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

PART 1:  
Conventional treatment of angina pectoris

PART 2:  
Treatment of refractory angina pectoris

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PART 3:  
Aim and structure of this thesis

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Atherosclerosis

Atherosclerosis is a complicated pathophysiologic process predominantly responsible for the development of the majority of cardiovascular diseases [1]. The combined action of different risk factors, such as hypertension, diabetes, hypercholesterolaemia and smoking together with a certain familial predisposition determine whether the process of atherosclerosis will lead to more or less circumscribed coronary lesions or to diffuse, so-called small vessel disease which can for example be seen in patients with type II diabetes mellitus. Examples of both types of coronary artery disease (CAD) are shown in figure 1. The type of lesion is not only important with respect to the clinical manifestations of the disease (abrupt complete occlusion after plaque rupturing of an unstable lesion leads to acute myocardial infarction while a stable stenosis leads to stable angina pectoris), but it also affects the appropriate treatment options in coronary artery disease. In refractory angina for example, multiple diffuse lesions are often found, on one hand being responsible for its clinical appearance, and on the other hand making the disease refractory for conventional treatment.

Figure 1. Two different types of coronary artery disease. 1A shows three circumscribed stenoses in a coronary artery; 1B shows a left internal mammary artery graft anastomosed to the left descending artery with very diffuse peripherally localised coronary artery disease, in a patient that was included in the TMLR trial described in chapters 5 and 6.
Introduction: treatment of (refractory) angina

Myocardial ischaemia

The underlying pathophysiology of myocardial ischaemia is well known. Normally increased energy demand is met by dilatation of arterioles, which is mediated by metabolic signals from the myocardium. This is amplified by the release of locally produced and locally acting nitric oxide. In healthy blood vessels this is a remarkably flexible system providing an accurate balance between oxygen demand and oxygen supply in the myocardium over a wide range of workloads. In atherosclerotic vessels however, especially in those with stenoses >50%, an increased oxygen demand cannot be fully compensated by an increased supply, thus causing myocardial ischaemia [2]. Myocardial ischaemia can lead to myocardial dysfunction, typical electrocardiographic changes and of course pain, the latter referred to as angina pectoris. The clinical importance of a stenosis depends not only on the reduction in luminal diameter but also on the length and number of stenoses [3]. Furthermore, stenoses are not fixed and may alter with changes in coronary tone due to local smooth muscle activity or with the presence of a thrombus.

Of all episodes of myocardial ischaemia, up to 70% may be asymptomatic. Even in case of myocardial infarction approximately 30% occurs silent [4]. This phenomenon is seen in most patients with CAD, but especially in patients with diabetes mellitus due to diabetic neuropathy. Important is the fact that there seems to be no correlation between the severity of the ischaemia and the degree of pain experienced by the patient [5].

Definitions of angina pectoris

Angina pectoris was first considered as a clinical identity by William Heberden in 1772 [6]. More than two centuries later, Heberdents description of angina pectoris: "A painful and most disagreeable sensation in the breast", still stands remarkably accurate. The painful sensation, which is caused by myocardial ischaemia, plays a major role in CAD and in definitions such as stable, unstable, refractory and non-refractory angina. Today there are several different definitions of angina pectoris, but most differ only in detail. According to the current guidelines of the American Heart Association (AHA) and the American College of Cardiology (ACC) "angina is a clinical syndrome characterised by discomfort in the jaws, chest, back, shoulders or arms. It is typically aggravated by exertion or emotional stress and is relieved by nitroglycerin. Angina usually occurs in
patients with CAD involving ≥ 1 coronary artery. However, it can also be present in patients with normal coronary arteries. Myocardial ischaemia is then related to spasm and/or endothelial dysfunction, or to causes like severe aortic stenosis and hypertrophic cardiomyopathy [3,7]. As shown in table 1, the severity of angina can be classified according to the classification of the Canadian Cardiovascular Society (CCS) or according to the classification of the New York Heart Association (NYHA) [8].

<table>
<thead>
<tr>
<th>Class</th>
<th>CCS functional classification</th>
<th>NYHA functional classification</th>
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<tbody>
<tr>
<td>I</td>
<td>Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina present with strenuous or rapid or prolonged exertion at work or recreation.</td>
<td>Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.</td>
<td>Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions.</td>
<td>Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.</td>
</tr>
<tr>
<td>IV</td>
<td>Inability to carry on any physical activity without discomfort - anginal syndrome may be present at rest.</td>
<td>Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

Table 1. Classification of angina pectoris according to the Canadian Cardiovascular Society (CCS) and the New York Heart Association (NYHA).

Furthermore, angina can be classified as 'stable' or 'unstable'. Anginal symptoms are regarded as stable if they have been present over several weeks without important deterioration. The angina attack occurs in circumstances associated with increased oxygen demand such as during exercise. Even in stable angina, symptoms may vary considerably from time to time due to fluctuations of factors like ambient temperature and emotional stress. Angina is classified as unstable if pre-existing angina
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worsens abruptly without any clear reason or when new angina develops at rest or at a relatively low workload [3]. Unstable angina is most often associated with fissuring or rupture of an atherosclerotic plaque followed by platelet aggregation at the same site. This intracoronary thrombus formation may lead to further impairment of the coronary blood flow or to thrombotic occlusion resulting in infarction. Activated platelets at the site of plaque rupture can release vasoconstricting prostaglandines. Together with thromboxane-A$_2$ this can increase the coronary artery tone or induce spasm at the site of the stenosis, thus further deteriorating the coronary blood flow [3].

Non-refractory angina is defined as angina that can be treated sufficiently by so-called conventional treatment. In this definition the word *sufficiently* is crucial, because it allows individual nuances. For example, a certain quality of life (QOL) may be acceptable for one person but totally unacceptable for another. Taking the above into account, refractory angina can, in our opinion, be defined as the *chronic* persistence of severe anginal symptoms despite maximal anti-anginal medication, while the option to use invasive revascularisation procedures such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) is excluded on the basis of recent coronary angiography (CAG) showing severe CAD. This definition of refractory angina is used in this thesis, thus excluding acute exacerbations of angina refractory to therapy. Patients with Syndrome-X are also excluded by this definition due to lack of significant CAD on angiography [9,10]. The European Society of Cardiology (ESC) Joint Study Group on the Treatment of Refractory Angina has agreed on the following definition of refractory angina pectoris: “Refractory angina pectoris is a chronic condition characterised by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty and coronary bypass surgery. The presence of reversible myocardial ischaemia should be clinically established to be the cause of the symptoms. Chronic is defined as a duration of more than 3 months” [11]. The presence of detectable myocardial ischaemia forms the difference between this definition and the one used in this thesis. In our experience a considerable number of patients with severe refractory angina and proven severe CAD shows no or only minimal myocardial ischaemia on myocardial perfusion scintigraphy. This issue will be discussed in chapter 8.
Other names for refractory angina used in the literature are for instance intractable angina pectoris and end-stage coronary artery disease. The term refractory angina, however, is more applicable in view of the development of new therapies for this specific condition.

**Coronary artery disease in the Netherlands**

The most recent data on morbidity and mortality due to cardiovascular diseases in the Netherlands, published by the Netherlands Heart Foundation, indicate that CAD is not only still the major cause of death but is also responsible for the majority of morbidity in the Netherlands [12], despite all primary and secondary preventive measures in CAD. In 2001, 48,437 persons died due to a cardiovascular disease, being 35% of all deaths. Cardiovascular mortality strongly increases with age, and so does cardiovascular morbidity. Of all persons between 55 and 64 years of age in 2001, 3,372 persons died because of cardiovascular diseases. Between 75 and 84 years of age 17,526 persons died by this cause and in the age category 85 years and older 15,836 persons [12]. Of all causes of cardiovascular death, ischaemic heart diseases and cerebrovascular diseases are the most important ones, together responsible for 59% of all cardiovascular death [12]. In table 2, the different causes of death due to cardiovascular disease are summarised. Thanks to improved therapy we have seen a remarkable reduction in mortality due to ischaemic heart diseases and cerebrovascular diseases over the last 20 years (see figure 2). In the Netherlands, this reduction in cardiovascular mortality is the major reason for improvement in life expectancy. Between 1980 and 2001, the life expectancy at birth for men has risen with 3.3 years and for women with 1.5 years to respectively 75.8 years and 80.7 years. In 2001, 18% (260,000) of all hospital admissions in the Netherlands were due to a cardiovascular cause, and 31.7% of these cardiovascular admissions were due to ischaemic heart disease [12]. These data demonstrate that despite all effort undertaken in terms of primary and secondary prevention, cardiovascular diseases, especially ischaemic heart diseases, still play a major role in our healthcare system. Reliable data on the incidence of refractory angina are scarce. In the United States per year about 100,000-200,000 patients with refractory angina are assumed eligible for new methods of revascularisation, including transmyocardial laser revascularisation (TMLR) and drug-induced angiogenesis [13]. In most European countries even the precise prevalence of angina pectoris is not known, and current
numbers are based on rough estimates. According to the literature approximately 5-10% of all patients with angina pectoris develop refractory angina [14,15]. In the Netherlands only the number of

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Male</th>
<th>Female</th>
<th>Male + Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>9,405</td>
<td>7,195</td>
<td>16,600 34.3%</td>
</tr>
<tr>
<td>of which acute myocardial infarction</td>
<td>6,632</td>
<td>5,265</td>
<td>11,897 24.8%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4,664</td>
<td>7,336</td>
<td>12,000 24.8%</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>98</td>
<td>73</td>
<td>171  0.4%</td>
</tr>
<tr>
<td>Rheumatic heart disease and valve vitiaie</td>
<td>543</td>
<td>901</td>
<td>1,444 3.0%</td>
</tr>
<tr>
<td>Infectious heart disease</td>
<td>207</td>
<td>281</td>
<td>488  1.0%</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>5,489</td>
<td>4,031</td>
<td>9,520 25.8%</td>
</tr>
<tr>
<td>of which heart failure</td>
<td>2,130</td>
<td>3,400</td>
<td>5,530 1.0%</td>
</tr>
<tr>
<td>Vascular disease – arterial</td>
<td>1,404</td>
<td>782</td>
<td>2,186 4.5%</td>
</tr>
<tr>
<td>Atherosclerosis and / or hypertension</td>
<td>1,032</td>
<td>1,212</td>
<td>2,244 4.6%</td>
</tr>
<tr>
<td>Vascular disease – venous</td>
<td>67</td>
<td>125</td>
<td>192  0.4%</td>
</tr>
<tr>
<td>Other vascular and lymph vessel disease</td>
<td>247</td>
<td>345</td>
<td>592  1.2%</td>
</tr>
<tr>
<td>Total</td>
<td>23,156</td>
<td>25,281</td>
<td>48,437 100%</td>
</tr>
</tbody>
</table>

Table 2. Absolute mortality due to cardiovascular disease in the Netherlands in 2001. Reproduced with permission of the Netherlands Heart Foundation. For further specification of the 'cause of death' categories see reference [12].

Ischaemic heart disease

Cerebrovascular attacks

Figure 2. Mortality of ischaemic heart disease and of cerebrovascular attacks (per 100,000 per year) in the Netherlands between 1980-2001. Reproduced with permission of the Netherlands Heart Foundation [12].
hospitalisations for angina pectoris is known: in 2001, there were 33,000 admissions. Some patients will be admitted several times during one year while other patients, even when they are suffering from refractory angina, are not admitted to a hospital. Considering the above, a guessed estimate of the incidence of refractory angina in the Netherlands would be at least 1,000 to 2,000 patients per year. With the improvement of the life expectancy and the amelioration of the treatment of acute coronary syndromes, one can expect that these numbers will rise. However, a systematic registration system is indispensable to assess the real burden of this disease and thus obtain accurate data on the prevalence and incidence of refractory angina.

Treatment of non-refractory angina pectoris

The treatment of angina pectoris aims for two different goals:

1. Improvement of prognosis by preventing myocardial infarction and death. To achieve this, treatment must be focussed on stopping or reducing the process of coronary atherosclerosis and on preventing complications, especially plaque rupture and thrombosis. In this respect, lifestyle changes and drugs play a key-role, but also revascularisation procedures may protect the myocardium by ameliorating myocardial perfusion;

2. Improvement of signs and symptoms caused by myocardial ischaemia and so improvement of QOL. In this respect, lifestyle changes, drugs and interventional techniques also play a role.

Lifestyle changes

The most important lifestyle changes as advised in almost all guidelines on the prevention and treatment of coronary artery disease involve:

*Smoking:* Cessation improves symptoms and prognosis, as well as therapeutic efficacy. Cigarette smoking is the most important reversible risk factor in the genesis of CAD [3]. Patients often need special help to stop smoking. Transdermal nicotine therapy has proven to be safe and effective.

*Diet:* A weight-reducing diet should be advocated in obese patients. A so-called Mediterranean diet with vegetables, fruit, fish and poultry is preferable especially in patients with lipid abnormalities. Moderate alcohol consumption (two to three glasses of wine a day) may be beneficial.
Excessive consumption however is harmful, especially in patients with concomitant hypertension, diabetes or heart failure.

*Physical activity:* Physical activity can increase exercise tolerance [3] and reduce anginal symptoms. Furthermore, it has favourable effects on weight, blood lipids, blood pressure and glucose metabolism. Physical activity should be encouraged, within the patient’s limitations. An exercise test can be helpful in this respect.

*Psychological stress:* This should be avoided as much as possible because it can provoke attacks of angina. Other psychological factors that deserve attention and that are often seen in patients with CAD are anxiety, feelings of unsafety and depressions.

*Hypertension, diabetes and other disorders:* Concomitant disorders like hypertension, anaemia, diabetes mellitus and hypercholesterolaemia should be managed as appropriately as possible. Ill controlled diabetes, hypertension and hypercholesterolaemia increase progression of CAD.

**Pharmacological treatment**

Pharmacological treatment aims to prevent complications and to induce relief of symptoms. Three classes of drugs are used in chronic stable angina to relieve symptoms: Nitrates, β-blockers and calcium channel-blockers. They try to reduce the myocardial oxygen demand or to increase the myocardial perfusion. In patients with severe anginal complaints a combination of all three classes is subscribed, called ‘triple medication’. In some patients a fourth or fifth drug is added, such as nicorandil, a potassium channel-activator with nitrate-like activity, or amiodarone, an anti-arrhythmic drug, which also has an anti-anginal effect [16].

In the last decade sufficient evidence has been gathered that drugs improving the lipid profile, especially statins, or drugs that decrease the risk of thrombosis, such as platelet aggregation inhibitors, improve prognosis substantially by lowering the incidence of myocardial infarction and death [17-19]. This is not the case with nitrates and calcium channel-blockers. Large trials have shown that, at least when started shortly after myocardial infarction, β-blockers reduce mortality and the number of re-infarctions [20].

**Conventional revascularisation techniques**

*Percutaneous transluminal coronary angioplasty (PTCA)*

PTCA was first performed in 1977 by Grüntzig [21]. Since that time the number of procedures has increased exponentially. For example, in the year 2000 approximately 16,000 patients were treated in the Netherlands.
Chapter 1

(70% of which received a coronary stent). This dramatic increase is largely the result of major changes in the technique, the materials and lesion selection criteria. Mostly, the PTCA procedure is achieved with a balloon tracking over a guidewire. For particular types of lesions alternative methods can be used, such as directional atherectomy or ablation with a Rotablator™ [22]. Intracoronary laser angioplasty has proven to be less effective, mainly because of a high incidence of restenosis [23]. At present, stents are used more and more in interventional cardiology. The use of stents has markedly decreased the rate of post-procedural myocardial infarction and restenosis, and the need for emergency CABG. In stable angina and anatomically suitable lesions the overall success rate of PTCA is 95% while the mortality rate is less than 0.2% in patients with one-vessel disease and 0.5% in patients with multi-vessel disease [24]. Procedural myocardial infarctions, defined as new Q-waves on the electrocardiogram (ECG), are seen in less than 1% of procedures, and emergency CABG is only necessary in less than 1% of cases. New developments are for example smaller catheters and drug-eluting stents [25,26], the latter to prevent restenosis that is a major concern in interventional cardiology. Despite these promising developments, until now there is no convincing evidence that PTCA in general is superior to medical treatment with regard to prognosis (myocardial infarction or death) in patients with stable angina pectoris [7].

Coronary artery bypass grafting (CABG)

CABG is known as a very effective method of myocardial revascularisation for more than 30 years. The coronary bypass operation is usually performed with cardiopulmonary bypass using the pump oxygenator. An important new development however is the so-called ‘off-pump’ surgery used to avoid complications related to the use of extracorporeal circulation [27]. A number of methods for minimising perioperative ischaemia as well as numerous strategies for optimal perioperative myocardial preservation have diminished the operation-related morbidity and mortality considerably. Initially, conduits used for CABG were almost only veins. The long saphenous vein is still widely used, however if possible arterial grafts are preferred because their long-term patency is much better compared to that of veins. The left internal mammary artery is used in almost all bypass procedures of the left coronary artery. Besides the right internal mammary artery, the right gastro-epiploic artery, the inferior epigastric artery and the radial artery are

- 20 -
used as conduits. In vessels with severe distal disease, which are not appropriate for distal grafts, endarterectomy is often performed. However, this procedure shows a higher peri-operative mortality and myocardial infarction rate, and a shorter graft patency. The major in-hospital peri-operative complications are predominantly determined by the extent of CAD, the ability to accomplish complete revascularisation, the left ventricular function and the presence of comorbidity, especially renal and/or respiratory insufficiency. At present, the in-hospital mortality rate is about 1% in one-vessel disease and increases up to 5% in multi-vessel disease combined with a poor left ventricular function. Peri-operative myocardial infarction diagnosed by the occurrence of new Q-waves is seen in 4-5% of procedures [28]. The patency of venous conduits is quite variable, but 10-20% of grafts are occluded within 1 week after surgery. Three to 5 years after the operation 60-70% of venous grafts show important atherosclerotic narrowing. In contrast, 90% of the internal mammary artery grafts anastomosed to the left anterior coronary artery are patent 10 years after the operation [29]. The peri-operative mortality of a re-CABG depends mainly on the left ventricular function but is as high as 5-11%. Compared to medical therapy CABG is only favoured in patients with left main disease or with severe three-vessel disease associated with an impaired left ventricular function. Many major randomised trials like RITA, GABI and BARI have compared PTCA and CABG [30-32]. The results of these trials are uniform and consistent. Both techniques of myocardial revascularisation are associated with a similar risk of non-fatal myocardial infarction and death although PTCA has a higher incidence of recurrent angina and necessity for coronary re-intervention. However, most comparative studies performed until now were underpowered to detect small differences or differences in specific subgroups. It is important to realise that in most patients with CAD the atherosclerotic process continues and indications for a re-intervention are very common. Angioplasty can be considered as a repeatable low-risk procedure while a repeated CABG has a much higher risk. Therefore, especially in younger patients, angioplasty becomes more and more the therapy of first choice.
PART 2:

TREATMENT OF REFRACTORY ANGINA PECTORIS

Introduction

As described in part 1, there is a substantial and growing number of patients with refractory angina pectoris. For these patients several different treatment regimens have been developed with often completely different and sometimes not fully understood working mechanisms. They include neuromodulating therapies and alternative revascularisation techniques, including TMLR, the subject of this thesis. These and other treatment regimens are described below, together with hypotheses on the working mechanism of TMLR.

Neuromodulating therapies

The neural aetiology of anginal pain is poorly understood. Activation of cardiac nociceptors is thought to be caused by ischaemia-induced release of specific substances (such as adenosine) [33]. The pain stimulus is transported through cardiac afferent fibres to the spinal cord. After converging with other afferent fibres the stimulus is transported to the somato-sensible cortex of the cerebrum where it is registered as typical angina pectoris [34]. The convergence of different afferent fibres from different dermatomes in the spinal cord is likely the reason why activation of cardiac nociceptors is not only experienced as pain in the cardiac region (chest) but also in other dermatomes, such as the jaw, arm or shoulder (‘referred pain’) [35].

Transcutaneous electric nerve stimulation (TENS)

TENS [36] is the least invasive neuromodulating therapy. The rationale for this technique (as well as for spinal cord stimulation (SCS), see below) is based on the ‘gate-control’ theory of Melzack and Wall [37]. In this theory, nociceptive nerve (C) fibres (transporting the anginal signal) are inhibited by stimulation of non-nociceptive (A) nerve fibres. With TENS, electrodes are placed on the chest wall. Using an external device, electric stimulation (at different levels) is applied to the chest through the electrodes, creating an area of paraesthesia. When placed correctly, it is possible to cover the entire area of anginal pain. A great advantage of this technique is the
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relative simplicity of the application. When instructed properly, patients can personally operate the device when angina occurs or is anticipated. The clinical results are good, but long-term use causes skin irritation in a large number of patients [38]. Nevertheless, because TENS is easy to apply and is reimbursed by the insurance companies, this therapy is relatively often used in the Netherlands. Furthermore, since non-ischaemia related pain reacts much less to TENS, it is also used to determine whether the pain is of ischaemic origin.

Spinal cord stimulation (SCS)

SCS has many similarities to TENS. However, the electrode is not placed on the chest wall but in the epidural space directly against those segments of the spinal cord that convey the anginal pain. The pulse generator is placed subcutaneously and stimulation can be controlled from the outside using a remote control. When placed correctly, stimulation produces paraesthesia that reduces the anginal pain. Besides the paraesthetic effect, the clinical efficacy of SCS has also been ascribed to a reduction of myocardial ischaemia caused by a redistribution of coronary blood flow between affected and unaffected myocardial regions (a phenomenon known as the “Robin Hood effect”) [39]. Interestingly, the anginal pain is not completely masked by stimulation and therefore the warning signal is not completely disabled. This is important since angina can be a warning signal for a pending myocardial infarction. Currently, approximately 2,000 patients have been implanted with a spinal cord stimulator [11]. Several clinical studies on safety as well as on efficacy have been published, and reduction in angina class and improvement in QOL have been reported [40]. Furthermore, in a comparative study in symptomatic high-risk surgical candidates with no prognostic benefit from CABG (according to the ACC / AHA guidelines [41]), SCS and CABG have shown similar effect in relieving anginal symptoms [42]. Due to these results SCS has obtained a Class IIb recommendation (Class IIb = usefulness/efficacy is less well established by evidence/opinion) in the recently published ACC / AHA guideline update on the treatment of chronic angina pectoris [43]. Adverse risks of SCS include dislocation of the electrodes and infections.

Thoracic epidural anaesthesia (TEDA)

TEDA was first introduced as a treatment for angina in 1989 by Blomberg et al. [44]. The technique works through insertion of an epidural catheter at the spinal cord level that corresponds with the cardiac area, i.e. C7-T4. An
anaesthetic is infused, aiming to achieve total bilateral anaesthesia of the spinal roots and sympathetic trunks. Treatment success is defined as complete anaesthesia of the dermatomes where anginal pain is experienced. Currently, a few hundred patients have been treated with this technique and the achieved results were satisfactory [45], especially for unstable angina. The use for chronic stable angina has been much less documented, mainly because of the many practical disadvantages of long-term use such as the repeated infusion (with risk of infection) and the fact that an infusion pump has to be carried around at all times.

**Left stellate ganglion blockade (LSGB)**
LSGB is a variation on thoracic epidural anaesthesia and was already described in 1966 [46]. Rather than infusion of the anaesthetic into the epidural space to work directly on the spinal cord as in TEDA, it is injected paravertebrally at the location of the left stellate ganglion. Like TEDA, the aim is to achieve anaesthesia in the area of anginal pain and thus decreasing this pain. Only few patients (around 100) have been treated with this technique and although good results were reported [47], the scientific evidence for efficacy remains scarce.

**Endoscopic thoracoscopic sympathectomy (ETS)**
ETS has been used for the treatment of angina pectoris for approximately a decade [48]. It is the most invasive and permanent method of neural modulation of anginal pain, creating a permanent afferent sympathetic block as well as disruption of afferent pathways leading to analgesia. Under general anaesthesia the sympathetic ganglia T1-T5 are coagulated. The procedure is often only performed on the left side, however if the result is unsatisfactory it can be performed bilaterally. Significant decrease of anginal symptoms has been reported for this treatment [48]. However, due to complications such as myocardial infarction and autonomic and sensory disturbances, less than 100 patients have currently undergone this therapy [11].

**Alternative revascularisation techniques**
Revascularisation is aimed at the reduction of angina-inducing ischaemia. Surgical techniques to ‘revascularise’ ischaemic myocardial regions have been under investigation for many decades. One of the first attempts was made by Beck in 1935 who grafted the pectoral muscle to the epicardial
surface of the heart [49]. After removing the pericardial fat, his aim was to create vascular connections between the myocardium and the overlying pectoral musculature and thus provide an alternative supply of blood to the myocardium. Almost 20 years later, Vineberg [50] described the treatment of coronary insufficiency using direct implantation of the left mammary artery into the myocardium. This ‘Vineberg procedure’ was not a direct arterial anastomosis but an implantation of the distal arterial end into a mechanically created myocardial channel. After a few weeks, microvascular connections were shown between the implanted artery and the native coronary circulation. Reports on follow up of patients who underwent the Vineberg procedure have demonstrated patent mammary artery grafts more than 20 years after the procedure [51].

Another approach to restore blood flow to ischaemic myocardium is the direct delivery of oxygenated blood from the left ventricular cavity into the myocardium. This concept originates from the work of Wearn et al. [52]. In 1935 they described the existence of vascular connections (‘myocardial sinusoids’) between human coronary arteries and the ventricular cavity. These connections may facilitate a flow from the ventricular cavity directly into the myocardium in the case of inadequately functioning coronary arteries. Open connections between the ventricular cavity and the myocardium are also known to be present in reptile hearts. In the reptilian heart, perfusion through these connections provides an important portion of blood delivery to the endocardium, and an underdeveloped coronary artery system only provides a small part of the myocardial perfusion [53]. Kohmoto et al. have investigated this perfusion system in alligator hearts and found that in the myocardium > 60% of the perfusion was derived directly from the ventricular chamber [54]. Myocardial oxygenation through direct ventriculo-myocardial perfusion has furthermore been described to be functional in children with hypoplasia of the left ventricle [55] and in patients with pulmonary atresia combined with proximal obstruction of the coronary arteries [56].

In the decades following Wearn’s description, many attempts have been made to mimic the reptilian cardiac anatomy by developing ways of delivering oxygenated blood directly from the left ventricle to the myocardium. The first attempt was described by Goldman et al. in 1956 [57]. They implanted perforated U-shaped carotid artery grafts in canine myocardium with both ends of the grafts in open connection with the left ventricular cavity. When the left anterior descending artery (LAD) was ligated 3 weeks after the implantation, mortality was only 5% versus 61%
after ligation in non-implanted (control) animals. Massimo et al. [58] slightly modified this concept and implanted T-shaped tubes of which the long leg was in open connection with the left ventricular cavity and both short legs were inside the myocardium. When Sen [53] later simplified this approach by using hollow needles to create channels in the myocardium, the first transmyocardial revascularisation (TMR) procedure was a fact. Although these channels appeared to be successful in protecting the myocardium against infarction after ligation of the LAD, the long-term effect of this ‘transmyocardial acupuncture’ technique was poor, which was attributed to rapid occlusion of the channels. Investigators such as Hershey [59] and Pifarré [60] further explored this revolutionary idea of transmyocardial revascularisation. However, the TMR approach was greatly overshadowed by the rapid development of PTCA and CABG, which were already described in part 1 of this chapter. Below we will discuss four alternative techniques: Long-term intermittent urokinase therapy, enhanced external counter pulsation, induction of angiogenesis and arteriogenesis using vascular growth factors, and finally TMLR, which is the major subject of investigation of this thesis.

**Long-term intermittent urokinase therapy (IUT)**

IUT has been reported to improve the haemodynamics of blood (decrease of viscosity) and has anti-thrombotic effects [61]. In short, up to 500,000 units of urokinase are administered intravenously 3 times per week for 12 weeks. The resulting haemodynamic and antithrombotic effects are thought to reduce anginal symptoms by a reduction of myocardial ischaemia. Drawbacks of this technique are the high costs and the occurrence of complications such as bleeding.

**Enhanced external counter pulsation (EEC)**

EEC is aimed at increasing arterial diastolic blood pressure and subsequent coronary perfusion. Pressure cuffs are placed around the patient’s legs and inflated sequentially in early diastole from the lower legs up to the thighs in order to propel blood to the heart in a retrograde direction. Decrease of anginal symptoms has been reported which has been suggested to result from a reduction in myocardial ischaemia [62]. In the recently published ACC / AHA guideline update for the management of patients with chronic stable angina this therapy received a Class IIB recommendation as an alternative therapy in patients with chronic refractory angina [43].
Introduction: treatment of (refractory) angina

*Induction of angiogenesis and arteriogenesis using vascular growth factors*

Angiogenesis, for which pioneering work in tumours has been performed by Folkman [63], refers to the sprouting of endothelial cells forming capillary networks. Insight in this mechanism has led to the start of clinical trials using vascular growth factors such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF). Initial promising results from small uncontrolled studies [64,65] could unfortunately not be confirmed in subsequent placebo-controlled multi-centre studies.

Arteriogenesis refers to the growth of pre-existent collateral arterioles into functional collateral arteries. Stimulating this process with substances such as monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-β (TGF-β) and granulocyte macrophage-colony stimulating factor (GM-CSF) may lead to the formation of natural bypasses that can serve as conduit arteries to compensate for the functional loss of atherosclerotic arteries. At present, much research in this interesting field is being performed [66], with very promising initial results.

*Transmyocardial laser revascularisation (TMLR)*

After more than a decade of silence, in 1981 Mirhoseini and Cayton reintroduced the myocardial acupuncture concept first described by Sen (see above). They reported on the creation of transmyocardial channels in canine hearts using a 400 Watt (W) carbon dioxide (CO$_2$) laser instead of needles [67]. Ligation of the LAD after creation of transmyocardial laser channels resulted in no mortality versus 100% mortality after ligation without laser channels. Two years later, these results led Mirhoseini to perform the first clinical TMLR as an adjunct to CABG in a 65-year old man [68]. From that moment on much research has been performed on this technique, both as a stand-alone procedure as well as in combination with other treatments [69].

The technique of TMLR is straightforward. Figure 2 shows a schematic drawing. In the vast majority of cases the heart is approached using a lateral thoracotomy in the fifth or sixth intercostal space. An approach using a sternotomy is often relatively contra-indicated since many TMLR-eligible patients have previously undergone bypass surgery through a sternotomy and they are likely to have extensive pericardial adhesions. No cardiopulmonary bypass is used and when the chest and pericardium have been opened the hand piece of the laser is placed on or close to the epicardial surface. Three different types of lasers are clinically used to create transmyocardial channels: The carbon dioxide (CO$_2$), the
holmium:yttrium-aluminum-garnet (Ho:YAG) and the xenon chloride (XeCl) excimer laser. Until June 2003, randomised controlled studies have only been published for the CO₂ and Ho:YAG laser, which are also the most widely used lasers for TMLR. However, in this thesis (chapters 5 and 6) we describe a randomised clinical trial of XeCl excimer TMLR versus medication. The Ho:YAG (wavelength 2.1 μm) and XeCl excimer laser (wavelength 308 nm) both use a flexible fibre-optic system in combination with a hand piece. The tip of the hand piece is placed on the epicardial surface of the beating heart and is gently advanced through the myocardium during multiple (ECG-triggered) laser pulses. The long wavelength of the CO₂ laser (10.6 μm) makes it unsuitable for fibre-based optics and therefore it operates with an articulated arm. This laser creates transmyocardial channels in one single pulse. During CO₂, Ho:YAG and excimer TMLR transmyocardial perforation can be confirmed with transoesophageal echocardiography (TEE) by the appearance of contrast bubbles in the ventricular cavity [70]. Furthermore, complete perforation can be felt (slight loss of resistance when the fibre has passed through the myocardium), heard (higher sound when laser is fired into the blood inside
the ventricular cavity) and seen (blood spurting from the epicardial entrance site).

The channel diameters are \( \sim 1 \) mm for the \( \text{CO}_2 \) and XeCl excimer lasers and \( \sim 2 \) mm for the Ho:YAG laser (larger diameter fibre tip). When a channel is created, bleeding can usually be stopped with the application of slight manual pressure at the epicardial opening. If this does not result in closure of the channel through formation of a blood clot, a suture can be used to close the epicardial channel opening. According to the current clinical standard, approximately one channel/cm\(^2\) is created. However, no absolute scientific evidence has been published indicating that this is the optimum channel density. The total number of channels mostly depends on the size of the reversibly ischaemic myocardium. Patients are usually dismissed from the hospital several days following the TMLR procedure.

**Hypotheses on the working mechanism of TMLR**

Clinical improvement after TMLR has been reported repeatedly [71-77]. Nevertheless a definitive mechanistic explanation still has to be found.

**The patent channels hypothesis**
The original theory, i.e. direct perfusion of oxygenated blood from the left ventricular cavity into the ischaemic myocardium, was based on the description of myocardial sinusoids as described above. In the ‘patent channels’ hypothesis the TMLR channels would endothelialise and connect to these sinusoids and possibly even to the native coronary artery system. Much research has been performed on this hypothesis, but in the past years conflicting experimental findings regarding the patency of laser channels and their (in)ability to increase the blood flow to ischaemic myocardium has gradually led to the rejection of this hypothesis [69].

**The angiogenesis hypothesis**
Angiogenesis as an explanation for the clinical efficacy of TMLR has two aspects: An increased vascular density in the ischaemic area followed by an increase in local perfusion.

An increase in vascular density in the treated area has been demonstrated in many animal studies as well as in human post-mortem observations (as described in chapter 3) and is believed to be induced by a local inflammatory response leading to a locally enhanced production of vascular growth factors by inflammatory cells. Several experimental
Chapter 1

studies showed the upregulation of angiogenic and inflammatory cytokines after TMLR [78,79]. Thus angiogenesis is probably a non-specific healing response to myocardial injury. It is not known what kind of damage (thermal, mechanical or other) gives the optimal angiogenic trigger. A recent study demonstrated that TMLR was superior to transmyocardial mechanical implants in inducing angiogenesis and arteriogenesis with enhanced regional myocardial blood flow measured by positron emission tomography (PET) [80]. Recently, alternative methods to create channels with enhanced angiogenesis have been explored using transmyocardial coils inside the channels [81] or, more promising, TMLR in adjunct with fibroblastic or vascular endothelial growth factors. Recent experimental studies in pigs using these growth factors showed a synergistic action when combined with TMLR [82,83].

An increase in perfusion following angiogenesis is essential when the angiogenesis hypothesis has to explain the clinical improvement after TMLR. None of the experimental animal studies that assessed perfusion (semi-)acutely after TMLR showed any increase in perfusion or flow. However, in contrast, all experimental studies that assessed perfusion 4 weeks after treatment or later demonstrated improved perfusion. This difference can logically be attributed to the time required for new vessels to grow. In humans only one [74] out of five randomised clinical trials [71-77] report an increase in perfusion. Therefore, at present it is doubtful and unclear whether and to what degree angiogenesis plays a role in the working mechanism of TMLR.

The denervation hypothesis

The third mechanistic explanation originates from the observation that many patients experience relief of angina within days after treatment. This acute improvement cannot be explained by angiogenesis but may be explained by myocardial denervation. The perception of anginal pain is believed to be transported to the brain through cardiac nociceptors and afferent sympathetic fibres [84]. These fibres are located superficially in the epicardium [85] and are easily accessible by epicardially orientated laser treatment. Indications that denervation may relieve angina are the reported beneficial effects on angina of neuromodulating therapies such as SCS [39] and TEDA [86]. Another interesting observation is the absence of anginal complaints in heart-transplant patients with extensive coronary artery disease. There is much evidence that TMLR can induce denervation, including three studies in humans (refs [87,88] and chapter 4 of this thesis).
Other hypotheses
Through the years, several other hypotheses for the mechanism of action have been suggested. They include scar production leading to an improved cardiac compliance and efficacy [89-91], myocardial destruction resulting in a redistribution of blood flow and improved oxygenation of surviving myocardium [92], a photo-acoustically induced change of conduction of ischaemic myocardium resulting in improved contractility and function [93], and a combination of mechanisms. Additionally, another mechanism has been suggested which might play a role in the long-term relief of anginal pain: TMLR relieves angina acutely by any of the working mechanisms suggested above, followed by an increase in exercise in individual patients, resulting in an increase of shear stress in myocardial vessels and stimulation of angiogenesis in the myocardium. Although they have been suggested as mechanisms, for these hypotheses no or little research has been performed and no or little evidence is available to make a funded statement on their (clinical) significance.
Chapter 1

PART 3:

AIM AND STRUCTURE OF THIS THESIS

The research presented in this thesis has the following aims:
1) To evaluate the efficacy and safety of TMLR in patients with refractory angina using a XeCl excimer laser;
2) To evaluate the effect of TMLR on myocardial perfusion and function and to provide insight into the main hypotheses of the working mechanisms responsible for the clinical improvement after TMLR;
3) To gain insight in the diagnostic value of myocardial perfusion scintigraphy and its implications for the clinical course and therapy in patients with refractory angina, contributing to a proposal for a treatment guideline.

To achieve these aims the literature was studied and clinical research has been performed.

Chapter 2 illustrates the use of echocardiography in TMLR.
Chapter 3 describes the histological findings in a patient that died 3 months after excimer TMLR, demonstrating angiogenesis in and around laser channel remnants.
Chapter 4 describes evidence of cardiac denervation due to TMLR in 8 patients using $^{123}$I-MiBG-SPECT scintigraphy.
Chapter 5 describes the results of the first randomised clinical trial using a XeCl excimer laser in 30 patients with refractory angina. This study shows the effects on angina class, QOL, myocardial perfusion and myocardial function.
Chapter 6 discusses in detail the improvement in QOL after XeCl excimer TMLR as seen in the randomised clinical trial described in chapter 5.
Chapter 7 gives an overview of the clinical literature on TMLR.
Chapter 8 discusses diagnostic limitations of myocardial perfusion scintigraphy and its impact on clinical course and consequences for treatment in patients with refractory angina.
Finally, in chapter 9 the clinical efficacy of XeCl excimer TMLR and the working mechanisms of TMLR are discussed, and TMLR is positioned in a guideline proposal for the treatment of refractory angina pectoris, incorporating the available treatment strategies.