Acute Ischemic Heart Disease

Refractory angina pectoris in end-stage coronary artery disease: Evolving therapeutic concepts

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Refractory angina pectoris in coronary artery disease is defined as the persistence of severe anginal symptoms despite maximal conventional antianginal combination therapy. Further, the option to use an invasive revascularization procedure such as percutaneous coronary balloon angioplasty or aortocoronary bypass grafting must be excluded on the basis of a recent coronary angiogram. This coronary syndrome, which represents end-stage coronary artery disease, is characterized by severe coronary insufficiency but only moderately impaired left ventricular function. Almost all patients demonstrated severe coronary triple-vessel disease with diffuse coronary atherosclerosis, had had one or more myocardial infarctions, and had undergone aortocoronary bypass grafting (70% of cases). We present three new approaches with antiischemic properties: long-term intermittent urokinase therapy, transcutaneous and spinal cord electrical nerve stimulation, and transmyocardial laser revascularization. (Am Heart J 1997;134:587-602.)

Therapeutic options for the management of angina pectoris in coronary artery disease have increased and improved impressively over the past 25 years. Scientific knowledge on the pathophysiologic characteristics of the underlying causes and mechanisms of myocardial ischemia has led to rational and well-documented therapeutic approaches. In addition to the three mainstays of medical treatment (nitrates, β-blockers, and calcium antagonists), two direct revascularization procedures have been introduced and are now well established: coronary artery bypass grafting (CABG)[1-3] and percutaneous transluminal coronary angioplasty (PTCA).[4]

Despite these advances, the practicing clinician increasingly sees patients who have refractory angina pectoris and end-stage coronary artery disease. These patients have highly symptomatic coronary artery disease, which leads to a severe impairment in the quality of life. Recurring symptoms at rest that suggest preinfarction angina result in numerous admissions to the hospital, where myocardial infarction is generally ruled out and clinical symptoms must be stabilized with intravenous drug therapy. The number of such patients will increase in the future because the long-term prognosis for patients with coronary artery disease continues to improve. These patients will live longer because of advances in secondary prevention (e.g., the introduction of β-blockers, platelet aggregation inhibitors, angiotensin-converting enzyme inhibitors, and lipid-lowering agents) and improvements in invasive revascularization procedures (PTCA, CABG).

The following review is based on actual scientific and clinical experiences from three independent study groups. We offer an updated definition of chronic refractory angina pectoris in end-stage coronary artery disease, including the clinical characteristics of this patient group as documented at our institutions (Clinic of Cardiology at the Heinrich-Heine University, Dusseldorf, Germany; the Department of Cardiology at the University Hospital, Groningen, The Netherlands; and the Texas Heart Institute, Houston, Texas). In addition, we present several evolving therapeutic approaches, namely long-term intermittent urokinase therapy, spinal cord stimulation, and transmyocardial laser revascularization, which have antiischemic prop-

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Supported in part by a federal grant from the German Scientific Society, special branch 242: "Coronary Artery Disease –Prevention and Therapy of Acute Complications."
Received for publication Sept. 13, 1996; accepted April 24, 1997.
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0002-8703/97/$5.00 + 0 **4/1/82871**

Table I. Classification of angina pectoris according to the criteria of the Canadian Cardiovascular Society

I. "Ordinary physical activity does not cause...angina," such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
II. "Slight limitation or ordinary activity." Walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals or in cold, in wind, or under emotional stress; or pain only during the few hours after awakening. Walking more than two level blocks and climbing more than one flight of ordinary stairs at a normal pace and under normal conditions.
III. "Marked limitation of ordinary physical activity." Walking one to two level blocks and climbing one flight of stairs under normal conditions and at a normal pace.
IV. "Inability to carry on any physial activity without discomfort—anginal syndrome may be present at rest."

From Campeau L. Grading of angina pectoris. Circulation 1997;54:522-3. Reproduced with permission from the American Heart Association.

Table II. Clinical characteristics of patients with refractory angina pectoris in end-stage coronary artery disease

	Leschke et al.[22] (*n* = 98)	Jessurun et al.[147] (*n* = 57)	Frazier et al.[21] (*n* = 21)
Age (yr)	61.9 ± 9.0	59.8 ± 7.6	62.6 ± 9.7
Male (%)	91	68	86
Patient history			
Previous myocardial infarction (%)	89	81	71
Previous CABG (%)	70	91	90
Time since CABG (months)	78 ± 43		82 ± 54
Angina CCS grade III (%)	37		24
Angina CCS grade IV (%)	63		76
Frequency of angina pectoris (events/week)	23.4 ± 11.6		
Intake of fast release nitrates (no./week)	13.9 ± 9.6		
Medication			
Nitrates (%)	100	92	71
β-Blocker (%)	69	81	57
Calcium antagonists (%)	98	94	67
Double combination therapy (%)	33	30	67
Triple combination (%)	67	68	29
Laboratory parameters			
Fibrinogen (mg/dl)	364 ± 67		
Plasma viscosity (mPa × s^{-1})	1.39 ± 0.07		
Red blood cell aggregation (U)	14.7 ± 2.9		
Data from invasive procedures			
Coronary triple-vessel disease (%)	99		95
Coronary double-vessel disease (%)	1		0
Coronary single-vessel disease (%)	0		5
No. of bypass vessels	3.3 ± 1.0		3.7 ± 1.3
No. of bypass vessels occluded	1.7 ± 1.2		3.2 ± 1.3
Left ventricular ejection fraction at rest (%)	47 ± 17	52 ± 13.8	47 ± 9
Left ventricular end-diastolic pressure (mm Hg)	18 ± 7		

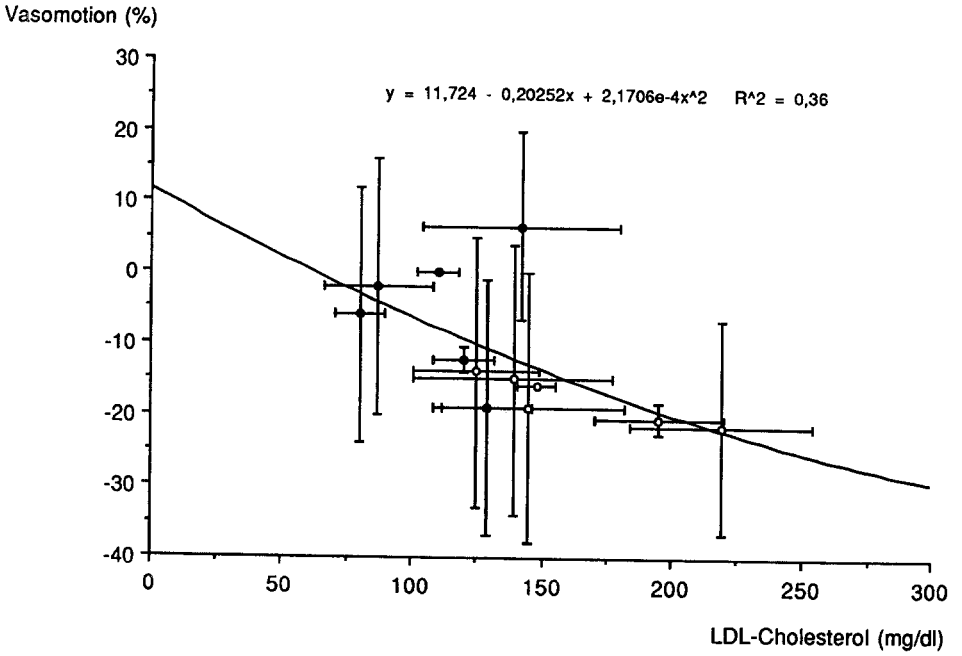
CCS, Canadian Cardiovascular Society.

erties beyond maximal medical treatment. It is not the purpose of this review to cover all new therapeutic options currently under investigation or to provide definite answers, but rather to point out perspectives for future developments in the treatment of this highly symptomatic patient group as viewed by clinical scientists who have had in-depth experience with these patients and with the treatment modalities presented.

Definition of refractory angina petoris and patient selection

Refractory angina pectoris in end-stage coronary artery disease is defined as persistence of angina pectoris class III and IV (Table I)[5] despite maximally tolerated conventional medical treatment (nitrates, β-blockers, calcium antagonists). To avoid withholding an established form of therapy, an experienced

Figure 1



Results from four different intervention trials on interrelation between LDL cholesterol levels and pathologic maximal coronary vasomotion (+, Vasorelaxation; –, vasoconstriction) after intracoronary administration of acetylcholine. *Open circles* denote results before intervention with diet, lipid-lowering medication, or both; *closed circles* depict results 6 to 12 months after initiation of therapy. (Data derived from references 13 through 16.)

team of cardiologists and cardiac surgeons must rule out conventional invasive revascularization procedures (CABG or PTCA) on the basis of a recent coronary angiogram.

Although most patients receive antianginal triple combination therapy (Table II), such therapy is not a necessary condition for the diagnosis of refractory angina pectoris: a considerable number of patients may only tolerate two drugs because of undesirable side effects (e.g., hypotension, symptomatic bradycardia, and subjective discomfort).[6] Nevertheless, a rigorous approach toward optimization of conventional antianginal therapy should be made based on current knowledge.[7] This is underlined by results from a recent study in which 44% of 117 patients initially referred for transmyocardial laser revascularization could be improved to angina class I or II with conventional medical therapy, whereas a further 18% could be successfully treated with interventional procedures (PTCA or CABG), even though this had been rejected by other centers.[8]

Furthermore, given the limited therapeutic perspectives for patients with refractory angina pectoris, potentially supportive measures should also be considered. These include modified medical treatment of secondary causes of myocardial ischemia, in particular episodes of arterial hypertension or hypotension such as increased myocardial demand or decreased coronary driving pressure, as evidenced by 24-hour blood pressure monitoring. In some cases further preload reduction, and hence decreased wall stress (e.g., with diuretics or high-dose molsidomine), may yield an additional benefit regardless of the state of left ventricular systolic function.[8,9]

Supportive measures should also include rigorous reduction of LDL cholesterol down to levels <110 mg/dl. This intervention, at least in the general population of patients with coronary artery disease, leads to a decrease in the rate of acute coronary events[10] and has antiischemic properties as documented by ST-Holter analysis during regular daily activities.[11,12] The antiischemic effect of LDL cholesterol reduction is probably mainly attributed to an improvement of endothelial dysfunction at the level of the epicardal conductance vessels (Fig. 1).[13-16]

This improvement decreases the often underrated dynamic component of arterial stenoses in the development of myocardial ischemia, for example intermittent vasoconstriction,[17] a phenomenon that occurs in at least 30% of the cases of patients with stable angina pectoris.[18] It is tempting to assume that LDL cholesterol reduction may also have antianginal properties. It remains to be seen whether it actually diminishes clinical symptoms, but results from uncontrolled secondary prevention trials with LDL apheresis in patients with familial hypercholesterolemia are promising.[19]

In particular, when alternative treatment modalities that may be costly and potentially harmful to the patient are considered, verification of myocardial ischemia is a crucial factor in proper patient selection. This allows only patients who may actually benefit from antiischemic measures to be treated and enables the therapeutic effect of the intervention to be objectively assessed. Nevertheless, because almost all patients with refractory angina pectoris have global and diffuse coronary insufficiency and have a low exercise capacity, detection of myocardial ischemia may be hard to achieve with conventional measures (ST-segment monitoring during exercise testing, thallium and technetium-sestamibi scan imaging). New techniques such as perfusion imaging with positron emission tomography, which also allows for reliable assessment of redistribution phenomena of blood flow,[20,21] or sensitive methods that measure the impact of myocardial ischemia on left ventricular diastolic and systolic function, including regional wall motion analysis of ischemic myocardium (Doppler echocardiography, radionuclide ventriculography, stress echocardiography), probably yield more reliable data.

Almost all patients with refractory angina pectoris have coronary triple-vessel disease, and approximately 70% have undergone coronary artery bypass grafting. Approximately 50% of implanted bypass vessels are occluded. In contrast to severe coronary insufficiency, a relatively large amount of viable myocardium is preserved as reflected by an only slightly to moderately impaired left ventricular systolic function at rest in most patients (Table II). Therefore heart transplantation is rarely a therapeutic option for this patient group. A major reason to refrain from conventional revascularization procedures is a coronary anatomy unsuitable for mechanical interventions. Diffuse coronary atherosclerosis, for example, extends to the periphery of the epicardial conductance vessels. Further criteria for exclusion include repeated, unsuccessful interventions on the culprit lesion, lack of graft material, and, in some cases, a high periinterventional risk because of severe left ventricular dysfunction.

One study group showed that a considerable number of patients with refractory angina pectoris seems to be characterized by disturbances of blood rheology (Table II),[22] including high elevations of fibrinogen concentrations and subsequent elevations of plasma viscosity and red blood cell aggregation. Pathologic elevations of fibrinogen are associated with an increased risk of future coronary events in the general population[23] and were higher in patients with refractory angina when compared with values in subjects who have no angiographic evidence of atherosclerotic disease and in patients who had coronary artery disease and nonrefractory angina pectoris.[24] This implies that improvement of rheologic blood properties may be of therapeutic benefit at least in a subset patients with refractory angina pectoris.

Currently, no valid data exist on the prevalence and prognosis of patients with refractory angina pectoris. Nevertheless, despite good left ventricular function, the life expectancy of these patients is likely to be more limited compared with patients with nonrefractory angina pectoris because of marked myocardial ischemia and accompanying severe clinical symptoms.[25,26] This assumption is confirmed by data from the yet unpublished phase III trial, which compared transmyocardial laser revascularization with medical treatment. It demonstrated a high annual mortality rate of 11% in the medical group during the first year after diagnosis when patients were excluded who were switched to transmyocardial laser revascularization later on as part of the intent-to-treat design of the study (PLC Medical Systems, Franklin, Mass.).

New therapeutic approaches in refractory angina pectoris

Alternative approaches in patients who have refractory angina pectoris and end-stage coronary artery disease should decrease anginal symptoms and increase functional capacity and thereby should result in an improved quality of life. Furthermore, an increased life expectancy in these patients is desirable. An analgesic approach is contraindicated because it may mask clinical warning signs of life-threatening myocardial ischemia.

Long-term intermittent urokinase therapy

Long-term intermittent urokinase therapy is clinically effective in a dose of 500,000 IU given as an intra-

venous bolus injection of 500,000 IU three times a week over a period of 12 weeks.27,28 Treatment is usually begun in the hospital with target fibrinogen concentrations of 200 to 250 mg/dl and is continued as an outpatient regimen. Clinical symptoms, fibrinogen concentrations, and activated partial thromboplastin time are assessed every 2 weeks. The clinical effectiveness of long-term intermittent urokinase therapy is probably based on three mechanisms: improvement in rheologic blood properties, thrombolysis, and possibly regression of coronary plaques.

Reduction of fibrinogen concentrations leads to an improvement in rheologic blood properties and subsequent increases in blood fluidity. Blood viscosity is mainly determined by plasma viscosity, red blood cell aggregation, red blood cell deformability, and hematocrit levels. In nonobstructed coronary arteries, the flow-limiting resistance caused by blood viscosity can be neglected.[29-31] However, in the poststenotic microcirculation of severe and successive multiple stenoses, occluded vessels, and collateral vessels,[32] blood viscosity (especially plasma viscosity and red blood cell aggregation) may limit flow and is therefore critical for oxygen delivery to the ischemic myocardium.[33] At the extremely low shear rates and almost zero flow in this area,[34] macromolecules, particularly fibrinogen, increase red blood cell aggregation and plasma viscosity, which in turn lead to an exponential increase in blood viscosity.[29,30,35]

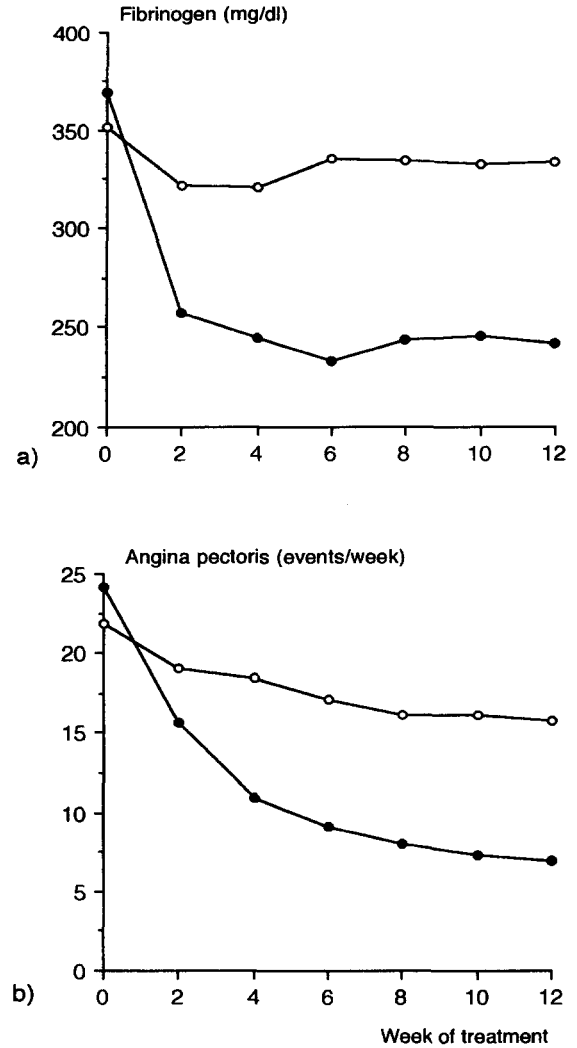
Apart from the acute coronary syndromes, plaque fissures or thrombi have been demonstrated in 22% of the patients with coronary artery disease who were clinically stable and died from noncardiac causes.[36] This figure has recently been confirmed by angioscopic studies in patients with stable coronary artery disease who underwent elective PTCA and who demonstrated coronary thrombus at the site of the target lesion in 11% to 19% of the cases before intervention.[37-39] Thrombi therefore may be of flow-limiting relevance in the epicardial conductance vessels[40] and the coronary microcirculation.[41,42] In patients who have refractory angina pectoris multiple, severe, and often successive coronary stenoses lead to regions of poststenotic nonlaminar flow and relative stasis of blood flow. With the reduction in blood fluidity resulting from increases in plasma viscosity and red blood cell aggregation, the fluid dynamic aspects of coronary stenoses favor intracoronary thrombus formation.[43] Furthermore, on the basis of pathogenetic considerations and evidence from epidemiologic trials, an increase in the fibrinogen concentration must be regarded as a promotor of intracoronary thrombus formation.[44-46]

These aspects of thrombogenic (and therefore dynamic) impairment of blood flow stress that the thrombolytic efficacy of long-term intermittent urokinase therapy may be a major factor in improving myocardial perfusion. Different therapeutic regimens of low-dose urokinase have demonstrated thrombolytic potential.[27,47,48] Furthermore, two recent studies on the antiischemic efficacy of low molecular weight heparin[49,50] support antithrombotic therapy for the improvement of myocardial perfusion in clinically stable (although not refractory) patients. Besides the induction of collateral angiogenesis and functional improvement of collaterals,[50-53] the antithrombotic efficacy of low molecular weight heparin may be relevant.[44,49]

Fibrinogen and fibrin are major constituents of atherosclerotic plaques,[54-56] and high levels of fibrinogen are positively correlated with the extent of atheroma in the coronary and carotid arteries.[57,58] This correlation is likely the result of repetitive plaque fissuring and the subsequent formation of coronary thrombus, that, because of incomplete endogenous lysis, becomes incorporated into the plaque. As a result a rapid, nonlinear morphologic plaque progression occurs.[40] In addition, high fibrinogen plasma levels increase the fibrin content of the plaque by direct permeation of fibrinogen.[54] It is therefore probable that long-term thrombolytic therapy may lead to a modification of plaque composition and even morphologic regression, which could be crucial for coronary blood flow in critically stenosed arteries. This effect of thrombolytic therapy on plaque regression may explain the clinical long-term results of a weekly dose of 3 × 500,000 IU urokinase past the duration of the treatment period.[28,59]

Several studies in patients with refractory angina pectoris[27,28] demonstrate a 70% reduction in frequency of angina and an increase in exercise capacity by 20% and an improvement of electrocardiographically and scintigraphically measured myocardial perfusion during ergometric exercise.[22] After 3 months of treatment, urokinase therapy statistically significantly decreases fibrinogen levels by about 35%, plasma viscosity by 7%, red blood cell aggregation by 19%, and plasminogen activity. The improvement of clinical symptoms lasts at least 3 months after the termination of therapy. A randomized dose-response study further validated this therapeutic approach[22]: it compared a rheologically effective weekly dose of 3 × 500,000 IU with a

Figure 2



Time course of fibrinogen *(a)* and clinical symptoms *(b)* during treatment with long-term intermittent urokinase therapy with dosage of 50,000 IU ($n = 43$; *open circles*) or 500,000 IU urokinase per injection ($n = 46$; *closed circles*). Reproduced with permission from the American College of Cardiology (Journal of the American College of Cardiology) 1996;27:575-84.

weekly dosage of 3 × 50,000 IU and found that the therapeutic effects were significantly dose dependent (Fig. 2). In a long-term follow-up of 121 patients who received the larger dose over a 3-month period, the reduction of symptoms (reduction of weekly anginal events >66%) persisted for an average of 12.7 ± 8.5 months after cessation of therapy.[59]

During the 3-month treatment period, therapy was discontinued in 5% of the 121 patients because of gastrointestinal bleeding (0.8%), lack of clinical effectiveness (3.3%), and subjective discomfort (0.8%).[59] This high-risk group had a 12% cardiac mortality rate during and after treatment. During the follow-up period, refractory angina pectoris recurred in 35% of the patients, most of whom were treated with long-term intermittent urokinase therapy. Four patients required high-risk aortocoronary bypass grafting because of severe bypass stenoses and, in one case, left main coronary disease; four patients underwent heart transplantation.

These data suggest that long-term urokinase therapy represents a safe and effective approach for the treatment of refractory angina pectoris, particularly in patients with elevated levels of fibrinogen, in whom marked rheologic improvements can be expected. Further trials will have to confirm these findings and supply data on the possible mechanisms. In particular the aspect of possible plaque regression is intriguing but needs to be substantiated by experimental and clinical data.

Neurostimulation

Two neurophysiologic treatment modalities, transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS), are currently being investigated in the treatment of patients with refractory angina pectoris. Results from these studies are compatible with those from earlier trials,[60,61] which demonstrated that neurostimulation increased microcirculatory blood flow in patients with peripheral arterial occlusive disease. Augustinsson et al.[62] described the efficacy and possible therapeutic mechanisms of neurostimulation in several clinical ischemic conditions. An increase in coronary blood flow results in an improved myocardial oxygen supply, and this effect is mediated by vasodilatation of coronary resistance vessels[63] in patients with either coronary artery disease or microvascular angina pectoris and normal epicardial coronary arteries. There were no concomitant changes in systemic hemodynamics during the vasodilatory effect.

Neurostimulation may affect these changes by either or both of two mechanisms: an indirect and a direct sympatholytic effect. The indirect effect is based on therapeutic analgesia, which may cause a secondary reduction of the adrenergic state. According to Melzack and Wall's "gate control theory,"[64] high-frequency stimulation of large nonnociceptive myelinated type A fibers inhibits the impulse transmission through smaller unmyelinated type C fibers, which subsequently reduces the activation of central pain receptors (Fig.

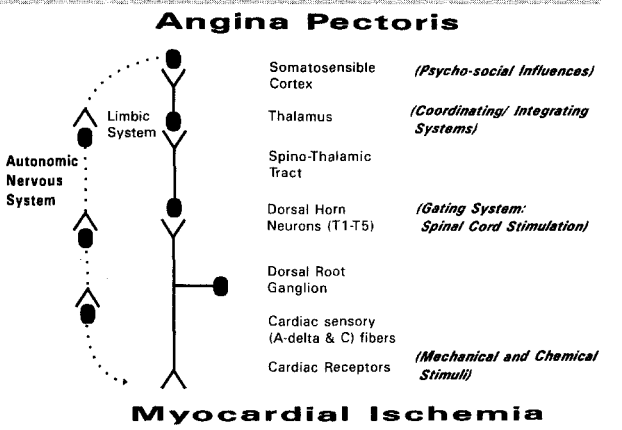
3). Experimental studies[65] demonstrated that the stimulation of the dorsal column may suppress the activity of cells in the tractus spinothalamicus, which leads to an inhibition of transmission at the segmental level.

In the direct sympathicolytic effect, stimulation of the dorsal roots leads to a number of segmental reflexes that induce an inhibition of the tonic sympathetic activity.[66-70] The reduction of sympathetic nerve activity, which is also reflected by a decrease in systemic concentrations of epinephrine,[63,71] causes a reduction of cardiac work load and a reduced myocardial oxygen demand. A reduction in the vasomotor tone of coronary resistance vessels also increases the myocardial oxygen supply. Furthermore, dilatation of coronary resistance vessels may also occur in patients with refractory angina pectoris because the coronary flow reserve is impaired but not completely abolished, regardless of the severity of coronary artery disease.[72]

In TENS treatment, two cutaneous electrodes are applied to the chest wall, one in the dermatome with the highest intensity of projected pain and the other in the contralateral dermatome.[73] The intensity of the stimulation is adjusted just below the individual pain threshold. In long-term therapy, TENS stimulation is given for 1 hour at least three times a day and, during episodes of angina pectoris, for an additional 10 minutes. These stimulation regimen results are similar to those of regimens from other studies.[74,75]

The SCS technique requires the device to be implanted while the patient receives local anesthetic.[75,76] The epidural space is punctured at the level of the fourth or sixth vertebra and a unipolar or bipolar electrode is advanced to the level of the first or second thoracic vertebra. The stimulator is implanted in a subcutaneous pocket in the upper left abdomen. The stimulator can be telemetrically manipulated and is adjusted in the same way as the TENS device. Given that the implantation of the electrode and the device is an invasive and therefore a potentially harmful approach, it is advisable to confirm that patients treated with SCS are fully cooperative and that their chest pain is related to reversible ischemia. Therefore those patients who receive SCS should have angiographically documented coronary artery disease and positive results in objective noninvasive tests for detection of myocardial ischemia. All other candidates should be primarily treated with TENS to omit unsuccessful invasive neurostimulation for a false indication, as in chest pain caused for example by esophageal disorders.

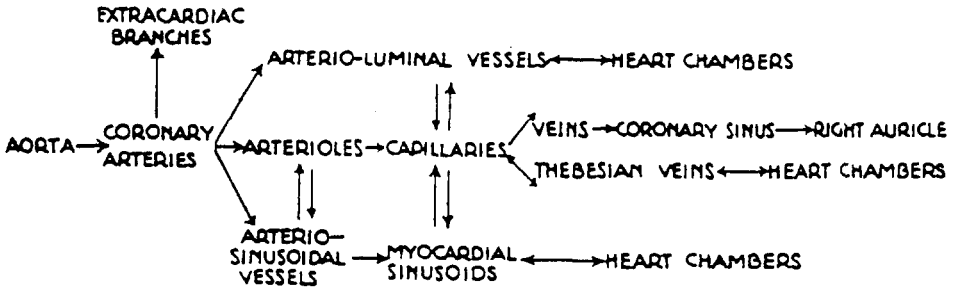
Figure 3



Sensory (afferent) and efferent cardiac neural pathways. Myocardial ischemia can stimulate both chemical and mechanical cardiac receptors. These receptors can elicit impulses in sensory cardiac nerves. These sensory fibers enter dorsal spinal cord at T1-T5 level, where they connect with neurons. According to gate control theory, these impulses can be modulated by descending and other impulses. Spinothalamic tract relays impulses to thalamus and limbic system. Cardiac sensory impulses are further modulated in higher brain centers, for example, by emotions. Limbic system is of paramount importance in modulation of pain perception. Pa5rceived in somatosensible cortex. Through these neuronal mechanisms, at different levels in brain, visceral nociceptive stimuli can induce autonomic reactions such as change in heart rate. Reprinted with permission from the BMJ Publishing Group.

Recent clinical studies confirmed that neurostimulation has an antiischemic effect in patients with end-stage coronary artery disease. During 48-hour ambulatory electrocardiography, both the total ischemic burden and the duration and number of ischemic episodes decreased.[77] Cardiac pacing that increases heart rate stepwise to the anginal threshold or until significant ST-segment depression showed improved coronary blood flow and oxygen delivery without side effects.[71,78,79] Exercise testing demonstrates an increase in exercise duration, time to angina, rate pressure product, and a reduction of ST-segment depression at comparable workloads.[73,79] The first positron emission tomographic study failed to demonstrate an improvement in myocardial blood flow during exercise.[80] In a more recent positron emission tomographic study, however, after 6 weeks of SCS, the ratio of perfusion during dipyridamole stress was significantly greater in ischemic regions than in nonischemic regions. Because there was no change in total

Figure 4



Blood supply of the heart.

perfusion, SCS may induce a rearrangement of flow patterns from the nonischemic to the ischemic regions.[20] During long-term follow-up, the frequency of spontaneous anginal episodes and intake of fast-release nitrates were consistently decreased.[78,79,81]

In clinical practice, TENS does not produce any major complications except local skin irritation.[82] SCS treatment may interfere with certain cardiac pacemaker systems,[76] and reoperation for battery replacement may be necessary after approximately 4 years. On the basis of clinical experience, SCS seems superior to TENS; however, pocket infection remains a potential complication of SCS. Recent studies indicate that neurostimulation delays rather than abolishes the occurrence of angina as an original warning signal for ischemia and therefore does not conceal the pain of the acute coronary syndromes.[83]

The aforementioned data underscore the improvement in the quality of life.[84] Moreover, the decrease in ischemia is probably related to a better life expectancy. However, a prospective mortality rate study is needed to confirm the safety of neurostimulation.

Transmyocardial laser revascularization

Transmyocardial laser revascularization (TMLR) is an indirect revascularization procedure that is aimed at establishing communications between the left ventricular cavity and the coronary microcirculation (ventriculocoronary anastomoses). The concept of transmyocardial revascularization is based on the early histopathologic work of Wearn et al.[85] on the potential sources of blood supply of the myocardium (Fig. 4).[86] The studies hypothesized the importance of epicardial conductance vessels, of extracardiac and ventriculocoronary anastomoses for myocardial perfusion, the latter of which have also been confirmed in their complexity by other investigations.[87,88] Early experimental studies demonstrated the positive antiischemic effects of implanted tubes or allogenous arterial segments,[89,90] endocardial incisions,[91] minimal endocardial abrasion,[92,93] and transmyocardial puncture.[94-97]

Transmyocardial mechanical puncture was first performed clinically in human beings in 1967[98] and was first published by White et al.[98] The approach was abandoned after the successful introduction of aortocoronary bypass grafting[3] and because some experimental findings showed fibrous occlusion of the channels induced by mechanical puncture.[99,100] On the basis of advances in medical laser technology, Mirhoseini later developed transmyocardial laser revascularization. He was the first to use the technique experimentally[101] and clinically.[102]

In transmyocardial laser revascularization, a left-lateral thoracotomy is performed, and usually as many as 40 transmural connections are established in the ischemic myocardium. Intraoperative transesophageal echocardiography demonstrates microcavities (so-called "bubbles") that enable immediate confirmation of successful transmyocardial penetration. A high-energy carbon dioxide laser, triggered electrocardiographically, perforates the myocardium in 50 msec; consequently, cardiopulmonary bypass and cardioplegia are not necessary.[21] The laser perforations (1 mm diameter) are completed in 15 to 45 minutes, and the entire operation requires approximately 2.5 hours. Although the epicardial openings close spontaneously or after a brief manual compression, the endocardial portion of the laser channel, which is connected to the left ventricular cavity, may remain patent as reported in postmortem cases (Fig. 5).[103-105]

The first clinical studies of TMLR investigated its use (in combination with CABG) in areas of the myocardium that could not be revascularized by CABG. Scintigraphic

studies showed an improvement in perfusion in the areas revascularized by TMLR and by CABG.[103] The use of TMLR as sole therapy in patients with refractory angina pectoris resulted in progressive improvement of clinical symptoms during a 6-month follow-up period[21] lasting at least 12 months in the majority.[106-108] This is in accord with results from studies on other indirect revascularization procedures, such as the Vineberg operation, which also led to increasing functional improvement for months after the operation.[109,110] In the latter case, this effect can be attributed to a progressive attachment of the mammary artery implant to the coronary circulation because of new formation of microvessels.

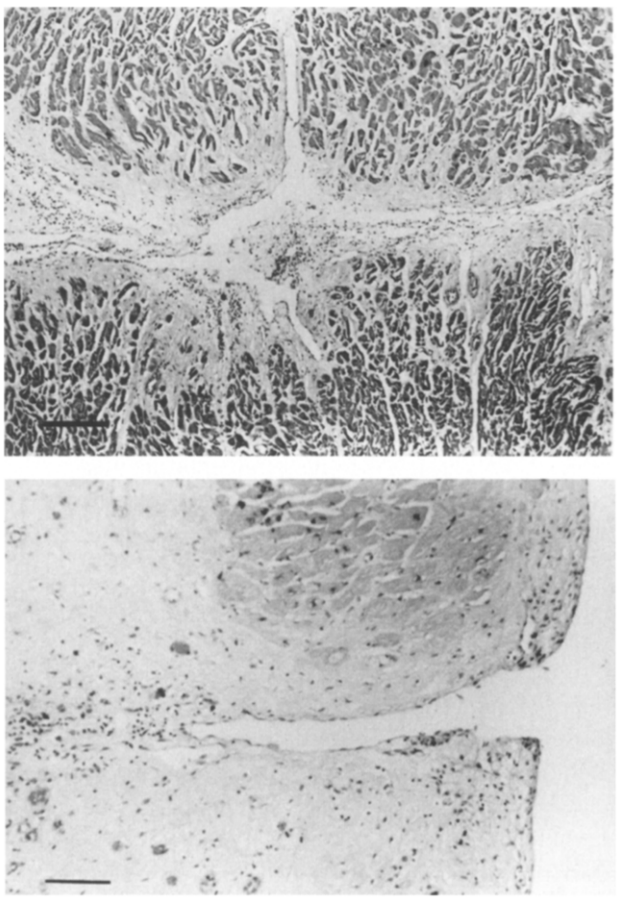
In addition to postoperative ventriculographic evidence of channel patency after TMLR,[103] postmortem histologic studies demonstrate endothelialization of laser channels and an increased density of microvessels in the revascularized region as many as 4 years after the operation.[103-105] Nevertheless, channel patency remains a controversial matter of discussion. It has been reported that human nonresponder myocardium may present different stages of wound healing resulting in scarred tissue without evidence of patent endothelialized laser-created channels.[111,112] Even though these studies derived data from postmortem investigations in nonresponder myocardium, they raise the question whether the clinical benefit from transmyocardial laser revascularization may at least result in part from a simple nonspecific histologic response to injury, which includes microvascular angiogenesis. On the other hand, channel perfusion could be visualized during systole by high-resolution contrast echocardiography.[113]

Regional perfusion analysis with positron emission tomography indicates that the relative subendocardial/subepicardial perfusion ratio at 6 months after TMLR significantly increases over baseline values.[21] This increase suggests a shift in myocardial blood supply from epicardial (coronary arterial) dominance to endocardial (ventriculocoronary) dominance, which is in accordance with the proposed mechanism of transmyocardial laser revascularization.

These positive results are further underscored by data from the FDA-approved phase II multicenter trial of TMLR in the United States, which stopped enrollment after 200 patients.[107] Of those who had completed follow-up during the 3-month (n = 159), 6-month (n = 143), and 12-month (n = 95) postoperative periods, clinical success as defined by a reduction from angina pectoris class III or IV to angina pectoris class 0, I, or II was achieved in 78%, 77%, and 79% of the cases, respectively, and 30%, 34%, and 30% of the patients were completely free from symptoms, respectively.[107] In this study the perioperative mortality rate could be reduced from 11% in the first 97 patients to 4% in the following 104 patients, most likely by identifying age and low left ventricular ejection as potential perioperative risk factors.

The FDA-approved phase III trial, which compared medical treatment and TMLR in patients with refractory angina pectons, stopped randomization after inclusion of 198 patients (101 medical, 97 TMLR) because TMLR proved superior in respect to clinical improve-

Figure 5



Histologic characteristics of laser channels in human myocardium 3 months after transmyocardial laser revascularization. *Top,* Laser channel (horizontal) connecting to intramyocardial vessels (vertical). (Original magnification ×40; bar = 150 μm.) *Bottom,* Laser channel connecting to endocardial surface. (Original magnification ×100; bar = 70 μm.) Reproduced with permission from the Texas Heart Institute Journal.

ment (PLC Medical Systems, Franklin, Mass.). On the basis of an intent-to-treat protocol, 12-month follow-up revealed a nonsignificant increase to the mortality rate of 33% in patients who were treated medically compared with 12% in patients who initially underwent TMLR (perioperative mortality rate 1%). The low rate of survival in medically treated patients has to be attributed to patients who were switched to TMLR after 6 months. According to the study protocol patients could be switched to TMLR 6 months after randomization in cases of unstable angina resulting in hospital admission, a stay in an intermediate-care unit beyond 48 hours, and the administration of intravenous antianginal medication. Corrected for these patients the actual rate of survival in medically treated patients was 11% after 12 months. It has to be stated critically that "unstable angina" may not have been an adequate selection criterion for a switch decision because unstable angina is often associated with an unstable coronary plaque and acute intracoronary thrombus formation. These patients are therefore at a high risk to develop perioperative complications.[114] It has to be kept in mind, therefore, that refractory angina pectoris as defined in this manner may result in an overlap that includes patients with the syndrome of primary unstable angina, which results from acute intracoronary thrombus formation. This overlap demands particular care in patient selection, especially when confronted with patients who are known to have a very high cardiovascular risk for myocardial infarction or cardiovascular death, for example, those who have had acute clinical changes within the last 48 hours before admission in conjunction with electrocardiographic ST-segment changes.[114] Furthermore it must be stated that unstable angina, even in patients without coronary thrombosis, signifies severe and critical myocardial ischemia, which may result in severe impairment of myocardial function and may be aggravated in the immediate postoperative period after TMLR because of the development of myocardial edema.

Chronic ischemia is probably a key factor in the success of indirect revascularization procedures such as TMLR (or the Vineberg operation[115-117]) because the compensatory increase of collaterals in the ischemic myocardium[118] improves the probability that laser channels will connect to the coronary circulation. In addition ischemia is a powerful promoter of angiogenesis mediated by vascular endothelial growth factor,[119] which could increase new vessel formation in the later stages after TMLR. This makes the consideration to use angiogenetic factors in combination with TMLR worthwhile.[120]

The type of laser used is also a factor in the success of TMLR. The high energy (50 J) of the carbon dioxide laser vaporizes tissue and therefore produces minimal thermal damage; the relatively long perforation time (50 msec) prevents the peak power from reaching particularly high levels, as is the case with the holium-yttrium aluminum-garnet or xenon-chloride, lasers, which operate at peak powers of 10 × 103 W or 10 × 106 W, respectively, compared with carbon dioxide lasers (800 W). In turn, keeping peak power relatively low allows for dissipation of excessive heat through conduction in the target tissue, a process called thermal relaxation. Thermal relaxation prevents an explosion caused by buildup of water vapor pressure, thereby minimizing collateral structural damage at high levels of energy. The relatively long pulse duration (50 msec) of the carbon dioxide laser, however, may constitute a problem of long exposure, which may tend to aggravate thermal damage at high levels of energy. However, recent experiments suggest that thermal damage with the carbon dioxide laser may be controlled by reducing the laser pulse energy to as low as 20 J/pulse, where the ability to create a transmural channel with one single pulse is still not jeopardized. The 10,600 nm wave length also has a high absorption in water, which enables precision cutting and, again, causes minimal collateral thermal damage.[121]

Current experimental data on the effects and mechanisms of transmyocardial laser revascularization are contradictory[122-126] and in most aspects not comparable. Two factors reduce the comparability of the aforementioned studies. First, study protocols differ with regard to the time at which the laser is used; in some studies, for example, the laser is used after ischemia has already resulted in irreversible structural damage of the myocardium. Second, some previous studies used low-energy lasers with little success; current studies are investigating the effects of a high-energy carbon dioxide laser with positive results.[126] Although some clinical and experimental studies demonstrate direct and indirect evidence of the antiischemic effectiveness of TMLR, a coherent model does not currently exist that explains the physiologic aspects of ventriculocoronary anastomoses or the timely course of perfusion in relation to myocardial tissue pressure.[122]

Conclusions and future perspectives

The definition of refractory angina pectoris presented includes the established treatment modalities for the relief of clinical symptoms and also implies the clinical limitations of those interventions. It therefore represents the frontier of scientific knowledge in respect to the pathophysiologic characteristics and treatment of myocardial ischemia. Even though the three new therapeutic approaches to myocardial ischemia, which have been presented in detail, may not be applicable for the general population of patients with symptomatic coronary artery disease, they are clinically effective and seem to improve stress-induced myocardial ischemia in refractory coronary insufficiency that results from end-stage coronary artery disease. These approaches therefore point to other pathophysiologically relevant mechanisms of myocardial ischemia that are not or only partially modified by the established antianginal agents (nitrates, β-blockers, and calcium antagonists). Whereas the established agents mainly modify blood supply at the level of the epicardial conductance vessels or reduce substrate demand at the level of the myocardium, the three new therapies at least partly influence myocardial perfusion at the level of the coronary microcirculation distal to severe coronary stenoses. The therapeutic effectiveness underlines the potential relevance of the coronary microcirculation for myocardial perfusion, which has been demonstrated also for other noncoronary diseases of the heart.[127-129]

Despite the promising results for the treatment modalities reported, rigorous further experimental and clinical evaluation has to be undertaken before general recommendations can be made. It has to be kept in mind that the past history of antiischemic therapy has seen numerous approaches, surgical and medical, that in the long run failed to survive in clinical practice.[87,130,131] Apart from the ineffectiveness of these therapeutic interventions themselves, this failure had to at least in some cases be attributed to improper patient selection and inadequate end points. For example, it has been shown that the Vineberg operation can be an effective procedure when viable myocardium, myocardial ischemia, and extensive collateralization in the area of revascularization could be demonstrated,[132,133] criteria not used in studies, which contributed to the abandonment of the procedure.[134] For interventions, which do not result in a stabilization of coronary atherosclerosis, antiischemic effectiveness may not be an adequate surrogate end point for a desirable improved survival rate. After all, coronary artery bypass grafting, the gold standard of revascularization, in randomized trials has only definitely improved survival in patients with left main disease as well as in patients with coronary triple-vessel disease and impaired left ventricular function, whereas results in other patient subgroups have been less convincing.[135] In contrast, antithrombotic and lipid-lowering agents have markedly decreased cardiovascular mortality rates in primary and secondary prevention. Therefore the influence of new therapeutic strategies on patient survival needs to be carefully evaluated, but prolongation of life is not necessarily to be expected even though desirable. For the known placebo effects of antianginal interventions, which range near 40%, caution is warranted when clinical symptoms are used as an end point in medical[130,131] and surgical approaches.[136,137] as stated by Effler et al.,[138] "Surgery may be a potent psychotherapy for the patient who has or thinks he has coronary insufficiency."

Arguments on the potential mechanisms of the approaches presented are in large part based on assumptions and currently available knowledge. In contrast to direct interventions in the epicardial conductance vessels, which can be made visible by coronary angiography, this evidence for the enhanced coronary perfusion is hard to achieve for the interventions presented because of methodologic shortcomings. Therefore particular care has to be taken in the further evaluation of indirect measures of improved blood supply such as positron emission tomography and functional evaluation of the left ventricle by means of Doppler echocardiography, radionuclide-ventriculography, and stress echocardiography.

In the particular case of long-term intermittent urokinase therapy, experimental models are needed that resemble the impairment of coronary perfusion, such as in patients with severe coronary artery disease, in addition to clinical studies that supply data on morphologic changes of atherosclerotic arteries. In contrast to the invasive approaches, which offer only limited opportunities to perform a double-blind sham-controlled study for ethical and practical reasons, a randomized, double-blind, placebo-controlled study would be desirable to establish long-term intermittent urokinase therapy beyond doubt. In SCS trials that include large series of consecutive patients from multiple centers are needed to supply additional data on safety and influences of this approach on survival. In TMLR the controversy

regarding channel patency and their functional properties during the cardiac cycle need to be settled.

Apart from the interventions presented, other evolving approaches, which so far have only been tested on smaller series of patients with refractory angina pectoris, will have to be further evaluated.[139,143] Cytoprotection at the cellular level represents a promising drug target, which so far has only partly been answered by conventional medication (β-blockers, diltiazem, verapamil). Particular attention will have to be paid to medical interventions such as L-carnitine and trimetazidine, which favorably modify the metabolic response of the myocytes to episodes of ischemia without major hemodynamic effects and which are currently tested in patients with nonrefractory angina pectoris.[144,145] Future investigations will also have to evaluate the benefit molecular biological approaches. The therapeutic use of vascular endothelial growth factor either as an adjunct to an indirect revascularization procedure such as TMLR or as a sole intervention, as currently tested in end-stage peripheral arterial disease,[146] offers a rational perspective for patient treatment.

The new therapies must be judged by their clinical efficacy and their side effects, practicability, and cost-effectiveness. Additional data from clinical and experimental studies on these treatment modalities should contribute to a more complete understanding of the therapeutic approaches presented in particular and of pathophysiologic mechanisms of myocardial ischemia in general.

We thank Sabine Meyer and Jerry Eastman for the careful preparation of the manuscript.

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