Transmyocardial laser revascularisation. Clinical experience in patients with refractory angina pectoris
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Cardiac denervation after clinical transmyocardial laser revascularisation: Short and long-term $^{123}$I-MiBG scintigraphic evidence

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Chapter 4

Abstract

This study was designed to investigate whether TMLR induces myocardial denervation, and to correlate this with myocardial perfusion and clinical status.

TMLR was performed using a Ho:YAG (n = 3) or XeCl excimer laser (n = 5). Pre- and post-operative $^{123}$I-MiBG SPECT scintigraphy to assess cardiac innervation and perfusion scintigraphy were performed. Furthermore, NYHA functional angina class and QOL were assessed.

In all patients, post-operative $^{123}$I-MiBG SPECT showed significantly decreased uptake and therefore sympathetic myocardial denervation up to 16 months follow up (average pre- and post-operative summed defect scores 14.8 ± 5.3 and 24.5 ± 4.2 respectively; p = 0.00005). In 86% of segments the decreased MiBG-uptake could be correlated to the treated area. In all patients, angina was reduced by ≥ 2 classes at 12 months follow up and QOL improved significantly.

In conclusion, TMLR-induced improvement of angina and QOL can be explained by destruction of nociceptors or cardiac neural pathways, changing the perception of anginal pain.
Introduction

TMLR is a therapy for severe angina pectoris refractory to anti-anginal medication, PTCA and CABG. At low operative risk, CO₂ and Ho:YAG TMLR relieves angina pectoris [72-76] and improves QOL [72-74,77] and exercise time [72,73,75,76]. Furthermore, non-randomised XeCl excimer TMLR achieves similar anginal relief [110,111]. However, the angina-relieving mechanism is still poorly understood and probably multifactorial, reducing acceptance of TMLR. The original idea that direct perfusion from the left ventricle through the laser channels improves myocardial perfusion [68] currently has little support [69]. Other hypotheses are TMLR-induced stimulation of angiogenesis [100] or destruction of cardiac nociceptors and afferent nerve fibres [99], which is investigated in the study reported here. Only one other clinical study has reported sympathetic myocardial denervation after Ho:YAG TMLR [87]. However, in that study 2 (of 8) patients post-operatively showed increased myocardial innervation and 5 patients had diabetes mellitus, introducing possible interference through diabetic neuropathy. Furthermore, denervation location was not correlated with the treated area.

In the present study we divided the heart in segments, and related changes in sympathetic innervation with treated area, perfusion and clinical performance in patients treated with Ho:YAG or XeCl excimer TMLR. We excluded confounding factors such as pre-operative myocardial infarction and diabetes mellitus in all but one patient.

Patients and methods

Study design

Patients were recruited from a randomised clinical trial investigating the clinical efficacy of Ho:YAG and XeCl excimer TMLR (see chapters 5 and 6). Inclusion criteria were angina pectoris NYHA functional class III-IV/IV (not eligible for PTCA or CABG as determined by an experienced cardiac surgeon and interventional cardiologist at the trial centre), a scintigraphically proven reversible perfusion defect, a LVEF ≥ 35%, and a life expectancy ≥ 1 year. Exclusion criteria were ventricular arrhythmias requiring treatment, clinically manifest heart failure, severe intrinsic haemorrhagic disorders and lack of informed consent.

Between March 1998 and June 2001, 30 of 118 patients screened for TMLR were included in the RCT of which eight were included in the study.
reported here. All other patients included in the randomised trial were excluded for this study either because of diabetic neuropathy or because of previously documented myocardial infarction (CK-MBmax > 25 µg/l), since denervation and regeneration of neural tissue occurs in varying degrees in viable myocardium adjacent to infarcted myocardium. 125Iodine-labelled meta-iodobenzylguanide (123I-MiBG) SPECT scintigraphy was performed at baseline and post-operatively at 1 (n = 5), 4 (n = 1), 9 (n = 1) or 16 (n = 1) months follow up. Myocardial perfusion was evaluated by 99mTc technetium-labelled tetrofosmin (99mTc-TF) SPECT scintigraphy at baseline (at 3 months ± 3 weeks before TMLR) and at 3 and 12 months follow up. Angina class, QOL and exercise time were assessed at baseline, 3, 6 and 12 months. The in-hospital medical ethical committee approved the study and all patients gave written informed consent. The funding agency played no role in data interpretation.

**Angina class, QOL and exercise tolerance**
Angina class was assessed by one investigator (JAPvdS), QOL was assessed using the Seattle Angina Questionnaire (SAQ) [112] and the EuroQol Standardised Questionnaire’s Visual Analogue Scale (VAS) [113], ranging from 0% (worst imaginable health) to 100% (best imaginable health), and exercise tolerance was assessed using a modified Bruce protocol.

**Myocardial perfusion scintigraphy (MPS)**
MPS was performed according to the guidelines of the American Society of Nuclear Cardiology [114], using 99mTc-TF and a 2-day stress/rest protocol. Stress was induced by exercise (bicycle ergometry) or, if exercise was not possible or suboptimal, or if patients had a left bundle branch block, it was induced pharmacologically (0.14 mg/kg/min adenosine for 6 minutes). For each individual patient, the stress modality used at baseline was also used at follow up.

All patients fasted four hours before perfusion scintigraphy. 99mTc-TF (approximately 500 MBq; Nycomed Amersham, Buckinghamshire, UK) was injected at maximal exercise or after 4 minutes of pharmacological stress, and also at rest. SPECT was performed one hour after 99mTc-TF injection. Images were obtained with the patient in prone position using a three-headed gamma camera (MultiSPECT-3, Siemens, Hoffman Estate, Illinois), using low energy high resolution collimators, a 20% energy window centred on the [99mTc] 140 keV photopeak, 20 views/camera-head, 45 s/view in a 64x64 matrix using the camera auto-contour facility and
standard filtered back projection without applying attenuation correction. Short axis slices were obtained and used for a segmental bull’s eye reconstruction (see figure 3F). Stress and rest images were scored using a validated and widely used three-dimensional sampling and analysis algorithm, which generates a five-point $^{99m}$Tc-TF uptake score (a measure for myocardial perfusion) for each myocardial segment [115]. Uptake was classified as normal (0), equivocal abnormal (1), mildly abnormal (2), moderately abnormal (3) or severely abnormal (4). With this classification, the algorithm used the stress and rest scans to calculate (per patient) a summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS, which is generated from the SSS and SRS). Since the two basal-septal segments represent the membranous part of the septum they were excluded from the SDS, leaving the sum of 18 segments. This 18-segment SDS was used in further analyses. The nuclear medicine physicians (HJV and BLFvE-S), blinded to treated area and $^{123}$I-MiBG SPECT, reviewed the generated scores per segment. In case of artefact scoring by the algorithm programme, scores were manually adjusted.

$^{123}$I-MiBG SPECT

MiBG and noradrenalin have similar molecular structures and both utilise the same uptake and storage mechanisms in sympathetic nerve endings [116]. $[^{123}I]$-labelling of MiBG enables scintigraphic visualisation of the cardiac sympathetic nervous system and uptake is therefore a measure of innervation. As β-blocker therapy affects MiBG-uptake, it is noteworthy that the dosage of β-blockers of each individual patient at pre-operative MiBG scintigraphy was identical to that at post-operative MiBG scintigraphy.

All patients received a single oral dose of 100 mg potassium-iodine to block thyroid uptake of free radioactive iodine one hour prior to the administration of the radiopharmaceutical. SPECT was performed 4 hours after intravenous administration of 185 MBq of $^{123}$I-MiBG (Nycomed Amersham, Buckinghamshire, UK) as described above for $^{99m}$Tc-TF SPECT, using medium energy collimators, an energy window centred on the $[^{123}I]$ 159 keV photopeak and 60s/view. Data reconstruction was performed using a Wiener filter. Short axis slices were obtained and used to construct the same segmental bull’s eye as described above. The fully automatic border-detection feature of a three-dimensional sampling and analysis algorithm [115] was used to delineate myocardial borders. Despite MiBG-uptake in the lungs and liver, in only one out of 16 scans manual
correction of the automatic delineation was required (performed by the two nuclear medicine specialists), and therefore in 15 $^{123}$I-MiBG SPECT scans the automatic delineation was successful.

The programme described above could not be used for the $^{123}$I-MiBG SPECT analysis because it is not validated for $^{123}$I-MiBG SPECT. Therefore, $^{123}$I-MiBG SPECT results before and after TMLR were visually analysed by the two nuclear medicine physicians, blinded to treated area and perfusion scintigraphy. However, for each segment, an identical five-point scorings system was used for MiBG-uptake: normal (0), equivocal abnormal (1), mildly abnormal (2), moderately abnormal (3) or severely abnormal (4). For each patient a pre-operative summed score, a post-operative summed score and a summed myocardial denervation score (SMDS), defined as post-operative summed score minus pre-operative summed score, was calculated for 18 segments.

**Operative technique and TMLR procedure**
A left lateral thoracotomy was performed in the fifth or sixth intercostal space and TMLR was performed in the ischaemic area of the left ventricular wall as pre-operatively assessed by perfusion scintigraphy. Approximately one channel per cm$^2$ was created with excimer TMLR and one per 1.5 cm$^2$ with Ho:YAG TMLR. Transmyocardial penetration was confirmed by transoesophageal echocardiography.

The Ho:YAG laser (*NSLX-6, CardioGenesis Corp., Sunnyvale, California; wavelength 2.1 µm, 2.0J/pulse, pulse duration 350 µs, 19 Hz*) was used with a 1.9 mm diameter spherically tipped fibre and its own trigger device. The myocardium was perforated by gently and manually advancing the fibre during 2-3 triggered cardiac cycles (3 pulses/cycle). With the XeCl excimer laser (*Max-20, Medolas, Munich, Germany; 308 nm, 37 - 40 mJ/pulse, 110 ns, 40 Hz*), which was combined with a hospital-built ECG-trigger device, the myocardium was perforated by gently and manually advancing a 1 mm diameter flat-tipped fibre during 3-4 triggered cardiac cycles (4-5 pulses/cycle).

Basal-septal and mid-septal segments were not treated to prevent damage to the bundle branches (see figure 3F). Apico-septal segments were sometimes treated through the apex. Immediately after the procedure the surgeon recorded the treated segments by drawing them into a bull’s eye presentation of the heart. Post-operative care was identical to that after open-heart surgery. Pre-operative anti-anginal medication was resumed on
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the first post-operative day. Myocardial damage was assessed by CK-MB$_{\text{max}}$.

**Statistical analysis**

Students’ t-tests (all paired and two-tailed) were used for statistical analyses of pre- and post-operative angina class, QOL, exercise time, myocardial perfusion scintigraphy (SDS) and $^{123}$I-MiBG SPECT scintigraphy (summed scores). $p < 0.05$ was considered significant. Results are given as mean ± SD.

**Results**

Tables 1 and 2 summarise pre-, peri- and post-operative patient characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>M:F</th>
<th>Age</th>
<th>Previous CABG</th>
<th>Previous PTCA</th>
<th>LVEF (%)</th>
<th>DM</th>
<th>Cardiac medication</th>
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</thead>
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<tr>
<td>1</td>
<td>M</td>
<td>61</td>
<td>+</td>
<td>-</td>
<td>56</td>
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<tr>
<td>2</td>
<td>M</td>
<td>51</td>
<td>+</td>
<td>-</td>
<td>53</td>
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<td>β-b/Ca</td>
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<td>3</td>
<td>M</td>
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<td>+</td>
<td>61</td>
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<td>+</td>
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<td>60</td>
<td>+</td>
<td>-</td>
<td>55</td>
<td>-</td>
<td>β-b/Ca/Ni</td>
</tr>
</tbody>
</table>

**Table 1. Pre-operative patient characteristics.** β-b = β-blocker; Ca = calcium-antagonist; CABG = coronary artery bypass grafting; DM = diabetes mellitus; F = female; LVEF = left ventricular ejection fraction; M = male; Ni = long-acting nitrate; PTCA = percutaneous transluminal coronary angioplasty.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Laser</th>
<th># of channels</th>
<th>CK-MB max</th>
<th>NYHA class pre-TMLR</th>
<th>NYHA class 3m</th>
<th>NYHA class 12m</th>
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<td>1</td>
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<td>23</td>
<td>3</td>
<td>2</td>
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<tr>
<td>2</td>
<td>Ho:YAG</td>
<td>43</td>
<td>36</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>excimer</td>
<td>59</td>
<td>101†</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>excimer</td>
<td>50</td>
<td>43</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
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<td>28</td>
<td>4</td>
<td>2</td>
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</tr>
<tr>
<td>6</td>
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<td>29</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
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<td>Ho:YAG</td>
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<td>4</td>
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<td>2</td>
</tr>
<tr>
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<td>excimer</td>
<td>42</td>
<td>25</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 2. Peri- and post-operative patient characteristics.** * $p < 0.05$ compared to pre-operative; † due to a small sub-endocardial infarction that did not affect $^{123}$I-MiBG scintigraphy; m = months; NYHA = New York Heart Association; SD = standard deviation.
Deliberately, the number of Ho:YAG laser channels was lower than with the excimer laser since, at the laser settings used, 1.9 mm Ho:YAG fibres induce more mechanical and thermal injury than 1 mm excimer fibres. Average in-hospital stay was 9 days for both Ho:YAG and XeCl excimer TMLR. None of the patients died during follow up.

**Angina class, QOL and exercise tolerance**

Angina improved ≥ 2 classes (NYHA) in 7 of 8 patients at 3 months and in all 8 patients at 12 months follow up (table 2). Overall, QOL (figure 1) was significantly improved at 3 months follow up in all 5 domains of the SAQ and in the VAS. These improvements were still significant at 12 months follow up with exception of the treatment satisfaction domain of the SAQ. No differences were seen between Ho:YAG and excimer laser patients. Overall, TMLR did not improve exercise time (526 ± 201 s pre-operative vs. 558 ± 217 s and 549 ± 222 s at 3 and 12 months respectively).

![Graph showing QOL score over time](image)

**Figure 1.** Results of the Seattle Angina Questionnaire (SAQ) and the EuroQol Questionnaire’s Visual Analogue Scale (VAS). *VAS and all SAQ domains; †VAS and SAQ domains with exception of treatment satisfaction.

**Myocardial segments treated by TMLR**

Of 144 segments (8 patients, 18 segments/patient), 74 were treated by TMLR (range 6-14 segments/patient). Furthermore, 63 of 144 segments demonstrated a reversible perfusion defect pre-operatively, 58 of these were eligible for TMLR (the other 5 were mid-septal segments), and 46 of these 58 segments (79%) were actually treated by TMLR. Consequently, 46 of 74 treated segments (62%) pre-operatively showed a reversible
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perfusion defect. Of the remaining 28 treated segments, 7 showed a minimal rest score (of 1 or 2) and the remaining 21 showed no defects. Figure 2 summarises the results.

![Venn diagram](image)

**Figure 2. Venn diagram of overlap of segments treated by TMLR (dark grey), pre-operatively showing a reversible perfusion defect (light grey) and showing a positive myocardial denervation score (white).** For example, 28 segments pre-operatively showed a reversible perfusion defect, were treated by TMLR and post-operatively did not show denervation. Of the 14 segments that pre-operatively showed a reversible perfusion defect, were not treated and did not show denervation, 5 were mid-septal segments that could not be treated. Consequently, a total of 58 reversible perfusion defect segments were eligible for TMLR.

**123I-MiBG SPECT and myocardial perfusion scintigraphy**

Table 3 summarises the scintigraphic results. Pre-operatively, 27 out of 62 segments with a decreased MiBG-uptake corresponded with areas at risk on perfusion scintigraphy. All patients showed a positive summed myocardial denervation score and MiBG-uptake decreased after TMLR in 45% of treated segments (figure 2). If we assume that there was no significant difference in the maximum pre- and post-operative MiBG-uptake

<table>
<thead>
<tr>
<th>Patient</th>
<th>123I-MiBG SPECT scintigraphy</th>
<th>Myocardial perfusion scintigraphy</th>
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<tbody>
<tr>
<td></td>
<td>Pre-TMLR</td>
<td>Post-TMLR</td>
</tr>
<tr>
<td></td>
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<td>Post-TMLR</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
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<td>24</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>mean ±</td>
<td>14.8 ± 5.3</td>
<td>24.5 ± 4.2*</td>
</tr>
</tbody>
</table>

Table 3. Results of 123I-MiBG SPECT and myocardial perfusion scintigraphy. *p = 0.00005 compared to pre-operative (and p = 0.0002 when excluding patient nr. 6 who had diabetes mellitus type II); SD = standard deviation; SDS = summed difference score; SMDS = summed myocardial denervation score; SS = summed score.
(that in each individual was in a non-treated basal segment and that pre-operatively was at the same cardiac location as post-operatively), we may conclude that none of the 144 segments showed increased innervation. Overall, in 50 segments, MiBG-uptake was decreased after TMLR and 33 of these (66%) had been treated. No significant differences in MiBG-uptake were found between Ho:YAG and excimer TMLR. On average, perfusion remained unchanged at 3 and 12 months. No post-operative increase in scar size was observed (average SRS was 4.4 ± 5.2 at baseline vs. 6.1 ± 5.0 at 3 months (p = 0.2) and 4.1 ± 4.6 at 12 months). Figure 3 shows a patient example.

![Figure 3](image_url)

**Figure 3.** Bull's eye representation of myocardial innervation and perfusion in a representative case (patient nr. 4) showing denervation after TMLR. Eight months post-operative $^{123}$I-MiBG scintigraphy (panel B) shows, compared to pre-operative (panel A), antero-laterally decreased uptake corresponding with the TMLR-treated area. Panel C displays the difference between pre- and post-operative $^{123}$I-MiBG scintigraphy, compatible with denervation in the TMLR-treated area. No improvement in ischaemia was observed in the TMLR-treated area 12 months post-operative (panel E) compared to pre-operative (panel D, both panels displayed as reversibility plots). The level of radioactivity (panels A and B) and difference (C, D and E) is encoded from low (black) via medium (yellow) to high (white). Panel F shows the 18-segment model of the left ventricle: 4 basal, 6 mid-ventricular, 6 pre-apical and 2 apical segments. The grey segments, representing the membranous part of the inter-ventricular septum, were excluded in all analyses. * segments never treated by TMLR; MPS = myocardial perfusion scintigraphy; ANT = anterior; LAT = lateral; INF = inferior; SEPT = septal.
Discussion

Our results support previous evidence that denervation plays a role in anginal relief after TMLR [87]. To our knowledge this is the first segmental analysis of innervation, correlated to perfusion and TMLR-treated area. Also, because no patient had diabetic neuropathy (because only one diabetic was included with no signs of neuropathy), the possible interference of diabetic neuropathy with the studied denervation effects is minimised.

Denervation hypothesis

The denervation hypothesis originates from the observation that TMLR can relieve angina within days. Since functional angiogenesis unlikely occurs within days, anginal relief through direct intervention in (neural) pain sensation by cardiac denervation is thought to play a role. Anginal perception is believed to be transported to the brain through cardiac nociceptors and afferent fibres [84]. The latter are located superficially in the epicardium [85] and thus easily accessible by TMLR. Other indications that interference in neural pathways may contribute to anginal relief are beneficial effects on angina of neuromodulating therapies such as SCS and TEDA [11,44]. Also, diabetics frequently experience silent ischaemia (without anginal complaints) because diabetic neuropathy often destroys sympathetic myocardial fibres [117]. Moreover, heart-transplant patients lack angina in the first years after transplantation despite the development of extensive coronary artery disease.

Experimental evidence

Experimental myocardial denervation studies after TM(L)R show conflicting results [69]. In a canine model, Kwong et al. reported that Ho:YAG TMLR destroys cardiac nerve fibres, as assessed by cardiac afferent nerve function (epicardial bradykinin) and tyrosine hydroxylase measurements 2 weeks post-operatively [99]. Using the same assessment and follow up, Yamamoto et al. reported radiofrequency TMR-associated denervation in canine comparable to TMLR [118]. In contrast, Minisi et al. [119] and Hirsch et al. [120] reported no effect of Ho:YAG TMLR in canine using various acute neural assessments. However, the group of Hirsch, i.e. Arora et al. [121], also studied TMLR-effects (after 4 weeks) and they concluded that remodelling of the intrinsic cardiac nervous system may account, at least in part, for delayed symptomatic benefits in TMLR patients. Finally, one study, using the same assessment techniques as
described in the clinical study reported here (MiBG SPECT) in a 3-day survival porcine model, has reported negligible effect of endocardial Ho:YAG channels (PMR) on denervation [122]. This may be explained by the epicardial location of the sympathetic fibres (less damaged by PMR) and because PMR affects myocardium to a lesser extent. These differences may also explain the reported difference in clinical efficacy between TMLR and PMR [123].

**Clinical evidence**

Al-Sheikh et al. have investigated sympathetic innervation and myocardial ischaemia with PET-imaging using $^{11}$C-hydroxyephedrine (HED) and $^{13}$N-ammonia respectively [87]. In 8 Ho:YAG patients, PET-imaging was performed at baseline and 2 months post-operatively. All patients experienced improvement of $\geq 2$ angina classes. As in our study, TMLR did not significantly affect myocardial perfusion. HED measurements showed decreased innervation after TMLR in 6 of 8 patients and, surprisingly, increased innervation in 2 patients. Pathophysiologically, this increase is difficult to explain. Nevertheless, the authors concluded that TMLR causes sympathetic myocardial denervation without affecting perfusion.

Compared to Al-Sheikh’s study, our design has several advantages. First, only one of our patients had diabetes (vs. 5 of 8 in Al-Sheikh’s study), which minimises possible interference of neuropathy with the scintigraphic results. In this patient (diabetes type II) no clinical signs of neuropathy were identified. Furthermore, even when excluding this patient from analyses, the observed denervation in the remaining 7 patients was still highly significant ($p = 0.0002$). Second, we assessed denervation at 1, 4, 9 and 16 months and found clinical benefit and denervation at all follow-up-times. Given the controversy concerning long-term efficacy of TMLR, this is an important finding, even though it was investigated in only few patients. Third, this study compares for each of 18 segments the areas that showed denervation vs. the TMLR-treated areas. Out of 74 TMLR-treated segments, 33 segments (45%) showed denervation. Apparently, not every transmyocardial laser perforation destroys nerves, or at least not enough to significantly decrease MiBG-uptake. However, since all patients post-operatively showed decreased MiBG-uptake, and all experienced significant clinical improvement, we hypothesise that this incomplete denervation of treated segments is sufficient to relieve angina. Inversely, 33 of 50 denervated segments (66%) were treated. Of the remaining
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17 non-treated segments, 10 were pre-apical or apical segments. As also postulated by Al-Sheikh et al., denervation of non-treated (pre-) apical segments may result from proximal ('upstream') lesions that interrupt sympathetic nerve fibres that connect with the apex. Consequently, we concluded that in 86% (43/50) of all segments that showed denervation, decreased MiBG-uptake could be attributed to TMLR. Why denervation occurred in the remaining 7 non-treated segments is unclear. Although myocardial ischaemia may play a role in cardiac neuronal damage [124], only 3 of the 7 remaining non-treated segments showed ischaemia, leaving unexplained denervation in 4 segments. These denervated segments were distributed over 3 patients (with 1 month follow up) and one segment showed a denervation score of 2 and 3 segments of only 1. Given our method of recording the treated area, it is entirely possible that a shift or uncertainty of some cm may occur in the TMLR polar plot compared to the scintigraphic scans. As a result, this could have led to minor errors in our analysis and this therefore may explain some of the inconsistencies. We have considered three other possible explanations for the denervation in the 4 segments: i) spontaneous denervation, ii) thoracotomy-related denervation or iii) a variation in observed MiBG-uptake. However, we rejected them because i) in our opinion spontaneous denervation is unlikely, given the short time span used in this study, ii) there is no theoretical basis for decreased MiBG-uptake solely induced by the thoracotomy and iii) any uptake-related variation would expected to be two-sided. Since none of the investigated segments showed increased innervation, this last explanation also seems unlikely.

Finally, we performed both Ho:YAG and excimer TMLR. Despite differences in laser-tissue interaction [69], no laser-specific differences in denervation or myocardial damage (CK-MB) were observed. However, for this comparison groups were too small to draw definite conclusions. If denervation would be the only working mechanism of TMLR, it is highly likely that the anti-anginal effect would decrease with re-innervation of the myocardium. Similarly, a return of anginal complaints is observed after re-innervation of transplanted hearts. However, a sustained relief might be induced if the initial TMLR-induced anginal relief due to denervation results in, for instance, a change in life style with increased exercise (inducing increased capillary shear rates and arteriogenesis).
Chapter 4

Conclusion
In all Ho:YAG and excimer patients, evidence of denervation was found, while no improvement was seen in perfusion. The coinciding improvement in angina and QOL suggests that myocardial denervation plays an important role in the efficacy of TMLR. Consequently, further research is indicated to investigate whether other methods to induce myocardial denervation might be at least as effective, simpler and cheaper in relieving angina and improving QOL in patients with severe refractory angina.