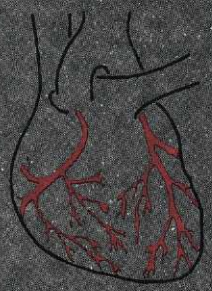
Refractory Angina Pectoris

Patient Characteristics

Safety and Long-Term Effects of Spinal Cord Stimulation

Paulin Andréll



Göteborg 2005

REFRACTORY ANGINA PECTORIS

PATIENT CHARACTERISTICS

SAFETY AND LONG-TERM EFFECTS OF SPINAL CORD STIMULATION

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin
vid Göteborgs Universitet kommer att offentligen försvaras i Centralklinikens aula,
Sahlgrenska Universitetssjukhuset/Östra Sjukhuset, Göteborg,
fredagen den 25 februari kl.13.00

av
PAULIN ANDRÉLL
LEG LÄKARE

Fakultetsopponent:
Professor Lars Rydén
Karolinska Institutet, Stockholm

Avhandlingen baserar sig på följande delarbeten:

I. Andréll P, Ekre O, Grip L, Albertsson P, Eliasson T, Mannheimer C. Incidence, Clinical and Angiographic Characteristics of Patients with Refractory Angina Pectoris – the Epidemiological study of Refractory Angina Pectoris (ERA). Manuscript.

II. Andréll P, Ekre O, Grip L, Albertsson P, Währborg P, Eliasson T, Mannheimer C. Fatality, Morbidity and Quality of Life in Patients with Refractory Angina Pectoris – A One Year Follow-Up of the ERA study. Manuscript.

III. Andréll P, Jensen C, Norrsell H, Ekre O, Ekholm S, Norrsell U, Eliasson T, Mannheimer C, Blomstrand C. Deep White Matter Disease in Magnetic Resonance Imaging Predicts Neurological and Neuropsychological Complications after Coronary Artery Bypass Grafting. Ann Thorac Surg; 2005:79(1):74-9.

IV. Andréll P, Ekre O, Eliasson T, Blomstrand C, Börjesson M, Nilsson M, Mannheimer C. Cost-Effectiveness of Spinal Cord Stimulation versus Coronary Artery Bypass Grafting in Patients with Severe Angina Pectoris – Long-term Results from the ESBY Study. Cardiology; 2003;99(1):20-4.

REFRACTORY ANGINA PECTORIS

PATIENT CHARACTERISTICS

SAFETY AND LONG-TERM EFFECTS OF SPINAL CORD STIMULATION

Paulin Andréll, Multidisciplinary Pain Centre, Sahlgrenska University Hospital/Östra
Cardiovascular Institute, Göteborg University, Göteborg, Sweden.

ABSTRACT

Refractory angina pectoris has been defined as severe angina pectoris due to coronary artery disease which cannot be controlled by conventional pharmacological or surgical therapy. The epidemiology of this condition is virtually unknown.

During the last decades, additional treatment options have been developed for this condition. One of these is spinal cord stimulation (SCS), which has been used for approximately 20 years as an additional symptom-relieving treatment for patients with severe angina pectoris. SCS has an anti-ischaemic effect and has been shown to be a safe and effective treatment modality.

The occurrence of refractory angina pectoris among patients who had undergone coronary angiography was assessed in a defined geographic area. In order to characterise the patients with regard to concurrent diseases, treatment, functional class, quality of life, morbidity and fatality, the refractory angina patients were compared with patients with severe angina pectoris who were accepted for revascularisation. Within three years, 146 patients were identified, comprising 2.1% of all patients undergoing coronary angiography due to stable angina pectoris. The patients with refractory angina pectoris had more severe cardiac disease as well as coronary artery disease than the patients in the revascularisation group. Some of the patients in the refractory group appear to be in a fairly good condition with regard to extracardiac diseases but there is a subpopulation in the refractory group with severe cardiac as well as extracardiac diseases. The main reasons for rejection for revascularisation were unsuitable coronary anatomy and a potential risk of damaging existing grafts. After one year of follow-up the refractory patients had a higher fatality rate but a lower frequency of cerebrovascular morbidity than the revascularisation group. The refractory patients had more severe angina and lower quality of life with regard to physical function and impact of angina symptoms, compared with the revascularisation group. However, the mental health of the refractory patients was not affected compared with the revascularisation group.

The patients in the so-called ESBY study (Electrical Stimulation versus Coronary Bypass Surgery in Severe Angina Pectoris, a randomised comparison of SCS and coronary artery bypass grafting (CABG) in 104 patients with severe angina pectoris and increased surgical risk) were followed up with regard to neurological and neuropsychological complications, morbidity and cost-effectiveness. There were more patients in the CABG group who developed neurological and neuropsychological complications than in the SCS group. Furthermore, presence of deep white matter disease on cerebral magnetic resonance imaging was shown to be a predictor of cerebrovascular complications after CABG. During two years of follow-up, health care costs and cardiac morbidity was lower in the SCS group than in the CABG group. However, the groups did not differ with regard to mortality or causes of death. There were no serious complications related to the SCS treatment.

CONCLUSION

Refractory angina pectoris appears to be a considerable problem. This patient group has a high fatality rate and low quality of life compared with revascularised patients. SCS, which is one of the recommended treatment option for these patients, was found to be safe (in terms of mortality, morbidity and absence of serious complications) and effective (in terms of symptom relief and cost-effectiveness) during long-term treatment. Furthermore, presence of deep white matter disease on cerebral magnetic resonance imaging seems to be a predictor of cerebrovascular complications after CABG.

Keywords: Angina pectoris, Deep white matter disease, Epidemiology, Health care costs, Morbidity, Mortality, Quality of life, Spinal cord stimulation.

ISBN 91-628-6388-6 Göteborg 2005

REFRACTORY ANGINA PECTORIS

PATIENT CHARACTERISTICS

SAFETY AND LONG-TERM EFFECTS OF SPINAL CORD STIMULATION

PAULIN ANDRÉLL, MD

From the Multidisciplinary Pain Centre

www.paincentre.se

Sahlgrenska University Hospital/Östra

Cardiovascular Institute

Göteborg University,

Göteborg, Sweden

GÖTEBORG 2005

ISBN 91-628-6388-6

To my family

REFRACTORY ANGINA PECTORIS

PATIENT CHARACTERISTICS

SAFETY AND LONG-TERM EFFECTS OF SPINAL CORD STIMULATION

Paulin Andréll, Multidisciplinary Pain Centre, Sahlgrenska University Hospital/Östra
Cardiovascular Institute, Göteborg University, Göteborg, Sweden.

ABSTRACT

Refractory angina pectoris has been defined as severe angina pectoris due to coronary artery disease which cannot be controlled by conventional pharmacological or surgical therapy. The epidemiology of this condition is virtually unknown.

During the last decades, additional treatment options have been developed for this condition. One of these is spinal cord stimulation (SCS), which has been used for approximately 20 years as an additional symptom-relieving treatment for patients with severe angina pectoris. SCS has an anti-ischaemic effect and has been shown to be a safe and effective treatment modality.

The occurrence of refractory angina pectoris among patients who had undergone coronary angiography was assessed in a defined geographic area. In order to characterise the patients with regard to concurrent diseases, treatment, functional class, quality of life, morbidity and fatality, the refractory angina patients were compared with patients with severe angina pectoris who were accepted for revascularisation. Within three years, 146 patients were identified, comprising 2.1% of all patients undergoing coronary angiography due to stable angina pectoris. The patients with refractory angina pectoris had more severe cardiac disease as well as coronary artery disease than the patients in the revascularisation group. Some of the patients in the refractory group appear to be in a fairly good condition with regard to extracardiac diseases but there is a subpopulation in the refractory group with severe cardiac as well as extracardiac diseases. The main reasons for rejection for revascularisation were unsuitable coronary anatomy and a potential risk of damaging existing grafts. After one year of follow-up the refractory patients had a higher fatality rate but a lower frequency of cerebrovascular morbidity than the revascularisation group. The refractory patients had more severe angina and lower quality of life with regard to physical function and impact of angina symptoms, compared with the revascularisation group. However, the mental health of the refractory patients was not affected compared with the revascularisation group.

The patients in the so-called ESBY study (Electrical Stimulation versus Coronary Bypass Surgery in Severe Angina Pectoris, a randomised comparison of SCS and coronary artery bypass grafting (CABG) in 104 patients with severe angina pectoris and increased surgical risk) were followed up with regard to neurological and neuropsychological complications, morbidity and cost-effectiveness. There were more patients in the CABG group who developed neurological and neuropsychological complications than in the SCS group. Furthermore, presence of deep white matter disease on cerebral magnetic resonance imaging was shown to be a predictor of cerebrovascular complications after CABG. During two years of follow-up, health care costs and cardiac morbidity was lower in the SCS group than in the CABG group. However, the groups did not differ with regard to mortality or causes of death. There were no serious complications related to the SCS treatment.

CONCLUSION

Refractory angina pectoris appears to be a considerable problem. This patient group has a high fatality rate and low quality of life compared with revascularised patients. SCS, which is one of the recommended treatment option for these patients, was found to be safe (in terms of mortality, morbidity and absence of serious complications) and effective (in terms of symptom relief and cost-effectiveness) during long-term treatment. Furthermore, presence of deep white matter disease on cerebral magnetic resonance imaging seems to be a predictor of cerebrovascular complications after CABG

Keywords: Angina pectoris, Deep white matter disease, Epidemiology, Health care costs, Morbidity, Mortality, Quality of life, Spinal cord stimulation.

ISBN 91-628-6388-6 Göteborg 2005

ORIGINAL PAPERS

This thesis is based on the following original articles, which will be referred to in the text by their Roman numerals:

I. Andréll P, Ekre O, Grip L, Albertsson P, Eliasson T, Mannheimer C. Incidence, Clinical and Angiographic Characteristics of Patients with Refractory Angina Pectoris – the Epidemiological study of Refractory Angina Pectoris (ERA). Manuscript.

II. Andréll P, Ekre O, Grip L, Albertsson P, Währborg P, Eliasson T, Mannheimer C. Fatality, Morbidity and Quality of Life in Patients with Refractory Angina Pectoris – A One Year Follow-Up of the ERA study. Manuscript.

III. Andréll P, Jensen C, Norrsell H, Ekre O, Ekholm S, Norrsell U, Eliasson T, Mannheimer C, Blomstrand C. Deep White Matter Disease in Magnetic Resonance Imaging Predicts Neurological and Neuropsychological Complications after Coronary Artery Bypass Grafting. Ann Thorac Surg; 2005:79(1):74-9.

IV. Andréll P, Ekre O, Eliasson T, Blomstrand C, Börjesson M, Nilsson M, Mannheimer C. Cost-Effectiveness of Spinal Cord Stimulation versus Coronary Artery Bypass Grafting in Patients with Severe Angina Pectoris – Long-term Results from the ESBY Study. Cardiology; 2003;99(1):20-4

TABLE OF CONTENTS

1. ABBREVIATIONS

ACS	Acute Coronary Syndrome
AED	Astheno-Emotional Disorder
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CHP	Cardiac Health Profile
CRF	Coronary Flow Reserve
ECG	Electrocardiogram
EECP	Enhanced External Counterpulsation
ESBY	Electrical Stimulation versus Coronary Artery Bypass Surgery in Patients with Severe Angina Pectoris
ESC	European Society of Cardiology
ETS	Endoscopic Thoracic Sympathicotomy
FBSS	Failed Back Surgery Syndrome
FFR	Fractional Flow Reserve
HRQOL	Health-Related Quality of Life
LAD	Left Anterior Descending artery
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonace Imaging
PCI	Percutaneous Coronary Intervention
PMR	Percutaneous Myocardial laser Revascularisation
QCA	Quantitative Coronary Angiography
SAQ	Seattle Angina Questionnaire
SF-36	Short Form 36
SCS	Spinal Cord Stimulation
TEDA	Thoracic Epidural Anaesthesia
TENS	Transcutaneous Electric Nerve Stimulation
TMR	Transmyocardial laser Revascularisation
WMD	White Matter Disease

2. INTRODUCTION

2.1 CORONARY ARTERY DISEASE

Coronary artery disease (CAD) is the main manifestation of arterial atherosclerosis in the vessels of the heart. The close association between CAD, dietary habits, low physical activity and tobacco smoking has been described in recent decades.[90,215] Diabetes mellitus, hypertension and hyperlipidemia are also well-known and strong risk factors for CAD. [90,215]

Arterial atherosclerosis is a process that starts in the intimal tissue of the arteries. Initially lipids and inflammatory cells are incorporated in the vessel wall. This is followed by a continuous formation of fibrosis and ultimately formation of atherosclerotic plaques.[114,189] As toxic and pro-inflammatory substances are accumulated in the atherosclerotic plaque, a degeneration process that might make the plaque unstable starts. Hence, the atherosclerotic plaques may rupture into the vessel lumen, causing an acute formation of a thrombus, which, in turn, will interrupt or drastically impair the blood flow in the affected vessel. Furthermore, activated platelets at the site of the plaque rupture may release a series of vascularly active substances that will lead to increased vasomotor tone or even spasm. This process is clinically referred to as acute coronary syndrome (ACS), including acute myocardial infarction and unstable angina pectoris.[54,189] In the chronic stage of CAD, the main problem is a relative and progressive narrowing of the arteries, due to atherosclerotic thickening of the vessel walls. This, in turn, impairs the arterial blood supply to the myocardium.[16,114] The chronic stage of CAD is clinically manifested as stable angina pectoris.

2.2 ANGINA PECTORIS

2.2.1 DEFINITION AND SYMPTOMATOLOGY OF ANGINA PECTORIS

Angina pectoris is a clinical syndrome characterised by discomfort in the chest, jaw, shoulder, back or arm. It is typically aggravated by exertion or emotional stress and commonly relieved by rest.[91] The syndrome was first described by William Heberden in the 18th century. Heberden described angina pectoris as a sense of strangling and anxiety in the chest, especially associated with exercise.[104] The cardiac origin was not established until a few years later, when Parry demonstrated CAD during the necropsy of patients who had experienced the symptoms.[162] The connection between angina pectoris and myocardial ischaemia was not established until the 20th century. [118] Hence, in modern medicine the term angina pectoris is used to describe chest discomfort due to myocardial ischaemia associated with coronary artery disease.[16] However, angina pectoris may also occur in persons with valvular heart disease, hypertrophic cardiomyopathy and uncontrolled hypertension. In addition, the symptoms may be present in patients with normal coronary arteries and myocardial ischaemia related to spasm or endothelial dysfunction. Angina-like chest pain may also be the main symptom in patients with non-cardiac conditions such as oesophageal, chest wall or lungsdisorders.[16,91]

Stable angina pectoris is defined as anginal symptoms occurring over several weeks without any major deterioration.[16] Even in stable angina the symptoms may vary considerably, depending on factors such as weather or emotional stress.

Unstable angina pectoris has been described by Braunwald and is divided into three classes; a) debut of anginal symptoms that markedly limit physical activities, b) abrupt worsening of pre-existing stable angina, for example, more anginal episodes and longer duration of the anginal attacks, and c) anginal symptoms occuring at rest.[38] However, some patients may present a mixed symptomatology. For this reason, sometimes it may be difficult to distinguish clinically between these conditions. Furthermore, pathologically the patients may have features of both stable and unstable angina.[16]

Prinzmetal angina is a rare condition that develops spontaneously with ST elevation on the electrocardiogram (ECG). It is believed that the pain and the ECG changes are due to an increase in coronary tone or epicardial spasm, often in combination with ventricular arrhythmias and atrioventricular block.[39,68,119] Prinzmetal angina is also referred to as vasospastic angina.[16]

Cardiac syndrome X is described as a syndrome in which angina pectoris occurs in the absence of apparent coronary atherosclerosis or other organic disease of the epicardial arteries according to angiographic findings, but where presents objective evidence of myocardial ischaemia in terms of ST segment depression on ECG during stress.[16] Recent studies indicate that the anginal symptoms occur due to endothelial dysfunction , sometimes referred to as "microvascular angina" in the literature.[57,79,160] However, patients with chest pain and normal coronary arteries have a good prognosis in contrast to patients with angina pectoris and CAD.[57,117]

The severity of anginal symptoms are commonly graded according the Canadian Cardiovascular Society's (CCS) classification (table 1).[45]

TABLE 1. Classification of angina pectoris according to the Candian Cardiovascular Society.

Class I	"Ordinary physical activity does not cause angina" – such as walking or climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Class II	"Slight limitation of ordinary activity" – walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, in cold, or in wind, 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 normal pace and in normal conditions.
Class III	"Marked limitations of ordinary physical activity" – walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
Class VI	"Inability to carry on any physical activity without discomfort" – anginal syndrome may be present at rest.

2.2.2 PREVALENCE OF ANGINA PECTORIS

The prevalence of angina pectoris increases with age, from 2-5% in men in the age group 45-54 years, to 11-20% in the age group, 65-74 years. Angina pectoris is less common in women in the same age groups: 0.5-1% and 10-14%, respectively.[16] The prevalence of angina pectoris in Sweden is estimated to be approximately 1-4.5% in men 40-55 year old and about 6% in 60-year old men.[164] In total, one per cent of the Swedish population is estimated to suffer from angina pectoris and the incidence of angina pectoris is approximately 16 000 new cases per year in Sweden.[3]

2.2.3 PATHOPHYSIOLOGY OF ANGINA PECTORIS

The heart is an aerobic organ, not designed for anaerobic work. The heart is dependent on almost complete oxidation of nutrients to obtain energy. At rest, the oxygen extraction fraction from the myocardial blood is approximately 75%, which is high compared with other kinds of tissue. Thus, the possible increase in oxygen extraction is quite limited.[209] Due to the inability of the myocardium to function without proper oxygen supply, balance between the supply and demand of oxygen is critical. Imbalance, and subsequent myocardial ischaemia, may be caused by poor myocardial perfusion (blood and oxygen supply), inreased oxygen demand or both. The cause may vary in the same patient on different occasions.

In healthy subjects cardiac stress will induce dilatation of the coronary arteries as a result of increased myocardial oxygen demand. As the myocardial blood flow increases to meet the increased demand, the balance between myocardial perfusion and oxygen demand is maintained. At rest and during myocardial stress, the myocardial perfusion will always be sufficient for maintaining an aerobic metabolism. In contrast, in persons with angina pectoris, usually during exercise with subsequent increased oxygen demand, the coronary arteries are not able to dilate sufficiently, due to thickening and stiffness in the vessel walls caused by atherosclerosis. The myocardial oxygen demand will be greater than the myocardial perfusion, an aerobic metabolism cannot be maintained and ischaemia occurs in the myocardium. Ischaemia is characterised by insufficient coronary blood flow, insufficient supply of oxygen and nutrients and insufficient removal of metabolic rest products.[39]

During ischaemia, glycolysis is accelerated and the glycogen is rapidly consumed in the myocardial tissue. The aerobic metabolism switches to anaerobic metabolism, resulting in decreased formation of ATP and accumulation of metabolites, especially lactate that reduces the pH in the myocardial tissue. The ischaemic pain probably arises from an increase in algogenic substances, such as lactate, protons, potassium, bradykinin and adenosine, which stimulate the pain-transmitting neurons.[204] The pain perception of the heart is believed to be transmitted mainly via chemoreceptors.[56]

2.2.4 CARDIAC PAIN

Pain occurs late in the progression of myocardial ischaemia.[141,204] The first result of myocardial ischaemia is impaired myocardial performance due to initial diastolic and then systolic dysfunction, leading to elevated left ventricular filling pressure. This is followed by electrographic changes and, finally, anginal pain may develop.[141]

Ischaemia is the pathophysiological stimulus of cardiac pain. When ischaemia develops, algogenic substances are formed which activate chemoreceptors in sensory nerve endings in the adventitia of the coronary arteries, in the subepicardial tissue and in the myocardium. The cardiac pain afferents mainly consist of small myelinated A delta fibres and unmyelinated C fibres.[47,204] These primary afferents from the three major cardiac nerves run together with the sympathetic and parasympathetic nerves to reach the cervical and stellate ganglia. Afferent nerves from the thoracic ganglia enter the dorsal column of the thoracic spinal cord via the thoracic dorsal spine roots. Just before entering the spinal cord, the heart's innervation spreads upwards and downwards over several segments, but the majority of the axons terminate in the Th1-Th5 segments of the spinal cord.[204] In the spinal cord the pain signal is transmitted via the spino-thalamic tract to the brain. In the brain the pain signal is processed in the thalamic nuclei and projected to the somato-sensory cortex, the pain signal is processed and the location of the pain is identified. Activity can be observed in the hypothalamus, the reticular formation and the amygdala in response to arousal, fear and autonomic activation. Cognitive appraisal of the pain

signal occurs in the parietal cortex and the anterior cingualte cortex, the situation will be assessed as intrusive and threatening, an unpleasant experience. This causes activation of the pre-frontal cortex and the limbic system, the pain signal is processed emotionally, resulting in apprehension and fear for the future, the pain signal is evaluated in terms of the threat it represents to well-being or life.[135]

2.2.4.1 Asymptomatic myocardial ischaemia

In many cases myocardial ischaemia is not accompanied by anginal pain. This condition is referred to as silent myocardial ischaemia. Up to 70% of the episodes of myocardial ischaemia in patients with CAD may be asymptomatic; for acute myocardial infarction, the incidence of painless events is estimated to be approximately 25%.[60,115,186] In addition, there is a group of patients who do not experience any anginal symptoms at all during myocardial ischaemia. The phenomenon has not yet been fully explained. It has been suggested that silent myocardial ischaemia might occur due to inconsistent processing of the pain signals in the central nervous system.[180] Studies of regional cerebral blood flow during myocardial ischaemia have suggested that cortical activation is necessary for the sensation of pain, while subcortical structures, for example the thalamic nuclei, may be affected during silent ischaemia as well as during painful ischaemia. [178-180] Furthermore, the distribution of cerebral blood flow during myocardial ischaemia seems to differ in patients with cardiac syndrome X from that in patients with CAD.[181] Results from a previous study indicate that the central neural handling of afferent signals may be altered in patients suffering from cardiac syndrome X, which may contribute to an abnormal pain perception in these patients.[181]

2.2.4.2 Referred pain

Pain from the heart, as well as from other visceral organs, is experienced as referred pain. The area of localisation corresponds to the dermatomes supplied by the thoracic spinal roots. There are several explanations for the phenomenon of referred pain. The most accepted hypothesis is "the convergence theory".[193] The convergence theory states that there are a great number of viscero-somatic convergences in the dorsal column. The brain is unable to determine the original visceral source of the pain and instead localises the pain to the corresponding somatic structure. Another theory explaining the referred phenomenon is "the occurrence of dichotomising afferents," i.e. one nerve supplies two or more axons to a visceral and somatic structure simultaneously.[47,193] Furthermore, another theory, proposed by MacKenzie, suggests that "irritable foci" are created in the dorsal column, making the neurons increasingly sensitised to normally physiologically non-painful stimuli from somatic structures, resulting in the brain localising the pain to those somatic structures instead of to the visceral organs.[193]

2.2.4.3 Differential diagnosis of chest pain

There are many diseases that may give rise to chest pain resembling angina pectoris.[34,39] Due to the referred pain phenomenon, anginal pain may be difficult to distinguish from pain from other visceral organs in the thorax.

Conditions in the oesophagus (gastro-oesophageal reflux, oesophageal dysmotility) may be especially difficult to differentiate from anginal pain, as disturbances in the organs may occur simultaneously and they are closely related anatomically. Furthermore, dysfunction in one of the organs may influence the other organ, either directly by reflex mechanisms, i.e. linked angina (a viscero-visceral reflex), or indirectly by modifying the afferent flow from the other organ.[33,49,204]

Other diseases of the heart, aorta and lungs, for example aortic stenosis, aortic dissection, thoracic aortic aneurysm, severe pulmonary hypertension and perimyocarditis, may give rise to chest pain, which may be difficult to differentiate form angina pectoris in the acute phase.

Pain from the chest wall, such as musculoskeletal pain, Tietze's syndrome and thoracic back pain with secondary neuralgia, may be difficult to distinguish from anginal pain. Post-CABG pain may be even more difficult to differentiate from angina pectoris. The former condition is primarly seen in patients who have undergone coronary artery bypass grafting (CABG) using the internal mammary artery. It is believed that this condition is due to damage to the intercostal nerves when the internal mammary artery is dissected, causing intercostal neuralgia that is associated with hypoesthaesia and mechanic allodynia (pain due to a stimulus that does not normally provoke pain).[53,70]

Visceral pain from the abdomen, e.g. peptic ulcer, gastritis, pancreatitis and gall bladder disease may also give rise to chest pain.

Functional pain, where there is no evidence of somatic pathology; for instance, anxiety disorders, often combined with depression, is another differential diagnosis in anginal pain.

2.2.5 Diagnosis of stable angina pectoris

In patients with chest pain that is considered to be of cardiac origin there is a need to assess whether the chest pain is due to myocardial ischaemia and CAD. The anginal pain is often characteristic, presenting four cardinal features; location (usually retrosternal with radiation to the chest and the arms), relationship with exercise (the symptoms are provoked by exercise), character (discomfort/feeling of pressure/strangling sensation), and duration (symptoms are relieved after rest within 1-3 minutes). Furthermore, patients with stable angina pectoris respond promptly, usually within 30 seconds, to sublingual nitrates. Hence, a clinical assessment and the patient's history often suffice to establish the diagnosis of stable angina pectoris.[16,91] After clinical assessment, non-invasive investigations, such as ECG stress testing, myocardial perfusion scintigraphy and stress echocardiography, are usually performed in order to confirm myocardial ischaemia, to assess the prognosis and to select the most appropriate therapies. However, non-invasive investigations are not always conclusive, or the patient may not be able to participate in the investigations properly so as to allow for conclusive results to be achieved. Thus, stable angina pectoris is ultimately a clinical diagnosis. In contrast, CAD is an angiographic diagnosis. CAD is often, but not always, associated with myocardial ischaemia and angina pectoris.

2.2.6 Non-invasive investigations

ECG exercise test (bicycle ergometer or treadmill tests) is the first choice of investigation after clinical assessment in most patients. ECG stress testing is a generally a safe procedure: it is a simple test and the least expensive investigation for confirming ischaemia. ECG changes during exercise are associated with the presence of CAD with a sensitivity of 50-80% and a specificity of 80-95%.[16,91] The greatest sensitivity can be found in patients with multi-vessel disease. Exercise testing is less sensitive in women than in men, and some studies have indicated that it is also less specific.[16,91] In addition, ECG changes in the absence of CAD are seen in patients with conditions such as cardiac syndrome X. A disadvantage with exercise tests is that they are dependent on the patient's ability to participate in the investigation for a conclusive result of the test to be obtained. For instance, conclusive results can usually not be obtained in patients with claudication, arthrosis of the knees/hips or obstructive pulmonary disease, as their exercise capacity is limited due to other reasons than myocardial ischaemia. Pharmacological stress tests, which do not require patient compliance, are more suitable in these patients.

Myocardial perfusion scintigraphy is often performed in association with a symptom-limited exercise test on a bicycle but can also be performed in association with pharmacological stress testing. The sensitivity (65-90%) and specificity (90-95%) is somewhat higher than those of exercise ECG test.[16,91] The test is used in patients who are unable to take part in exercise testing, or as an additional test when the results of the ECG stress test are inconclusive. Myocardial perfusion scintigraphy is also recommended for patients who have previously been revascularised. Myocardial perfusion scintigraphy allows more precise localisation of the vascular territories involved, particularly identification of single-vessel disease.

Stress echocardiography, like myocardial perfusion scintigraphy, is an alternative to classical exercise testing with ECG. The test is suitable for the same patient groups as those for whom myocardial perfusion scinitgraphy is the test of choice. Stress echocardiography has the same sensitivity (65-90%) and specificity (90-95%) as myocardial perfusion scintigraphy and is less expensive.[16,91] The method has a high sensitivity of detection of single-vessel and multi-vessel disease. However, proper interpretation of the test requires considerable experience and expertise.

2.2.7 INVASIVE INVESTIGATIONS

In order to assess whether clinically important obstructive coronary atherosclerosis is the cause of the patient's anginal symptoms and in order to determine whether the CAD is available for treatment with revascularisation procedures such as percutaneous coronary intervention (PCI) or CABG, a coronary angiography is usually performed. During the coronary angiography narrowing of the vessels caused by atherosclerosis is assessed visually. A stenosis in the epicardial vessels is usually considered clinically significant, i.e. the coronary blood flow is inadequate to meet the metabolic demands of the heart during exercise or stress, if the vessel lumen is narrowed by at least 50% of the lumen diameter.[16] However, the clinical importance of the stenosis is also dependent on the length and relative percent narrowing of the stenosis as well as the number of stenoses. Furthermore, the luminal diameter of the stenoses is not fixed and may alter with changes in coronary tone due to local smooth muscle constriction or dilatation.

Visual interpretation of coronary angiography is known to carry a high interobserver variability.[221] Furthermore most interventionists tend to overestimate the degree of stenosis prior to an intervention such as PCI and underestimate the residual narrowing after the treatment..[29] To handle these problems quantitative coronary angiography (QCA) has been developed.[168] With this method, using automatic contour detection with minimal manipulation by the operator, stenoses can be measured with high accuracy and low intraobserver as well as interobserver variability. Even though coronary angiography is the cornerstone for assessment of epicardial coronary lesions, the method is limited since complex plaque morphology is difficult to assess and since the method does not provide any physiological information.[208] Hence, Gould et al. developed coronary flow reserve (CRF) as a method for assessing the haemodynamic consequences of coronary stenoses. During the 1990s, the CRF has developed into fractional flow reserve (FFR), which has emerged as an important physiologic adjunct to coronary angiography for the assessment of intermediate lesions.[30] Haemodynamic studies have indicated that the resting coronary flow is not altered until a constriction of at least 85% by diameter is present but the maximal coronary flow is affected by a constriction as small as 30%.[93]

Even if a stenosis is considered clinically significant according to coronary angiography and haemodynamic measurements, the stenosis significance to the patient is dependent on collateral flow. A plaque rupture with a sudden formation of a stenosis, even if moderate, might cause severe symptoms if there is no collateral flow. On the other hand, a severe stenosis, or even an occlusion, which have been formed successively might be well tolerated as a collateral flow in most cases already has been established.

Despite the shortcomings of visual assessment of coronary angiographies this method is, to date, the most feasible to assess the overall distribution and severity of CAD.

2.3 Conventional treatment of stable angina pectoris

The aim of treatment is to minimise or to abolish angina symptoms and to prevent further progress of the CAD. The two main determinants for myocardial ischaemia are myocardial perfusion and myocardial oxygen consumption. Thus, these factors are the main targets for the therapeutic approach in the treatment of angina pectoris.

Before, or in connection with initiation of pharmacological therapy, lifestyle changes, in terms of smoking cessation, dietary changes, weight reduction and increased physical activity, should be applied. Furthermore, concomitant diseases such as hypertension, dyslipidaemia and diabetes (as the diseases affect the progression of CAD), should be appropriately treated.

2.3.1 Pharmacological treatment

Pharmacological treatment of angina pectoris encompasses both the prevention of complications of CAD and symptom relief. Conventional symptom-relieving pharmacological treatment in angina pectoris consists of nitrates, beta-blockers and calcium antagonists.

Nitrates are one of the cornerstones in the symptomatic treatment of angina pectoris. Short-acting nitrates work rapidly and usually relieve the anginal pain within minutes. Long-acting nitrates are used for prophylactic treatment of angina pectoris. Nitrates decrease myocardial oxygen consumption by causing vasodilatation, predominantly venodilatation, which leads to a decrease in ventricular pre-load. In addition, nitrates produce less pronounced systemic arterial dilatation (resulting in a decrease in afterload) and coronary artery dilatation (increasing myocardial perfusion). A disadvantage is the rapid development of tolerance to the substance.[16,91] The development of tolerance can be overcome by the use of nitrate-free intervals between dosing.

Beta-blockers act mainly by blocking the $beta_1$-receptor. "Non-selective" beta-blockers also block the $beta_2$-receptor but even "selective" beta-blockers also have an effect upon this receptor. Beta-blockers slow down the heart rate, reduce myocardial contractility and decrease arterial pressure.[16,91] These effects reduce the myocardial oxygen demand. Beta-blockers have been shown to improve survival in patients with previous myocardial infarction.[9,159] In addition, beta-blockers are used in the treatment of hypertension, arrhythmias, cardiomyopathy and congestive heart failure.[107,169]

Calcium antagonists act by blocking calcium channels, causing a decrease in intracellular calcium levels which produces arterial smooth muscle relaxation and decreases the systemic blood pressure through coronary and peripheral vasodilatation. The reduced intracellular calcium levels cause a reduction in myocardial contractility, which, in turn, reduces oxygen consumption. It has also been shown that calcium antagonists increase coronary blood flow.[16,98] However, the clinical significance of this finding has been debated. The calcium antagonists are a heterogeneous group with important differences in terms of pharmacological action. The three main classes are phenylalkylamines, benzothiazepines and dihydropyridines. In stable angina pectoris, long-acting dihydropyridines (e.g. felodipine, amlodipine) seem to be useful, as they are more vascular-selective and have less negative inotropic effects.[98] However, the present consensus is that short-acting dihydropyridines should no longer be used in the treatment of CAD.[98] Calcium antagonists are generally as effective as beta-blockers at relieving angina.[91] However, the efficacy of adding a calcium antagonist to patients already medicated with beta-blockers has been discussed during

the last few decades. There are studies, however, supporting the theory that addition of calcium antagonists to beta-blockers may be of value.[88,123,166]

Platelet inhibitors, such as aspirin and clopidogrel, are anti-thrombotic and are used in angina pectoris in order to prevent complications of CAD. Aspirin may also be active through anti-inflammatory effects on the atherosclerotic process. Clopidogrel is used as an alternative for patients who are allergic or intolerant to aspirin. Platelet inhibitors have been shown to reduce vascular events in patients with stable angina pectoris and to improve survival in the ACS.[12,172] Benefits of the combination of aspirin and clopidogrel have been demonstrated in patients with ACS and patients undergoing percutaneous coronary intervention (PCI).[145,219] Furthermore, platelet inhibitors seem to have beneficial effects on the occlusion rate of vein grafts after CABG.[91]

Lipid-lowering agents, such as statins, have been shown to reduce the risk of myocardial infarction, death and the need of coronary bypass surgery in patients with stable angina pectoris and elevated total cholesterol level.[13] Furthermore, there are reports indicating anti-ischaemic effects of statins at least in the acute phase of CAD. The mechanisms that have been suggested are plaque stabilisation, anti-inflammatory effects, anti-thrombotic effects and improved endothelial function. These mechanisms may be independent of lipid levels, suggesting that all patients with CAD might benefit from statin therapy, regardless of cholesterol levels.[23,69,198,211]

ACE inhibitors have been shown to reduce the incidence of cardiovascular death, myocardial infarction and stroke in high-risk patients with diabetes or vascular disease and one cardiovascular risk factor, even in the absence of heart failure.[218] Furthermore, results from previous studies indicate that ACE inhibitors may increase coronary blood flow.[122] However, the clinical importance of this effect has not yet been demonstrated. Treatment with ACE inhibitors is indicated in patients with CAD who also have diabetes and/or left ventricular systolic dysfunction according to the American guidelines for management of patients with chronic stable angina.[90]

2.3.2 INVASIVE TREATMENT

When pharmacological therapy fails to reduce the anginal symptoms, invasive treatments - i.e. revascularisation procedures, such as CABG or PCI - may offer further symptom relief. In addition, CABG is indicated in patients with impaired left ventricular ejection fraction (LVEF), three-vessel disease and/or left main stenosis irrespective of the patient's symptoms, as several studies have shown favourable effects on survival in this patient group after surgery. [6,11,78,113,220]

CABG has been used in the treatment of angina pectoris for more than 30 years. The treatment modality is considered beneficial, including a survival benefit in patients with left main stenosis or proximal three-vessel disease or two-vessel disease including proximal stenosis of the left anterior descending (LAD) artery.[113,220] CABG efficiently improves the symptoms in patients with angina pectoris: freedom from angina up to five years after surgery in 80% of the patients has been described.[11,83] A disadvantage of CABG is that it involves major surgery, which in especially in patients with more progressive CAD and/or extracardiac disease results in a risk of adverse outcome.[100,106,200] Hence, CABG is a treatment modality associated with a non-negligble risk of complications in connection with the procedure. The in-hospital mortality rate is about 1 to 5% of the cases, depending on the preoperative extent of CAD and on preoperative LVEF.[16] The mortality rate in connection with repeat revascularisation in patients who have previously undergone CABG is high. After prior CABG, the one year mortality rate after consecutive PCI is approximately 11-12 percent, compared with 5-21 percent after repeat CABG.[16,151]

Perioperative myocardial infarction may be observed in approximately 5% of the patients and major neurological complications in patients undergoing CABG occur in about 2% of the patients, although there have been reports of complication rates ranging from 1% to 5%.[16,42,143,173] Furthermore, the percentage of patients suffering from neuropsychological dysfunctions is high at hospital discharge, approximately 50 to 90 percent.[155,190] During the first decades, the CABG procedure was performed using extracorporeal circulation with a pump oxygenator and cardioplegia. However, the outcome after CABG seems to have improved due to the development of surgical and anaesthesiological management.[16,91] A problem with CABG is low patency rate of the vein grafts. Within one week of surgery 10-20% of the grafts are occluded from thrombosis and by three to five years after the operation, 60-70% of the vein grafts show evidence of atherosclerotic narrowing and after ten years, 50% are occluded.[16,91,97] In contrast, 90% of the internal mammary artery grafts anastomosted to the LAD are patent ten years after surgery.[132]

PCI is a less invasive procedure that was introduced in the treatment of angina pectoris in the late 1970s. In this strategy a catheter-borne balloon, introduced percutaneously via the femoral or radial artery, is inflated at the point of the coronary stenosis, dilating the stenosis. The number of procedures has increased dramatically and PCI has surpassed the frequency of CABG as it is a less costly treatment modality than CABG and the patients can return to activity earlier. PCI is considered suitable for patients with single-vessel or two-vessel disease, which does not involve the left main stem or the proximal LAD. Compared with medical treatment, studies have indicated that PCI is more efficient at relieving symptoms of angina pectoris.[161] Jones et al. demonstrated improved survival of PCI versus medical treatment in patients with single-vessel disease without LAD stenosis, but there is no evidence of a reduced risk of myocardial infarction by PCI treatment compared with medical treatment.[113,161]

The mortality rate in connection with the procedure is 0.2% in patients with single-vessel disease and 0.5% in patients with multi-vessel disease.[16] However, there is a risk of acute coronary occlusion during PCI. This risk has been reduced due to the advent of stents and improved antithrombotic therapies. To date, perioperative myocardial infarctions occur in less than 1% of the cases. A major disadvantage of PCI treatment is the high frequency of restenosis, which occurs in 30-40% of cases treated with ballon angioplasty.[16,91]

The general usage of stents and platelet inhibitors have decreased the frequency of restenosis compared with ballon angioplasty solely.[19,126,145] Furthermore, the recent development of drug eluting stents, with capability to release antiproliferative drugs to the vessel wall, carry the possibility of reducing the restenosis problem to only a few percent. The risk complications in connection to reintervention is low and repeat PCI, with our without stent implantation, can be performed with a high success rate.[16]

CABG and PCI are both effective at reducing anginal symptoms by re-establishing the blood and oxygen supply to the affected myocardium. In randomised studies, early and late survival rates as well as the frequency of myocardial infarction have been equivalent for PCI and CABG.[14,15,99,105,121] Patients undergoing CABG present fewer angina symptoms and require fewer anti-anginal drugs than patients undergoing PCI.

The CABG involves longer hospitalisation and convalescence thereafter, but PCI requires more reinterventions. Thus, the choice of approach, besides coronary anatomy factors, rests on weighing the more invasive nature of CABG against the greater risk of recurrent angina and reintervention over many years after PCI.

2.4 REFRACTORY ANGINA PECTORIS

2.4.1 DEFINITION AND DIAGNOSIS

Despite conventional pharmacological and invasive therapy, there is a group of patients who suffers from chronic severe disabling angina pectoris. This condition has been described with different terms such as intractable angina pectoris, end-stage CAD and refractory angina pectoris.[120,135,188] The terms end-stage CAD and intractable angina pectoris are less suitable, as they imply a condition that is inaccessible to any further treatment. The refractory patients do suffer from end-stage CAD, as further revascularisation procedures are not feasible due to their coronary anatomy. However, refractory angina pectoris is a more appropriate term, as it indicates that the condition is refractory or resistant to conventional treatment modalities, but may be available for other treatment options.[135] Hence, the refractory patients' angina pectoris disease should not be considered an end-stage disease.

According to a report by the European Society of Cardiology (ESC) joint study group on the treatment of refractory angina pectoris, which is based on the European Heart Journal's guidelines for management of stable angina pectoris and the American guidelines for the management of patients with chronic stable angina, refractory angina pectoris is defined as follows:

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.

In order to be considered refractory the patient has to have optimum medication. The word "optimum" is used rather than "maximum" as a considerable number of patients do not tolerate triple combination therapy (nitrates, beta-blockers, calcium antagonists) due to side effects: for example, hypotension, bradycardia and subjective discomfort.[207] Furthermore, conventional revascularisation procedures (PCI or CABG) must be ruled out on the basis of a recent coronary angiogram and the presence of CAD must be established. In addition, the presence of myocardial ischaemia should be established before alternative treatment modalities are considered. However, as most patients with refractory angina pectoris have global and diffuse coronary insufficiency and a low exercise capacity, detection of myocardial ischaemia may be difficult to achieve with conventional investigations (ECG exercise testing, myocardial perfusion scintigraphy).[188] It has been suggested that stress echocardiography might be a more suitable investigation method in this patient group as it includes regional wall motion analysis of the ischaemic myocardium.[188] However, stress echocardiography is not always available and the result and conclusiveness of the investigation is dependent on the performer. Hence, the report by the joint study group's on the treatment of refractory angina pectoris underlines that myocardial ischaemia as a cause of angina pectoris is ultimately a clinical diagnosis.[135] According to the report, the patients suffering from refractory angina pectoris must have severe angina pectoris. The majority of patients with mild to moderate angina (CCS class 1-2) can be adequately treated with conventional anti-anginal medication.[120] Furthermore, due to the potential risk of complications in connection with revascularisation procedures, invasive treatment is usually not considered as an option for symptomatic treatment only, in patients with mild to moderate angina. Hence, only patients with severe angina (CCS class 3-4) are considered refractory when rejected for revascularisation as invasive treatment is indicated for symptom relief in theses patients.

Secondary prevention of CAD, including improved drug therapy (aspirin, beta-blockers and lipid-lowering agents) and the development of revascularisation techniques seem to have reduced

mortality among patients with CAD in the last decades.[188,213] It has been suggested that the number of patients with refractory angina pectoris increases, partly due to this improvement in survival.[135,188] According to Yang et al. the number of patients suffering from refractory angina pectoris is estimated at 300 000 to 900 000 patients in the United States and 25 000 to 75 000 new cases are diagnosed each year.[216] In a Swedish survey of patients referred for coronary angiography due to stable angina pectoris, performed by the Swedish Council of Technology Assessment in Health Care in 1994-1995, it was shown that 9.6% of the patients referred for angiography were rejected for revascularisation despite severe angina.[40]

Until recently, this patient group seems to have been more or less ignored, probably because they are not available for conventional treatment. The responsible physician often informs the patient that "nothing more can be done", which is very depressing for the patient. However, additional symptomatic treatment modalities for refractory angina pectoris have been developed during the last few decades. The epidemiology of refractory angina pectoris is virtually unknown and the patient group has not been described in terms of co-morbidity, nor have the reasons for rejection for revascularisation been systematically characterised. In order to form a basis for specific guidelines concerning the management and treatment of patients with refractory angina pectoris, there is a need for further studies of this patient group.

2.4.2 Additional symptomatic treatment modalities for stable angina

Several therapeutic approaches have been developed for symptom control in refractory angina pectoris during the last decades and numerous reviews have been published on the treatment of refractory angina pectoris.[63,120,135,188,203,216] In the field of pharmacological treatment, therapy with opioids, intrathecally applied anaesthetics and opioids, additional antiplatelet agents, low-molecular-weight heparins, thrombolytic agents and partial fatty acid oxidation inhibitors (e.g. ranolazine and perhexiline), are being discussed as additional pharmacological therapy options in patients with refractory angina pectoris. [63,120,188,216] However, the documentation regarding the efficacy and safety of these treatments in refractory angina pectoris is so far limited. Furthermore, some of the pharmacological treatments have major drawbacks as long-term therapies; for example, opioids, because of the risk of development of dependence and the gastro-intestinal side effects of the treatment, and intrathecal treatment because of the risk of intraspinal infection.

In addition, there are several non-invasive non-pharmacological and invasive treatment modalities available for the treatment of refractory angina pectoris. In Europe, neuromodulation techniques (i.e. transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS)), enchanced external counterpulsation (EECP), thoracic epidural anaesthesia (TEDA), endoscopic thoracic sympathicotomy (ETS), stellate ganglion blockade (SGB) and laser revascularisation, i.e. transmyocardial revascularisation (TMR) and percutaneous myocardial revascularisation (PMR) are being used.[27,51,84,95,135,137,154,171,206,214]

The main effect of neuromodulation is decreasing myocardial oxygen consumption. It has been suggested that the main effect of TEDA, ETS and SGB is modulation of sympathetic activity. Laser revascularisation and EECP aim at increasing myocardial perfusion, but the documentation to date regarding long-term effect of these treatments on myocardial perfusion is limited. Another evolving therapeutic concept is vascular endothelial growth factor (VEGF).[131,205] Furthermore, cardiac rehabilitation programmes, including stress management and regular physical exercise might be of value in this patient group.[63,135]

In the report by the ESC joint study group on the treatment of refractory angina pectoris, neuromodulation (TENS and SCS) is recommended as the first choice of treatment in refractory

angina pectoris, as neuromodulation seems to be the treatment with the best documentation concerning the efficacy and safety in angina pectoris.[135]

2.5 Background of neuromodulation

The neuromodulation techniques have evolved from Melzack and Wall's "gate control theory". This theory was proposed in 1965 to explain the modulation of afferent pain signals in the spinal cord. According to the gate control theory activation of large afferent, non-nociceptive myelinated type A fibres (transmitters of mechanic stimuli) inhibit the transmission of nociceptive impulses through smaller unmyelinated type C fibres in the relaying areas of the dorsal horn of the spinal cord, thereby "closing the gate" for the nociceptive impulses.[146] On the basis of this theory, dorsal column stimulation, later called spinal cord stimulation (SCS) was developed (Fig.1). The technique was introduced in humans in the late 1960s, when low voltage current was applied to the dorsal part of the spinal cord, thereby mimicking the effect of activation of the type A fibres.[192] Transcutaneous electrical nerve stimulation (TENS) was introduced during this time, but it was only meant to be used for selection of patients for subsequent SCS treatment.[149] However, to date TENS is used for treatment in variety of pain conditions.

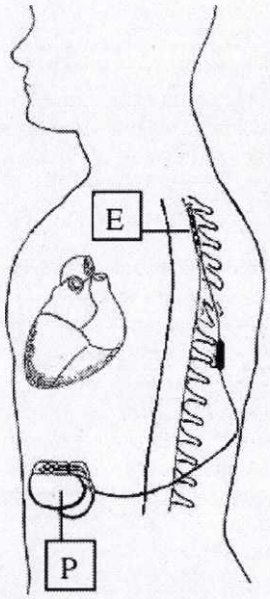


FIGURE 1. An implanted SCS system. E= epidural electrode, P= pulse generator.

SCS is used in the treatment of a number of different pain conditions. The four main indications are neuropathic pain, so called failed back surgery syndrome (FBSS), peripheral vascular disease, and angina pectoris. The characteristics of the pain-relieving effect of SCS are different in these conditions, implying that SCS may have different mechanisms of action. Thus, in peripheral neuropathic pain the symptoms decline after 10-20 minutes and this effect is subtotal. In contrast, in ischaemic pain conditions, such as angina pectoris, the pain-relieving effect occurs within 30-60 seconds and is usually complete. This difference can be used clinically to differentiate between ischaemic pain and pain from of non-ischaemic origin.

Approximately 50-60% of the patients treated with SCS for neuropathic pain experience adequate pain relief.[43,74] Studies have indicated that the main mechanism of pain relief in neuropathic pain is SCS-induced modulation of the neural activity in the spinal cord, involving changes in local transmitter systems.[128] It has also been suggested that activation of supraspinal loops may be of importance.[128]

In the 1970s, SCS was introduced by Cook et al. as treatment of pain due to peripheral vascular disease.[55] SCS was found to relieve pain in patients with nonreconstructable peripheral vascular disease, resulting in improved mobilisation which enhanced the blood flow, leading to ulcer healing and reduced need to amputate.[25,108] It has been suggested that the underlying mechanism of pain relief by SCS in peripheral vascular disease is the improvement in the microvascular blood flow and a decrease in sympathetic tone.[111,127-129] In patients treated with SCS for peripheral vascular disease, about 60-70% of the patients experience pain relief.[41,74,111]

2.6 NEUROMODULATION IN REFRACTORY ANGINA PECTORIS

TENS and SCS were introduced in the early 1980s as a therapeutic option in severe angina pectoris.[134,137,152] Although initially met by great scepticism, TENS and later SCS have gained acceptance as a therapeutic possibility in severe angina. To date, SCS in refractory angina pectoris is regarded as the most successful application of SCS. More than 80% of the patients experience pain relief in terms of less angina attacks and less consumption of short-acting nitrates.[65,74,217] Furthermore, the anti-anginal effect of SCS in refractory angina pectoris is due to decreased myocardial ischaemia during stimulation, rather than to an inhibition of the pain transmission.[59,61,62,75,101,103,124,134,139,182,183]

Even if SCS and TENS have similar effects with regard to symptom relief, there are several practical issues regarding TENS treatment. The electrodes sometimes fall off and in 10-15% of the patients the electrodes causes skin irritation, which makes the method impractical for long-term treatment. To date, TENS is mainly used in the screening process of angina pectoris, in order to determine whether the patient's chest pain is due to myocardial ischaemia and to determine whether the patient is sufficiently compliant to manage the SCS treatment adequately. In addition, TENS is also used alone in patients with anginal pain where SCS is not regarded as the optimum treatment for different reasons. In conclusion, SCS is a more suitable method for continuous treatment of angina pectoris, as it is a fully implanted system.

2.6.1 SAFETY AND SHORT-TERM EFFECTS OF NEUROMODULATION

When neuromodulation was introduced the safety of the treatment was a major concern. One concern was that the electrical stimulation in the vicinity of the heart would induce arrhythmias. This was shown not to be the case as long-term ECG studies (Holter monitoring) demonstrated that arrhythmias were not increased during stimulation.[61,75]

Another major concern was that neuromodulation might conceal symptoms of ischaemia and thus deprive the patient of a warning signal by solely inhibiting the pain signal. However, the long-term ECG studies showed that neuromodulation reduced the number of ischaemic attacks and several short-term experimental studies (described below) has shown that the mechanism of action by neuromodulation is rather an anti-ischaemic effect than a pain inhibiting effect.[61,75] In addition, clinical studies have shown that SCS do not conceal symptoms of myocardial infarction.[22] TENS has been demonstrated to reduce the number of episodes of silent ischaemia. in unstable angina pectoris.[35]

A further concern has been whether SCS is feasible in patients with cardiac pacemakers: an increasing number of patients with cardiac disease are treated with cardiac pacemakers and SCS may be indicated also among these patients.[67] One study has demonstrated that cardiac pacemakers and bipolar SCS can be safely combined in patients with refractory angina pectoris.[72] However, individual testing is mandatory to confirm safety in each patient and unipolar SCS should not be used in combination with cardiac pacemakers.[72,177]

Results from animal studies have suggested that SCS might have a protective effect on the cardiomyocytes (for example a decrease in oxygen-dependent metabolism) as there are indications that SCS might induce protective effects in tissues totally deprived of their oxygen supply.[86,89] In addition, there are data implying that SCS might induce modulation of neuronal activity within the heart, which in turn would protect the heart from arrhythmias and thus lead to less generalised ischaemic threat to the heart.[24,87]

However, the effect of neuromodulation in humans preceded animal experiments. Since 1982 several studies have been publish on the short-term effect of TENS and SCS on the relationship between myocardial ischaemia and angina pain from different centres.[59,61,62,75,96,101,103,124,134,136,137,139,182,183] Different methods for ischaeamia provocation, for example bicycle ergometer exercise tests, pharmacological stress testing and atrial pacing have been used. Irrespective of the stress method used, the relationship between anginal pain and myocardial ischaemia is unchanged. In summary, the results from these studies indicate that stimulation does not induce any changes in coronary haemodynamics or myocardial metabolism at rest (Fig 2). At a comparable stress level during stimulation, myocardial ischaemia and anginal pain disappears. However, at maximum stress level myocardial ischaemia and anginal pain reoccurs. Thus, myocardial ischaemia during stimulation induces anginal pain and the patient is not deprived of the warning signal.

As earlier discussed, the two main determinants for myocardial ischaemia is coronary blood flow and myocardial oxygen consumption. Hence, the anti-ischaemic effect of neuromodulation should affect either, or both of the main determinants.

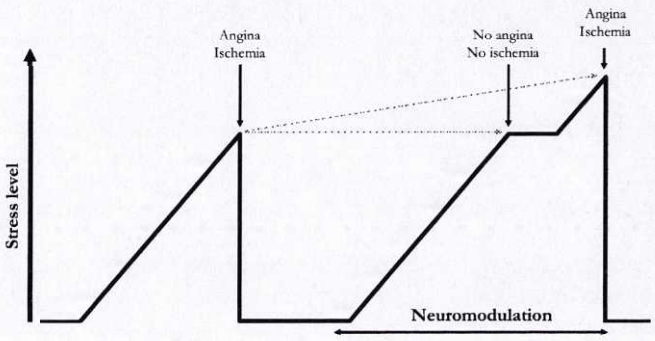


FIGURE 2. "Ischaemic shift". SCS elevates the ischaemic threshold.

Results from invasive studies using intra coronary Doppler technique are contradictional. The results from one report indicated a general decrease in the coronary blood flow velocity by TENS treatment at rest.[50] However, these findings have never been reproduced in later studies.[156,185] According to experimental studies, the anti-ischaemic effect of TENS and SCS at comparable stress level seems rather to be secondary to decreased myocardial oxygen consumption, than to an increase in myocardial blood flow.[136-139]

The mechanism behind the reduced oxygen consumption during stimulation has not yet been fully elucidated. Animal studies have indicated the existence of local opioid receptors in the myocardium. Agonistic effects on the opioid receptors will give rise to decreased myocardial oxygen consumption.[44] Beta-endorphin is a highly selective endogenous μ-agonist. In one report, it was shown that myocardial extraction of beta-endorphin during control session was turned into release during SCS stimulation, indicating that this release of beta-endorphin might contribute to the decreased myocardial oxygen consumption via agonistic effects on the μ-receptor.[76]

Studies on heart rate variability and invasive studies on catecholamine release from the coronary circulation indicates that that SCS do not have any effect on the local effects on sympathetic activity in the myocardium..[21,102,157,158] However, it has been demonstrated that general sympathetic activity is decreased during stimulation, which might be beneficial in terms of reducing the oxygen demand.[77,157,184]

There are conflicting results regarding SCS's effect on myocardial perfusion during stress, by means of positrion emission tomography. In one study, no effect of SCS on the myocardial perfusion could be demonstrated.[59] Results form another study was interpreted by the authors as

SCS altering the perfusion to benefit the ischaemic regions, even in the absence of increased total blood flow, i.e. a "homogenisation" of the coronary blood flow was induced during stimulation.[101]

In summary, SCS seems to act by inducing a shift of the ischaemic threshold to higher levels of myocardial performance. This phenomenon is referred to as "ischaemic shift". The mechanism is not fully elucidated but seems to mainly depend on a reduction of myocardial oxygen consumption although several mechanisms might contribute to the effect involving changes in myocardial blood flow and neurohormonal mechanisms.

2.6.2 LONG-TERM EFFECTS OF NEUROMODULATION

Several reports of the long-term effects of SCS in severe angina pectoris have been published. They have shown positive effects on symptoms in terms of decrease of anginal attacks, improvement of quality of life as well as beneficial effects on myocardial ischaemia. [65,96,176,183,217]

However, many of these studies have drawbacks such as a limited number of patients, short follow period and lack of randomisation. To date, no study has indicated that a prognostic benefit of SCS treatment. Hence, SCS can not replace any of the pharmacological or invasive therapies above that have been shown to produce prognostic benefit.

2.6.2.1 The ESBY study

Before the ESBY study (Electrical Stimulation versus Coronary Artery Bypass Surgery in Severe Angina Pectoris) was initiated, SCS had only been used to treat angina in patients who were rejected for revascularisation. The aim of the ESBY study was to compare the results of SCS treatment with CABG in patients with severe angina (CCS class 3 or 4) and increased surgical risk who were accepted for CABG on a strict indication of symptom relief, i.e. with no anticipated prognostic benefit from CABG.[140]

Over a period of three years, 1992-1995, 104 patients were randomised to SCS (n=53) or CABG (n=51). After six months of follow-up, both groups showed an improvement in angina symptoms in terms of fewer anginal attacks and reduced consumption of short-acting nitrates ($p<0.0001$), without any differences between the groups. The SCS group had lower cerebrovascular morbidity ($p=0.03$) than the CABG group, but there were no differences between the groups with regard to cardiac morbidity. At the six-month follow-up, the SCS group had a lower mortality rate ($p=0.02$): one patient died in the SCS group compared to seven in the CABG group.[140]

After six months, during bicycle ergometer tests, there was a decrease in myocardial ischaemia in the CABG group in contrast to the SCS patients, where no significant ischaemic changes at comparable stress level were detected. However, the SCS patients had their stimulators "off" since 24 hours before the stress tests. The reason for this was to investigate potential long-term anti-ischaemic effects of SCS without ongoing stimulation, as the actue effects during stimulation had been appropriately addressed in previous studies. However, a long-term effect of SCS could not be demonstrated. Hence, continuous active treatment is needed to obtain the positive effects of SCS on myocardial ischaemia.

Furthermore, the ESBY patients were assessed with regard to quality of life, after six months of follow-up and after 4.8 years.[73] Quality of life was assessed using generic and disease-specific quality of life questionnaires. On both these occasion, quality of life was improved compared with before the intervention, with no differences between the groups ($p<0.001$). Furthermore,

there were no differences between the groups with regard to mortality after 5 years, 13 patients in the SCS group had died compared to 16 patients in the CABG group.[73]

The conclusion from the results of the ESBY study was that SCS may be a therapeutic alternative for patients with severe angina and increased risk of surgical complications in connection with CABG.

As all the patients in the ESBY study were considered eligible for CABG, they were not suffering from refractory angina pectoris. The possible symptomatic improvement from surgery must be related to the risk associated with the intervention. Table 2 describes patient groups in relation to prognostic and symptomatic aspects of CABG, possibilities of intervention and surgical risks. Group "A" are patients with an anticipated prognostic benefit from CABG according to the guidelines, "B" have only symptomatic indications, "C" have a risk of adverse outcome after CABG (i.e. the ESBY patients), and "D" are refractory angina patients.[16,71,91]

TABLE 2. Patient groups in relation to prognostic and symptomatic aspects of CABG, as well as possibility of intervention and surgical risks.

Patient group	A	B	C	D
Prognostic benefit	+	-	-	-
Symptomatic indication	+/-	+	+	+
Revascularisation possible	+	+	+	-
Increased surgical risk	-/+	-	+	-/+

CABG indicates coronary artery bypass grafting.

2.7 CONCLUDING REMARKS

The prevalence of refractory angina pectoris is so far unknown. This patient group has not been described in terms of co-morbidity and the reasons for rejection for further revascularisation have not been systematically characterised, in terms of concomitant diseases as well as extent of CAD. Furthermore, there are no data available regarding the prognosis, progress of angina symptoms or quality of life in patients with refractory angina pectoris. Studies are therefore needed to explore and describe this patient group, as the number of patients with refractory angina seems to increase due to improved secondary prevention of CAD.

Most of the previous studies regarding the long-term effect of SCS suffer from drawbacks in terms of being, retrospective, limited in size and/or non-randomised. Consequently, to evaluate the safety and long-term effects of SCS, systematic follow-up assessments are needed. The long-term safety aspects of SCS include mortality, hospitalisations, cerebral complications and treatment complications. In addition, the health care costs of long-term SCS treatment need to be described.

3. AIMS OF THE THESIS

The general aims of the thesis were to study the epidemiological characteristics of patients with refractory angina pectoris and to assess the applicability of SCS in patients with severe angina pectoris, with special attention to safety and long-term efficacy. More specifically, the aims can be defined as follows:

- To estimate the incidence of refractory angina pectoris in a defined geographic area;
- To describe the reasons why patients with refractory angina pectoris are considered inappropriate for further revascularisation;
- To characterise patients with refractory angina pectoris in terms of general health characteristics, concomitant diseases, previous and ongoing treatment as well as extent of CAD;
- To describe the progress of refractory angina pectoris with regard to fatality, cerebrovascular morbidity, angina symptoms and quality of life;
- To study the safety aspects of SCS in terms of cerebral complications, treatment complications and causes of death;
- To study the long-term effects of SCS with regard to morbidity and health care costs.

4. METHODS AND METHODOLOGICAL CONSIDERATIONS

4.1 EPIDEMIOLOGICAL ESTIMATIONS (PAPER I AND II)

According to the report by the European Society of Cardiology's (ESC) joint study group on the treatment of refractory angina pectoris, refractory angina pectoris is defined as severe stable angina pectoris (CCS class 3-4) in the presence of CAD that cannot be controlled by conventional pharmacological treatment and that is not available to further revascularisation. In addition, the decision that the patient is inappropriate for further revascularisation should be made on the basis of a recent coronary angiogram.[135]

According to this definition, only patients with severe angina pectoris who undergo coronary angiography and are subsequently considered inappropriate for revascularisation can be considered to suffer from refractory angina pectoris. Hence, follow-up of revascularisation conferences, where an interventional cardiologist and a cardiac surgeon evaluate the coronary angiograms and decide whether revascularisation is appropriate or not, would make it possible to identify patients fulfilling the criteria for refractory angina pectoris (Table 3). This would provide an estimate of the incidence of refractory angina pectoris in the catchment area of the participating centres. The letter of referral for coronary angiography should contain all the relevant data regarding the patient's general health status and any concomitant diseases. By obtaining this information from the patients' medical records it would be possible to characterise this patient group. Patient telephone interviews, performed by a research nurse, would also give complementary information. Further information regarding the characteristics of this patient group could be obtained by comparing the patients with refractory angina pectoris with patients with angina pectoris who were accepted for revascularisation. Thus, the refractory patients were matched by age and gender to a group of patients with severe stable angina pectoris (CCS class 3-4), and CAD, who were accepted for revascularisation after the revascularisation conference.

TABLE 3. Inclusion criteria for the patients in the studies in Paper I and II.

Criteria	Refractory group	Revascularisation group
History of stable angina pectoris, CCS class 3-4	Yes	Yes
CAD on a recent coronary angiogram	Yes	Yes
Accepted for further revascularisation after revascularisation conference	No	Yes
Patient consent	Yes	Yes

CAD indicates coronary artery disease; CCS, Canadian cardiovascular society.

There is most likely a number of patients who suffer from severe angina pectoris, despite optimum pharmacological treatment, who are not referred for coronary angiography at all. These patients might fulfil the criteria for refractory angina pectoris, provided they undergo a coronary angiography, but they are disqualified *a priori* due to concomitant disease and/or advanced age. It is also known that acute angiographies are not reported at the revascularisation conferences. This means that an acute event in a patient with possible refractory angina pectoris may occassion an

acute coronary angiography, which may not be evaluated according to the routines for stable angina pectoris.

However, as a recent coronary angiography is necessary to establish the diagnosis refractory angina pectoris according to the current definition by the ESC, this approach would be the most appropriate in order to obtain an estimate of the incidence of refractory angina pectoris.

4.2 Assessment of coronary angiographies (Paper I and II)

In order to verify the presence of CAD in patients with angina pectoris and to assess whether a revascularisation procedure is appropriate, a coronary angiography is usually performed. If a lesion is present a qualitative assessment is made, involving grading of the diameter stenosis, in order to assess the lesion's impact on the coronary blood flow and, ultimately the myocardial perfusion. Despite the shortcomings of visual assessment of coronary angiographies (as previously discussed), this method is the most feasible to assess the overall distribution and severity of CAD, especially in a retrospective analysis. For this purpose scoring systems have been developed taking into account both severity of and distribution of stenoses within the coronary tree.[113,125]

Thus, in order to characterise the refractory patients with regard to extent of CAD, the coronary angiograms were scrutinised by one of two experienced interventional cardiologists. The epicardial arteries were divided into 18 segments, based on the classification by Austen et al., and were evaluated as to the presence of lesions.[26] If a lesion was present, visual qualitative assessment was carried out with grading of the diameter stenosis (DS) as "insignificant stenosis" (<50% DS), "significant stenosis" (>50%), "severe stenosis" (>70%DS or >90%DS) or "total occlusion" (100% DS and Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1).[8]

Five different scores were used for assessing the extent of the CAD and the subsequent impact on myocardial perfusion:

The *stenosis score* is a description of the extent of the CAD and assesses the number of segments with significant stenoses as well as non-significant stenoses (not only stenoses >70%). All segments present are assessed and the score is adjusted for the stenosis grade. A disadvantage of the stenosis score is that the location of the stenoses is not taken into account by the scoring system.

The *Leaman coronary score* is a continuous score that assesses the severity of the underlying CAD based on the fact that different coronary vessels carry different volumes of blood to the left ventricle.[125] The more severe the stenosis and the larger the blood volume provided by the vessel to the left ventricle, the higher the coronary score. The Leaman score is weighted for the location as well as the grade of the stenoses, relating the impact of the stenoses to subsequent prognosis. However, not all coronary segments are assessed in this score and only stenosis >70% are assessed. In addition, the score does not assess whether or not all three main vessels are affected. However, the score has been validated and found to correlate to prognosis of the distribution of CAD on a population level.

The coronary angiograms were also assessed according to the *modified Duke coronary anatomy score* described by Jones et al.[113] The score is divided into nine prognostic groups representing a continuum of one-vessel, two-vessel, and three-vessel CAD, with the greatest emphasis laid on the presence of lesions in the LAD. As the Leaman score, the Duke score has been validated and found to correlate to prognosis of the distribution of CAD on a population level. The score is

weighted with regard to stenosis in LAD, but the location of the stenoses in other segments is not taken into account. Furthermore, all segments are not evaluated and only stenoses >70% are assessed.

More than half of the patients in the refractory group had previously undergone CABG. Thus, in order to be able to assess the burden of CAD in patients with prior CABG, a score modified from the Duke coronary anatomy score was used. In this *modified Duke score for previously CABG-operated patients*, the lesions were adjusted for the current result of any previous CABG. In this modified score, a lesion is disregarded if the periphery of the artery is supplied by a graft without a stenosis.

According to clinical experience, peripheral stenoses are one of the main anatomical reasons for rejection for further revascularisation. As none of the scoring systems specifically assess peripheral stenoses, the *peripheral stenosis score* was developed as a modification of the stenosis score. The peripheral stenosis score only assesses whether there is a lesion in the peripheral segments of the coronary arteries and the grade of the stenosis is not taken into account.

4.3 Assessment of quality of life (Paper II)

Quality of life is defined as the subjective perception of the degree of physical, psychosocial and social well-being. It is recommended that patients suffering from specific diseases should be assessed using two different kinds of questionnaires: generic and disease specific. Generic questionnaires measure health-related quality of life (HRQOL) in general.[64] They are designed to assess health-related quality of life in different patient groups as well as in healthy populations. Any disease can be evaluated using generic quality of life questionnaires. However, changes in specific symptoms may not be detectable with these instruments.[64] On the other hand, disease-specific questionnaires measure the impact on quality of life of a specific disease. These instruments are not applicable to other patient groups or healthy subjects, but they are more sensitive to changes in symptoms of a specific disease over time.

Quality of life questionnaires have to be carefully validated to ensure their accuracy. [64,197,201,210] Three factors are of importance when evaluating the validity of a quality of life questionnaire:

1. The instrument's discriminative ability, i.e. the ability to distinguish between different patient groups.

2. The reliability/stability of the instrument, i.e. consistent results in repeated measurement..

3. Sensitivity to change/the evaluative ability, i.e. adequate detection of change in relation to an intervention.

Furthermore, as the validation of quality of life questionnaires is a lengthy process, choosing one of the most frequently used questionnaires is recommended.

The SF-36 is a generic health status questionnaire. It is a validated, well-known and widely used generic health status questionnaire.[48,64,201,212] The 36 items in the questionnaire are grouped into eight scales: physical functioning, social functioning, role limitations caused by physical problems, role limitations caused by emotional problems, mental health, energy/vitality, bodily pain, and general health. However, the SF-36 is generic, i.e. not disease-specific, and may thus fail to discriminate between classes of angina, and may be insensitive to changes in cardiovascular health.[66,197]

The SAQ is a disease-specific quality of life questionnaire assessing the functional status of patients with angina pectoris. The questionnaire consists of 19 items measuring five dimensions of CAD: physical limitation (how daily activities are limited by symptoms of CAD), anginal stability (assesses change in angina symptoms at the most strenuous level of activity), anginal frequency (frequency of angina episodes and consumption of short-acting nitrates), treatment satisfaction, and disease perception (assesses the burden of the CAD on the patient's quality of life). The result for each patient comprises five separate scores, one for each dimension, in a range from zero to 100. The SAQ has been used in several follow-up studies of angina pectoris patients to assess benefits from interventions but also to assess symptomatic changes in patients with stable angina pectoris.[36,195-197]

The CHP is a disease-specific, HRQOL questionnaire, tested for reliability and validity in a Swedish population with ischaemic heart disease.[210] The questionnaire consists of three parts. In part I, the presence and degree of angina pectoris according to the CCS classification are assessed by the patient. Part II assesses HRQOL (16 items) and part III is disease-specific assessing quality of life with regard to angina pectoris. Four factors have been extracted: Emotional, Social, Somatic functioning and Emotional Control. The second and third parts of the CHP consist of a visual analogue scale with verbal "anchors" at each side expressing the extremes. The scores in part II and III are summed up and divided by the number of answered items. Low values indicate a better quality of life. The CHP has been used for assessing benefits from interventions.[210]

In contrast to the SAQ, the CHP questionnaire describes the impact of angina pectoris on the emotional and social aspects of quality of life, whereas the SAQ rather describes the impact on function of the angina symptoms. However, the CHP questionnaire is less frequently used than the SAQ.

4.4 Cerebrovascular morbidity and white matter disease (Paper III)

Neurological and neuropsychological complications frequently occur in connection with CABG.[42,143,155,173,190,202] Previous studies have indicated that there is a relationship between subcortical brain ischaemia (white matter disease, WMD), caused by small-artery disease in the brain, and neuropsychological decline after CABG.[52,80-82,92,167,170] Ischaemic WMD is visible on T2-weighted magnetic resonance images as signal hyperintensities in the brain's white matter. Post-mortem examinations have shown that the grade of magnetic resonance imaging (MRI) hyperintensities corresponds to the severity of ischaemic tissue damage.[81]

In the study presented in Paper III, neurological complications were defined as focal cerebral ischaemia, i.e. stroke and/or transient ischaemic attacks (TIA). The diagnoses of stroke and TIA were classified according to the criteria presented in the report by the WHO Task Force on Stroke and Other Cerebrovascular disorders.[10] The neurological examinations were performed by one and the same experienced neurologist before and six months after the primary intervention (i.e. CABG or SCS).

Neuropsychological complications were defined as presence of astheno-emotional disorder (AED). The AED diagnosis is validated and has a high inter-rater reliability.[174,175] Symptoms of AED; enhanced psychic fatigability, diminished power of concentration, amnaesic problems, irritability and emotional instability, were identified during the neurological examination.[46,130,174,175] The symptoms of AED must not be secondary to a depressed mood disorder. Each symptom was judged separately and graded as "non-existent to a pathological extent" or "existent to a moderate to severe extent". If all symptoms were present to a "moderate to severe extent", the patient was considered to have AED. Furthermore, neuropsychological function was also

assessed in the patients pre- and post-operatively by means by a battery of 14 neuropsychological tests. The tests encompass encompassing attention, memory functions and psychomotor performance, a simple reaction time test and Trail Making Tests A and B.[199] The tests were performed by a licensed neuropsychologist.

Presence of WMD before intervention was identified by cerebral magnetic resonance imaging. MRI examination before treatment was planned for all the patients. All examinations were performed on a 0.5 Tesla magnet (Philips Gyroscan NT5, Eindhoven, the Netherlands). The protocol included a double spin-echo sequence. The slice thickness was 7 mm in the axial projection and the in-plane pixel size was 0.9 x 0.9 mm.

Fazekas' rating scale was used to grade the lesion load of MRI hyperintensities in the white matter of the brain.[80,82] Fazekas' rating scale has been developed as a simple method for classification of the hyperintensities on MRI to reflect the severity of the WMD.[80] The MRI hyperintensities are rated as punctate, early confluent and confluent lesions. [82] The Fazekas' rating scale is a well-known and validated method for grading WMD, but a disadvantage of the scale is that it does not differentiate between the causes of the lesions [82,116,187] The presence and grade of the WMD according to Fazekas' rating scale were assessed before intervention by one and the same neuroradiologist, who was blinded to the treatment allocation. The WMD was defined as punctate foci of MRI hyperintensities, beginning confluence of foci and large confluent areas.

The MRI changes according to Fazekas' rating scale might be due to "pure" WMD, but also to cerebral infarctions or to non-specific periventricular changes around the posterior horns, a common finding in the elderly.[144] To be able to relate "pure" WMD to cerebral complications, one and the same neuroradiologist scrutinised the white matter changes to exclude isolated periventricular areas around the posterior horns and focal solitary infarctions. In this manner a "modified" Fazekas' rating scale was obtained for the evaluation of the patients.

4.5 Mortality and causes of death (Paper II and IV)

Data on mortality and causes of all deaths in Sweden are continuously collected by the Centre of Epidemiology at the Swedish National Board of Health and Welfare. The rate of missing data on causes of death in this register is claimed to be 0.6%.[1]

The cause of death is established by clinical examination by a physician or by autopsy. The number of autopsies in Sweden has decreased from about 50% at the beginning of the 1970s to about 15% in 2001. The decrease varies with different age. Among patients over 85 years of age the number has decreased by about 85%, from 30% in 1970 to 4% in 2001. Consequently, the examinations made to define the underlying causes of death are a source of unreliability.

Data regarding the cause of death and death dates were obtained from the cause of death register for the patients participating in the ERA study (Paper II) and for the ESBY patients (Paper IV).

4.6 Health care costs and hospitalisation (Paper IV)

The Centre of Epidemiology at the Swedish National Board of Health and Welfare also continuously collects data on hospitalisations and surgical interventions carried out in Sweden.[2] The rate of missing data on hospital admissions in this register is claimed to be less than 2% and missing data on diagnosis less than 1%. Data from this register were collected for the patients participating in the ESBY study (Paper IV). In addition, data on costs and days in hospital in

connection with the primary intervention were collected prospectively from the hospital databases by a hospital economist. In order to assess the costs incurred by each hospitalisation, a certain amount was ascribed to each in-patient-day in the accounts. Interventions due to coronary heart disease, i.e. angiography, PCI, CABG, SCS implantation and re-operations related to SCS were also accounted for.

As the ESBY patients were recruited from different parts of western Sweden, with a variety of approaches to out-patient care, nursing-home stay and medication data regarding these costs were not collected. Even though information about these costs would have been of interest, the data would have been inconsistent in terms of quality.

In order to further estimate the cost of the SCS treatment, the pulse generator life span was analysed for up to five years after implantation. The pulse generator life span was calculated from implantation until either the pulse generator had to be replaced or the last occasion of active stimulator function noted in the patient file.

4.7 Long-term efficacy of spinal cord stimulation (Paper IV)

Information regarding treatment effect, need for intervention to restore stimulator function and treatment complications (i.e. infections, electrode fractures and electrode displacements) could be obtained for all patients treated with SCS in the ESBY study, as they were all regularly followed up at the Multidisciplinary Pain Centre at Östra Hospital, Göteborg.

4.8 Surgical Techniques (Paper III and IV)

The CABG operations were performed as open-heart surgery with extracorporeal circulation according to the standard clinical practice during the study period. The cardiopulmonary bypass circuit included a membrane oxygenator and non-pulsatile flow during bypass, typically 2.4 l/m2 of body surface area per minute (reduced to 2.0 l/m2 per minute during hypothermia). The mean arterial pressure was maintained in the range of 50-70 mmHg. Hypothermia (28-32°C) and cardioplegia were applied. The duration of extracorporeal circulation, aorta cross-clamping, surgery and anaesthesia were monitored and related to the development of cerebral complications.

The patient is awake and placed in a prone position during SCS implantation. An incision is made at the mid-thoracic level after administration of local anaesthesia. The epidural space is identified and punctured using a Touhy needle. A quadripolar electrode is introduced through the needle into the epidural space and is guided to the level of the Th1-Th2 vertebrae during X-ray monitoring. The electrode is placed at the midline and the patient experiences paraesthesiae during the intraoperative test stimulation. It is important to adjust the position of the electrode so that the paresthesiae in the chest cover the area to which the patient localises the anginal pain. This is to ensure that the area of the spinal cord innervating the heart is stimulated. When adequate paraesthesiae are obtained, the electrode is fixed to the ligaments and an extension wire is tunnelled subcutaneously to below the left costal arch, where it is connected to a subcutaneous pulse generator.[74] The system is fully implanted and is programmed telemetrically (Fig 1). The treatment is completely managed by the patient, who can switch on and off the stimulation as well as regulate the amplitude (within preset limits). In the present studies, all patients had 4-polar epidural electrodes. The SCS systems used were all Medtronic Itrel pulse generators (model II or III), connected to an epidural 4-polar Pisces Quad electrode (Medtronic, Minneapolis, MN,

USA). Implantation is usually performed by a neurosurgeon or an anaesthesiologist, the latter being the case in Göteborg.

4.9 Statistical methods

In Paper I, paired non-parametric tests were used when comparing the two groups, i.e. the Wilcoxon Sign Rank Test and the Sign Test were used for analysing continuous and categorical variables respectively. When these tests were not applicable, the Mann-Whitney U test and the $\chi 2$ test were used. Non-parametric test were used since the data had a skewed distribution. Paired tests were used as they are considered to be more reliable than non-paired tests.[18]

In Paper II, survival analysis was performed using Kaplan-Meier probabilities, employing the log-rank test. Paired non-parametric tests were used when comparing the two groups, i.e. the Wilcoxon Sign Rank Test and the Sign Test were used for analysing continuous and categorical variables respectively. When these tests were not applicable, the Mann-Whitney U test and the $\chi 2$ test were used when comparing the two groups with regard to quality of life data, anginal function class, extent of CAD, cerebral morbidity and pharmacological treatment. Non-parametric test were used since the data had a skewed distribution. Paired tests were used as they are considered to be more reliable than non-paired tests. [18]

In Paper III, non-parametric tests were used due to the small number of patients and events.[18] Categorical data were analysed using $\chi 2$ tests and Fisher's exact test: relative risk and 95% confidence intervals (CI) are quoted. Continuous variables were analysed using the Mann-Whitney-U test. The data were analysed on an intention-to-treat basis.

In Paper IV, the Mann-Whitney U test was employed compare the costs of the treatment groups and the number of hospital days, as these data had a skewed distribution.[18] The Fisher's exact test was used to analyse differences in the number of events and causes of death, as the event were few. The data were analysed on an intention-to-treat basis.

5. PRESENTATION OF THE STUDIES

5.1 PAPER I

Incidence, Clinical and Angiographic Characteristics of Patients with Refractory Angina Pectoris – the Epidemiological study of Refractory Angina pectoris (ERA)

BACKGROUND AND DESIGN

The epidemiology of refractory angina pectoris is virtually unknown. However, according to previous estimations, a considerable number of patients may suffer from this condition. The aim of the study was to assess the incidence of refractory angina pectoris and to characterise the patient group in terms of concomitant diseases, treatment and angiographic findings. This was a multicentre observational study, with seven participating centres. Patients who underwent coronary angiography but were considered inappropriate for further revascularisation (i.e. coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)) despite severe stable angina pectoris of Candian Cardiovascular Society (CCS) class 3-4 were included in the study. The refractory patients were matched by gender and age to a group of patients with coronary artery disease (CAD) and severe angina pectoris who were accepted for revascularisation after angiography. The two patient groups were compared with regard to health history, concomitant diseases, previous and current treatment. The extent of CAD on the coronary angiograms was also assessed using the stenosis score, the peripheral stenosis score, the Leaman coronary score, he Duke coronary score and the Duke coronary score modified for previous CABG.

RESULTS

During the inclusion period of three years, 146 patients with refractory angina pectoris were identified and evaluated at the revascularisation conferences at the seven participating centres. This number corresponds to 2.1% of all patients who underwent coronary angiography due to angina pectoris and were evaluated at the revascularisation conference (1% of all patients undergoing angiography also including angiographies for emergency reasons).

The refractory group had more pronounced cardiac disease than the revascularisation group. More patients in the refractory group had CCS class 4 (27% vs. 16%), had previously suffered one or more myocardial infarctions (26% vs. 13%), had undergone a previous revascularisation procedure (CABG and/or PCI) (63% vs. 21%) and/or had pharmacologically treated heart failure (19% vs. 6%) than the patients in the revascularisation group. Furthermore, the average left ventricular ejection fraction was lower in the refractory group than in the revascularisation group (0.52 vs. 0.59). In 38% of the patients, current myocardial ischaemia had not been confirmed before angiography. The majority of patients in both groups received beta-blockers, short-acting nitrates and aspirin, while only about one fourth of patients received calcium antagonists.

A considerable number of the patients had extracardiac disease such as diabetes, obstructive pulmonary disease of clinical importance and cerebrovascular disease, with no differences between the groups, except for insulin-treated diabetes (20% vs. 6%) and renal dysfunction (15% vs. 3%), which were more common in the refractory group than in the revascularisation group.

More patients in the refractory group than in the revascularisation group had three-vessel disease (59% vs. 39%). The mean stenosis score (1.6 vs. 1.0) and the number of significant stenoses (5.1 vs. 4.1) were higher in the refractory group compared with the revascularisation group. Furthermore, the patients in the refractory group had a higher peripheral stenosis score (0.37 vs. 0.20). The refractory group had also a higher Leaman coronary score (17.7 vs. 9.4) and Duke coronary score (6.4 vs. 4.5) than the revascularisation group. However, when the Duke coronary anatomy score was adjusted for previous CABG, there was no difference between the groups.

One of the most important issues concerning the patients with refractory angina is the reason why they are rejected for further revascularisation. In the present study, the most common reasons for rejection were unsuitable coronary anatomy and a potential risk of damaging pre-existing graft. However, in patients with no previous CABG, unsuitable coronary anatomy in combination with extracardiac diseases was the most common cause of rejection.

LIMITATIONS OF THE STUDY

Since the study inclusion period was limited to three years, only a limited number of patients were included in the study. The incidence of refractory angina pectoris may be underestimated in this study, possibly due to the fact that only patients evaluated at the revascularisation conferences were not included.

CONCLUSIONS

A considerable number of patients seem to suffer from refractory angina pectoris. Compared with patients accepted for revascularisation, the patients with refractory angina pectoris have more pronounced CAD as well as cardiac disease. Some of the patients appear to be in fairly good condition with respect to extracardiac health compared with revascularised patients. However, there seems to be a subpopulation in the refractory group with severe cardiac as well as extracardiac diseases. The main reasons why further revascularisation is not appropriate are unsuitable coronary anatomy and a potential risk of damaging pre-existing grafts. In addition, several patients were rejected for revascularisation due to concomitant severe extracardiac diseases, despite no previous heart surgery. A significant number of patients showed no recent evidence of current myocardial ischaemia, which could be considered a prerequisite for referral for coronary angiography in most cases. Furthermore, there are probably a number of patients who would benefit from optimised medication.

5.2 PAPER II

Fatality, Morbidity and Quality of Life in Patients with Refractory Angina Pectoris – A One Year Follow-Up of the ERA study

BACKGROUND AND DESIGN

Refractory angina pectoris is defined as severe angina pectoris (CCS class 3-4) due to coronary artery disease that cannot be controlled by pharmacological or invasive therapy. To date, the prognosis in refractory angina pectoris is unknown. The present study is a one-year follow-up of the patients in the so called ERA study (Epidemiologic study of Refractory Angina pectoris) aiming at assessing fatality, morbidity, development of anginal symptoms and quality of life. The quality of life was assessed by using one generic (Short Form 36; SF-36) and two disease-specific quality of life questionnaires (Seattle Angina Questionnaire; SAQ and Cardiac Health Profile; CHP).

RESULTS

Fourteen patients in the refractory group died during the one-year follow-up period compared to one in the revascularisation group ($p<0.001$). More patients in the revascularisation group developed stroke or transient ischaemic attacks than the patients in the refractory group (12 vs. 3; $p<0.05$). The refractory group had a higher CCS class ($p<0.0001$) than the revascularisation group after one year of follw-up.

Compared with the revascularisation group the refractory group had more impaired quality of life with regard to physical function, physical well-being and impact of angina symptoms. In contrast, there were no difference between the groups with regard to social function, emotional function and mental health. When compared to a normative Swedish population, the refractory group had lower scores in all the dimensions of SF36 except for social function and mental health. However, compared to patients with fibromyalgia, the refractory group had a better quality of life in the dimensions of bodily pain, social functioning and mental health

LIMITATIONS OF THE STUDY

A limited number of patients were included in the study. In addition, one year of follow-up is a limited period of time. The CHP questionnaire is a validated questionnaire but has not been extensively used compared to SAQ and SF36. A limited number of patients in the refractory group answered the quality of life questionnaires at both of the two occasions. Furthermore, there was a limited number of matched controlled pairs who answered the questionnaires in both the refractory group and the revascularisation group.

CONCLUSION

Patients with refractory angina pectoris have a high fatality rate and their quality of life is markedly impaired compared with a group of patients with CAD who have undergone revascularisation. The quality of life of both these groups of angina pectoris patients seems to be largely linked to the patient's CCS class. The angina symptoms seem to inflict limitations of physical activity and impair physical well-being in the refractory group. However, social function, emotional function and mental health do not seem to be affected by the severity of the anginal pain. This is in contrast with patients with chronic pain syndromes, whose quality of life is severely impaired physically as well as mentally and socially. There are additional treatment modalities that may be appropriate for patients with refractory angina pectoris aiming at symptom relief and improvement in quality of life.

5.3 PAPER III

Deep White Matter Disease in Magnetic Resonance Imaging Predicts Neurological and Neuropsychological Complications after Coronary Artery Bypass Grafting

BACKGROUND AND DESIGN

The ESBY study (Electrical Stimulation versus Coronary Artery Bypass Surgery in Severe Angina Pectoris) included 104 patients with severe angina pectoris, increased surgical risk and, no prognostic benefit from revascularisation who were randomised coronary artery bypass grafting (CABG) or spinal cord stimulation (SCS). Cerebral complications in connection with SCS have previously not been described. Thus, the aim of the study was to assess neurological and

neuropsychological complications in CABG with those following SCS. An additional objective of the study was to assess whether preoperative white matter disease (WMD) might predict cerebral complications, as previous studies have shown that there is a relationship between WMD and neuropsychological decline after CABG. The WMD was identified by preoperative cerebral magnetic resonance imaging (MRI). Neurological and neuropsychological complications were assessed by the same experienced neurologist before and six months after intervention.

RESULTS

More patients in the CABG group than in the SCS group developed focal cerebral ischaemia ($p<0.05$) and astheno-emotional disorder ($p<0.001$). More patients with WMD undergoing bypass were affected by focal cerebral ischaemia ($p<0.01$) and astheno-emotional disorder ($p<0.001$) after the intervention compared to patients with WMD undergoing spinal cord stimulation. In patients with no WMD there were no differences between the CABG group and SCS group with regard to cerebral complications.

LIMITATIONS OF THE STUDY

The ESBY study was not blinded because the two procedures differ significantly, i.e. the treatment allocation was known by patient and the surgeon. Furthermore, the study included a limited number of patients.

CONCLUSION

White matter disease may be a previously unobserved surgical risk factor for cerebral complications. Patients with preoperative WMD developed cerebral complications to a higher extent following CABG than following SCS. Thus, presence of WMD might indicate an increased risk of cerebral complications for a patient after CABG. It may be valuable to perform a MRI and assess the extent of WMD before CABG and avoid surgery in patients with WMD, to prevent cerebral complications. Further studies are needed to evaluate the predictive potential of WMD. The present study further supports the results from the ESBY study; that SCS might be a therapeutic alternative in patients with severe angina pectoris and surgical risk factors.

5.4 PAPER IV

Cost-Effectiveness of Spinal Cord Stimulation versus Coronary Artery Bypass Grafting in Patients with Severe Angina Pectoris – Long-term Results from the ESBY Study

BACKGROUND AND DESIGN

The ESBY study (Electrical Stimulation versus Coronary Artery Bypass Surgery in Severe Angina Pectoris) included 104 patients with severe angina pectoris, increased surgical risk and, no prognostic benefit from revascularisation who were randomised to coronary artery bypass grafting (CABG) or spinal cord stimulation (SCS). The aim of this study was to assess cost-effectiveness of SCS and CABG in the patients participating in the ESBY study, since the cost-effectiveness of SCS treatment compared with CABG previously not had been assessed. Furthermore, the study aimed at assessing morbidity and causes of death during two years of follow-up. The efficacy of SCS treatment and the complication rate of the treatment during the study period were also assessed.

Results

SCS proved to be a less expensive symptomatic treatment modality of angina pectoris than CABG ($p<0.01$). The SCS group had fewer hospitalisation days related to the primary intervention ($p<0.0001$) and fewer hospitalisation days due to cardiac events ($p<0.05$). The groups did not differ with regard to causes of death. There were no serious complications related to the SCS treatment.

Limitations of the study

The limitations of the present study are identical to those of Paper II, i.e. the ESBY study was not blinded because the two procedures differ significantly, i.e. the treatment allocation was known by patient and the surgeon. Furthermore, the study included a limited number of patients.

Conclusion

Previous studies have shown that SCS is effective at relieving myocardial ischaemia and severe angina pectoris. The present study suggests that SCS is a more cost-effective symptomatic treatment modality in angina pectoris than CABG in a selected patient group, i.e. patients with coronary artery disease, severe angina pectoris, no anticipated prognostic benefit from CABG and increased surgical risk. Taking into account that previously presented data from the ESBY study have found SCS and CABG to be comparable in terms of symptom relief, quality of life and survival, this study further supports the results from the ESBY study; that SCS may be a therapeutic alternative for these patients.

6. Discussion

6.1 Incidence of refractory angina pectoris

The majority of patients suffering from angina pectoris can be adequately treated by conventional pharmacological therapy and/or invasive therapy in terms of CABG and PCI. There are, however, patients who suffer from severe angina pectoris due to coronary insufficiency, despite optimum pharmacological treatment, and who are not accessible for any further revascularisation (refractory angina). It has been suggested that this patient group is increasing in number as a result of improved secondary prevention of CAD.[135,188,213]

However, the epidemiology and the characteristics of this patient group have never been fully explored. Thus, one of the aims of the study presented in Paper I was to estimate the incidence of refractory angina pectoris in a defined geographic area during a defined time period. The study confirms that there seems to be a considerable number of patients who suffer from refractory angina pectoris.

Refractory angina pectoris is defined in the report by the ESC joint study group on the treatment of refractory angina.[101] According to the report, the patient's angina symptoms have to be due to coronary insufficiency and the decision that the patient is inaccessible for further revascularisation procedures should be based on a recent coronary angiogram. Hence, the only way to obtain the diagnosis refractory angina pectoris is to undergo a coronary angiography and subsequently be considered inappropriate for further revascularisation. Thus, the method used in Paper I may be regarded as an adequate way to find patients fulfilling the criteria for refractory angina pectoris. Using this method to identify patients suffering from refractory angina pectoris in a defined area during a defined time period would consequently provide an estimate of the incidence.

As a recent coronary angiogram is needed to confirm the diagnosis refractory angina pectoris, a cross-sectional study in the population in order to estimate the prevalence would not be possible for ethical and practical reasons. Coronary angiography is associated with risks and should only be performed if considered necessary for further therapeutic intervention.[58,112]

In earlier estimations, approximately 10% of all patients undergoing coronary angiography are rejected for revascularisation despite severe angina.[40,135] Compared with these estimations, the incidence of refractory angina pectoris found in the study in Paper I was low. There are reasons for a possible underestimation. An acute event in patients with possible refractory angina pectoris may necessitate an emergency angiography, which may not be evaluated according to the routine for stable angina pectoris, as emergency angiographies are rarely presented at the revascularisation conferences in the participating institutions. In addition, patients may have been accepted for revascularisation at the conference, but were in spite of this rejected later. On the other hand, the surgical and anaesthesiological management in relation to revascularisation procedures has improved since the mid-nineties, when one of the earlier estimations was made.[40] Hence, patients previously considered inappropriate for revascularisation, such as elderly patients, may now be available for revascularisation today.[17,94] This development of the techniques involved in revascularisation has probably shifted the boundary between refractory and non-refractory angina pectoris. In addition, during the last few years, the number of angiographies due to stable angina pectoris has been decreasing in Sweden.[4,5] Instead, an increasing number of angiographies are preformed on the indication of unstable angina pectoris. Hence, the change in

the clinical management of angina pectoris is a contributing factor to the lower frequency of refractory angina pectoris reported in Paper I.

According to the results of the study in Paper I, a considerable number of patients seem to suffer from refractory angina pectoris, approximately 2.5-3 persons per 100 000 inhabitants per year. This would correspond to approximately 250 patients per year in Sweden. The refractory patients comprised 1% of all patients undergoing angiography, including angiographies for emergency reasons, at the participating centres.

There are probably patients suffering from disabling angina pectoris who are not referred for angiography at all, because of advanced age and/or concurrent diseases. According to clinical experience, patients suffering from obstructive pulmonary disease, renal failure and severe congestive heart failure may be found in this group. For some of these patients, the angiography itself may pose a risk of complications. These patients might suffer from refractory angina pectoris, but the diagnosis cannot be established as verification of CAD on a recent angiogram is not possible. Nevertheless, this patient group may be in need of additional symptom-relieving treatment modalities.

6.2 Characteristics of patients with refractory angina pectoris

The patients with refractory angina pectoris seemed to have more pronounced cardiac disease as well as CAD, compared with the patients who were accepted for revascularisation. A considerable part, 54%, of the refractory patients had previously undergone CABG. When the extent of CAD was adjusted for previous CABG, there were no differences between the refractory angina patients and the patients accepted for revascularisation. Hence, patients with refractory angina pectoris have CAD which is as severe, or even more severe, than the patients accepted for revascularisation. In addition, the patients in the revascularisation group were not representative of the "ordinary" population undergoing revascularisation, which is generally younger and have less pronounced CAD.

Even though the refractory group in Paper I had advanced CAD – 59% had three-vessel disease and 54% previous CABG - patients accepted for SCS treatment due to refractory angina seem to have even more severe CAD, according to previous studies. In populations of patients with refractory angina pectoris treated with SCS, 70-80% have three-vessel disease and 60-70% of the patients have previously undergone CABG procedure.[65,206] Hence, patients who are referred for treatment with SCS seem to have even more severe CAD than the refractory patients identified after referral for coronary angiography. This might be secondary to the fact that the more progressive disease the disease of a patient, the greater the readiness to refer the patients for additional treatment.

The reasons for rejection for revascularisation have previously not been systematically characterised. According to clinical experience unsuitable coronary anatomy, impaired LVEF and extracardiac diseases, such as obstructive pulmonary disease and renal failure, are the main reasons for rejection for revascularisation There were more patients with impaired LVEF, insulin-treated diabetes and renal dysfunction in the refractory group than in the revascularisation group, but there was no difference between the groups with regard to obstructive pulmonary disease or cerebrovascular disease.

According to the study in Paper I the main reason for rejection was unsuitable coronary anatomy. In patients who had previously undergone CABG the main contributing factor was a potential risk of damaging pre-existing grafts and in patients who had not had previous surgery,

extracardiac disease was the main contribution factor. The anatomy was considered unsuitable due to multiple and peripheral stenoses and due to the localisation of the stenosis. This was confirmed by the scrutiny of the coronary angiograms, where the patients in the refractory group had a higher stenosis score as well as higher peripheral stenosis score than the revascularisation group.

However, impaired LVEF does not seem to be a major cause of rejection. This might be explained by that the patients with the most impaired LVEF not being referred for coronary angiography at all. This may also be a possible explanation of the fact that few patients were diagnosed with obstructive pulmonary disease in the refractory group.

According to the definition of refractory angina pectoris, presence of CAD is mandatory for the diagnosis.[135] In the study in Paper I, patients were considered to have CAD if they had non-significant or significant diameter stenosis in the epicardial vessels according to the medical records. There is an ongoing debate regarding about what extent of atherosclerosis in the coronary vessels that can be considered "normal" for age and gender and what should be considered CAD. In the present study, patients with non-significant stenosis were considered to suffer from CAD, as interobserver variability is known to be present and it has been shown that the maximum coronary flow may be affected by a constriction as small as 30%.[93,221]

Previous CABG seems to be a factor that is crucial for whether or not further revascularisation is possible in patients with refractory angina pectoris. In approximately 40% of the patients, a potential risk of damaging pre-existing grafts, which may be functioning in some parts but occluded in other parts, is a contributing factor or the main reason why further revascularisation is considered inappropriate.

6.3 Management of refractory angina pectoris

In Paper I a majority of the patients received anti-anginal pharmacological treatment in the form of beta-blockers and nitrates. Only 26% of the patients in the REFRACT group were treated with calcium antagonists. The additional effect of a calcium antagonist to patients already medicated with beta-blockers has been demonstrated in exercise studies.[88,123] Furthermore, the results from the ACTION study indicate that addition of calcium antagonists to conventional symptomatic treatment of angina pectoris may have long-term beneficial effects in terms of a reduction of the need for coronary angiographies and interventions.[166] However, more studies are needed to confirm the beneficial effects of adding calcium antagonists to beta-blockers. Many patients do not tolerate triple therapy with beta-blockers, nitrates and calcium antagonists due to side effects. Nevertheless, calcium antagonists are an alternative for patients who do not tolerate beta-blockers.[83,91,98]Sixty-eight percent of all the patients were on lipid-lowering therapy, which is similar to the usage of lipid-lowering treatment in a population of patients with stable angina pectoris and that of a post-CABG population.[37,166] However, this might be below optimum, considering the suggestion of the beneficial prognostic effect of statins. ACE inhibitors are not recommended to date in the treatment of refractory angina pectoris. Considering the frequency of heart failure and insulin-treated diabetes in the patients with refractory angina pectoris, there are probably subgroups of patients with refractory angina pectoris who might benefit from treatment with ACE inhibitors.

Before referring a patient with stable angina pectoris for coronary angiography, optimisation of medication should be the first step, as coronary angiography and revascularisation procedures involve a certain risk of complications. In a previous study by Nägele et al. it was demonstrated that in 50% of patients with refractory angina pectoris partial symptom relief can be obtained by

optimisation of the pharmacological treatment.[154] However, that patient group's pharmacological treatment was not as optimised as that given to patients suffering from refractory angina pectoris presented in Paper I.

The results of the study in Paper I indicated that there may be additional possibilities for optimisation of the pharmacological therapy, in both in the group of patients with refractory angina pectoris and to patients accepted for revascularisation.

It is also of importance to establish myocardial ischaemia as the cause of chest pain before referring the patient for a coronary angiography. In the study in Paper I, approximately 40% of all the patients had no any verified myocardial ischaemia on stress tests before being referred for coronary angiography, which may be considered quite remarkable. The patients were probably referred for a coronary angiography based on a history of known CAD and/or previous evidence of myocardial ischaemia. Nevertheless, some of the patients, in both the refractory and the revascularisation group, may have had chest pain of other origin, such as gastro-oesophageal disorders, which may be difficult to distinguish from patients with chest pain secondary to myocardial ischaemia.[33,34,70] Even though the patients have known CAD or previously demonstrated myocardial ischaemia, the current chest pain may be due to other causes or the patient may suffer from two diseases that both give rise to chest pain.

Bicycle ergometer/treadmill tests have low sensitivity for different reasons as described in the introduction. Pharmacological stress tests, such as myocardial perfusion scintigraphy or stress echocardiography, may be more suitable for the evaluation of ischaemia in this patient group. Even if these stress tests are more sensitive than exercise tests in this patient group, a negative stress test does not exclude myocardial ischaemia as the cause of the chest pain. Hence, angina pectoris is ultimately a clinical diagnosis.[16,91]

If CAD that is unavailable for further revascularisation is demonstrated on coronary angiography, the patient can be considered to suffer from "verified" refractory angina pectoris. As mentioned above, there is a group of patients who are unable to undergo coronary angiography in order to establish the diagnosis refractory angina pectoris. It would be of clinical benefit if patients with "probable" refractory angina pectoris (not verified by coronary angiography) could be diagnosed on clinical criteria only, in line with the guidelines for the management of stable angina pectoris issued by the ESC and the American College of Cardiology/American Heart Association. There is a need to acknowledge this patients group as the same additional symptomatic treatment modalities available for patients with "verified" refractory angina, might also be used for symptom relief in this patient group.

Until recently, patients with refractory angina pectoris seem to have been disregarded, probably because of a lack of knowledge of additional treatment possibilities. The responsible physician often informs the patient that "nothing more can be done", which is very disheartening for the patient. This situation is most likely to have a negative impact on the patient's psychological well-being.

Several reports concerning additional treatment modalities have been presented in recent decades.[63,120,135,188,203,216] Thus, it is of great importance to identify patients with refractory angina pectoris and patients who might be suffering from refractory angina pectoris. The choice of treatment demands individual evaluation and is dependent on the patient's physical as well as mental condition. According to the report by the ESC joint study group on the treatment of refractory angina pectoris, neuromodulation techniques, TENS and SCS, were recommended as the treatment of choice in refractory angina pectoris.[135] In addition, cardiac rehabilitation in terms of risk factor management, such as smoking cessation and weight reduction is important.

Furthermore, regular physical activity, as an element in the cardiac rehabilitation, may also improve anginal symptoms.[85]

6.4 Prognosis and quality of life in patients with refractory angina pectoris

The prognosis in patients with refractory angina pectoris has so far not been described. In Paper II, patients with refractory angina pectoris were followed up for one year with regard to fatality rate and cause of death. Approximately 10% of the patients in the refractory angina pectoris group died during the follow-up period and the main cause of death was cardiac disease. Compared with other patients group with stable angina, the fatality rate is high.[109,110] However, the fatality rate was comparable those of other populations of patients with refractory angina pectoris treated with SCS or patients with severe angina pectoris and increased surgical risk (the ESBY patients).[65,206]

Both the refractory group and the revascularisation group suffered from severe angina pectoris at the time of the revascularisation conference. After one year of follow-up, the anginal functional class of the patients in the revascularisation group was markedly improved compared with the refractory patients. The improvement in the refractory angina pectoris group may reflect a spontaneous variation in anginal symptoms, and that patients are more likely to be referred for coronary angiography at a time when the symptoms are more pronounced. In addition, 29 of the patients in the refractory group received symptomatic treatment after the revascularisation conference.

The angina symptoms seem to have a great impact on the patients' quality of life with regard to physical function and physical well-being (bodily pain, general health and somatic function) as these dimensions of quality of life were impaired in the refractory group compared with the revascularisation group after one year of follow-up. The relationship between anginal symptoms and quality of life has been demonstrated in, for example, the RITA trial; the more pronounced the angina pectoris, the greater the negative impact on quality of life.[165] In the RITA trial symptom relief also appeared to be related to increased mobility as well as general well-being.

Compared to a normative Swedish population using SF-36, the refractory patients have impaired quality of life in most of the dimensions, except social function and mental health, after one year of follow-up (Fig. 3). The revascularisation group, which obtained adequate symptom relief, presented quality of life scores comparable to those of the normative Swedish population after one year of follow-up.

The dimensions assessing mental health, social and emotional function do not seem to be affected by the severity of the anginal pain in the refractory group. According to studies and clinical experience, this is in contrast with patients with other chronic pain syndromes, such as low back pain, fibromyalgia and whiplash disorders, where the patients' mental as well as physical health is seriously affected.[28,32,133,142,147,163] For example, compared with fibromyalgia patients, the patients in the refractory angina pectoris group seem to have a better quality of life according to the SF-36, especially with regard to bodily pain, social functioning and mental health (Fig. 3).[133,142]

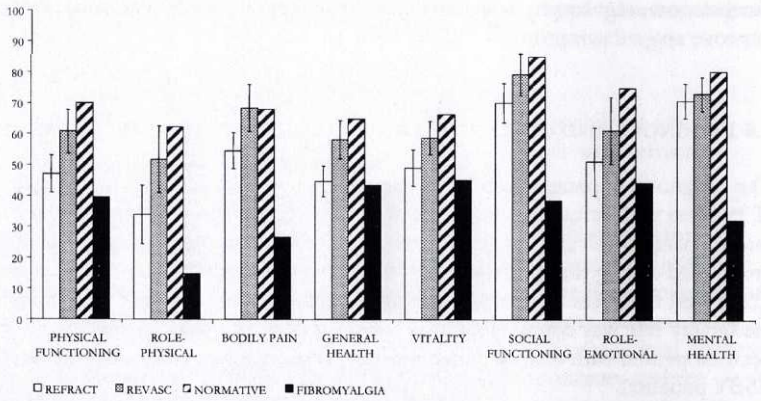


FIGURE 3. Quality of life according to the SF-36 in the REFRACT group and the REVASC group one year after the revascularisation conference, compared with a normative Swedish population and a group of patients with fibromyalgia.[23] Higher values indicate better quality of life.

These results are in accordance with the clinical impression that patients with refractory angina pectoris seem to have better coping strategies compared with patients with long-term pain conditions. This is quitea contradiction, as it would be reasonable to assume that patients suffering from refractory angina pectoris would have poorer quality of life than patients with long-term pain conditions, as the refractory patients' pain – unlike long-term pain - might actually be lethal. A possible rationale for this may be that severe angina pectoris is well defined and more readily accepted by the physicians and by the society in general and thus considered a "high status" diagnosis. In contrast, other chronic pain conditions, such as fibromyalgia and low back pain, are less well defined and often lack objective physical findings. These conditions have considerably "lower status".

As shown in the revascularisation group and in previous studies, symptom relief is of the outmost importance for the quality of life in patients with refractory angina pectoris.[73,165] As mentioned above, neuromodulation techniques, such as TENS or SCS, are the treatment of choice in patients with refractory angina pectoris.[135] The results from the ESBY study indicate that SCS is effective, with regard to symptom relief and improvement in quality of life, in a group of patients with severe angina pectoris, no prognostic benefit from CABG and with an increased surgical risk.[73,140] Thus, patients with "verified" as well as "probable" refractory angina pectoris should be considered for additional treatment modalities aiming at symptom relief and improvement in quality of life.

6.5 When is revascularisation appropriate for symptomatic relief in patients with stable angina pectoris?

According to the results form the ESBY study patients with increased surgical risk undergoing CABG and SCS, have long-lasting symptom relieving effect of the treatment as well as long-lasting improvement in their quality of life.[73,140] The risk of developing complications in connection with revascularisation procedures is not negligible. [16,42,143,173] Redo CABG has an estimated mortality rate of 5-21%.[16,151]

In the ESBY study (Paper III), a considerable number of the CABG patients (n=7) died in connection with the primary intervention and in nine of the eleven patients with focal cerebral ischaemia in the CABG group, the event was related to the surgery (in total 17.6% of the CABG patients). Furthermore, 27.5% of the CABG patients developed neuropsychological deficit after the intervention in terms of astheno-emotional disorder (AED). The patients in the ESBY study, undergoing CABG had a higher cerebrovascular morbidity in terms of stroke and TIA than what

has been reported for patients in other studies.[42,143,173,191,202] However, the frequency of neuropsychological complications in the CABG group was comparable to that reported in other studies.[155,190,194] These patients were considered patients high-risk patients in terms of complications in connection with surgery. Thus, a high morbidity of focal cerebral ischaemia was expected.

In patients without increased surgical risk, in the revascularisation group (Paper II), six patients (4.3%) developed stroke and nine patients (6.5%) suffered serious perioperative and postoperative cardiac complications in the revascularisation group. Hence, neurological complications in association with revascularisation procedures are not negligible in patients without a previously known increased surgical risk. Patients who underwent SCS (Paper III) or additional symptomatic treatment (Paper II), did not develop any cerebral complications in connection with the interventions.

In Paper III, the results indicate that preoperative presence of small artery disease in the brain, i.e. white matter disease (diagnosed by cerebral MRI), might be a predictor of development of neurological (i.e. focal cerebral ischaemia) and neuropsychological complications (i.e. AED) after CABG. However, patients with WMD undergoing SCS did not have an increased risk of developing neurological or neuropsychological complications compared with the CABG group. Thus, in order to assess the risk of cerebral injury, a preoperative cerebral MRI might be of value in patients with increased surgical risk.

A question that was not addressed in Paper III was whether the patients with and without WMD diseases differed with regard to risk factors for developing neurological and neuropsychological complications. There were no differences between the patients with and without WMD with regard to age, gender distribution, presence of clinically significant carotid stenosis, previous CABG or previous AED, but the groups differed with regard to pre-existing cerebrovascular disease (i.e. focal cerebral ischaemia) ($p<0.01$). It is reasonable to assume that patients with previous focal cerebral ischaemia have a more generalised atherosclerotic disease. Hence, these patients may also have an increased risk of developing WMD, as it is a manifestation of atherosclerosis in the small arteries in the brain. However, there were no differences between the SCS and the CABG groups with regard to pre-existing cerebrovascular disease. Thus, the patients with WMD in both the CABG and the SCS groups could be considered to be equally at risk of developing cerebral complications. Nevertheless, more patients with WMD undergoing CABG developed neurological as well as neuropsychological complications compared with the SCS group.

When assessing whether a patient is suitable for undergoing a revascularisation procedure or not, technical feasibility, indication for surgery as well as the risk of developing cerebral complications and the risk of death, should be taken into account. The increased mortality rate in connection with repeat revascularisation in patients who have previously undergone CABG should be considered, as mentioned above.[16,151]

TABLE 4. Risk factors for developing focal cerebral ischemia and AED in the patients with and without WMD before intervention.

	WMD (n=71)	No WMD (n=25)	P value
Age (mean)	69	66	0.24
Gender; female/male (n)	14/57 (20/80%)	4/21 (16/84%)	0.68
Carotid artery stenosis ≥70% (n)	14 (20%)	4 (16%)	0.72
Previous CABG (n)	15 (21%)	8 (32%)	0.27
Pre-existing AED (n)	21 (30%)	4 (16%)	0.18
Pre-existing cerebrovascular disease (n)	19 (27%)	0	<0.01

AED indicates Astheno-Emotional Disorder; CABG, Coronary Artery Bypass Grafting; WMD, White Matter Disease.

Considering the high risk of complications in connection with revascularisation procedures, patients suffering from mild or moderate stable angina pectoris (CCS class 1-2) should not be endangered by undergoing revascularisation procedures for symptomatic relief only. In these patients, symptomatic relief can usually be obtained by optimising the medication.[120] In contrast, patients with severe angina pectoris (CCS class 3-4) might benefit from revascularisation procedures for symptomatic relief. However, if the indication for revascularisation is strictly symptomatic, patients with a high risk of developing complications in connection with the procedure need to be identified. In these patients the potential benefit of symptom relief does not correspond to the risk of developing complications. In Paper III, it was suggested that preoperative cerebral WMD may be a predictor for the development of cerebral complications, in addition to other known risk factors for cerebrovascular lesions. Hence, preoperative cerebral MRI may be a tool for identifying patients with increased of cerebral complications in connection with surgery. If investigations indicate that the patient have a too high risk of complications in connection with a revascularisation procedure, additional symptomatic treatments should be considered as an option.

In patients with severe angina pectoris who are considered inappropriate for further revascularisation (patients with refractory angina pectoris) and in patients with increased surgical risk of developing cerebral complications, additional symptomatic treatment modalities, such as neuromodulation techniques (TENS and SCS) may be a therapeutic alternative.[135,140] These treatment modalities are effective for symptomatic relief of angina pectoris and as the SCS implantation is only a minor surgical procedure, unconnected with development of cerebral complications, SCS is suitable for somatically diseased patients with increased risk surgical risk. Figure 4 suggests a flow-chart for the management of patients with severe angina pectoris.

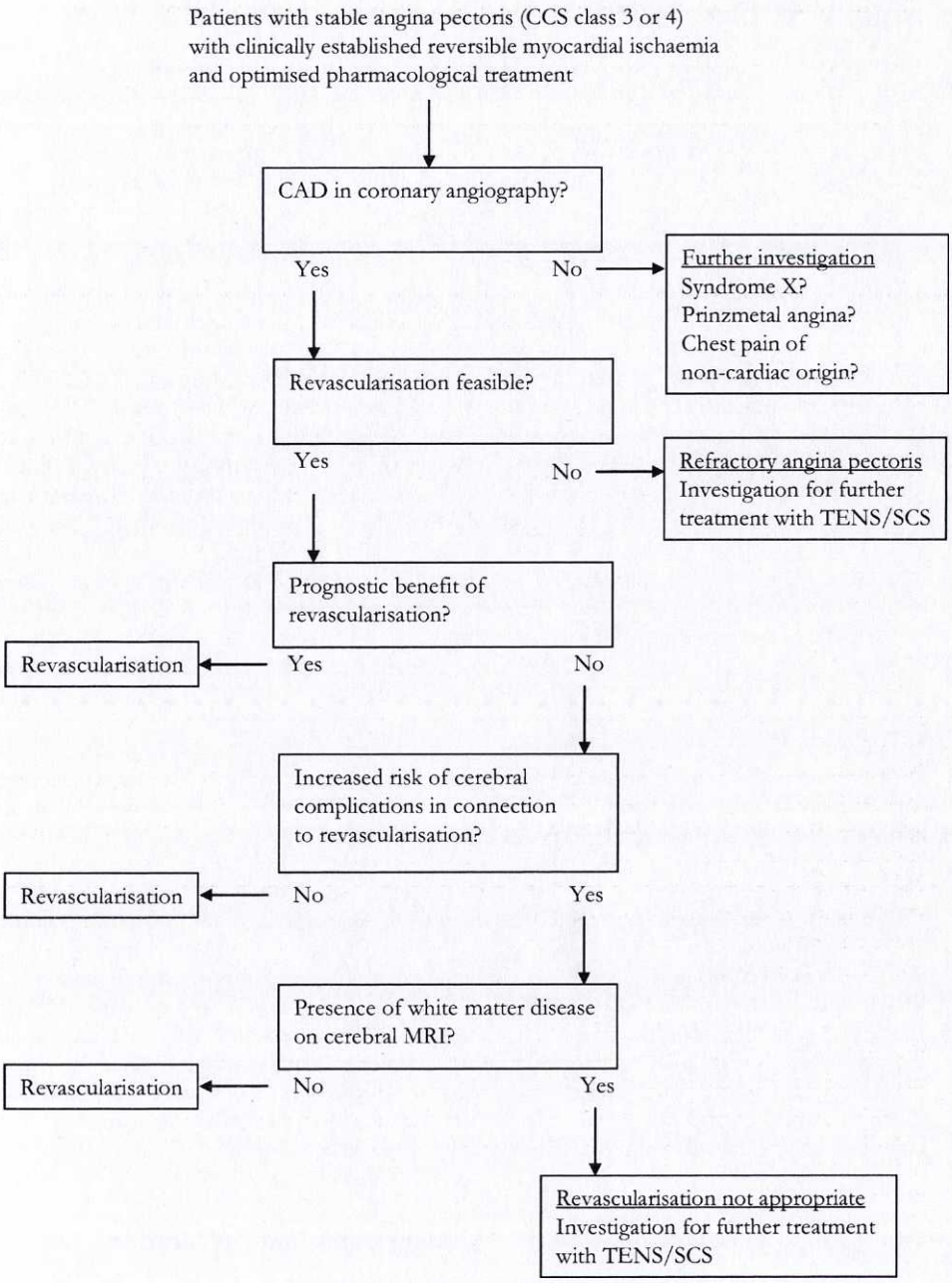


FIGURE 4. A suggestion of a flow-chart for the management of patients with severe angina pectoris.

6.6 SAFETY OF SPINAL CORD STIMULATION IN ANGINA PECTORIS

There have been previous reports regarding the long-term effects and safety of SCS.[65,96,176,183,206] However, most of these studies have drawbacks in terms of being too small, retrospective and/or non-randomised. Further long-term studies regarding the safety of SCS treatment were therefore needed. Despite previous results from the ESBY study, the long-term mortality of SCS in comparison with CABG has previously not been described. Hence, the aim of the study presented in Paper IV was to assess the long-term effects and safety of SCS treatment compared with CABG treatment.

CABG is associated with a certain mortality risk in connection with the intervention, whereas implantation of the SCS device is a minor surgical procedure. This was reflected in the higher mortality rate in the CABG group after six months of follow-up.[140] According to previous results from the ESBY study, and the results presented in Paper IV, the SCS group and the CABG group had comparable mortality after two years of follow-up and after five years of follow-up. On these two follow-up occasions, the total mortality rate of the ESBY patients was 10.7% and 27.9 %.[73] This is a higher mortality rate than that described in other studies of patients with pharmacologically treated angina pectoris.[7,78,213] However, when compared with a Swedish angina population with similar extent of CAD and pharmacological treatment, the mortality rate (4.3% at 12 months and 9.1% at 21 months) was comparable with that of the ESBY study patients.[40] As mentioned above, the high mortality rate was not unexpected, as these patients were considered to have an increased surgical risk due to generalised atherosclerosis and concomitant diseases. In addition, there were no differences between the groups with regard to the number of deaths due to cardiac or cerebrovascular disease after two years of follow-up. Furthermore, when compared to patients with risk factors for CABG randomised to PCI or CABG, the three-year survival in both these groups was comparable to that of the ESBY study patients.[73,150]

Data from the ESBY study indicate that SCS is as safe as CABG in the long-term perspective, with regard to mortality and causes of death. However, CABG seems to be associated with an increased mortality in the short-term perspective.

The long-term safety of the SCS treatment was also evaluated in terms of complications in connection with the treatment (Paper IV). The most feared complication of SCS is intraspinal infection and subsequent serious neurological sequelae. There were no cases of intra spinal infection in the ESBY study. In addition, there has been no case of intraspinal infection in Göteborg in any of the over 800 patients implanted since 1985, when SCS for angina pectoris was introduced. One patient, out of the 57 patients who were implanted with a SCS device during the two-year follow-up period, developed a postoperative subcutaneous infection in the pulse generator skin pocket. As the SCS system is fully implanted, without percutaneous connections, the risk of late occurring infections is small. Other centres report a similar frequency of complications in connection with SCS treatment for angina.[20,96,176]

6.7 LONG-TERM EFFECTS OF SPINAL CORD STIMULATION IN ANGINA PECTORIS

After two years of follow-up, more than 80% of the patients implanted with a SCS device experienced symptomatic improvement in terms of reduced frequency and severity of angina attacks. The success rate of the SCS treatment in the ESBY patients is comparable to results from other studies.[65,217] Hence, SCS seems to be an effective treatment modality also in the long-term perspective, which may also be reflected by the long-lasting improvement in quality of life.[73]

Several studies have demonstrated that SCS reducess hospitalisation due to cardiac disease after implantation and that SCS in refractory angina pectoris is more cost-effective than pharmacological treatment in terms of the number of hospital days and/or hospital admissions.[31,148,153,217] According to a study by Yu et al., the cost of SCS was balanced after 16 months, including costs of hospitalisation, additional investigations and device related costs. However, SCS has not previously been compared with invasive procedures for symptomatic treatment of severe angina pectoris.

According to Paper IV, the hospitalisation rate in the SCS group and CABG group was similar. The CABG group had more hospital days due to cardiac events, but there were no differences between the groups with regard to the number of cardiac events. However, the CABG group needed twice as many days of hospital care in connection with the primary intervention as the SCS group (11 days compared to 5 days). At present, the average length of stay in hospital in connection with SCS implantation is approximately 2.5 days, compared with 9 days for CABG surgery. Hence, the long-term morbidity is comparable in SCS- treated patients and in patients with increased surgical risk surgical risk undergoing CABG.

In addition, SCS was shown to be less expensive than CABG, not only with regard to the primary intervention cots, but also with regard to the total cost during the two-year follow-up period. Previous studies have shown that the total health-service costs over five years are similar for patients undergoing CABG and patients undergoing PCI.[105] However, there are no studies comparing the health costs of PCI and SCS. However, "the cost of impaired quality of life" or "the cost of suffering" caused by a stroke or AED is not measurable. According to Paper III, by undergoing a preoperative MRI and assessing the presence of WMD, the risk of cerebral complications may be predicted before undergoing CABG is carred out on high-risk patients. Thus, theoretically, the relatively low cost of a cerebral MRI may prevent suffering for the patient as well as increased health care costs for society.

Thus, since the cost of symptom relief appears to be similar for revascularisation procedures and SCS in patients with severe angina pectoris, it is of great importance to evaluate carefully which method of symptom relief might be the most beneficial for the patient, in terms of technical feasibility, risk of cerebral complications and death. Symptom relief seems to be crucial for the quality of life of patients with severe angina pectoris and can successfully be obtained either by conventional revascularisation procedures or with SCS.

7. Conclusions

- A significant number of patients seem to suffer from refractory angina pectoris. This patient group has advanced cardiac disease as well coronary artery disease. Even though the majority of patients have coronary artery disease, some patients need further evaluation to confirm current myocardial ischaemia. Furthermore, there are probably a number of patients who would benefit from optimised medication. The refractory patients appear to suffer from severe cardiac disease as well as severe coronary artery disase.

- The main reason why the refractory patients are considered inappropriate for further revascularisation is unsuitable coronary anatomy. In patients with prior CABG, the main contributing factor is a potential risk of damaging pre-existing grafts and in patients who not have undergone any previous CABG, extracardiac disease is the main contributing factor for rejection.

- Patients with refractory angina pectoris have a high fatality rate and impaired quality of life. In contrast, cerebrovascular morbidity seems not to be pronounced. The anginal pain seems to limit their physical activity and impair their physical well-being, while social function, emotional function and mental health seem to be unaffected. This is in contrast with patients with chronic pain syndromes, whose quality of life is severely impaired physically as well as mentally and socially. This observation is in accordance with the clinical impression, that patients with refractory angina pectoris seem to have better cooping strategies compared with patients with long-term pain conditions.

- Preoperative presence of white matter disease, identified by cerebral MRI, seems to be a predictor of cerebral complications after CABG. Hence, preoperative cerebral MRI might be used as a screening tool in patients with increased surgical risk and no prognostic benefit from CABG, in order to choose the most appropriate symptomatic treatment modality.

- SCS, one of the treatments of choice in refractory angina pectoris, is concluded to be a safe treatment modality in terms of cerebral complications in connection with the implantation, long-term morbidity, mortality and frequency of treatment complications.

- Long-term treatment with SCS is concluded to be effective in terms of symptom relief. In addition, SCS is concluded to be less expensive than CABG in patients with increased surgical risk and no prognostic benefit from surgery.

8. CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

This thesis demonstrates that there seems to be a considerable number of patients who suffer from refractory angina pectoris and that there is a need to acknowledge this patient group. Before confirming the diagnosis the application of symptomatic treatment, an attempt should be made to optimise the medication and myocardial ischaemia should be confirmed. It is of the outmost importance that this patient group is identified and subsequently treated with additional symptom-relieving treatment modalities, irrespective of whether the patient suffers from "verified" or "probable" refractory angina pectoris. Refractory angina pectoris is an important issue for cardiologists as well as for specialists in pain medicine, as many of the available treatment modalities for symptomatic relief are frequently used in pain medicine.

Furthermore, the guidelines concerning refractory angina pectoris need to be regularly updated, as reports regarding research on additional treatment modalities providing new information on the efficiency, safety and side effects of these methods, are constantly published. In addition, further studies regarding the long-term prognosis of patients with refractory angina pectoris, as well as randomised treatment studies are needed in order to improve the understanding and treatment of this condition.

Even when matched for age and gender, the refractory patients had more severe coronary artery disease than patients accepted for revascularisation. Studies regarding the genetical characteristics of this patient groups would be of value in order to investigate whether patients with refractory angina pectoris might have a genetic predisposition for coronary artery disease.

In patients with severe angina pectoris, symptom relief seems to be of great importance with regard to quality of life. In patients with refractory angina pectoris, the quality of life seems to be impaired with regard to physical function and physical well-being, but not with regard to mental health and social function. This is in contrast with patients suffering from chronic pain conditions, whose quality of life is impaired with regard both to physical function as well as mental health. Thus, patients with refractory angina pectoris seem to have better coping strategies for managing their pain. Studies to further characterise and compare these patients groups would be of value.

Spinal cord stimulation can be considered to be a safe and effective therapeutic option for patients with refractory angina pectoris as well as patients with severe angina pectoris and increased surgical risk. However, approximately 20% of patients treated with neuromodulation do not receive adequate symptom relief. Thus, further treatment strategies for patients with refractory angina pectoris are needed.

When assessing the risk of cerebral complications, it can be concluded that the presence of white matter disease on cerebral magnetic resonance imaging may be a predictor of a risk of cerebral injury after CABG.

This thesis underlines the importance of carefully evaluatating which therapeutic symptom-relieving method may be the most beneficial for patients with severe angina pectoris who do not have a prognostic benefit from revascularisation.

Finally, further studies are needed in order to fully elucidate the mechanisms of SCS in angina pectoris.

9. ACKNOWLEDGEMENTS

There are a lot of people who have helped me, in various ways, to complete this thesis. In particular I wish to express my gratitude to:

Clas Mannheimer, my mentor, for friendship, inspiration and enthusiasm, guidance in the academic jungle, for making me perform my very best and for many laughs.

Caterina Finizia and Ulla Strandman, director of studies and staff secretary respectively for the interns at Sahlgrenska University Hospital, for making research possible during my internship at Sahlgrenska University Hospital, for encouragement and continuous efforts to improve the research climate.

Tore Eliasson, supervisor and co-author, for guidance, stimulating discussions and for being "the linguistic oracle".

Christian Blomstrand, supervisor and co-author, for expert advice in the neurological field, much advice and encouragement.

Olof Ekre, supervisor and co-author, for much practical advice, inspiration and making me interested in this field of research in the first place.

Lars Grip, co-author, for expert guidance regarding coronary angiographies, stimulating discussions, constructive criticism and most of all, "for finding the white Opel".

Henrik Norssell, co-author, for advice and encouragement.

Mats Börjesson, co-author, for inspiration and encouragement.

Peter Währborg, co-author, for teaching me quality of life.

Dag Thelle, co-author, for expert guidance in the epidemiological field.

Per Albertsson, co-author, for introducing me to coronary angiography and assisting in "finding the white Opel".

Sven Ekholm and Christer Jensen, co-authors, for fruitful collaboration and for introducing me to magnetic resonace imaging and white matter disease.

Ulf Norrsell, co-author, for expert advice and guidance in the field of neuropsychology.

Michael Nilsson, co-author, for expert advice in economical issuses.

Lillian Alnäs, Marita Snällman, Gunilla Norman for collaboration, zealous work and for pleasant journeys in Western Sweden.

Annika Odell, for enthusiasm and assistance in retrieving coronary angiograms and medical records.

Thomas Karlsson, for expert statistical advice and many instructive discussions.

Margareta Johansson, for skilful secretarial assistance.

Tage Nilsson, for providing instant information from the SCAAR and for stimulating discussions.

Agneta Ståhle, for constructive criticism and encouragement.

Lars-Erik Dyrehag, for introducing me to the team at the Multidisciplinary Pain Centre.

Johan Herlitz, Karin Manhem and Karl Swedberg, for constructve criticism and much good advice in connection with my pre-dispuation.

All my colleagues at the Multidiscplinary Pain Centre: Tommy Berglund, Tobias Carlson, Karin Dahlén-Wetter, Ann-Charlotte Eliasson, Marie Escar, Mahnaz Gholipor, Eva-Lotte Karlsson Lena Mattsson, Kerstin Moberg, Yakoub Noubhany Tomas Schultz and Reza Tajy for friendship and encouragement..

All the patients who have participated in the different studies.

My friends from "The summer Research School in Biomedicine at Karloinska Institutet 1997", especially Linda Holmbjer, for inspiration and many laughs.

My fellow researchers and colleagues in "the working group for research during internship at Sahlgrenska University Hospital" for practical advice and encouragement..

My close friends for all support and encouragement.

My siblings, Juni and Hampus, for always being there for me and making me laugh.

My parents, for "helping me to do it myself", endless support and for the design of my thesis.

10. REFERENCES

1. The Centre for Epidemiology at the Swedish National Board of Health and Welfare. The Cause of Death Register. Stockholm 2004; http://www.sos.se/epc.
2. The Centre for Epidemiology at the Swedish National Board of Health and Welfare. The Hospital Discharge Register. Stockholm 2003; http://www.sos.se/epc.
3. Nationella riktlinjer för kranskärlssjukvård. Socialstyrelsen (the Swedish National Board of Health and Welfare), Stockholm 1998. http://www.sos.se/fulltext/9800-063/9800-063.htm.
4. SCAAR (1999) Swedish Coronary Angiography and Angioplasty Registry. Årsrapport 1999. Socialstyrelsen (the Swedish National Board of Health and Welfare), MARS. http://www.sos.se/mars/kva053/kva053.htm.
5. SCAAR (2003) Swedish Coronary Angiography and Angioplasty Registry. Årsrapport 2003. Socialstyrelsen (the Swedish National Board of Health and Welfare), MARS. http://www.sos.se/mars/kva053/kva053.htm.
6. Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. N Engl J Med. 1984;311:1333-9.
7. Myocardial infarction and mortality in the coronary artery surgery study (CASS) randomized trial. N Engl J Med. 1984;310:750-8.
8. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. N Engl J Med. 1985;312:932-6.
9. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomized trials in post infarction patients. The Beta-Blocker Pooling Project Research Group. Eur Heart J. 1988;9:8-16.
10. Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke. 1989;20:1407-31.
11. Guidelines and indications for coronary artery bypass graft surgery. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Coronary Artery Bypass Graft Surgery). J Am Coll Cardiol. 1991;17:543-89.
12. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. Bmj. 1994;308:81-106.
13. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383-9.
14. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants. Lancet. 1995;346:1179-84.
15. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease. A multicenter randomized trial. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Jama. 1997;277:715-21.

16. Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. Eur Heart J. 1997;18:394-413.

17. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. Lancet. 2001;358:951-7.

18. Altman DG. Practical Statistics for Medical Research. London: Chapman & Hall; 1991.

19. Altmann DB, Racz M, Battleman DS, Bergman G, Spokojny A, Hannan EL, Sanborn TA. Reduction in angioplasty complications after the introduction of coronary stents: results from a consecutive series of 2242 patients. Am Heart J. 1996;132:503-7.

20. Andersen C. Complications in spinal cord stimulation for treatment of angina pectoris. Differences in unipolar and multipolar percutaneous inserted electrodes. Acta Cardiol. 1997;52:325-33.

21. Andersen C. Does heart rate variability change in angina pectoris patients treated with spinal cord stimulation? Cardiology. 1998;89:14-8.

22. Andersen C, Hole P, Oxhoj H. Does pain relief with spinal cord stimulation for angina conceal myocardial infarction? Br Heart J. 1994;71:419-21.

23. Andrews TC, Raby K, Barry J, Naimi CL, Allred E, Ganz P, Selwyn AP. Effect of cholesterol reduction on myocardial ischemia in patients with coronary disease. Circulation. 1997;95:324-8.

24. Armour JA, Linderoth B, Arora RC, DeJongste MJ, Ardell JL, Kingma JG, Jr., Hill M, Foreman RD. Long-term modulation of the intrinsic cardiac nervous system by spinal cord neurons in normal and ischaemic hearts. Auton Neurosci. 2002;95:71-9.

25. Augustinsson LE, Carlsson CA, Holm J, Jivegard L. Epidural electrical stimulation in severe limb ischemia. Pain relief, increased blood flow, and a possible limb-saving effect. Ann Surg. 1985;202:104-10.

26. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation. 1975;51:5-40.

27. Bagger JP, Hall RJ, Koutroulis G, Nihoyannopoulos P. Effect of enhanced external counterpulsation on dobutamine-induced left ventricular wall motion abnormalities in severe chronic angina pectoris. Am J Cardiol. 2004;93:465-7.

28. Bergman S, Jacobsson LT, Herrstrom P, Petersson IF. Health status as measured by SF-36 reflects changes and predicts outcome in chronic musculoskeletal pain: a 3-year follow up study in the general population. Pain. 2004;108:115-23.

29. Bertrand ME, Lablanche JM, Bauters C, Leroy F, Mac Fadden E. Discordant results of visual and quantitative estimates of stenosis severity before and after coronary angioplasty. Cathet Cardiovasc Diagn. 1993;28:1-6.

30. Bishop AH, Samady H. Fractional flow reserve: critical review of an important physiologic adjunct to angiography. Am Heart J. 2004;147:792-802.

31. Bladt Rasmussen M, Andersen C, Andersen P, Frandsen F. Cost-utility analyse af elektrisk rygmarvsstimulation til behandling af angina pectoris. Ugeskr Laeger. 1992;154:1180-1184.

32. Bono G, Antonaci F, Ghirmai S, D'Angelo F, Berger M, Nappi G. Whiplash injuries: clinical picture and diagnostic work-up. Clin Exp Rheumatol. 2000;18:S23-8.

33. Börjesson M, Albertsson P, Dellborg M, Eliasson T, Pilhall M, Rolny P, Mannheimer C. Esophageal dysfunction in syndrome X. Am J Cardiol. 1998;82:1187-91.

34. Börjesson M, Dellborg M. "Before intervention - is the pain really cardiac?" Scand Cardiovasc J. 2003;37:124-7.

35. Börjesson M, Eriksson P, Dellborg M, Eliasson T, Mannheimer C. Transcutaneous electrical nerve stimulation in unstable angina pectoris. Coron Artery Dis. 1997;8:543-50.

36. Borkon AM, Muehlebach GF, House J, Marso SP, Spertus JA. A comparison of the recovery of health status after percutaneous coronary intervention and coronary artery bypass. Ann Thorac Surg. 2002;74:1526-30; discussion 1530.

37. Bradshaw PJ, Jamrozik K, Gilfillan I, Thompson PL. Preventing recurrent events long term after coronary artery bypass graft: suboptimal use of medications in a population study. Am Heart J. 2004;147:1047-53.

38. Braunwald E. Unstable angina. A classification. Circulation. 1989;80:410-4.

39. Braunwald E. HEART DISEASE: A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia: W.B. Saunders Company; 1997.

40. Brorsson B, Persson H, Landelius P, Werkö L. Smärtor i bröstet: Operation, ballongvidgning, medicinsk behandling. Stockholm, Sweden: Statens beredning för utvärderning av medicinsk metodik; 1998. Report No.: 140.

41. Broseta J, Barbera J, de Vera JA, Barcia-Salorio JL, Garcia-March G, Gonzalez-Darder J, Rovaina F, Joanes V. Spinal cord stimulation in peripheral arterial disease. A cooperative study. J Neurosurg. 1986;64:71-80.

42. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, Metz S, Falk V, Mohr FW. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg. 2003;75:472-8.

43. Burchiel KJ, Anderson VC, Brown FD, Fessler RG, Friedman WA, Pelofsky S, Weiner RL, Oakley J, Shatin D. Prospective, multicenter study of spinal cord stimulation for relief of chronic back and extremity pain. Spine. 1996;21:2786-94.

44. Caffrey JL, Gaugl JF, Jones CE. Local endogenous opiate activity in dog myocardium: receptor blockade with naloxone. Am J Physiol. 1985;248:H382-8.

45. Campeau L. Letter: Grading of angina pectoris. Circulation. 1976;54:522-3.

46. Carlsson GE, Moller A, Blomstrand C. Consequences of mild stroke in persons <75 years -- a 1-year follow-up. Cerebrovasc Dis. 2003;16:383-8.

47. Cervero F. Sensory innervation of the viscera: peripheral basis of visceral pain. Physiol Rev. 1994;74:95-138.

48. Charlier L, Dutrannois J, Kaufman L. The SF-36 questionnaire: a convenient way to assess quality of life in angina pectoris patients. Acta Cardiol. 1997;52:247-60.

49. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Cardioesophageal reflex: a mechanism for "linked angina" in patients with angiographically proven coronary artery disease. J Am Coll Cardiol. 1996;27:1621-8.

50. Chauhan A, Mullins PA, Thuraisingham SI, Taylor G, Petch MC, Schofield PM. Effect of transcutaneous electrical nerve stimulation on coronary blood flow. Circulation. 1994;89:694-702.

51. Chester M, Hammond C, Leach A. Long-term benefits of stellate ganglion block in severe chronic refractory angina. Pain. 2000;87:103-5.

52. Chui H. Dementia due to subcortical ischemic vascular disease. Clin Cornerstone. 2001;3:40-51.

53. Conacher ID, Doig JC, Rivas L, Pridie AK. Intercostal neuralgia associated with internal mammary artery grafting. Anaesthesia. 1993;48:1070-1.

54. Conti CR. Updated pathophysiologic concepts in unstable coronary artery disease. Am Heart J. 2001;141:S12-4.

55. Cook AW, Oygar A, Baggenstos P, Pacheco S, Kleriga E. Vascular disease of extremities. Electric stimulation of spinal cord and posterior roots. N Y State J Med. 1976;76:366-8.

56. Crea F, Gaspardone A. New look to an old symptom: angina pectoris. Circulation. 1997;96:3766-73.

57. Crea F, Lanza GA. Angina pectoris and normal coronary arteries: cardiac syndrome X. Heart. 2004;90:457-63.

58. de Bono D. Complications of diagnostic cardiac catheterisation: results from 34,041 patients in the United Kingdom confidential enquiry into cardiac catheter complications. The Joint Audit Committee of the British Cardiac Society and Royal College of Physicians of London. Br Heart J. 1993;70:297-300.

59. De Landsheere C, Mannheimer C, Habets A, Guillaume M, Bourgeois I, Augustinsson LE, Eliasson T, Lamotte D, Kulbertus H, Rigo P. Effect of spinal cord stimulation on regional myocardial perfusion assessed by positron emission tomography. Am J Cardiol. 1992;69:1143-9.

60. Deanfield JE, Maseri A, Selwyn AP, Ribeiro P, Chierchia S, Krikler S, Morgan M. Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet. 1983;2:753-8.

61. DeJongste MJ, Haaksma J, Hautvast RW, Hillege HL, Meyler PW, Staal MJ, Sanderson JE, Lie KI. Effects of spinal cord stimulation on myocardial ischaemia during daily life in patients with severe coronary artery disease. A prospective ambulatory electrocardiographic study. Br Heart J. 1994;71:413-8.

62. DeJongste MJ, Hautvast RW, Hillege HL, Lie KI. Efficacy of spinal cord stimulation as adjuvant therapy for intractable angina pectoris: a prospective, randomized clinical study. Working Group on Neurocardiology. J Am Coll Cardiol. 1994;23:1592-7.

63. DeJongste MJ, Tio RA, Foreman RD. Chronic therapeutically refractory angina pectoris. Heart. 2004;90:225-30.

64. Dempster M, Donnelly M. Measuring the health related quality of life of people with ischaemic heart disease. Heart. 2000;83:641-4.

65. Di Pede F, Lanza GA, Zuin G, Alfieri O, Rapati M, Romano M, Circo A, Cardano P, Bellocci F, Santini M, Maseri A. Immediate and long-term clinical outcome after spinal cord stimulation for refractory stable angina pectoris(*). Am J Cardiol. 2003;91:951-5.

66. Dougherty CM, Dewhurst T, Nichol WP, Spertus J. Comparison of three quality of life instruments in stable angina pectoris: Seattle Angina Questionnaire, Short Form Health

Survey (SF-36), and Quality of Life Index-Cardiac Version III. J Clin Epidemiol. 1998;51:569-75.

67. Ector H, Rickards AF, Kappenberger L, Linde C, Vardas P, Oto A, Santini M, Sutton R. The World Survey of Cardiac Pacing and Implantable Cardioverter Defibrillators: calendar year 1997--Europe. Pacing Clin Electrophysiol. 2001;24:863-8.

68. Egashira K, Araki H, Takeshita A, Nakamura M. Silent myocardial ischemia in patients with variant angina. Jpn Circ J. 1989;53:1452-7.

69. Egashira K, Hirooka Y, Kai H, Sugimachi M, Suzuki S, Inou T, Takeshita A. Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. Circulation. 1994;89:2519-24.

70. Eisenberg E, Pultorak Y, Pud D, Bar-El Y. Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). Pain. 2001;92:11-7.

71. Ekre O. Severe Angina Pectoris and Spinal Cord Stimulation. Long-term effects and safety aspects. Göteborg, Sweden: Thesis Göteborg University, 2003.

72. Ekre O, Borjesson M, Edvardsson N, Eliasson T, Mannheimer C. Feasibility of spinal cord stimulation in angina pectoris in patients with chronic pacemaker treatment for cardiac arrhythmias. Pacing Clin Electrophysiol. 2003;26:2134-41.

73. Ekre O, Eliasson T, Norrsell H, Wahrborg P, Mannheimer C. Long-term effects of spinal cord stimulation and coronary artery bypass grafting on quality of life and survival in the ESBY study. Eur Heart J. 2002;23:1938-45.

74. Eliasson T, Augustinsson LE, Mannheimer C. Spinal cord stimulation in severe angina pectoris -presentation of current studies, indications and clinical experience. Pain. 1996;65:169-79.

75. Eliasson T, Jern S, Augustinsson LE, Mannheimer C. Safety aspects of spinal cord stimulation in severe angina pectoris. Coron Artery Dis. 1994;5:845-50.

76. Eliasson T, Mannheimer C, Waagstein F, Andersson B, Bergh CH, Augustinsson LE, Hedner T, Larson G. Myocardial turnover of endogenous opioids and calcitonin-gene-related peptide in the human heart and the effects of spinal cord stimulation on pacing-induced angina pectoris. Cardiology. 1998;89:170-7.

77. Emanuelsson H, Mannheimer C, Waagstein F, Wilhelmsson C. Catecholamine metabolism during pacing-induced angina pectoris and the effect of transcutaneous electrical nerve stimulation. Am Heart J. 1987;114:1360-6.

78. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR, Jr., Chaitman BR, Kaiser GC, Alderman E, Killip T, 3rd. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation. 1994;90:2645-57.

79. Fabian E, Varga A, Picano E, Vajo Z, Ronaszeki A, Csanady M. Effect of simvastatin on endothelial function in cardiac syndrome X patients. Am J Cardiol. 2004;94:652-5.

80. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol. 1987;149:351-6.

81. Fazekas F, Kleinert R, Offenbacher H, Payer F, Schmidt R, Kleinert G, Radner H, Lechner H. The morphologic correlate of incidental punctate white matter hyperintensities on MR images. AJNR Am J Neuroradiol. 1991;12:915-21.

82. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Radner H, Lechner H. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology. 1993;43:1683-9.

83. Fihn SD, Williams SV, Daley J, Gibbons RJ. Guidelines for the management of patients with chronic stable angina: treatment. Ann Intern Med. 2001;135:616-32.

84. Fitzgerald CP, Lawson WE, Hui JC, Kennard ED. Enhanced external counterpulsation as initial revascularization treatment for angina refractory to medical therapy. Cardiology. 2003;100:129-35.

85. Fletcher GF, Balady G, Blair SN, Blumenthal J, Caspersen C, Chaitman B, Epstein S, Sivarajan Froelicher ES, Froelicher VF, Pina IL, Pollock ML. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation. 1996;94:857-62.

86. Foreman RD, DeJongste MJ, Linderoth B. Integrative Control of Cardiac Function by Cervical and Thoracic Spinal Neurons. In: Armour JA, Ardell JL, eds. Basic and Clinical Neurocardiology. New York: Oxford Univeristy Press; 2004.

87. Foreman RD, Linderoth B, Ardell JL, Barron KW, Chandler MJ, Hull SS, Jr., TerHorst GJ, DeJongste MJ, Armour JA. Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. Cardiovasc Res. 2000;47:367-75.

88. Fox KM, Mulcahy D, Findlay I, Ford I, Dargie HJ. The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. The TIBET Study Group. Eur Heart J. 1996;17:96-103.

89. Gherardini G, Lundeberg T, Cui JG, Eriksson SV, Trubek S, Linderoth B. Spinal cord stimulation improves survival in ischemic skin flaps: an experimental study of the possible mediation by calcitonin gene-related peptide. Plast Reconstr Surg. 1999;103:1221-8.

90. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB, Jr., Fihn SD, Fraker TD, Jr., Gardin JM, O'Rourke RA, Pasternak RC, Williams SV. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina--summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). J Am Coll Cardiol. 2003;41:159-68.

91. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, Grunwald MA, Levy D, Lytle BW, O'Rourke RA, Schafer WP, Williams SV. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). Circulation. 1999;99:2829-48.

92. Goto T, Baba T, Honma K, Shibata Y, Arai Y, Uozumi H, Okuda T. Magnetic resonance imaging findings and postoperative neurologic dysfunction in elderly patients undergoing coronary artery bypass grafting. Ann Thorac Surg. 2001;72:137-42.

93. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol. 1974;33:87-94.

94. Graham MM, Ghali WA, Faris PD, Galbraith PD, Norris CM, Knudtson ML. Survival after coronary revascularization in the elderly. Circulation. 2002;105:2378-84.

95. Gray TJ, Burns SM, Clarke SC, Tait S, Sharples LD, Caine N, Schofield PM. Percutaneous myocardial laser revascularization in patients with refractory angina pectoris. Am J Cardiol. 2003;91:661-6.

96. Greco S, Auriti A, Fiume D, Gazzeri G, Gentilucci G, Antonini L, Santini M. Spinal cord stimulation for the treatment of refractory angina pectoris: a two-year follow-up. Pacing Clin Electrophysiol. 1999;22:26-32.

97. Grondin CM, Campeau L, Thornton JC, Engle JC, Cross FS, Schreiber H. Coronary artery bypass grafting with saphenous vein. Circulation. 1989;79:I24-9.

98. Grossman E, Messerli FH. Calcium antagonists. Prog Cardiovasc Dis. 2004;47:34-57.

99. Hamm CW, Reimers J, Ischinger T, Rupprecht HJ, Berger J, Bleifeld W. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). N Engl J Med. 1994;331:1037-43.

100. Hammermeister KE, Burchfiel C, Johnson R, Grover FL. Identification of patients at greatest risk for developing major complications at cardiac surgery. Circulation. 1990;82:IV380-9.

101. Hautvast RW, Blanksma PK, DeJongste MJ, Pruim J, van der Wall EE, Vaalburg W, Lie KI. Effect of spinal cord stimulation on myocardial blood flow assessed by positron emission tomography in patients with refractory angina pectoris. Am J Cardiol. 1996;77:462-7.

102. Hautvast RW, Brouwer J, DeJongste MJ, Lie KI. Effect of spinal cord stimulation on heart rate variability and myocardial ischemia in patients with chronic intractable angina pectoris--a prospective ambulatory electrocardiographic study. Clin Cardiol. 1998;21:33-8.

103. Hautvast RW, DeJongste MJ, Staal MJ, van Gilst WH, Lie KI. Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. Am Heart J. 1998;136:1114-20.

104. Heberden W. Some account of a disorder of the breast. Med Trans. 1772;2:59-67.

105. Henderson RA, Pocock SJ, Sharp SJ, Nanchahal K, Sculpher MJ, Buxton MJ, Hampton JR. Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Lancet. 1998;352:1419-25.

106. Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Paranandi L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. Jama. 1992;267:2344-8.

107. Hjalmarson A, Fagerberg B. MERIT-HF mortality and morbidity data. Basic Res Cardiol. 2000;95 Suppl 1:I98-103.

108. Horsch S, Schulte S, Hess S. Spinal cord stimulation in the treatment of peripheral vascular disease: results of a single-center study of 258 patients. Angiology. 2004;55:111-8.

109. Hueb W, Soares PR, Gersh BJ, Cesar LA, Luz PL, Puig LB, Martinez EM, Oliveira SA, Ramires JA. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol. 2004;43:1743-51.

110. Jackson G. Stable angina: drugs, angioplasty or surgery? Eur Heart J. 1997;18 Suppl B:B2-10.

111. Jacobs MJ, Jorning PJ, Beckers RC, Ubbink DT, van Kleef M, Slaaf DW, Reneman RS. Foot salvage and improvement of microvascular blood flow as a result of epidural spinal cord electrical stimulation. J Vasc Surg. 1990;12:354-60.

112. Jansson K, Fransson SG. Mortality related to coronary angiography. Clin Radiol. 1996;51:858-60.

113. Jones RH, Kesler K, Phillips HR, 3rd, Mark DB, Smith PK, Nelson CL, Newman MF, Reves JG, Anderson RW, Califf RM. Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. J Thorac Cardiovasc Surg. 1996;111:1013-25.

114. Kadar A, Glasz T. Development of atherosclerosis and plaque biology. Cardiovasc Surg. 2001;9:109-21.

115. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. N Engl J Med. 1984;311:1144-7.

116. Kapeller P, Barber R, Vermeulen RJ, Ader H, Scheltens P, Freidl W, Almkvist O, Moretti M, del Ser T, Vaghfeldt P, Enzinger C, Barkhof F, Inzitari D, Erkinjunti T, Schmidt R, Fazekas F. Visual rating of age-related white matter changes on magnetic resonance imaging: scale comparison, interrater agreement, and correlations with quantitative measurements. Stroke. 2003;34:441-5.

117. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. J Am Coll Cardiol. 1995;25:807-14.

118. Keefer C, Resnik W. Angina pectoris; a syndrome caused by anoxemia of the myocardium. Arch Intern Med. 1928;41:769.

119. Kerin NZ, Rubenfire M, Naini M, Wajszczuk WJ, Pamatmat A, Cascade PN. Arrhythmias in variant angina pectoris. Relationship of arrhythmias to ST-segment elevation and R-wave changes. Circulation. 1979;60:1343-50.

120. Kim MC, Kini A, Sharma SK. Refractory angina pectoris: mechanism and therapeutic options. J Am Coll Cardiol. 2002;39:923-34.

121. King SB, 3rd, Lembo NJ, Weintraub WS, Kosinski AS, Barnhart HX, Kutner MH, Alazraki NP, Guyton RA, Zhao XQ. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). N Engl J Med. 1994;331:1044-50.

122. Kitakaze M, Asanuma H, Funaya H, Node K, Takashima S, Sanada S, Asakura M, Ogita H, Kim J, Hori M. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers synergistically increase coronary blood flow in canine ischemic myocardium: role of bradykinin. J Am Coll Cardiol. 2002;40:162-6.

123. Klein WW, Jackson G, Tavazzi L. Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a meta-analysis. Coron Artery Dis. 2002;13:427-36.

124. Kujacic V, Eliasson T, Mannheimer C, Jablonskiene D, Augustinsson LE, Emanuelsson H. Assessment of the influence of spinal cord stimulation on left ventricular function in patients with severe angina pectoris: an echocardiographic study. Eur Heart J. 1993;14:1238-44.

125. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation. 1981;63:285-99.

126. Lincoff AM, Califf RM, Moliterno DJ, Ellis SG, Ducas J, Kramer JH, Kleiman NS, Cohen EA, Booth JE, Sapp SK, Cabot CF, Topol EJ. Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. N Engl J Med. 1999;341:319-27.

127. Linderoth B, Fedorcsak I, Meyerson BA. Peripheral vasodilatation after spinal cord stimulation: animal studies of putative effector mechanisms. Neurosurgery. 1991;28:187-95.

128. Linderoth B, Foreman RD. Physiology of spinal cord stimulation: review and update. Neuromodulation. 1999;2:150-164.

129. Linderoth B, Herregodts P, Meyerson BA. Sympathetic mediation of peripheral vasodilation induced by spinal cord stimulation: animal studies of the role of cholinergic and adrenergic receptor subtypes. Neurosurgery. 1994;35:711-9.

130. Lindqvist G, Malmgren H. Organic mental disorders as hypothetical pathogenetic processes. Acta Psychiatr Scand Suppl. 1993;373:5-17.

131. Losordo DW, Vale PR, Hendel RC, Milliken CE, Fortuin FD, Cummings N, Schatz RA, Asahara T, Isner JM, Kuntz RE. Phase 1/2 placebo-controlled, double-blind, dose-escalating trial of myocardial vascular endothelial growth factor 2 gene transfer by catheter delivery in patients with chronic myocardial ischemia. Circulation. 2002;105:2012-8.

132. Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor PC. Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. J Thorac Cardiovasc Surg. 1985;89:248-58.

133. Mannerkorpi K, Nyberg B, Ahlmen M, Ekdahl C. Pool exercise combined with an education program for patients with fibromyalgia syndrome. A prospective, randomized study. J Rheumatol. 2000;27:2473-81.

134. Mannheimer C, Augustinsson LE, Carlsson CA, Manhem K, Wilhelmsson C. Epidural spinal electrical stimulation in severe angina pectoris. Br Heart J. 1988;59:56-61.

135. Mannheimer C, Camici P, Chester MR, Collins A, DeJongste M, Eliasson T, Follath F, Hellemans I, Herlitz J, Luscher T, Pasic M, Thelle D. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J. 2002;23:355-70.

136. Mannheimer C, Carlsson CA, Emanuelsson H, Vedin A, Waagstein F, Wilhelmsson C. The effects of transcutaneous electrical nerve stimulation in patients with severe angina pectoris. Circulation. 1985;71:308-16.

137. Mannheimer C, Carlsson CA, Ericson K, Vedin A, Wilhelmsson C. Transcutaneous electrical nerve stimulation in severe angina pectoris. Eur Heart J. 1982;3:297-302.

138. Mannheimer C, Carlsson CA, Vedin A, Wilhelmsson C. Transcutaneous electrical nerve stimulation (TENS) in angina pectoris. Pain. 1986;26:291-300.

139. Mannheimer C, Eliasson T, Andersson B, Bergh CH, Augustinsson LE, Emanuelsson H, Waagstein F. Effects of spinal cord stimulation in angina pectoris induced by pacing and possible mechanisms of action. Bmj. 1993;307:477-80.

140. Mannheimer C, Eliasson T, Augustinsson LE, Blomstrand C, Emanuelsson H, Larsson S, Norrsell H, Hjalmarsson A. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris: the ESBY study. Circulation. 1998;97:1157-63.

141. Marcassa C, Galli M, Baroffio C, Campini R, Giannuzzi P. Ischemic burden in silent and painful myocardial ischemia: a quantitative exercise sestamibi tomographic study. J Am Coll Cardiol. 1997;29:948-54.

142. Martinez JE, Barauna Filho IS, Kubokawa K, Pedreira IS, Machado LA, Cevasco G. Evaluation of the quality of life in Brazilian women with fibromyalgia, through the medical outcome survey 36 item short-form study. Disabil Rehabil. 2001;23:64-8.

143. McKhann GM, Goldsborough MA, Borowicz LM, Jr., Mellits ED, Brookmeyer R, Quaskey SA, Baumgartner WA, Cameron DE, Stuart RS, Gardner TJ. Predictors of stroke risk in coronary artery bypass patients. Ann Thorac Surg. 1997;63:516-21.

144. Meguro K, Yamaguchi T, Hishinuma T, Miyazawa H, Ono S, Yamada K, Matsuzawa T. Periventricular hyperintensity on magnetic resonance imaging correlated with brain ageing and atrophy. Neuroradiology. 1993;35:125-9.

145. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358:527-33.

146. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971-9.

147. Merkesdal S, Busche T, Bauer J, Mau W. Changes in quality of life according to the SF36 Health Survey of persons with back pain six months after orthopedic in- and outpatient rehabilitation. Int J Rehabil Res. 2003;26:183-9.

148. Merry AF, Smith WM, Anderson DJ, Emmens DJ, Choong CK. Cost-effectiveness of spinal cord stimulation in patients with intractable angina. N Z Med J. 2001;114:179-81.

149. Meyerson B, Linderoth B. Spinal cord stimulation. In: Loeser J, ed. Bonica's management of pain. Philadelphia: Lippincott Williams and Wilkins; 2001:1857-1876.

150. Morrison DA, Sethi G, Sacks J, Henderson W, Grover F, Sedlis S, Esposito R, Ramanathan K, Weiman D, Saucedo J, Antakli T, Paramesh V, Pett S, Vernon S, Birjiniuk V, Welt F, Krucoff M, Wolfe W, Lucke JC, Mediratta S, Booth D, Barbiere C, Lewis D. Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). J Am Coll Cardiol. 2001;38:143-9.

151. Morrison DA, Sethi G, Sacks J, Henderson WG, Grover F, Sedlis S, Esposito R. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. J Am Coll Cardiol. 2002;40:1951-4.

152. Murphy DF, Giles KE. Dorsal column stimulation for pain relief from intractable angina pectoris. Pain. 1987;28:365-8.

153. Murray S, Carson KG, Ewings PD, Collins PD, James MA. Spinal cord stimulation significantly decreases the need for acute hospital admission for chest pain in patients with refractory angina pectoris. Heart. 1999;82:89-92.

154. Nagele H, Stubbe HM, Nienaber C, Rodiger W. Results of transmyocardial laser revascularization in non-revascularizable coronary artery disease after 3 years follow-up [ssee comments]. Eur Heart J. 1998;19:1525-30.

155. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344:395-402.

156. Norrsell H, Eliasson T, Albertsson P, Augustinsson LE, Emanuelsson H, Eriksson P, Mannheimer C. Effects of spinal cord stimulation on coronary blood flow velocity. Coron Artery Dis. 1998;9:273-8.

157. Norrsell H, Eliasson T, Mannheimer C, Augustinsson LE, Bergh CH, Andersson B, Waagstein F, Friberg P. Effects of pacing-induced myocardial stress and spinal cord stimulation on whole body and cardiac norepinephrine spillover. Eur Heart J. 1997;18:1890-6.

158. Norrsell H, Pilhall M, Eliasson T, Mannheimer C. Effects of spinal cord stimulation and coronary artery bypass grafting on myocardial ischemia and heart rate variability: further results from the ESBY study. Cardiology. 2000;94:12-8.

159. Olsson G, Rehnqvist N, Sjogren A, Erhardt L, Lundman T. Long-term treatment with metoprolol after myocardial infarction: effect on 3 year mortality and morbidity. J Am Coll Cardiol. 1985;5:1428-37.

160. Osamichi S, Kouji K, Yoshimaro I, Tadashi U, Hiroichi T, Seiyu K, Shinji O, Noboru T. Myocardial glucose metabolism assessed by positron emission tomography and the histopathologic findings of microvessels in syndrome X. Circ J. 2004;68:220-6.

161. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. N Engl J Med. 1992;326:10-6.

162. Parry CH. An inquiry into the symptoms and causes of syncope angiosa, commonly called angina pectoris. 1799. Edinburgh; Bryce. London: Murray and Callow.

163. Penny KI, Purves AM, Smith BH, Chambers WA, Smith WC. Relationship between the chronic pain grade and measures of physical, social and psychological well-being. Pain. 1999;79:275-9.

164. Persson S. Kardiologi - hjärtsjukdomar hos vuxna. Lund: Studentlitteratur; 2003.

165. Pocock SJ, Henderson RA, Seed P, Treasure T, Hampton JR. Quality of life, employment status, and anginal symptoms after coronary angioplasty or bypass surgery. 3-year follow-up in the Randomized Intervention Treatment of Angina (RITA) Trial. Circulation. 1996;94:135-42.

166. Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, Just H, Fox KA, Pocock SJ, Clayton TC, Motro M, Parker JD, Bourassa MG, Dart AM, Hildebrandt P, Hjalmarson A, Kragten JA, Molhoek GP, Otterstad JE, Seabra-Gomes R, Soler-Soler J, Weber S. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet. 2004;364:849-57.

167. Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. Neurobiol Aging. 2002;23:421-31.

168. Reiber JH, van der Zwet PM, Koning G, von Land CD, van Meurs B, Gerbrands JJ, Buis B, van Voorthuisen AE. Accuracy and precision of quantitative digital coronary

arteriography: observer-, short-, and medium-term variabilities. Cathet Cardiovasc Diagn. 1993;28:187-98.

169. Reiter MJ. Cardiovascular drug class specificity: beta-blockers. Prog Cardiovasc Dis. 2004;47:11-33.

170. Restrepo L, Wityk RJ, Grega MA, Borowicz L, Jr., Barker PB, Jacobs MA, Beauchamp NJ, Hillis AE, McKhann GM. Diffusion- and perfusion-weighted magnetic resonance imaging of the brain before and after coronary artery bypass grafting surgery. Stroke. 2002;33:2909-15.

171. Richter A, Cederholm I, Jonasson L, Mucchiano C, Uchto M, Janerot-Sjoberg B. Effect of thoracic epidural analgesia on refractory angina pectoris: long-term home self-treatment. J Cardiothorac Vasc Anesth. 2002;16:679-84.

172. Ridker PM, Manson JE, Gaziano JM, Buring JE, Hennekens CH. Low-dose aspirin therapy for chronic stable angina. A randomized, placebo-controlled clinical trial. Ann Intern Med. 1991;114:835-9.

173. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med. 1996;335:1857-63.

174. Rodholm M, Hellstrom P, Bilting M, Starmark JE. Diagnostic classification of organic psychiatric disorders after aneurysmal subarachnoid hemorrhage: a comparison between ICD-10, DSM-IV and the Lindqvist & Malmgren classification system. Acta Psychiatr Scand. 2003;108:222-31.

175. Rodholm M, Starmark JE, Svensson E, Von Essen C. Astheno-emotional disorder after aneurysmal SAH: reliability, symptomatology and relation to outcome. Acta Neurol Scand. 2001;103:379-85.

176. Romano M, Auriti A, Cazzin R, Chiaranda G, Circo A, De Luca A, Di Pede F, Fiume D, Greco S, Grieco A, Mangiameli S, Maritano M, Mazzarino F, Pinato G, Raciti S, Raviele A, Santini M, Zucco F, Zuin G. Epidural spinal stimulation in the treatment of refractory angina pectoris. Its clinical efficacy, complications and long-term mortality. An Italian multicenter retrospective study. Ital Heart J. 2000;1:97-102.

177. Romano M, Zucco F, Baldini MR, Allaria B. Technical and clinical problems in patients with simultaneous implantation of a cardiac pacemaker and spinal cord stimulator. Pacing Clin Electrophysiol. 1993;16:1639-44.

178. Rosen SD, Camici PG. The brain-heart axis in the perception of cardiac pain: the elusive link between ischaemia and pain. Ann Med. 2000;32:350-64.

179. Rosen SD, Paulesu E, Frith CD, Frackowiak RS, Davies GJ, Jones T, Camici PG. Central nervous pathways mediating angina pectoris. Lancet. 1994;344:147-50.

180. Rosen SD, Paulesu E, Nihoyannopoulos P, Tousoulis D, Frackowiak RS, Frith CD, Jones T, Camici PG. Silent ischemia as a central problem: regional brain activation compared in silent and painful myocardial ischemia. Ann Intern Med. 1996;124:939-49.

181. Rosen SD, Paulesu E, Wise RJ, Camici PG. Central neural contribution to the perception of chest pain in cardiac syndrome X. Heart. 2002;87:513-9.

182. Sanderson JE, Brooksby P, Waterhouse D, Palmer RB, Neubauer K. Epidural spinal electrical stimulation for severe angina: a study of its effects on symptoms, exercise tolerance and degree of ischaemia. Eur Heart J. 1992;13:628-33.

183. Sanderson JE, Ibrahim B, Waterhouse D, Palmer RB. Spinal electrical stimulation for intractable angina -long-term clinical outcome and safety. Eur Heart J. 1994;15:810-4.

184. Sanderson JE, Tomlinson B, Lau MS, So KW, Cheung AH, Critchley JA, Woo KS. The effect of transcutaneous electrical nerve stimulation (TENS) on autonomic cardiovascular reflexes. Clin Auton Res. 1995;5:81-4.

185. Sanderson JE, Woo KS, Chung HK, Chan WW, Tse LK, White HD. The effect of transcutaneous electrical nerve stimulation on coronary and systemic haemodynamics in syndrome X. Coron Artery Dis. 1996;7:547-52.

186. Schang SJ, Jr., Pepine CJ. Transient asymptomatic S-T segment depression during daily activity. Am J Cardiol. 1977;39:396-402.

187. Scheltens P, Erkinjunti T, Leys D, Wahlund LO, Inzitari D, del Ser T, Pasquier F, Barkhof F, Mantyla R, Bowler J, Wallin A, Ghika J, Fazekas F, Pantoni L. White matter changes on CT and MRI: an overview of visual rating scales. European Task Force on Age-Related White Matter Changes. Eur Neurol. 1998;39:80-9.

188. Schoebel FC, Frazier OH, Jessurun GA, De Jongste MJ, Kadipasaoglu KA, Jax TW, Heintzen MP, Cooley DA, Strauer BE, Leschke M. Refractory angina pectoris in end-stage coronary artery disease: evolving therapeutic concepts. Am Heart J. 1997;134:587-602.

189. Shah PK. Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol. 2003;41:15S-22S.

190. Shaw PJ, Bates D, Cartlidge NE, French JM, Heaviside D, Julian DG, Shaw DA. Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. Stroke. 1987;18:700-7.

191. Shaw PJ, Bates D, Cartlidge NE, Heaviside D, Julian DG, Shaw DA. Early neurological complications of coronary artery bypass surgery. Br Med J (Clin Res Ed). 1985;291:1384-7.

192. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg. 1967;46:489-91.

193. Sinclair D, Weddel G, Feindel W. Referred pain and associated phenomena. Brain. 1948;71:184-211.

194. Smith PL, Treasure T, Newman SP, Joseph P, Ell PJ, Schneidau A, Harrison MJ. Cerebral consequences of cardiopulmonary bypass. Lancet. 1986;1:823-5.

195. Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health status predicts long-term outcome in outpatients with coronary disease. Circulation. 2002;106:43-9.

196. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Fihn SD. Monitoring the quality of life in patients with coronary artery disease. Am J Cardiol. 1994;74:1240-4.

197. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol. 1995;25:333-41.

198. Spin JM, Vagelos RH. Early use of statins in acute coronary syndromes. Curr Atheroscler Rep. 2003;5:44-51.

199. Spreen O, Strauss E. A compendium of neuropsychological tests: administration, norms and commentary. New York: Oxford University Press; 1991.

200. Stahle E, Bergstrom R, Holmberg L, Nystrom SO, Hansson HE. Risk factors for operative mortality and morbidity in patients undergoing coronary artery bypass surgery for stable angina pectoris. Eur Heart J. 1991;12:162-8.

201. Sullivan M, Karlsson J. The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population. J Clin Epidemiol. 1998;51:1105-13.

202. Svedjeholm R, Hakanson E, Szabo Z, Vanky F. Neurological injury after surgery for ischemic heart disease: risk factors, outcome and role of metabolic interventions. Eur J Cardiothorac Surg. 2001;19:611-8.

203. Svorkdal N. Treatment of inoperable coronary disease and refractory angina: spinal stimulators, epidurals, gene therapy, transmyocardial laser, and counterpulsation. Semin Cardiothorac Vasc Anesth. 2004;8:43-58.

204. Sylven C. Angina pectoris. Clinical characteristics, neurophysiological and molecular mechanisms. Pain. 1989;36:145-67.

205. Sylven C, Sarkar N, Insulander P, Kenneback G, Blomberg P, Islam K, Drvota V. Catheter-based transendocardial myocardial gene transfer. J Interv Cardiol. 2002;15:7-13.

206. TenVaarwerk IA, Jessurun GA, DeJongste MJ, Andersen C, Mannheimer C, Eliasson T, Tadema W, Staal MJ. Clinical outcome of patients treated with spinal cord stimulation for therapeutically refractory angina pectoris. The Working Group on Neurocardiology. Heart. 1999;82:82-8.

207. Tolins M, Weir EK, Chesler E, Pierpont GL. "Maximal" drug therapy is not necessarily optimal in chronic angina pectoris. J Am Coll Cardiol. 1984;3:1051-7.

208. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation. 1995;92:2333-42.

209. Tune JD, Richmond KN, Gorman MW, Feigl EO. Control of coronary blood flow during exercise. Exp Biol Med (Maywood). 2002;227:238-50.

210. Wahrborg P, Emanuelsson H. The cardiac health profile: content, reliability and validity of a new disease-specific quality of life questionnaire. Coron Artery Dis. 1996;7:823-9.

211. van Boven AJ, Jukema JW, Zwinderman AH, Crijns HJ, Lie KI, Bruschke AV. Reduction of transient myocardial ischemia with pravastatin in addition to the conventional treatment in patients with angina pectoris. REGRESS Study Group. Circulation. 1996;94:1503-5.

212. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol. 1998;51:903-12.

213. Varnauskas E, Aberg T, Brorsson B, Karlsson T, Olsson B, Werko L. Five-year mortality for stable angina in a medical practice study and a randomized trial. Scand Cardiovasc J. 2002;36:209-14.

214. Wettervik C, Claes G, Drott C, Emanuelsson H, Lomsky M, Radberg G, Tygesen H. Endoscopic transthoracic sympathicotomy for severe angina. Lancet. 1995;345:97-8.

215. Wood D. Established and emerging cardiovascular risk factors. Am Heart J. 2001;141:S49-57.

216. Yang EH, Barsness GW, Gersh BJ, Chandrasekaran K, Lerman A. Current and future treatment strategies for refractory angina. Mayo Clin Proc. 2004;79:1284-92.

217. Yu W, Maru F, Edner M, Hellstrom K, Kahan T, Persson H. Spinal cord stimulation for refractory angina pectoris: a retrospective analysis of efficacy and cost-benefit. Coron Artery Dis. 2004;15:31-7.

218. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342:145-53.

219. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494-502.

220. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet. 1994;344:563-70.

221. Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. Circulation. 1976;53:627-32.

På grund av upphovsrättsliga skäl kan vissa ingående delarbeten ej publiceras här.
För en fullständig lista av ingående delarbeten, se avhandlingens början.

Due to copyright law limitations, certain papers may not be published here.
For a complete list of papers, see the beginning of the dissertation.

GÖTEBORGS UNIVERSITET

Vasastadens
Bokbinderi AB

Bokbinderi & Tryckeri

Tel: 031 - 29 20 45 • Mail: info@vasastadensbokbinderi.se