9

GENERAL DISCUSSION

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Introduction

Coronary Artery Disease (CAD) is still the major cause of morbidity and mortality in the western world, despite all efforts in primary and secondary prevention during the last decades. Thanks to new treatment modalities in modern cardiology, i.e. treatment of acute coronary syndromes as well as of arrhythmias and of congestive heart failure, and thanks to advancement of healthcare in general, patients with a cardiac illness have an improved life expectancy. However, improved treatment of CAD has also resulted in a growing number of patients with refractory angina pectoris. In this thesis, research was focussed on this type of patient and now we will focus on the three main topics of this thesis. Firstly, clinical efficacy and safety of TMLR using a XeCl excimer laser are discussed. Secondly, our findings are discussed with respect to effect of TMLR on myocardial perfusion and function and our work on the working mechanism of TMLR. Thirdly, the demonstrated diagnostic limitation of myocardial perfusion scintigraphy to detect ischaemia in patients with refractory angina is discussed, as well as its implications for the clinical course and therapy in these patients. Finally, a guideline is proposed for the treatment of refractory angina in general.

Clinical efficacy and safety of XeCl excimer TMLR

In previous studies, the clinical efficacy (i.e. the reduction of angina) of CO₂ and Ho:YAG TMLR has been demonstrated. Since CO₂ and Ho:YAG lasers have a different mechanism of tissue destruction than XeCl excimer lasers, XeCl excimer TMLR may be more effective and safer than CO₂ or Ho:YAG TMLR [69].

In our study, 79% of patients in the TMLR group showed a decrease of ≥ 2 angina classes at 12 months follow up, versus 0% of patients in the control group. Although assessed in a smaller number of patients, this result is at least as good as the outcome of earlier randomised TMLR studies using CO₂ and Ho:YAG lasers. In these latter studies, angina decreased with ≥ 2 classes in 24% to 76% of TMLR patients and with ≥ 1 class in at least 63% of TMLR patients (versus 86% in our study). As could be expected, improvement was most pronounced in patients with functional class IV/IV angina (see chapters 5 and 7).

The improvement in QOL in our study was comparable with results reported earlier for CO₂ or Ho:YAG TMLR. The scores of the physical
limitation domain, angina frequency domain and disease perception domain of the Seattle Angina Questionnaire improved significantly after TMLR compared to the controls. Also the EuroQol and MOS-SF24 questionnaires showed improvement of quality of life (see chapter 6). As in our opinion an increased QOL is the major goal of treatment of refractory angina, these significant improvements are clinically even more important than the observed improvement in angina class.

In contrast to other investigators, we did not find any evidence for increased exercise time. This is remarkable in view of the demonstrated relief of anginal complaints. This might be explained by use of the modified Bruce protocol to assess exercise time. This protocol includes the use of an incremental workload that has the disadvantage that small differences in exercise capacity cannot be detected.

In our study, the peri-operatively mortality after XeCl excimer TMLR was 6.8% (which was similar to the 7.7% that we observed in our results with Ho:YAG TMLR). During the first year of follow up none of the control patients died and no additional patient died in the TMLR group. In the other randomised trials, when including cross-over, mortality during the first year of follow up varied from 5-21% after TMLR vs. 4-26% in the controls. Total one-year mortality after TMLR in the other randomised trials was 14% (74 out of 545 patients). The peri-operative morbidity was low, except for the occurrence of TMLR-related myocardial infarctions (4 in 15 excimer TMLR patients or 27%).

We concluded that the treatment of refractory angina with excimer TMLR gives similar results as earlier CO₂ and Ho:YAG studies, showing a relief of angina and improved quality of life without evidence of improved cardiac perfusion or function. Consequently, TMLR is primarily a symptomatic treatment for patients with refractory angina with no known prognostic benefit, with improvement in angina and QOL that are comparable to results after other approaches, including revascularisation strategies such as PTCA and CABG. In view of the demonstrated clinical improvement, peri-operative mortality and morbidity is acceptable. Therefore, in patients with severe refractory angina, TMLR is a valuable option. However, careful patient selection is mandatory since TMLR is still an invasive procedure requiring general anaesthesia and a thoracotomy. Finally, long-term results for excimer TMLR have to be awaited, although persisting favourable results have been reported with respect to angina, quality of life and hospitalisations for unstable angina up to 5 years after CO₂ and Ho:YAG TMLR [109,160].
Chapter 9

Working mechanism of TMLR

The initial hypothesis from which the treatment has originated was based on the description of myocardial sinusoids and the observation that in reptilian and some amphibian hearts, perfusion through these sinusoids provides the majority of blood delivery to the myocardium. Currently, this hypothesis has been dismissed because in most post-mortem histology, fibrotic scars with an epicardial to endocardial orientation were observed instead of open channels. At present, angiogenesis and denervation are considered the two main hypotheses to explain the clinical efficacy of TMLR. In this section, after the paragraph on angiogenesis, also the effect of TMLR on perfusion and function is discussed.

Angiogenesis

In TMLR, using any of the three clinically available lasers, thermal damage and scar formation is induced, which are likely part of the normal healing response to the inflicted injury. Not surprisingly, as in any lesion resulting in scar formation, angiogenesis plays a role in tissue healing and remodelling. In 1 of our patients, who died 3 months after TMLR, we have observed angiogenesis (see chapter 3). An interesting finding was that new vessels sprouted into the myocardial tissue adjacent to the channel remnant. However, whether these newly formed vessels attribute to local perfusion remains doubtful. The histological appearance of the new vessels suggests that the contribution to local perfusion is probably minimal. Although the mechanistic importance of angiogenesis is probably limited, it might be that angiogenesis does play a role in redistribution of local flow and relief of anginal complaints following TMLR.

Perfusion

Only one randomised TMLR study claimed an improvement in myocardial perfusion [74]. In this study an unusual endo-to-epicardial perfusion ratio was used, which hampers the interpretation of the findings. Conflicting clinical results on the effect of TMLR on perfusion are reported in uncontrolled studies. Different detection methods for ischaemia were used, e.g. MPS, stress-echocardiography, PET and MRI. In our study, scans showed sustained ischaemia on MPS at 3 and 12 months follow up. In individual patients, local perfusion remained unchanged or even decreased whilst these patients improved clinically (see chapter 5). In contrast to MPS, however, after TMLR stress-echocardiography showed a small but significant decrease in reversible wall motion abnormalities, as well as an
increase in fixed wall motion abnormalities. However, compared to the controls, the LVEF was unchanged 12 months after TMLR. Our findings may indicate a reduced sensitivity of stress-echocardiography for the detection of ischaemia in this specific patient group. It remains speculative whether the increase in fixed wall motion abnormalities reflects the presence of dysfunctional but viable myocardium. Nevertheless, considering that angina pectoris occurs late in the cascade of events following an ischaemic insult, it can be hypothesised that although an increase in perfusion may be too small to be detected by perfusion scintigraphy, it may be sufficient to decrease the severity of an ischaemic insult below the level of sensitisation of cardiac nociceptors. Overall, we conclude that TMLR does not improve myocardial perfusion and function.

Denervation
Myocardial denervation as a mechanism of anginal pain reduction following TMLR, has been much less investigated clinically. Besides our own work, two studies have been published so far. In the first study using PET, denervation after TMLR was demonstrated in 6 patients, while increased innervation was seen in 2 patients [87]. Recently, in a second study, denervation after TMLR was demonstrated in 14 patients (whilst 2 patients remained unchanged) using MiBG SPECT scintigraphy, as in our own study. This study was published sometime after the acceptance for publication of our own MiBG study (see chapter 4) in the same journal. The method of this and our study were almost identical, especially with regard to the use of MiBG scintigraphy and semiquantitative analysis of segmental results. Although the general conclusion of this paper was that TMLR induces denervation, several differences should be noted. Firstly, 3 months after TMLR, 14 patients had decreased anginal complaints and in only 10 of these patients (71%) denervation was demonstrated. Results on the number of patients showing persisting denervation at 12 months are lacking. Overall, 60% (15 of 25) of the treated areas showed denervation, vs. 45% in our study. Secondly, partial reinnervation was observed at 12 months follow up. To what extent this finding corresponded with increase of angina is unclear. Thirdly, although also untreated segments were evaluated for denervation, the authors fail to report on this item. A remarkable finding in our study was that 34% of segments showing denervation were not treated. Finally, in contrast to our study, a positive effect of TMLR on myocardial perfusion was observed at 3 and 12 months after TMLR [88]. Contrary to the findings in these two studies, in the
Chapter 9

Clinical denervation study described in this thesis (see chapter 4), clear evidence for TMLR-induced local myocardial denervation was observed in all investigated patients. Furthermore, in the majority of denervated segments, the location of denervation correlated with treated area. Finally, diabetes can influence the biodistribution of MiBG and influence the outcome of the scans. In the other studies diabetes was present in 5 out of 8 (63%) and 6 out of 16 (38%) patients respectively, vs. one out of 8 (13%) in our study.

All patients in our study experienced significant relief of angina and improved quality of life, suggesting a correlation between local changes in innervation and symptomatic status. Another observation, which provides support for the denervation hypothesis, is that many patients who are treated with TMLR experience relief of angina already within days after treatment. This early relief of angina cannot be explained by the angiogenesis hypothesis since it takes some time for new vessels to grow. However, it is in agreement with the quickly induced damage on which the denervation hypothesis is based. The denervation-evidence seems even more convincing when the results of TMLR are compared with results of percutaneous myocardial revascularisation (PMR), which showed disappointing relief in angina [123,177]. We hypothesise that this is because the relatively large bundles of epicardially located nerve fibres are unaffected by PMR, in contrast to TMLR. Overall, we conclude that denervation plays a major mechanistic role in inducing the observed decrease of anginal symptoms following TMLR.

Treatment proposal for refractory angina in the Netherlands

Refractory angina pectoris is usually defined as a chronic condition of angina that cannot by controlled by medication, PTCA or CABG, in which reversible myocardial ischaemia should be clinically established to be the cause of the symptoms, e.g. by the Joint Study Group of the European Society of Cardiology on refractory angina. In our opinion, some aspects of this definition of refractory angina need further specification or adjustment. First, optimisation of life style and medication should be included in the definition. Even after optimising of life style and medication, the patient should still experience severe angina, functional class III to IV/IV according to the NYHA classification. Second, in our opinion, detectable ischaemia is not mandatory for the diagnosis of refractory angina (see below).
Based on the limited evidence available in the literature and a number of clinical considerations, a guideline for treatment of refractory angina is proposed (figure 1). This proposal only considers management of stable refractory angina. In the following section, the consecutive levels of the guideline will be discussed in separate paragraphs.

**Optimisation of life style and medication**
Life style changes remain important in this type of patients with refractory angina to delay the process of atherosclerosis. Weight reduction with a Mediterranean diet, cessation of smoking and excessive alcohol consumption, adjustment of physical activity to a moderate level and avoiding mental stress, are recommended. Optimisation of medication includes maximal tolerable dosages of β-blockers, long-acting nitrates and calcium-antagonists, besides aspirin and lipid-lowering drugs. Concomitant disorders such as hypertension, diabetes and hypercholesterolaemia should be managed as optimal as possible. In some patients, adding amiodarone in a low dosage or a potassium channel-activator is recommended.

**Life expectancy**
In patients with a life expectancy of less than one year, choice of treatment should be focussed on palliation in general and also on relief of anginal complaints. Consequently, therapy should not burden the patient with frequent visits to their physicians or obligatory hospital admissions. Only minimally invasive surgery should be considered. The choice for TENS and SCS has the additional benefit that the patient, to some extent, can manage his own degree of pain reduction.

**Operative risk**
The strongest parameters determining the operative risk in an individual patient are cardiac, renal and pulmonary function. There is an increased peri-operative risk in case of left ventricular dysfunction (LVEF < 40%) [74,157], renal insufficiency (arbitrarily, at creatinin ≥ 175 μmol/l), and chronic obstructive pulmonary disease (CO diffusion < 40%, FEV₁ < 40% of normal) [178,179]. Therefore, to guide treatment choices, in the guideline proposal patients are primarily divided into patients with a low operative risk and patients with a high operative risk. However, the patient's perception of the complaints and the patient's preferences and expectations must also be taken into account. Patients with very severe
Chapter 9

Severe complaints of stable angina > 3 months due to significant CAD, not amenable for PTCA or CABG, based on CAG < 3 months

Optimisation of lifestyle and medication

**Angina class I or II / IV**
- Continue medication

**Angina class III or IV / IV**
- Life expectancy < 1 yr
- Continue maximal medication combined with 1) TENS 2) SCS

**Angina class III or IV / IV**
- Life expectancy ≥ 1 yr
- Continue maximal medication combined with options below

**Relative low operative risk:**
- EF ≥ 35%
- Creatinine < 175 µmol/l
- CO diffusion > 40% and/or FEV₁ ≥ 40%N

- No or minimal detectable ischaemia at testing
  - 1) TENS
  - 2) SCS
  - random PMR
  - IUT
  - TEDA
  - random TMLR

**Relative high operative risk:**
- EF < 35%
- Renal insufficiency: creatinine ≥ 175 µmol/l
- Severe COPD:
  - CO diffusion < 40% and/or FEV₁ < 40%N

- No or minimal detectable ischaemia at testing
  - 1) TENS
  - 2) SCS
  - random PMR
  - IUT
  - TEDA
  - random TMLR

**Moderate or severe ischaemia at testing**
- 1) TENS
  - 2) TMLR
  - 3) SCS

**Figure 1. Guideline proposal for treatment of patients with stable severe refractory angina (dashed lines for experimental treatments).** CABG = coronary artery bypass grafting; CAG = coronary angiography; CO = carbon monoxide; COPD = chronic obstructive pulmonary disease; ETS = endoscopic thoracoscopic sympathectomy; FEV₁ = forced expiratory volume in 1 s (40%N = 40% of normal); IUT = intermittent urokinase therapy; LSGB = left stellate ganglion blockade; PTCA = percutaneous transluminal coronary angioplasty; random (TMLR / PMR) = (TMLR / PMR) of the whole ventricular wall; SCS = spinal cord stimulation; TMLR = transmyocardial laser revascularisation; TEDA = thoracic epidural anaesthesia; TENS = transcutaneous electric nerve stimulation.
complaints, patients who cannot accept the constraints of a sedentary life, or patients with more risk-prone behaviour might be willing to accept higher operative risks. The ultimate decision, therefore, is taken with the patient by carefully balancing the operative risk with the potential alleviation of symptoms and the ensuing gain in quality of life.

**Myocardial ischaemia**

Patients were furthermore deliberately divided into a group with no or minimal ischaemia, and a group with moderate to severe ischaemia, as tested with currently available diagnostic modalities (e.g. MPS, stress-echocardiography, PET or MRI). As we have stressed above, detectable ischaemia is not mandatory for the diagnosis refractory angina. In these patients, ischaemia is certainly the cause of their complaints, even if you cannot detect the ischaemia, given the following patient characteristics. Most patients with refractory angina have a long history of CAD, always proven by angiography, and found to be not amenable for revascularisation by intervention cardiologists and cardiac surgeons. These patients do recognise their symptoms, due to their experiences, and feel whether their complaints are due to a cardiac cause or due to something else. If in this type of patients ischaemia cannot be demonstrated, ischaemia should still be considered to be the cause of their anginal complaints. In our own study as much as 33% of patients with anginal complaints refractory to conventional treatment had no detectable ischaemia (see chapter 8). In other words, these patients had refractory angina pectoris according to all features of the definition, except for detectable ischaemia. Therefore, we propose to treat patients with refractory angina, irrespective of the presence of detectable ischaemia at testing. However, the inability to localise ischaemia excludes targeted TMLR to a specific region of the heart. This clinical point of view is integrated in the above proposal for management of refractory angina.

**Treatment modalities**

Note that of all alternative treatments of refractory angina, transcutaneous electric nerve stimulation (TENS) is relatively well accepted without appropriate clinical evidence and only spinal cord stimulation (SCS), TMLR and PMR have been studied in a randomised fashion. Unfortunately, the major randomised study on SCS has been performed in patients with a high operative risk that were eligible for CABG [42]. Consequently, these patients did not have true refractory angina. TMLR demonstrated a beneficial effect in all six randomised trials that to date
have been published. Of these four treatments, only TENS, SCS and TMLR are considered first choice treatment options. PMR has not been included as a first choice treatment option in the proposal as such because randomised trials either did not demonstrate a beneficial effect, or were stopped prematurely, except for one study [177]. Consequently, PMR and several other therapeutical approaches (i.e. IUT, TEDA, ETS and LSGB) included in the proposal have to be classified as experimental. Also TMLR (or PMR) of the whole ventricular wall (random TMLR, random PMR) in patients with diffuse ischaemia and a low operative risk should be classified as such. New therapeutic strategies, such as gene therapy and injection of growth factors [63-65]) were excluded, although very promising, because of minimal clinical experience as were other experimental treatments with limited clinical applicability, such as enhanced external counterpulsation (EEC). Finally, at present refractory angina with preserved left ventricular function is no indication for heart transplantation.

Centres for the management of refractory angina
An additional objective of the guideline proposal is to initiate a broader discussion on optimising management of refractory angina. Because of the complexity of the clinical problems concerning refractory angina pectoris and the necessity to search for and to investigate new treatment modalities, it is recommended to create specialised centres for treatment of patients with refractory angina pectoris. Such centres need to be suitably equipped to adequately compare various therapeutical approaches. Such comparisons are currently lacking, e.g. a randomised comparison of SCS and TMLR. Furthermore, in such centres new approaches could be evaluated in a sufficient number of patients, i.e. application of growth factors and combinations of different therapies. Given the results of our denervation study, further research focussed on epicardial, non-transmyocardial laser applications might be indicated. Furthermore, other methods to induce epicardial denervation as well as other approaches to induce local denervation are potential future investigation projects. In these centres of expertise, a multidisciplinary staff should treat the patients on an individual basis according to properly updated guidelines and participate in studies concerning research in refractory angina. Such a multidisciplinary staff should be composed of cardiologists, intervention cardiologists, cardiac surgeons, nuclear medicine physicians, anaesthesiologists specialised in treatment of pain, psychologists, social workers and nurses trained in
specific care for patients with refractory angina. In these centres TENS, TMLR and SCS should be available. Given the estimated incidence of refractory angina in the Netherlands (at least 1000 to 2000 patients / year) and the geographic and demographic situation, two or three of such centres probably would be sufficient.

**Interest in TMLR**

Despite clinical success, approval by the Food and Drug Administration and insurance coverage in the USA, there is a remarkable reduction in interest in TMLR. After a period with a high number of publications per year, the number of annual publications on TMLR is gradually declining (see figure 2). Editors of international journals are less willing to accept papers for publication, the number of patients treated by TMLR seems to decrease rather than increase and TMLR companies have problems to survive. Several reasons can explain this decline of interest. The second

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Number of publications on TMLR and PMR per year between 1981 and 2003. Included are all forms of publications (clinical and experimental), including journal articles, (meeting) abstracts, letters, replies to letters, conference discussions, reviews and editorials. For 2003 the number of publications in the first 6 months have been doubled to get an annual estimate. PMR = percutaneous myocardial revascularisation; TMLR = transmyocardial laser revascularisation.
published controlled TMLR trial [75] was of great importance and considerable impact. This study, published in 1999, overall showed a significant relief of angina, while none of the other results reached significance. In spite of their promising clinical outcome, a (non-significant) difference in mortality prompted the investigators to conclude that “the adaptation of TMLR cannot be advocated”. This publication, in combination with lack of consensus on the working mechanism of TMLR, has made acceptance of the therapy problematic. Increasing evidence to support the denervation hypothesis probably will have a limited effect on current sentiments. Moreover, pioneers in TMLR research aimed at increasing local perfusion. Increasing perfusion is one of the pillars of anti-anginal therapy. The idea that TMLR induces minimal or no effect on local perfusion and ‘only’ induces denervation evidently affects clinical interest negatively. As TMLR involves major surgery with substantial morbidity and mortality, TMLR nowadays is rarely advocated and other treatment options are preferred although not always available. As a result, treatments other than medication are often withheld.

Given the impressive clinical improvement in the majority of patients treated with TMLR, it is beyond doubt that this treatment modality still deserves a place in the treatment arsenal of physicians caring for patients with refractory angina and be the therapy of choice in a carefully selected group of patients. In the recently published ACC / AHA 2002 guideline update for the management of patients with chronic stable angina, this opinion is shared, given their Class IIa recommendation for TMLR (Class IIa = weight of evidence/opinion is in favour of usefulness/efficacy) [43].

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 after TMLR no improved myocardial perfusion was found 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 risks are decisive.