
EVIDENCE-BASED MEDICINE

Evidence-Based Interventional Pain Medicine
According to Clinical Diagnoses

24. Chronic Refractory Angina Pectoris

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■ **Abstract:** Angina pectoris, cardiac pain associated with ischemia, is considered refractory when optimal anti-anginal therapy fails to resolve symptoms. It is associated with a decreased life expectancy and diminishes the quality of life. Spinal cord stimulation (SCS) may be considered for patients who have also undergone comprehensive interventions, such as coronary artery bypass graft (CABG) and percutaneous transluminal coronary angioplasty (PTCA) procedures.

The mechanism of action of SCS is not entirely clear. Pain reduction is related to the increased release of inhibitory neuropeptides as well as normalization of the intrinsic nerve system of the heart muscle, and may have a protective myocardial effect.

SCS in patients with refractory angina pectoris results in reduced anginal attacks as well as improved rate pressure product prior to the occurrence of ischemic events. This may be the result of reduced Myocardial Volume Oxygen (MVO₂) and possibly the redistribution of the coronary blood flow to

ischemic areas. There are a number of studies that demonstrate that SCS does not mask acute myocardial infarction.

The efficacy of the treatment has been investigated in two prospective, randomized studies.

The long-term results showed an improvement of the symptoms and of the quality of life. SCS can be an alternative to surgical intervention in a selected patient population. In addition, SCS is a viable option in patients in whom surgery is not possible.

SCS is recommended in patients with chronic refractory angina pectoris that does not respond to conventional treatment and in whom revascularization procedures have been attempted or not possible, and who are optimized from a medical perspective. ■

Key Words: evidence-based medicine, angina pectoris, spinal cord stimulation

INTRODUCTION

This review on refractory angina pectoris is part of the series “Evidence-Based Interventional Pain Medicine according to Clinical Diagnoses.” Recommendations formulated in this chapter are based on “Grading strength of recommendations and quality of evidence in clinical guidelines” described by Guyatt et al.¹ and adapted by van Kleef et al.² in the editorial

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Table 1. Summary of Evidence Scores and Implications for Recommendation

Score	Description	Implication
1 A+	Effectiveness demonstrated in various RCTs of good quality. The benefits clearly outweigh risk and burdens	Positive recommendation
1 B+	One RCT or more RCTs with methodologic weaknesses, demonstrate effectiveness. The benefits clearly outweigh risk and burdens	
2 B+	One or more RCTs with methodologic weaknesses, demonstrate effectiveness. Benefits closely balanced with risk and burdens	
2 B±	Multiple RCTs, with methodologic weaknesses, yield contradictory results better or worse than the control treatment. Benefits closely balanced with risk and burdens, or uncertainty in the estimates of benefits, risk and burdens.	Considered, preferably study-related
2 C+	Effectiveness only demonstrated in observational studies. Given that there is no conclusive evidence of the effect, benefits closely balanced with risk and burdens	
0	There is no literature or there are case reports available, but these are insufficient to suggest effectiveness and/or safety. These treatments should only be applied in relation to studies.	Only study-related
2 C-	Observational studies indicate no or too short-lived effectiveness. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	Negative recommendation
2 B-	One or more RCTs with methodologic weaknesses, or large observational studies that do not indicate any superiority to the control treatment. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	
2 A-	RCT of a good quality which does not exhibit any clinical effect. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	

RCT, randomized controlled trial.

accompanying the first article of this series (Table 1). The latest literature update was performed in September 2010.

Angina pectoris is severe chest pain that is often accompanied by a heavy oppressive feeling. Angina pectoris occurs because of insufficient blood supply to the heart muscle. In most cases, this is caused by a constriction of the coronary arteries. It often coincides with physical exertion or emotional strain, which causes the heart to beat more rapidly and is associated with higher oxygen consumption. The pain occurring in case of a sudden occlusion of a coronary artery because of a thrombus or embolus is usually more severe. A complete occlusion eventually leads to a myocardial infarction. Risk factors of angina pectoris include smoking, obesity, hypertension, diabetes mellitus, and hypercholesterolemia. Besides coronary obstruction, coronary spasms may also cause symptoms of angina pectoris.

Angina pectoris can be treated with vasodilating drugs or by the reduction of exertion. A reduction of the blood pressure also leads to a lower cardiac workload and to decreased angina symptoms. Presently, a large number of pharmacological therapies are available. In addition, revascularization procedures, such as percutaneous coronary angioplasty and coronary bypass surgery (CBS), can help with angina attacks if a single or several discrete areas of obstruction can be identified.

Angina pectoris is termed refractory if the conventional therapies mentioned above have insufficient or no

effect. Patients with refractory angina pectoris generally have a long history of coronary disease and are usually clearly limited in their physical activities. In addition to extensive anti-anginal pharmacological treatment, these patients have often undergone one or more percutaneous coronary angioplasties or even CBS. Strikingly, most patients with refractory angina pectoris are relatively young, predominantly male, and sometimes have a limited ejection fraction.^{3,4}

In Europe, the annual prevalence of class III and class IV Canadian Cardiovascular Society (CCS; angina pectoris upon mild exertion and at rest, respectively; CCS classification) symptoms are estimated to be approximately 100,000.⁵

Spinal cord stimulation is considered a reasonable treatment option for patients with chronic angina not responsive to more conservative strategies who are not candidates for coronary revascularization surgery. Since its first publication in 1987, several publications have demonstrated the safety and efficacy in patients with severe coronary artery disease.⁶

I. DIAGNOSIS

I.A HISTORY

The clinical signs of angina pectoris are typical: They are provoked by exertion and disappear at rest. Patients with severe coronary disease may experience various symptoms during exertion, usually located substernally and sometimes radiating to adjacent areas, especially

on the left side, such as the arms, neck, throat, jaw, or even the teeth. The pain sensation is often accompanied by other symptoms such as perspiration, nausea, and, sometimes, vomiting. Some patients suffering from angina pectoris are able to estimate the amount of exertion that will cause an attack of angina pectoris. The maximum exercise tolerance is closely related to the degree of coronary constriction in the main vessels. At rest, the angina pectoris threshold is clearly influenced by emotional stress, exposure to cold, meals, and smoking. These aspects of pain sensation suggest a dynamic stenosis of the coronary artery. The variability of the angina pectoris threshold suggests that a combination of fixed and variable obstructions of the coronary vessels plays a role. Therefore, it can generally be stated that angina pectoris is not a specific indicator of the degree of coronary constriction but that angina pectoris can be an inconsistent, nonspecific phenomenon, determined by a variety of causes.

Angina pectoris is considered refractory if constant reversible myocardial ischemia and pain occur despite optimal anti-anginal therapy in cases with substantial stenosis of a significant coronary artery (more than 75% stenosis in one or more of the main coronary arteries).

I.B PHYSICAL EXAMINATION

Physical examination is mainly directed at excluding other disorders in the differential diagnosis. By the time the neuromodulation specialist is involved, the patient will have had an extensive workup by a cardiologist.

I.C ADDITIONAL TESTS

Angina pectoris can be diagnosed when ischemia is identified on an electrocardiogram when the patient is experiencing symptoms. Exercise stress tests, such as a bicycle ergometer test or a stress echo test and angiography, are examples of the wide variety of options that cardiologists can apply to evaluate the symptoms. The gold standard for the diagnosis of coronary disease is a coronary angiogram or a computed tomography angiogram.

I.D DIFFERENTIAL DIAGNOSIS

All patients considered for SCS with refractory angina pectoris should have been seen by a cardiologist. In practice, patients who are eligible for SCS have often undergone comprehensive interventions, such as CABG and PTCA procedures. Patients with small vessel disease should be considered for SCS if medical treatment is

unsatisfactory. The differential diagnosis includes but is not limited to⁷:

- Pulmonary disorders: pulmonary hypertension, pulmonary embolism, pleuritis, pneumothorax, and pneumonia.
- Nonischemic cardiac disease, mitral valve prolapse, and cardiac syndrome X.
- Gastrointestinal disorders: peptic ulcer, pancreatitis, esophageal spasms, esophageal reflux, cholecystitis, and cholelithiasis.
- Musculoskeletal related: costochondritis, Tietze's syndrome, thoracic trauma, cervical arthritis with or without radiculopathy, myositis, and cancer.
- Spinal cord injury and thoracic radiculopathy.
- Acute aortic dissection.
- Herpes zoster with post-herpetic neuralgia.
- Panic disorder.

II. TREATMENT OPTIONS

II.A CONSERVATIVE MANAGEMENT

All therapies for (refractory) angina pectoris aim to improve the myocardial ischemia by means of either the reduction of oxygen demand (β blockers, calcium channel blockers) or the increase of oxygen supply (nitrates, revascularization procedures, coronary angioplasty, or CBS). In addition, the patients are often treated with anticholesterol drugs and platelet aggregation inhibitors.

II.B INTERVENTIONAL MANAGEMENT

Spinal Cord Stimulation

A therapy that has anti-anginal effects, enhances the quality of life of patients with refractory angina pectoris, and is not harmful is a valuable treatment. An additional argument is that patients in this category show an annual mortality between 5% and 8%.³ The population that should be treated includes patients who experience substantial limitations because of their angina pectoris despite exhaustive conservative and surgical intervention.

The mechanism of action of SCS remains as yet unsolved. The obtained pain reduction is related to the increased release of inhibitory neuropeptides such as GABA, dopamine, and glycine, and a reduced release of stimulating neuropeptides such as substance P and acetylcholine.^{8,9}

It has recently been suggested that the effects of SCS in angina pectoris are in part attributed to the protection

of the myocardium and the normalization of the intrinsic nerve system of the heart muscle.¹⁰ Studies have shown that patients treated with SCS have less angina symptoms, a lower use of short-acting nitrates, and an improved exercise tolerance.^{11,12} Moreover, clear anti-ischemic effects have been demonstrated, such as an increased exercise time without a deterioration of the myocardial symptoms and an increased tolerance for arterial pacing. The reduced myocardial ischemia and reduced myocardial oxygen consumption (MVO₂) result in delayed angina pectoris symptoms.^{13,14}

SCS in patients with refractory angina pectoris results in reduced attacks that may be caused by the increased angina pectoris threshold as a result of the reduced MVO₂ and possibly the redistribution of the coronary blood flow.

It has also been suggested that angiogenesis would take place under the influence of SCS.¹⁵ Redistribution of the myocardial blood flow has been demonstrated in three studies,^{13,14,16} and it is proposed that some of the redistribution may be because of the formation of collaterals. Also, there are a number of studies that demonstrate that SCS does not mask acute myocardial infarction.¹⁷⁻¹⁹

Efficacy of Spinal Cord Stimulation Treatment

The efficacy of the treatment has been investigated in two prospective, randomized studies.^{11,12} The first study was a prospective, randomized clinical study in 17 patients conducted between 1990 and 1994. One group was implanted immediately after inclusion. The other group was implanted after a period of 8 weeks. Inclusion criteria of both studies were: (1) angina pectoris, (2) coronary angiogram in which coronary angioplasty or CBS was no longer an option, (3) New York Heart Association classification 3 or 4, (4) an exercise test with reversible ischemia, and (5) optimal pharmacological treatment for at least 1 month. The results demonstrated that the exercise capacity in the SCS group was better than in the control group and that the quality of life variables in both groups were better after 12 months compared with baseline.

Mannheimer et al.'s Electrical Stimulation versus coronary artery Bypass surgery in severe angina pectoris study¹¹ was a prospective, randomized study in 104 patients. The inclusion criteria were patients with angina pectoris refractory to pharmacological treatment in cases with no proven benefit from CABG and with an increased risk of surgical complications. Group 1, consisting of 51 patients, was treated with CBS, and group 2, consisting

of 53 patients, received SCS. This study had a remarkably long follow-up of 5 years.²⁰ The results of this study showed improvement of symptoms in both groups after 1 year. There was reduced myocardial ischemia, but only in the CABG surgery group. The mortality in the CABG group was higher than in the spinal cord stimulation group (seven and one cases of death, respectively). It should be mentioned that three patients died before their operation took place. With respect to morbidity, slightly more cerebrovascular accidents were reported in the CABG group. The long-term results demonstrated an improvement in anginal symptoms and of the quality of life in both groups. A prospective Italian publication of spinal cord stimulation in 104 patients with severe refractory angina showed a significant improvement of angina symptoms in 73% of the patients after a 13.2-month follow-up.²¹ Based on the above studies of efficacy, it can be concluded that SCS can be considered an alternative to surgical intervention in a select patient population. SCS may also be a viable option in patients in whom surgery is not possible.

The indications for SCS in angina pectoris are controversial. An open-label, randomized study compared the efficacy of SCS to percutaneous myocardial laser revascularization. In this study, two groups of 30 patients each were followed for 1 year. Both groups demonstrated improved pain control and improved exercise tolerance. However, no significant difference of efficacy was observed between the groups.²² Critics point out that the available randomized controlled trials are rather dated (10 to 14 years old). During that time, it is possible that the improvement in the anticholesterol drugs or anti-anginal drugs may have made SCS for angina obsolete. Also, the quality of percutaneous angioplasty has clearly improved, which makes the comparative therapy less definitive. A recent cohort study shows that this therapy may have good results on a longer term as well.²³ It can be concluded that there is a need for a new prospective, randomized study.

II.C COMPLICATIONS OF INTERVENTIONAL MANAGEMENT

The complications of SCS treatment are limited to minor complications in approximately 6.8% of the patients receiving the treatment and include lead migrations, electrode fractures, battery failure, and subcutaneous infection.^{3,12,20,24}

Major complications have not been described in previously published studies. There are, of course, absolute contraindications for this treatment, including implant-

able cardioverter defibrillator pacemaker, irreversible bleeding diathesis, neuraxial malignancy, or cognitive disorders, that do not allow the patient to operate the spinal cord stimulator.

II.D EVIDENCE FOR INTERVENTIONAL MANAGEMENT

The summary of the evidence for the interventional management for chronic refractory angina pectoris is given in Table 2.

Table 2. Summary of the Evidence for Interventional Management

Technique	Evaluation
Spinal cord stimulation	2 B+

III. RECOMMENDATIONS

Based on the present literature, SCS is recommended in patients with chronic refractory angina pectoris that does not respond to conventional therapy who are referred by a cardiologist.

III.A CLINICAL PRACTICE ALGORITHM

Figure 1 represents the treatment algorithm for refractory angina pectoris based on the available evidence.

III.B TECHNIQUE(S)

The intervention takes place under strictly sterile conditions and antibiotic prophylaxis, eg, 1,000 mg of a cephalosporin intravenously. The patient is placed in a prone position on an operating table suitable for X-

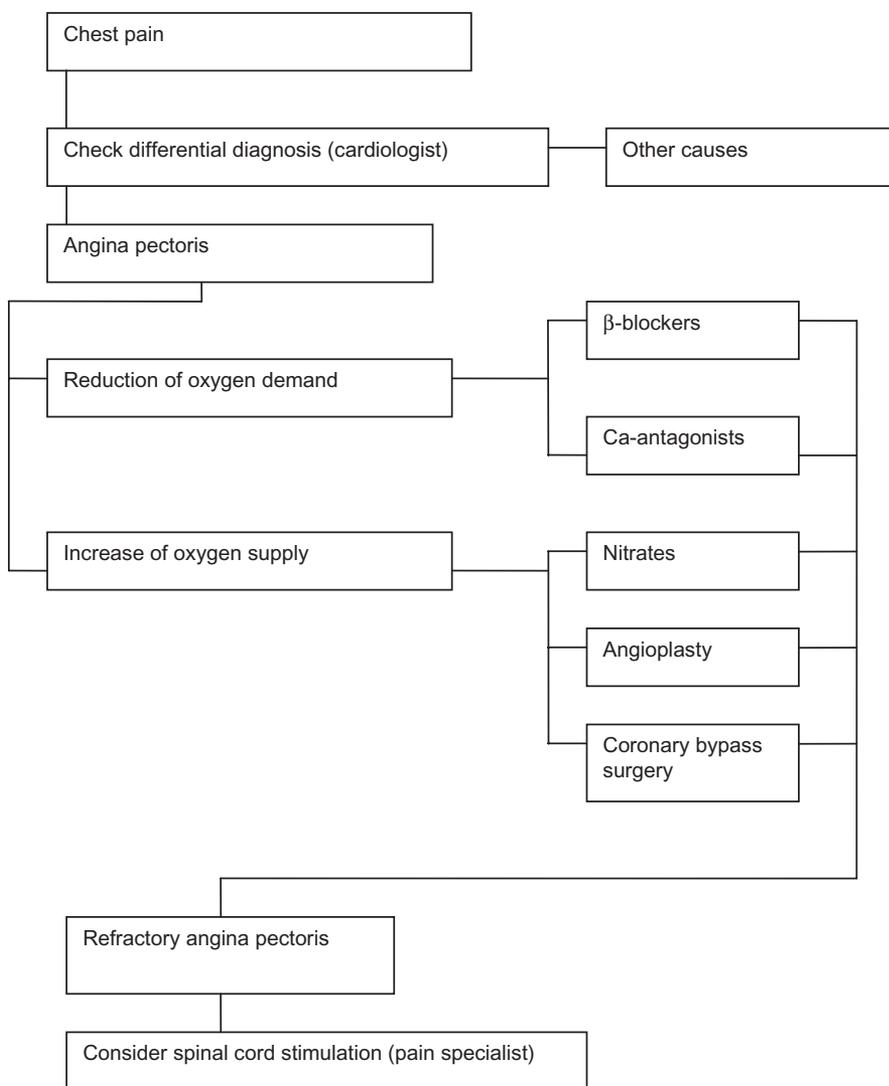


Figure 1. Algorithm for the treatment of refractory angina pectoris.

ray screening. The T8–T9 vertebral level is identified by means of a C-arm. A Tuohy needle is inserted under X-ray guidance to find the epidural space, and a four-contact or eight-contact electrode array is placed with its cephalad tip at the T2–T3 level left of midline. Subsequently, test stimulations are performed; the test stimulations should overlap the areas that are painful during angina attacks. The electrode is normally located in the T1–T4 area. When the correct level has been found, the lead is fixated, and the pacemaker is inserted in the left or right buttock, or in the upper abdomen. The electrical continuity is then restored via an extension lead. The patient is hospitalized and treated with antibiotics for 24 hours. The patient can be discharged the following day. The treatment does not include a period of test stimulation. The system is implanted directly.

IV. SUMMARY

Angina pectoris is termed refractory if conventional treatment fails.

In case of persisting symptoms, spinal cord stimulation can be recommended after extensive multidisciplinary evaluation.

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