# Laser revascularization in the management of coronary artery disease

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**In recent years, laser therapy has been evaluated for the treatment of patients with angina who have coronary artery disease which is not amenable to conventional revascularization techniques. The results of transmyocardial revascularization and percutaneous myocardial revascularization are reviewed.**

The medical and surgical treatments which are currently available for the management of patients with coronary artery disease are usually successful. There are, however, a growing number of patients with angina which is not controlled by medication, who have diffuse and distal disease in their coronary circulation which is not suitable for treatment by coronary angioplasty/stenting or by coronary artery bypass surgery. The surgical approaches of transmyocardial laser revascularization (TMR) and more recently percutaneous myocardial revascularization (PMR) have been evaluated for the treatment of this group of patients.

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There have been attempts to provide direct myocardial perfusion in the past based on the description of a sinusoidal network in the left ventricular myocardium. Vineberg (1954) introduced thoracic artery implantation, which met with success in some patients. Later, Sen et al (1965) proposed the creation of transmural channels in the left ventricular wall to permit direct perfusion of ischaemic myocardium with oxygenated blood from the left ventricular cavity. This concept was based on the model of the reptilian heart, in which the left ventricle is directly perfused from endothelium-lined channels that radiate out from the cavity of the left ventricle. Mirhoseini et al (1982, 1986) subsequently used laser energy rather than mechanical energy to create the transmural channels.

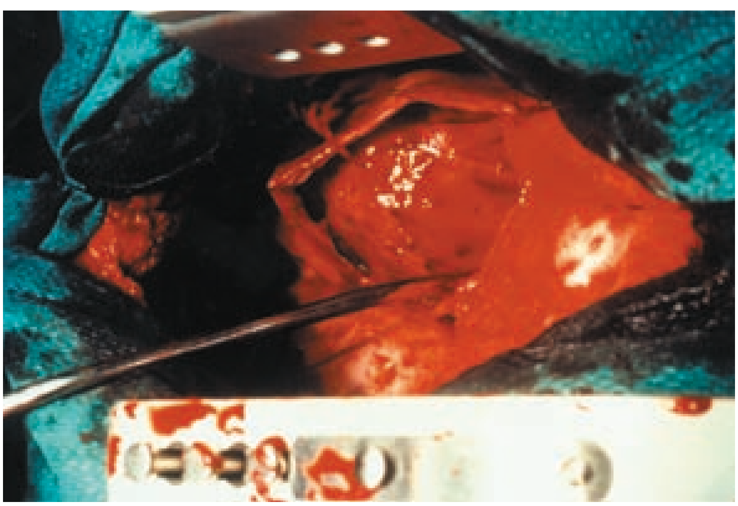

*Figure 1. The surface of the left ventricle intraoperatively showing sites of transmural laser channels.*

## TRANSMYOCARDIAL LASER REVASCULARIZATION

### Technique

TMR involves the creation of transmural channels in ischaemic myocardial using laser ablation. It is usually carried out through a left anterolateral thoracotomy. The area to be treated is determined preoperatively from myocardial perfusion scanning (nuclear techniques or positron emission tomography) in conjunction with the coronary angiographic findings. There is no requirement for cardiopulmonary bypass.

The laser probe is placed on the surface of the left ventricle in the ischaemic area and activated. Initially high-energy carbon dioxide lasers were used and more recently holmium:yttrium-aluminium-garnet (YAG) lasers have been used. The laser energy is absorbed by the blood within the left ventricle and an acoustic image is created which can be seen on transoesophageal echocardiography. The channels which are created are about 1 mm in diameter and they are created in a 'grid' of approximately one per square centimetre. Usually, haemorrhage from the channel can be controlled by direct finger pressure, although occasionally an epicardial suture is required (*Figure 1*).

## Results

Initially, non-randomized trials of TMR were undertaken to establish safety and efficacy of the procedure. In a multicentre trial of 200 patients, there was an operative mortality of 9% (Horvath et al, 1997). The patients had angina refractory to medical therapy, evidence of reversible myocardial ischaemia and disease which was not suitable for conventional revascularization techniques. There was an improvement in Canadian Cardiovascular Score (CCS) for angina at 12 months by at least 2 classes in 75% of patients. In a registry report from European and Asian centres undertaking TMR using a carbon dioxide laser, involving over 960 patients, the operative mortality was 9.7% (Burns et al, 1999). Fewer than 50% of patients achieved an improvement of at least 2 angina classes. Complications of the technique include perioperative bleeding and infection, left ventricular failure in the early postoperative phase and cardiac arrhythmias. The commonest arrhythmia was transient atrial fibrillation.

**TABLE 1. Improvements in angina after transmyocardial revascularization**

| | Angina score at 12 months | Control group |
|---|---|---|
| Horvath et al (1997) | 75% ↓ 2 classes | – |
| Burns et al (1999) | 34% ↓ 2 classes | – |
| March (1999) | 72% ↓ 2 classes | 13% ↓ 2 classes |
| Schofield et al (1999) | 25% ↓ 2 classes | 4% ↓ 2 classes |
| Burkhoff et al (1999) | 61% ↓ 2 classes | 11% ↓ 2 classes |

**TABLE 2. Treadmill exercise time after transmyocardial revascularization**

| | Exercise time at 12 months | Control group |
|---|---|---|
| Burns et al (1999) | +110 seconds (baseline 360 seconds) | – |
| Schofield et al (1999) | +70 seconds | +12 seconds |
| Burkhoff et al (1999) | +65 seconds (baseline 360 seconds) | −46 seconds |

**TABLE 3. Perioperative mortality with transmyocardial revascularization**

| | Laser | No of patients | Perioperative mortality |
|---|---|---|---|
| Horvath et al (1997) | $CO_2$ | 200 | 9% |
| Burns et al (1999) | $CO_2$ | 967 | 10% |
| March (1999) | $CO_2$ | 97 | 8% |
| Schofield et al (1999) | $CO_2$ | 94 | 5% |
| Burkhoff et al (1999) | Ho:YAG | 92 | 1% |

$CO_2$ = carbon dioxide; Ho:YAG = Holmium:yttrium-aluminium-garnet

There have now been several large randomized controlled trials of TMR reported (Burkhoff et al, 1999; March, 1999; Schofield et al, 1999). An American trial randomized 198 patients to either continued medication or TMR plus continued medication (March, 1999). Unfortunately, there was a high cross-over rate from medical therapy to TMR which complicates the analysis. At 12 months, there was an improvement in angina of at least 2 classes in 72% of the TMR group and 13% of control patients. There was an operative mortality for TMR of 8%.

The results of a UK randomized trial were less favourable (Schofield et al, 1999). In this study, 188 patients were randomized to either continued medical therapy or TMR plus continued medical therapy. There were no cross-overs in this trial and almost complete data collection. At 12 months, the angina score fell by at least 2 classes in 25% of the TMR patients and 4% of the control group. There was a perioperative mortality of 5% for TMR, with no significant difference in survival at 12 months between the two groups. The morbidity associated with TMR included wound/respiratory infection (33%), transient arrhythmia (usually atrial fibrillation) (15%) and transient left ventricular failure (12%). Exercise capacity measured using treadmill exercise times and 12-minute walking distance was greater in the TMR patients, although the difference between the two groups did not reach statistical significance.

The study by Burkhoff et at (1999) involved use of a holmium:YAG laser. They found an improvement of at least 2 angina classes in 61% of the TMR and 11% of the control group, with a low perioperative mortality (only 1%). At 12 months, the treadmill exercise time was significantly improved in the TMR group compared with controls, the result of an increase in exercise time in the TMR group and a fall in the control group.

## Summary

Most studies have shown a beneficial effect on angina following TMR (*Table 1*). Typically, this involves an improvement in at least 2 angina classes in 25–75% of patients. A significant increase in treadmill exercise time has been demonstrated in some but not all studies (*Table 2*). The procedure carries a significant perioperative mortality as well as morbidity: perioperative mortality is usually between 5 and 10%, although one study has reported a figure of only 1% (*Table 3*).

In an individual patient, therefore, one has to carefully consider the potential benefits in terms of angina improvement and increased exercise capacity of TMR against the morbidity and mortality associated with the procedure.

## PERCUTANEOUS MYOCARDIAL REVASCULARIZATION

In view of the morbidity and mortality associated with the surgical approach of TMR, attempts have been made to develop a less invasive technique. A holmium:YAG laser has been developed which enables laser energy to be delivered to the endocardial surface of the left ventricular cavity. From the patient's viewpoint, it does not involve a general anaesthetic or a thoracotomy and the length of hospital stay is much less. Following PMR, patients are usually discharged within 24 hours, but after TMR patients may be in hospital for 7–10 days.

### Technique

At the moment, the two most commonly used holmium:YAG techniques for catheter-based treatment are the percutaneous myocardial revascularization (PMR, Eclipse/Cardiogenesis, Amsterdam, Netherlands) and the direct myocardial revascularization (DMR, Biosense, Johnson & Johnson, Ascot, England) systems.

**PMR**: The Eclipse/Cardiogenesis PMR system uses a 9F 'aligning catheter' which is introduced from the femoral artery and positioned within the left ventricle. A 'laser catheter', which has a right-angled bend at its tip is advanced through this, and a 'laser fibre' is then advanced through the laser catheter to make contact with the endocardium of the left ventricle. The right-angled bend in the laser catheter facilitates access to different parts of the left ventricle (*Figure 2*).

The procedure is usually carried out using two radiological views, typically 40° right anterior oblique and 50° left anterior oblique with 10° of cranial angulation. Once the aligning catheter has been advanced into the left ventricular cavity, angiograms are taken in these two views and the outline of the left ventricle is traced onto acetate sheets which have been fixed over the viewing screens. These outlines then act as 'maps' during the procedures. As with TMR, the region to be treated by PMR is determined beforehand from the coronary angiogram and myocardial perfusion scan (either nuclear technique or positron emission tomography).

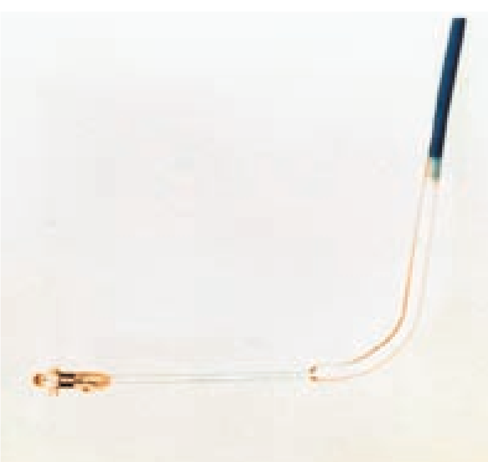

*Figure 2. The equipment for percutaneous myocardial laser revascularization. This includes the 'guiding catheter' (blue), the 'laser catheter' with a right angled bend (white) and the 'laser fibre'.*

It is possible to access the various regions of the left ventricle using PMR: the anterior, lateral and inferior walls as well as the apex and septum can be treated. The right anterior oblique view is used to show contact with the anterior and inferior walls and the left anterior oblique for contact with the lateral wall and septum. Once the laser fibre has made contact with the endocardial surface of the ventricle, the laser is activated. This produces a channel into the myocardium which is approximately 3 mm deep. The laser fibre is then advanced slightly and reactivated, resulting in a channel which is around 6 mm deep.

Once the channel is created, the site is marked on the acetate sheet in both views. The laser fibre is then retracted into the laser catheter and a different site is then selected by further manipulation of the laser catheter and/or aligning catheter. The channels are usually created at about 1 cm intervals (*Figure 3*). Since the apex of the left ventricle tends to be thinner, typically only one 'burst' of laser energy is used when treating the apical region. A transthoracic echocardiogram is performed before the procedure to ensure that the thickness of the left ventricular wall in the region to be treated is at least 8 mm. The left anterior oblique view provides the best 'map' of the channels when treating the anterior and inferior walls, whereas the right anterior oblique view is preferred for mapping the lateral wall and septum.

**DMR:** The Biosense DMR system enables both a functional assessment of the left ventricle as well as catheter-based intramyocardial treatment. The diagnostic system uses an ultra-low magnetic field energy source and sensor-tipped catheter electrodes to locate the exact position of the mapping catheter in three-dimensional space. The location of the mapping catheter is gated to end-diastole and recorded relative to the location of the fixed reference catheter at the time, thus compensating for patient or cardiac movement. By moving the tip of the mapping catheter to multiple left ventricular endocardial sites, the NOGA system (workstation) is able to reconstruct the left ventricular anatomy. Intra-cardiac electrical signals are acquired simultaneously and superimposed on the three-dimensional anatomical map. Normal regional myocardial function is characterized by high electrical and mechanical activity. Endocardial zones with low electrical and impaired mechanical activity usually represent previously infarcted areas. In sites where electrical activity is preserved but mechanical activity is impaired, there is typically severe ischaemia associated with hibernating myocardium (*Figure 4*).

The electromechanical maps can therefore be used to identify target zones for the DMR laser therapy. The navigation system, by using the location sensors, is useful for catheter guidance during DMR. The distal laser catheter tip location and orientation are detected in real time in order to achieve optimal laser-tissue contact and guidance to the selected site for therapy. The channels are created using holmium:YAG laser energy and their location is indicated in real time on the electromechanical map. The Biosense technique therefore integrates the identification of target zones (by electromechanical maps), catheter guidance (by location sensors) and the delivery of ablative laser therapy (by the laser system) with minimal X-ray radiation exposure. The Biosense DMR laser system is currently undergoing clinical evaluation. The system also allows for the local intramyocardial delivery of pharmacological therapy (e.g. growth factors).

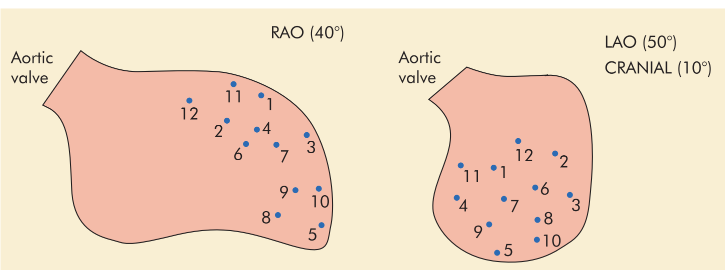


*Figure 3. The outline of the left ventricle in the right anterior oblique (RAO) and also in the left anterior oblique (LAO) with cranial angulation are shown. Twelve channels have been created by percutaneous myocardial laser revascularization in the anterior wall of the left ventricle.*

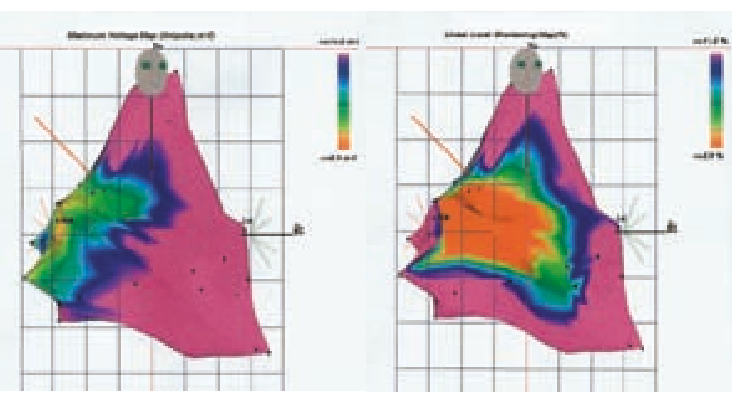

*Figure 4. Biosense map showing (a) preserved electrical activity but (b) reduced mechanical activity in the ventricular septum.*

**Results**

A multicentre randomized prospective trial of PMR has been completed using the Eclipse/Cardiogenesis system — the PACIFIC trial (Oesterle et al, 1999a). A total of 221 patients were randomized; 111 to medication alone and 110 to PMR and continued medication. All had angina refractory to medical therapy and had coronary artery disease which was not amenable to conventional revascularization.

At 6 months there was a mean reduction of 1.4 CCS angina classes in the PMR group as compared with 0.125 in the control group ($P$=0.001). There was also a 30% increase in treadmill exercise time in the PMR group as compared with 5% in the control group ($P$=0.001), from baseline values of around 400 seconds. The 12-month follow-up results have shown that the improvements in CCS angina class and exercise capacity noted at 6 months are maintained (Oesterle et al, 1999b) (*Figures 5* and *6*).

There were no perioperative deaths in the PMR group, which is encouraging in the light of the experience with TMR. The morbidity associated with PMR was also low. Of the 110 patients undergoing PMR, one developed cardiac tamponade requiring percutaneous drainage and one developed atrioventricular block requiring permanent pacing. There are ongoing studies of PMR, including a randomized trial in which the control group undergo a 'sham' procedure. The results of the trials using the Biosense DMR system are also awaited with interest.

## MECHANISM OF ACTION

The mechanism of action of TMR and PMR remains unclear. Suggested mechanisms include direct perfusion of the myocardium, angiogenesis, denervation and placebo effect. The channels tend to close following laser treatment, and therefore direct perfusion seems unlikely. Angiogenesis seems to be the most likely explanation for the symptomatic benefit which occurs. There is evidence of new vessel formation associated with the laser channels (Hughes et al, 1998). However, the clinical data demonstrating improved myocardial perfusion is not consistent. Laser treatment does destroy some cardiac nerve fibres and this may, at least in part, account for some of the symptomatic improvement. Finally, in this 'end stage' group of patients with severe symptoms, any treatment which is offered has the potential for a placebo effect.

## CONCLUSIONS

If the techniques of PMR and DMR are proven to be effective, and the results of the PACIFIC trial are encouraging, then it is likely that the catheter-based approach will be preferred to TMR in patients who have no other option for revascularization. The techniques of PMR and DMR are much less invasive and the PACIFIC trial confirms a much lower morbidity and mortality.

There is a group of patients who have some vessels which are suitable for coronary artery grafting and some which are not. TMR may have a role in this patient population, as an adjunct to coronary artery bypass surgery. In a similar manner, PMR and DMR may be undertaken in conjunction with coronary angioplasty/stenting in the future — for example with stenting of a stenosed left anterior descending artery and PMR to the inferior wall as a result of diffuse distal disease in the right coronary artery. It is likely that the use of laser revascularization, especially using the catheter-based approach, will increase in the future. It may also be combined with intra-myocardial delivery of angiogenic growth factors. **HM**

*Conflict of interest: none.*


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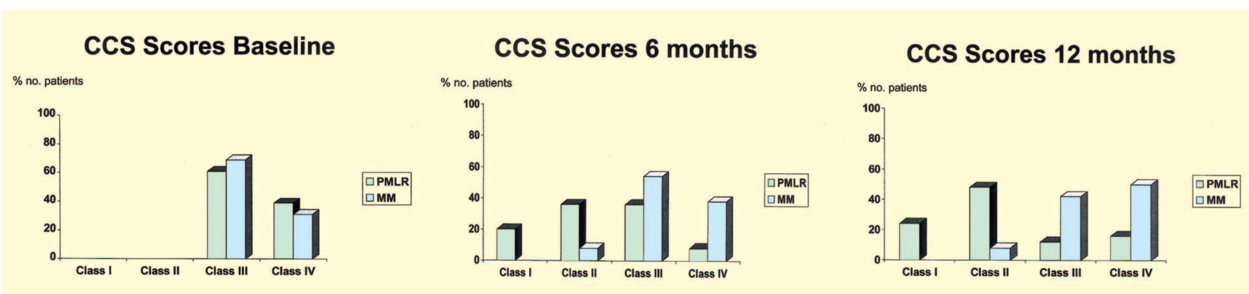


*Figure 5. The results of percutaneous myocardial revascularization — Canadian Cardiovascular Scores (CCS). These are shown (a) at baseline, (b) at 6 months and (c) at 12 months.*

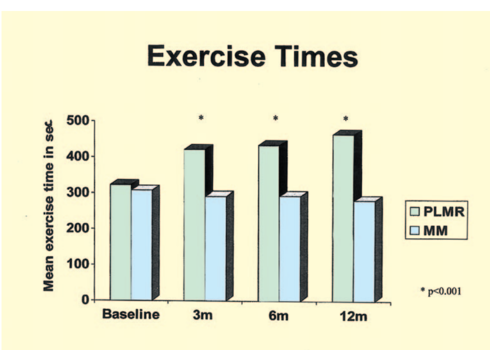


*Figure 6. The results of percutaneous myocardial revascularization — exercise times. These are shown at baseline, at 3 months, at 6 months and at 12 months.*

### KEY POINTS

- Transmyocardial revascularization (TMR) improves angina and increases exercise capacity in patients with end-stage coronary artery disease.
- TMR is associated with significant perioperative morbidity and mortality.
- Percutaneous myocardial revascularization (PMR) improves angina and increases exercise capacity in patients with end-stage coronary artery disease.
- PMR is associated with a low procedural morbidity and mortality.
- PMR may be a useful treatment in patients with severe angina caused by coronary artery disease who have no option for conventional revascularization.