refractory angina: a pilot feasibility study. G Ital Cardiol 1999; 29: 1020-6.
13. Dowling RD, Allen KB, Fudge T, et al. Recent experience of transmyocardial revascularization in a prospective randomized trial demonstrates dramatic symptoms relief and excellent safety profile. (abstr) J Am Coll Cardiol 1999; 33 (Suppl A): 380.
14. Laurer B, Stahl F, Junghans U, Kluge R, Shuler G. Long-term results after percutaneous myocardial laser revascularization in patients with end-stage coronary artery disease. (abstr) J Am Coll Cardiol 1999; 33 (Suppl A): 381.
15. Shawl FA, Domanski MJ, Kaul U, et al. Procedural results and early clinical outcome of percutaneous transluminal myocardial revascularization. Am J Cardiol 1999; 83: 498-501.
16. Oesterle SN, Sanbor TA, Ali N, et al. Percutaneous transmyocardial laser revascularization for severe angina: the PACIFIC randomised trial. Lancet 2000; 356: 1705-10.
17. Galli M, Bonatti R, Molteni S, et al. Percutaneous transmyocardial revascularization with holmium laser (PTMR) pilot study on the use of 6F/7F mono-directional catheter. (abstr) Am J Cardiol 1999; 84 (Suppl 6A): 92.