Current Cardiology Reports (2019) 21: 46
https://doi.org/10.1007/s11886-019-1134-8

ISCHEMIC HEART DISEASE (D MUKHERJEE, SECTION EDITOR)

Refractory Angina: the Current State of Mechanical Therapies

Amod Amritphale[1] · Nupur Amritphale[2]

Published online: 22 April 2019

Abstract

Purpose of Review Refractory angina (RA), which is characterized by tissue ischemia along with neurological, mitochondrial, and psychogenic dysfunction, is becoming a major cause of morbidity in patients with advanced coronary artery disease. In this review, we discuss in detail the invasive mechanical non-cell therapy–based options, the evidence behind these therapies, and future trends.

Recent Findings There is extensive ongoing research in the areas of spinal-cord stimulation, transmyocardial laser revascularization, sympathectomy, angiogenesis, and other non-cell-based therapies to explore the best therapy for refractory angina. There is conflicting data in the literature suggesting subjective improvement in angina, but very few studies boast improvement in core objective parameters such as myocardial blood flow, survival, or rehospitalizations.

Summary Patients with refractory angina are a complex group of patients that need novel approaches to help alleviate their symptoms and reduce mortality. A carefully selected sequence of therapies may provide the best results in this patient population.

Keywords Refractory angina · Coronary artery disease · Spinal-cord stimulation · Transmyocardial laser revascularization · Sympathectomy · Angiogenesis

Abbreviations

RA	Refractory angina
CAD	Coronary artery disease
SCS	Spinal-cord stimulation
TMLR	Transmyocardial laser revascularization
CABG	Coronary artery bypass grafting
RCT	Randomized controlled trial
SNA	Sympathetic nervous activity

Introduction

Refractory angina (RA) has been defined as the presence of persistent angina or angina equivalents extending over a period of more than or equal to 3 months. This mainly consists of tissue ischemia along with neurological, mitochondrial, and psychogenic dysfunction leading to persistent precordial pain and other symptoms. It is often identified as being a result of an untreatable coronary artery disease (CAD) in patients with objective evidence of myocardial ischemia [1].

The statistics have sky rocketed with the average number of patients suffering from RA are over a million per year in the elderly patients, not to mention the increasing hospitalization costs due to advancement in technology [2, 3].

It is pertinent to reduce risk factors as a preventative measure including smoking cessation, regular exercise, and lifestyle changes. Besides that, multiple pharmacological therapies like coronary vasodilators nitrates, nicorandil; those modifying heart rate and contractility like beta blockers, calcium channel blockers and ivabradine have proven themselves with strong evidence to treat stable angina [4]. Despite these therapies, a considerable portion of patients remain suffering from RA.

In invasive options for RA, there are two major areas. Primarily, it is the cell-based therapies and other areas, including enhanced external counterpulsation (EECP), gene therapy, spinal cord stimulation (SCS), transmyocardial laser revascularization (TMLR), angiogenesis, coronary sinus reduction, and sympathectomy. The cell-based therapies for RA are an extensive topic and have been recently reviewed in detail by

This article is part of the Topical Collection on *Ischemic Heart Disease*

✉ Amod Amritphale
amod.amritphale@gmail.com

Nupur Amritphale
nupurs.88@gmail.com

[1] Oklahoma University Health Sciences Center, Oklahoma City, OK, USA

[2] Texas Tech University Health Sciences Center, El Paso, TX, USA

Bassetti et al. [5•]. In this review, we discuss invasive mechanical non-cell therapy–based options, the evidence behind these therapies, and future trends.

Enhanced External Counterpulsation

The premise of this technique is based on the concept similar to that of intra-aortic balloon pump. It increases arterial blood pressure and retrograde aortic blood flow during diastole (diastolic augmentation). The hypothesis behind this technique includes improvements in endothelial function, stress-induced myocardial perfusion, diastolic filling, and peripheral arterial flow-mediated dilation [6–11].

MUST-EECP trial evaluated this technique and did show benefit on time to ≥ 1 mm ST segment depression compared with baseline (379 versus 337 s) but showed no statistical significant difference in terms of exercise duration or nitroglycerine use [12]. Similar effects were seen in multicenter registries, but no study has till date shown benefit in terms of absolute indices like coronary blood flow or mortality benefit. Based on these data, ACC 2014 focused update on stable ischemic heart disease gives a IIb recommendation to EECP for refractory angina [13].

It is important to understand that EECP has peripheral effects that need to be evaluated in detail. EECP has been shown to cause a decrease in wall stiffness both in the central and in the peripheral vasculatures [6, 14], improved peripheral endothelial function as shown with increased reactive hyperemia in the fingers [15], mobilization of circulating progenitor cells leading to improved angiogenesis and peripheral oxygen utilization [16], and by altering the levels of proinflammatory biomarkers such as tumor necrosis factor-alpha and monocyte chemoattractant protein-1 [17]. These widespread effects suggest that there is a niche where EECP may help improve patient outcomes. Further studies are necessary to refine our understanding of the same.

Spinal-Cord Stimulation

Spinal-cord stimulation (SCS) is a therapeutic option of stimulating the spinal cord to relieve pain with a low voltage current. It is generally applied to T1-T2 level causing reduction in the capacity of cardiac neurons to generate activity during an ischemic episode. Melzack and Wall in 1965 were the first ones to propose the "pain gate control" theory, which was based on the assumption that impulse was transmitted in the small nociceptive C-fibers of the central nervous system [18]. It took a long time for this therapy to be first used for refractory angina in 1987 [19]. Along with reducing the functionality of the cardiac neurons, this therapy also causes redistribution of blood flow from non-ischemic to ischemic areas [20, 21]. The therapy has been known to improve NYHA functional class, reduces hospital admissions, and increases quality of life with no adverse clinical rebound phenomenon when stimulation is stopped [22–24].

In the largest trial (ESBY), 104 patients at high risk for surgery were randomly assigned to CABG or spinal cord stimulation [25]. Both modalities reduced angina and the use of nitrates to a similar extent. Although CABG group had a greater increase in exercise capacity, less ST segment depression at maximum and comparable workloads, and an increase in the rate-pressure product both at maximum and comparable workloads compared with the group receiving spinal cord stimulation, the SCS group had a lower 6-month mortality (1.9 versus 13.7% with CABG) and fewer cerebrovascular events (3.8 versus 15.7%). On long-term follow-up, cessation of therapy in SCS group was associated with a lack of effect on ischemic ST changes but a reduction in anginal symptoms, suggesting a primary analgesic effect or a placebo effect only [26–28].

In another RCT with patients suffering with cardiac syndrome X that were refractory to maximal antianginal therapy, spinal cord stimulation therapy was seen to reduce the number, duration, and severity of spontaneous anginal episodes along with prolonging the time to angina/ST depression during dobutamine stress testing [29].

In summary, SCS significantly relieves the symptoms of angina pectoris without increasing the nitroglycerin consumption to some extent. Future larger outcome studies for finding the appropriate intensity of stimulation are worthy of further investigation.

Transmyocardial Laser Revascularization

The concept of creating transmural channel in the myocardium trying to replicate reptilian type myocardial direct perfusion has been tried since 1965 [30]. This involves the use of 800 W carbon dioxide laser to drill 1-mm-diameter channels into a beating heart after left thoracotomy. The first attempt at creating transmural channels using lasers was demonstrated by Mirhoseini and associates [31, 32]. Besides using a carbon dioxide laser [33–39], a holmium:yttrium–aluminum–garnet laser [40–42] has also been used that demonstrated significantly improved transmyocardial revascularization (TMR) and therefore better outcomes in patients who were not candidates for conventional therapies.

In a study by Horvath et al., it was demonstrated that TMLR reduces infarct size and preserves myocardial function after an infarction. However, there has been little objective evidence of improvement in myocardial perfusion as assessed by nuclear perfusion imaging. It has been proven that essentially all channels are closed by 24 h, possibly within the first hour, and direct measurement of channel-supplied myocardial

blood flow suggests that the increase in myocardial blood flow is minimal [43–45]. Henceforth, the concept of passive myocardial perfusion of oxygenated blood via newly developing channels is almost non-existential. The lack of improved blood flow has also been observed clinically. In one study, positron emission tomography prior to and at 7.5 and 34.6 weeks after TMLR in seven patients showed no difference in absolute coronary flow despite a reduction in angina suggesting majorly placebo effect of the procedure. In fact, there was no change in myocardial blood flow at rest and during dobutamine infusion or in coronary vasodilator reserve in lasered and unlasered regions [46] further faulting the premise of this hypothesis. This situation places patients at high risk for perioperative morbidity and mortality while providing questionable if any significant benefit.

There have been several clinical trials reported following TMLR in patients with refractory angina who had lesions not amenable to revascularization or high risk which have shown encouraging results [35, 47–53]. An initial trial involving 192 patients with refractory angina and left ventricular free-wall ischemia, all of them not candidates for coronary revascularization, demonstrated that, after 1 year follow-up, patients who underwent TMLR improved by at least two Canadian Cardiovascular Society (CCS) classes (72 versus 13% for continued medical therapy), and they also had a significant improvement in quality of life [47]. Myocardial perfusion, as assessed by thallium scanning, improved by 20% in the TMLR group compared with a 27% worsening in the medical group. Overall survival at 1 year was the same in the two groups (85 versus 79%), but there was a marked reduction in hospitalization for unstable angina with TMLR.

The other trial by Allen et al. with a moderate sample size of 275 showed an improvement in angina (76 versus 32% with medical therapy), a higher rate of survival free of cardiac events that was primarily due to freedom from cardiac related hospitalizations (61 versus 31%), and higher exercise tolerance and quality-of-life scores. There was however no difference in myocardial perfusion with thallium imaging or in 1-year survival (84 versus 89%). At 5 years follow-up, these people continued to show improvements in angina compared with those treated medically (88 versus 44% improvement by two or more angina classes). The survival rate was also significantly higher for patients initially assigned to TMLR; however, this difference disappeared when patients crossing over were analyzed separately [54].

Aaberge et al. established the reduction of angina symptom and hospitalization following TMLR in a long follow-up trial of 100 Norwegian patients [53]. However, there were no differences in the number of myocardial infarctions or mortality (22 versus 24%).

There still remains an element of uncertainty among the various trials. Schofield et al. randomly assigned 188 patients with refractory angina due to severe coronary disease not amenable to revascularization with TMLR plus usual medication or to medical management only but failed to show any objective difference in treadmill exercise capacity. The only favorable feature was an improvement in angina which again can have confounding factors [55]. The fact that this procedure puts patients at a risk of multitude of cardiac-related complications including but not limited to myocardial infarction, left ventricular failure, atrial fibrillation, and ventricular arrhythmias questions the true benefit of this modality in its current form. Risk factors for an adverse event include CCS class IV status, unprotected left main stenosis, and diabetes mellitus [57]. There can also be peri-operative mortality associated to the tune of 3 to 5% per most reports, going up to a maximum of 12% [28, 56–59]. The eventual 4-year follow-up was however remained equal as compared with other strategies [53, 55].

Another study evaluated the safety and efficacy of TMLR combined with CABG in patients with coronary disease not amenable to complete revascularization. Two hundred sixty-three patients were randomly assigned to bypass grafting of suitable vessels plus TMLR of areas not graftable or bypass surgery alone, with nongraftable areas left unrevascularized. This study boasts of lower operative mortality in the combined approach (1.5 versus 7.6% for bypass surgery alone) and decreased need for inotropic support post-operatively [60–62]. Short term there was significant freedom from major adverse cardiac events (death or myocardial infarction), but the disease progression rendered this effect nullified at 1-year mark. In a follow-up analysis published in 2004, there was no residual survival benefit at 5 years although the angina scores remained significantly improved in the experiment group [63].

It was thought that the technological development of using the holmium:yttrium-aluminum garnet laser will bring down the perioperative mortality associated with surgical transmyocardial laser revascularization (TMLR) as it can channel energy through flexible fibers hence creating channels in the presence of blood, but phase I and open-label phase II studies found similar results to those seen with the open chest CO2 TMLR studies suggesting improvement on angina but no change in nuclear perfusion objective data [62–65].

PACIFIC and DIRECT were two of the biggest trials that evaluated TMLR. While, in the PACIFIC trial, 221 patients randomly assigned the patients to percutaneous TMLR or conventional medical therapy, the DIRECT trial was the only major blinded study [66, 67]. The study population in the PACIFIC trial had a median increase in exercise tolerance in the experiment cohort, but there was no difference in survival or the combined end points of mortality, MI, or rehospitalization [68].

In the DIRECT trial, 298 patients with refractory angina who were suboptimal candidates for coronary artery bypass graft surgery or percutaneous coronary intervention (PCI)

were randomly assigned to low- or high-dose laser channels or no laser channels. The important aspect of this trial was the use of sham procedure as a blinding mechanism to prevent bias or confounding. No benefit was seen in TMLR arm in terms of patient survival, angina class, quality-of-life assessment, exercise duration, or nuclear perfusion imaging [69].

We believe that continued clinical research on the hypotheses is essential to obtain a complete understanding of the working mechanism of TMR, and that this will ultimately provide the best possibility to optimize TMR as an adjunctive therapy to achieve a more complete revascularization.

Endoscopic Thoracic Sympathectomy

Surgical procedures on the autonomous nervous system of the heart have been performed for more than a century. Although it was originally utilized as palliative procedures to relieve angina, later through various studies, we were able to identify its utility in the treatment of refractory angina. Since experimental studies have shown that stimulation of the sympathetic ganglion induces constriction of coronary arteries, stellate ganglion blockade has been tried for refractory organic angina in some reports in the past.

It is a well-established fact that a long-term increase of sympathetic nervous activity (SNA) correlates with coronary, cardiovascular, and general mortality of a population. Patients with unstable angina tend to have higher levels of norepinephrine. It is well known that left ventricular dysfunction is associated with the highest increase of catecholamines during ischemia along with an increased incidence of malignant arrhythmias and lowering of ventricular fibrillation threshold. Heart rate (SNA activity marker) and its variability in patients who suffered myocardial infarction are strong predictors of death [70, 71]. To outline the anatomy of the vessels, there is a rich sympathetic network in the walls of coronaries. In standard circumstances, the muscular layers of these walls lead to dilatation under the sympathetic influence. However, vasoconstriction prevails in the atherosclerotic artery. Reflex contraction associated with the loss of endothelial integrity and transmitter changes at the terminal sympathetic endings is probably the cause of vasoconstriction. Serotonin is linked with the late effect. Serotonin is released in foci of aggregation, i.e., the site of turbulent flow. This vasoconstriction effect is successfully reduced by sympathetic blockage. Decreased myocardial oxygen consumption, dilatation of the atherosclerotic artery, and spread of the myocardial capillary bed were the most important outcomes of these studies that were used lately in clinical practice. A follow-up of a larger group of patients after the treatment is needed to determine whether this method is only palliative or if it can even improve the prognosis of patients with refractory angina.

Reduction of Coronary Sinus

The concept behind coronary sinus reduction is by creating a trans-sinusal pressure gradient that in turn is considered as the force to cause a redistribution of coronary arterial blood from the epicardium to the underperfused endocardium. This subsequently counteracts the abnormal decrease in adaptive vasoconstriction in severe CAD, inadequate increase in blood flow secondary to the abnormally high resistance at the level of the large conductance coronary arteries, hence preventing subendocardial ischemia. Beck and Leighninger performed the original surgery in the 1950s that was eventually adapted to restrict the venous drainage of the heart using percutaneous devices [72, 73].

Jolicoeur et al. in 2013 published a trial design to evaluate this device using a sham control. The COSIRA trial (coronary sinus reducer for treatment of refractory angina) demonstrated that, in patients with advanced CAD unsuitable for revascularization and refractory CCS III or IV angina, patients in the experiment group had shown improvement of at least two CCS angina classes at 6 months compared with patients assigned to a sham implantation (35% vs. 15%, $p = 0.02$). This group also had increased exercise duration measured by stress test and improved angina-related quality of life. The cons of this procedure come from the fact that it only targets the myocardial ischemia originating from the left coronary system, as the right coronary system does not drain by the coronary sinus. Further trials looking at this caveat and hypothesis are necessary before it can be offered to the population in general [74, 75••].

Therapeutic Angiogenesis

The term "angiogenesis" broadly refers to formation of new vessels. Therapeutic angiogenesis is the term used when the formation of new vessels or vasculogenesis can be of benefit to us, especially for the treatment of refractory angina [76]. By this process, we can induce the formation of new coronary arterial vessels that can perfuse areas of diseased myocardium where the native arteries cannot provide a normal blood supply. Hence, in other words, this contribute to improved ventricular performance and better patient prognosis [77].

To understand the process of vasculogenesis, it is pertinent to go into the history. Studies in the 1990s and early 2000s suggested that there may be circulating endothelial progenitor cells (EPCs) that can form vasculature in mature adult tissue [78]. Other studies have also brought to light that EPCs are circulating adult endothelial cells which can never cause angiogenesis [79]. However they do have some role for angiogenesis by the paracrine release of growth factors [80]. The most important factor contributing to angiogenesis is ischemia. This causes local activation of VEGF, mediated by the

Hypoxia inducible factor (HIF) pathway [81]. It has also been proposed that recruitment of certain circulating mononuclear cells is of critical importance for vascular angiogenesis as they serve as reservoirs [82, 83]. Angiogenesis thus causes wound healing along with supporting new tissue formation and also increasing blood supply in case of ischemia.

Angiogenesis can be pathological in a number of situations where it does not contribute to increasing the functioning of perfusion. It can be seen in premature newborn babies in the form of retinopathy of prematurity as well as seen in adults in the form of diabetic retinopathy. The process of growth of cancer cells also involves pathological angiogenesis.

Besides angiogenesis, arteriogenesis also plays an eminent role in the restoration of blood supply. For a typical patient with atherosclerotic coronary disease, the arterial blood supply to a particular area of the myocardium is compromised due to a high-grade stenosis or occlusion of the coronary artery supplying that region. The most effective strategy to restore the arterial blood supply would be to provide an alternative bypass around the occlusion or in other words another route for perfusion to be maintained. Since atherosclerotic lesions primarily affect epicardial coronary arteries, the required "bypass" should be in the same size range to be able to carry bulk flow [84].

There are a few angiogenic factors that contribute to stimulate blood vessel growth such as fibroblast growth factors (FGFs), VEGFs, and platelet-derived growth factor (PDGF), all of which have different and poorly understood biologic properties. The vascular endothelial growth factor causes capillary tissue growth along with synthesis of new arteries. Interestingly, even a 50% reduction in its expression during development leads to lethality [85, 86]. The fibroblastic growth factors; type 1, 2, 4, 5 are also expressed by various types of cells. Secretion and cell death lead to the accumulation of these long-lived proteins in the extracellular matrix. Further, in contrast to VEGFs, their expression is not sensitive to ischemia or hypoxia. In contrast to VEGFs, FGFs appear to be particularly important in arteriogenesis with growing collaterals demonstrating abundant expression of FGF2 in surrounding monocytes [87].

There have always been challenges facing researchers in developing effective revascularization strategies using biologic agents. The various parameters for randomization of patients include age, sex, extent of hypercholesterolemia, and the extent of endogenous collateralization. Thus, it is necessary to recruit a large size of population so that other unknown factors can be evenly distributed [88]. It might also be important to exclude patients who have undergone administration of these factors in the past, such as the cancer population. Also, it may be interesting to know that certain populations can be resistant to VEGF signaling [89–92].

It is critical to determine how to effectively and safely we can deliver growth factors. In therapeutic trials, it was seen that IV infusions have either not been effective when used short term or have not been tried long term because of the fear of side effects. Methods of local delivery to the heart have included simple intracoronary infusion, which has been ineffective for both proteins and viruses, intramyocardial injections, pericardial administration, and locally applied polymer-based delivery. The consensus points towards the fact that, for an effective intervention, it may be required that the therapeutic agent should be present for at least 4–6 weeks at the desired site of action. For this reason, we will need multiple injections at the same site due to a shorter half-life. It may also be worthwhile to use a sustained release polymer for the same.

According to the VIVA trial, the infusions were given into coronary arteries for 10 min, followed by three repeat intravenous infusions over the following 9 days. It was noted that, at 60 days, there were no significant differences in exercise tolerance or angina class between the treated and control groups. However, at 120 days, patients receiving high-dose VEGF showed a significant improvement in angina class compared with the other two groups. However, nuclear perfusion imaging yielded similar results among the three groups, raising doubt about the improvement in angina. This suggests that angina class may not be a good end point for trials of this intervention. The Euroinject One trial randomly assigned 80 patients with advanced CHD but not further medical or revascularization options to receive either phVEGF-A or placebo plasmid in the myocardial region showing stress-induced myocardial perfusion defects [93]. At 3 months, it was seen that there were no significant differences between the various groups for analysis of myocardial stress perfusion in the treated region as compared with the remaining.

The largest trial, the FGF Initiating Revascularization Support Trial (FIRST) trial, consisted of a sample size of 337 patients who were ineligible for angioplasty to undergo an intracoronary infusion of recombinant FGF-2 in either of the three doses (0.3, 3, or 30 μg/kg) [94]. It was demonstrated that, at 90 days, there was no significant improvement in exercise treadmill time or nuclear perfusion parameters among the treatment groups. However, there was an improvement in patient and physician perception of angina as assessed by special criteria under the Seattle Angina Questionnaire and the Canadian Cardiovascular Society angina classification. A smaller trial of 24 patients evaluated the efficacy of local application of an FGF-2-containing polymer during bypass surgery in the area of myocardium unable to be revascularized. Patients receiving high dose of FGF-2 (100 mg) had a significant improvement in perfusion of the target area compared with low-dose FGF-2 (10 mg) or placebo controls [95]. Three years later, the patients receiving high-dose FGF-2 had significantly less angina than placebo controls [96]. Another well-known trial known as the AGENT-1 trial included 79 patients who were randomly assigned to various doses of Ad-FGF4

[97]. Out of the two groups, there was a trend towards a greater increase in exercise time at 4 weeks compared with the placebo group (1.3 versus 0.7 min). It was also found that the patients with a baseline exercise time ≤ 10 min had a significant increase in the same after the therapy (1.6 versus 0.6 min).

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine secreted by a wide variety of cell types that acts broadly upon hematopoietic cells. Activated macrophages can induce vascular proliferation, suggesting a role for the administration of recombinant human GM-CSF (rhGM-CSF). Compared with placebo, rhGM-CSF improved collateral flow, measured by intracoronary sensor guidewires, and reduced electrocardiogram signs of ischemia during coronary balloon inflation. Various animal studies have shown that heparin can expedite the formation of coronary collaterals induced by ischemia [98]. Clinical studies have shown that the use of heparin to treat repeated episodes of exercise-induced ischemia can improve myocardial perfusion and reduced electrocardiographic evidence of ischemia [99, 100].

To address the downside, there are a number of potential complications associated with therapeutic angiogenesis: it can cause aberrant vascular proliferation in adjacent and perhaps distant non-targeted tissues. It may also produce increased vascular permeability, activating the coagulation cascade thus leading to the deposition of fibrin gel and the development of edema, induction of new blood vessels, and fibroblast activation. It may also activate neoplasmic growth by triggering of growth factors. There can sometimes be a pro-atherogenic effect by causing smooth muscle proliferation or increasing neointimal mass [101]. There may also be hazards associated with direct myocardial delivery of angiogenic factors. However, only a very few of these have actually been observed.

Conclusion

With growing options including noninvasive and invasive mechanical therapies and cell-based therapies to opt from, there are complex questions that currently practicing cardiologists face. There is no one size fits all answer when it comes to effectively treating patients with advanced CAD and RA. As discussed above, all modalities have shown some promise in terms of angina reduction but have not been able to come across in terms of absolute objective data like myocardial blood flow, survival, or rehospitalizations.

There are multiple ongoing trials that are looking into these therapies to help find those answers. A novel Neovasc Coronary Sinus Reducer System is being tested in Israel [102], and REDUCER-I study is underway with results to be expected by 2024 [103]. PHOENIXTM system is evaluating TMR with Holmium YAG laser plus the patient's own stem cells extracted from bone marrow [104]. More blinded studies are needed to further evaluate the questions raised by the current evidence before these therapies are ready to be introduced for the general population.

Compliance with Ethical Standards

Conflict of Interest Amod Amritphale and Nupur Amritphale declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina. Report from the ESC Joint Study Group on the treatment of refractory angina. Eur Heart J. 2002;23(5):355–70.
2. Povsic TJ, Broderick S, Anstrom KJ, et al. Predictors of longterm clinical endpoints in patients with refractory angina. J Am Heart Assoc. 2015; vol. 4, no. 2, article e001287.
3. McGillion M, Arthur HM, Cook A, et al. Management of patients with refractory angina: Canadian Cardiovascular Society/Canadian Pain Society Joint Guidelines. Can J Cardiol. 2012;28(2, Supplement):S20–41.
4. Mukherjee et al. Eur Heart J. 2013; Volume 34, Issue 34, Pages 2655–2657.
5. • Bassetti B, Nigro P, Catto V, et al. Cell therapy for refractory angina: a reappraisal. Stem Cells Int. 2017;2017:5648690. **Excellent overview of the key elements, options, and efficacies of cell-based therapies for refractory angina**.
6. Braith RW, Conti CR, Nichols WW, Choi CY, Khuddus MA, Beck DT, et al. Enhanced external counterpulsation improves peripheral artery flow-mediated dilation in patients with chronic angina: a randomized sham-controlled study. Circulation. 2010;122:1612–20.
7. Urano H, Ikeda H, Ueno T, Matsumoto T, Murohara T, Imaizumi T. Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia and improves left ventricular diastolic filling in patients with coronary artery disease. J Am Coll Cardiol. 2001;37:93–9.
8. Stys TP, Lawson WE, Hui JC, et al. Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and exercise capacity in chronic stable angina pectoris. Am J Cardiol. 2002;89:822–4.
9. Shechter M, Matetzky S, Feinberg MS, Chouraqui P, Rotstein Z, Hod H. External counterpulsation therapy improves endothelial function in patients with refractory angina pectoris. J Am Coll Cardiol. 2003;42:2090–5.
10. Akhtar M, Wu GF, Du ZM, et al. Effect of external counterpulsation on plasma nitric oxide and endothelin-1 levels. Am J Cardiol. 2006;98:28–30.

11. Nichols WW, Estrada JC, Braith RW, Owens K, Conti CR. Enhanced external counterpulsation treatment improves arterial wall properties and wave reflection characteristics in patients with refractory angina. J Am Coll Cardiol. 2006;48:1208–14.
12. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, McKiernan T, 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.
13. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014;64:1929.
14. Casey DP, Beck DT, Nichols WW, Conti CR, Choi CY, Khuddus MA, et al. Effects of enhanced external counterpulsation on arterial stiffness and myocardial oxygen demand in patients with chronic angina pectoris. Am J Cardiol. 2011;107:1466–72.
15. Bonetti PO, Barsness GW, Keelan PC, Schnell TI, Pumper GM, Kuvin JT, et al. Enhanced external counterpulsation improves endothelial function in patients with symptomatic CAD. J Am Coll Cardiol. 2003;41:1761–81.
16. Barsheshet A, Hod H, Shechter M, Sharabani-Yosef O, Rosenthal E, Barbash IM, et al. The effects of external counter pulsation therapy on circulating endothelial progenitor cells in patients with angina pectoris. Cardiology. 2008;110:160–6.
17. Casey DP, Conti CR, Nichols WW, Choi CY, Khuddus MA, Braith RW. Effect of enhanced external counterpulsation on inflammatory cytokines and adhesion molecules in patients with angina pectoris and angiographic CAD. Am J Cardiol. 2008;101:300–2.
18. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–9.
19. Murphy DF, Giles KE. Dorsal column stimulation for pain relief from intractable angina pectoris. Pain. 1987;28:365–8.
20. Foreman RD, Linderoth B, Ardell JL, Barron KW, Chandler MJ, Hull SS Jr, et al. Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. Cardiovasc Res. 2000;47:367–75.
21. Murray S, Collins PD, James MA. Neurostimulation treatment for angina pectoris. Heart. 2000;83:217–20.
22. TenVaarwerk IA, Jessurun GA, DeJongste MJ, et al. Clinical outcome of patients treated with spinal cord stimulation for therapeutically refractory angina pectoris. The Working Group on Neurocardiology Heart. 1999;82:82.
23. Murray S, Carson KG, Ewings PD, et al. Spinal cord stimulation significantly decreases the need for acute hospital admission for chest pain in patients with refractory angina pectoris. Heart. 1999;82:89–92.
24. Jessurun GA, DeJongste MJ, Hautvast RW, et al. Clinical follow-up after cessation of chronic electrical neuromodulation in patients with severe coronary artery disease: a prospective randomized controlled study on putative involvement of sympathetic activity. Pacing Clin Electrophysiol. 1999;22:1432–9.
25. Mannheimer C, Eliasson T, Augustinsson LE, Blomstrand C, Emanuelsson H, Larsson S, et al. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris: the ESBY study. Circulation. 1998;97:1157–63.
26. Norrsell H, Pilhall M, Eliasson T, Mannheimer C. Effects of spinal cord stimulation and coronary artery bypass grafting on myocardial ischemia and heart rate variability: further results from the ESBY study. Cardiology. 2000;94:12–8.
27. McNab D, Khan SN, Sharples LD, Ryan JY, Freeman C, Caine N, 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.
28. Leon MB, Kornowski R, Downey WE, Weisz G, Baim DS, Bonow RO, 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;46:1812–9.
29. Lanza GA, Sestito A, Sgueglia GA, Infusino F, Papacci F, Visocchi M, et al. Effect of spinal cord stimulation on spontaneous and stress-induced angina and 'ischemialike' ST-segment depression in patients with cardiac syndrome X. Eur Heart J. 2005;26:983–9.
30. Sen PK, Udwadia TE, Kinare SG, Parulkar GB. Transmyocardial acupuncture: a new approach to myocardial revascularization. J Thorac Cardiovasc Surg. 1965;50:181–9.
31. Mirhoseini M, Muckerheide M, Cayton MM. Transventricular revascularization by laser. Lasers Surg Med. 1982;2:187–98.
32. Mirhoseini M, Cayton MM, Shelgikar S, Fisher JC. Laser myocardial revascularization. Lasers Surg Med. 1986;6:459–61.
33. Frazier OH, Cooley DA, Kadipasaoglu KA, et al. Myocardial revascularization with laser: preliminary findings. Circulation. 1995;92(Suppl II):II-58–65.
34. Horvath KA, Mannting F, Cummings N, Shernan SK, Cohn LH. Transmyocardial laser revascularization: operative techniques and clinical results at two years. J Thorac Cardiovasc Surg. 1996;111:1047–53.
35. Horvath KA, Cohn LH, Cooley DA, Crew JR, Frazier OH, Griffith BP, et al. Transmyocardial laser revascularization: results of a multicenter trial with transmyocardial laser revascularization used as sole therapy for end-stage coronary artery disease. Thorac Cardiovasc Surg. 1997;113:645–54.
36. Cooley DA, Frazier OH, Kadipasaoglu KA, Pehlivanoglu S, Shannon RL, Angelini P. Transmyocardial laser revascularization: anatomic evidence of long-term channel patency. Tex Heart Inst J. 1994;21:220–4.
37. Cooley DA, Frazier OH, Kadipasaoglu KA, Lindenmeir MH, Pehlivanoglu S, Kolff JW, et al. Transmyocardial laser revascularization: clinical experience with twelve-month follow-up. J Thorac Cardiovasc Surg. 1996;111:791–9.
38. Vincent JG, Bardos P, Kruse J, Maass D. End stage coronary artery disease treated with the transmyocardial CO2 laser revascularization: a chance for the 'inoperable' patient. Eur J Cardiothorac Surg. 1997;11:888–94.
39. March RJ, Boyce S, Cooley DA, et al. Improved event survival following transmyocardial laser revascularization versus medical management in patient with unreconstructed coronary artery disease. In: Program and abstracts of the 77th Annual Meeting of the American Association of Thoracic Surgery, Washington, D.C., May 4–7, 1997; 94. abstract.
40. Allen KB, Dowling RD, Heimansohn DA, Reitsma E, Didelot L, Shaar CJ. Transmyocardial revascularization utilizing a holmium: YAG laser. Eur J Cardiothorac Surg. 1998;14(Suppl 1):S100–4.
41. Dowling RD, Petracek MR, Selinger SL, Allen KB. Transmyocardial revascularization in patients with refractory, unstable angina. Circulation. 1998;98(Suppl II):II-73–6.
42. Allen KB, Fudge FL, Schoettle GP Jr, Selinger SL, Shaar CJ, Dowling RD. Prospective randomized multi-center trial of transmyocardial revascularization versus maximal medical management in patients with refractory class IV angina: 12-month results. Circulation. 1998;98(Suppl I):I–476 abstract.
43. Kohmoto T, Fisher PE, Gu A, Zhu SM, Yano OJ, Spotnitz HM, et al. Does blood flow through holmium:YAGtransmyocardial laser channels? Ann Thorac Surg. 1996;61:861–8.

44. Kohmoto T, Fisher PE, Gu A, Zhu SM, DeRosa CM, Smith CR, et al. Physiology, histology, and 2-week morphology of acute transmyocardial channels made with a CO2 laser. Ann Thorac Surg. 1997;63:1275–83.
45. Burkhoff D, Fisher PE, Apfelbaum M, Kohmoto T, DeRosa CM, Smith CR. Histologic appearance of transmyocardial laser channels after 4 1/2 weeks. Ann Thorac Surg. 1996;61:1532–5.
46. Rimoldi O, Burns SM, Rosen SD, et al. Measurement of myocardial blood flow with positron emission tomography before and after transmyocardial laser revascularization. Circulation. 1999;100:II134.
47. Frazier OH, March RJ, Horvath KA. Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease. N Engl J Med. 1999;341:1021–8.
48. Allen KB, Dowling RD, Fudge TL, Schoettle GP, Selinger SL, Gangahar DM, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. N Engl J Med. 1999;341:1029–36.
49. Burkhoff D, Schmidt S, Schulman SP, et al. Transmyocardial laser revascularisation compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomised trial. ATLANTIC Investigators Angina Treatments-Lasers and Normal Therapies in Comparison. Lancet. 1999;354:885.
50. Diegeler A, Schneider J, Lauer B, Mohr FW, Kluge R. Transmyocardial laser revascularization using the Holium-YAG laser for treatment of end stage coronary artery disease. Eur J Cardiothorac Surg. 1998;13:392–7.
51. Burns SM, Sharples LD, Tait S, et al. The transmyocardial laser revascularization international registry report. Eur Heart J. 1999;20:31–7.
52. March RJ. Transmyocardial laser revascularization with the CO2 laser: one year results of a randomized, controlled trial. Semin Thorac Cardiovasc Surg. 1999;11:12.
53. Aaberge L, Rootwelt K, Blomhoff S, Saatvedt K, Abdelnoor M, Forfang K. Continued symptomatic improvement three to five years after transmyocardial revascularization with CO(2) laser: a late clinical follow-up of the Norwegian randomized trial with transmyocardial revascularization. J Am Coll Cardiol. 2002;39:1588–93.
54. Allen KB, Dowling RD, Angell WW, Gangahar DM, Fudge TL, Richenbacher W, et al. Transmyocardial revascularization: 5-year follow-up of a prospective, randomized multicenter trial. Ann Thorac Surg. 2004;77:1228–34.
55. Schofield PM, Sharples LD, Caine N, Burns S, Tait S, Wistow T, et al. Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial. Lancet. 1999;353:519–24.
56. Nägele H, Stubbe HM, Nienaber C, Rödiger W. Results of transmyocardial laser revascularization in non-revascularizable coronary artery disease after 3 years follow-up [ssee comments]. Eur Heart J. 1998;19:1525–30.
57. Tjomsland O, Aaberge L, Almdahl SM, Dragsund M, Moelstad P, Saatvedt K, et al. Perioperative cardiac function and predictors for adverse events after transmyocardial laser treatment. Ann Thorac Surg. 2000;69:1098–103.
58. Aaberge L, Nordstrand K, Dragsund M, et al. Transmyocardial revascularization with CO2 laser in patients with refractory angina pectoris. Clinical results from the Norwegian randomized trial. J Am Coll Cardiol. 2000;35:1170.
59. Burkhoff D, Wesley MN, Resar JR, Lansing AM. Factors correlating with risk of mortality after transmyocardial revascularization. J Am Coll Cardiol. 1999;34:55–61.
60. Hughes GC, Shah AS, Yin B, Shu M, Donovan CL, Glower DD, et al. Early postoperative changes in regional systolic and diastolic left ventricular function after transmyocardial laser revascularization: a comparison of holmium:YAG and CO2 lasers. J Am Coll Cardiol. 2000;35:1022–30.
61. Hattler BG, Griffith BP, Zenati MA, Crew JR, Mirhoseini M, Cohn LH, et al. Transmyocardial laser revascularization in the patient with unmanageable unstable angina. Ann Thorac Surg. 1999;68:1203–9.
62. Allen KB, Dowling RD, DelRossi AJ, et al. Transmyocardial laser revascularization combined with coronary artery bypass grafting: a multicenter, blinded, prospective, randomized, controlled trial. J Thorac Cardiovasc Surg. 2000;119:540–9.
63. Allen KB, Dowling RD, Schuch DR, Pfeffer TA, Marra S, Lefrak EA, et al. Adjunctive transmyocardial revascularization: five-year follow-up of a prospective, randomized trial. Ann Thorac Surg. 2004;78:458–65.
64. Kim CB, Oesterle SN. Percutaneous transmyocardial revascularization. J Clin Laser Med Surg. 1997;15:293–8.
65. Kornowski R, Hong MK, Haudenschild CC, Leon MB. Feasibility and safety of percutaneous laser revascularization using the biosense system in porcine hearts. Coron Artery Dis. 1998;9:535–40.
66. Lauer B, Junghans U, Stahl F, Kluge R, Oesterle SN, Schuler G. Catheter-based percutaneous myocardial laser revascularization in patients with end-stage coronary artery disease. J Am Coll Cardiol. 1999;34:1663–70.
67. Shawl FA, Domanski MJ, Kaul U, Dougherty KG, Hoff S, Rigali GE, et al. Procedural results and early clinical outcome of percutaneous transluminal myocardial revascularization. Am J Cardiol. 1999;83:498–501.
68. Oesterle SN, Sanborn TA, Ali N, et al. Percutaneous transmyocardial laser revascularisation for severe angina: the PACIFIC randomised trial. Potential Class Improvement From Intramyocardial Channels. Lancet. 2000;356:1705.
69. Stone GW, Teirstein PS, Rubenstein R, Schmidt D, Whitlow PL, Kosinski EJ, 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.
70. Blomberg S, Emanuelsson H, Kvist H, Lamm C, Ponten J, Waagstein F, et al. Effects of thoracic epidural anesthesia on coronary arteriesand arterioles in patients with coronary artery disease. Anesthesiology. 1990;73:840–7.
71. Gillman MW, Kannel WB, Belanger A, D'Agostino RB. Influence of heart rate on mortality among persons with hypertension: the Framingham Study. Am Heart J. 1993;125:1148–54.
72. Beck CS, Leighninger DS. Operations for coronary artery disease. J Am Med Assoc. 1954;156:1226–33.
73. Beck CS, Leighninger DS. Scientific basis for the surgical treatment of coronary artery disease. J Am Med Assoc. 1955;159:1264–71.
74. Jolicoeur EM, Banai S, Henry TD, et al. A phase II, sham-controlled, doubleblinded study testing the safety and efficacy of the coronary sinus reducer in patients with refractory angina: study protocol for a randomized controlled trial. Trials. 2013;14:46.
75.•• Verheye S, Jolicoeur EM, Behan MW, et al. Eficacy of a device to narrow the coronary sinus in refractory angina. N Engl J Med. 2015;372:519–27. **This is a well-conducted, phase 2, multicenter, randomized, double-blind, sham-controlled clinical trial to test the safety and efficacy of the coronary-sinus reducing device**.
76. Mukherjee, et al. Current clinical perspectives on myocardial angiogenesis. Mol Cell Biochem. 2004;264(1–2):157–67.
77. Simons M, Ware JA. Therapeutic angiogenesis in cardiovascular disease. Nat Rev Drug Discov. 2003;2:863–72.
78. Simons M. Angiogenesis: where do we stand now? Circulation. 2005;111:1556–66.

79. Yoder MC, Mead LE, Prater D, Krier TR, Mroueh KN, Li F, et al. Redefining endothelial progenitor cells via clonal analysis and hematopoietic stem/progenitor cell principals. Blood. 2007;109:1801–9.
80. Pearson JD. Endothelial progenitor cells - hype or hope? J Thromb Haemost. 2009;7:255–62.
81. Helisch A, Schaper W. Arteriogenesis: the development and growth of collateral arteries. Microcirculation. 2003;10:83–97.
82. Schaper W, Scholz D. Factors regulating arteriogenesis. Arterioscler Thromb Vasc Biol. 2003;23:1143.
83. Heil M, Eitenmüller I, Schmitz-Rixen T, Schaper W. Arteriogenesis versus angiogenesis: similarities and differences. J Cell Mol Med. 2006;10:45–55.
84. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003;9:669–76.
85. Carmeliet P, Ferreira V, Breier G, Pollefeyt S, Kieckens L, Gertsenstein M, et al. Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. Nature. 1996;380:435–9.
86. Ferrara N, Carver-Moore K, Chen H, Dowd M, Lu L, O'Shea KS, et al. Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. Nature. 1996;380:439–42.
87. Simons M. Integrative signaling in angiogenesis. Mol Cell Biochem. 2004;264:99–102.
88. Arras M, Ito WD, Scholz D, Winkler B, Schaper J, Schaper W. Monocyte activation in angiogenesis and collateral growth in the rabbit hindlimb. J Clin Invest. 1998;101:40–50.
89. Simons M, Bonow RO, Chronos NA, et al. Clinical trials in coronary angiogenesis: issues, problems, consensus: an expert panel summary. Circulation. 2000;102:E73.
90. Tchaikovski V, Olieslagers S, Böhmer FD, Waltenberger J. Diabetes mellitus activates signal transduction pathways resulting in vascular endothelial growth factor resistance of human monocytes. Circulation. 2009;120:150–9.
91. Simons M. Angiogenesis, arteriogenesis, and diabetes: paradigm reassessed? J Am Coll Cardiol. 2005;46:835–7.
92. Hedman M, Hartikainen J, Syvänne M, et al. Safety and feasibility of catheter-based local intracoronary vascular endothelial growth factor gene transfer in the prevention of postangioplasty and in-stent restenosis and in the treatment of chronic myocardial ischemia: phase II results of the Kuopio Angiogenesis Trial (KAT). Circulation. 2003;107:2677.
93. Kastrup J, Jørgensen E, Rück A, Tägil K, Glogar D, Ruzyllo W, et al. 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.
94. Simons M, Annex BH, Laham RJ, Kleiman N, Henry T, Dauerman H, et al. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2: double-blind, randomized, controlled clinical trial. Circulation. 2002;105:788–93.
95. Laham RJ, Sellke FW, Edelman ER, Pearlman JD, Ware JA, Brown DL, et al. Local perivascular delivery of basic fibroblast growth factor in patients undergoing coronary bypass surgery: results of a phase I randomized, double-blind, placebo-controlled trial. Circulation. 1999;100:1865–71.
96. Schumacher B, Pecher P, von Specht BU, Stegmann T. Induction of neoangiogenesis in ischemic myocardium by human growth factors: first clinical results of a new treatment of coronary heart disease. Circulation. 1998;97:645–50.
97. Seiler C, Pohl T, Wustmann K, Hutter D, Nicolet PA, Windecker S, et al. Promotion of collateral growth by granulocyte-macrophage colony-stimulating factor in patients with coronary artery disease: a randomized, double-blind, placebo-controlled study. Circulation. 2001;104:2012–7.
98. Unger EF, Sheffield CD, Epstein SE. Heparin promotes the formation of extracardiac to coronary anastomoses in a canine model. Am J Phys. 1991;260:H1625.
99. Melandri G, Semprini F, Cervi V, Candiotti N, Palazzini E, Branzi A, et al. Benefit of adding low molecular weight heparin to the conventional treatment of stable angina pectoris. A double-blind, randomized, placebo-controlled trial. Circulation. 1993;88:2517–23.
100. Barron HV, Sciammarella MG, Lenihan K, Michaels AD, Botvinick EH. Effects of the repeated administration of adenosine and heparin on myocardial perfusion in patients with chronic stable angina pectoris. Am J Cardiol. 2000;85:1–7.
101. Drinane M, Mollmark J, Zagorchev L, Moodie K, Sun B, Hall A, et al. The antiangiogenic activity of rPAI-1(23) inhibits vasa vasorum and growth of atherosclerotic plaque. Circ Res. 2009;104:337–45.
102. As assessed on Clinicaltrials.gov on 12/24/2018. https://clinicaltrials.gov/ct2/show/study/NCT01566175?cond=Refractory+Angina&rank=3
103. As assessed on Clinicaltrials.gov on 12/24/2018. https://clinicaltrials.gov/ct2/show/NCT02710435?cond=Refractory+Angina&rank=31
104. As assessed on Clinicaltrials.gov on 12/24/2018. https://clinicaltrials.gov/ct2/show/NCT01214499?cond=Refractory+Angina&rank=22