The transmyocardial laser revascularization international registry report

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Aims This report aimed to provide an analysis of the data submitted from Europe and Asia on transmyocardial laser revascularization.

Methods and Results Prospective data was recorded on 967 patients with intractable angina not amenable to conventional revascularization in 21 European and Asian centres performing transmyocardial laser revascularization using the PLC Medical Systems CO2 laser. Patient characteristics, operative details and early complications following transmyocardial laser revascularization were recorded. The in-hospital death rate was 9.7% (95% confidence interval 7.8% to 11.6%). Other early complications were consistent with similar cardiothoracic surgical procedures. There was a decrease of two or more Canadian Cardiovascular Score angina classes in 47.3%, 45.4% and 34.0% of survivors at 3, 6 and 12 months follow-up, respectively (P=0.001 for each). Treadmill exercise time increased by 42 s at 3 months (P=0.008), 1 min 43 s at 6 months (P<0.001) and 1 min 50 s at 12 months (P<0.001) against pre-operative times of 6 min.

Conclusion Uncontrolled registry data suggest that transmyocardial laser revascularization may lead to a decrease in angina and improved exercise tolerance. It does, however, have a risk of peri-operative morbidity and mortality. Definitive results from randomized controlled trials are awaited.

(Eur Heart J 1999; 20: 31–37)

Key Words: Transmyocardial laser revascularization, Transmyocardial Laser Revascularization Registry.

Introduction

There is increasing interest around the world in the use of transmyocardial laser revascularization. Transmural channels are created using a high powered CO2 laser to provide a potential source of myocardial perfusion directly from the left ventricle. This procedure was pioneered by Mirhoseini and Cayton in 1981[1] and investigators have since shown improved mortality, reduced infarction size, preservation of contractile function and channel patency in animal models[2,3]. Following these early positive results, case reports of transmyocardial laser revascularization combined with coronary artery bypass grafting (CABG) in human subjects were reported[4–6]. It is now being studied as a form of treatment for patients with intractable angina despite medical management who are not suitable for conventional revascularization with CABG or angioplasty (PTCA). A number of centres around the world are performing transmyocardial laser revascularization either as sole therapy or in combination with CABG or PTCA.

In 1994 European, Asian and U.S. registries were established to prospectively record patient characteristics, operative details and early complications following transmyocardial laser revascularization using the PLC Medical Systems CO2 laser. Results from the central registry for data collected from Europe and Asia are presented.

Method

Operative details have been described previously[7] Briefly, a high powered CO2 laser is placed directly onto the myocardium, firing during diastole, when the heart is electrically inactive and full of blood. The extent of reversible ischaemia determines the number of channels. Holes are around 1 mm in diameter and about 1 cm apart. Transmural channels may be confirmed by
Transoesophageal echo or carotid Doppler. Haemostasis is achieved by epicardial digital pressure or purse-string sutures.

Twenty-two centres are registered with the Transmyocardial Laser Revascularization International Registry, of which 16 have supplied registration data on 1023 patients. One centre declined to be included in this report which reduced the number of patients to 967 — their exclusion did not influence any of the outcomes. Transmyocardial laser revascularization operative details are available on 932 patients. Eligibility criteria for transmyocardial laser revascularization may vary among centres to some extent, however, all centres are requested to record the following information as a minimum: patient characteristics, risk factors and cardiac history, operative details, combined procedures and in-hospital complications. In addition, centres are encouraged to supply the following details if available: laboratory results, cardiac function, current angiographic findings, exercise test times and follow-up episodes. Completed data are submitted to the coordinating centre at 6 monthly intervals and regular contact with centres is maintained to encourage compliance.

Initial outcome of the procedure is assessed using in-hospital mortality and other complications. For survivors, the clinical outcome of the procedure is assessed using Canadian Cardiovascular Society (CCS) and New York Heart Association (NYHA) angina classification, left ventricular ejection fraction and treadmill exercise times, using the modified Bruce protocol, at 3, 6, and 12 months after the procedure where these measures had been recorded.

Statistical analysis
Background data and operative details are summarized using the mean and standard deviation or the median and inter-quartile ranges, as appropriate, for continuous measurements. For categorical data, the number in each group and the percentage as a proportion of those responding is presented. The number of responses for each field was taken as the denominator throughout and, therefore, varied, with no attempt to treat missing values as negative responses.

Early complications and mortality following transmyocardial laser revascularization are presented as the percentage of patients for each event. For clinical outcome, changes between pre- and 3, 6 and 12 months post-transmyocardial laser revascularization were assessed: those patients who had both pre-procedure and follow-up data were compared using paired statistical tests; for change in angina scores the sign test was used; for change in left ventricular ejection fraction the paired Student t-test; and for exercise time the Wilcoxon signed ranks test was used. Due to the varying number of respondents supplying follow-up data at each time point Bonferroni adjustments were used in preference to repeated measures analysis of variance and Friedman tests.

Results
Patient characteristics and history
A total of 932 transmyocardial laser revascularization procedures were reported. Gender was reported on 929, 148 (16%) female and 781 (84%) males. The mean age at operation was 62 years (SD 8.7 years, range 32–84, 74% aged between 50 to 70 years, n=830). Most cases (874, 94%) had coronary artery disease alone but 26 (3%) had concomitant mitral valve disease, eight (1%) aortic valve disease, three (<1%) had both and five (1%) had other aetiologies. Eleven percent (65/596) of patients reported a history of congestive heart failure. Of 849 responses, peripheral vascular disease, cerebral vascular disease or both were reported in 157 (18%), 37 (4%) and 36 (4%) cases, respectively.

Of 904 responses, 437 (48%) had a history of unstable angina and 467 (52%) stable angina at the time of surgery. The majority of patients (713/865, 82%) reported at least one previous myocardial infarction (range 1 to 7). Most transmyocardial laser revascularization operations were performed in patients who had already had established revascularization procedures, 500/712 (70%) reported previous CABG, 209/649 (32%) reported previous PTCA, including 159 who reported both CAGB and PTCA. Patient history data were not always recorded so that denominators differ.

Treatment for hypertension was recorded for 339/578 (59%) of cases. Insulin-dependent diabetes was reported for 101/777 (13%) patients, 111/777 (14%) had non-insulin dependent diabetes. Of 692 responses, transmyocardial laser revascularization was performed in 105 (15%) current smokers and 359 (52%) previous smokers. At the time of surgery, 95/589 (16%) patients had impaired renal function defined as a serum creatinine >200 μmol l−1. Pulmonary co-morbidity, defined as forced expiratory volume in 1 s of <50% of that predicted for age and size, was recorded in 39/523 (7%) of cases.

Mean left ventricular ejection fraction was 49% (SD 14.9%, range 11–90%, n=596). Ninety percent of patients had an left ventricular ejection fraction of 30% or more and 12 of 15 centres, which reported left ventricular ejection fraction at assessment, had patients with values <30%. Three centres used multigated acquisition radionuclide ventriculography scanning, eight used left ventricular angiography and one small centre used both in equal numbers.

At registration, CCS was recorded for 694 cases and NYHA for 626 cases (Fig. 1). The majority of cases were in CCS class III or IV (78%) and NYHA class III or IV (81%). Sixty-four cases (9%) recorded a CCS of zero or one, of whom 53 had an angina NYHA score of two or above. Similarly, 16 cases (2.5%) recorded an...
NYHA of zero or one, of whom 12 had a CCS score of two or above; the remaining four are included in the former 11 cases identified above. Therefore, only 11 patients had minor symptoms — the justification for transmyocardial laser revascularization in these patients was not stated. Of the cases recorded as CCS or NYHA zero or one, 13 such patients had transmyocardial laser revascularization in combination with conventional surgical revascularization and the remaining cases were concentrated in three countries (Germany, India and Saudi Arabia).

Transmyocardial laser revascularization procedure

Between November 1993 and April 1997, the details of 932 transmyocardial laser revascularization procedures were reported to the registry. Of the 867 cases in whom this information was recorded, 177 (20%) were combined with CABG and 11 (1%) with PTCA. Of those done in combination with surgery the number of grafts reported were one (27%), two (34%), three (15%), four (2%) and five (1%) with 21% failing to record this detail. Twenty-four out of 928 (3%) were reported as emergency procedures of which four were in combination with either CABG or PTCA.

The mean number of channels was 28·6 (SD 12·2, n=902), with mean total energy used of 38·7 joules (SD 9·2, n=653). Support mechanisms used peri-operatively were intravenous adrenaline (109/893, 12%), dopamine (64/893, 7%), dobutamine (69/893, 8%), dopamine+dobutamine (27/893, 3%), an intra-aortic balloon pump (72/893, 8%), a left ventricular assist device (4/893, <1%) and 24 had other forms of support. The remaining 524 (59%) patients did not require additional support mechanisms. The mean left ventricular ejection fraction in patients requiring peri-operative support mechanisms was 46·4 ± 15·7% and in patients requiring no support was 49·9 ± 14·3% (P<0·01). Therefore, there is some evidence of lower left ventricular ejection fraction predicting the need for support. Immediate post-operative stay in an Intensive Care Unit was median 2 days, inter-quartile range 1–3 days, range 0–45 days (n=810). Total post-operative hospital stay was median 9 days, inter-quartile range 7–11 days, range 0–139 days (n=843).

Information on immediate post-operative complications is given in Table 1. Where ‘no complications’ had been checked we assumed that all listed complications were absent irrespective of the completeness of the data sheet. Otherwise, no response was assumed for incomplete data. Complication rates for infection,
cardiac arrhythmias, cardiac failure, ischaemia/myocardial infarction and tamponade and other vascular complications such as stroke and pulmonary embolism, were comparable with those for redo CABG (Table 1). Bleeding was recorded in 7-6% of cases. This was higher than the rate of 2-7% of cases reported from a large series of 2760 operations on lungs and mediastinal organs which required reoperation for bleeding\(^5\). However, in the registry data there is no indication of how many of the cases who bled actually required reoperation or transfusion, nor does it define the nature of the bleeding. The registry does not define whether treatment was required or not for the infections, left ventricular dysfunction or arrhythmias, nor does it provide any standard definition as to the criteria for diagnosing myocardial infarction.

In-hospital mortality following the procedure was 90/932 (9-7%, 95% confidence interval 7-8% to 11-6%). A test for heterogeneity between individual centre death rates was not significant (chi-squared (13), \(P=0.54\)), indicating consistency of results. Since procedures are not reported to the registry until discharge this information is expected to be complete. If the 11 patients who had minor pre-operative symptoms are excluded, the mortality rate changes marginally to 9-5% (95% CI 7-6% to 11-4%). After the initial discharge only 36 deaths have been reported to the registry, during which time reporting is not complete in the majority of cases.

**Clinical follow-up**

Ten centres supplied follow-up data at pre-set intervals after the transmyocardial laser revascularization procedures. The following results relate to changes in clinical measurements from pre-operation for those patients who survived and returned to hospital for post-operative assessment.

Seven centres provided post-operative CCS and NYHA scores. Table 2 shows the change in scores after the procedure. There is a statistically significant improvement in CCS at 3, 6 and 12 months (Sign tests with Bonferroni adjustment, \(P=0.001\) for each). It has been suggested that a reduction of at least two classes is clinically significant\(^3\) and this was achieved by 47-3% at 3 months, 45-4% at 6 months and 34-0% at 12 months, respectively. Similarly, surviving patients reported a significantly lower NYHA score after transmyocardial laser revascularization (\(P<0.001\), Sign test with Bonferroni correction). Assuming that a decrease of at least two classes is a clinically significant improvement, this was achieved by 38-0% of patients at 3 months, 42-4% at 6 months and 49-1% at 12 months. It may be felt by some that an improvement of two or more angina classes is a strong criteria to meet. An improvement in one or more CCS classes was seen in 70-3% at 3 months, 70-5% at 6 months and 55-4% at 12 months. Similarly, NYHA score improved at 3, 6 and 12 months by 76-0%, 79-3% and 83-9% respectively.

For cases who had both pre-operative and follow-up measurements, there were very small changes in left ventricular ejection fraction at 3, 6 and 12 months (Table 3). A statistically significant drop in mean left ventricular ejection fraction of 4-3% was recorded at 12 months (\(P<0.01\), paired Student t-test with Bonferroni correction). Within patient change was not influenced by the different methods used in different centres. Only one patient had a combined procedure and 12 month left ventricular ejection fraction, which did not change the outcome.

Four centres provided exercise test results both before and after the procedure (Table 3). Comparing post-operative to pre-operative treadmill exercise times in those patients with paired data, exercise performance increased significantly by 42 s at 3 months (\(P=0.008\), 1 min 43 s at 6 months (\(P<0.001\)) and 1 min 50 s at 12 months (\(P<0.001\)), against a baseline performance of approximately 6 min. An increase of 25% over baseline is the minimum improvement considered of clinical significance. There were only four patients who had combined procedures included in these results: none at 3 months; 3 at 6 months; and one at 12 months. If these patients are excluded, exercise performance increased by 2 min 9 s at 6 months and 2 min 6 s at 12 months.

There was no Thallium or MIBI scan data to report and the only angiographic data available was pre-operative.

**Discussion**

Uncontrolled human studies using the CO\(_2\) laser have suggested an overall improvement both subjectively and
The first use of a CO₂ laser in human subjects objectively following transmyocardial laser revascularization was published by Mirhoseini et al.[4]. In a patient with severe coronary disease they used the laser in conjunction with coronary bypass grafting (CABG) in an arrested heart. The patient did well, with relief of angina coupled with improved myocardial perfusion scans. A Phase I trial followed on 12 patients who underwent concomitant CABG and laser revascularization. Clinical improvement was noted in all patients; eight out of 10 patients showed an improvement in left ventricular function; follow-up studies consistently found increased uptake of thallium isotope in the lasered areas; and left ventriculography demonstrated patent channels in six out of 10 patients[5]. A further very similar study with 16 patients feeling well, there is a potential for bias. Assessments or decreased compliance to follow-up in patients requiring additional revascularization procedures. This should be contrasted with a significant improvement in the CCS for angina at 3, 6 and 12 months after the procedure in those who survived. Taking a decrease of 2 CCS classes as a clinically significant improvement, 75% of those assessed post-operatively achieved this. In addition, there was a significant decrease in the number of perfusion defects in the treated left ventricular wall. Patients who had at least one year of follow-up experienced a significant decrease in the number of admissions for angina from 2.5 per patient-year in the year before treatment to 0.5 per patient-year in the year after.

This report reviews results submitted to the registry from European and Asian centres performing transmyocardial laser revascularization using a CO₂ laser. One limitation is that data submitted to registries is less well monitored than in a clinical trial. Consequently, records are subject to individual centre variation in reporting and interpretation which is not blinded since most patients are not in clinical trials and records are often incomplete. For example, less than 30% of transmyocardial laser revascularization patients who had the procedure also had follow-up CCS/NYHA class recorded and less than 10% had either left ventricular ejection fraction or exercise test results at both pre- and post-transmyocardial laser revascularization assessments. Since some of the reasons for this are death following the procedure, inability to undergo follow-up assessments or decreased compliance to follow-up in patients feeling well, there is a potential for bias.

It is questionable whether the drop in left ventricular ejection fraction of 4-3% is clinically significant or indeed whether the measurements themselves are reproducible considering the different methods used by different centres for measuring left ventricular ejection fraction. The inter-programme measurement of left ventricular ejection fraction by multigated acquisition radionuclide ventriculography scanning is poorly reproducible — the difference in value may be as high as 5%[11]. Also, left ventricular ejection fraction
measurements by this method are significantly more accurate than those based on angiographic ventriculography\cite{12}. This highlights further limitations of the results.

Operative mortality was 9.7% (7.8% to 11.6%) for procedures reported to the registry, which agrees closely with the U.S. uncontrolled study. Previous studies have reported one year mortality in medically treated patients with triple vessel disease as 11–20\%\cite{13,14}. Benefit in terms of improvement in exercise performance was clinically significant, but much less impressive than that observed in the U.S. study and less than benefits observed following other revascularization procedures\cite{15–17}. Indeed, the 1 min 50 s improvement was clinically significant, but much less than benefits observed following other revascularization procedures. The complication rate may reflect a learning curve. If the data on the first 10 patients from each centre are removed the hospital death rate alters only very slightly, 82/797, 10·3% (95% Confidence Interval 8·2% to 12·4%). The complication rates and CCS/NYHA scores are summarized in Tables 4 and 5.

Transmyocardial laser revascularization is still a very new technology but is now being used widely in Europe, Asia and the U.S. It is becoming increasingly clear that the benefits of this method, in terms of improvements in angina and exercise tolerance, will need to be sufficient to outweigh the initial risk of death and other operative complications if the procedure is to become universally accepted. If this technology is used for patients with end-stage coronary artery disease, with severe limiting angina and for whom there are no other revascularization options, then these may be acceptable risks to the patient if there is a significant chance for improvement in health-related quality of life. Publication of further studies to assess this are awaited.

On the basis of the Phase II results, two U.S. multicentre randomized controlled trials were set up; one comparing transmyocardial laser revascularization against medical management, the other transmyocardial laser revascularization against redo-CABG. Following a review of results from the first trial and enthusiastic reports of success in relieving symptoms, the U.S. Food and Drug Administration advisory committee recommended in July 1997 that the PLC transmyocardial laser revascularization laser system should not be approved for use in the U.S. Their decision was based on the lack of a definitive explanation for the underlying mechanism (although many other well accepted techniques in clinical practice still lack full insight into the pathophysiological mechanism) and lack of rigour in the conduct of the trial in that the design allowed crossover from medical therapy to transmyocardial laser revascularization, data was missing for more than half of the patients and there was only short-term follow-up of 6 months\cite{20,21}. On 24 April 1998 the FDA recommended approval but with stringent conditions of use, recommending labelling restrictions, post-market surveillance, that it be limited to patients with stable class 3–4 angina and not used concurrently with other revascularization techniques\cite{22,23}.

### Table 4 Peri-operative complications following transmyocardial laser revascularization after 'a learning curve period'

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (%)</td>
</tr>
<tr>
<td>No complications</td>
<td>541 (70.7%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>52 (6.9%)</td>
</tr>
<tr>
<td>Infection</td>
<td>29 (4.0%)</td>
</tr>
<tr>
<td>LV dysfunction</td>
<td>63 (8.6%)</td>
</tr>
<tr>
<td>Arrhythmia:</td>
<td></td>
</tr>
<tr>
<td>Supraventricular</td>
<td>29 (4.2%)</td>
</tr>
<tr>
<td>Ventricular</td>
<td>45 (6.5%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>26 (3.6%)</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Others (miscellaneous)</td>
<td>68 (9.3%)</td>
</tr>
</tbody>
</table>

### Table 5 Change in Canadian Cardiovascular Society and NYHA angina classes following transmyocardial laser revascularization after 'a learning curve period'

<table>
<thead>
<tr>
<th>Change in score</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+3</td>
<td>1 (0.4%)</td>
<td>1 (0.6%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>+2</td>
<td>2 (0.9%)</td>
<td>3 (1.9%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>+1</td>
<td>16 (7.0%)</td>
<td>13 (8.1%)</td>
<td>7 (7.9%)</td>
</tr>
<tr>
<td>0</td>
<td>49 (21.6%)</td>
<td>34 (23.1%)</td>
<td>29 (32.6%)</td>
</tr>
<tr>
<td>−1</td>
<td>51 (22.5%)</td>
<td>39 (24.4%)</td>
<td>19 (21.3%)</td>
</tr>
<tr>
<td>−2</td>
<td>50 (22.0%)</td>
<td>32 (20.0%)</td>
<td>14 (15.7%)</td>
</tr>
<tr>
<td>−3</td>
<td>33 (14.5%)</td>
<td>21 (13.1%)</td>
<td>9 (10.1%)</td>
</tr>
<tr>
<td>−4</td>
<td>25 (11.0%)</td>
<td>17 (10.6%)</td>
<td>8 (9.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>227 (100.0%)</td>
<td>160 (100.0%)</td>
<td>89 (100.0%)</td>
</tr>
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<table>
<thead>
<tr>
<th>NYHA</th>
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<tbody>
<tr>
<td>+2</td>
<td>1 (0.8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>+1</td>
<td>5 (3.9%)</td>
<td>5 (2.7%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>0</td>
<td>27 (20.9%)</td>
<td>26 (17.6%)</td>
<td>14 (14.6%)</td>
</tr>
<tr>
<td>−1</td>
<td>51 (39.5%)</td>
<td>62 (41.9%)</td>
<td>36 (37.5%)</td>
</tr>
<tr>
<td>−2</td>
<td>41 (31.8%)</td>
<td>51 (31.7%)</td>
<td>43 (44.8%)</td>
</tr>
<tr>
<td>−3</td>
<td>4 (3.1%)</td>
<td>4 (3.4%)</td>
<td>2 (2.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>129 (100.0%)</td>
<td>148 (100.0%)</td>
<td>96 (100.0%)</td>
</tr>
</tbody>
</table>

($P<0.001$).
The U.K. randomized controlled trial, funded by the Medical Research Council, is currently comparing the benefits and costs of transmyocardial laser revascularization and medical therapy. This trial has now recruited the 188 patients needed to show any difference between the groups, it does not allow crossover from medical to surgical treatment and follow-up is at least one year. A recent interim analysis of results was reviewed by the independent data monitoring committee and their recommendation was that the trial should be completed as planned. There is an obvious need for a large, randomized, controlled trial of transmyocardial laser revascularization to evaluate risks and benefits accurately using the most scientifically valid methodology. Definitive information on which to base future clinical practice in the use of this technology will be available from the U.K. trial towards the end of 1998.

References


Appendix

Contributors to the Registry

Germany: Prof. Dr W. P. Klövekorn, Herzchirurgie, Bad Neuen; Prof. Dr Roland Hetzer, Deutsches Herzzentrum, Berlin; Prof. Dr Beyersdorf, Universitätssklinik Freiburg, Freiberg; Prof. Dr Hans H. Sievers, Universitätssklinik, Lübeck; Prof. Dr Rainer Moosdorf, Klinikum der Philipps-Universität, Marburg; Dr Hartmut Oster, Klinik für Herz und Gefäßchirurgie, Rotenburg; Dr Helmut Isringhaus, Herzzentrum Völklingen, Völklingen.
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Interests

The registry is sponsored by PLC Medical Systems and is held in the Research & Development Unit at Papworth Hospital, Cambridge. The analysis and report were prepared independently by members of the Cardiology Unit and R&D Unit at Papworth Hospital and the authors take responsibility for errors and omissions.