Treatment of chronic refractory angina pectoris—light at the end of the tunnel?

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This editorial refers to 'An open label, single-centre, randomized trial of spinal cord stimulation vs. percutaneous myocardial laser revascularization in patients with refractory angina pectoris: the SPIRIT trial† by D. McNab et al., on page 1048

Despite increasing number of coronary interventions over recent years, there is still a considerable number of patients suffering from chronic refractory angina pectoris. The volume of no option patients is not exactly known, but has been suggested to be 30 per million inhabitants per year; other estimates are 2.5–5% of coronary angiography procedures. The group of no option patients includes those who have angina despite optimal medical therapy; they may not have been offered PCI or CABG because of severe diffuse coronary artery disease, or they who continue to experience severe angina after CABG, PCI, or both.

A considerable number of therapeutic strategies have been investigated to treat severe chronic angina, such as transcutaneous electric nerve stimulation (TENS), left stellate ganglion blockade (LSGB), endoscopic thoracoscopic sympathectomy (ETS), thoracic epidural anaesthesia (TEDA), external balloon counter pulsation (EECP), stem cell therapy, and finally myocardial laser revascularization by surgical (TMR) or percutaneous (PMR) technique or spinal cord stimulation (SCS).†

These interventions have been suggested to have primary effect on pain; there is no valid evidence that any of these procedures reduces any clinical major cardiac endpoints. Only a few of these options have undergone the test of randomized studies, so the impact of a placebo effect on pain is largely not known.

When trying to orientate in the jungle of mechanical or implant options to decide on how to advice patients, it may be helpful to look at the natural course of chronic refractory angina. We know that this group of patients often are in agony with severe coronary artery disease. It is therefore natural to first look at the data on mortality with drug therapy only. The suggestion of a mortality over 1-year of up to 17% is often quoted, however, there is other evidence suggesting that this figure may be too high. If we look at the medically treated placebo groups of previous myocardial laser studies that did not allow crossover, the 1-year mortality was 1–5% for percutaneous myocardial laser studies and 4–8% for surgical myocardial laser, and 3-year mortality of up to 24%.‡

Spontaneous remissions of even severe angina do occur. Again, looking at the medically treated groups of randomized studies, between 0–19% of patients included in PMR trials and 0–32% for TMR studies had a reduction of at least two CCS angina classes over 12 months, and 0–44% at 3 years. About 7–69% of patients may expect to be re-admitted to hospital for cardiac causes during the first 12 months, but there is no consistent finding in the studies that re-admissions may be reduced by intervention beyond drug therapy. Thus, when considering treatment options that may have their own inherent complications and may be mortality, this must be weighed up against the possible therapeutic benefit and data on the natural course of the disease. We may learn from the past studies that chronic refractory angina is probably not an inert situation but rather has a large variation in symptoms over time.

McNab et al. report the results of an open label, single centre, parallel group randomized comparison of SCS and percutaneous myocardial laser (SPIRIT trial). The primary goal was to compare exercise treadmill time; secondary goals were comparison of angina functional class and quality-of-life measurements. They found no difference after 12 months between the two treatments in the main endpoint exercise time, nor in the secondary angina endpoint. PMR/SCS-related events during 12 months were 3 vs. 27, respectively. There were no serious events related to therapy. Neither of the two treatment options used in the study is widely used, both treatment procedures carry a certain risk. SCS procedure requires co-operation between anaesthetists and cardiologist, and the study was conducted in a tertiary referral centre. Consequently, the study population is rather small, but the statistical power calculation must be accepted; hence, we accept the main conclusion that there is little evidence of a difference between the two therapies. The interpretation of the comparison of angina is not so clear because the impact of placebo or the validation of interpretation of angina after a one-time procedure vs. a permanent implant may be uncertain. Another drawback with this trial is that it was

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not powered to show an increase in exercise time between baseline and 12 months. By looking at the exercise figures in Table 3, there was no numerical difference for either therapy between baseline and 12 months; this is in line with the negative results of multicentre myocardial laser trials. In summary, the SPIRIT trial showed that there was no difference between the treatment groups, while the important question of an improvement between baseline and 12 months is left open.

Has this question been answered by other studies? There is large volume of previous basic and clinical studies on SCS and PMR. The main mechanisms that have been suggested to explain the effects of myocardial laser are blood supply directly via channels, denervation, angiogenesis, placebo, and injury with scarring. The idea of supplying the myocardium with blood via channels was conceived in the 1960s. There is still debate both on long-term patency of the channels and on whether the intramyocardial pressure exceeds that of the left ventricular cavity impeding filling of the myocardium. There is ample evidence to suggest that the channels are invaded by granulation tissue and close in a matter of few weeks. The same controversy exists on the formation of new blood vessels after intervention with laser. However, it is questionable whether vessels formed by angiogenesis have the capacity to nourish the myocardium and if the newly formed vessels have a communication with the left ventricle. Denervation as a mechanism for laser benefits has not been convincingly proven. Suggested mechanisms for SCS have been such as functional sympathectomy, reduced lactic acid production, reduced cardiac oxygen need, and increased coronary blood flow. Basic research on SCS have in general elucidated its physiological effects. There is no clear evidence from the previous animal research that either myocardial laser or SCS should reduce ischaemia and thereby improve left ventricular function in chronic ischaemia.

Data from early uncontrolled clinical studies indicated that myocardial laser improved left ventricular function. The controlled studies are not consistent on this issue. A reduction in reversible ischaemia has been suggested, but follow-up was incomplete. When only studies without crossover and with adequate follow-up are taken into account, it is fair to conclude that myocardial laser does not improve the left ventricular function indicated by exercise time, ejection fraction, or ST changes in the EKG. The ESBY study randomized SCS vs. CABG in a selected cohort of patients with angina pectoris. There was no increase of exercise time in patients randomized to SCS. Thus, clinical studies indicate that neither myocardial laser nor SCS improves left ventricular function.

What is the evidence that these treatment options really relieve pain? All the randomized clinical studies on myocardial laser delivered via open chest surgery show a highly significant reduction of at least two angina classes in 25–78% of patients. Percutaneous myocardial laser has also been effective with a reduction of two CCS angina classes at 12 months in 35% of patients in two randomized studies. Two randomized studies have been able to evaluate percutaneous myocardial laser in a blinded way, one had a true sham-controlled group. The results were conflicting. This may be attributed to differences between the studies in terms of design and type of laser, but such post hoc interpretation of studies is always difficult. Unless another study is performed to strengthen the evidence in one direction, the question is really left open. The ESBY study showed that SCS had a significant effect on reduction of angina and was comparable to CABG, but CABG increased exercise time in contrast to SCS. Both SCS and PMR have been shown to have lasting effects over 3–5 years, but such follow-up has only been open label.

Do we have to know how devices work to be able to believe in efficacy? There is probably general agreement among the cardiologists and cardiac surgeons that every new device or treatment modality should be based on an idea validated in basic laboratory research to elucidate mechanisms. For myocardial laser, it has been shown that the original mechanism—the creation of myocardial channels—is most probably not valid. In spite of this, application of the method on patients continued parallel with the search for new mechanisms in the animal laboratory. There is not enough evidence to conclude that SCS reduces ischaemia, and even the mechanism of pain relief is not exactly known. The device’s suggested effect on pain relief has not been evaluated in randomized blinded studies. Such studies may be difficult to perform because of the parasthesia and vibration sensation of the active device. On the other hand, if blinding is claimed to be difficult then even more scrutiny must be applied to the methods and results of the available studies.

Should these treatment options be offered to patients with chronic refractory angina pectoris? The answer is definitely no to a large-scale use. The European guidelines assign SCS a level A recommendation, in the American Heart Association/American College of Cardiology guidelines TMR (not PMR) has a IIa recommendation. Clearly, it is prudent to inform patients about the large variability of symptoms over time and the frequent occurrence of spontaneous improvement. Furthermore, device treatment is not without risk and the price to pay in the form of complications may in many cases be too high for a treatment, which only at the very best may modulate pain. Finally, it cannot be excluded that a highly selected small cohort of patients with persistent severe angina over time may benefit from SCS or myocardial laser performed on a palliative indication in specialized centres with low complication rates. Consequently, some hospitals may choose to include SCS or PMR as a part of their palliation strategies. However, future research on chronic refractory angina should be directed towards new emerging therapies.

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References


Clinical vignette

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Septic peripheral embolization from *Haemophilus parainfluenzae* endocarditis

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A 40-year-old, previously healthy lady with good dentition, presented with pyrexia of unknown origin for 6 weeks. Physical examination was unremarkable. Initial cultures were negative. Rheumatoid factor was elevated but she did not have any joint symptoms. Because of severe thrombocytopenia which developed during hospitalization, bone marrow examination was done, which showed normal megakaryocytic activity and reactive haemophagocytosis. Marrow cultures subsequently yielded *Haemophilus parainfluenzae*. However, transthoracic and transesophageal echocardiogram did not show any vegetation. She then developed a painful localized erythematous swelling on her right foot (Panel A). In view of unabating fever and unknown primary focus of infection, a positron emission tomography (PET) scan was performed, which revealed a splenic embolic infarct and intense uptake at cardiac fibrous ring near aortic root (Panels B and C). A computed tomography (CT) of the heart demonstrated a vegetation 0.7 x 1.3 cm² at tip of anterior mitral valve leaflet (ventricular surface) which extended into the chordae (Panel D). The evolving clinical picture was suggestive of infective endocarditis with septic peripheral embolization. She eventually underwent mitral valvul surgery because of suboptimal clinical response and post-operatively, made an uneventful recovery.

*Haemophilus endocarditis* often produces bulky valvular lesions and is frequently complicated by arterial embolization. Special culture medium is necessary for isolation of *Haemophilus* species because it is a slow growing microorganism.

Panel A. Focal area of inflammation on right foot (encircled) due to septic microemboli.
Panel B. PET scan showing wedge-shaped hypodense area at anterior aspect of spleen with no metabolism with adjacent focus of increased glycolysis (white arrow).
Panel C. PET scan showing hypermetabolic focus at base of left ventricle near aortic root (white arrow).
Panel D. Dynamic gated CT of the heart showing large vegetation at anterior mitral valve leaflet (black arrow).