EDITORIAL

Alternative treatments for angina

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Angina pectoris in patients with ischaemic heart disease is usually treated successfully with anti-ischaemic drugs and percutaneous or surgical coronary interventions. In some patients, however, angina attacks are not prevented by optimal medical treatment and coronary lesions are judged unsuitable for coronary revascularisation. These patients with refractory angina have recurrent, disabling symptoms, which markedly limit daily activities.

The precise prevalence of refractory angina is not known. However, the number of patients with angina not suitable for coronary interventions is likely to increase in the future, in particular, because of the prolonged survival of patients with extensive, complex coronary artery lesions, often already treated by multiple coronary revascularisation procedures.

Although several alternative treatments have been proposed for refractory angina[1] (box 1), a sufficiently large number of studies and results are available only for some treatment options. The most widely assessed treatments are briefly discussed here.

SPINAL CORD STIMULATION

In spinal cord stimulation (SCS), an electrocatheter is introduced into the epidural space through an intervertebral dorsal puncture to stimulate the dorsal horn segments of the spinal cord receiving cardiac nerve fibres (usually C7–T2). The electrocatheter is connected through a subcutaneous lead extension to a pacemaker-like pulse generator, which is usually implanted in a subcutaneous abdominal pouch.

The therapeutic mechanisms of SCS are not fully understood, but both an antalgic effect, mainly due to modulation of pain signal in the spinal cord, and an anti-ischaemic effect, mainly related to modulation of adrenergic activity, have been suggested.

There are no substantial clinical contraindications to SCS, and no severe complications related to the treatment have been reported. However, side effects including catheter dislodgement requiring repositioning, pain at the device site and device migration may occur in a large proportion of patients; furthermore, infection of the device system may also occur.

Several studies spanning >20 years have consistently shown beneficial effects of SCS on angina and quality of life in patients with refractory angina.[2 3] Yet, the real benefits of SCS could be questioned because of the lack of placebo-controlled trials. Indeed, appreciation of paraesthesias in the chest area of referred angina during SCS has until now been considered indispensable for its antianginal effects, precluding the inclusion of unbiased placebo control groups in clinical studies.

Interestingly, a randomised trial of SCS versus coronary bypass surgery[4] has already suggested that the benefits of SCS are unlikely to be explained by a placebo effect only. Indeed, patients treated by SCS showed clinical improvement comparable to that of patients treated by bypass surgery both at short-term[4] and long-term follow-up.[5]

In a recent prospective controlled study, we have also shown that SCS maintains its effects on episodes of refractory angina and quality of life at long-term (3-year) follow-up in patients with microvascular angina (syndrome X),[6] further suggesting that the clinical benefits are unlikely to be related to a mere placebo effect, which usually decreases over a few months.

Stronger evidence of the antianginal effect of SCS comes now from a study by Eddicks *et al*[7], in which, for the first time, a ''placebo'' group of SCS has been included. In this study, 12 patients with refractory angina underwent four different kinds of SCS treatment, each lasting 4 weeks, in a random sequence: intermittent (2 h three times a day) paraesthetic SCS; continuous paraesthetic SCS; intermittent subthreshold SCS (ST-SCS, at 85% of paraesthetic threshold); and continuous 0.1 V (inactive) stimulation. The latter was a ''placebo'' control of ST-SCS. Indeed, patients did not feel any sensation during both these phases of the study, but the stimulation intensity during ST-SCS could be sufficient to cause active SCS, which could not occur, instead, with the 0.1 V intensity. Thus, the study was based on the novel hypothesis that ST-SCS could be effective on angina. Compared with the inactive phase, ST-SCS did improve the primary end point of the study (the distance in the 6-min walking test) and several secondary end points, thus excluding a mere placebo effect of the treatment. Furthermore, the clinical improvement was in several aspects similar during the three active phases of SCS, suggesting that ST-SCS could be as effective as paraesthetic SCS.[7]

Some caution, however, is required in the interpretation of these findings, because of the small number of patients. In particular, the similar efficacy of ST-SCS and paraesthetic SCS deserves further assessment, as data on relevant secondary end points (angina frequency, nitrate use, Canadian Cardiovascular Society (CCS) angina

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Abbreviations: CCS, Canadian Cardiovascular Society; EECP, enhanced external counterpulsation; MLR, myocardial laser revascularisation; SCS, spinal cord stimulation; ST-SCS, subthreshold spinal cord stimulation

Box 1: Main proposed treatment options for refractory angina pectoris

- Spinal cord stimulation (SCS)
- Surgical/percutaneous myocardial laser revascularisation
- Angiogenic therapy
- Enhanced external counterpulsation
- Neuromodulatory treatments other than SCS (transcutaneous electrical nerve stimulation, left stellate ganglectomy)
- Epidural anaesthesia
- Intermittent urokinase treatments
- Chelation treatments
- Heart transplantation

class) suggest better results with paraesthetic than with subthreshold SCS.[7]

MYOCARDIAL LASER REVASCULARISATION

Myocardial laser revascularisation (MLR) creates small channels through the myocardium (from the epicardium to the endocardium in the surgical approach and in the inner-mid myocardial layers in the percutaneous approach) with the purpose of directly bringing oxygen to ischaemic areas through them. Owing to the early closure of these channels, however, other mechanisms for the antianginal effect of MLR have been suggested, including cardiac denervation and stimulation of local angiogenesis.[1 8]

Surgical MLR resulted in improvement in angina status and effort tolerance compared with maximal medical treatment in several randomised clinical trials, but it is associated with a significant occurrence of serious peri-procedural adverse events, including death (3% in selected low-risk patients, but up to 20% in unselected populations).[8]

The development of percutaneous MLR consistently reduced procedure-related complications, but relevant clinical events, including death, myocardial infarction, heart failure, cardiac perforation and stroke, may still occur. Moreover, in two randomised blind studies, percutaneous MLR showed no benefits with regard to angina status compared with sham interventions,[9 10] although a significant improvement in angina symptoms was reported in a third small study.[11]

Notably, in a recent small randomised trial, SCS and percutaneous MLR showed similar beneficial effects on the primary end point of exercise tolerance; SCS, however, showed better results for angina status, as assessed by changes in CCS angina class.[12]

ANGIOGENIC THERAPY

Angiogenic therapy includes a heterogeneous group of therapeutic techniques that aim to stimulate the formation of new coronary vessels in ischaemic myocardial regions, in an attempt to improve myocardial perfusion.[1]

Placebo-controlled trials have been performed involving intracoronary or intramyocardial delivery of angiogenic factors or of virus vectors leading modified genes encoding for angiogenic factors and able to colonise ischaemic myocardial areas in the attempt to increase local angiogenesis. Disappointingly, these studies have shown no or negligible effects of active treatment on symptom relief and myocardial ischaemia, compared with controls.[13 14]

As invasive procedures are usually required for angiogenic therapy, a small, but significant, number of serious adverse events may occur. Furthermore, stimulation of angiogenesis in other organs, potentially favouring proliferative diseases, and immunological reactions to extraneous material are further matters of concern.[1]

ENHANCED EXTERNAL COUNTERPULSATION

Enhanced external counterpulsation (EECP) consists of the sequential inflation of three pairs of cuffs, wrapped around the calves, the lower thighs and the upper thighs, during diastole, at a pressure of 250–300 mm Hg. The cuffs are simultaneously released at the onset of systole. An EECP treatment usually consists of 35 one-hour sessions over a period of 7 weeks.[15]

During diastole, EECP increases blood pressure and blood venous return to the heart, whereas cuff deflation during systole decreases peripheral vascular resistance and cardiac workload. Suggested mechanisms for the antianginal effect of EECP include improvement in endothelial function, stimulation of coronary collateral vessels, and changes in peripheral circulation.[15]

The best evidence of the effect of EECP in refractory angina comes from the Multicentre Study of EECP, which randomised 139 patients to standard EECP or ''inactive'' counterpulsation (pressure applied to the cuffs of 75 mm Hg).[16] EECP, but not the ''sham'' treatment, significantly improved time to 1 mm ST segment depression in the exercise stress test and reduced angina episodes, compared with the pre-treatment test. Accordingly, registry data show improvement of $\geqslant$1 CCS angina class in 70–80% of patients with refractory angina treated by EECP.[15]

In some clinical conditions, however, including marked aortic regurgitation, uncontrolled hypertension, aortic aneurysm or dissection and peripheral venous disease, EECP is potentially dangerous, and is therefore contraindicated. Furthermore, caution is required in patients with low left ventricular ejection fraction, in whom EECP can precipitate acute heart failure and appears to be associated with an appreciable occurrence of serious adverse events, including death and myocardial infarction.[17] However, when patients with increased procedure-related risks are excluded, EECP appears to be sufficiently safe, although some unpleasant side effects, including local pain, swelling, oedema and skin lesions, may occur in a significant number of patients.

WHAT KIND OF TREATMENT FOR REFRACTORY ANGINA?

Refractory angina is an emerging issue in clinical practice, which is also receiving appropriate consideration in international guidelines.[18 19] As there is no suggestion that any of the alternative treatments for refractory angina may improve prognosis, indications about the choice of treatment should be mainly based on a careful assessment of the balance between the benefits for the disabling symptoms of patients and the risk associated with the different treatment options. In this evaluation, evidence that angina relief is not merely related to a placebo effect, which is probably an important component of the increased symptomatic benefits in all proposed treatments, should be taken into appropriate account.

The evidence, at present, indicates that, the adequately assessed treatments for refractory angina, SCS has the best efficacy/safety profile, because of the substantial absence of contraindications and severe adverse events, which makes it applicable to almost all patients with refractory angina. SCS has been shown to be effective also in patients with microvascular angina[6] and the suggestion from several studies that its antianginal efficacy goes beyond a mere placebo effect[4–6] is now supported by the data of the first placebo-controlled study of SCS by Eddicks *et al*.[7]

Also for EECP there is evidence that the antianginal efficacy is not merely related to a placebo effect.[16] Furthermore, when

patients with contraindications or potential procedure-related risks are excluded, EECP presents a favourable efficacy/safety profile and is, therefore, a valid treatment for refractory angina. In patients with increased risk of EECP-related adverse events,[17] however, SCS seems to be the first-choice treatment.

Current evidence, on the other hand, does not support the utilisation of MLR and angiogenic therapy in the treatment of patients with refractory angina.

REFERENCES

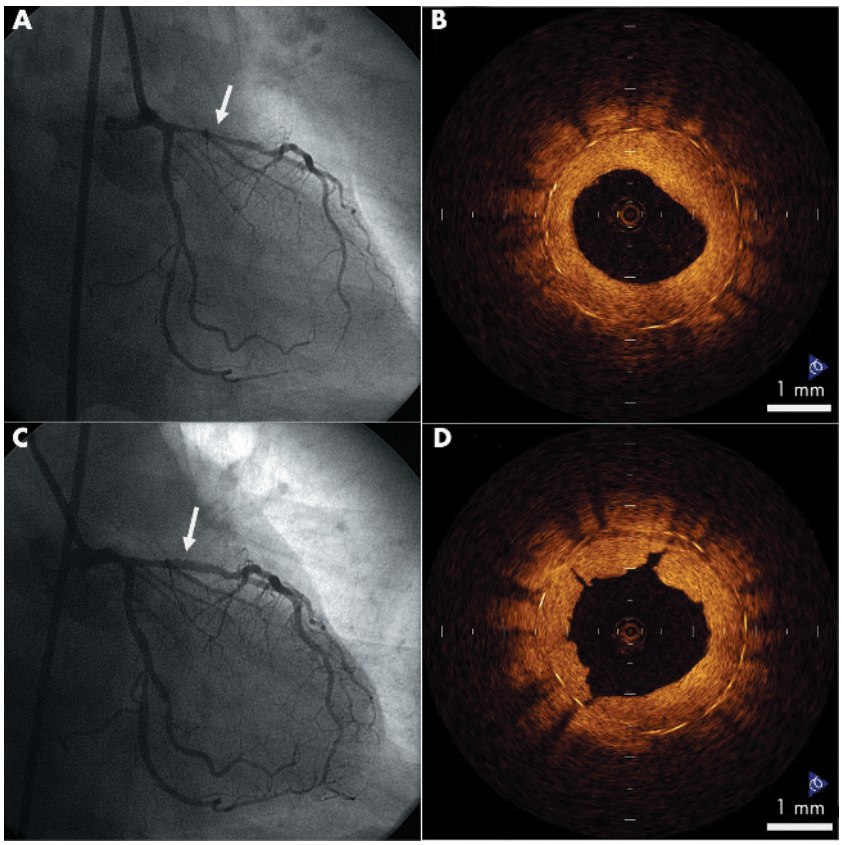
1 **Kim MC**, Kini A, Sharma SK. Refractory angina pectoris. *J Am Coll Cardiol* 2002;**39**:923–34.
2 **TenVaarwerk AM**, Jessurun GAJ, DeJongste MJL, for the Working Group on Neurocardiology, *et al.* Clinical outcome of patients treated with spinal cord stimulation for therapeutically refractory angina pectoris. *Heart* 1999;**82**:82–8.
3 **Di Pede F**, Lanza GA, Zuin G, *et al.* Spinal cord stimulation for refractory angina pectoris patients: data on clinical outcome from the prospective Italian registry. *Am J Cardiol* 2003;**91**:951–55.
4 **Mannheimer C**, Eliasson T, Augustinsson LE, *et al.* Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris The ESBY Study. *Circulation* 1998;**97**:1157–63.
5 **Ekre O**, Norsell H, Währborg P, *et al.* Spinal cord stimulation and coronary artery bypass grafting provide equal improvement in quality of life. Data from the ESBY study. *Eur Heart J* 2002;**23**:1938–45.
6 **Sgueglia GA**, Sestito A, Spinelli A, *et al.* Long-term follow-up of patients with cardiac syndrome X treated by spinal cord stimulation. *Heart* 2007;**93**:591–7.
7 **Eddicks S**, Maier-Hauff K, Schenk M, *et al.* Thoracic spinal cord stimulation improves functional status and relieves symptoms in patients with refractory angina pectoris: the first placebo-controlled randomised study. *Heart* 2007;**93**:585–90.
8 **Saririan M**, Eisenberg MJ. Myocardial laser revascularization for the treatment of end-stage coronary artery disease. *J Am Coll Cardiol* 2003;**41**:173–83.
9 **Stone GW**, Teirstein PS, Rubenstein R, *et al.* A prospective, multicenter, randomized trial of percutaneous transmyocardial laser revascularization in patients with nonrecanalizable chronic total occlusions. *J Am Coll Cardiol* 2002;**39**:1581–7.
10 **Leon MB**, Kornowski R, Downey WE, *et al.* A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. *J Am Coll Cardiol* 2005;**46**:1812–19.
11 **Salem M**, Rotevatn S, Stavnes S, *et al.* Usefulness and safety of percutaneous myocardial laser revascularization for refractory angina pectoris. *Am J Cardiol* 2004;**93**:1086–91.
12 **McNab D**, Khan SN, Sharples LD, *et al.* 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, *Eur Heart J* 2006;**27**:1048–53.
13 **Grines CL**, Watkins MW, Helmer G, *et al.* Angiogenic Gene Therapy (AGENT) trial in patients with stable angina pectoris. *Circulation* 2002;**105**:1291–7.
14 **Kastrup J**, Jorgensen E, Ruck A, *et al.* Euroinject One Group. Direct intramyocardial plasmid vascular endothelial growth factor-A165 gene therapy in patients with stable severe angina pectoris A randomized double-blind placebo-controlled study: the Euroinject One trial, *J Am Coll Cardiol* 2005;**45**:982–8.
15 **Bonetti PO**, Holmes DR, Lerman A, *et al.* Enhanced external counterpulsation for ischemic heart disease. What's behind the curtain? *J Am Coll Cardiol* 2003;**41**:1918–25.
16 **Arora RR**, Chou TM, Jain D, *et al.* The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J Am Coll Cardiol* 1999;**33**:1833–40.
17 **Soran O**, Kennard ED, Kfoury AG, Kelsey SF, for the IEPR Investigators. Two-year clinical outcomes after enhanced external counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction (report from the International EECP Patient Registry). *Am J Cardiol* 2006;**97**:17–20.
18 **Gibbons RJ**, Abrams J, Chatterjee K, *et al.* 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. *J Am Coll Cardiol* 2003;**41**:159–68.
19 **Fox K**, Garcia MA, Ardissino D, *et al.* Guidelines on the management of stable angina pectoris: executive summary. *Eur Heart J* 2006;**27**:1341–81.

IMAGES IN CARDIOLOGY

Optical coherence tomography after cutting balloon angioplasty

Optical coherence tomography (OCT) is a recently developed optical imaging technique that provides high-resolution (approximately 10–20 μm) cross-sectional images of vessels.

A 74-year-old man was admitted for chest pain. A coronary angiogram showed diffuse in-stent restenosis of an Express (Boston Scientific Corporation and Medinol Ltd) 2.75 × 15 mm stent which had been implanted in the left anterior descending coronary artery six months earlier (panel A; arrow). Using OCT (Image Wire, LightLab Imaging, Inc) imaging, well-apposed stent struts and neointima formation around the stent were clearly visualised (panel B). We performed angioplasty by using Cutting Balloon Ultra (Boston Scientific Corporation and Medinol Ltd) for this lesion. After the cutting balloon procedure, a coronary angiogram showed a very smooth lumen border (panel C; arrow). However, OCT imaging showed that the lumen surface was irregular with fissures of neointima formation. OCT imaging may be useful in assessing small structural details of the coronary artery, such as neointima formation after stent implantation and the presence of fissures after angioplasty.



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