Refractory Angina—Unsolved Problem

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KEYWORDS

• Refractory angina pectoris • Neuromodulation • Spinal cord stimulation • Coronary sinus reducer • Enhanced external counter-pulsation

KEY POINTS

- Refractory angina affects up to 5% to 10% of patients with coronary artery disease and is a lingering problem in everyday clinical practice.
- The recommendations for management are based on registries, not on randomized clinical trials, which are restricted to small groups of patients.
- Management of patients with refractory angina should be carried out in or supervised by experienced centers with access to multiple pharmacologic and interventional options. Decisions to disqualify patients from coronary revascularization should be made by the heart team individually and should consider patients' needs and expectations.
- Introduction of new drug compounds and new interventional methods increases therapeutic options for this difficult-to-treat group of patients.

EPIDEMIOLOGY

Based on European Society of Cardiology (ESC) Joint Study Group on the Treatment of Refractory Angina estimation, the incidence of refractory angina ranges from 5% to 10% of patients with coronary artery disease.[1] In the Andrell and colleagues[2] study, refractory angina affects 2% of patients with stable angina pectoris who were referred to coronary angiography. Refractory angina pectoris (RAP) decreases the quality of life, increases the number of hospitalizations, and is linked to increased cost for health care systems.[2] The mortality rate in this subgroup of patients differs significantly among studies, ranging from 1% to 22%.[3–8] According to centers specialized in RAP treatment, 1-year mortality is 3.9%, and up to 29.4% after 9 years of follow-up.[9]

PATHOPHYSIOLOGY

Traditionally, the pathomechanism of angina pain in coronary artery disease is attributed to oxygen supply-demand imbalance. Ischemia of cardiomyocytes leads to the release of the compounds stimulating nerve endings (substance P, adenosine, histamine, bradykinin, and lactic acid). Stimulation of nociceptive fibers in heart muscle leads to the conducting of the impulses to the central nervous system, thereby creating ischemic pain. The mechanism of the transmission of pain signals from the cell to nerve fibers is not fully elucidated. It is proposed that changes in potentials of membrane receptors are caused by neurotransmitter release.[10–12] It is stated that the chemosensitivity of receptors and their voltage changes, which could be translated to pain stimuli.[10,12]

Nociceptive endings are located in myelinated (A) and unmyelinated (C) fibers, forming cardiac visceral sensory nerves creating sympathetic and vagal systems.[13,14] Sympathetic fibers travel via dorsal root ganglion to posterior thalamus. Vagal afferents fibers also reach posterior thalamus via the nucleus of tractus solitarius. Based on PET, several cortical structures from posterior thalamus

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are activated during anginal pain.[15] Little or even no peripheral stimulus could provoke severe cardiac pain.[16] Some observations in patients with microvascular angina show enhanced activation in the area connected with pain perception on brain level, which suggests central abnormalities in pain mechanism.

There is evidence that peripheral neuropathy can impair pain signaling; classic examples are diabetic patients who can experience silent ischemic episodes.[17,18] There is no straightforward correlation between the intensity of pain sensation and the severity of ischemia.[19] The intervention method depends on the pain source and its transmission.

PHARMACOLOGIC TREATMENT

The aim of the optimal medical treatment of refractory angina is symptom reduction, an increase of exercise tolerance, and prevention of further cardiovascular events. The group of patients with refractory angina presents various comorbidities that also should be taken into consideration while choosing the most appropriate treatment method.[20,21] β-Blockers, calcium channel blockers, and long-acting and short-acting nitrates are traditional antianginal first-line drugs recommended by guidelines.[22] Patients after myocardial infarction, especially those with reduced ejection fraction, benefit from β-blockers,[23] whereas nondihydropyridine calcium channel blockers are associated with increased mortality in this particular group.[23]

Drugs that improve prognosis in coronary artery disease are acetylsalicylic acid (ASA), 75 mg daily; or in cases of contraindications, clopidogrel, 75 mg daily; and statins. Statin dose should be adjusted to achieve treatment goal, which is low-density lipoprotein cholesterol levels below 1.8 mmol/L (70 mg/dL).[22]

Prasugrel and ticagrelor are given together with ASA (if not contraindicated), in the long term, secondary prevention in following doses (prasugrel, 10 mg daily, or 5 mg daily in cases of body mass 75 years old; ticagrelor, 60 mg twice a day). Also 2.5 mg of rivaroxaban, twice a day, can be administered to lower mortality.[24]

In cases of a combination of ASA with clopidogrel, prasugrel, ticagrelor, or rivaroxaban, the risk of hemorrhagic complications should be assessed. Drug combination increases anticoagulant effect in patients with refractory angina (patients with type 2 diabetes mellitus, renal insufficiency, or atherosclerosis–peripheral artery disease) decrease rate of ischemic events.[25–27] In cases of hypersensitivity to ASA, drug desensitization should be taken into consideration because ASA is a treatment of choice and patients require lifelong treatment with the compound.[28]

In 1 small randomized controlled trial, the beneficial effect of the uric acid–lowering compound, allopurinol (600 mg daily), was found. Allopurinol treatment increased the time to the ischemic event and the appearance of angina during exertion.[29] In a study by Singh and Yu,[30] a reduction of myocardial infarction rate was found, especially in the elderly and especially if allopurinol was given for longer than for 2 years.

In large clinical trials, the percentage of patients adherent to prescribed treatment (including β-blockers) varies between 50% and 90%. An increase in the heart rate above 70 beats per minute at rest in a group of patients with decreased ejection fraction was linked to increased risk of death due to cardiovascular events.[31] The most frequent contraindications to β-blockers include bradycardia, conduction disorders, and bronchial spasm (both asthma and chronic obstructive pulmonary disease). In cases of induction of bronchoconstriction after this class of drugs, a switch to calcium blockers is indicated. Calcium blockers do not lead to proper control of the heart rate; in that case, ivabradine may be helpful.[22] In cases of atrial fibrillation and poor rate control, addition of digoxin is recommended. In critical cases, when the control rate in atrial fibrillation is difficult or impossible despite pharmacologic therapy, ablation of an atrioventricular node with pacemaker (optimal His bundle stimulation or resynchronization therapy) implantation is an option.[32]

Long-acting and short-acting nitrates are basal antianginal therapy. The problems appearing during nitrate treatment are tachyphylaxis and drug tolerance. In some cases, it is useful to combine nitrates, once daily, with molsidomine. Sometimes, a useful method is temporarily withdrawing nitrates with an exchange, for example, to nicorandil. Nicorandil is a nitrate-like drug that vasodilates coronary arteries and has cardioprotective potentials.[33] Efficacy of nicorandil was demonstrated in the Impact Of Nicorandil in Angina (IONA) trial, with major cardiovascular events (MACEs) reduction compared with the placebo group.[34]

Ivabradine blocks If channels, which regulate sinoatrial node chronotropic function. This drug is ideal for patients in whom β-blockers or calcium channels blockers are contraindicated. Ivabradine decreases heart rate, not affecting the systemic pressure; it also can be used together with a β-blocker to achieve a pulse rate below 70 beats per minute[35] or with a calcium channel blockers in cases of contraindications to β-blockers. The

drugs are effective compared with β-blockers in angina reduction[36] and increase free of angina time during exercise.[35]

The anti-ischemic mechanism action of ranolazine is not fully understood. Probably, the drug affects channels similarly to amiodarone mainly via inhibition of late sodium currents.[37] In a few trials in patients with stable angina, ranolazine increases exercise time and ischemic threshold.[38–40] It is supposed that ranolazine improves coronary flow in areas of myocardial ischemia.[41]

Trimetazidine is a metabolic drug that acts on the cellular level by blocking thiolase (an enzyme involved in the β-oxidation of fatty acids) and increases glucose oxidation.[42,43] In the cells in ischemic conditions, in which oxygen supply is not sufficient, oxidation of glucose requires 10% to 15% less oxygen than β-oxidation of fatty acid to create the same amount of energy (adenosine triphosphate). In this way, the drug helps the cell to maintain basic functions in ischemic cells. There is evidence that trimetazidine improves exercise time to ischemia occurrence and decreases angina frequency.[44] In a meta-analysis of 23 randomized trials with trimetazidine, however, this anti-ischemic effect and reduction of MACEs were not confirmed.[45] In cases of comorbid hypertension, heart failure, and type 2 diabetes mellitus, the addition of angiotensin-converting enzyme I inhibitors or angiotensin receptor II blockers is recommended.[22]

Other drugs, like perhexiline, L-arginine, testosterone, thrombolytic agents (urokinase), and chelation therapy, are available; however, their efficacy and safety in refractory angina have not been confirmed.

ROLE OF THE HEART TEAM

Patients with refractory angina should be treated in specialized centers, where wide spectrum of treatment methods are available. Detailed analysis of each case allows personalizing the treatment and increasing its efficacy. Proper assessment of the pathogenesis of pain in individual patients plays a pivotal role in the choice of the optimal management plan.

The first step to be taken is coronary angiography. Cardiologists performing coronarography, in cases of advanced lesions in coronary arteries, should refer patients to a heart team consultation, to make a shared decision on further steps. In each case, better control of concomitant diseases is recommended (ie, glycemia, blood pressure, lipids, and body weight). Patients are obliged to cease smoking, control body weight, and adjust their diet. Each patient disqualified from the revascularization procedure should be supplied with psychological help and should be included in a cardiac rehabilitation program. The Hospital Anxiety and Depression Scale can be useful to screen patients.[46] Complex analysis of each case, adjustment to patient expectations, and psychological support are crucial components of patients' management.[47]

Reevaluation of contraindications for revascularization also is pivotal. The center for treatment of refractory angina should have available various modalities of percutaneous coronary intervention (including chronic total occlusion atherectomy and shockwave balloon) and coronary artery bypass graft (especially minimally invasive procedure on heart beating). The heart team, with experienced surgeons and interventional cardiologists, should decide, based on current angiogram and patient clinic, on referral or exclusion from further revascularization. In selected cases (after risk assessment), it even is possible to perform not complete revascularization. Next, based on careful examination, concomitant abnormalities that could mimic angina, like anemia, chronic obstructive pulmonary disease, and hyperthyroidism, should be excluded.

CARDIAC REHABILITATION

Changes in lifestyle and cardiac rehabilitation reduce cardiac mortality.[48,49] Physical training adjusted to patients' state, brings effects in long-term observation, improves quality of life, and should be implemented in each patient ok the program or the treatment program.[50–52] In elderly and disabled patients, musculoskeletal disorders can hamper rehabilitation and rehabilitation programme should be adjusted to a patient's disability level.

In cases of a lack of efficacy of pharmacologic treatment, some invasive techniques can be implemented (**Table 1**).[22]

Enhanced external counter-pulsation (EECP) is a noninvasive method using 3 sets of pneumatic cuffs around the lower extremities, which work in a coordinated manner with the heart pump. In diastole, they fill, increasing vein backflow, imitating muscle pump; in systole, they deflate and therefore decrease afterload.[53,54]

The benefits of this method include not only mechanical support but also the proangiogenic effect, with an increase of the growth factors levels and circulating $CD34^+$ cells that can stimulate the growth of the collateral circulation.[55–58] Also, some beneficial effects on the factors regulating vessel tonus were observed, that is, increase in the concentration of nitric oxide and decrease in the endothelin levels.[59] Reduction of the vasoconstriction increases control of blood pressure and

Table 1
Nonpharmacologic treatment options in refractory angina

Therapy	Mechanism of Action	Strength of Evidence
Coronary sinus reducer	Coronary flow redistribution	ESC: IIb/B ACC/AHA: NA
SCS	Pain termination	ESC: IIb/B ACC/AHA: IIb/B
EECP	Mechanic support, vascular relaxation	ESC: IIb/B ACC/AHA: IIB/B
Transmyocardial laser revascularization (surgical or percutaneous)	Angiogenesis, myocardial denervation	ESC: III/A ACC/AHA: IIb/B

Abbreviation: AHA, American Heart Association.
Data from Knuuti, J., et al., 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J, 2020. 41(3): p. 407-477.

reduces angina.[60] In the multicenter study of enhanced external counterpulsation, the improvement of ischemia-induced pain by physical exercise was observed.[61]

EXTRACORPOREAL SHOCKWAVE THERAPY

Low-energy extracorporeal shockwave therapy (ESWT) is similar to lithotripsy but with lower energy. It is possible to stimulate in situ expression of proangiogenic vascular endothelial growth factor and nitric oxide.[62,63] In a few small randomized trials, ESWT confirmed positive results in increasing exercise time and reduction of angina.[64,65]

NEUROMODULATION

Neuromodulation is a method using chemical or electrical stimuli to break the pain signal pathway from heart to brain. The reduction of sympathetic afference stimulation, besides termination or alleviation of pain sensation, also decreases vasoconstriction.[66,67]

Spinal cord stimulation (SCS) is an invasive method used by neurosurgeons for treating patients with persistent pain that is refractory to medical therapy. This method is wildly available in many countries. For angina pain treatment, surgically epidural space is reached and a multipolar electrode is positioned between the C7 and T4 vertebrae. In this position, electrical stimulation has an impact on afferent sympathetic fibers and affects regional neurochemistry changes, which finally leads to pain elimination or reduction. There is evidence of the increase in γ-aminobutyric acid, that limits nociceptive afference.[68] The electrode is connected with a device that is placed subcutaneously. The therapy requires stimulation for 1 hour, 2 times per day, and on patient demand. Based on the results of several trials, the method reduces angina and nitrate consumption and improves exercise capacity and the quality of life.[69–72]

Other therapeutic options use neuromodulation: subcutaneous electrical nerve stimulation (SENS), thoracic epidural anesthesia, left stellate ganglion blockade (LSBG), and endoscopic thoracic sympathectomy are available. These methods are used successfully in specialized centers, but they still need validation in the randomized trials. The SENS method was tested in a small pilot study and demonstrated safety and feasibility using the same protocol as in SCS.[73] Reduction of angina and sublingual nitrate consumption was observed in all studied patients. The method seems safer in patients requiring anticoagulation or dual antiplatelet therapy compared with SCS, in which an electrode has to be positioned in epidural space. There are some concerns about safety in patients with other implantable electrical devices like implantable cardioverter defibrillators.

The methods of the left stellate ganglion blockade and endoscopic thoracic sympathectomy are feasible but data on its efficacy are scarce.[74,75] These methods require further randomized studies to confirm their usefulness and safety profiles.

CORONARY SINUS REDUCER

The idea of heart revascularization by grafting a systemic artery into coronary sinus was described by Beck and colleagues in 1948.[76] Nowadays, the possibility of narrowing coronary sinus by a special hourglass-shaped stent is a novel method of treating patients with refractory angina in a less traumatic way. The method was tested positively in a few studies.[77,78] The sinus reducer mechanism of action increases the trans-sinusal gradient

pressure of blood and redistribution from less ischemic epicardium to the ischemic endocardium.[79–83] In the Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA) study, angina pain was decreased effectively by reducer compared with the control group.[84] An improvement in quality of life also was stated.[84] The efficacy of coronary sinus reducer therapy was confirmed in a group of patients with nonrevascularized chronic total occlusions. They had better outcomes than patients without chronic total occlusions (CTO);[85] higher efficacy in this subgroup may be the consequence of the better collateral flow.[86,87] Chronic ischemia may stimulate neoangiogenesis. Redistribution of coronary flow through increased resistance in sinus may be beneficial and may lead to the development of collateral flow by stimulation of neoangiogenesis.

Until now, an adequate response to RAP treatment has not been defined. In a study by Andrell and colleagues,[69] 18% of patients received adjunctive nonpharmacologic treatment, but, in more than 50% of patients, there was no method that used in monotherapy would be sufficient enough to reduce angina symptoms.[69] Nevertheless, safety and efficacy aspects of all invasive procedures should be evaluated carefully in prospective optimally randomized trials.

GENE THERAPY AND STEM CELLS

Stem cell treatment and gene therapy still are considered experimental treatments.

Improvement of systolic fraction of left ventricle and reduction of angina and mortality were observed in some studies using $CD34^+$ and $CD133^+$ cell therapy.[88–93] These changes were observed even 2 years after the procedure.[89] In the RENEW: Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects With Refractory Angina study, treatment with autologous stem cells also increased the pain-free exercise time.[94] The results of placebo-controlled trials, however, are less encouraging.[8,95,96]

TRANSMYOCARDIAL LASER REVASCULARIZATION

The idea of creating channels into ischemic myocardium to restore perfusion is based on an animal model of a reptile heart. In this method, using a surgical or percutaneous approach, 20 to 40 transmural 1-mm channels from epicardium to endocardium are created. An analysis of 7 trials conducted by the National Institute for Health and Care Excellence showed a statistically significant increase in mortality, heart attack rate, progression to heart failure, and thromboembolic complications.[97]

SUMMARY

Refractory angina increases mortality, impairs quality of life, and increases cost caused by repeated hospitalizations. The real number of patients with refractory angina is hard to assess. In Andrell and colleagues'[2] study, the prevalence of RAP was 2.1% but that seems underestimated because elderly and patients with comorbidities often are excluded from the studies.

In most patients, angina symptoms can be reduced by optimal pharmacologic treatment. Introduction of ivabradine, ranolazine, more efficient antiplatelet treatment, and anticoagulation increased angina treatment options. Only those in whom another alternative diagnosis was excluded, who did not respond to pharmacologic treatment (approximately 20%–30% of RAF), are qualified for intervention therapies. The term, *untreatable angina*, should be avoided because it suggests that there is no treatment option available for the patients. In recent years, novel intervention modalities were introduced and are included to present ESC and American College of Cardiology (ACC) recommendations. In RAP patients, the effect of a placebo cannot be neglected. In the TLRM study, a 30% improvement in exercise duration and a significant decrease in angina symptoms were reported in the control group. There is evidence that even placebo interventions alone could improve exercise duration and reduce angina. These strong placebo effects make the performance of reliable randomized interventional studies difficult.

A diagnostic and therapeutic process of patients with RAP should be conducted in specialized centers. Angina clinics should cover all diagnostic procedures and have a team experienced in percutaneous and surgical treatment and access to a full range of pharmacotherapy. A step-by-step process, starting from pharmacologic treatment, is pivotal. Each center performing revascularization procedures should be able to consult with a center specialized in RAP treatment. Because each case should be analyzed individually, a decision on further steps should be taken by a multidisciplinary heart team and should be accepted by the patient. The decision should be based on optimal benefit-risk balance. Despite a wide range of therapeutic options, elimination or reduction of angina sometimes is impossible; therefore, close cooperation with a psychologist also should be taken into consideration.

DISCLOSURE

The authors declare no conflicts of interest.

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