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Nonpharmacological approaches to refractory angina

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Abstract

An increasing number of patients have advanced coronary artery disease with ischemic symptoms that are refractory to medical therapy and revascularization. With the increasing adoption of percutaneous revascularization of chronic total occlusions, previously nonrevascularizable vessels may now be targets for revascularization, which may change the landscape of refractory angina. Several nonpharmacological approaches to refractory angina have emerged, including novel interventional, noninvasive, neuromodulatory, and angiogenic approaches. Enhanced external counterpulsation remains the mainstay of noninvasive therapy, increasing time to exercise-induced ischemia and reducing frequency of angina episodes. Cardiac shockwave therapy is a promising noninvasive therapy, but randomized data remain limited. Neuromodulatory approaches include spinal cord stimulation, which has demonstrated a reduction in frequency of angina episodes; however, randomized, double-blind clinical trials have yielded conflicting results. Cell-based therapies have shown a reduction in angina and an improvement in exercise tolerance, but advancement of such therapies awaits adequately powered phase 3 trials. Coronary sinus reduction is a novel interventional approach in which an hourglass-shaped device is implanted in the coronary sinus, creating a narrowing that increases upstream pressure, relieving angina. The recently reported COSIRA phase 2 randomized trial showed improvements in angina class and quality of life metrics, setting the stage for a larger definitive trial. In summary, novel nonpharmacological therapies are emerging as promising options for the growing population of formerly "no-option" patients. ■ *Heart Metab*. 2017;72:18-24

Keywords: enhanced external counterpulsation; neuromodulation; PCI; refractory angina

Introduction

As the population ages and with improvements in outcomes for coronary artery disease (CAD), a growing number of patients experience angina that is refractory to usual attempts at revascularization and medical therapy. The term refractory angina is defined as "a chronic condition caused by clinically established reversible myocardial ischemia in the presence of CAD, which cannot be adequately controlled by a combination of medical therapy, angioplasty or coronary artery bypass graft," and as a "debilitating disease characterized by severe, unremitting cardiac pain, resistant to all conventional treatments for [CAD]".[1,2]

Epidemiology and natural history

Refractory angina is increasing in frequency, with angiography revealing an estimated 10% to 15% of patients with CAD that is not amenable to revascularization, resulting in an estimated prevalence of 1.8 million

Abbreviations

ACC: American College of Cardiology; **ACT-34:** Autologous CD34+ cell Therapy; **AHA:** American Heart Association; **CAD:** coronary artery disease; **CCS:** Canadian Cardiovascular Society; **COSIRA:** COronary SInus Reducer for treatment of refractory Angina; **CSWT:** cardiac shockwave therapy; **CTO:** chronic total occlusion; **DIRECT:** DIrect myocardial laser revascularization (DMR) in Regeneration of Endomyocardial Channels Trial; **EARL:** European Angina Registry Link; **EECP:** enhanced external counterpulsation; **ESC:** European Society of Cardiology; **MACE:** major adverse cardiac events; **MUST-EECP:** MUlticenter STudy of Enhanced External Counterpulsation; **PCI:** percutaneous coronary intervention; **PMLR:** percutaneous myocardial laser revascularization; **QOL:** quality of life; **RASCAL:** Effectiveness and Cost-Effectiveness of Spinal Cord Stimulation for Refractory Angina; **RCT:** randomized controlled trial; **RENEW:** Efficacy and Safety of Intramyocardial Autologous CD34+ Cell Administration in Patients With Refractory Angina; **SCS:** spinal cord stimulation; **STARTSTIM:** Stimulation Therapy for Angina RefracTory to Standard Treatments, Interventions, and Medications; **TMLR:** transmyocardial laser revascularization

patients in the United States alone.[2-4] Potential mechanisms behind anginal pain are summarized in *Figure 1*.[5] Historically, survival was reported to be poor.[6] Outcomes from a contemporary cohort at a specialized refractory angina clinic in the United States are more optimistic, with 1-year and 9-year survival of 96.1% and 71.6%, respectively, highlighting the importance of aggressive risk factor modification, antiplatelet therapy, and the use of novel therapies.[7]

Revascularization

Stable ischemic heart disease guidelines recommend revascularization for obstructive CAD to improve symptoms that are persistent despite maximally tolerated goal-directed medical therapy (GDMT) and also for select anatomical subsets in asymptomatic patients to improve prognosis.[1,8] With the increasing adoption of percutaneous revascularization (ie, percutaneous coronary intervention [PCI]) of chronic total occlusions (CTO) leading to increasing success rates and safety, previously nonrevascularizable vessels are now intervenable, which may change the landscape of refractory angina management. However, randomized controlled trials (RCTs) are still needed.[9,10]

Guideline-directed medical therapy and pharmacological approaches

β-Blockers, calcium-channel blockers, and long-acting nitrates are mainstays of GDMT,[1,8] although their ability to demonstrably reduce ischemic burden is limited. These agents improve symptoms by reducing heart rate, blood pressure, and myocardial contractility, but are often limited by a patient's ability to tolerate them. Ranolazine has recently been approved in the United States and appears to decrease angina in refractory angina patients.[10] The pathophysiology

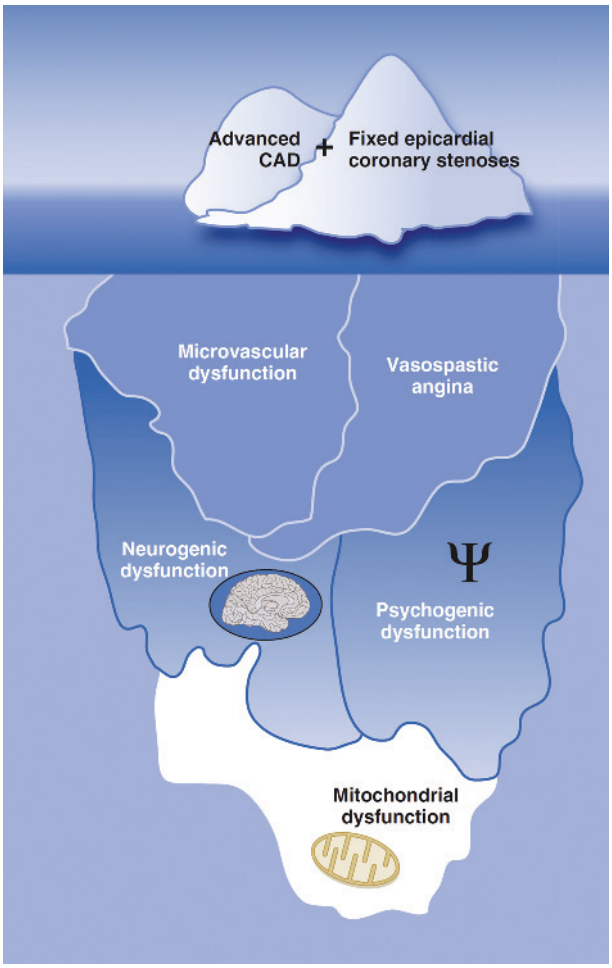

Fig. 1 *Potential mechanisms for refractory angina extend beyond epicardial coronary artery disease (CAD)—the tip of the iceberg—to microvascular dysfunction and vasospastic angina. Neurogenic, psychogenic, and mitochondrial dysfunction may further drive angina and may be potential targets for intervention.*
Reproduced from reference 5: *Jolicoeur EM and Henry TJ. Refractory angina. In: de Lemos J and Omland T, eds.* Chronic Coronary Artery Disease: A Companion to Braunwald's Heart Disease. *Elsevier Health Sciences; 2017:412-432. © 2017 Elsevier.*

and clinical efficacy of established and novel pharmacological approaches to refractory angina have been previously summarized.[5,10,11]

Chronic total occlusions

CTO are occluded or near-occluded coronary blockages lasting at least 3 months. Their corresponding myocardium may be supplied by collaterals, leading to jeopardized but viable myocardium, with resultant ischemic pain. However, the occlusion may be calcified and/or have anatomy not amenable to traditional antegrade approaches. Advances in CTO PCI, including CTO-specific equipment and retrograde approaches have increased procedural success, and a recent meta-analysis of 25 nonrandomized studies and 24 486 patients suggested successful CTO PCI to be associated with lower mortality, lower risk of stroke, less need for subsequent coronary artery bypass grafting, and lower risk for major adverse cardiac events (MACE) than unsuccessful CTO PCI.[9] In nine studies reporting on angina, there was less residual angina (odds ratio, 0.38; 95% confidence interval, 0.24-0.60).[9] A smaller study at a single institution with propensity matching did not replicate the mortality benefit seen in the unmatched pooled study,[12] and randomized data is needed. Nonpharmacological approaches to refractory angina, including CTO PCI, are summarized in *Table I*.

European Society of Cardiology (ESC) guidelines recommend that PCI may be considered in patients with "expected ischemia reduction in a corresponding myocardial territory and/or angina relief."[1]

Noninvasive approaches to refractory angina

Enhanced external counterpulsation

A mainstay of noninvasive therapy, enhanced external counterpulsation (EECP) utilizes pneumatic cuffs around the lower extremities; the cuffs inflate during diastole, augmenting coronary blood flow, and deflate during systole, decreasing afterload. The landmark trial MUST-EECP (MUlticenter STudy of Enhanced External Counterpulsation) randomized 139 patients with refractory angina to 35 hours of active versus inactive counterpulsation. Time to exercise-induced ST-segment depression was increased, and angina was less frequent in the active counterpulsation group[13]; results supported by a meta-analysis of 18 nonrandomized studies including 1768 patients showed 85% of patients who underwent EECP had a reduction of at least one Canadian Cardiovascular Society (CCS) angina class.[14] The anti-ischemic mechanistic benefits of EECP were further investigated in 42 patients randomized to EECP versus sham treatment. EECP improved flow-mediated dilation of the brachial and femoral arteries and increased the endothelial-derived vasoactive agents nitric oxide and 6-keto-prostaglandin, whereas it decreased endothelin-1 and the inflammatory markers tumor necrosis factor α and high-sensitivity C-reactive protein, among others.[15] Moreover, in a perfusion stress test study of 175 patients, 83% of patients had improvement in perfusion images after a 35-hour course of EECP.[16] EECP is approved and reimbursed for 35 hours over 7 weeks in the United States.

American College of Cardiology (ACC) and American Heart Association (AHA) joint guidelines recommend that EECP may be considered for relief of refractory angina,[8] whereas ESC guidelines recommend it *should* be considered.[1,17]

Cardiac shockwave therapy

Also known as extracorporeal shockwave therapy, cardiac shockwave therapy (CSWT) delivers low-energy shockwaves applied to the borders of ischemic zones under ultrasound guidance, creating mechanical stress, which may promote neovascularization. Although there have been several small RCTs, they have been limited by small sample size and lack of consistent use of sham control. In a recent meta-analysis of a mixture of randomized and nonrandomized trials, CSWT was associated with improvements in CCS angina class, quality of life (QOL) metrics, nitroglycerin dosage, New York Heart Association functional class, left ventricular ejection fraction, 6-minute walk test (6MWT), left ventricular (LV) end diastolic dimensions, and myocardial viability.[18] However, there was significant heterogeneity across trials highlighting the need for more randomized data.

Neuromodulatory approaches to refractory angina

Patients with a prominent neurogenic component to their cardiac pain may benefit from neuromodulation, which uses chemical, mechanical, or electrical means to interrupt pain signals, with therapies ranging from noninvasive to invasive approaches.[5,10]

Transcutaneous electrical nerve stimulation

Low-voltage electrical currents are administered through electrodes placed on pain points and can be used to ameliorate angina before taking more definitive approaches. ESC guidelines recommend that transcutaneous electrical nerve stimulation may be considered for refractory angina, though acknowledging the evidence is very limited.[17]

Spinal cord stimulation

In cardiac spinal cord stimulation (SCS), a multipolar electrode is implanted in the epidural space at the

	Indication	Reported benefits	Guidelines	Future directions
PCI of chronic total occlusions	CAD; evidence of ischemia in corresponding myocardial territory; angina	↑ Survival ↓ Stroke ↓ CABG ↓ MACE ↓ Angina	• ESC 2013: IIb, B	• Randomized trials ongoing in DECISION-CTO, EURO-CTO
Enhanced external counterpulsation	CAD; refractory angina	↑ Time to exercise-induced ischemia* ↓ Angina* ↓ Nitroglycerin use* ↑ Flow-mediated dilation* ↑ Endothelial-derived vasoactive agent profile* ↓ Inflammatory markers* ↓ Perfusion defect	• ACC/AHA 2012/2014: IIb, B • ESC 2013: IIa, B • CCS 2012: may be considered, weak, low-quality evidence	• Approved and reimbursed for 35 h over 7 weeks in the United States and parts of Europe
Cardiac shockwave therapy	CAD; ischemic heart disease; refractory angina	↓ Angina* ↑ LVEF* ↑ 6MWT* ↓ Perfusion defect*	-	• Further randomized data needed
Transcutaneous electrical nerve stimulation	Angina	↓ Angina	• ESC 2013: IIb, C	• Further randomized data needed
Spinal cord stimulation	CAD; refractory angina	↑ Exercise capacity* ↑ QOL* ↓ Angina ↓ Nitroglycerin use	• ACC/AHA 2012: IIb, B • ESC 2013: IIb, B • CCS 2012: may be considered, weak, moderate-quality evidence	• STARTSTIM and RASCAL failed to fully enroll • Further randomized data needed
Transmyocardial laser revascularization	CAD; refractory angina	↓ Angina* ↑ 30-d mortality*	• ACC/AHA 2012: IIb, B • ESC 2013: III, A • CCS 2012: not recommended, strong, high-quality evidence	• No further studies planned
Percutaneous myocardial laser revascularization	CAD; refractory angina	± Exercise duration*† ± Angina*† ± Perfusion imaging scores*† ↑ 30-d myocardial infarction*†	• CCS 2012: may be considered, weak, moderate-quality evidence	• Negative DIRECT phase 2 study • No further studies planned
Coronary sinus reduction	CAD; refractory angina	↓ Angina*† ↑ QOL*† ↓ Perfusion defect	-	• Successful COSIRA phase 2 study with sham control
Cell-based therapies	CAD; refractory angina	↓ Angina*† ↑ Exercise tolerance*† ↓ MACE*†	-	• $CD34^+$: RENEW phase 3 trial terminated early for financial reasons, • Meta-analysis strongly positive

Table I *Summary of nonpharmacological approaches to refractory angina. *Randomized data, †Sham intervention control arm included*
Abbreviations: *6MWT, 6-minute walk test; ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; COSIRA, COronary SInus Reducer for treatment of refractory Angina; DECISION-CTO, Drug-Eluting Stent Implantation versus Optimal Medical Treatment in Patients with Chronic Total Occlusion; ESC, European Society of Cardiology; DIRECT, DIrect myocardial laser revascularization (DMR) in Regeneration of Endomyocardial Channels Trial; EURO-CTO, European Study on the Utilization of Revascularization vs Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; QOL, quality of life; RASCAL, Effectiveness and Cost-Effectiveness of Spinal Cord Stimulation for Refractory Angina; RENEW, Efficacy and Safety of Intramyocardial Autologous $CD34^+$ Cell Administration in Patients With Refractory Angina; STARTSTIM, Stimulation Therapy for Angina RefracTory to Standard Treatments, Interventions, and Medications.*

C7/T1 level near the afferent nerves. In a meta-analysis of seven RCTs encompassing 270 patients with refractory angina, SCS was compared with coronary artery bypass grafting, percutaneous myocardial laser revascularization (PMLR), and SCS off control. As compared with SCS off control, cardiac SCS demonstrated improvements in exercise capacity and QOL.[19] However, trial heterogeneity and lack of a usual care control limited their results. In a subsequently published EARL registry (European Angina Registry Link) of 235 patients, the 121 patients with implanted devices reported fewer angina episodes, reduced nitrate use, and improved CCS angina class.[20]

STARTSTIM (Stimulation Therapy for Angina RefracTory to Standard Treatments, Interventions, and Medications), a contemporary RCT, randomized patients to high-stimulation versus low-stimulation control, but due to slow enrollment, the study was terminated early after 68 randomized patients. Although both groups saw decreases in angina episodes, the decreases were not different between groups, nor were improvements in total exercise time and time to angina onset.[21] Similarly, RASCAL (Effectiveness and Cost-Effectiveness of Spinal Cord Stimulation for Refractory Angina) sought to randomize patients to SCS versus usual care but failed to meet enrollment targets. Of 29 randomized patients, there was a trend toward larger improvements in angina frequency and the 6-minute walk test in the SCS group.[22]

These two recent negative RCTs have dampened the enthusiasm for cardiac SCS. ACC/AHA and ESC guidelines published before such RCT results were available both recommend that SCS may be considered for relief of refractory angina and, in the ESC guidelines, also for improving QOL.[1,8,17]

Transmyocardial laser revascularization

Although the exact mechanism behind its efficacy is unknown, transmyocardial laser revascularization (TMLR) employs high-powered carbon dioxide or xenon monochloride lasers by thoracotomy or sternotomy to create multiple transmural channels in the LV myocardium. A recent Cochrane Review meta-analysis of seven nonblinded RCTs with 1137 patients demonstrated superiority of TMLR in reducing angina by two angina classes (43.8% versus 14.8%). However, 30-day mortality by as-treated analysis was alarmingly higher in the TMLR group (6.8%) than in the control group (0.8%).[23] ACC/AHA guidelines recommend that TMLR may be considered for relief of refractory angina,[8] but CCS and ESC guidelines both recommend against its use, as the risks outweigh the potential benefit.[1,2]

An alternative delivery method using an endovascular catheter-based laser system showed promise in the early 2000s, and DIRECT (DIrect myocardial laser revascularization (DMR) in Regeneration of Endomyocardial Channels Trial), a phase 2 multicenter RCT, enrolled 298 patients to test the efficacy of PMLR against sham control. Exercise duration, angina class, and perfusion imaging scores were not different between PMLR and sham control groups, and there was an increase in morbidity in PMLR-treated patients.[24] It is not clear whether the lack of efficacy as compared with TMLR was due to differences in energy delivery, endocardial versus epicardial delivery, or the removal of a placebo effect when a sham control arm was used.

Novel interventional technique

Coronary sinus reduction

The Reducer is an hourglass-shaped device that is implanted in the coronary sinus, creating a stenosis that modulates endocardial versus epicardial flow (*Figure 2*).[5,25] At 3-year follow-up in first-in-human trials, the device was shown to have maintained patency, and angina symptoms were reduced.[26] The recently reported COSIRA (COronary SInus Reducer for treatment of refractory Angina) phase 2 trial was a double-blind, sham-controlled RCT randomizing 104 patients with CCS class III or IV refractory angina to treatment versus sham. At 6-month follow-up, improvement of two CCS angina classes was achieved in 35% (treatment) versus 15% (sham), and improvement of one CCS angina class occurred in 71% versus 42%.[25] QOL metrics were also improved, along with improvements in perfusion imaging.[25,26] A multicenter, randomized phase 3 trial (COSIRA) will begin in the United States in 2017.

Cell-based therapies

Cardiovascular cell therapy is a novel approach designed to promote neovascularization and en-

dothelial repair. A recent meta-analysis of six RCTs with 353 patients randomized in cell therapy trials showed improvements in angina episodes, use of antianginal medications, CCS angina score, exercise tolerance, myocardial perfusion, MACE, and arrhythmias in cell-treated patients.[27] ACT-34 (Autologous CD34+ cell Therapy), the largest double-blind, placebo-controlled trial (N=167) included in that analysis, compared intramyocardial-delivered CD34+ cells versus placebo and demonstrated significant reduction in angina along with a significant improvement in exercise time.[28,29] These results were maintained at 24 months, with a trend toward decreased MACE.[29] The phase 3 RENEW trial (Efficacy and Safety of Intramyocardial Autologous CD34+ Cell Administration in Patients With Refractory Angina), which compared CD34+-cell injection, no intervention, or placebo injection was terminated early, unfortunately, due to financial reasons; however, it confirmed the improvements in exercise time and angina frequency seen in phase 1 and phase 2 trials.[30] A definitive phase 3 trial is still needed.

Future directions and conclusions

Multiple nonpharmacological therapies are emerging as promising options for what have been previously considered "no-option" refractory angina patients. EECP remains a cornerstone noninvasive therapy; meanwhile, CTO revascularization, CSWT, and SCS require further randomized data. Moreover, novel approaches in coronary sinus reduction and cell-based therapies have demonstrated promising results in rigorously conducted double-blinded, sham-controlled randomized studies, and definitive trials are urgently needed. ■

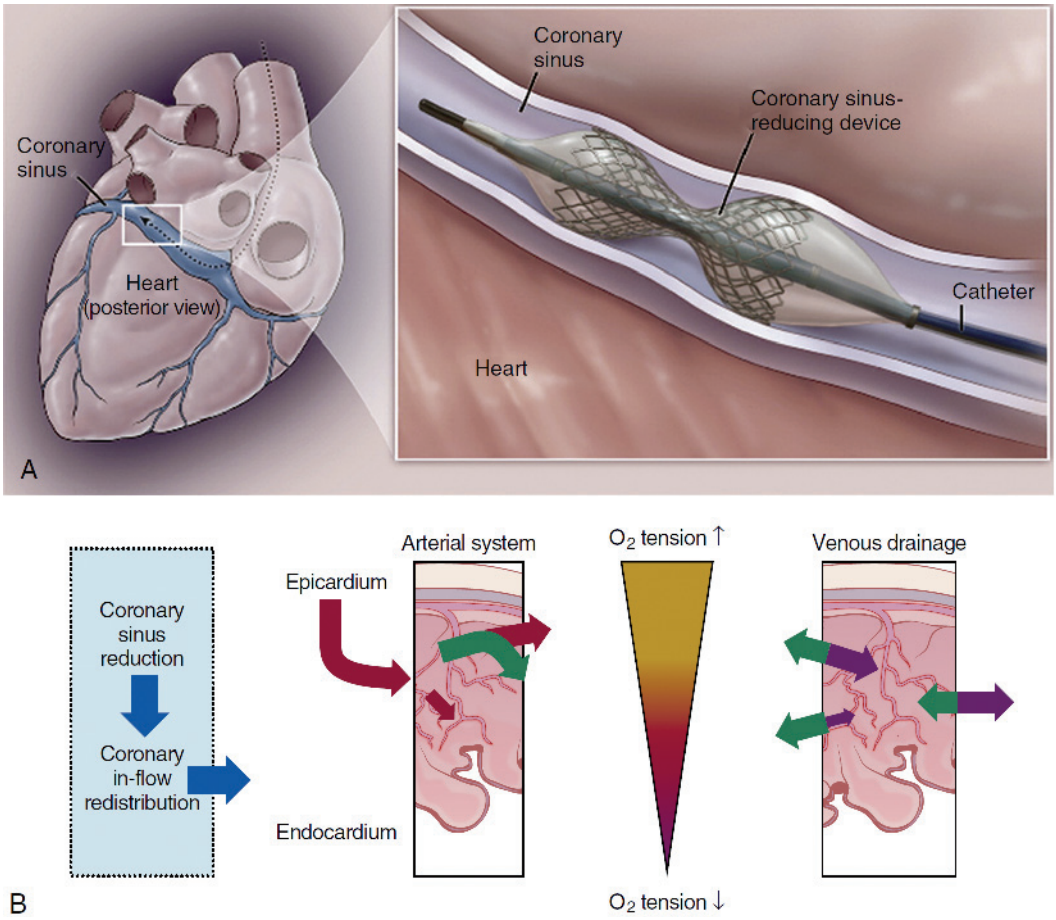

Fig. 2 *Coronary sinus-reducer system (**A**), an hourglass-shaped metal mesh device mounted on a balloon catheter, expanded, and implanted in the coronary sinus. The vessel wall grows into the fenestrations in the metal mesh. The central orifice of the device remains patent, leading to a narrowed channel for blood flow, increased upstream pressure, and favorable coronary blood flow redistribution (**B**).*
Panel (A) reproduced from reference 25: *Verheye S, Jolicoeur EM, Behan MW, et al. Efficacy of a device to narrow the coronary sinus in refractory angina.* N Engl J Med. *2015;372:519-527. © 2015, Massachusetts Medical Society.*
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