Invited review

Refractory angina – current therapeutic challenge

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Abstract

Refractory angina is a common, growing problem in cardiology due to the effective treatment of coronary disease, which improves prognosis. Significant progress has been confirmed in the current guidelines on the management of stable angina pectoris. The article discusses the present value of haemodynamic treatment and new directions of pharmacotherapy, i.e. bradycardic and metabolic agents. High-risk patients, i.e. diabetic and elderly patients, are also considered. Invasive procedures in refractory angina for no-option patients are briefly presented. Their implementation in common practice is still controversial and requires further investigations.

Key words: refractory angina, therapy, high-risk patients.

Introduction

The population of people aged over 50 years increased between 1997 and 2005 to 222 million worldwide. The estimated incidence of MI for 2005 is 10.7 million. The prevalence of chronic refractory angina is 30 000 to 50 000 patients/year in Europe, generally 30 per million. The total cost of health care of these patients will grow [1]. Annual mortality in this group of patients is up to 17% [2]. Now it is possible to improve prognosis by modification of lifestyle and use of medications: statins, ACE-inhibitors and aspirin. So-called haemodynamic drugs for managing symptoms are in many cases not sufficient so there is still a need to look for novel anti-anginal drugs. Results of the studies evaluating the efficacy of PTCA and CABG on the quality of life 6-12 months after revascularization show that angina symptoms may remain in 50 to 70% of patients [3-5]. In the ARTS study angina had been present in 7.3, 10.5, 12.8% of CABG patients and in 24.5, 21.1, 18.4% of PCI patients after 6 months, 1 year and 3 years, respectively, since intervention [6]. The problem with the full evaluation of benefits either from CABG and PTCA or medical therapy is that we cannot use the double blind method. Even after invasive procedures it is often necessary to consider the indications for another coronary angiography to exclude the restenosis of the coronary artery or graft stenosis. Some of these patients do not have patent revascularized arteries and they need to be medically treated. Low calibre arteries with stenoses not suitable for intervention or incomplete revascularization procedures can still be a source of angina attacks. Other possible causes of ischaemic pain are lack of arterial and venous conduits, comorbidities, low ejection fraction and advanced age, i.e. numerous risk factors, making every invasive procedure very risky.

The major problem in these patients is recurrent angina, resistant to medical therapy with classical haemodynamically acting agents (nitrates, beta

blockers, calcium antagonists). They have significant disability, multiple medications and frequent hospitalizations. Prevalence is estimated at 5-15% of angina patients. The management of recurrent angina is more difficult, since the risk that is associated with a second procedure is increased and the outcome is worse [7]. For these patients apart from individual coronary artery pharmacotherapy, treatment of concomitant conditions such as hypertension, anaemia, arrhythmias, thyreotoxicosis, diabetes and renal insufficiency is extremely important.

Aims of treatment

According to the ESC Guidelines, the basic aim of therapy is to improve prognosis by preventing myocardial infarction and death. Maximal possible lifestyle changes, proper medical therapy and optimal revascularization if necessary should be introduced in every patient. Other disorders such as hypertension, diabetes, renal insufficiency and others should be treated very carefully. Pharmacological therapy to improve prognosis at the highest level of evidence (A) should consist of aspirin, statin, ACE inhibitor in patients with coincident indications (hypertension, heart failure, LV dysfunction, prior infarction and diabetes) and oral beta blocker in patients post infarction and with heart failure. Clopidogrel is treated as an alternative agent in patients with aspirin intolerance (level of evidence, B). Some of the patients with coronary disease and other risk factors would require high-dose statin therapy to maximal possible lowering LDL level (i.e. 70 mg%) [8].

Haemodynamic treatment

For patients with angina pectoris, impaired left ventricle and no possibilities of further procedures of myocardial revascularization, the optimal medical therapy is crucial. In stable coronary artery disease patients the relief of angina attacks may be achieved with conventional haemodynamic treatments. The ESC guidelines recommend using beta blocker to the highest possible dose taking into consideration patient tolerance and heart rate (level A). In case of beta blocker intolerance or still low efficacy, monotherapy with calcium channel blocker [CCB] (level A), long acting nitrate (level C) or nicorandil (level C) can be considered. If the therapy with beta blocker is not sufficient, dihydropyridine calcium channel blocker can be added (level B) [8]. Some studies have demonstrated additional beneficial anti-anginal effects after combination of beta blocker with a calcium channel blocker or nitrate, or all of them. But large multi-centre trials such as TIBET or IMAGE, as well as smaller studies, showed no significant differences between monotherapy and combined therapy for mild chronic stable angina [9-12]. In a practical setting, because of quick development of invasive procedures now we can observe low frequency of nitrates and CCB use in patients with coronary disease. But taking into consideration patients with refractory angina, it often happens that we use beta blockers, long-acting nitrates, molsidomine during tolerance preventive periods and calcium channel blockers concomitantly. There are no randomized studies comparing therapy with 3-4 drugs: nitrates, beta blockers, CCB and molsidomine. Its usefulness is established by everyday practice in individual patients. One meta-analysis of several clinical studies demonstrated that combination of classical haemodynamic agents failed to prove a real additive efficacy over monotherapy [13]. It often happens that coronary angiography shows severe three-vessel disease with diffuse peripheral lesions, not suitable for CABG. Exercise treadmill tests and SPECT perfusion study demonstrate low coronary reserve in these patients. Numerous risk factors are usually present in these patients: advanced age, comorbidities, arterial hypertension, hypercholesterolaemia, often cigarette smoking, diabetes. So the therapy becomes more and more complicated.

New possibilities of therapy in ESC Guidelines

For the first time in the ESC Guidelines in the part of pharmacological therapy to improve symptoms and/or reduce ischaemia new classes of drugs have appeared: sinus node inhibitor (ivabradine), potassium channel activator (nicorandil) and metabolic agents. In case of beta blocker intolerance, sinus node inhibitor therapy can be attempted (Class IIa, level of evidence B). If combination therapy with CCB and beta blocker is not sufficient, CCB can be replaced by long-acting nitrate or nicorandil (Class IIa, level of evidence C). If conventional drugs are not tolerated or they are not sufficient, metabolic drugs can be used (Class IIb, level of evidence B) [8].

Metabolic treatment

Trimetazidine

New therapeutic approaches such as metabolic treatment appear to be a rational choice since they aim to optimize cardiac metabolism. An alternative treatment to oppose consequences of myocardial ischaemia is to optimize cardiac metabolism. In patients with angina refractory to therapy with haemodynamically acting agents, the addition of a metabolic agent, such as trimetazidine, which is devoid of any haemodynamic effect and acts at the cellular level, would be expected to have an additive effect [14]. It has been demonstrated in experimental studies that trimetazidine, the first 3-keto acyl coenzyme A thiolase inhibitor, is an effective cytoprotective agent that shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation, improving the efficient use of oxygen [15].

This results in enhancement of ATP production, improvement in cardiac contractile work and protection of the myocyte towards ischaemic damage [16]. The anti-anginal activity of trimetazidine has been shown in various double blind studies. In several double-blind trials, trimetazidine significantly improved the exercise test parameters of patients with effort angina [17, 18]. In comparative studies, trimetazidine has been as effective as CCB or beta blocker and better tolerated [19, 20]. The anti-ischaemic efficacy of trimetazidine has been established in numerous studies, in which it was added in patients uncontrolled by one conventional haemodynamic agent [21-24]. In combination treatment it provides additive benefits to beta blockers or diltiazem and exerts superior efficacy to isosorbide dinitrate [21, 22, 25]. Trimetazidine delays the ischaemic threshold and improves ventricular function in patients with ischaemic cardiomyopathy [26]. It was proved that therapy with trimetazidine has beneficial effects in patients with ischaemic cardiomyopathy [27, 28]. Anti-ischaemic and anti-anginal efficacy of trimetazidine was confirmed in meta-analyses [29]. The latest of them, by Ciapponi et al., included 23 studies (1378 patients) and showed significant reduction in angina attacks and longer exercise time to ST-depression after trimetazidine therapy [30].

As a result, the European Society of Cardiology guidelines have, for the first time in 1997 and then in 2006, mentioned trimetazidine as a metabolic agent in the treatment of stable angina [8, 31]. Efficacy of metabolic therapy as an adjunctive treatment of refractory angina has been proved so far.

The efficacy of trimetazidine in patients with recurrent angina was previously shown in the Trimpol I study [32]. The study population comprised 700 patients. In 331 of them trimetazidine was added to existing monotherapy with long-acting nitrate, in 293 to beta blocker and in 76 to calcium antagonist. Among them were 109 post-revascularized patients (45 received PTCA, 59 CABG, and 5 both procedures) remaining with angina symptoms while receiving a haemodynamically acting agent. In these patients the addition of trimetazidine to existing monotherapy improved all exercise test parameters and reduced clinical symptoms. All 3 sub-groups – TMZ and nitrate, TMZ and beta blocker, TMZ and CCB – were comparable in improving the exercise test and clinical parameters. Trimetazidine proved to be effective in improving exercise tests and relieving angina symptoms in these angina patients for whom a repeated surgical procedure appears to be inappropriate.

A subgroup of 94 patients was analyzed in the TRIMPOL II study, a multicentre, double-blind randomized placebo-controlled trial in 426 patients with stable effort angina. These patients had a history of revascularization in the course of coronary disease and they were still symptomatic after 6 months despite treatment with metoprolol (50 mg twice daily). They were randomly allocated to receive either trimetazidine (20 mg three times daily) or placebo for 12 weeks, on top of the beta blocker. Compared to placebo, the 12-week treatment with trimetazidine significantly improved: time to 1 mm ST segment depression, exercise test duration, total workload and time to onset of angina ($p=0.031$). Weekly number of angina attacks and nitrate consumption were significantly reduced in the trimetazidine group compared to placebo. These results show that trimetazidine provides anti-anginal efficacy in post-revascularized patients with recurrent angina despite monotherapy with metoprolol. The treatment was well tolerated [33].

Recurrent angina in diabetic patients

Diabetic patients suffer from a high incidence of morbidity and mortality from cardiovascular disorders. The incidence of mortality due to cardiac disease is two-fold higher in diabetic men and four-fold higher in diabetic women than in non-diabetic patients [34, 35]. Diabetic patients have two to three times higher risk of atherosclerosis compared with non-diabetic subjects. After PTCA they have greater risk of restenosis. Diabetic coronary patients who undergo CABG are at high risk of stenosis of vein grafts [36]. Because of more diffuse coronary lesions and high intra-operative risk these patients are not qualified for repeated surgery. In spite of that, in these patients recurrent angina occurs relatively often in comparison with a non-diabetic population. Diabetes not only affects the coronary macro- and micro-circulation but also myocyte function, leading to more severe myocardial dysfunction [37]. Thus, there is a need to use novel drugs which not only reduce symptoms of angina, but will protect myocardial function as well. In the diabetic heart several metabolic disturbances appear. Transport of glucose is impaired and the rate of glycolysis is significantly decreased, resulting in a greater reliance on free fatty acids (FFA) as a source of ATP. The high plasma FFA level and increased FFA oxidation result in metabolic disorders and impaired left ventricular function during and after an ischaemic episode in both the normal and diabetic heart [38-40]. Consequently, there is a rationale for improving patients' clinical status and contractile function by suppressing FFA oxidation. Due to decrease of insulin sensitivity and elevation of FFA metabolism in diabetes, drugs that inhibit fatty acid oxidation may be especially useful. Recent experimental studies have shown that trimetazidine, through selective inhibition of long-chain 3-ketoacyl CoA thiolase activity, reduces FFA oxidation and increases glucose oxidation, which optimizes energy production and

protects the ischaemic heart [15]. The results of experimental and clinical studies suggest that trimetazidine may be especially recommended for coronary diabetic patients. Long- and short-term trimetazidine treatment in patients with diabetes and ischaemic cardiomyopathy improved clinical symptoms, glucose metabolism, endothelial function and left ventricular ejection fraction [41, 42].

Among the TRIMPOL I study population there were 50 diabetic patients with angina pectoris not controlled by conventional anti-anginal drugs. The subanalysis of this group shows an improvement in treadmill test parameters and clinical symptoms of angina pectoris, along with an excellent tolerability [32]. In the prospective, open-label, observational DIETRIC study, 580 patients with diabetes and coronary disease were treated with trimetazidine (dose: 3 x 80 mg a day). After six-month follow-up, treatment reduced incidence of angina episodes and consumption of nitrate tablets. The time of total exercise ($p<0.001$) and time to significant ST depression ($p=0.02$) were longer. Tolerance of the treatment was good [43].

The rationale for metabolic therapy in elderly patients with recurrent angina

In elderly patients, several years after revascularization, recurrent angina may occur because of degenerative changes in vein bypasses and progression of atherosclerosis in native coronary arteries. Conventional anti-anginal agents may be associated with significant adverse effects in this group, often because of direct consequences of their haemodynamic action. The use of maximal doses of haemodynamically acting agents may be limited by hypotension. In elderly patients treated with beta blockers and CCB, sinus bradycardia and atrio-ventricular blocks may occur. Trimetazidine, which exerts an anti-ischaemic effect in the absence of haemodynamic changes, influence on sinus node and conduction system of the heart, may be a particularly valuable drug in the elderly. The anti-ischaemic efficacy and good tolerability of trimetazidine in 71 patients aged >65 years was shown in a sub-study from TRIMPOL I [44].

Ranolazine

Ranolazine is the only metabolic agent approved in United States. It inhibits the late inward sodium current. The most important mechanism of action is prevention of both sodium and calcium overload in ischaemic myocytes and the subsequent increase in diastolic tension [45]. In the MARISA study monotherapy with ranolazine increased exercise performance at trough and peak for the doses 500, 1000 and 1500 mg bid [46]. In the CARISA study combination regimen of ranolazine doses 750 mg bid and 1000 mg bid with atenolol 50 mg qd, or diltiazem 120 mg qd, or amlodipine 5 mg qd caused at trough significant exercise duration and time to angina prolongation in exercise test. At peak therapy significant exercise duration, time to angina and time to 1-mm ST depression prolongation in exercise test were observed [47]. In the ERICA study the effect of ranolazine in patients with refractory angina despite maximum amlodipine therapy was studied. Concomitant treatment of amlodipine and ranolazine reduced the number of angina episodes ($p=0.028$) and NTG consumption per week ($p=0.014$) [48].

The use of other metabolic agents – carnitine palmitoyl transferase inhibitors (CPT-1), etomixir, perhexiline, oxphenicine – is limited because of insufficient clinical evidence and side effects.

Other possibilities of drug therapy

Nicorandil

Another alternative therapy is nicorandil, a novel drug with a unique mechanism of action. The drug activates ATP-sensitive potassium channels, causing dilatation of peripheral and coronary resistant arterioles. It also contains an NO2 moiety which dilates systemic veins and epicardial coronary arteries [49]. Nicorandil decreases cardiac preload and afterload and increases coronary blood flow. In a randomized, double-blind IONA study of 5126 patients with coronary disease and other risk factors, active treatment for 1.6 years caused significant (21%) reduction of secondary end-point: coronary disease mortality or non-fatal infarction [50].

An original, clinically efficient therapeutic option is using the serotonin blocker sarpogrelate [51].

Bradycardic agents

Reduction of heart rate is a very important therapeutic approach in patients with high cardiovascular risk, which was proved in epidemiological studies. It is crucial in beta blockers' mechanism of action. In some patients there are some problems with side effects of beta blockers and non-dihydropyridine calcium antagonists diltiazem and verapamil, so the idea of developing novel drugs with other mechanisms of action is very exciting. Some inhibitors of calcium and potassium channels – alindine, zetabradine and falipamil – have not been further studied. Another one, ivabradine, successfully passed experimental and clinical trails and is mentioned as an alternative to beta blockers in the ESC 2006 Guidelines. It inhibits funny current (mixed sodium/potassium inward current, If) in the sinus node which is activated by hyperpolarization. Its anti-ischaemic activity was confirmed in experimental and clinical trials [52].

Invasive procedures in refractory angina: no-option patients

The problem with these procedures is that there are no large randomized trials which could establish their position as an effective and cost-benefit clinical therapy.

Enhanced External Counterpulsation [EECP] is based on the principle of intra-aortic counter pulsation. It augments coronary blood flow during diastole and facilitates left ventricular flow in systole and improve function of the endothelium. Treatment is based on 1-hour daily sessions for 7 weeks and is rather expensive. The EECP method has been approved for clinical use. Registry of patients treated with this method showed improvement in angina class and reduction of angina episodes in 75% of patients [53]. ACC/AHA has given B/IIb recommendation to this method [54].

Neurologically based therapies are palliative methods aimed at pain reduction. In the past acupuncture, thoracic epidural anaesthesia, stellate ganglion block and sympathectomy were reported as methods for the prevention of angina episodes. Transcutaneous nerve stimulation (TENS) improves exercise tolerance, prolongs time to ischaemia during provocation and reduces sympathetic discharge. Electrodes are placed in the chest in the dermatome with the highest pain intensity. The placebo effect in this method may be strong [55]. Another method is spinal cord stimulation (SCS), proposed in the 1980s. It is based on low voltage (2-7 volts, 30-90 Hz) electric stimulation of the spinal cord. An electrode is placed at the level of Th4 and Th5 and a lead at T1 and T2 level. The stimulation device is implanted under the skin in the abdomen or lower thorax. The patient can control device activity. Open studies showed reduction of angina frequency and ischaemic episodes and better exercise tolerance. No benefit on hard end points and no long-term follow-up have been presented so far. Randomized studies are ongoing to establish this method as a guideline therapy. It is used mostly in Scandinavia. According to AHA/ACC it has B/IIB recommendations [55, 56].

Transmyocardial Laser Revascularization (TMR), surgical or percutaneous (PMR), is based on the principle of provoking angiogenesis by creating 1 mm diameter channels from epicardium to endocardium per cm^2 of the myocardia surface during the surgical procedure. One of the mechanisms is cardiac denervation. Hypotheses about angiogenesis were not confirmed. Also some types of laser devices were approved by FDA and in other countries for the therapy of recurrent angina. There are no randomized studies of this method because of methodological difficulties. Studies with percutaneous transmyocardial revascularization did not confirm the beneficial effects of this method of therapy [57]. AHA/ACC give the method IIa class recommendation. Results of the SPIRIT trial comparing SCS and PMR did not show any significant differences in the two methods of therapy. SCS patients had more adverse episodes during 1-year follow-up [58].

Angiogenesis is another promising option. There are many ongoing studies of potential factors stimulating angiogenesis in the myocardium. But present results remain controversial. Other methods investigated in refractory angina patients are: left stellate ganglion blockade (LSGB), endoscopic thoracoscopic sympathectomy (ETS), thoracic epidural anaesthesia (TEDA) and stem cell therapy with autologous bone marrow cells and autologous muscle cells [8].

In conclusions recurrent angina is already a major healthcare problem due to its growing prevalence. Because of successful revascularization procedures and growing length of life, the number of patients will grow as well. In stable coronary artery disease patients, control of symptoms and improvement in exercise tolerance may be achieved with haemodynamically acting agents such as nitrates, beta blockers and calcium channel antagonists. If one anti-anginal agent is ineffective, a combination of two or more agents can be used. But angina episodes may occur despite therapy with full doses of these haemodynamically active agents. Using metabolic drugs such as trimetazidine or ranolazine is a promising option, because they are free of any haemodynamic mechanisms of action and act at the cellular level, so an additive effect can be expected [14]. Because of no influence on heart rhythm, blood pressure and good tolerance, trimetazidine may be safely used as an alternative therapy or in combination with haemodynamic agents in elderly patients with numerous concomitant diseases. The beneficial effect of trimetazidine on cardiac metabolism suggests that it can be recommended to relieve current angina symptoms in coronary diabetic patients and/or with impaired left ventricular function. This has been shown in post-revascularized or no-options patients whose angina was not controlled with conventional anti-anginal drugs.

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