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Nonconventional therapeutic modalities in refractory angina pectoris

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Abstract

Despite sophisticated conventional medical treatment and the continued development and improvement of coronary revascularization modalities in recent years, a significant number of patients still suffer from refractory angina pectoris and cannot be successfully managed. Advances in therapeutic options have led to an increase in the average of life expectancy even in such no-option patients. Management of these patients is a challenging problem because most of them have already undergone multiple coronary interventions or surgeries and therefore are not suitable candidates for further procedures. In this situation, cardiologists who frequently face the patients are limited in their decision making when all therapeutic methods have been exhausted. The aim of this review article was to draw attention to the novel therapeutic strategies currently available for this condition, including nonconventional medical treatment, improving myocardial perfusion, neuromodulation, new vessel formation and eventually heart transplantation. Unfortunately, these therapies have only a complementary role because of inadequate experience. Therefore, maximal conventional treatment along with these options should be used on an individual basis.

Keywords
refractory angina, nonconventional treatment, end stage angina

Refractory angina pectoris definition

Patients must have three criteria before labeling with refractory angina :

1. They should have class 3 or 4 angina, based on Canadian Cardiovascular Society (CCS) functional class, despite optimal tolerable medical treatments, traditional percutaneous coronary interventions (PCIs) or coronary bypass surgery (CABG) and life-style modifications.

2. Duration of angina should be more than three months[1].

3. There must be objective evidence of myocardial ischemia on exercise tolerance test, radionuclide myocardial perfusion scan, stress echocardiography or PET scan.

Most of these patients could not be good candidate for further revascularization procedures, because of one of the following: unsuitable coronary anatomy such as diffuse disease or distal lesions, several prior PCIs or CABGs, lack of appropriate vascular conduit for CABG, severe left ventricular dysfunction, concomitant diseases that increase surgical morbidity and mortality, and aging which often associated with other factors [1].

Ten characteristics of patients with chronic refractory angina pectoris are 70 years old, predominantly male, long term (±10 years) coro-

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nary artery disease, three vessel disease, previous myocardial infarction, previous revascularization procedure, maintenance of left ventricular function, no serious arrhythmias, 5% annual cardiac mortality and raised fibrinogen level [2].

Prevalence of angina pectoris increases with age in both genders. It has been estimated that 2-4% of the adult European population is affected by angina pectoris [3]. This number is likely to increase further since life expectancy continues to improve worldwide. As many as 15% of the patients suffer from refractory angina [1]. The estimated annual incidence of patients with the refractory angina is around 30,000-50,000 in Europe [1] and 100,000 in the USA [4].

Patients with refractory angina have severely restricted lives and frequent hospital admissions due to acute coronary syndrome, intractable angina or pulmonary edema. Although adjunctive therapy have been suggested to have primary effect on pain and there is no obvious evidence that any of these treatments reduces cardiac mortality, but reduction of angina attacks in these patients not only improve their quality of life but will also ameliorate their psychological status. We review these nontraditional techniques in four section; nonconventional medical treatment, improving myocardial perfusion, neuromodulation, new vessel formation and eventually heart transplantation.

A. Nonconventional medical treatment

1. Ranolazine: It is a metabolic agent and has recently been shown to work by first inhibiting fatty acid oxidation that maximize glucose utilization of oxygen versus fatty acid oxidation which is more efficient and second inhibition of the slow sodium channel in myocytes that reduces sodium-dependent calcium entry into the cytosol which decreases diastolic stiffness, thereby improving diastolic blood flow and improvement of ischemia [5]. CARISA trial has shown benefits in treated patients with or without other antianginal drugs, including reduction of anginal attacks and functional capacity improvement [6]. Trimetazine and Perhexiline are also metabolic antianginal drugs which used in refractory angina.

2. Nicorandil: It is a nicotinamide ester and ATP-dependent potassium channel activator which dilates peripheral and coronary resistance vessels. It reduces preload and afterload and results in an increase in coronary blood flow. It has been shown to reduce major coronary events in IONA trial [7].

3. Ivabradine: It is a specific and selective inhibitor of the If channel, the principle determinant of the sinoatrial node pacemaker current to cause heart rate reduction without negative inotropic effect [8]. It gives a dose-dependent exercise tolerance improvement in BEAUTIFUL trial [9].

4. Fasudil: It is an orally available inhibitor of rho kinase, an intracellular signaling molecule that participates in vascular smooth muscle contraction [10].

5. Corticosteroids: It may be considered as a choice treatment of refractory chest pain in patients with vasospastic angina, particularly when the patient has an allergic tendency such as bronchial asthma [11].

6. Urokinase: Long term intermittent therapy with urokinase may be an option. Urokinase at a dose of 500,000 IU intravenously 3 times/week over a period of 12 weeks could reduce angina episodes and the need for sublingual nitrates. Mannheimer et al. proposed that the therapeutic effectiveness of urokinase is at least in part mediated by the improved rheological properties of the blood with consequent increase in blood flow in the myocardial microcirculation and reduced thrombus formation on atherosclerotic plaques in stenotic vessels [1].

B. Improving myocardial perfusion:

-Noninvasive procedures:

1. Enhanced external counterpulsation (EECP):

It is a non-invasive counterpulsation technique which uses three sets of pneumatic cuffs wrapped around the lower exterimities. The cuffs are inflated at the onset of diastole and are deflated at the onset of systole. Diastolic inflation produces aortic counter pulsation, diastolic augmentation, increased venous return and improved cardiac output. Systolic deflation of cuffs lead to decrement of systolic pressure.

EECP is generally administered as 35 1-hour treatments over 7 weeks [13]. The mechanisms underlying the effects of EECP on cardiovascular system are poorly understood. The immediate benefits are similar to those provided by intra-aortic balloon pumping (IABP) namely increased diastolic coronary blood flow and decreased afterload during systole [14]. Indeed increament of transmyocardial pressure probably lead to open collaterals. EECP has been shown to be more efficient than IABP in increasing venous return and enhancing cardiac output [15] In contrast to IABP, EECP provides long-lasting increase in coronary blood flow [14]. Long term effects of EECP treatment are thought to be mediated through shear stress on the vascular endothelium, which in turn triggers angiogenesis and improves vascular endothelial function due to modulated release of vasoactive substances [16] such as endothelin [17], nitric oxide [17] and vascular endothelial growth factor [18].

MUST-EECP trial has evaluated the efficacy of EECP in patients with refractory angina and showed improved functional capacity and myocardial perfusion in these groups [19].

2. Cardiac rehabilitation: In the recent updated American Heart Association (AHA) recommendations for exercise and training is recommended for patients with ongoing angina, previous history of CABG, PTCA, myocardial infarction and patients with existing cardiomyopathy in order to promote a reduction in myocardial ischemia at rest and during submaximal exercise [20].

-Invasive:

1. Transmyocardial laser revascularization (TMLR): Laser revascularization creates channels through muscle to the purpose of directly revascularizing ischemic myocardium. The development of laser revascularization dates back to 1993, when Wearn et al. hypothesized the importance of epicardial conductance vessels and extracardiac and ventriculocoronary anastomoses (sinusoidal network) in myocardial perfusion [4]. Although all channels are closed by 24 hours, possibly within the first hour, and direct measurement of channel-supplied myocardial blood flow suggests that the increase in myocardial blood flow is minimal [21]. Thus, the mechanism of the observed clinical benefit following TMLR remains uncertain. A number of possibilities have been proposed to explain these results: myocardial angiogenesis, myocardial sympathetic denervation and myocardial fibrosis that promote favorable remodeling [22]. TMLR is the only Food and Drug Administration-approved device used for the treatment of refractory angina pectoris.

a) Surgical (TMR): TMR is done via a left anterior thoracotomy to drill holes on the heart muscle using a high energy carbon dioxide laser beam, with the aim of enabling blood flow from the heart chambers into the heart muscle, to relieve myocardial ischemia and reduce chest pain. The epicardial channel opening usually closes spontaneously or after brief manual compression and the entire procedure can be performed within 2 to 3 hour. There is no need for cardiopulmonary bypass or cardioplegia. The National Institute for Health and Clinical Excellence (NICE) is announced that current evidence of TLMR shows no efficacy, based on objective measurements of myocardial function or survival but seems to be effective on quality of life [23].

b) Percutaneous (PMR): Some trials have shown symptomatic benefit in TMR with significant peri-operative mortality and morbidity.

But in this context, PMR, in which channels are created from the endocardium partially through the myocardium, is an attractive alternative as the peri-procedural complication rate is significantly lower. For PMR, biplane ventriculography is performed to provide landmarks for laser tip placement. A 9F Axcis guiding catheter is used to position the optical fiber attached to a Holmium: YAG laser, which can channel energy through flexible fibers, unloke the CO2 laser, creating channels in the presence of blood. Each position is checked in two radiographic views to ensure placement of channels at least 1 cm apart and 9-12 channels is created [24].

2. Percutaneous in situ coronary venous arterialization (PICVA): It is an interventional procedure which redirects arterial blood flow from the occluded, offending artery into an adjacent coronary vein, thereby arterializing the vein and providing retroperfusion to ischemic myocardium. Access is from the internal jugular vein. The procedure requires that the occluded artery and corresponding great vein be imaged. A needle is advanced proximal to the occlusion in the artery and into the adjacent vein under ultrasound guidance [25]. After delivery, the body of the stent is expanded to fit securely within the coronary sinus. The leading end of the stent is positioned in the left ventricle, and the trailing end is positioned in the right atrium [26]. And thereafter venous retroperfusion may occur without significant left to right shunt.

3. Percutaneous in situ coronary artery bypass (PICAB): It is also an advancing technology for these patients in whom arterial blood flow is redirected form diseased artery to an adjacent coronary vein, and then rerouted back to the artery after the lesion. Thus coronary vein acts as an in situ coronary bypass conduit rather than as a means of retroperfusion. This technology requires that two arteriovenous fistula be created, one on either side of the artery blockage, and that the vein be blocked both distally and proximally[27].

4. Coronary sinus reducer stenting: In the setting of coronary arteries obstruction, increased coronary sinus (CS) pressure can reduce myocardial ischemia by redistribution of collateral blood flow from nonischemic to ischemic myocardium [28]. The coronary sinus reducer is a percutaneous implantable device designed to establish CS narrowing and to elevate CS pressure. The diameter at its mid portion is 3 mm, and it can reach a diameter of 7-13 mm at both ends using inflation pressure of 2-4 bars. The reducer is introduced into the CS through the right internal jugular vein. In preclinical experiments, implantation of the reducer was safe and was associated with improved ischemic parameters [29]. The subendocardium is more vulnerable to ischemic damage than the other part of myocardium. Epicardial coronary stenosis are associated with reduction in the subendocardial to subepicardial flow ratio. This reducer, by increasing backpressure into the precapillary arteriolar system, will facilitate dilatation of the constricted subendocardial capillaries. Any change in the diameter of these vessels will be more pronounced than the changes taking place in the already-dilated vessels in the epicardial territory, thereby facilitating the directional changes in flow toward the subendocardial segments [29].

C. Neuromodulation:

Patients with refractory angina often exhaust conventional treatment, therefore they usually need opioids and still have angina pectoris despite prior PCI or CABG and full dose medical treatment. In these cases, neuromodulation techniques often are successful.

1. Transcutaneous electrical nerve stimulation (TENS):

Based on the gate control theory, high frequency stimulation of large non-nociceptive

myelinated type A fibers inhibits the impulse through smaller, unmyelinated type C fibers, thereby reducing the activation of central pain receptors. In addition, there is a reduction in sympathetic discharge, leading to decrease in cardiac work and myocardial oxygen demand. Mannheimer et al. first described the beneficial effects of TENS in the early 1980s [30]. In this procedure, two electrodes are applied to the chest, one in the dermatome with highest intensity of projected pain and other in the contralateral dermatome. The stimulus intensity is adjusted to just below the individual's pain threshold [4]. Covering the pain area with electrically induced paraesthesia leads to reduction in angina incidence, better functional capacity and better quality of life. Side effects included skin irritation and limited physical activity during treatment. Today, TENS is primarily used as a test method for planned implantation of spinal cord stimulator [1].

2. Spinal cord stimulation (scs):

It is an under-utilized but well-established modality for the treatment of intractable angina. After a period of TENS, these patients are usually treated with implantation of a single electrode SCS-system. Spinal cord stimulation has been claimed as a valuable therapeutic option for this difficult population of patients. The SCS device implantation was performed in two sessions, one for the lead insertion and one to implant the permanent pulse generator.

Under local anesthesia a lead is inserted into the epidural space at the level of T6, through a needle. The tip of the lead is positioned often at the C6-T2 level in order to cover pain area. Usually one month later, the lead is connected to an extension wire which is tunneled subcutaneously below the left costal arch and connected to a permanent pulse generator placed in a subcutaneous packet in the lateral abdominal region. The neurostimulator is set to give a continuous paresthetic stimulation at the minimal level perceived by the patient [31].

Two large studies, the Electrical Stimulation versus Coronary Bypass Surgery (ESBY) trial (32) and Greco's study [33] evaluating SCS have shown more convincing evidence, but both modalities improve functional capacity and ischemia.

3. Videothoracoscopic sympathectomy (VTSY):

An anti-ischemic effect of thoracic sympathetic blockage is clearly recorded in several studies, and antiarrhythmic and positive influences on ischemic myocardium were demonstrated in several other studies. Thoracic sympathectomy in these patients has high mortality and morbidity but the use of minimally invasive surgical techniques spread the range of effective treatments even in the high risk patients [31]. The goal of this method is to increase oxygen supply to a diseased myocardium and to relieve angina. The procedure is carried out under general anesthesia or combined anesthesia with selective single-lung ventilation. Three or four ports is inserted for VTSY and a rigid 30° endoscope is used for visualization. The usual site for optical port is the 3rd intercostal space lateral to pectoralis major muscle and instrumental ports is in 5th intercostals spaces in posterior axillary line. Bilateral gangliectomy at the levels th2-th4 or transaction of interganglia fibers are done. Few studies have shown a decrease in the frequency of angina and an increase in exercise tolerance [34].

D. New vessel formation

1. Stem cell injection:

Recently, cell therapy has evolved as an option for the treatment of ischemic heart disease. Several cell types including skeletal myoblasts, bone marrow stem cells, endothelial progenitors, mesenchymal stem cells, resident cardiac stem cells and embryonic stem cells are under pre-clinical and clinical investigations [35].

Within those different cell types, autologous BMSCs have raised the interest of many re-

search and clinical investigators. So far, clinical data suggest that autologous BMSCs seem to have the potential to improve myocardial perfusion and contractile performance in patients suffering from myocardial infarction, severe ischemic heart disease and chronic heart failure. Unselected autologous BMSCs have been injected into the myocardium during open-chest surgical procedures [36] or via percutaneous intervention using injection catheters [37]. Most of the patients undergoing surgery together with the cell injection had received a coronary artery bypass graft (CABG). The choice of the bone marrow-derived cell type and even the cell isolation procedure will ultimately depend greatly on the cardiac injury to be treated. Highly selected haematopoietic progenitor cells might have angiogenic potential only, whereas mesenchymal stem cells were shown to represent subsets with cardiomyogenic and angiogenic potential. Also critical is the stem cell dose that can be obtained from bone marrow using various techniques. Recent investigations suggest that there may be a dose-response relationship, which it has not been possible to test in clinical trials so far because of the limited number of stem cells isolated from autologous bone marrow using current available technology. Increasing evidence from cardiac surgery studies suggests that therapy with certain bone marrow-derived stem and progenitor cells improves myocardial perfusion and LVEF [38].

Endothelial stem cells have been identified in the adult and shown to participate in new blood vessel formation in normal and pathological states [38]. Therefore, several groups are investigating the potential of selected progenitor cell fractions from bone marrow for cellular therapy in cardiac diseases. Defined surface markers such as CD3415 and CD13316-18 are used for immunomagnetic selection of progenitor cells under good manufacturing practice (GMP) conditions. While the majority of patients within Stamm et al studies have received the selected stem cells in addition to revascularisation by CABG [39] substantial improvement of cardiac function was also found in patients who received CD133-selected cells as sole therapy [40].

In order to improve the efficacy of CABG and stem cell therapy, Klein et al have been using transmyocardial laser revascularization (TMLR) for many years. The intention is to restore tissue viability by taking advantage of the synergistic angiogenic effects of TMLR and stem cell injection. The local inflammatory reaction induced by TMLR should serve as an informational platform for stem cells and may trigger their angiogenic differentiation [41].

2. Gene therapy:

One of its potential roles is treating refractory angina. Losordo et al. showed the safety of intramyocardial delivery of VEGF plasmid in humans with myocardial ischemia. Using a left anterior thoracotomy, the plasmid VEGF-DNA is directly injected into myocardium. [42] The true efficacy of gene therapy cannot be definitively evaluated because there is a lack of randomized, placebo-controlled trial [4].

3. Shock wave therapy:

Low intensity shockwaves have been proven in animal studies to induce local growth of new blood vessels from existing ones. Shockwave therapy hypothesis is that it could improve the symptoms of patients with refractory angina not amenable to revascularization with angioplasty or bypass surgery [43].

Low intensity shockwaves (1/10 the ones used in Lithotripsy) are delivered to myocardial ischemic tissue. Shockwaves are created by a special generator and are focused using a shockwave applicator device. The treatment is guided by standard echocardiography equipment. The shockwaves are delivered in synchronization with Patient R-wave to avoid arrhythmias. The treatment is painless. At first, the patient undergoes stress- SPECT testing to identify the ischemic areas. Following that, the

same area is localized by the ultra-sound device and the shockwaves are focused to the ischemic area. Several treatments are required for optimal results [44].

E. Heart transplantation

For patients who have disabling angina an in whom all conventional and alternative treatments have failed, heart transplantation should be considered.

References

1. Mannheimer C, Camici P, Chester MR, Collins A, DeJongste M, Eliasson T, Follath F, Hellemans I, Herlitz J, Luscher T, Pasic M, Thelle D. 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. Mike J L DeJongste, René A Tio, and Robert D Foreman. Chronic therapeutically refractory angina pectoris. Heart 2004; 90(2): 225-230.

3. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, et al. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006; 27:1341-1381.

4. Kim MC, Kinu A, Shara SK. Refractory angina pectoris; Mechanism and therapeutic options. J Am Coll Cardiol 2002; 39:923-934.

5. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. Circulation 2006; 113:2462.

6. Chaitman B, Anaheim, CA. Presented at American Heart Association Scientific Sessions. Late breaking trial results: the CARISA trial. 2001 November.

7. IONA study group. Effect of nicorandil on coronary events in patients with stable angina: the impact of Nicorandil in angina (IONA) randomized trial. Lancet 2002; 359:1269-1275.

8. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I(f) current inhibition with Ivabradine: A new therapeutic perspective in cardiovascular disease. Drugs 2004; 64:1757.

9. Lionel Opie, Bernard J. Gersh. Drugs for the heart. 2009; Saunders Elsevier: NY. pp. 390.

10. Vicari RM, Chaitman B, Keefe D. Efficacy and safety of fasudil in patients with stable angina: a double blind, placebo controlled, phase 2 trial. J Am Coll Cardiol 2005; 46:1803.

11. S Takagi, Y Goto, E Hirose, M Terashima, S Sakuragi, S Suzuki, Y Tsutsumi, S Miyazaki, H Nonogi. Successful treatment of refractory vasospastic angina with corticosteroids: coro. Circ J 2004 Jan; 68(1):17-22.

12. Thomas Pettersson, Susanne Bondesson, Diodor Cojocaru;, Ola Ohlsson, Angelica Wackenfors, Lars Edvinsson. One year follow-up of patients with refractory angina pectoris treated with enhanced external counterpulsation. BMC Cardiovasc Disord 2006; 6: 28.

13. Soran O, Kennard ED, Kfoury AG, Kelsey SF. Two-year clinical outcomes after enhanced external counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction. Am J Cardiol 2006; 97:17.

14. Michaels AD, Accad M, Ports TA, Grossman W. Left ventricular systolic unloading and augmention of intracoronary pressure and doppler flow during enhanced external counterpulsation. Circulation 2002; 106:1237-1242.

15. Taguchi I, Ogawa K, Oida A, Abe S, Kaneko N, Saiko H. Comparison of hemodynamic effects of enhanced external counterpulsation and intra-aortic balloon pumping in patients with acute myocardial infarction. Am J Cardiol 2000; 86(10):1139-1141.

16. Bonetti PO, Barsness GW, Keelan PC, Schnell TI, Pumper GM, Kuvin JT, Schnall RP, Holmes DR, Higano ST, Lerman A. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. J Am Coll Cardiol 2003; 41:1761-1768.

17. Akhtar M, Wu GF, Du ZM, Zheng ZS, Michaels AD. Effect of external counterpulsation on plasma nitric oxide and endothelin-1 levels. Am J Cardiol 2006; 98:28-30.

18. Kersten JR, Pagel PS, Chilian WM, Warltier DC. Multifactorial basis for coronary collateralization: a complex adaptive response to ischemia. Cardiovasc Res 1999; 43:44-57.

19. Rohit R. Arora, Tony M. Chou, Diwakar Jain, Bruce Fleishman, Lawrence Crawford, Thomas McKiernan and Richard W. Nesto. 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; 33:1833-1840.

20. second Joint Task Force of European and other Societies on Coronary Prevention. Prevention of coronary heart disease in clinical practice. Eur Heart J 1998; 19:1434-1503.

21. Kohmoto T, Fisher PE, Gu A, Zhu SM, Yano OJ, Spotnitz HM, Smith CR, Burkhoff D. Does blood flow through holmium: YAG transmyocardial laser channels?

Ann Thorac Surg 1996; 61(3):861-8.

22. Horvath KA, Chiu E, Maun DC, Lomasney JW, Greene R, Pearce WH, Fullerton DA. Up-regulation of vascular endothelial growth factor mRNA and angiogenesis after transmyocardial laser revascularization. Ann Thorac Surg 1999; 68(3):825-9.

23. Tasse J, Arora R. Transmyocardial revascularization: peril and potential. J Cardiovasc Pharmacol Ther 2007 Mar; 12(1):44-53.

24. Duncan McNab, Sadia N. Khan, Linda D. Sharples, Judy Y. Ryan, Carol Freeman, Noreen Caine, 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. European Heart Journal 2006; 27(9):1048-1053.

25. Kay EB, Suzuki A. Coronary venous retroperfusion for myocardial revascularization. Ann Thorac Surg 1975; 69:63-72.

26. Patel, N.H. Percutaneous transmyocardial intracardiac retroperfusion shunts: Technical feasibility in a canine model. Journal of vascular and interventional radiology 2000; 11(3):382-390.

27. Fitzgerald PJ, Hayase M, Yeung AC, Virmani R, Robbins RC, Burkhoff D, Makower J, Yock PG, Oesterle SN. New approaches and conduits: in situ venous arterialization and coronary artery bypass. Curr Interv Cardiol Rep 1999; 1:127-137.

28. A, Hasbe N, Matsuhashi H, Kikuci K. Coronary sinus occlusion enhances coronary collateral floe and reduces subendocardial ischemia. Am J Physiol Heart Circ Physiol 2001; 280:H1361-H1367.

29. Banai S, Ben Muvhar S, Parikh KH, Medina A, Sievert H, Seth A, Tsehori J, Paz Y, Sheinfeld A, Keren G. Coronary sinus reducer stent for the treatment of chronic refractory angina pectoris: a prospective, open-label, multicenter, safety feasibility first-in-man study. J Am Coll Cardiol 2007 May 1; 49(17):1783-9.

30. Mannheimer C, Carlsson CA, Emanuelsson H, Vedin A, Waagstein F, Wilhelmsson C. The effects of transcutaneous electrical stimulation in patients with severe angina pectoris. Circulation. 1985; 71:308-316.

31. E. Lapenna, D. Rapati, P. Cardano, M. De Bonis, F. Lullo, A. Zangrillo, and O. Alfieri. Spinal Cord Stimulation for Patients With Refractory Angina and Previous Coronary Surgery. Ann Thorac Surg 2006; 82(5): 1704 - 1708.

32. Mannheimer C, Eliasson T, Augustinsson LE, Blomstrand C, Emanuelsson H, Larsson S, Norrsell H, Hjalmarsson A Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris: the ESBY study. Circulation 1998; 37:1157-1163.

33. Greco S, Auriti A, Fiume D, Gazzeri G, Gentilucci G, Antonini L, Santini M. Spinal cord stimulation for the treatment of refractory angina pectoris: a two-year follow up. Pacing Clin Electrophysiol 1999; 22:26-32.

34. Khogali SS, Miller M, Rajesh PB, Murray RG, Beattie JM. Video-assisted thoracoscopic sympathectomy for severe intractable angina. Eur J Cardiothorac Surg 1999; 16:1:S95-98.

35. Laflamme MA, Murry CE. Regenerating the heart. Nat Biotechnol 2005; 23:845-56.

35. Hendrikx M, Hensen K, Clijsters C, Jongen H, Koninckx R, Bijnens E, Ingels M, Jacobs A, Geukens R, Dendale P, Vijgen J, Dilling D, Steels P, Mees U, Rummens JL. Recovery of regional but not global contractile function by the direct intramyocardial autologous bone marrow transplantation: results from a randomized controlled clinical trial. Circulation 2006; 114(1 Suppl) :I101-7.

36. Briguori C, Reimers B, Sarais C, Napodano M, Pascotto P, Azzarello G, et al. Direct intramyocardial percutaneous delivery of autologous bone marrow in patients with refractory myocardial angina. Am Heart J 2006; 151(3): 674-80.

37. Hans-Michael Klein. Ischaemic Heart Disease - Alternative Treatment Options. European Cardiovascular Disease 2007; 1:32-5.

38. Loges S, Fehse B, Brockmann MA, Lamszus K, Butzal M, Guckenbiehl M, et al. Identification of the adult human hemangioblast. Stem Cells Dev 2004; 13(3): 229-42.

39. Stamm C, Kleine HD, Choi YH, Dunkelmann S, Lauffs JA, Lorenzen B, David A, Liebold A, Nienaber C, Zurakowski D, Freund M, Steinhoff G. Intramyocardial Delivery of CD133+ Bone Marrow Cells and CABG Surgery for Chronic Ischemic Heart Disease: Safety and Efficacy Studies. Thorac Cardiovasc Surg 2007; 133 (3):717-25.

40. Pompilio G, Cannata A, Pesce M, Capogrossi MC, Biglioli P. Long-lasting improvement of myocardial perfusion and chronic refractory angina after autologous intramyocardial PBSC transplantation. Cytotherapy 2005; 7(6):494-6.

41. Klein HM, Ghodsizad A, Borowski A, Saleh A, Draganov J, Poll L, Stoldt V, Feifel N, Piecharczek C, Burchardt ER, Stockschl der M, Gams E. Autologous Bone Marrow-Derived Stem Cell Therapy in Combination with TMLR. A Novel Therapeutic Option for End-stage Coronary Heart Disease: Report on 2 Cases. Heart Surg Forum 2004; 7(5):E416-9.

42. Losordo DW, Vale PR, Symes JF, Dunnington CH, Esakof DD, Maysky M, Ashare AB, Lathi K, Isner JM. Gene therapy for myocardial angiogenesis: initial clinical results with direct myocardial injection of ph VEGF 165 as sole therapy for myocardial ischemia. Circulation 1998; 98:2800-2804.

43. Ito K, Shimokawa H. Extracorporeal cardiac

shock wave therapy for angina pectoris. Nippon Rinsho 2008; 66(10):2019-26.

44. Leibowitz D. Extracorporeal shock wave therapy myocardial ischemia refractory angina. Clinical Trials. GOV processed this record on 2009 May 01.