

CHRONIC THERAPEUTICALLY REFRACTORY ANGINA PECTORIS

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In contrast to the tremendous increase in practical opportunities and theoretical knowledge in the western world, resulting in a doubling of our average life expectancy, the number of diseases has not been reduced during the last 150 years. This apparent contradiction, secondary to changes in environmental influences and sociocultural developments such as smoking habits, sedentary lifestyles, fast food meals, stressful jobs, etc, have led to the introduction of newer definitions for illnesses. From this perspective, the illness pattern has changed during the last century and a half from infectious diseases to more culturally influenced diseases, such as coronary artery disease (CAD). However, to date, following thorough research, no evidence is available that these cultural influences are the sole initiators in the process of atherosclerotic plaque formation. Albeit that plaque formation is the result of a variety of processes culminating in CAD, the search for the initial trigger is ongoing. During the last few years, more and more evidence has become available that an inflammatory response plays a key role in atherosclerotic plaque formation leading to CAD.

These mediators of inflammation interact with nervous signalling transduction pathways arising from the environment of the atherosclerotic plaque. The inflammatory substances released during myocardial ischaemia are relevant to progression of the atherosclerotic process in the narrowed coronary arteries. In contrast, the recruited nervous and neurohumoral pathways during cardiac ischaemic challenges are thought to be involved in maintaining the integrity of the myocytes.

Subsequently, myocardial ischaemia, angina pectoris signalling pathways, and neurohumoral and inflammatory responses are considered to be key players in atherosclerotic heart disease.

This article discusses newer insights into the pathophysiology of chronic (refractory) angina pectoris, resulting from stable atherosclerotic CAD, and suggests some potential additional treatments.

ATHEROSCLEROSIS, ANGINA PECTORIS, AND MYOCARDIAL ISCHAEMIA

Atherosclerosis

During the initial phase in the atherosclerotic process, the vascular wall thickens in conjunction with luminal dilatation (that is, vascular remodelling). Though in stable situations many (risk) factors determine the velocity of progression to plaque formation, before a critical stenosis in a coronary artery is formed an occlusion may already occur, resulting from an unstable plaque. Given the gradual reduction in luminal diameter of a coronary artery caused by atherosclerotic plaque formation, the increased oxygen demand of the heart during exercise ultimately results in a perturbation of the balance between myocardial oxygen consumption (O_2 demand) and coronary blood flow (O_2 supply), the so-called ischaemic threshold.¹ Subsequently, during a physical work out, the ischaemic threshold is determined at the moment coronary flow and myocardial oxygen consumption become disproportional. Pharmacological treatments and revascularisation procedures are meant to improve this ischaemic threshold, by reducing the myocardial oxygen demand, or by improving the oxygen supply to the myocardium.

Recruited pathways following myocardial ischaemia

Before the disturbance in oxygen supply and demand balance occurs in the heart, in stable circumstances and predominantly during physical exercise, sensitisation of high threshold nerve endings in the myocardium takes place through a variety of metabolic substances such as potassium, lactate, adenosine, bradykinin, and prostaglandins.² These substances induce various kinds of sensations such as fatigue, muscle pain, and shortness of breath. The cardiorespiratory threshold that limits exercise is determined by metabolic excitation–contraction (Na^+K^+) alterations inducing muscle tension, sensation of weakness or fatigue, and finally the responsiveness of motor neurone commands.³ The responsiveness of motor neurones, depending on impulses relayed by the spinothalamic tract to medullar neurones of the cardiorespiratory centres, is influenced by central (that is, reflexes in the spinal cord) and peripheral factors (that is,

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receptors in the muscles). Furthermore, exercise in cardiovascular compromised patients initiates stimulation of the β sympathetic nervous system, resulting in partial counteraction of the limited exercise by an increased heart rate and ventilation frequency. However, the adaptive effect to ischaemic challenges in humans appears to be coordinated by α adrenergic receptors.⁴ It has been reported that a specific G_i protein, connected to the α_2 receptors, induces atherosclerotic related impairment of endothelium dependent relaxation. Furthermore, α receptors, localised on primary afferents, sympathetic postganglionic neurones, and dorsal laminae of the spinal cord and of the brainstem are involved in analgesia and play a role in vasomotor control. In brief, the role of α adrenergic receptors in myocardial ischaemia, by controlling vasomotor tone, is well established.

The role of the vagus nerve in processing noxious cardiac information remains controversial. While both vagal and sympathetic afferent fibres contribute to the increased activity of spinothalamic tract cells and spinal neurons in the C1–C3 segments of the spinal cord, vagal stimulation is a more potent stimulus. Activation of vagal afferent fibres can modulate the processing of information of the thoracic spinothalamic tract cells receiving afferent input from the heart, by activating supraspinal pathways and nuclei. Contrary to the idea that activation of vagal afferent fibres may lead to visceral pain, except in the neck and jaw regions, the vagal afferents may serve as an important rapid signalling pathway for communicating the immune changes from the periphery to the areas in the brain that respond to infection and inflammation. Infection and inflammation elicit the production of vasoactive and neurohumoral compounds.

Depending on the integrity of the vagal afferent pathway, the release of inflammatory cytokines like interleukin (IL)-1, IL-6, IL-1 β , and tumour necrosis factor α , trigger several systemic responses. This reaction induces alterations in pain sensitivity and metabolism, hyperthermia, and increased release of adrenocorticotropin, glucocorticoids, and liver acute phase proteins. Furthermore, vagal afferent stimulation activates the hypothalamus–pituitary–adrenal axis. Finally, the activation of this vagal pathway to supraspinal structures, such as the hypothalamus and the amygdala, may activate descending antinociceptive pathways that may provide projections of a visceral organ against local inflammatory reactions.

Based on this information, it is possible that vagal activation resulting from the release of cytokines might produce the inhibition of spinothalamic tract cells and spinal neurones in the thoracic segments. In summary, the vagal afferent pathway to supraspinal structures might be important for eliciting the immune responses resulting from systemic infections and inflammation, and might not be the pathway that contributes to the perception of angina pectoris.

Angina pectoris

The clinical manifestations of angina pectoris are typically provoked through exercise and abate during rest. Usually the patient suffering from effort angina can predict the amount of physical exercise that causes his or her angina. At maximal exercise the faltering blood flow through the diseased coronaries implies a fixed narrowing (stenosis) in the coronary arteries. At rest, the anginal threshold is influenced by, among other factors, emotional stress, exposure to cold

weather, superfluous meals, and smoking. These aspects suggest a dynamic stenosis in a coronary artery. As a consequence, the variability of the anginal threshold is determined by the interplay between the fixed and the variable obstruction in the coronary arteries. Angina pectoris is not a very specific indicator for occlusive coronary disease, since it is a relatively late, inconsistent, and non-specific phenomenon. In contrast, in the sequence of events resulting from myocardial ischaemia, angina pectoris is a sensitive parameter. Myocardial ischaemia may occur in the presence of at least 60% narrowing of the diameter of a coronary artery, while anginal complaints may begin when the stenosis is already more than 75%. Only 75 years ago the momentary angina “pain” was linked to myocardial ischaemia.⁵ To date, from anatomical, pathophysiological, and neurocardiological viewpoints, angina pectoris is considered to be the symptomatic result of ischaemic atherosclerotic coronary artery disease, associated with an impaired residual coronary blood flow (reserve). In a patient suffering from exercise induced angina pectoris this ischaemic threshold is determined by systolic blood pressure, heart rate, and contraction force.⁶

During exercise, patients with advanced CAD often experience a crushing, constrictive, suffocating discomfort, usually in the upper substernal area, sometimes radiating to adjacent areas (predominately the left side), such as arms, neck, throat, jaw, and teeth. The provoked visceral nociception is characterised by its vaguely distributed, “emotionally” charged aspects, and the influence of emotions on the experience of the anginal pain. The “vaguely” localised and “loaded” nociceptive information of the elicited angina pectoris is conveyed by visceral afferent nerve fibres, following sensitisation of cardiac (C and A delta) nerve endings.⁷ Sensitisation of multireceptive nerve endings is believed to be effected through substances such as adenosine and prostaglandins. The latter sensitise cardiac sympathetic afferents for bradykinin. Other vasoactive and neurohumoral substances involved in ischaemic pain are endorphins, vascular intestinal protein, γ amino butyric acid, neuropeptide Y, and serotonin.⁸ Transmitters are released by pressure (stretch), infection (irritation), nervous and chemical stimuli, and (myocardial) ischaemia.

After induction of the stimulus, a neuro-hierarchic complex of gating at multiple levels, overlapping receptive fields, and ascending and descending nervous pathways modulate the propagation of information to the cortex and hence determines the ultimate nociception. The involvement in the perception of angina pectoris of the limbic system and predominantly the (hypo)thalamic area has recently been demonstrated, making use of positron emission tomography.⁹ In this perspective it is illustrative that mental stress and physical exercise induced myocardial ischaemia produces the same alterations in higher brain centres. Moreover, the hierarchical organisation of the nervous system enables it to settle with compromised balances and so restore the integrity of cardiomyocyte function. Consequently, the afferent and efferent cardiac nervous system may be considered as a hierarchical nervous loop from which one limb is interacting with the other. In addition to this neural feedback pathway, a (neuro)humoral circuit is suggested. In response to stress, the efferent humoral pathway induces the release of glucocorticoids, noradrenaline (norepinephrine), and adrenaline (epinephrine). The humoral afferent limb has only recently been

Criteria for chronic refractory angina pectoris

- ▶ Debilitating angina pectoris
- ▶ Inadequately controlled by medication
- ▶ Results from significant coronary artery disease
- ▶ Paralleled by reversible myocardial ischaemia
- ▶ No options for revascularisation

postulated and links the ischaemic heart to cognitive brain centres via cytokines (fig 1).¹⁰

CHARACTERISTICS OF PATIENTS WITH (CHRONIC REFRACTORY) ANGINA PECTORIS

Patients with chronic refractory angina lead severely restricted lives and perform only limited activities.

Moreover, the psychological stress caused by awareness of the increased risk of a myocardial infarction often places an additional burden on the patient and his or her family. These patients are usually characterised by a long history of coronary artery disease. During this part of their life, patients have therefore often experienced numerous hospital admissions, caused by an acute worsening of their coronary artery disease expressed as either a period of unstable angina or a myocardial infarction.

Treatments that reduce these patients' angina not only improve their quality of life but will also ameliorate their psychosocial status. In addition to antianginal medication, they have often been treated with one or more percutaneous transluminal coronary angioplasty (PTCA) procedures or coronary artery bypass graft surgery (CABG). Most patients

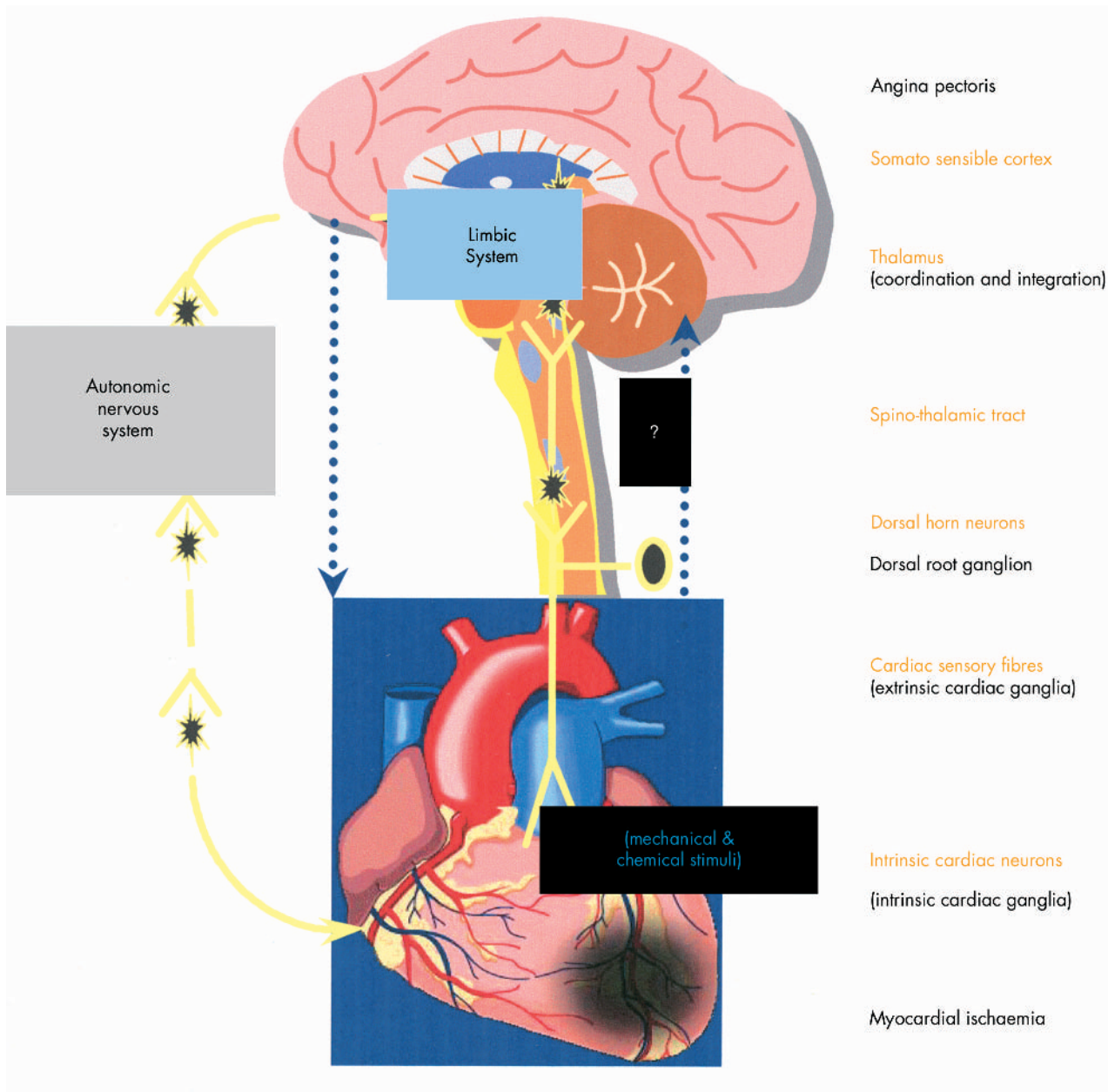


Figure 1 Schematic drawing of afferent and efferent nervous (solid lines) and efferent and suggested (question mark) afferent neurohumoral (dotted lines) pathways. Heart: mechanical and chemical polymodal receptors. Spino-thalamic tracts: gating and modulation. Thalamus: gating, coordination, and integration. Cerebral cortex: psychological influence.

suffering from chronic refractory angina pectoris are relatively young, predominantly male, with a moderately hampered left ventricular ejection fraction and elevated fibrinogen values^{11 12} (table 1). The increased fibrinogen is most likely to be an epiphenomenon, related to chronic inflammation induced by coronary artery disease.

However, an increasing number of patients, surviving various ischaemic events, are suffering from chronic angina pectoris, most likely as a result of sensitisation (that is, a reduced pain threshold), refractory to conventional strategies. The prevalence is estimated to be 100 000 patients in the USA, with an equal number in Europe.¹³ Their angina is considered to be refractory when, despite optimal antianginal pharmacological treatment and the presence of persistent reversible myocardial ischaemia, revascularisation is no longer feasible. Patients suffering from angina pectoris, resistant to conventional treatments, may be considered as survivors of their coronary artery disease. Since they are invalidated by their anginal pain, without conventional treatment options the patients have unmet medical needs. Subsequently, any additional treatment that relieves their complaints without adversely affecting their chronic disease is worth taking into consideration. The argument for focusing attention on improving these patients' quality of life is particular valid with respect to the prognosis of those who survive with end stage heart disease for a long period of time, as expressed in the low annual cardiac mortality of about 5%.¹¹

TREATMENT FOR ANGINA

In addition to improvement in lifestyle, the conventional way to improve myocardial ischaemia is by either reducing the oxygen demand (β blockers, calcium channel blockers) or by improving the supply (nitrates, revascularisation procedures such as PTCA or CABG). Additive measures, such as lipid lowering, inhibition of platelet aggregation, and interference in the renin-angiotensin system have become established treatments for stable angina pectoris. In the vast majority of patients these strategies are sufficient to control the symptoms.

Adjunctive treatments for chronic refractory angina pectoris

If conventional treatments fail to control the patient's condition, many adjunctive therapies are available. In

general, four types of additional treatment can be offered to patients with therapeutically refractory angina (fig 2).

First, the *application of additional medication*, administered either systemically such as cordarone, chelation, opioids, and (intermittent) urokinase, or locally, such as intrathecally applied anaesthetics or opioids. In general, the use of adjunctive medication for long term treatment is withheld because of its drawbacks (opioids), because it is only suitable for short term application (intrathecally applied anaesthetics), it is costly (urokinase), or it has not proven to be effective for this indication (chelation, cordarone). Medications targeting inflammation and thrombosis are considered to be more potent options in the near future.

Second, *treatments aimed at improving myocardial perfusion*, by means of a rehabilitation programme or by affecting the haemodynamic system. The trade-off of the beneficial effects of cardiac rehabilitation programmes on cardiac performance is the need for continuation of the programme.¹⁴ Angina pectoris may also be treated by enhanced external counterpulsation. This method is directed at diastolic augmentation of blood flow in the coronary arteries through an increase in aortic retrograde blood flow, induced by compression of cuffs that are wrapped around the legs. Recently, enhanced external counterpulsation has been reported to be effective in improving myocardial perfusion during stress in patients with chronic stable angina.¹⁵ However, experience is limited and the equipment costly.

Third, *modulation of the nervous system*. The nervous system can be modulated through spinal cord stimulation or transcutaneous electrical nerve stimulation. Neuro-modulation appears to be one of the most successful adjunctive treatments. It is a reversible therapy and has been reported to be effective, without concealing angina pectoris during an acute myocardial infarction. The beneficial effects of neuromodulation, expressed in a reduction in the number and severity of anginal attacks in conjunction with an improvement in exercise capacity and quality of life, have been reported to last for several years. Evidence that spinal cord stimulation exerts an additional anti-ischaemic effect is provided by studies on exercise testing, ambulatory ECG monitoring, positron emission tomography, and coronary flow measurements. The explanation for the reduction in

Table 1 Characteristics of patients (n = 517) suffering from chronic refractory angina pectoris. Modified from TenVaarwerk *et al.*¹¹

Sex	71% male
Age (years)	63.9 (10.1)
Clinical presentation	
Duration of angina pectoris (years)	8.1 (6.3)
NYHA class (mean)	3.5 (0.7)
LVEF \leq 40%	24%
Previous myocardial infarction	66%
Three vessel disease	68%
PTCA	17%
CABG	58%
Risk factors	
Family CAD	61%
Hypertension	39%
Hypercholesterolaemia	28%
Smoking	21%
IDDM	14%

CAD, coronary artery disease; CABG, coronary artery bypass graft surgery; IDDM, insulin dependent diabetes mellitus; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PTCA, percutaneous transluminal coronary angioplasty.

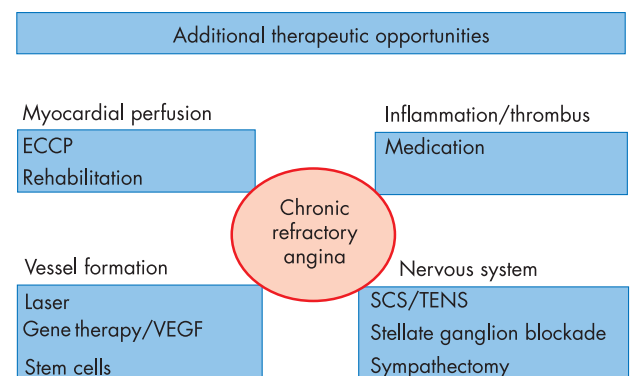


Figure 2 Schematic representation of additional therapeutic options for patients with chronic refractory angina pectoris. ECCP, enhanced external counterpulsation; SCS, spinal cord stimulation; TENS, transcutaneous electrical nerve stimulation; VEGF, vascular endothelial growth factor.

myocardial ischaemia may be a homogenisation of the myocardial perfusion.¹⁶ Furthermore, there is evidence that electrical stimulation of the dorsal aspect of the spinal cord stabilises the intrinsic cardiac nervous system and may therefore prevent deleterious consequences, such as electrical instability of the ventricles.¹⁷ Finally, research performed by Kanno and colleagues in 1999 may shed new insights into the influence of electrical stimulation on the concentration of vascular endothelial growth factor (VEGF). From his investigations on low intensity (10% of contraction threshold) electrical stimulation in ischaemic hind paw muscles of rabbits and in muscle cells *in vitro* it may be concluded that VEGF mRNA concentration after stimulation is increased significantly. Denervation of the heart by endoscopic trans-thoracic sympathectomy has also been reported in a very limited number of publications over the last decade. The drawback of these destructive experimental treatments is a relatively high mortality and morbidity, ranging from 5–10%.¹⁸ Arbitrarily, these latter adjunctive treatments could also be classified into the next category.

Fourth, *treatments aimed at vessel formation* through up-regulation of vascular endothelial growth factors inducing angiogenesis, making use of stem cells, or applying either transmyocardial (TMR) or percutaneous laser (PMR). Restoration of function by means of angiogenesis is a stepwise experimental procedure, best studied by making use of gene therapy. Gene therapy can be applied by direct intramyocardial injection of naked DNA encoding for VEGF, a heparin binding glycoprotein, as well as adenoviral transfection with VEGF. Regulation of VEGF mainly takes place via oxygenation of tissues. Ischaemia enhances both the expression and production of VEGF. Furthermore, since an increased concentration of VEGF mRNA has been demonstrated in ischaemic tissues, this suggests a negative feedback system. When oxygen concentration in the tissues increases, VEGF gets down regulated. At the onset of the angiogenesis process, endothelial cells produce metalloproteinases to digest the basement membrane. Next, the endothelial cells may disconnect from the basement membrane, and are able to migrate, proliferate, and form a network of “endothelial tubes”. To become functionally important the vessels then need to mature. During the following arteriogenesis, nascent vessels become extensively covered by a muscular coat creating blood vessels with viscoelastic and vasomotor properties.¹⁹ Studies on gene therapy have demonstrated a remarkable improvement in flow to ischaemic areas in peripheral arteries as well as in the heart.²⁰ Although the clinical results are encouraging, there is a need for further validation in placebo controlled trials. With

respect to angiogenesis most concerns relate to the vehicle, usually a genetically manipulated virus, delivering the growth factor. Though the long term effects of these genetic therapies are not yet known, the vehicle issue should be of minor concern in the case of plasmid based delivery. In conclusion, gene therapy induced new blood vessel formation, making use of angiogenetic growth factors, is a recent and promising development.

TMR and PMR are meant to improve the flow through the myocardium by channelling with laser beams. Mirhoseini was the first to advocate direct laser therapy of the myocardium as a treatment for refractory angina pectoris, in 1981. The idea initially was to create transmural channels from the left ventricular cavity into the myocardial muscle to improve myocardial perfusion. Although some animal studies have suggested patency of lasered channels, most recent studies and necropsy reports showed occlusion of the lasered channels within one day, making neo-“revascularisation” as a mechanism of action unlikely. Also denervation of the heart or laser induced angiogenesis with subsequent collateralisation causing improvement of perfusion is not proven. Initially the myocardium was lasered from the epicardial side during heart surgery, both as an adjunct to bypass surgery and as a stand alone procedure. Early studies showed a high post-operative mortality. Randomised controlled studies comparing laser therapy with medical treatment reported inconsistent findings. The majority showed a reduction of anginal complaints, some an improvement in exercise capacity, and only one study demonstrated an improved perfusion. Developments in catheter based technology made it possible to deliver the laser energy from the endocardial side. Preliminary data show that efficacy is in the same range as surgical based laser therapy. However, in view of the unknown underlying mechanism of action, to date laser therapy is not recommended for this subset of patients. Finally, heart transplantation is not considered a feasible treatment for this group of patients.

Some of the discussed adjuvant treatments have class 2A or class 2B indications, according to the recent American Heart Association/American College of Cardiology guidelines.²¹

CONCLUSIONS

The numbers of patients suffering from angina pectoris chronically resistant to conventional treatments are increasing. Patients with chronic refractory angina differ from the ordinary angina patient in three ways: first, patients with chronic refractory angina pectoris maintain their left ventricular function despite severe three vessel disease; second, they do not experience severe arrhythmias and therefore their mortality is only about 5%; and third, their angina is debilitating. New and often promising treatments for this condition are worth taking into consideration.

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Ten characteristics of patients with chronic refractory angina pectoris

- ▶ < 70 years old
- ▶ Predominantly male
- ▶ Long term (± 10 years) coronary artery disease
- ▶ Three vessel disease
- ▶ Previous myocardial infarction(s)
- ▶ Previous revascularisation procedure(s)
- ▶ Maintenance of left ventricular function
- ▶ No serious arrhythmias
- ▶ Annual cardiac mortality $\sim 5\%$
- ▶ Raised fibrinogen values

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