Evolving treatment strategies for chronic refractory angina

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Chronic refractory angina is a term used to describe patients who, despite optimal medical therapy, have both angina and objective evidence of ischaemia. It is estimated that 5 – 15% of the 12 million patients with chronic angina in the US meet the criteria for having refractory angina. This review focuses on the following evolving pharmacological therapies for chronic refractory angina: L-arginine, ivabradine, ranolazine, nicorandil and trimetazidine. Evolving devices and invasive procedures including enhanced external counterpulsation, spinal cord stimulation, and transmyocardial revascularisation are also briefly discussed.

Keywords: counterpulsation, refractory angina, spinal stimulation, therapy


1. Introduction

Coronary artery disease is one of the leading causes of morbidity and mortality worldwide. Although many advances have been made in both surgical and percutaneous revascularisation strategies over the past two decades, many patients with severe coronary artery disease cannot be revascularised. Refractory angina is a term used to describe patients who are not considered candidates for revascularisation and who, despite optimal medical therapy, have both angina and objective evidence of ischaemia. It is estimated that 5 – 15% of patients with chronic angina meet the criteria for having refractory angina [1]. In the US, ~ 300,000 – 900,000 patients have refractory angina, and it is estimated that 25,000 – 75,000 new cases will be diagnosed per year [2].

The purpose of this review is to discuss the evolving pharmacological treatment strategies for patients with chronic refractory angina. Although the term ‘evolving’ is used, some of the agents have been in use for a significant period of time and have been proven to be clinically effective. Three nonpharmacological therapies; enhanced external counterpulsation (EECP), spinal cord stimulation (SCS) and transmyocardial revascularisation (TMR), will also be discussed briefly.

2. Goal of therapy

Angina pectoris occurs when there is an imbalance between myocardial oxygen supply and demand. The goals of therapy for chronic refractory angina are to improve both subjective symptoms (Table 1) and objective evidence of myocardial ischaemia (exercise duration, time to ST-depression during exercise and myocardial perfusion). These goals can be accomplished by either decreasing myocardial oxygen demand or by increasing myocardial oxygen supply. Prognostic benefits are difficult to demonstrate and are not considered a therapeutic goal using currently available modalities.

3. Traditional standard therapy

A detailed review of standard therapy is beyond the scope of this review and has been published elsewhere [3]. In general, the standard treatment for symptomatic relief in
chronic stable angina should include β-blockers and/or long-acting nondihydropyridine calcium channel blockers titrated to the lowest heart rate and blood pressure tolerated to decrease oxygen demand. A long-acting nitrate using an interrupted dose schedule to prevent nitrate tolerance should also be given to increase oxygen supply. Aggressive risk-factor modification with smoking cessation, cholesterol modifying agents and exercise training should also be offered to these patients along with chronic aspirin and/or a thienopyridine, such as clopidogrel or ticlopidine. Patients who continue to have angina despite optimal standard therapy should be considered as candidates for evolving therapies in chronic refractory angina.

4. Evolving therapies

4.1 L-Arginine

L-Arginine is a positively charged amino acid (Figure 1) that is the metabolic precursor for nitric oxide synthesis. It has been proposed as a therapy for chronic refractory angina because it increases coronary blood flow by improving endothelium-dependent vasodilation [4]. Although it is completely absorbed by the brush border, it has a bioavailability of ~ 30% due to extensive metabolism by enterocytes. L-Arginine is metabolised by the liver, has a half-life of 1.5 – 2.0 h and is generally well tolerated. Adverse reactions to arginine include hypotension, hyperkalaemia and abdominal bloating (Table 2).

One single-centre trial has investigated the use of L-arginine in patients with chronic refractory angina. The results of this randomised, double-blinded, placebo-controlled trial showed that oral L-arginine resulted in an increase in exercise duration and maximum workload during stress testing, as well as a decrease in the amount of ST-segment depression [5].

4.2 Ivabradine

Ivabradine (Procoralan®, Servier) is a selective and specific inhibitor of the If ion channel that is responsible for the primary sinoatrial node pacemaker current [6]. Its ability to decrease heart rate and myocardial oxygen demand without having any negative inotropic effects has made ivabradine a potential therapy for chronic stable angina. When given orally, ivabradine has a bioavailability of 40% and is eliminated by hepatic clearance. The half-life is unknown and the main adverse reaction is visual disturbance, which can occur in ~ 15% of patients (Table 2).

Two clinical trials have investigated the effects of ivabradine in patients with angina. Borer et al. conducted a randomised, double-blind, placebo-controlled trial investigating the use of ivabradine in patients with stable angina [7]. Compared with placebo, ivabradine resulted in a statistically significant 9.5% increase in exercise duration and a 12% increase in time to ST depression during treadmill testing. There was also a 77% reduction in anginal symptoms during the study period of 3 months. Another study by Tardif compared ivabradine with atenolol in 932 patients with stable angina [8]. Patients taking ivabradine had a significantly greater increase in exercise duration than those taking atenolol. Ivabradine is not currently approved by the FDA for use in the US (Table 3).

4.3 Ranolazine

Ranolazine (Ranexa™, CV Therapeutics) is an orally active piperazine derivative (Figure 1). Its mechanism of action is not completely understood but most likely involves its ability to inhibit sodium entry through the late I_{Na} channels. Inhibition of sodium entry through these channels results in a reduction in sodium loading in cardiac myocytes and an attenuation of the rise in intracellular calcium. The end result is a reduction in myocardial oxygen demand via a reduction in the change in pressure per unit time (dP/dt) and an improvement in diastolic function [9,10]. Ranolazine is eliminated by hepatic metabolism and has a half-life of 2 h. The most common adverse reactions to ranolazine are constipation, dizziness, nausea and asthenia, which occurred in 8% of patients. Ranolazine has also been associated with a prolongation of the QT interval in some patients (Table 2).

The use of ranolazine in patients with angina has been studied in two clinical trials. The MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) trial investigated the effects of ranolazine in 191 patients [11]. Treatment with ranolazine resulted in a 56% improvement in exercise tolerance. The CARISA (Combination Assessment of Ranolazine in Stable Angina) trial investigated the effects of ranolazine in combination with other antianginal agents [12]. In this Phase III clinical trial, 823 patients with refractory angina already receiving standard therapy with atenolol, diltiazem or amiodipine were randomised in a double-blind, placebo-controlled manner to receive placebo or ranolazine. After 12 weeks, patients in the ranolazine arm were found to have a significant 26% increase in total exercise time, as well as a decrease in the number of anginal episodes per week. The time to onset of 1 mm of ST-segment depression during exercise testing did not change (Table 4). The FDA is currently reviewing ranolazine for approval for use in patients with chronic refractory angina (Table 3).
4.4 Nicorandil
Nicorandil is a nicotinamide ester (Figure 1) that has both nitrate-like and ATP-potassium channel-activating properties [13]. Its pharmacological effects include the ability to reduce both preload and afterload by vasodilating the arterial and venous systems. In addition, the ATP-potassium channel activation of nicorandil may offer cardioprotection via a preconditioning effect on the myocardium. Nicorandil is rapidly absorbed and has a > 75% bioavailability. The compound has a half-life of 45 min and is eliminated by hepatic metabolism. The main adverse reactions to treatment are headaches and gastrointestinal discomfort (Table 2).

Several small randomised trials have shown that nicorandil prolongs the time to the onset of ST depression and exercise duration during stress testing in patients with stable angina [14-17]. Nicorandil has also been shown to improve myocardial perfusion at rest and with exercise [18] (Table 4). It is currently approved for use in Europe and Japan (Table 3).

4.5 Trimetazidine
Trimetazidine is a piperazine derivative (Figure 1) that blocks the β-oxidation of fatty acids by inhibiting the enzyme 3-koero-acyl-CoA thiase [19]. Inhibition of the metabolism of fatty acids results in an increase in glucose metabolism that is more energy efficient and reduces myocardial oxygen demand. Trimetazidine is excreted by the kidneys and has a half-life of 6 h. The most common adverse reaction is a sensation of gastrointestinal burning (Table 2).

Trimetazidine has been extensively studied in multiple clinical trials. A meta-analysis of 12 trials showed that trimetazidine results in a significant reduction in weekly anginal episodes and a prolongation of time to the onset of ST-depression during exercise testing [20]. There was a trend toward prolongation of total exercise duration and no improvement in myocardial perfusion (Table 4). Trimetazidine is currently approved for clinical use in several European and Asian countries, but is not yet approved for use in the US (Table 3).

5. Nonpharmacological therapies

5.1 Enhanced external counterpulsation
EECP is comprised of three pairs of pneumatic cuffs placed around the lower extremities at the levels of the calves, lower and upper thighs. An electrocardiographic trigger is used to sequentially inflate the cuffs from distal to proximal during the onset of diastole and simultaneously deflate all cuffs before the onset of systole. A standard course of EECP therapy consists of...
Evolving treatment strategies for chronic refractory angina

Table 2. Pharmacokinetic properties of evolving pharmacological agents for the treatment of chronic refractory angina.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism of action</th>
<th>Clearance</th>
<th>Half-life</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Arginine</td>
<td>Improves coronary blood flow by</td>
<td>Hepatic</td>
<td>1.5 - 2.0 h</td>
<td>Hypotension, hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>endothelium-dependent vasodilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Decreases heart rate by specific inhibition</td>
<td>Hepatic</td>
<td>NA</td>
<td>Visual disturbances, abdominal</td>
</tr>
<tr>
<td></td>
<td>of the L_{ion} channel</td>
<td></td>
<td></td>
<td>bloating</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Inhibits sodium entry through the late L_{Na}</td>
<td>Hepatic</td>
<td>2 h</td>
<td>Constipation, dizziness, nausea</td>
</tr>
<tr>
<td></td>
<td>channels</td>
<td></td>
<td></td>
<td>and asthenia, prolongation of QT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>interval</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>Nitrile-like and ATP-potassium channel</td>
<td>Hepatic</td>
<td>45 min</td>
<td>Headaches and gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>activating properties</td>
<td></td>
<td></td>
<td>discomfort</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>Inhibits 3-keto-acyl-CoA thiolase</td>
<td>Renal</td>
<td>6 h</td>
<td>Gastrointestinal burning</td>
</tr>
</tbody>
</table>

NA: Not available.

Table 3. Summary of clinical approval and use in the US.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FDA status</th>
<th>AHA/ACC indication for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Arginine</td>
<td>Approved</td>
<td>NA</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Not approved</td>
<td>NA</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Not approved</td>
<td>NA</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>Not approved*</td>
<td>NA</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>Not approved*</td>
<td>NA</td>
</tr>
<tr>
<td>Enhanced external counterpulsation</td>
<td>Approved</td>
<td>IIb</td>
</tr>
<tr>
<td>Spinal cord stimulator</td>
<td>Approved</td>
<td>IIb</td>
</tr>
<tr>
<td>Transmyocardial revascularisation</td>
<td>Approved</td>
<td>Ila</td>
</tr>
</tbody>
</table>

*Approved for use in Europe and Asia.

ACC: American College of Cardiology; AHA: American Heart Association; FDA: Food and Drug Administration; NA: Not available.

35 1-h sessions over a 7-week period. The mechanism by which EECP improves anginal symptoms is not completely understood. EECP has been shown to improve coronary blood flow during diastole [21], and improve endothelial function [22]. In addition, it has been associated with the release of growth factors, such as VEGF that promote the formation of collaterals in the coronary circulation [23]. Finally, EECP may result in a ‘training effect’ by decreasing peripheral vascular resistance in the same manner as exercise training. The net result is an increase on coronary blood flow and a decrease in myocardial oxygen demand.

The MUST-EECP (Multicenter Study of Enhanced External Counterpulsation) trial conducted by Arora and colleagues was a double-blind, sham-controlled study in which 139 patients with chronic stable angina were randomised to either active EECP therapy or sham treatment with subtherapeutic cuff inflations [24]. After 35 sessions, patients in the active treatment arm had a significant 15% increase in time to the onset of 1 mm ST-depression, and 25% fewer anginal symptoms per week. Several other trials have also shown that EECP results in both subjective and objective improvements in patients with chronic refractory angina [25-35]. EECP is approved by the FDA and is currently recommended by the American Heart Association and American College of Cardiology as a therapy for patients with chronic refractory angina [36].

5.2 Spinal cord stimulator

SCS comprises of an epidural lead placed at the level of C7-T1, which is connected to a pulse generator that is implanted in the abdomen. It is believed that SCS blocks pain by stimulating the dorsal columns, which inhibits transmission through the pain-conducting spinothalamic tract [37-41]. Stimulation by the device occurs at scheduled intervals and at the demand of the patient. Pain from an acute coronary syndrome, however, has not been shown to be blocked in clinical trials [42].

Several clinical trials have investigated the use of SCS in refractory angina [43-46]. These trials have shown that SCS results in a significant improvement in anginal symptoms, as well as an increase in exercise duration and time to onset of ST-depression during treadmill testing. The main adverse reactions to SCS are the risk of epidural haematoma and infection that occurs in ~ 1% of patients. In addition, SCS may interfere with the function of pacemakers and implantable
Table 4. Clinical effects of evolving pharmacological agents for the treatment of chronic refractory angina.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improvement in time to ST-depression</th>
<th>Improvement in total exercise time</th>
<th>Reduction in anginal class</th>
<th>Improvement in myocardial perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Arginine</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+; Yes; -; No; NA: Not available. Adapted from [2].

defibrillators. SCS is currently approved by the FDA and, like EECP, has been recommended by the American Heart Association and American College of Cardiology as a therapy for patients with chronic refractory angina [50].

5.3 Transmyocardial revascularisation

The concept of myocardial revascularisation began in the 1950s when Goldman proposed that the formation of artificial conduits in the subendocardium would improve oxygen delivery to myocytes [47]. Initially, needles were used, but in 1986 Okada and colleagues became the first to use laser technology to generate myocardial channels [48]. In TMR, a surgical incision is made and the laser is placed directly on the myocardium to generate channels. The actual mechanism by which TMR improves anginal symptoms is unknown. Proposed mechanisms have included: improved myocardial perfusion through direct channels; promotion of angiogenesis through the release of growth factors; and denervation of pain fibres [49-51]. A placebo effect is also possible.

Several randomised trials have investigated the clinical use of TMR in patients with chronic refractory angina [52-57]. In general, TMR has been shown to improve anginal symptoms and exertional tolerance, but does not seem to improve mortality or myocardial perfusion. None of these trials, however, were randomised sham-controlled trials. The perioperative mortality rate of TMR ranges from 1.1 to 5.3%. Although TMR is FDA approved for use in the US, the rates of TMR procedures have been decreasing.

6. Combination therapy and drug interactions

Most patients with refractory angina will require combination therapy with multiple pharmacological agents. Long-acting nitrates used in combination with L-arginine or nicorandil can cause hypotension and may increase the likelihood of headaches. β-Blockers used in combination with ivabradine may cause bradycardia and should be used with caution. Combination therapy using drugs with different mechanisms of action, such as long-acting nitrates in conjunction with ranolazine or trimetazidine, is suggested. Pharmacological therapy can also be used in conjunction with nonpharmacological therapy, such as EECP or SCS.

7. Expert opinion and conclusion

A significant number of patients worldwide suffer from chronic refractory angina and the treatment of these patients can be challenging. All patients with chronic refractory angina should be treated with standard therapy consisting of aspirin and/or a thienopyridine, β-blocker and/or a nondihydropyridine calcium channel blocker titrated to the lowest tolerated heart rate and blood pressure. A long-acting nitrate should also be given, in addition to aggressive risk factor modification with smoking cessation, cholesterol modifying agents and exercise training. Patients who continue to have angina despite optimal standard therapy should receive L-arginine and be considered for EECP. Those who continue to have symptoms should be considered for SCS. TMR is now recommended as a stand-alone procedure in most patients due to the potential for increased peri-procedural morbidity and mortality. Patients who desire an invasive device or are not eligible for SCS will be candidates for the evolving therapies discussed in this review. Of these therapies, nicorandil and trimetazidine are approved for use in parts of Europe and Asia, whereas ivabradine and ranolazine await approval for use in the US and Europe. Gene therapy may be a promising therapy and the results of ongoing trials are eagerly awaited.
Evolving treatment strategies for chronic refractory angina

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** Excellent review of standard therapy for refractory angina.**


** Landmark trial of EECP.**


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Evolving treatment strategies for chronic refractory angina

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