Transmyocardial laser revascularisation. Clinical experience in patients with refractory angina pectoris
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Summary

Chapter 1 provides an introduction of this thesis and is composed of three parts:

Part 1, entitled ‘conventional treatment of angina pectoris’, describes the different definitions of angina pectoris and gives some insight in the epidemiology of coronary artery disease in the Netherlands. Despite all efforts concerning primary and secondary prevention of cardiovascular diseases, they are still the leading cause of morbidity and mortality in the Netherlands. For example in 2001 more than 34% of all deaths were due to ischaemic heart disease. Furthermore the different conventional treatment regiments of stable angina pectoris, i.e. medication, PTCA and CABG, are shortly described.

Part 2, called ‘treatment of refractory angina pectoris’ discusses several different treatment modalities that are available for the treatment of refractory angina with special attention for transmyocardial laser revascularisation (TMLR) and the main hypotheses of its working mechanism: Patent channels, angiogenesis and denervation.

Part 3 provides an overview of the aims and the structure of this thesis.

Chapter 2 shows two-dimensional echocardiographic images of laser-made channels in the myocardium in an experimental model and in a patient treated with TMLR.

Chapter 3 describes a histological case report of a patient that died 3 months after XeCl excimer TMLR. In the treated myocardium, no patent channels were found but scars were seen with a linear distribution and in continuity with circumscribed small fibrotic endocardial and epicardial scars. The scars were highly vascularised by new vessels, ranging from small capillaries to large thin-walled, and sometimes branching ectatic vessels. Sprouting of vessels into the adjacent myocardium was also observed. These results support the hypothesis that angiogenesis plays some role in the clinical improvement after TMLR.

In chapter 4 a clinical study investigating TMLR-induced changes in innervation is described. In 8 patients, Ho:YAG or XeCl excimer TMLR was performed and myocardial innervation (using $^{123}$I-MiBG SPECT scintigraphy), perfusion (using $^{99}$Tc-TF SPECT scintigraphy), and function (using stress echocardiography) were assessed pre- and post-operatively. Post-operative $^{123}$I-MiBG SPECT scintigraphy demonstrated myocardial
denervation in all 8 patients (p = 0.00005). Using a segmental comparison of denervation and TMLR-treated area, we found that 86% of denervated segments could be correlated to TMLR. Myocardial perfusion scintigraphy and stress-echocardiography did not change significantly. In all patients angina was reduced with ≥ 2 classes at 12 months follow up and quality of life improved significantly. In conclusion, TMLR-induced improvements of angina and quality of life may be explained by destruction of nociceptors or cardiac neural pathways.

Chapters 5 and 6 describe the results of a randomised clinical trial investigating XeCl excimer TMLR as a treatment for severe refractory angina pectoris. Thirty patients with New York Heart Association (NYHA) functional class III-IV/IV angina, a reversible defect on \(^{99}\)Tc-TF SPECT perfusion scintigraphy, a left ventricular ejection fraction ≥ 35% and no option for PTCA or CABG were randomised to excimer TMLR with maximal anti-anginal medication (n = 15) or continued maximal anti-anginal medication alone (n = 15). Patients were followed during one year with assessment of angina class, quality of life (described separately in chapter 6), myocardial perfusion scintigraphy, exercise tolerance and stress-echocardiography. One TMLR patient died peri-operatively vs. none in the controls. In the TMLR group angina decreased from class 3.8 ± 0.4 at baseline to 1.9 ± 0.9 at 12 months, versus 3.9 ± 0.3 to 3.7 ± 0.6 respectively in the control group (p < 0.0001). At 12 months, a decrease of ≥ 2 angina classes was found in 11 out of 14 (79%) TMLR patients versus none of the controls (p < 0.01). At 12 months, improvement in the three used QOL questionnaires was significantly higher in the TMLR group vs. the control group. A decrease in wall motion abnormality score was found without improvement in myocardial perfusion or exercise time. The results of this study show that XeCl excimer TMLR is very effective in reducing anginal symptoms and improving QOL in the selected patient group, with results that are comparable to CO\(_2\) and Ho:YAG TMLR.

Chapter 7 gives an overview of the current clinical TMLR literature. Since its first clinical application in 1981, many reports have described the use of TMLR as a treatment for refractory angina pectoris. In the current chapter both uncontrolled and controlled stand-alone TMLR studies (using CO\(_2\), Ho:YAG and XeCl excimer lasers) that have been published are reviewed. For uncontrolled TMLR, a total of 721 CO\(_2\), 251 Ho:YAG and 34 XeCl excimer patients have been described. Overall, in respectively 349, 222 and 27 patients with a completed one-year follow up, angina decreased from
class $3.2 \pm 0.5$ to $2.2 \pm 0.9$ after $\text{CO}_2$, $3.7 \pm 0.3$ to $2.0 \pm 0.7$ after $\text{Ho:YAG}$ and $3.5 \pm 0.5$ to $1.8 \pm 0.5$ after $\text{XeCl}$ excimer TMLR. Mortality at 8-12 months was 25% after $\text{CO}_2$ TMLR, 12% after $\text{Ho:YAG}$ TMLR and 7% after $\text{XeCl}$ excimer TMLR.

In six randomised TMLR trials (3 $\text{CO}_2$, 2 $\text{Ho:YAG}$, 1 $\text{XeCl}$ excimer), angina decreased $\geq 2$ classes in 24-72% of $\text{CO}_2$ treated patients, in 61-76% of $\text{Ho:YAG}$ treated patients and in 79% of $\text{XeCl}$ excimer treated patients (all significant compared to medication). Including cross-over, one-year mortality was 12-21% after $\text{CO}_2$, 5-13% after $\text{Ho:YAG}$ TMLR and 7% after $\text{XeCl}$ excimer TMLR (no differences compared to medication).

A meta-analysis of the six randomised TMLR trials was also performed. In a total of 967 patients, 57.1% (197 out of 345) of the TMLR patients improved $\geq 2$ classes in angina compared to 14.2% (40 out of 282) in the maximal medication group (absolute difference 42.9%, 95%CI: 35%-51%, $p < 0.0001$). The relative risk of mortality was 1.16 (95%CI: 0.80-1.71, $p = 0.43$) comparing TMLR with maximal medication.

In conclusion, all studies with the three clinically used lasers demonstrate relief of angina in the majority of patients, combined with an acceptable peri-operative mortality. Therefore, after a proper selection of patients, TMLR can be performed safely and effectively and should be the treatment of choice in selected patients. Clinically, as there was no important difference between the three types of laser, currently any of these lasers is suitable for TMLR.

Chapter 8 discusses the diagnostic limitations of myocardial perfusion scintigraphy (MPS) in refractory angina pectoris, as well as its consequences for therapy. Refractory angina pectoris is defined as a chronic condition characterised by severe angina caused by coronary insufficiency that cannot be controlled by conventional therapies. By definition, the presence of detectable ischaemia should be established. We investigated the diagnostic value of myocardial MPS in patients with refractory angina evaluated for inclusion in a randomised trail of TMLR and the consequences for therapy and clinical course.

Of 67 patients with severe angina refractory to conventional treatment and with proven severe coronary artery disease, as much as 22 (33%) were excluded for TMLR because of the lack of detectable ischaemia on MPS (both visually and quantitatively). However, a subanalysis in 9 of these 22 patients showed a significantly increased lung/heart ratio, suggesting the presence of generally impaired myocardial perfusion. Thirty out of
67 patients showed ischaemia on MPS and were randomised to immediate (n = 15) or delayed TMLR after one year (n = 15). The one-year morbidity in patients with ischaemia who were randomised to delayed TMLR and patients without detectable ischaemia was identical, except for the number of hospitalisations and alternative treatments that were significantly higher in patients without detectable ischaemia. TMLR resulted in a significant reduction in angina class (3.6 ± 1.0 to 1.9 ± 0.8), which persisted during the mean follow up of 36 months, in contrast to patients excluded for TMLR. Peri-operative mortality of TMLR was 7.2% and 8 patients experienced a peri-operative myocardial infarction (28.6%). During follow up the number of hospitalisations for angina remained significantly higher in patients without detectable ischaemia.

These results indicate that (i) the sensitivity of MPS for the detection of ischaemia in patients with refractory angina is lower than expected, (ii) the application of alternative treatment options for symptomatic relief is justified in all patients with refractory angina irrespective of detection of ischaemia and (iii) TMLR is an effective palliative treatment for refractory angina in patients with detectable ischaemia, although with considerable peri-operative morbidity and mortality.

Finally, in chapter 9 the outcome of the research in this thesis is evaluated in a general discussion resulting in the following conclusions:

Firstly, TMLR using a XeCl excimer laser is highly effective in relieving refractory angina pectoris and improving quality of life, at least up to 12 months after the procedure. With careful consideration of the operative risks, TMLR should not be withheld in a selected group of patients.

Secondly, since no improved myocardial perfusion was found after TMLR and our study showed signs of denervation, clinical improvement is induced by denervation rather than by angiogenesis.

Thirdly, patients with the clinical syndrome of refractory angina without documented ischaemia should not be excluded from alternative treatment strategies. A guideline for patient selection, treatment and future research in specialised centres is proposed. For the final choice of treatment, the patient’s opinion and perception of complaints together with his physical status and treatment-related risk are decisive.