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# Alternative Non-Medical, Non-Surgical Therapies for the Treatment of Angina Pectoris

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## 1. Introduction

The treatment of angina pectoris as an important symptom of coronary artery disease is usually focused on restoring the balance between myocardial oxygen demand and supply by administration of drugs interfering in heart rate, preload, afterload, and coronary vascular tone. For non responders to drug therapy or for those with jeopardized myocardium, revascularization procedures such as coronary artery bypass graft surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA) are at hand. However, these therapies cannot stop the disease process and, at longer terms, angina may recur. It is not always possible to revascularize all the patients who do not sufficiently react to medical treatment. In these group patients alternative therapies are more effective. A major difference between alternative therapies versus traditional therapies is that alternative therapy tends to look at the entire patient rather than simply treating a disorder as traditional treatments do. Some kinds of these therapies are applicable in all patients with coronary artery disease irrespective of their symptoms and the other ones would be considered in patients with refractory angina who are not suitable for revascularization.

## 2. General alternative therapy

These therapies are applicable in all patients with coronary artery disease whether they are symptomatic or not.

### 2.1 Heart healthy lifestyle

#### 2.1.1 Goals

Preventing heart disease, living heart healthy, and overcoming stress-related heart illness requires more than just a physical approach to heart problems. Whether or not patients had an interventional angioplasty or bypass surgery, it's obvious that some changes in lifestyle will need to be made. To continue living a normal active life, one needs to begin making heart healthy lifestyle changes that include eating a heart healthy diet. Maintaining a healthy diet and lifestyle offers the greatest potential of all known approaches for reducing the risk for CVD in the general public. Specific goals are to consume an overall healthy diet;

aim for a healthy body weight; recommended levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides; normal blood pressure; normal blood glucose level; be physically active and avoid use of and exposure to tobacco products.

**Consume a Healthy Diet:**

An emphasis on whole diet should be done to ensure nutrient adequacy and energy balance. Hence, rather than focusing on a single nutrient or food, individuals should aim to improve their whole or overall diet. (1) The American Heart Association has provided dietary recommendations and recommendations for an overall healthy lifestyle to the American public with the goal of reducing risk for cardiovascular diseases. (1)

**Achievement or maintaining an ideal body weight:**

A healthy body weight is currently defined as a body mass index (BMI) of 18.5 to 24.9 kg/m<sup>2</sup>. Overweight is a BMI between 25 and 29.9 kg/m<sup>2</sup>, and obesity is a BMI 30 kg/m<sup>2</sup>. Achieving and maintaining a healthy weight throughout life is particularly difficult and are critical factors in reducing CVD risk in the general public. Great emphasis should be put on prevention of weight gain (2), because achievement and maintenance of weight loss, although certainly possible, require more difficult behavioral changes ie, greater calorie reduction and more physical activity, than prevention of weight gain in the first place.

**Prevention of excess weight gain:**

Prevention of excess weight gain relies on the maintenance of energy balance, whereby energy intake equals energy consumption over the long term.(1, 2) This means maintaining a relatively stable weight across life stages. A positive imbalance will increase energy storage, deposited as body fat and observed as weight gain. Although the concept is seemingly simple, the physiological systems that regulate body weight through energy intake and consumption mechanisms are complex, interactive, homeostatic, and still poorly understood. Furthermore, the components of energy balance are not weighed easily or with adequate precision to be practical as a guide to help individuals maintain energy balance. In theory, a small persistent energy imbalance of 50 kcal per day could result in a 5-lb weight gain in 1 year, provided that all other things being equal. (2)

**Treatment of obesity:**

Although prevention and treatment of obesity both depends on the same principles of energy balance, the application of the principles is completely different. For treatment of obesity, a large reduction in calorie intake of about 500 to 1000 kcal per day, along with increased physical activity, can result in a loss of approximately 8- 10% of body weight over the relatively short period of about 6 months. Although the types of low-calorie diets that best promote weight loss are the subject of current investigations, behaviors for weight loss focused on caloric reduction such as decreasing overall food intake, reducing portion sizes, substituting lower-calorie for higher calorie foods, and increasing physical activity. Weight loss is best achieved by participation in a behavioral program using self-monitoring, goal-setting, and problem-solving techniques. Motivation levels may be high for appearance reasons or if adverse health consequences and quality of life impairments associated with obesity are readily perceived.(2) However, because weight regain after weight loss is common, motivations and strategies to maintain weight may differ largely from those initiating weight loss.(2)

**A diet rich in vegetables and fruits:**

Most vegetables and fruits are rich in nutrients, low in calories, and high in fiber. Diets high in fiber, especially from cereal sources, substantially reduce the risk of coronary heart disease. Short-term randomized trials have shown that diets rich in vegetables and fruits not only provide micronutrient, macronutrient, and fiber requirements, but also lower BP and improve other CVD risk factors. Vegetables and fruits that are deeply colored, for example, spinach, carrots, peaches and berries, ought to be emphasized because they tend to be higher in micronutrient contents compared to other vegetables and fruits such as potatoes and corn. Equally important is the method of preparation which includes techniques preserving nutrient and fiber content without adding unnecessary calories, saturated or trans fat, sugar, and salt.(1)

**2.2 Supplements**

It is ideal to get the body nutritional needs in foods .When that is not enough, a registered dietitian may also start a series of supplements to make up for nutrients not getting through the diet. Some of the more popular supplements for both healthy and those at risk for coronary artery disease include antioxidants such as vitamins C and E, B-complex, omega-3 fish oil and coenzyme Q10. The American Heart Association recommends 2-4 grams of Omega-3 per day for anyone with high triglycerides and at least 1 gram per day for anyone with documented coronary heart disease. (1) According to the results of many clinical trials performed to clear the role of dietary supplements in the prevention and /or slowing the progression of cardiovascular diseases , the long-term effects of most dietary supplements other than for vitamins and minerals are not known, so these agents should be prescribed under professional supervision of physician or a registered dietitian.

**Essential Fatty Acids****Omega-3 and Flaxseed oil**

Flaxseed oil comes from the seeds of the flax plant (*Linum usitatissimum*, L.) which contains both omega-3 and omega-6 fatty acids, which are vital for health. They are composed of essential fatty acid alpha-linolenic acid (ALA), which the body turns into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the omega-3 fatty acids found in fish oil. Some researchers argue that flaxseed oil might have some of the same usefulness as fish oil, but the body is not very efficient at converting ALA into EPA and DHA, however, the benefits of ALA, EPA, and DHA are not necessarily the same. The human body is not able to make its own omega-3 fatty acids, so it is important that they are part of everyone's dietary intake. (3) The consumption of 2 servings (8 ounces) per week of fish high in EPA and DHA can result in a reduction of risk of mortality and morbidity from coronary artery disease. In addition to providing EPA and DHA, regular fish consumption may facilitate the displacement of other foods higher in saturated and trans fatty acids from the diet, such as fatty meats and full-fat dairy products.(1) Omega-3 fatty acids seem to have a small, dose-dependent, hypotensive effect, the extent of which seems to be dependent on the degree of hypertension.(4) In a meta-analysis, Morris et al found a significant reduction in blood pressure of  $\leq 3.4/2.0$  mmHg in studies with hypertensive subjects who consumed 5.6 g/d of omega-3 fatty acids.(4) Likewise, Appel et al found that blood pressure was decreased  $\leq 5.5/3.5$  mmHg in trials of untreated hypertensives given 3 g/d of omega-3 fatty acids. DHA seems to be more effective than EPA in lowering blood pressure. (4) Getting a

good balance of omega 3 and 6 fatty acids in the diet is important which are examples of polyunsaturated fatty acids (PUFAs). Omega 3 fatty acids help reduce inflammation, while most omega 6 fatty acids tend to contribute to inflammation. A healthy diet should consist of roughly 2 to 4 times fewer omega 6 fatty acids than omega 3 fatty acids. Some species of fish may contain significant levels of methylmercury, polychlorinated biphenyls (PCBs), dioxins, and other environmental contaminants which is a potential concern for using them.(1,4) Subgroups of the population, primarily children and pregnant women are advised by the FDA to avoid eating those fish with the potential for the highest level of mercury contamination. Eating up to 12 ounces (2 average meals) per week of a variety of fish and shellfish that are lower in mercury is also recommended. (1) The American Heart Association recommends inclusion of omega 3 fatty acids in patients with stable CAD because of evidence from randomized controlled trials. The recommended daily dose in patients with stable coronary artery disease is 1 gram of eicosapentaenoic acid/docosahexaenoic acid (EPA/DHA) by capsule supplement, the equivalent amount in alpha-linolenic acid (LNA) from vegetable source, or by eating daily fatty fish(1). Since maintaining daily fish meals can be difficult, capsule supplements may be preferred although there is no uniformity of EPA/DHA content or purity.

### Niacin

Niacin (nicotinic acid) is a B vitamin that has been used in high doses (1.0–4.5 grams per day) as a treatment for hyperlipidemia which is associated with increased risk of CAD. Niacin reduces cholesterol and TG levels, and increases the concentration of high-density lipoprotein (HDL). (5) It is also effective at modulating blood lipids, but side effects sometimes dampen enthusiasm for therapy. Although side effects are dose-related, few studies have determined an optimal dose of nicotinic acid that alters lipid levels with the fewest side effects. Martin-Jadraque et al. (6) found improvement in blood lipid levels in 75% of subjects who tolerated low-dose nicotinic acid therapy. Nicotinic acid may also be useful in combination drug therapy for prevention of CAD if higher doses cannot be tolerated. Use of a lower dose should still be beneficial for producing a moderate rise in HDL levels. Women seem to have a greater LDL response to niacin, but experience more side effects at higher dosages. (7)

Long-term treatment with nicotinic acid (4 g/day for 6 weeks) not only corrects serum lipoprotein abnormalities, but also reduces the fibrinogen concentration in plasma and stimulates fibrinolysis. (8) Although most medications used to treat dyslipidemias will raise HDL levels modestly; however, niacin appears to have the greatest potential to do so, increasing HDL up to 30%. (9)

### Vitamin C

A widely publicized study showed that men who took 800 mg daily of vitamin C lived about 6 years longer than those consuming of 60 mg per day. (10) A study of elderly subjects; being supplemented by vitamin C and vitamin E to subjects using no vitamin supplements showed that use of vitamin E alone reduced death from myocardial infarction (MI) by 63% and overall mortality by 34%. When the vitamin C and E were used together, overall mortality was reduced by 42%. (11)

A proper supply of nutrients will allow the cellular damage to vascular walls to be repaired properly and prevent further cracks and lesions. The results of a clinical studies, published in the Journal of Applied Nutrition (12), determine the effect of a nutritional supplement program, consisting of vitamin C therapy, on the natural progression of coronary artery



disease. The study used Ultrafast Computed Tomography to document the level of coronary artery disease and the sample of patients composed of people with early and advanced stages of the disease. During the course of the 12-month study, the rate of coronary artery calcification decreased in all patients by an average of 15%. In the subset of early stage patients, the progression of calcification was stopped completely. In some cases, calcification was actually reversed, including a case of the disappearance of all calcification deposits.

### **Vitamin E**

Evidence demonstrates that vitamin E protects against development of atherosclerosis by reducing oxidation of LDL, inhibiting proliferation of smooth muscle cells, decreasing platelet adhesion and aggregation, and changing the expression and function of adhesion molecules. The biological functions of vitamin E (attenuating the synthesis of leukotrienes and potentiating release of prostacyclin) which reduces platelet aggregation and acts as a vasodilator may protect against the development of atherosclerosis. (13)

A large study that examined the relationship between the intake of dietary carotene, vitamin C, and vitamin E and subsequent coronary mortality found an inverse association between dietary vitamin E and coronary mortality, supporting the hypothesis that antioxidant vitamins provide protection against CAD. (14) Large epidemiological studies revealed that higher vitamin E levels in plasma result in a reduced incidence of CAD. Dose-response studies in humans have demonstrated that 400 IU per day of vitamin E increased vitamin E plasma levels twofold and delayed oxidation of LDL, while the length of time was more important than the amount of the nutrient used. (15) The type and blend of vitamin E selected for supplementation can affect the end results. Studies show that  $\alpha$ -tocopherol may offer better protection against CAD when it is combined with gamma tocopherol, which has a greater activity. Unfortunately, gamma tocopherol is poorly retained in body because it is excreted in urine following liver metabolism, whilst  $\alpha$ -tocopherol is more abundant in body tissues which does not provide for maximum protection against free radical attack. So complexing  $\alpha$ -tocopherol (80%) with gamma tocopherol (20%) is an ideal blend for individuals seeking protective cardiovascular effects from vitamin E tocopherol.

### **Coenzyme Q10**

Coenzyme Q10 (CoQ10; ubiquinone) is a fat-soluble cofactor substance. It is a naturally occurring substance that prevents cell damage due to myocardial ischemia (hypoxia) or subsequent to reestablishment of blood flow to the heart after temporary ischemia. CoQ10 is involved in several key enzymes in energy production within a cell, and has membrane-stabilizing activity. Numerous studies provide details of the efficacy of CoQ10 in the prevention and treatment of heart disease, as detailed below. Oral CoQ10 (150 mg daily in 3 doses) was given for 4 weeks to exercising angina patients. Average levels of CoQ10 in plasma increased after CoQ10 treatment and were significantly related to an increase in exercise duration. The study suggested that: "CoQ10 is a safe and promising treatment for angina pectoris". (16) Pretreatment with intravenous CoQ10 minimized myocardial injury caused by cardiac bypass graft (CABG) surgery and improved heart function. In patients undergoing CABG pretreatment with intravenous CoQ10 (5 mg/kg, intravenously 2 hours before cardiopulmonary bypass) prevents left ventricular depression in early reperfusion and minimizes myocardial cellular injury during CABG following reperfusion. (17)

In comparison with younger individuals, the outcome of surgery in the elderly, is compromised by age-related reduction of cellular energy production in the myocardium during surgery. Fibers from subjects over age 70 showed poor recovery of force after

simulated ischemia compared to younger patients. This age-associated effect was prevented by pretreatment with CoQ10 (18), in addition CoQ10 pretreatment prior to stress improved recovery of the myocardium after stress (19). Because of the popular use of "statin" drugs (Zocor, Lipitor, Pravachol, Lescol, and Mevacor) it is important to emphasize that statins act by inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. Drugs inhibiting HMG-CoA reductase activity decrease CoQ10 levels (20) because HMG-CoA reductase is required for CoQ10 synthesis. Individuals using statins ought to increase their intake of CoQ10 to negate the decrease in CoQ10 biosynthesis caused by the statin drugs. So it is recommended to administer it with statin therapy. CoQ10 is free of toxicity and typically produces no side effects and may change the insulin requirements of people with diabetes.

### **2.3 Mind-body relaxation techniques**

While living a type A lifestyle isn't typically categorized as a main risk factor for heart disease, learning how to deal with life and lower stress levels can help down road to recovery.

Mind-body approach aimed at diminishing excess activation in the nervous system and thereby improving one's own ability to modulate emotional and behavioral responses.

Relaxation therapy is a broad term used to describe a number of techniques that promote stress reduction, the elimination of tension throughout the body, and a calm and peaceful state of mind.

Relaxation techniques include behavioral therapeutic approaches that differ widely in philosophy, methodology, and practice. There are two basic methods, deep methods include autogenic training, progressive muscle relaxation, and meditation (although meditation is sometimes distinguished from relaxation based on the state of "thoughtless awareness" that occurs during meditation). Brief methods include self-control relaxation, paced respiration, and deep breathing. Brief methods generally are less time consuming and often represent a summarized form of a deep method. In order to be able to evoke the relaxation, several months of practice (at least three times per week) is required.

Some of the more popular relaxation techniques include massage therapy, yoga, listening to music, pray and meditation.

#### **Massage therapy**

Massage therapy is the scientific manipulation of the soft tissues of the body, consisting primarily of manual (hands-on) techniques such as applying fixed or movable pressure, holding, and moving muscles and body tissues.

Various forms of therapeutic superficial tissue manipulation have been practiced for thousands of years across cultures. Chinese use of massage dates to 1600 BC, and Hippocrates made reference to the importance of physicians being experienced with "rubbing" as early as 400 BC. There are references to massage in ancient records of the Chinese, Japanese, Arabic, Egyptian, Indian, Greek, and Roman nations. Many different therapeutic techniques can be classified as massage therapy. Most involve the application of fixed or moving pressure or manipulation of the muscles/connective tissues of clients. Practitioners may use their hands or other areas such as forearms, elbows, or feet. Used techniques during massage therapy include (1) superficial stroking away from the heart or deep stroking towards the heart; (2) kneading in a circular pattern using fingers and thumbs; (3) deep muscle stimulation; (4) rhythmic movements such as slapping or tapping; and (5) vibration. Scientific research of massage is limited, and existing studies use a variety

of techniques and trial designs. Firm evidence-based conclusions about the effectiveness of massage cannot be drawn at this time for any health condition.

### **Shiatsu**

Shiatsu literally means 'finger pressure'. Shiatsu is based on the same principles as acupuncture concentrating on meridians or energy lines but without the needles. Everything is related to the five elements that correspond to different parts of the body: *Heart: Fire, Kidney: Water, Spleen: Earth, Lungs: Metal, Liver: Wood.*

The idea, as in acupuncture, is to balance the life energy in the body which is disturbed when we become ill. Through a series of finger pressures all over the body along the specific pathways, Shiatsu can rebalance the body's energies, regulate the organs' function and improve circulation. Shiatsu last up to 1 hour during which practitioners often use their elbows, knees and feet as well as their fingers for palpation of the abdomen and other areas which may be lacking energy, but they seldom use the hands' palms unlike other traditional Western contact therapies.

### **Yoga**

The term "Yoga" comes from a Sanskrit word meaning "union." Yoga combines physical exercises, mental meditation, and breathing techniques to strengthen the muscles and relieve stress. The first known work is "The Yoga Sutras," written more than 2,000 years ago, although yoga may have been practiced up to 5,000 years ago. Yoga has been described as "the union of mind, body, and spirit," which addresses physical, mental, intellectual, emotional, and spiritual dimensions towards an overall harmonious state of being. It works towards self-realization and control of mental, physiological, and psychological parameters. Yoga is often practiced by healthy individuals with the aim to achieve relaxation, fitness, and a healthy lifestyle. Yoga has also been recommended and used for a variety of medical conditions and consists 30 to 90 minutes sessions.

### **Meditation**

Meditation is usually suggested as a stress management technique used to cause a tranquil and relaxed state of mind. However, researchers have lately found that meditation offers other significant health benefits by changing deeper and more dynamic processes in the body, even so far as being able to strengthen the heart. Researchers at the Margaret and H.A. Rey Laboratory, Boston, USA discovered that meditation impacts prominent heart rate variability traditionally associated with practicing slow breathing during specific traditional forms of Chinese Yoga meditation techniques. (21) The magnitude of this variability during meditation was much far greater than when compared to those not practicing any meditation in healthy young adults and even elite athletes during sleep. These results uncovered that meditation can have a profound effect on the heart and its activity. The researchers observed that the variability of beat-to-beat heart rate was directly affected by meditation. The report concluded that meditation should not be seen as just a method of relaxation and stress management, but also as an aid to strengthen the heart and create a more active state in the body. (21)

## **2.4 Cardiac rehabilitation and exercise training**

### **I. Cardiac rehabilitation definition**

Cardiac rehabilitation (CR) is welcomed not only as integral in the management of patients with coronary artery disease, but also as the primary means in delivering secondary



prevention which consists of a number of activities or measures that may be adapted by patients so as to reduce the symptoms or the risk of a further event.

More recently CR has been redefined as follows: "Cardiac rehabilitation is the process by which patients with cardiac disease, in partnership with a multidisciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychosocial health". (22,23)

According to guidelines, CR including exercise training, patient education, psychological support, risk factor management, and clinical assessment, is indicated for patients with ischemic heart disease (IHD), chronic heart failure, patients with a high risk for developing IHD (24-27), patients with valvular heart diseases, cardiac transplantation, Implanted cardioverter defibrillators, and congenital heart diseases (23).

## II. Cardiac rehabilitation phases

Cardiac rehabilitation is divided into four phases, ranging from the acute hospital admission stage to long-term maintenance of lifestyle changes, as follows (23,25,26):

*Phase I (in patient period):* is started after a 'step change' in cardiac condition including myocardial infarction, onset of angina, any emergency hospital admission for coronary heart disease, cardiac surgery or angioplasty and/or stenting, and first diagnosis of heart failure. This should begin as soon as possible after admission. Phase I consists of assessment, education, exercise/mobilization.

*Phase II (Early post-discharge):* exercise consultation and behavior change strategies are beneficial at this stage to improve adherence to both lifestyle change and maintenance of exercise in phase II and uptake of phase III in the future. This is the stage for risk factors modification and goal setting in phase I (lasting over a period of between 8 and 12 weeks).

*Phase III (supervised out-patient):* at this stage, risk factor changes and education are continued. Phase III usually consists of at least two supervised exercise sessions per week, lasting over a period of between 6 and 12 weeks. Patients may be provided with one session of education per week. Physical training is often the essential part of phase III, while psycho-social counseling and education considering risk factors and lifestyle are of primary importance. In addition to the aerobic conditioning phase, resistance training is part of CR exercise. Home-based exercise is also prescribed with self monitoring skills being used by the patients.

*Phase IV (long-term maintenance of exercise and other lifestyle changes):* For the benefits of physical activity and lifestyle change to be sustained, the available evidence suggests that both are necessary to be retained. As clinically indicated, referral to specialist clinicians, such as smoking cessation or psychological support, may still be needed. Continuation and progression of appropriate physical activities are persuaded outside the hospital setting. By this time it is looked forward that individuals will be aware of their exercise capabilities and be able to monitor themselves properly.

## III. Cardiac rehabilitation and exercise training in Ischemia

There are several mechanisms by which regular exercise training may improve myocardial oxygen supply and thereby result in an anti ischemic effect. Exercise training reduces cardiac workload at a given (sub maximal) exercise level by improved adaptation of the peripheral circulation. A alternative external work can be gained with a lower heart rate and blood pressure, thereby reducing myocardial oxygen demands and

coronary blood flow requirements in areas with a potentially critical perfusion deficit. Since myocardial perfusion is related to the length of the diastole, the time for perfusion of the myocardium decreases with increasing heart rate. Thus, exercise training improves the economy of the heart work and facilitates myocardial perfusion in patients with coronary artery stenoses. A lower heart rate and a lower systolic blood pressure during exercise is a usual though somewhat transient phenomenon after exercise training in normal persons as well as in patients with CAD. To maintain this training effect exercise needs to be incorporated into the daily routine – such as medication. (22, 25) Many studies have revealed that the symptomatic improvement as a result of exercise training is mainly owing to a decrease in the rate-pressure product at sub maximal workloads with no change in the rate-pressure product at the onset of angina (22, 28) Later reports also showed a rise in the rate-pressure product at the onset of angina along with a reduction in the ischemic response measured as angina or ST-segment depression, at a given rate-pressure product, suggesting that exercise training improves myocardial oxygen delivery. There are controversial aspects about improvement in angiographic collateralization or regression of coronary atherosclerosis- that might be a reason for less ischemia- despite the endurance exercise training program. However, some surveys showed a significant tendency toward decreasing progression after prolonged rather intense, particularly in those patients who took part more sessions of the structured training program (22,29,30).

The question whether ischemia should be avoided during endurance training in stable patients is open to question. The studies of Ehsani et al. suggest that in selected patients significant ST-segment depression can be borne without adverse effects (31). However, for safety reasons it is usually recommended to avoid ischemia during endurance training in order to minimize risks and maximize benefits. In patients with symptoms suggesting instability, exercise is not recommended until the phase of instability has resolved. (32)

Randomized clinical trials (RCTs) and meta-analyses have demonstrated significant (14% to 24%) relative reductions in all-cause mortality over 1 to 2 years in patients with coronary artery disease randomized to cardiac rehabilitation programs. Women, elderly patients, low-income groups, and ethnic minorities tend to be under-represented in RCTs. (33 - 35) CR also resulted in a comparable effects in terms of cardiac overall survival, event-free survival and other secondary outcome measures like cardiac morbidity. (36,37) Stukel et al argued whether the true size of the effect is 10% or 30%, but both are large when translated into absolute population numbers. (38)

### **The effects of Cardiac rehabilitation on Endothelial function**

One of the positive effects of exercise is the improvement of endothelial dysfunction. Endothelial dysfunction is a precursor of clinically significant atherosclerotic disease and is a signal for an increased cardiovascular event rate.(39-41)

Different efforts have been made to correct the impaired endothelium-dependent vasodilatation. In recent years it has become apparent that exercise affects the functional activity of the vascular endothelium. Whereas normal coronary arteries dilate, atherosclerotic coronary arteries often exhibit a paradoxical vasoconstriction in response to exercise, thereby causing critical ischemia even in moderate epicardial stenosis. Endothelium-derived NO is the main mediator of improved endothelial function and enforces a multitude of anti atherosclerotic functions. Acting on the endothelial cell itself, NO inhibits endothelial cell apoptosis, suppresses inflammatory activation, and increases the activity of oxygen radical-scavenging enzymes. Furthermore NO inhibits platelet aggregation via luminal release from

the endothelium and also inhibits vascular smooth muscle cell proliferation and promotion of positive arterial remodeling. Studies using cultured endothelial cells and animal experiments suggest that increases in endothelial NO synthesis expression and protein phosphorylation are possible mechanisms. Exercise training in stable CAD leads to an improved agonist-mediated endothelium-dependent vasodilatory capacity. (42-45) Exercise training induces adaptations in cellular mechanisms of nitric oxide regulation in collateral-dependent coronary arteries of chronically occluded vessels that contribute to enhanced nitric oxide production (46). Also arterial production of reactive oxygen species could significantly reduced by exercise training.

### **Improvement in Exercise Capacity**

Physical activity is seen as a behavior that generally has advantages on exercise capacity and many of the physiologic processes involved in the development of primary prevention of coronary artery disease. (26) Lavie et al reported a 34% improvement in exercise capacity after cardiac rehabilitation participation. (47) Some newer studies showed every one MET increase in exercise capacity can induce more than 17% improvement in survival rate, it is especially important in heart failure patients .(25,26)

### **Improvement in Left Ventricular Function (systolic and diastolic)**

Ehsani et al studied 25 patients, 52 ( $\pm 2$ ) years old with coronary artery disease and mildly impaired LV function (ejection fraction 53%)[31], They compared these to 14 patients with comparable maximal exercise capacities and ejection fractions who did not undergo an exercise training program. The exercise group completed a 12- month program of very intense endurance exercise training of progressively increasing intensity, frequency, and duration. Ejection fraction did not change during maximal supine exercise before training ( $52 \pm 3\%$ ),but after training it increased during exercise to  $58 \pm 3\%$  ( $P < 0.01$ ), despite a higher rate-pressure product during maximal exercise, providing some evidence for an improvement in contractile state after training – or also for improved perfusion with less ischemic impairment of myocardial function during exercise. (22,31)

In one of the first small prospective studies of endurance training in HF patients, Sullivan et al confirmed that 4 to 6 months of training did not deteriorate LV ejection fraction and tended to improve maximal cardiac output. (48) Another larger randomized clinical trial provided evidence for a training- induced reverse remodeling with modest improvements of LVEF and reductions of LV end-diastolic diameter in a mixed population of ischemic and dilated cardiomyopathy.(49)

Heart failure with preserved left ventricular ejection fraction (HFPEF) is the most popular form of HF in the older population. Exercise intolerance is the primary chronic symptom in patients with HFPEF and is a strong determinant of their reduced quality of life (QOL). Exercise training improves exercise intolerance and diastolic function and QOL in patients with HF with preserved and reduced ejection fraction. (50)

### **Improvement of quality of life**

Cardiac rehabilitation is increasingly known as an integral part of comprehensive cardiac care. The evidence supporting its effectiveness in reducing morbidity and mortality and improving quality of life (51) Frank suggested that those who have greater physical functionality, the confidence to perform physical activities, and are not restricted clinically, may more readily adjust to cardiac rehabilitation and progress more rapidly. Those patients

with the poorest exercise capacities at entrance to the program tended to make the greatest gains in health related quality of life. (52)

#### **Improvement in risk factors profile**

Regular physical activity is associated with favorable modification of cardiovascular risk factors such as hypercholesterolemia, hypertension, diabetes, and obesity. (22,53-57)

#### **Cost- benefit**

Cardiac rehabilitation is one of the most effective treatments of secondary prevention for patients with heart disease. These standard training programs are safe and cost-effective. (37)

### **IV. Cardiac rehabilitation components**

#### **IV.a Exercise program**

Not only a universal understanding of patient's medical history, current status, and medication regimen need to be taken into account, while prescribing an exercise, but also a solid understanding of exercise physiology as relates to recreational and vocational activities. Experience and individualization of exercise prescription are essential for optimal success in activity programming. A staged exercise test (preferably Ramp protocols) is recommended for exercise prescription. Every activity program should be consist of a warm-up, conditioning, and cool-down periods. (25,58)

**Warm up:** is a 5 to 15 minutes period, during which the musculature and joint structures are stimulated gently with a series of static stretches and dynamic range of motion (ROM) activities. A large group of muscle is involved in the warm-up stretches. The stretch should be maintained 15-30 seconds and should not result in discomfort or pain. Patients should be encouraged to continue to breathe to avoid Valsalva maneuver that can cause exaggerated BP responses.

**Conditioning period:** The conditioning period may be designed to focus on the following activities:

1. To increase caloric expenditure to aid with weight management
2. To improve overall functional capacity
3. To delay the onset of symptom
4. To improve muscle tone and strength
5. To optimize job or vocational abilities
6. To optimize recreational activity performance
7. To optimize ability to perform activities of daily living (ADL)

It must address 5 keys factors: Frequency, Intensity, Mode, Duration, Rate of progression

**Frequency:** Typically, the exercise stimulus must be done at least three times per week. It is recommended that the sessions be allocated equally throughout the week. From an FC improvement standpoint, there is trivial achievement by extending the program beyond 5 days per week. It is recommended that the average rehabilitation program being with an exercise frequency of 3 times per week for at least the first 3-6 months, if after this time the patient has remained free of musculoskeletal complications and expresses an interest in increasing the frequency, the program can reach to four to five times per week.

**Intensity:** According to ACSM guideline the intensity threshold for healthy adults is between 60-90% of HR max in a staged exercise test or 50-85% of Vo<sub>2</sub>max or heart rate reserve (HRR). The typical range of exercise intensity for patients involved in cardiac rehabilitation is between 40% and 85%. Exercise intensity is not static. The cost of the activities varies slightly from day to day, depending on the time of day, environmental



factors, and time since medications were last taken. Medications, especially  $\beta$ -blockers, can alter the patient's FC significantly. If significant stable ischemic changes or symptoms occur with activity, the exercise intensity must be established at a level adequately below the threshold for these findings (usually 10-15 beat/min below the onset of ischemic changes). If possible, to minimize any flaw in prescribing exercise intensity, it is advised to carry out the exercise test for exercise prescription on all usual medications and the same approximate time of day as patients exercise.

**Mode:** Any activity that engages a mass of muscle group in a rhythmic and repetitive fashion (dynamic exercises) at the approximate intensity and duration leads to improved FC. The most common sorts of the activity used in CR are walking and appropriate jogging. Cycling, swimming, rowing, stair climbing, and aerobic dancing are other popular activities used in CR programs. Recent studies, however, have demonstrated the safety and benefit of isotonic and weight training programs. Strengthening is recommended 2-3 times per week.

**Duration:** The duration of conditioning period is typically 15 and 60 minutes. A minimum of 15 minutes is necessary to achieve an improvement in FC. The optimal duration is 20-40 minutes. It can be extended if the intensity is reduced and a goal of the program is increased caloric consumptions. Patients with significant claudication, low FC, or marked weakness may require an interval program (limited by symptoms), until the total time of all intervals equals the prescribed duration.

**Rate of progression:** The first scale developed by Borg ranges from 6 to 20 and is linear, with word anchors that describe the exercise intensity equally spaced along the length of the scale. On average, a perceived exertion of 12 to 14 (somewhat hard), on the 6 to 20 scale, corresponds with a HR response of between 60% and 85%, respectively. The second scale has an exponential design to the spacing of the word anchors and runs from 0 to 10. For ratings on the 10 point scale; values between 3 and 6 correspond to a similar HR response.

**Cool- down:** this period should promptly follow the conditioning period in an activity session. It lasts 3-10 minutes. The patients should perform low- level, rhythmic, aerobic activities during period. After the active aerobic cool- down, static stretching and fine ROM activity included again. Stretching exercises are essential segment in each training session.

#### IV.b Education

Patient education can play an integral role in accomplishment of any CR program, provided that it is done properly. The inclusion of the patient education program changes, depending on the background of the patient and on the phase of CR. Some topics which should be taken into consideration are the following: management of risk factors through lifestyle modifications of smoking, diet, stress management and exercise behavior; return to work; medications; sexual activity; exercise prescription and psychological issue.

#### IV.c Psychological consideration and stress management

**Depression:** The relationship between depression and CAD is well atated. Depression is highly prevalent in cardiac patients, and is a considerable risk factor for cardiac outcomes. Patients should be screened for depression at entry to CR programs, using either a few verbal screening questions or a standardized depression questionnaire. Depressed patients enrolled in CR programs will need more attention to insure continued adherence and close monitoring to rapidly intervene provided that depressive symptoms worsen. (22,23,25,59) Several treatments have shown some success in treating depression in cardiac patients, including antidepressant medication (sertraline), psychological interventions (such as



cognitive behavioral therapy), and exercise training. Other psychological disorders such as type A personality behavior, anger and hostility should be managed in CR setting. (23, 25, 26) Treatment with cardiac rehabilitation can improve mental health related quality of life in a significant way. (60)

**Stress management:** The previous researches has indicated that mental and emotional stress can result in myocardial ischemia and is associated with a several fold increase in occurrence of subsequent fatal, and nonfatal, cardiac events. Although the efficacy research on stress management in cardiac rehabilitation is fraught with methodological issues, it appears that psychological interventions that are successful in reducing distress are also successful in reducing morbidity and mortality. Key components for providing sufficient stress management interventions include involving patients through joining the process of heart disease to their own experiences, assisting them to understand the ability they have in slowing or reversing the process through the choices they make in dealing with responses, providing adequate training and opportunities for guided practice in producing the relaxation response, and teaching patients to shift perceptions and beliefs that tend to increase stress and effect healthy coping.

**Relaxation Training:** Relaxation training has also been found to reduce heart rate, respiratory rate and muscle tension. The patients can take advantage of relaxation training that instructs them to use abdominal breathing and visual imagery to focus attention on healing stimuli, memories, or fantasies.

## V. Home- based cardiac rehabilitation

Home-based secondary prevention programs for CAD are an effective and fairly low-cost alternative measure to hospital-based CR and should be noticed for stable patients unlikely to access or adhere to hospital-based services.(61,62)

## VI. Safety of exercise training

In the meanwhile, the benefits of comprehensive cardiac rehabilitation have been obviously demonstrated, but the exercise training-induced complications and benefit-risk ratio of cardiac rehabilitation remains poorly understood. Screening procedures can be used to identify subjects at increased risk for an exercise-related cardiac event. These are patients who are generally at increased risk of sudden cardiac death; particularly patients with severe LV dysfunction or ischemia at low levels of exercise. The results of studies reporting the risks of sudden cardiac arrest during exercise training depict that this risk is low even during vigorous exercise. These studies strongly suggest that the incidence of sudden cardiac arrest across a variety of activities, with the exception of jogging, is similar to that expected by chance alone. In summary, the risk of cardiac events during exercise testing and training appears to be very low, but such events seem difficult to for see. Finally, although risk stratification remains necessary at the beginning of a CR program, the occurrence of a severe cardiac event seems to be difficult to predict in most cases. This difficulty emphasizes the role of the cardiologist in the prescription and supervision of CR sessions. (63-66)

## VII. Problems exist in cardiac rehabilitation

### Underutilization of cardiac rehabilitation

Unfortunately despite the obvious benefits and effectiveness of CR on quality of life and mortality, and regardless of the class I indication from AHA/ACC (67-69), the majority of

people who would benefit from this program fails to participate in it and right now the main present problem with exercise-based cardiac rehabilitation is its underutilization. (37,70,71)

### **Barrier to cardiac rehabilitation**

There are multiple interrelated factors that influence a patient's decision to use cardiac rehabilitation services. These factors divided into environmental and individual categories. (72) The healthcare delivery systems and policies within hospitals and cardiac rehabilitation programs represent factors within the internal environment. These factors are amenable to improvement. The external environment which includes factors that affect the patient's ability to use healthcare services are not as amenable to change, such as where they reside or their access to these services. Individual factors (at the patient and provider level) are composed of 4 categories. 1) Predisposing factors are socio-demographic characteristics and prior experiences with cardiac rehabilitation. 2) Enabling factors are any skill or resource required to enroll and participate regularly (income, social support, work/personal schedules, transportation, knowledge, attitude, and beliefs). 3) Reinforcing factors strengthen or lessen the motivation for program attendance and adherence (strength of physician endorsement, encouragement and support of healthcare providers, family, and friends). 4) Need factors in term of physician's and patient's perceptions are influenced by the clinical condition, psychological factors, and anticipated benefits of the service. Many of the barriers that arise from these categories provide opportunities for healthcare professionals to attempt to improve rates of CR referral, registration, and completion. (72-79)

## **3. Specific alternative therapy**

Treatment of patients with refractory angina pectoris has still remained challenging in patients with end-stage coronary artery disease not suitable for revascularization (even bypass surgery or angioplasty with stent).

### **3.1 ESMR (Extracorporeal Shockwave Myocardial Revascularization)**

Extracor Extracorporeal Shock Wave Therapy (ESWT) was introduced in the early 1990s as a spin-off of urological lithotripsy.(80) Since then, ESWT has been applied to treat various musculoskeletal conditions. Right now Shockwave Myocardial Revascularization (ESMR) is a breakthrough in management of refractory angina pectoris with end-stage coronary artery disease not suitable for revascularization (81). The treatment is performed using a special generator that produces low intensity shockwaves, a kind of sound waves similar to, but of lower strength than Extracorporeal Shock Wave Lithotripsy (ESWL) that is used in the treatment of kidney stones . These acoustic shock waves are not dissolving plaque in the same way that lithotripsy breaks up a stone, instead, these waves result in release substances which stimulate the formation of new blood vessels in the heart.( 82) The shock wave schedule consists of three 20-minute sessions per week over nine weeks.

The patient must first undergo cardiac SPECT (single photon emission computed tomography) testing to identify the location of the ischemic areas. Afterwards a handheld device called a transducer is placed over the skin and shockwaves will then be delivered directly to the ischemic region under echocardiographic guidance. (83)The therapy sessions that have already been conducted have yielded positive results among treated patients who claim they have had their pain alleviated since the beginning of the treatment. ESMR is an alternative therapy for patients who have angina, even though they take medicine, and are not suitable candidates for coronary angioplasty or bypass surgery.

### 3.2 EECp (Extracorporeal Electrical Counter pulsation)

EECP is sometimes known as a "natural bypass" since it optimizes the body's ability to develop new vessels around stenotic arteries. EECp seems to be a noninvasive, well-tolerated therapeutic option for patients with coronary artery disease (CAD) and refractory angina who are not amenable to standard revascularization procedures. (84-86) The EECp device consists of three paired pneumatic cuffs applied to the lower extremities. Patients are typically treated for 1 hour daily program for a total of 35 sessions over 7 weeks. The cuffs are inflated in sequence, placing pressure on the legs which pushes blood flow from the lower limbs up towards the heart. The inflation of the cuffs occurs during diastole so it increases blood flow delivery to the heart at the precise moment it is relaxing. Then, just before the heart pumps, the cuffs deflate, reducing resistance and decreasing the heart's workload.

Prospective clinical trials and large treatment registries have shown major reductions in anginal symptoms and improvements in objective measures of myocardial ischemia in response to EECp in patients with symptomatic CAD. Its potential role in heart failure management, which improves quality of life and reduces symptoms, has been also shown. (84)

EECP treatment is associated with an immediate increase in blood flow in multiple vascular beds including the coronary artery circulation and causes acute changes in hemodynamics including an increase in preload and a decrease in afterload. (87-90) Several published studies were designed to assess objective evidence of improvement in myocardial perfusion and beneficial hemodynamic effects. They have also shown improvements in various organ system perfusions and LV diastolic filling after EECp treatment and it is even recommended as initial revascularization treatment for refractory angina. The abrupt drop in intra-aortic pressure unloads the left ventricle during systole, thus reducing the cardiac workload in ejection period and reducing myocardial oxygen demands.

EECP greatly accelerates the formation of collateral vessels, helping restore adequate circulation to organs and tissues that have been deprived of blood and oxygen. EECp was developed at Harvard University almost 50 years ago as a therapy for angina. Several studies have shown that patients who undergo a course of EECp experience fewer episodes of angina, experience less intense episodes of angina, need less anti-angina medication, can walk farther without experiencing angina, and resume work and enjoy more social activities. (86, 91)

In a recent study by Esmailzadeh et.al, the effects of EECp on regional myocardial function were evaluated. Given their findings, EECp can improve global and regional LV systolic and diastolic functions by means of strain and strain rate imaging. (91)

Unlike drugs that are prescribed for angina, EECp is completely safe and without side effects. And unlike angioplasty and bypass surgery, EECp can be done on an outpatient basis and requires no post-treatment recovery period. Patients suffering a heart attack or enduring one or even several surgeries for coronary artery disease are best candidates for this kind of treatment. In some cases, EECp is their only option. Yet this noninvasive therapy is so safe and effective that it should be considered as a first-line treatment for angina, not just a last resort after surgery has been ruled out.

For a growing number of patients, who are imposed a potentially dangerous surgical procedure, recommending EECp is a wise decision; because in less time than it takes to recover from bypass surgery, these patients can complete a full course of EECp and begin enjoying an active, pain-free life.

### 3.3 Neurostimulation

For the first time healing power of electric current was described by Scribonius Largus, the physician of the Roman emperor Claudius, in the treatment of headache and gout.(92)

Because of the very promising results of neurostimulation in different ischemic syndromes, it seemed obvious to try electrical neurostimulation therapy as an adjuvant therapy in patients suffering from medically refractory angina pectoris. The beneficial effects of transcutaneous electrical nerve stimulation (TENS) were described by Mannheimer and colleagues. (93,94)

For patients not responding to adequate medication and not being suitable anymore for revascularization and suffering from refractory angina pectoris, neurostimulation has been described repeatedly as an effective and safe therapy.(95,96) The mechanism of action of neurostimulation is not completely known, however, recent studies suggest that anti-ischemic effect expressed by decrease in the serum catecholamine level, exerted by reducing sympathetic tone. (97-99)

The effect of TENS on coronary flow was not accomplished in patients with a heart transplant which suggests that neurostimulation employs its effect through neural mechanisms employed at the microcirculatory level. (100) Considering the lack of resting heart rate and blood pressure variability under neurostimulation, it's unlikely that beta-adrenergic mechanisms are involved. (101) Moreover, beta-mediated coronary dilatation is of less importance in the ischemic myocardium. (102) On the other hand, alpha- adrenergic receptors may play a role in the anti-ischemic mechanism of action of neurostimulation. Inhibition of the alpha receptors may cause relative vasodilation at the subendocardial coronary level,(103) which in turn may cause a redistribution effect.

At present it is unknown which neural pathways are involved in neurostimulation for angina pectoris. It is discovered that angina begins with stimulation of cardiac nerve endings.(104,105) by visceral afferent nerve fibers, converging in common pathways into the dorsal spinal cord at C7-T5 level, where they have synaptic connections with other neurons.(106) Afferent fibers from the heart and cutaneous input are assumed to cover specific interneurons in the same segment of the spinal cord, explaining the ensuing referred projection of pain to the related dermatome.(107, 108) Consequently, angina is felt in areas of the chest that refer to the dermatome from which afferent nerves project to the same segment of the spinal cord (C7-T5) as the heart. For an optimal clinical result of neurostimulation it is of great importance to achieve paresthesia in the same dermal regions. Although there is increasing evidence that neurostimulation is effective in angina pectoris, its safety needs to be established. In a 5-year follow-up study of 23 patients on spinal cord stimulation (SCS), Sanderson reported that it is a safe therapy based on the fact that; (109) only three patients died during this follow-up. In another follow up study, out of 46 patients with severe coronary artery disease who were treated at the Groningen University Hospital Department of Cardiology with SCS; only six patients died during a 7- year period. (110)

However, despite declining mortality rates in patients with coronary artery disease, little is known about mortality rates in patients with refractory angina due to severe coronary artery disease. It is estimated that 3% (about 7 million) of Americans have active coronary artery disease implying an annual death rate of 7 %. (111)

Another important issue which needs further attention before the general acceptance of neurostimulation as an alternative therapy in angina pectoris is its complication rate. Because of the high skin impedance, TENS is frequently complicated by persistent skin



irritation, which makes adequate continuation of therapy difficult. Meanwhile, SCS has a rather high incidence of dislocation of the epidural lead,(112) and this often impairs its effect.

Once the safety of neurostimulation in angina pectoris is convincingly established and the aforementioned side effects can be further reduced, both TENS and SCS may be commonly used as alternatives in the therapeutic spectrum of intractable angina pectoris.

### 3.4 Acupuncture

Acupuncture involves the insertion of extremely thin needles in skin at strategic points of body. Acupuncture originated in China six thousands of years ago, but during the past three decades it was grown significantly as a popular therapy within the world.

It works by stimulating the body to naturally correct the imbalances of energy. This is done by inserting ultra-fine, disposable needles, underneath the skin at specific points of the body. (113) These acupuncture points are related to energy pathways that run throughout the entire length of the body. Acupuncture points are also related to specific internal organs. The earliest known text on acupuncture was published more than 4,500 years ago.

Acupuncture has been traditionally used to treat a wide variety of cardiovascular diseases, and recent controlled studies have demonstrated that it is particularly beneficial for angina pectoris by offering a proven option to drug therapy.

Traditional Chinese theory explains acupuncture as a technique for balancing the flow of energy through specific pathways (meridians) in the body. In contrast, many Western practitioners believe the acupuncture points as places to stimulate nerves, muscles and connective tissue. This stimulation seems to boost the activity of natural painkillers and increase blood flow. (114)

Basically, acupuncture is a method of encouraging the body to enhance its own natural healing. The idea is to balance overall energy in order to establish or re-establish well-being. Research has shown that the body response to acupuncture is releasing endorphins (neurotransmitters that stop pain), increasing blood cell counts, and heightening the immune system. Acupuncture is used worldwide both as a primary and complementary form of medical treatment. The frequency of treatment depends greatly on the condition. Most people will begin to see results from acupuncture in approximately 4-10 treatments. Treatments are generally administered once per week until improvement is made and then follow-up appointments may range from a few times per year to monthly to bi-weekly.

In one study (115) at the Human College of Traditional Chinese Medicine, forty patients with stable type of angina pectoris were assessed during and after acupuncture treatments and compared to a control group. After only one acupuncture treatment, 15 (37.5%) of the patients were already noticing a marked improvement in degree and area of pain, but after 7 treatments 25 (63%) of the patients recorded significant reductions both in extent and area of pain, and they also experienced a reduction in the number and the duration of attacks. Furthermore the patients in the acupuncture group who did get angina attacks recovered much faster than the patients in the control group.

Similar findings were reported in another study, this time in Sweden (116), where 21 patients with stable effort angina pectoris were treated with acupuncture. All of the patients had a history of at least five anginal attacks per week despite intensive conventional medical treatment. They were given three acupuncture treatments per week which led to a 40% reduction in the number of anginal attacks and the researchers also observed that the patients were able to exercise for longer before the onset of pain. All the patients completed



a life quality questionnaire which confirmed that they all felt better as a result of the acupuncture treatment. The report concluded that acupuncture should be considered a beneficial treatment even for patients with severe, intensively treated angina pectoris.

Other studies have come to the same conclusion (117,118) in the treatment of angina. In one research project at the Nanjing Medical College involving 267 patients, all suffering from angina pectoris, acupuncture treatment was shown to have a 93.3% success rate with no harmful side effects (119).

There are some possible side effects and risks that could be involved in patients and depend completely upon the experience and expertise of the acupuncturist, but these are relatively less when compared to other forms of treatment. Some of the common acupuncture side effects or inconveniences experienced during or after acupuncture are: a regular sensation of warmth, tenderness, and tingling when the acupuncture needles reach the acupoint or trigger point, mild bruising and bleeding, temporary drop in blood pressure which may result in fatigue and rarely fainting, allergic reactions to stainless steel acupuncture needles, infections, and perforation of some of the vital organs by needles.

Acupuncture is safe and complications are extremely rare and side effects, if any, are limited. There are a number of guidelines, however, which govern the use of particular acupuncture points. A precaution may be related to use in certain conditions, with particular techniques, or because of a points location, however, in some cases, practitioner may still use a point or technique even if it is listed as a precaution.

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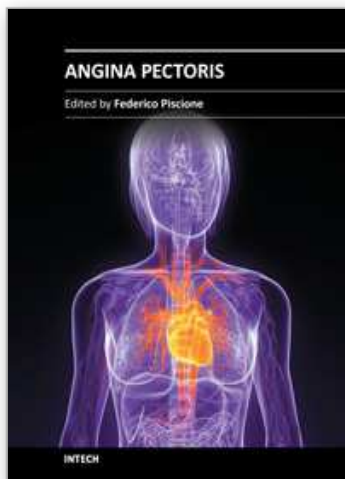
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Angina is the most common disorder affecting patients with ischemic heart disease. This book provides a thorough review of fundamental principles of diagnosis, pathophysiology and treatment of angina pectoris, representing an invaluable resource not only for cardiologists, but also for general practitioners and medical students.

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