

## Refractory Angina: The Magnitude of the Problem, Ayurvedic Approach and Emerging Novel Therapies: A Holistic Approach

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### Editorial

Many patients present debilitating symptoms related to myocardial ischemia which cannot be controlled by a rational combination of anti-anginal drugs due to uncontrolled progression of disease with arterial occlusion and diffuse involvement of previous grafts or post-angioplasty restenosis, preventing new attempts of myocardial revascularization. This condition is defined as refractory angina, which greatly impairs the quality of life of the affected. The goal of rehabilitative therapy in such a situation is directed towards the improvement in the quality of the life as the disease is chronic and the person has to lead a quality life in the presence of the disease.

Their goal is to be able to perform any physical activity (no matter how trivial it seems like walking a few meters or even bathing) without anginal pain. Some patients are frequently awakened during the night by angina. Presently, all major Cardiology Societies (American Heart Association and American College of Cardiology [1], Canadian Cardiovascular Society [2] and the European Society of Cardiology acknowledge the need to seek new therapeutic strategies for this growing population of patients in whom maximally tolerated conventional treatment has failed.

The Indian traditional medicinal system as mentioned in *Sushruta Samhita* had recognized this situation in 600 BC whereby the pupils of the guru used to feel the pulse of the diseased person and used to time their massage on the thighs and the leg of the person for a considerable duration so as to maximize venous return, analogous to the present day Enhanced external- counter pulsation technique.

Ayurveda describe cardiovascular disorder in many details. *Charak samhita*, *Sushrut samhita* has clearly mentioned about cardiovascular disorder and have classified them in *vataj*, *pittaj*, *kaphaj*, *krumij* types. The word *dhamanipratichaya* has occurred in the context of atherosclerosis in *Sushrut samhita*. Ayurvedic scholars have clearly mentioned the causes of coronary artery disease. Their focus is mainly on diet, anger and emotions, which are the causative factors of coronary artery disease [3], the patient who are diagnosed or desire to prevent coronary artery disease has to keep a control on all these factors.

Herbs like Garlic (*Allium sativum L.*) and its various forms reduce cardiovascular risk, including abnormal plasma lipids, oxidized low density lipoproteins (LDL), abnormal platelet aggregation and a high blood pressure. Stimulation of nitric oxide generation in endothelial cells seems to be the critical preventive mechanisms.

Garlic may promote an anti-inflammatory environment by cytokine modulation in human blood. Cardio protective effects of dietary garlic are mediated in large part via the generation of hydrogen sulfide. Garlic derived organic polysulphides are converted by erythrocytes into hydrogen sulfide which relaxes vascular smooth muscles, induces vasodilatation of blood vessels and significantly reduces blood pressure [4]. *Tinospora cordifolia* possess a dose dependent cardio protection against ischemia -reperfusion induced myocardial injury and the cardio protection may be due to its free radical scavenging activity or indirectly by enhancing the endogenous antioxidant levels or by protecting Mg<sub>2</sub> dependent Ca<sub>2</sub> ATPase enzyme or by antagonizing free radical mediated inhibition of sarcolemma Na, K ATPase activity or by Ca<sub>2</sub> channel blocking activity [5]. Saponins of *Tibullus terrestris* have the action of dilating coronary artery and improving coronary circulation.

In a clinical trial 406 patients with coronary heart disease were treated, results showed that the total efficacious rate of remission angina pectoris was 82.3 percent and efficacious rate of ECG improvement (52.7 percent) was even higher than that of control group (35.8 percent) were observed [6], *Terminalia arjuna* lowered systolic blood pressure and body mass index to a significant level and rise High density lipoprotein cholesterol only somewhat along with marginal improvement in left ventricular ejection fraction instable angina patients [7].

Herbo-mineral drug like Prabhakar vati along with *lekhana basti* possesses potent antianginal and cardio protective activities and it can be used effectively in the management to slow down the progress of pathogenesis of atherosclerosis leading to various coronary artery diseases especially stable angina [8].

Supplementation of Shilajit significantly reduces serum triglycerides level, cholesterol, LDL cholesterol and VLDL cholesterol levels and significant improvement in HDL cholesterol level [9]. *Commiphora mukul* decreased the total cholesterol level, LDL, triglycerides and the total cholesterol and HDL cholesterol ratio [10], *Curcuma longa* is useful in endothelial inflammation and also helps to keep interleukins and TNF under control. Draksharishta is useful in keeping the oxidation of LDL under control [11], the herb *Gymnema sylvestre* possesses cardioprotective activity [12]. The present day cardiologist has the following emerging therapies in his armament to offer to the group of patients suffering from refractory angina.

Therapy	Current status for clinical use (class of recommendation/level of evidence)
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Gene therapy	Investigational
Stem cell therapy	Investigational
Transmyocardial laser revascularization	Approved ( IIb/B) <sup>a</sup>
Enhanced external counter-pulsation	Approved ( IIb/B) <sup>a</sup> (IIa/B) <sup>b</sup>
Spinal cord stimulation	Approved ( IIb/C) <sup>a</sup> (IIa/B) <sup>b</sup>
Extracorporeal shock wave myocardial revascularization	Approved in a few countries in Europe and Asia
	Investigational in the USA
<sup>a</sup> According to the American Heart Association/American College of Cardiology Guidelines, <sup>b</sup> According to the European Society of Cardiology Guidelines	

**Table 1:** New therapeutic options for patients with refractory angina.

### a) Gene therapy

Gene therapy can be defined as a medical intervention for transferring genetic material to somatic cells in vivo, allowing the in situ expression of the transferred gene with therapeutic effect. Administration of therapeutic genes requires the use of a vehicle, called a vector, capable of carrying the gene of interest and guiding it to the target cell, thereby facilitating the transfer of genetic material into somatic cells.

Symes et al. [13], Rosengart et al. [14] and others reported the results of the VEGF 165 gene transfer by direct intra-myocardial injection in patients with refractory angina. Documented a significant reduction in the frequency of angina attacks, a significant decrease in the number of hypoperfused myocardial segments, and an increased Rentrop score (number of collateral vessels) in all patients.

VIVA trial (Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis) [14]. In this trial, clinical evaluation performed at 120 days after treatment showed that the group receiving the highest dose of VEGF had a significant reduction in angina (functional class improvement) with only a favorable trend towards better exercise performance. Because of the lack of consistent, replicable data in terms of efficacy in controlled randomized clinical trials, much of the initial interest in gene therapy for the treatment of patients with refractory angina has faded away.

### b) Cell therapy

The therapeutic potential of transplantation of stem cells and/or progenitor cells has been explored experimentally for over a decade aiming to induce the growth of new blood vessels (angiogenesis) [15] and/or to regenerate cardiomyocytes after myocardial infarction [16].

### c) Trans myocardial laser revascularization (TMLR)

It is a surgical procedure in which intramyocardial channels (1 mm in diameter) are created through the application of high-energy CO<sub>2</sub> laser beams on the heart, without cardiopulmonary bypass, (CPB) through a left anterolateral thoracotomy. The procedure is based on the hypothesis that myocardial perfusion will increase as blood flows from the myocardial ventricular cavity through the channels created to the ischemic areas.

### d) Enhanced external counter-pulsation

Enhanced external counter pulsation (EECP) is a non-invasive physical therapy designed to increase venous return, raise cardiac preload, increase cardiac output, and decrease systemic vascular resistance [17]. EECP therapy is usually offered at daily sessions with 1 h duration, five times a week for 7 weeks, totaling 35 sessions. Clinical benefits were observed in over 80% of those who underwent this therapeutic strategy including a decrease in the number of angina attacks and consumption of sublingual nitrate, increased exercise tolerance, improved quality of life, objectively demonstrable increase in time for the onset of ischemia and improvement in myocardial perfusion defects [18-20].

### e) Spinal cord stimulation

In theory, SCS decreases myocardial ischemia by one or more of the following mechanisms: an increase of coronary blood flow, reduction of O<sub>2</sub> demand, and direct inhibition of nociception with consequent reduction in the consumption of O<sub>2</sub>. In this treatment modality neuromodulation plays a pivotal role to increase the pain threshold, possibly by redistributing coronary flow [21]. Briefly, this technique involves inserting a cable into the epidural space connected to an implanted stimulation pulse generator in the subcutaneous tissue. Electrical stimulation can be generated in a continuous, cyclical or intermittent mode.

### f) Extracorporeal shockwave myocardial revascularization

Extracorporeal shockwave myocardial revascularization (ESMR) is a non-invasive therapy that, through the application of low energy shock waves directed to the ischemic areas of the myocardium, the induction of growth of new blood vessels (neovascularization) may occur, increasing tissue perfusion and leading to relief of symptoms.

The author believes that a coordinated effort must be undertaken with collaboration of Ayurvedic and herbal preparations, which are affordable, low cost and free from side effects and available at home along with the recently evolved therapies of modern cardiology, like spinal cord stimulation, enhanced external counter pulsations, gene therapy and Trans-myocardial laser. The role of fiber rich and low fat diet cannot be underemphasized. The emotional component of the disease can be best managed by Yoga and meditation. All these together would converge in perfect synchrony to serve as a holistic approach to the management of refractory angina and will greatly improve the quality of the life of the patients.

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