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Electrical Stimulation Versus Coronary Artery Bypass Surgery in Severe Angina Pectoris

The ESBY Study

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Background—Spinal cord stimulation (SCS) has been shown to have antianginal and anti-ischemic effects in severe angina pectoris. The present study was performed to investigate whether SCS can be used as an alternative to coronary artery bypass grafting (CABG) in selected patient groups, ie, patients with no proven prognostic benefit from CABG and with an increased surgical risk.

Methods and Results—One hundred four patients were randomized (SCS, 53; CABG, 51). The patients were assessed with respect to symptoms, exercise capacity, ischemic ECG changes during exercise, rate-pressure product, mortality, and cardiovascular morbidity before and 6 months after the operation. Both groups had adequate symptom relief ($P < .0001$), and there was no difference between SCS and CABG. The CABG group had an increase in exercise capacity ($P = .02$), less ST-segment depression on maximum ($P = .005$) and comparable ($P = .0009$) workloads, and an increase in the rate-pressure product both at maximum ($P = .0003$) and comparable ($P = .03$) workloads compared with the SCS group. Eight deaths occurred during the follow-up period, 7 in the CABG group and 1 in the SCS group. On an intention-to-treat basis, the mortality rate was lower in the SCS group ($P = .02$). Cerebrovascular morbidity was also lower in the SCS group ($P = .03$).

Conclusions—CABG and SCS appear to be equivalent methods in terms of symptom relief in this group of patients. Effects on ischemia, morbidity, and mortality should be considered in the choice of treatment method. Taking all factors into account, it seems reasonable to conclude that SCS may be a therapeutic alternative for patients with an increased risk of surgical complications. (*Circulation*. 1998;97:1157-1163.)

Key Words: bypass ■ angina ■ electrical stimulation

Spinal cord stimulation (SCS), or epidural spinal electrical stimulation, has been used in the treatment of chronic neurogenic pain for several years.^{1,2} SCS has also been used in the treatment of peripheral vascular disease with satisfactory clinical results in terms of increased local blood flow and promoted healing of ischemic ulcers.³⁻⁵ Since 1985, SCS has been used to treat intractable angina pectoris with promising clinical results in terms of symptom relief and reduction in myocardial ischemia.⁶⁻¹⁰ Eighty percent of the patients treated with SCS at our center enjoy a lasting, good effect of the treatment in terms of reduced frequency of anginal pain and consumption of short-acting nitrates.⁹ In a similar study from The Netherlands, the reported mortality rate was similar to that of patients with coronary artery disease and stable angina pectoris.¹¹ The antianginal effect is secondary to an anti-ischemic effect, which in turn seems to be due to a reduction in myocardial oxygen consumption⁶; however, a redistribution of coronary blood flow cannot be excluded.¹² Further-

more, it has been shown unequivocally that ongoing myocardial ischemia during stimulation treatment gives rise to anginal pain. Thus, the treatment does not deprive the patient of a warning signal.^{6,7,9,13,14}

Revascularization procedures, ie, coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA), are standard treatments in severe angina pectoris. There are several groups of patients for whom CABG is known to be associated with an increased complication risk, eg, patients with unsuitable coronary anatomy requiring extended surgical procedures¹⁵; patients with low ejection fractions¹⁶; patients with concomitant extracardiac disease such as diabetes mellitus,¹⁷ renal dysfunction,¹⁸ cerebrovascular disease,¹⁸⁻²⁰ or peripheral vascular disease²¹; and patients who have previously undergone CABG.^{15,17} Until now, SCS has been used in the treatment of severe angina pectoris despite optimum medication in patients who are not accessible for revascularization.

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TABLE 1. Factors Considered Important for Surgical Outcome

| |
|--|
| Cerebrovascular disease |
| Complicated coronary anatomy (ie, peripheral coronary atherosclerosis) |
| Diabetes mellitus |
| Low ejection fraction (<40%) |
| Peripheral vascular disease |
| Previous coronary artery bypass graft surgery |
| Renal dysfunction |

The SCS device is implanted under local anesthesia, and the complication risk is therefore considered to be lower than in CABG, in which the patient must be subjected to cardiopulmonary bypass/extracorporeal circulation and cardioplegia.

Therefore, the aim of the present study was to compare the results of SCS and CABG in patients accepted for CABG who had an increased intraoperative and postoperative complication risk and lack of prognostic benefit from CABG in a randomized, prospective trial.

Methods

The present study was designed as a randomized, prospective, open comparison between CABG and SCS in a selected patient group, ie, patients with no proven prognostic benefit from CABG and with an increased risk of complications. Patients were included over a period of 36 months from January 1992 to March 1995.

Because the criteria stated above limited the number of patients eligible for the study, the number of patients enrolled was based on an estimate of the realistic enrollment frequency over a 3-year period. The inclusion period was limited because surgical and anesthesiological techniques develop rapidly. A longer inclusion period could have resulted in differences between patients included early and late in the study, which would have made the results more difficult to interpret.

Eligibility

All patients being evaluated for revascularization procedures by a team consisting of cardiac surgeons, interventional cardiologists, and the referring physician at the routine daily revascularization conferences at Östra Hospital and Sahlgren's Hospital, Gothenburg, Sweden, were evaluated for eligibility in the study. These physicians were not involved in this study. The evaluation was based on strict conventional clinical criteria in which several factors were considered.

Patients who were considered to have only symptomatic indication for CABG according to the American College of Cardiology/American Heart Association guidelines (ie, no prognostic benefit),²² to run an increased risk of surgical complications (Table 1), and to be unsuitable for PTCA were invited to participate in the study. Patients with coronary anatomy who were considered unavailable for complete revascularization with PTCA treatment because of either diffuse, extensive coronary artery disease or chronic multiple stenoses were considered unsuitable for this procedure and thereby eligible for inclusion in this study.

One hundred sixteen patients were selected from the patient population accepted for CABG. These patients were subjected to a second assessment, including a thorough physical examination and case history by the two cardiologists conducting the study in which inclusion and exclusion criteria were carefully weighed. These cardiologists have extensive experience of SCS treatment in ischemic heart disease.

Patients were excluded if they were considered unsuitable for CABG, unable to manage the SCS device, or unable to follow the

study protocol. Patients with myocardial infarction within the last 6 months were excluded.

After these examinations, 104 patients who complied with the inclusion criteria remained, which amounted to 3.2% of 3272 patients accepted for CABG in the region during the inclusion period.

The study was approved by the ethical committee of the University of Gothenburg. The patients received both written and thorough verbal information. After informed consent, each patient was randomized.

Patients

One hundred four patients were included in the study (mean age, 68.9 years; 21 women with a mean age of 69.4 years and 83 men with a mean age of 68.9 years). Mean ejection fraction was 57.5% (range, 19% to 86%). Fifty-one patients were randomized to CABG (mean age, 68.7 years; 9 female patients [18%]), and 53 were randomized to SCS (mean age, 72.2 years; 12 female patients [23%]). The time from inclusion to operation was on average 1.9 months in the CABG group and 1.0 month in the SCS group. This difference was statistically significant ($P < .0001$).

At the time of inclusion, 2 of 104 subjects worked full-time, 5 worked part-time, 21 were on sick leave due to cardiac disease, and 76 had retired. Additional patient data are presented in Table 2.

Stratified randomization was not used. A retrospective scoring for risk of surgical complications according to Higgins et al¹⁸ was performed and yielded a mean of 4.2 points. However, differences between the two groups were negligible except for current smoking and nephrologic disease.

End Points

The aim of the ESBY study was to compare CABG with SCS on the basis of an "intention-to-treat" design. The primary goal was to compare the effect on the end points of symptoms and myocardial ischemia. Effects on symptoms were assessed in terms of frequency of anginal attacks, consumption of short-acting nitrates, and self-estimated symptom relief. Myocardial ischemia was assessed by means of exercise tests before and 6 months after surgery. Secondary end points were total mortality and morbidity. Mortality was subgrouped into cardiac death and death from other causes. Morbidity was subgrouped into cardiovascular and cerebrovascular morbidity.

Spinal Cord Stimulation: Surgical Technique and Equipment

The stimulation equipment was implanted by use of a sterile technique. The patient was placed on an x-ray-translucent table. The operation was performed under local anesthesia to allow the patient and the surgeon to communicate during the perioperative test stimulation. The electrode was positioned so that the patient felt a pricking sensation in the region of anginal pain. The adequate position is when the stimulation produces paresthesia covering the area of radiation of anginal pain, ie, confirming that the spinal segments in which the cardiac innervation is located are stimulated.

The skin incision was made at the midline in the midthoracic region. The epidural space was punctured at the level of T6. A Tuohy-type needle was advanced in the midline through the intervertebral spaces into the epidural space. The electrode tip was placed at the level of T1 to T2. The pulse generator was placed in a subcutaneous pouch below the left costal arch. An extension lead was tunneled subcutaneously to the midline incision and connected to the electrode. The pulse generator was telemetrically programmed with two preset stimulation strengths, one stronger that was used in case of established anginal pain and one weaker that was used as prophylactic treatment. The latter was used for at least 2 hours four times daily. A commercially available electrical device (Medtronic) was used. The pulse generator is turned on or off when the patient quickly touches the skin over the pulse generator with an external magnet. The patient can also use the magnet to switch between the two preset stimulation strengths.

TABLE 2. Patient Characteristics

| | CABG (n=51) | SCS (n=53) |
|---|----------------|----------------|
| Male, n | 42 | 41 |
| Female, n | 9 | 12 |
| Mean age (range), y | 68.7 (40–81) | 72.2 (42–82) |
| Angina class, n (%) | | |
| Class 3 | 47 (94) | 50 (94) |
| Class 4 | 3 (6) | 3 (6) |
| Current medication, n (%) | | |
| Short-acting nitrates | 48 (94) | 51 (96) |
| β -blocker | 43 (84) | 48 (91) |
| Anticoagulants | 3 (6) | 4 (7.5) |
| ACE inhibitors | 8 (16) | 9 (17) |
| Long-acting nitrates | 43 (84) | 39 (74) |
| Calcium channel inhibitor | 25 (49) | 21 (40) |
| Aspirin | 42 (83) | 46 (87) |
| History | | |
| Current smoking | 10 (20%) | 2 (4%) |
| Myocardial infarction | 34 (67%) | 36 (68%) |
| Diabetes | 13 (25%) | 14 (26%) |
| Cerebrovascular disease | 9 (18%) | 11 (21%) |
| Carotid artery stenoses | 11 (22%) | 12 (23%) |
| Nephrologic disease | 6 (12%) | 12 (23%) |
| Hypertension | 19 (37%) | 23 (43%) |
| Peripheral vascular disease | 14 (27%) | 13 (25%) |
| Hyperlipidemia | 10 (20%) | 8 (15%) |
| Previous CABG | 11 (22%) | 14 (26%) |
| Mean Higgins score (range) | 4.1 (0–10) | 4.2 (0–11) |
| Coronary angiogram, n (%) | | |
| One-vessel disease | 1 (2) | 5 (9) |
| Two-vessel disease | 10 (20) | 14 (26) |
| Three-vessel disease | 39 (76) | 34 (64) |
| Complicated anatomy (ie, peripheral coronary atherosclerosis) | 30 (59) | 29 (55) |
| Mean ejection fraction (range) | 58.0% (26–82%) | 57.0% (19–86%) |

CABG indicates coronary artery bypass graft surgery; SCS, spinal cord stimulation.

Exercise Tests

Exercise tests were performed according to a standardized protocol with a 12-lead ECG on a bicycle ergometer. The tests were of a stepwise, continuous, and maximum design, starting at 30 or 50 W, depending on the patient's estimated capacity. The workload was increased by 10 W/min. Blood pressure, heart rate, and ECG changes were recorded at each level. Exercise was stopped when the patient experienced maximum effort, chest pain rated 6 to 7 of 10 on the Borg scale or dyspnea rated 6 to 7 of 10, or showed signs of severe myocardial ischemia (>3-mm ST-segment depression) or hypotension. The calculated measures were exercise capacity, ischemic ECG changes (ie, degree of ST-segment depression), and the rate-pressure products at comparable and maximum workloads. Patients randomized to SCS had stimulation treatment discontinued 24 hours before the second exercise test.

Comparable workload was defined as the lowest individual maximum workload that a patient achieved in both tests and thus represents the highest workload that can be used for a comparison at a similar level of cardiac stress.

Symptom Relief

Clinical outcome was recorded on a questionnaire given to the patient shortly after the exercise tests. Patients reported their frequency of anginal attacks and consumption of short-acting nitrates per week. At follow-up, the subjective treatment effect was recorded with the use of a scale ranging from 1 (better or free from symptoms) to 2 (unchanged or worse).

Mortality and Morbidity

Mortality was characterized as a fatality occurring between the inclusion examination date and 6 months thereafter. Cardiac events were monitored as myocardial infarction, angina pectoris, or heart failure that was fatal or required hospital admission. A cerebrovascular event was characterized as acute focal cerebral ischemia lasting >24 hours (definite stroke) and corresponding focal signs at the separate follow-up neurological examination that were not noted at the preinclusion examination.

Statistical Methods

Efficacy parameters (ischemia and symptom variables) were analyzed by use of repeated measures ANOVA, with randomization as the grouping variable. Tests were conservatively calculated as described by Greenhouse and Geisser.²³

Differences in mortality and morbidity were assessed by use of Kaplan-Meier probabilities and Cox proportional hazard models.²⁴ Morbidity was assessed as a combined end point, ie, including both fatal and nonfatal cardiac and cerebrovascular events. In each Cox regression calculation, a patient was allowed to participate with only one event.

Results

Effects on Symptoms and Myocardial Ischemia

In both groups, a majority of the patients (79.5% in the CABG group and 83.7% in the SCS group) had a good self-estimated treatment effect, and the treatment methods did not differ in this respect. Both treatment methods caused a decrease in the frequency of anginal attacks ($P<.0001$) and consumption of short-acting nitrates ($P<.0001$). There were no differences between the groups in these respects (Table 3).

The CABG group had an increase in exercise capacity ($P=.02$) and less ST-segment depression on maximum ($P=.005$) and comparable ($P=.0009$) workloads than the SCS group. The rate-pressure products on maximum ($P=.0003$) and comparable ($P=.03$) workloads were higher for CABG than for SCS subjects (Table 4).

Follow-up

Fifteen patients did not participate in the follow-up examination. Eleven of these were in the CABG group. Of these, 7 died before the follow-up appointment and 2 were not operated on, one because the risk was reconsidered (unacceptably high) after the first evaluation and the other because he became free from anginal symptoms before surgery.

In the SCS group, four patients were lost to follow-up. Two patients had emergency CABG because of unstable angina and were lost to follow-up. One patient died before follow-up. The reasons for the loss of the remaining three patients (two CABG and one SCS patient) to follow-up were lack of compliance or medical complications not related to the study.

TABLE 3. Effect on Anginal Symptoms

| | Preoperative | Follow-up | P | |
|---|--------------|------------|---|---------------------------|
| | | | Comparison of Preoperative vs Postoperative | Comparison of CABG vs SCS |
| Nitrate consumption, doses/week | | | | |
| CABG | 13.7 (12.1) | 3.1 (8.7) | <.0001 | |
| SCS | 15.2 (18.8) | 4.1 (10.5) | <.0001 | NS |
| Anginal attack frequency, attacks/wk | | | | |
| CABG | 16.2 (12.6) | 5.2 (10.3) | <.0001 | |
| SCS | 14.6 (13.5) | 4.4 (7.4) | <.0001 | NS |
| Self-estimated treatment effect, % better or symptom free | | | | |
| CABG | | 79.5% | | |
| SCS | | 83.7% | | NS |

CABG indicates coronary artery bypass graft surgery; SCS, spinal cord stimulation. Values are given as mean (1 SD).

Cardiac and Cerebrovascular Mortality and Morbidity

Eight patients died between randomization and follow-up. Seven patients in the CABG group died, three before surgery. Six deaths were cardiac in nature, and the seventh patient had both myocardial as well as computer tomography-verified cerebral infarctions. One patient in the SCS group died of a myocardial infarction 3 months after implantation. The mortality rate was 13.7% in the CABG group and 1.9% in the SCS group,

respectively. This difference in mortality was significant ($P=.02$) on an intention-to-treat basis (Tables 5 and 6).

Cardiac events did not differ between the groups. There were 8 cerebrovascular events in the CABG group and 2 in the SCS group. This difference in cerebrovascular morbidity was statistically significant ($P=.03$). Three patients in the CABG group and 2 patients in the SCS group had both cardiac and cerebrovascular events. Total cardiac and cerebrovascular morbidity (including patients who had one or

TABLE 4. Exercise Tests

| | Preoperative | Follow-up | P | |
|---|--------------|--------------|---|---------------------------|
| | | | Comparison of Preoperative vs Postoperative | Comparison of CABG vs SCS |
| Maximum workload capacity, W | | | | |
| CABG | 86.2 (23.1) | 99.0 (28.0) | .002 | |
| SCS | 90.6 (29.2) | 92.2 (33.7) | NS | .02 |
| ST-segment depression on maximum workload, mm | | | | |
| CABG | -1.46 (1.36) | -0.68 (1.52) | .0009 | |
| SCS | -2.01 (1.17) | -1.95 (1.18) | NS | .005 |
| ST-segment depression on comparable workload, mm | | | | |
| CABG | -1.40 (1.39) | -0.46 (1.13) | .0001 | |
| SCS | -1.73 (1.14) | -1.66 (1.24) | NS | .0009 |
| RPP on maximum workload, mm Hg/min $\times 10^3$ | | | | |
| CABG | 21.6 (5.4) | 25.4 (5.6) | <.0001 | |
| SCS | 21.4 (5.8) | 21.2 (6.9) | NS | .0003 |
| RPP on comparable workload, mm Hg/min $\times 10^3$ | | | | |
| CABG | 21.3 (5.4) | 23.0 (5.4) | .034 | |
| SCS | 20.9 (5.7) | 20.6 (6.5) | NS | .03 |

CABG indicates coronary artery bypass graft surgery; SCS, spinal cord stimulation; and RPP, rate-pressure product. Values are given as mean (1 SD).

TABLE 5. Mortality and Morbidity

| | CABG | SCS | P |
|--------------------|------|-----|----------|
| Mortality | 7 | 1 | .02 |
| Nonfatal morbidity | 7 | 7 | NS |
| Total morbidity | 14 | 8 | NS (.08) |

CABG indicates coronary artery bypass graft surgery; SCS, spinal cord stimulation.

Mortality and morbidity tabulated as number of patients suffering one or more of the events listed.

more fatal or nonfatal cardiac or cerebrovascular event) was 14 patients in the CABG group and 8 in the SCS group, which was not statistically significant ($P=.08$).

Crossover

Three patients randomized to CABG received SCS instead; one patient refused CABG and one was reevaluated immediately before CABG and considered to present an unacceptably high perioperative risk. The third patient was implanted with an SCS device 2 months after CABG surgery because of a quick relapse of severe angina. Three patients randomized to SCS had a CABG because of unstable angina.

Discussion

The patients included in the present study were selected by use of the criteria mentioned above: no prognostic indication for CABG and increased risk of surgical complications. This selection was made after a thorough individual evaluation of all the factors known to be associated with an increased risk of surgical complications (see introduction and Table 1). Stratified randomization was not used owing to the limited number of patients. A retrospective scoring for surgical risk according to Higgins et al¹⁸ was performed to further describe the patients. This yielded a mean score of 4.2 points, which is above the reported cutoff point for increased morbidity. However, because the scoring was done retrospectively, it should be interpreted with caution. This scoring system was not in use at the start of the study, and one of the factors considered of importance for surgical outcome at inclusion was complicated coronary anatomy, which is not considered in this scoring system. However, differences between the two groups were negligible except for current smoking, which had a higher representation in the CABG group, and nephrologic disease, which occurred more frequently in the SCS group.

Both treatment methods had a similar effect on symptom relief, decrease in anginal attack frequency, and consumption of short-acting nitrates. However, CABG led to increased exercise capacity and decreased ST-segment depression at

TABLE 6. Causes of Mortality and Morbidity

| | CABG | SCS | P |
|------------------------|------|-----|-----|
| Cardiac events | 9 | 8 | NS |
| Cerebrovascular events | 8 | 2 | .03 |

CABG indicates coronary artery bypass graft surgery; SCS, spinal cord stimulation.

Note that the number of events are listed in this table. Five patients suffered two events (both cardiac and cerebrovascular).

follow-up compared with SCS. The mortality in the CABG group was significantly higher on an intention-to-treat basis.

The treatment of patients with severe angina pectoris and increased complication risk in association with cardiac surgery is a clinical problem because the success rate in this patient group is considered to be limited and the mortality rate is elevated. Still, these patients have disabling symptoms, and therapeutic alternatives to CABG have previously been lacking.

Both methods had satisfactory effects on symptom relief, decrease in anginal attacks, and consumption of short-acting nitrates. In these respects, the strategies did not differ. This is a crucial observation because the indications for invasive procedures were based only on symptoms in all patients.

CABG had a significant effect on ischemic variables such as exercise capacity and ST-segment depression, whereas SCS did not affect these variables. These effects of CABG were as expected and are in accordance with those reported in previous studies.^{25,26} The lack of effect of SCS on exercise capacity and ST-segment depression in the present study was in contrast with previous studies on the immediate effects of electrostimulation on experimentally induced myocardial ischemia, in which a consistent and highly reproducible anti-ischemic effect has been observed.^{6-10,12-14,27-44}

In the present study, SCS was discontinued for 24 hours before the exercise test. This was different from the design used in previous studies, in which ischemia monitoring has been performed during ongoing stimulation. The reason for choosing to discontinue the stimulation in the present study was the need to assess the possible long-term effects on myocardial ischemia,⁹ because the anti-ischemic effect during ongoing stimulation has been thoroughly documented in earlier studies.^{6-10,12-14,27-44} The results of the present study indicate that there are no long-term effects on myocardial ischemia after treatment has been discontinued for 24 hours. This should be considered when the results of the present study are evaluated, ie, exercise tests should be performed during ongoing stimulation. Furthermore, in the clinical setting, it is essential to continue daily stimulation even if the patient is free from cardiac symptoms. The study design of the above-mentioned studies on the immediate effects of SCS on myocardial ischemia is more similar to the daily-life setting, in which the patient uses the stimulator in situations in which myocardial ischemia occurs.

Mortality was significantly higher in the CABG group when calculated on a strict intention-to-treat basis. However, three of seven patients died while waiting for surgery.

Cardiac morbidity did not differ between the two strategies. Cerebrovascular morbidity was significantly higher in the CABG group. This was expected because stroke is a well-known complication in connection with bypass surgery.⁴⁵

Study Limitations

This study included a limited number of patients and a limited follow-up time, and the mortality and morbidity results should therefore be interpreted cautiously.

The study was not blinded because the surgical procedures differ significantly. Thus, it was not possible to blind the

treatment to either patient or physician. However, tasks were strictly divided among the investigators to minimize bias, ie, the investigators involved in the tests were not engaged in patient contact and follow-up and vice versa.

As pointed out, it would have been an advantage to have two exercise tests at follow-up, the second one during ongoing stimulation to evaluate the well-known immediate anti-ischemic effects of SCS compared with CABG. This was not done for practical reasons.

Conclusions

The results of the present study indicate that SCS is an equivalent alternative to bypass surgery in this patient group to obtain symptom relief. The more pronounced anti-ischemic effect of CABG could be explained by the fact that treatment was discontinued for patients in the SCS group, unlike the CABG patients. When all aspects are taken into consideration, it seems reasonable to conclude that SCS may be a therapeutic alternative for patients with an increased risk of surgical complications and no prognostic benefit from surgery. However, these results warrant further research in this field.

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