Summary

In spite of the tremendous improvement in treatment of patients with angina pectoris due to significant coronary artery disease, there remains a group of patients who cannot adequately be treated. These patients are considered as having 'intractable angina'. Patients, suffering from intractable ischemic heart disease have never been defined as a separate group and no data are available regarding their morbidity and mortality. Furthermore, since their angina was 'intractable', no therapy was offered to improve their quality of life or their life expectancy.

In this thesis the efficacy of neurostimulation, a possible adjuvant therapy for these patients, is evaluated.

Neurostimulation is usually applied on the skin (transcutaneous electrical nerve stimulation = TENS) or via an implanted device on the dorsal spinal cord (spinal cord stimulation = SCS). If the only effect of neurostimulation is a reduction in, or an abolishment of, the anginal warning signal, this treatment may not be safe because of a possible increase in myocardial ischemia. Therefore, we investigated the additional potential mechanisms of action of neurostimulation on the heart. Optional mechanisms have been studied from an anatomical, a physiological and a biochemical points of view.
Protocol for the evaluation of spinal cord stimulation (Chapter I). In a pilot study we have demonstrated the efficacy of neurostimulation by an increase in activities of daily living (ADL), although maximal exercise capacity was not altered. In addition, it appears that transcantaneous electrical nervous stimulation (TENS) improves the ADL more gradually than spinal cord stimulation. In the pilot study the patients performed the exercise testing without active neurostimulation. To allow us to compare our findings with other investigators, exercising their patients during active neurostimulation, we changed our protocol.

During neurostimulation the patients were aware of the paresthesias and the physician saw the artifacts on the ECG, which made it impossible to undertake a double-blind or cross-over study. However, a randomization into a Treatment and a Control group was still possible. Originally, the Treatment group, the Spinal Cord Stimulator was implanted at the beginning of the study period, and in the Control group after the study period. The patients equipped with a Spinal Cord Stimulator needed 6 weeks to learn the procedure of activating the spinal cord stimulation device. Consequently, the study protocol was extended from 2 to 3 months. In addition, to prevent an operation bias, we implanted the device in the Control group at the beginning of the study, without the device activated in the Control group during the 3-months study period. After the 3-month study period, the device was switched to active stimulation mode in the Control group. The patients were no longer randomized and served as their own controls during the follow-up period.

Efficacy of spinal cord stimulation (Chapter II, III). In a prospective randomized study with a two months' follow-up, the efficacy of spinal cord stimulation was evaluated through exercise capacity and quality of life in patients with intractable angina. Exercise capacity was assessed by treadmill exercise tests, and quality of life by registering the short acting nitrate intake and the number of anginal attacks in a diary, and scoring of activities of daily living (ADL). The conclusion was that spinal cord stimulation improved both exercise capacity and quality of life. The increase in exercise capacity and rate pressure product, in conjunction with the reduction in ST segment depression, suggested that spinal cord stimulation improved the oxygen supply to the heart. It is uncertain whether spinal cord stimulation employs its electro-analgesic effect as a result of its anti-ischemic property on the heart, or vice versa.

Anti-ischemic effect of spinal cord stimulation (Chapter IV). To study a potential anti-ischemic effect, the patients performed treadmill exercise tests and had 48 hour ambulatory ECG monitoring. Exercise capacity was assessed by a standardized treadmill protocol in patients randomly assigned into a Treatment group and a Control group. To evaluate a potential operation bias we implanted the spinal cord stimulator in half of the Control group patients before the 3-month study period and in the other half of the Controls after the study period. The exercise capacity of patients treated with spinal cord stimulation increased with a concomitant reduction in ST segment depression. Moreover, we could not explain the significant improvement in the Treatment group only by an operation bias.

A significant reduction in ST segment depression was also found in our study on 48 hour ECG recordings, after implantation of the spinal cord stimulation device. The beneficial effect of neurostimulation on the ST segment depression, observed during exercise testing and 48 hour ECG recording, favors for the safety of the therapy in the treated group.

Spinal cord stimulation and quality of life aspects (Chapter VI). The quality of life is difficult to measure because subjective observations are hard to quantify. For patients with angina resulting from coronary artery disease, the New York Heart Association (NYHA) classification is a commonly accepted rating scale for clinical symptoms of cardiac patients. A problem related to the NYHA functional classification is that it is poorly related to quality of life. Furthermore, NYHA classification indicates the patient's condition only at one single point in time. Therefore, we developed and validated a questionnaire on activities of daily life specifically tailored to this subset of patients with intractable angina. After implantation of the spinal cord stimulator in a subset of patients with intractable angina, the ADL increased significantly. This increase in ADL was measured during the 1-year follow-up period.

Technical follow-up and complications (Chapter V). To study the complications of spinal cord stimulation devices (Chapter V). To study the complications of spinal cord stimulation devices, we implanted the device in the Control group at the beginning of the study, without having the device activated in the Control group during this 3 months' study period. After the 3-month study period, the device was switched to active stimulation mode in the Control group. To evaluate a potential operation bias we implanted the spinal cord stimulator in half of the Control group patients before the 3-month study period and in the other half of the Controls after the study period. The exercise capacity of patients treated with spinal cord stimulation increased with a concomitant reduction in ST segment depression. Moreover, we could not explain the significant improvement in the Treatment group only by an operation bias.

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Clinical evaluation of TENS in pain syndromes (Chapter VIII). In some patients, severe angina, resulting from coronary artery disease, may not be demonstrated by treadmill electrocardiographic (ECG) recordings. These patients may benefit from transcutaneous electrical nerve stimulation (TENS). Among patients treated with TENS, the patients with angina showed the best results after 6 months, whereas 1 out of 3 patients experienced temporary irritation of the skin at the electrode positioning.

Studies on mechanisms of neurostimulation (Chapter IX, X, XI). To date, it is not known how the higher structures in the central nervous system are involved in spinal cord stimulation. For example, the periaqueductal gray (PAG), a structure coordinating pain modulation and the structures involved in the pathways of pain transmission, has been demonstrated that parts of the PAG produce an increase in carotid- and coronary- blood flow,
implantation of the spinal cord stimulation device the ADL increased significantly. This increase was maintained during the 1-year follow-up period.

**Technical follow-up and complications of spinal cord stimulation devices** (Chapter VII). The implantation of a spinal cord stimulator can be considered as a standardized surgical procedure similar to the implantation of a pacemaker.

The variable settings for the various medical applications have been fine-tuned over the past few years. During 1-year follow-up the stimulation threshold did not change significantly. This implies that no adaptation in the provoked paresthesias occurred. The consequences of micro-dislocation can usually be restored by reprogramming the device. Reoperations to position the dislodged electrodes have occurred rather frequently in our group of patients.

**Clinical evaluation of TENS in different pain syndromes** (Chapter VIII). In some patients with severe angina, resulting from coronary artery disease, documented by coronary angiography, ischemia could not be demonstrated by treadmill exercise or ambulatory ECG recordings. These patients were not included in the study on spinal cord stimulation; they were treated with transcutaneous electrical nerve stimulation (TENS). Among patients treated with TENS for different pain syndromes, the patients with angina pectoris showed the best results after 6 months follow-up. Albeit that 1 out of 3 patients experienced a problem, usually a temporary irritation of the skin at the sites of electrodes positioning.

**Studies on mechanisms of neurostimulation** (Chapter IX, X, XI). To date, it is not yet known which higher structures in the central nervous system are involved in spinal cord stimulation. The periaqueductal gray (PAG), a structure coordinating survival behavior and pain modulation of the individual, might be one of the structures involved (Chapter IX). In animal experiments we have demonstrated that stimulation in specific parts of the PAG produces an increase in femoral-, carotid- and coronary- blood flow, usually accompanied by a change in heart rate. During PAG-stimulation myocardial blood flow increased 3-fold, after temporary occlusion of a coronary artery, compared to no PAG-stimulation.

From a physiological point of view we studied myocardial perfusion during and without spinal cord stimulation by means of a positron emission tomography (PET). During every session scans were made at rest and during the dipyridamole stress. We found an increase at rest in myocardial perfusion in the ischemic regions during spinal cord stimulation, with a concomitant increase in perfusion ratio. The perfusion ratio is the perfusion in the ischemic regions divided by the perfusion in non-ischemic regions. During active stimulation a reduction in ST segment depression was observed, accompanied by a decrease in angina when ischemia was induced by the dipyridamole stress test.

We concluded that spinal cord stimulation employs its action through a redistribution of blood flow from non-ischemic to ischemic regions (chapter X).

Finally, we studied the expression of biochemical compounds in the brain, to evaluate the involvement of the autonomic nervous system when spinal cord stimulation is applied. In rats electrodes were introduced into the epidural space and fixated at the T1 level. By stimulation of the spinal cord we could study the expression of the immediate early gene: c-fos and the stress hormone: Heat Shock Protein (HSP72) in the central nervous system. We found c-fos labelling in specific parts of the PAG, indicating a nervous system damage (Chapter XI).

Regarding the clinical efficacy of neurostimulation in this group of patients and the observed reduction in myocardial ischemia, neurostimulation can be considered a safe additional treatment for this subset of patients.