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Aims and Scope

Heart and Metabolism is a quarterly journal focusing on the management of myocardial ischemia. Its aim is to inform cardiologists and other specialists about the newest findings of the role of metabolism in cardiac disease and to create awareness of its potential clinical implications. The management of patients with angina, as well as those with heart failure and hypertrophic or dilated cardiomyopathy, will also be discussed. Moreover, the effects of metabolic diseases such as diabetes mellitus on the heart will be highlighted. Each issue will include an editorial, followed by articles on a key topic. Experts in the field will explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and non-ischemic heart disease.

The figure on the cover shows PET images of rubidium-82 (Rb) and F18 fluorodeoxyglucose (FDG) uptake in the left ventricle of a patient with stable angina. In each image the left ventricle free wall is in the 6 to 10 o'clock position, the anterior wall and septum are in the 1 to 3 o'clock position and the remaining open area is the plane of the mitral valve. The perfusion scan recorded at peak exercise (top right) shows a severely reduced Rb uptake in the anterior left ventricle wall compared to the scan recorded at rest (top left). The FDG scan recorded following an injection of FDG in the recovery phase (bottom right), when Rb had normalized (bottom left), shows a higher (1.90 times) tracer concentration in the previously ischemic region as compared to the nonischemic tissue (free wall). From: Camici PG, Araujo L, Spinks T et al. Increased uptake of F18 flurodeoxyglucose in postischemic myocardium of patients with exercise-induced angina. Circulation 1986;74:81-88.

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Refractory angina is defined as severe disabling angina in spite of optimal therapy and where percutaneous intervention or coronary artery surgery is not feasible. It is equivalent to class III or IV of the Canadian Cardiovascular Society classification [1].

As both percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) are effective in relieving symptoms [2], these options should have been excluded by experienced interventional cardiologists or cardiac surgeons, and their decision based on a recent coronary angiogram, preferably performed within the preceding 3 months. This may seem to be self-evident, but in a study evaluating transmyocardial laser revascularization, 72 (62%) of 117 patients initially referred because of refractory angina responded to changing their medical therapy (44%) or intervention by PTCA or CABG (18%) [3]. As long ago as 1975 [4], the problem of suboptimal medical therapy was highlighted and it has been the focus of recent reviews [2, 5].

Establishing that angina is truly refractory to conventional therapy requires a detailed evaluation of each individual patient, the nature of their symptoms (is it really angina?), and the exclusion of secondary causes [6]. We must also be sure that they are taking their medication in the doses prescribed, and that the prescribed medication has been optimized for the individual concerned.

Whilst coronary artery disease (CAD) is clearly the commonest cause of angina, the symptoms may be exacerbated by other factors.

– If the patient is hypertensive, has the blood

pressure been controlled effectively to a target of 140/90 mm Hg or less [7], and have the preferred agents for coexisting angina and hypertension (β -blockers and calcium antagonists) been utilized?

– Has anemia been ruled out?

– Is there any evidence of significant aortic valve disease? If in doubt, an echocardiogram will clarify and also give important information on left ventricular function.

– Is there evidence of rapid or slow arrhythmias (especially atrial fibrillation in the elderly)? Either may render angina difficult to control.

– Has thyrotoxicosis been ruled out?

When treating refractory angina, we must be clear that the symptoms reflect ischemia and we must have ruled out exacerbating causes. Patients usually have diffuse CAD affecting all major coronary arteries and may have undergone unsuccessful CABG or PTCA (see the case report in this issue).

Unlike cardiac failure, the patient with refractory angina may not have substantially impaired left ventricular function.

General measures [8]

– Cigarette-smoking should stop, as cessation may improve symptoms and will improve prognosis.

– Obesity should be corrected with the help of a qualified dietitian and, if necessary, a course of carefully supervised drug therapy.

– Physical activity should be encouraged. Although exercise in these patients is likely

to be very limited, it does help with weight loss and may reduce ischemic symptoms.

- Patients may be anxious about their condition and/or depressed. Relaxation techniques, specific counseling and antidepressant therapy may be helpful in reducing the adverse impact of psychological factors on symptoms.

Compliance

Many patients do not take their medication, or take it incorrectly. They may stop their medication because of depression. Complex regimens may be too demanding and create a feeling of helplessness in the patient.

Written material providing details of how to use medication correctly, counseling the patient and their closest relative (usually spouse), treating depression, and emphasizing the positive aspects of the therapy may enhance adherence to therapy [9].

Refractory angina: key questions

- Is it ischemic pain?
- Have precipitating causes been excluded?
- Is the patient taking the medication?
- Is the medication at an optimal dosage?
- Have PTCA and CABG been discussed with experienced operators?
- Has a combination of a hemodynamic and metabolic agent been tried?
- Have research protocols been explored?
- Have the psychosocial aspects been addressed?

Management

After asking several key questions, listed above, a practical strategy needs to be adopted. In this issue of *Heart and Metabolism* the important aspects of management are considered. Dr Paolo Camici discusses the role of positron emission tomography as a noninvasive means of defining viable myocardium which is relevant to the management of

refractory pain. Interestingly, he concludes that transmyocardial laser revascularization may reduce angina but not by improving perfusion or coronary reserve in the lasered areas. This raises important issues about pain perception which is comprehensively covered by Dr Robert Foreman. He highlights the huge variations in perception which, while currently undergoing detailed study, leave us at present with the difficulties of individualized care with regard to response to therapy. The evaluation and mechanism of cardiac ischemic pain are covered from a different perspective by Professor Filippo Crea and Dr Achille Gaspardone who again point out how elusive the connection is between objective evidence of myocardial ischemia and cardiac ischemic pain.

We can clearly see the difficulties in management because of the lack of direct objective evidence of ischemia in relationship to the clinical endpoint of pain. Dr Duncan McNab and Dr Peter Schofield explore new therapeutic approaches, focusing on mechanical means of pain relief, and providing a comprehensive and very useful overview. However, once more the mechanisms of benefit remain unclear. Dr M. Chester provides us with a clinical assessment which alerts us to the need for a comprehensive strategy given that the incidence and prevalence of refractory angina will increase within the next decade.

Incorporating a metabolic approach with trimetazidine may be in part preventative, as discussed by Dr Holban, but importantly it offers a different evidence-based approach to improving the quality of life of those disabled by chronic cardiac pain [10]. My case report illustrates its potential. Refractory angina is a time-consuming management problem with a deleterious psychosocial impact on quality of life, requiring counseling and support to the patient and close relatives or friends. This means the approach must be multidisciplinary, involving specialized nurses and health care workers, both in the hospital and the community. ■

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Cardiac ischemic pain

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Abstract

At the turn of this century, Colbeck proposed that ischemic cardiac pain may be related to distension of the ventricular wall (“mechanical hypothesis”). Three decades later, Lewis hypothesized that ischemic pain may be elicited by the intramyocardial release of pain-producing substances induced by ischemia (“chemical hypothesis”). Studies carried out in the last 10 years have lent strong support to the chemical hypothesis, as they have consistently shown that adenosine is a mediator of ischemic cardiac pain. Adenosine-induced ischemic cardiac pain is mainly mediated by stimulation of A₁ receptors located in cardiac nerve endings and is potentiated by substance P. Conversely, the magnitude and rate of left ventricular dilatation during ischemia do not predict the severity of angina. It is worth noting, however, that stretching of epicardial coronary arteries appears to potentiate the severity of angina caused by myocardial ischemia. The nervous activity generated by myocardial ischemia is modulated in intrinsic cardiac, mediastinal, and thoracic ganglia. It is then further modulated in the central nervous system and projects bilaterally to the cortex, as demonstrated in humans using PET, where it is decoded as a painful sensation. The causes responsible for the lack of angina during myocardial ischemia are probably different in patients presenting with either painless or painful myocardial ischemia, in patients with predominantly painless ischemia, and in diabetic patients. ■ *Heart Metabol.* 2002;16:5–8.

Keywords: Angina, adenosine, bradykinin, ischemic heart disease

Introduction

Although patients with ischemic heart disease usually consult their doctor because of angina symptoms, transient myocardial ischemia or even necrosis can occur without pain, and, conversely, severe angina-like pain may occur in the absence of detectable myocardial ischemia. Thus the occurrence of pain can serve the useful purpose of eliciting a protective reaction, but can also become a major component of the disease when it is disproportionate to the severity of the ischemic insult.

Causes of cardiac ischemic pain

In 1903, Colbeck proposed that cardiac ischemic pain may be related to distension of the ventricular wall (the “mechanical hypothesis”) [1]. Three decades later, Lewis hypothesized that ischemic pain may be elicited by the intramyocardial release of algogenic substances induced by ischemia (the “chemical hypothesis”) [2].

Mechanical hypothesis

Ventricular dilatation is unlikely to be responsible for anginal pain, as the rate and magnitude of left ventricular dilatation during

ergonovine-induced or spontaneous transient ischemic episodes were found to be similar during both painful and painless episodes [3]. Mechanical factors, however, may play a role in activating nociceptors localized at the level of the coronary arteries. The distension of the coronary arterial wall can cause pain: at the end of two sequential balloon inflations during coronary angioplasty, pain severity, normalized for the severity of ischemia, is similar when the two inflations are carried out using the same pressure, yet is more severe during the second inflation when the latter is carried out at a higher pressure [4].

Furthermore, we have recently observed that in a substantial proportion of patients complaining of angina-like chest pain after stent implantation, the pain may be related to a transient increase in vascular tone at the site of the implanted stent which stretches the arterial wall causing nociceptor activation [5].

Chemical hypothesis

Although several substances have been investigated as potential mediators of anginal pain, at present only two molecules have been convincingly demonstrated to be involved in the genesis of cardiac ischemic pain in man: adenosine and bradykinin.

Adenosine

Adenosine is rapidly formed during myocardial ischemia and is released into the vascular bed. The intravenous administration of adenosine causes a dose-dependent angina-like pain in normal subjects [6]. Adenosine-induced pain is increased by dipyridamole, which reduces adenosine cellular uptake, and reduced by theophylline, which is an adenosine antagonist [6]. Infusion of a similar dose of adenosine into the right atrium fails to elicit pain, thus proving that pain elicited by the intracoronary infusion of adenosine originates from the heart [7].

Adenosine-induced cardiac pain is not secondary to myocardial ischemia, as it generally occurs in the absence of ischemic ECG-like changes and it can be induced by infusing adenosine in angiographically normal coro-

nary branches and in vascular beds, such as brachial or femoral arteries, where ischemia caused by steal cannot occur [8–10]. In patients with exercise-induced angina, the severity of anginal pain is significantly reduced by pretreatment with theophylline, a potent nonselective adenosine receptor antagonist, in the presence of a similar severity of myocardial ischemia [11]. This finding indicates that the improvement of anginal pain produced by theophylline is likely to be due also to the direct inhibition of the algogenic effects of adenosine. Adenosine-induced pain is not prevented by β -blockade, atropine, naloxone, nitroglycerine, nifedipine, clonidine, cyclooxygenase inhibitors, or steroids [12, 13], and is potentiated by substance P [14].

In humans, the intravenous infusion of bamifylline, a selective A_1 receptor antagonist [15], reduces adenosine-induced muscular and cardiac pain without affecting adenosine-induced coronary vasodilatation, which is an A_2 receptor-mediated effect [16]. Furthermore, in patients with exercise-induced angina, bamifylline reduces the severity of anginal pain normalized for maximal ST-segment depression, thus suggesting that the improvement in anginal pain produced by bamifylline is likely due to the direct inhibition of the algogenic effect of endogenous adenosine of the A_1 adenosine receptors [17]. These findings indicate that in humans the algogenic effects of adenosine are mainly mediated by A_1 receptors.

Bradykinin

Among substances released by ischemic myocardium, bradykinin has been in vogue for more than 20 years as a potential mediator of cardiac ischemic pain. Recently, we have shown that the intracoronary infusion of bradykinin in patients with angina and coronary artery disease causes cardiac pain that is similar to their habitual angina [18]. Interestingly, bradykinin-induced pain is abolished or reduced by acetylsalicylate, thus suggesting that acetylsalicylate-sensitive mediators, such as prostaglandins, are involved in the pathogenesis of bradykinin-induced pain. As bradykinin is released in large amounts by the heart during ischemia, it can be a natural

stimulus for causing, via arachidonic acid metabolites, excitation of the sensory receptors signaling pain during myocardial ischemia.

Significance of cardiac ischemic pain in different coronary syndromes

Cardiac ischemic pain does not provide information on the causes of myocardial ischemia. However, information on the causes of ischemic episodes and on the possible evolution of myocardial ischemia can be obtained from the pattern of pain recurrence and from the circumstances in which the pain occurs. A stable pattern of occurrence of ischemic episodes with pain suggests a stable cause of ischemia. Conversely, a recent onset of ischemic episodes and/or a rapid worsening of their severity and duration, or the presence of pain at rest suggest an unstable cause.

Chronic stable angina

Although this form of angina is characterized by a stable pattern of symptoms over months and years, a detailed history of the circumstances in which anginal attacks develop can provide useful information on the actual cause of ischemia. Attacks that occur predictably only when a certain level of physical activity is exceeded, suggest a fixed impairment of coronary flow reserve. Attacks that occur unpredictably during levels of effort that are usually well tolerated, suggest a variable impairment of coronary flow reserve caused by “dynamic” coronary stenoses [19]. The range of this modulation can be confirmed by assessing the heart rate at which ischemic episodes occur during Holter monitoring or exercise test after acute nitrate administration [20].

Unstable angina

The sudden onset and rapid worsening of angina with more severe and longer lasting attacks, and attacks occurring at rest or during minimal physical effort, are a signal of an unstable cause of ischemia and therefore

demand prompt medical attention and aggressive management. The diagnosis of instability is easy when symptoms are rapidly worsening but cannot easily be made only on the basis of the occurrence of angina at rest or angina that occurs unpredictably during a degree of effort well tolerated on other occasions. On the one hand, variability of the anginal threshold and even occasional episodes of angina at rest can occur over periods of months and years in patients with chronic stable, predominantly effort-related, angina [21]. On the other hand, episodes of angina at rest, usually with preserved effort tolerance, are typical of variant angina. In this latter syndrome the attacks are typically nocturnal, or occur in the early morning hours, sometimes associated with palpitation due to arrhythmias. The attacks sometimes occur in clusters within a 30- to 60-min period, leaving the patient angina-free throughout the rest of the day whilst engaged in normal activities [21].

Acute myocardial infarction

In acute myocardial infarction, pain is usually, but not always, more severe and more frequently accompanied by *angor animi*. The severity of pain is in itself a reason for alarm; but even when symptoms are not severe, it is the persistence of pain that demands prompt attention. Despite the extreme severity of ischemia, which characterizes myocardial infarction, the Framingham study showed that about 34% of acute myocardial infarctions were not associated with pain that could be recognized by the patient. The proportion of painless myocardial infarctions was higher in diabetic and hypertensive patients. In men, but not women, there was a tendency to an increase in the proportion of painless infarctions with age. An intriguing observation of the Framingham study was that 24% of men and 33% of women with painless myocardial infarction had episodes of angina pectoris [22]. As the algogenic stimuli operating during myocardial infarction are likely to be much more powerful than those operating during episodes of transient myocardial ischemia, these findings further emphasize how the cen-

tral modulation of algogenic messages plays a pivotal role in determining the perception of cardiac ischemic pain.

Conclusions

Mechanical stimuli are unlikely to play a major role in the genesis of anginal pain during daily life, but they may play a role in patients undergoing percutaneous interventions. At present, the clinical evidence indicates that adenosine, via activation of A₁ adenosine receptors, and bradykinin, via arachidonic acid metabolites, are algogenic substances involved in the pathogenesis of cardiac ischemic pain.

The relationship between myocardial ischemia and cardiac ischemic pain is rather elusive, as the severity of pain is not necessarily proportionate to the severity of ischemia and as only the pattern and duration of pain can provide clues to the actual causes of ischemia. ■

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Diagnosis, incidence, epidemiology, and treatment of refractory angina

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Abstract

Angina that is refractory to the orthodox cardiac management paradigm is becoming a significant clinical problem. The chronic refractory angina patient is usually a major burden on their family, their family doctors and 'clog up' secondary and tertiary service providers. Such recidivist patients who do not improve using conventional models of care commonly earn the epithet "heart-sink". Faced with such patients the physician is faced with two options. Abandon the conventional paradigm or abandon the patient. The future for these expanding group patients is grim unless we do the right thing. This article sets out a simple, pragmatic and unorthodox approach that merits serious consideration. ■ *Heart Metabol.* 2002;16:9–14.

Key words: Angina, patient centered, holistic, multidisciplinary, guidelines

Introduction

Stable angina that persists despite optimal conventional treatment is a major clinical headache. In the past the terminology used to describe this condition included: intractable angina, therapy-resistant angina, uncontrolled angina, and refractory angina. This made any attempt to define the epidemiology of the problem difficult. In 1997, the UK National Refractory Angina Guideline Group recommended that the term chronic refractory angina should be used to describe all patients with a clinical diagnosis of stable angina pectoris that is not controllable with optimal medication and where revascularization is unfeasible or the risks cannot be justified [1]. It does not include syndrome X. This definition was presented at both the World Congress of Pain meeting in 1999 and the European Congress of Cardiology in 1999 and 2000. The term "intractable angina" is best reserved for the tiny minority of patients with continuous unremitting angina.

Prevalence

The prevalence of chronic refractory angina is unknown; however, in a given population it is likely to be related to the size of the main at-risk population, namely CABG patients. In our own series of over 500 patients with chronic refractory angina, over 95% were referred with recurrent angina following revascularization, the remaining 5% being patients with inoperable disease from the outset. The majority of patients (80%) had previously undergone CABG, many of whom had also undergone angioplasty (PTCA) to native disease or vein graft. Only 15% had undergone PTCA only. Eight patients had undergone the now largely discredited transmyocardial laser procedure.

Data from key angioplasty vs coronary artery surgery studies reveal that more than 20% of angioplasty patients and more than 10% of bypass surgery patients have angina a year after the procedure, often despite repeat revascularization [2, 3]. Vein graft attrition [4], native disease progression [5], and long-term survival [6–8] combine to ensure a steady

increase in recurrent angina over time until the death rate matches or exceeds the rate of recurrence. Data from post-CABG angiogram activity and disposal in our own center confirm that there is a strong correlation between the prevalence of post-CABG recurrent angina and the number of CABG survivors multiplied by time after surgery [9].

Management of recurrent angina

Angina recurrence rates and the proportion of patients undergoing repeat revascularization in key PTCA vs CABG trials are shown in *Table I*. In these trials the decision to revascularize for recurrent angina was at the clinician's discretion; comparison with registry data reveals a consistent pattern of practical decision-making. Thus, repeat revascularization rates at 7 years for angioplasty and surgery were 60% and 12%, respectively, and were the same in the BARI trial and registry patients [13]. It is clear from the data that most cardiologists are comfortable with managing recurrent angina whilst angioplasty or surgery is an option. In the absence of any comparative trial data, the preference for PTCA over repeat CABG is based on extrapolation, supported by audit [15], that PTCA is safer though less effective than CABG in the management of postrevascularization recurrent angina.

The lack of prospective clinical trials represents a major challenge for evidence-based cardiology and cardiac surgical practice in determining when repeat revascularization is justified and when alternatives should be tried. There is growing evidence of the safety

and efficacy of low-risk nonrevascularization strategies, and the dogged attachment to the anti-ischemia revascularization approach is becoming increasingly hard to justify especially when high-risk palliative procedures are under consideration. Clearly, availability and clinical confidence in the alternatives will vary between centers. In our center the number of patients referred for repeat CABG has fallen dramatically as patients are instead referred to the refractory angina program for outpatient management. Consequently, the prevalence of clinically defined chronic refractory angina will be partly reflected by the availability of low-risk alternatives.

Management of chronic refractory angina

There are a number of nonrevascularization treatment options available for the management of chronic refractory angina and they vary enormously in terms of cost, safety, efficacy, and evidence. The lack of a coherent treatment strategy and consequent gross variation in clinical practice prior to 1998 prompted the inauguration of the UK National Chronic Refractory Angina Guideline Group. This group, jointly commissioned by the UK Pain Society and the British Cardiac Society, has formal representation from the Royal College of General Practitioners, the British Cardiac Patients' Association, and the International Association for the Study of Pain, and meets regularly to review the guideline in the light of new evidence. In the absence of comparative trials, therapies are ordered pragmatically

Table I. Percentage of patients with recurrent angina in angioplasty vs coronary bypass studies.

	PTCA (%)	Need for repeat revascularization (%)	CABG	Need for repeat revascularization (%)	Study
1 Year	29	48	12		BARI [2]
1 Year	25	34	15	7	CABRI [3]
2 Years	32	38	22	4	RITA [10]
3 Years	20	63	12	14	EAST [11]
5 Years	21	52	15	12	BARI [12, 13]
5 Years	49	53	34	12	RITA [14]

according to relative risk, reversibility, and simplicity of application. Relative cost is used when therapies are otherwise equally ranked. The first consultation guideline document was produced in November 1998 and was endorsed by the British Cardiovascular Interventional Society, forming the basis for the European Society of Cardiology Refractory Angina Study Group document [16]. The guideline was first published in the *British Journal of Cardiology* [1] and is available at www.angina.org.

Below is a brief description of the treatment stages. Patients advance through successive stages until they have achieved their objectives or are unwilling to proceed.

A best management stepwise algorithm for patients suffering from chronic refractory angina

Diagnosis

- 1a Requires a cardiological and cardiothoracic surgical opinion that the patient has angina of ischemic origin and that revascularization is unfeasible or the risks unjustifiable. Regular angiographic review is recommended to exclude the development of "new" revascularizable disease.
- 1b Outpatient assessment to include:
 - review of pain history, drug history, and physical exam;
 - evaluation of additional/complicating noncardiac causes of pain (common);
 - assessment of functional impairment;
 - consideration of depression as a component of the patient's total pain experience;
 - realistic and achievable "treatment targets" should be agreed at this and each subsequent stage.
- 1c Outpatient therapy to include:
 - (re)-education;
 - standard risk factor modification;
 - explanation of management plan;
 - medication optimization.
- 2 Rehabilitation based on recommended guidelines involving a combination of education, modification of mistaken

- beliefs in the patient and carer, stress management, and an individually tailored graduated exercise program [17].
- 3 Transcutaneous electrical nerve stimulation [18].
- 4 Temporary sympathectomy, stellate ganglion block [19, 20], T3/4 paravertebral block [21], or high thoracic epidural [22].
- 5 Spinal cord stimulation (SCS) [23–25]: implant data and outcome should be recorded in a registry. *Note: Although SCS is licensed for use in "pain," it does not yet have approval for use in angina in the USA. Conversely, SCS has a grade A SERNIP classification for use in angina in the UK and is in widespread use across the European Union.*
- 6 Opiate analgesia: there is limited evidence of the effectiveness of strong analgesics in refractory angina. Introducing opiates requires extensive pretreatment counseling and careful follow-up. Opiates should be avoided in patients with a history of addiction. Trial of epidural followed by intrathecal opioids may be beneficial if side effects are intolerable [26].
- 7 Destructive sympathectomy [27].
- 8 External enhanced counterpulsation [28] undoubtedly has a role in refractory angina management and is currently under review.

Whilst all therapies require further evaluation in clinical trials, the therapies in the following section were considered too high-risk to justify their use in routine clinical practice. We recommend that these therapies should only be undertaken as part of a formal clinical trial except in experienced centers in exceptional circumstances.

- 1 Myocardial (percutaneous or transmural) laser [29–33].
- 2 Gene therapy.

Cardiac transplantation has no place in routine management.

Practical tip

There is no doubt that psychology plays a major part in the syndrome, and the starting point of successful management often hinges on an in-depth understanding of how the angina is affecting the life of the individual patient. This takes time and is not suited to a routine follow-up appointment in a busy clinic. By the time the diagnosis is reached, the typical patient will have been revascularized at least once and have been through the mill of cardiological investigations following angina recurrence. It is worth seeing the patient afresh with plenty of time in a new patient clinic. Extra time is needed because by definition the chronic refractory angina patient is unresponsive to the conventional ischemia-centered approach, and a different and unfamiliar holistic patient-centered approach is required.

Since 1997 we have treated over 550 patients with chronic refractory angina in a multidisciplinary clinic, and a useful and illuminating trick is to consider angina as an entity, the primary purpose of which is to erode the patient's (and his or her carer's) quality of life. In nearly all patients, angina uses a relatively small number of tools: pain, fear, avoidance behavior ("it hurt so I won't do it again"), and vicarious avoidance behavior ("it hurts him so I won't let him do it again"). Understanding which is the dominant tool in a particular clinical situation helps to direct therapy. Anxiety and avoidance behavior are almost always influenced by misconceptions about angina and it is important to address the angina beliefs of the patient and main carers at the initial clinic visit. For example, it is commonly believed that each episode of angina permanently damages the heart and that the patient's heart must therefore be dangerously weak. Many patients complain that their lives are ruined by angina because they cannot function normally, whereas the truth is that they rarely attempt to function normally for fear of further damaging their already dangerously weakened heart. On the rare occasion that they do try to do something, their spouses, certain that they will do themselves

harm, stop them. When such patients, who are usually obese and very unfit, present at the clinic, clinicians often wrongly assume that their condition is the result of laziness rather than of a genuine, though misguided, belief that they will live longer if they do not provoke the angina through regular exercise.

A thorough explanation of the cardiac-neurological-psychological interactions that produce the angina syndrome is invaluable and enables the patient and carer to understand the logic behind the therapies and the order in which they are offered.

Ask one or two patients how they felt when they were told that they were "inoperable."

Summary

All the available evidence indicates that the size of the chronic refractory angina population will grow inexorably to present a major clinical problem within a decade. Faced with patients who are refractory to the conventional treatment paradigm, the cardiologist can either admit defeat or change strategy. A significant minority of patients will improve once their irrational fears have been identified and confronted. The UK National Refractory Angina Consensus Guideline sets out a logical order in which alternative therapies should be tried, based on the available evidence, and recommends the provision of complex treatment within a patient-centered multidisciplinary framework. The provision of refractory angina management programs makes clinical and economic sense, especially in centers with relatively high rates of palliative repeat CABG surgery and complex graft angioplasty. ■

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PET imaging in refractory angina

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Abstract

Positron emission tomography (PET) is a noninvasive tool that provides accurate quantitative information on regional perfusion, metabolism, and autonomic function in different human organs in vivo. Classically, PET has been applied to cardiology for the investigation of myocardial blood flow and flow reserve, and for the assessment of myocardial glucose utilization and tissue viability. However, PET has also been applied very successfully to the study of human brain function. In this review, the contribution of PET to our understanding of the pathophysiology of cardiac pain as well as its role in the assessment of transmyocardial laser revascularization in patients with refractory angina will be discussed. The former issue is particularly relevant in these patients in whom persisting chest pain is the key feature. Since relief of ischemia is often technically difficult in refractory angina, a better understanding of the mechanisms involved in chest pain perception may help develop alternative therapeutic measures for these patients.

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Key words: Coronary artery disease, angina, brain, cardiac imaging, transmyocardial laser revascularization

Positron emission tomography (PET) is a non-invasive tool that provides accurate quantitative information on regional perfusion, metabolism, and autonomic function in different human organs in vivo. Classically, PET has been applied to cardiology for the investigation of myocardial blood flow and flow reserve, and for the assessment of myocardial glucose utilization and tissue viability [1].

In this brief review, the contribution of PET to our understanding of the pathophysiology of cardiac pain as well as its role in the assessment of transmyocardial laser revascularization (TMLR) in patients with refractory angina will be discussed. The former issue is particularly relevant in these patients, in whom persisting chest pain is the key feature. Since relief of ischemia is often technically difficult in refractory angina, a better understanding of

the mechanisms involved in chest pain perception may help the development of alternative therapeutic measures for these patients.

Painful and painless myocardial ischemia

Up to 70% of episodes of myocardial ischemia in patients with coronary artery disease may be asymptomatic; for acute myocardial infarction, the incidence of painless events is estimated to be 30% [2–6]. Silent ischemia often coexists with painful ischemia in the same patient, and the evidence suggests that there is no correlation between the degree of pain and the severity of the ischemia [2].

The higher incidence of myocardial ischemia in diabetics implicates peripheral neuropathy in the process; differences in autonomic nerve function have also been described in nondiabetic patients with silent myocardial ischemia [3, 4]. Conversely, silent ischemia can be shown in many nondiabetics with no evidence of neuropathy.

There is no pathophysiological hypothesis to fully explain these findings. Such a hypothesis should take into account two interrelated phenomena. Firstly, the development of ischemia is a dynamic process in which the determinants of the imbalance between oxygen supply and demand are not fixed but can be modulated by a number of factors [5]. Secondly, the sensation of angina pectoris is the result of activity in neural circuits with potential for modulation of the message at all levels of the process [6].

Peripheral mechanisms involved in the transduction of chest pain perception

An adequate stimulus (eg, mechanical and/or chemical) at the level of the myocardium will lead to the release of numerous neurotransmitters, among which adenosine [7] and substance P [8] have been shown to be particularly important in the case of cardiac pain. There is disagreement as to whether these ligands activate receptors on specific nociceptors (*specificity theory*), or whether particularly intense stimulation of receptors for other modalities, such as proprioception, will constitute a nociceptive signal (*intensity theory*) [9]. It is important, however, that we do not label these signals as "painful." Pain is a conscious experience triggered by activity in the peripheral nervous system. Prior to the peripheral signal being processed in the brain, it is perhaps best thought of as "ischemia-induced afferent activity" [6].

This afferent activity occurs in anatomically sympathetic fibers, which have their primary synapses in the dorsal horn of the spinal cord [10, 11], and vagal fibers, which synapse first in the nucleus of the solitary tract [12]. At these synapses, there is potential for modula-

tion of the message. Other sensory input to the spinal cord, descending control mechanisms from the brain, and mechanisms integral to the spinal cord, will act together to either amplify or diminish ongoing afferent activity [13]. After the primary synapse, second order neurons ascend in multiple pathways, including the spinothalamic tract, the spinoamygdaloid pathway, and the spinohypothalamic pathway [14].

Central nervous pathways mediating anginal pain

The pain experience is multidimensional, composed of a sensory-discriminative component (represented by the ability to identify the stimulus within spatiotemporal and intensive domains) and a hedonic component (through which the intrusive and unpleasant qualities of pain are experienced). Additionally, a cognitive component reflects the ability to evaluate the pain in terms of the threat that it represents to wellbeing or survival. A great deal of information on central processing of visceral pain and angina has been derived from animals, and the following summarizes this work.

The sensory-discriminative component of the experience is expressed through the S-1 and S-2 somatosensory cortex and the posterior cingulate gyrus. These areas receive input from third order neurons from the ventroposterior lateral thalamus. Arousal, fear, and autonomic activation are expressed through activity in the reticular formation, the amygdala, and the hypothalamus. The latter two areas receive third-order projection fibers from the parabrachial nuclei of the pons.

Cognitive appraisal occurs in the parietal cortex and the anterior cingulate cortex. Such appraisal will assess the situation to be intrusive and threatening, and there will be the appropriate affective sequelae of difficulty, apprehension, and fear for the future mediated by increased activity in the prefrontal cortex and limbic system. These areas receive diffuse projections via third-order neurons from medial thalamic nuclei [14].

This operational separation of the compo-

nents of pain helps us understand the experience, but we must be aware that these are semantic constructs. The experience of angina is a dynamic, integrated, subjective phenomenon which is unique to the individual.

PET studies of the central pathways mediating angina in humans

Recently, PET has been used to trace the central pathways mediating angina in humans [15]. PET permits noninvasive assessment of regional cerebral blood flow (rCBF), which is a reliable indicator of regional cerebral neuronal activity. PET was used to assess rCBF in patients with stable angina pectoris and angiographically proven coronary artery disease during dobutamine stress.

Painful myocardial ischemia

Compared with the resting state, the development of angina was associated with increased rCBF in the hypothalamus, periaqueductal gray, bilaterally in the thalamus and lateral prefrontal cortex, and left inferior anterocaudal cingulate cortex. In contrast, rCBF was reduced bilaterally in the mid-rostrocaudal cingulate cortex, fusiform gyrus, and right posterior cingulate, and left parietal cortices. Thalamic activity could be detected several minutes after stopping dobutamine infusion and after the disappearance of anginal pain and ECG changes. Therefore, it is proposed that the activated central structures constitute the pathways which map the experience of anginal pain and that the thalamus acts as a gate to nociceptive information, with activation of many other areas of the brain being necessary before angina is experienced.

Silent myocardial ischemia

The same PET methodology has been used to study patients with silent myocardial ischemia [16]. In this study a difference in the pattern of cerebral cortical activation was observed when symptomatic patients were compared with those with silent myocardial ischemia;

however, the flow pattern in the thalamus was similar when the groups were compared. It was concluded that since bilateral activation of the thalamus can be shown in both angina and silent ischemia, peripheral nerve dysfunction cannot serve as a full explanation for silent ischemia. In addition, activity in the frontal cortex appears necessary for the sensation of anginal pain.

PET for the assessment of transmural laser revascularization (TMLR)

TMLR has been proposed for the treatment of refractory angina. It has been hypothesized that transmural left ventricular channels created by laser improve myocardial blood flow in the treated zones. Recently we conducted a study to assess the effect of TMLR on myocardial blood flow and coronary vasodilator reserve [17].

We measured myocardial blood flow (mL/min per g) by means of PET with oxygen-15-labeled water in seven patients with refractory angina, CCS class 3.6 ± 0.5 , on three occasions: before and at 7.5 ± 2.8 weeks (follow-up 1, FU-1) and at 34.6 ± 4.7 weeks (follow-up 2, FU-2) after TMLR performed with a synchronized high-powered CO₂ laser. In each study, myocardial blood flow was measured at rest and during maximal IV dobutamine. The coronary vasodilator reserve was computed as dobutamine/rest myocardial blood flow. After TMLR, the CCS class was 2.2 ± 1.7 at FU-1 and 2.4 ± 1 at FU-2 ($P = 0.04$ vs pre-TMLR). Resting myocardial blood flow, both in lasered and nonlasered regions, was unchanged after TMLR. Dobutamine myocardial blood flow at baseline was 1.45 ± 0.52 in lasered and 1.55 ± 0.52 in nonlasered regions ($P = \text{NS}$). At FU-1, dobutamine myocardial blood flow in nonlasered regions had increased significantly to 1.89 ± 0.82 ($P < 0.05$) and was higher than in lasered regions (1.51 ± 0.61 , $P < 0.05$ vs nonlasered). At FU-2, dobutamine myocardial blood flow in nonlasered regions was still higher than in lasered regions (1.56 ± 0.54 vs 1.21 ± 0.44 , $P < 0.01$). The coronary vasodilator reserve was

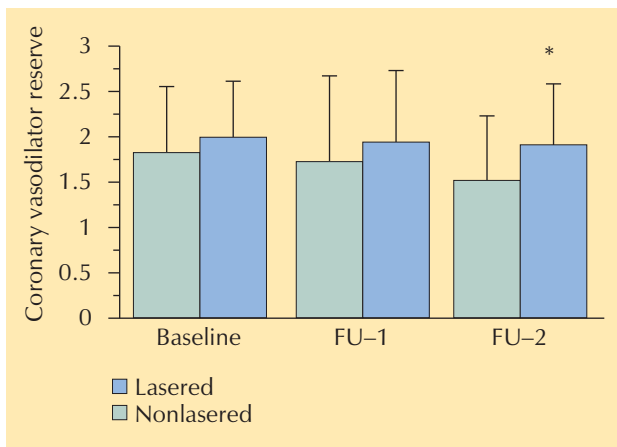


Figure 1. Coronary vasodilator reserve in lasered and nonlasered regions at baseline, FU-1, and FU-2. * $P < 0.05$. (Adapted from [17].)

comparable in nonlasered and lasered regions at baseline and FU-1, whereas it was higher in nonlasered regions at FU-2 (1.86 ± 0.67 vs 1.53 ± 0.72 , $P < 0.05$) (Figure 1).

In conclusion, TMLR has been shown to reduce angina in severely diseased patients. The results of our study do not support the hypothesis that the symptomatic benefit of TMLR can be ascribed to improved myocardial perfusion or the coronary vasodilator reserve in the lasered areas. ■

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New therapeutic approaches: TMR, PMR, and SCS

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Abstract

Many patients with symptomatic coronary artery disease can be effectively treated through a combination of medication and percutaneous or surgical revascularization. Unfortunately, some patients cannot be adequately managed by these conventional strategies and suffer severe angina. Three of the most promising therapies for these patients are transmyocardial laser revascularization (TMR), percutaneous myocardial laser revascularization (PMR), and spinal cord stimulation (SCS). Although the mechanisms of action for each of these modalities remain unclear, their use appears to confer symptomatic benefit to patients with chronic refractory angina. In this article we review and compare the clinical evidence for TMR, PMR, and SCS. ■ *Heart Metabol.* 2002;16:19–22.

Key words: Myocardial revascularization, therapies

Introduction

Ischemic heart disease (IHD) remains one of the greatest health burdens in developed countries [1]. Most patients suffering from IHD can be treated adequately through a combination of medication and revascularization strategies including CABG or angioplasty and stent implantation, but a subgroup has coronary artery disease that is not amenable to conventional therapies. Typically these patients either demonstrate diffuse coronary disease unsuitable for revascularization or have undergone previous revascularization, with a lack of graft options preventing a repeat procedure.

We review the clinical evidence for three of the most promising new therapeutic modalities for chronic refractory angina: transmyocardial laser revascularization (TMR), percutaneous myocardial laser revascularization (PMR), and spinal cord stimulation (SCS).

Transmyocardial laser revascularization (TMR)

In 1981, Mirhoseini and Cayton reported their experience with the use of lasers to create transmyocardial channels in animals [2]. Within 5 years TMR had been performed in humans [3]. During TMR, a laser is placed on the epicardial surface of the left ventricle via a left lateral thoracotomy and a variable number (10–50) of small transmural channels is created. The proposed potential mechanisms of action include direct flow of blood from the left ventricle into the ischemic myocardium via the laser-created channels, laser-induced angiogenesis, and laser-induced denervation.

Initial observational data were encouraging [4–6] and these stimulated the conduct of a number of trials comparing TMR with medical therapy. Five large trials of TMR and medical therapy have been published [7–11] and their results are summarized in *Table 1*.

Unfortunately, two of these trials [8, 9] suffered from profound methodological deficiencies.

Table I. Results of randomized trials of TMR (12 months).

Authors	Year	Laser	Procedural mortality	Change in angina status ^a		Exercise time (s)		12-Month survival		Myocardial perfusion		Left ventricular ejection fraction	
				TMR	Medical	TMR	Medical	TMR	Medical	TMR	Medical	TMR	Medical
Schofield et al [7]	1999	CO ₂	5%	25%	4% ^b	TMR 40 s better		89%	96%	NSD		-1%	-2%
Frazier et al [8]	1999	CO ₂	3%	72%	13% ^b	Not assessed		85%	79%	+20%–27% ^b		Not assessed	
Allen et al [9]	1999	Ho:YAG	5%	76%	32% ^b	Not assessed		84%	89%	NSD		Not assessed	
Burkhoff et al [10]	1999	Ho:YAG	1%	61%	11% ^b	+65	-46 ^b	95%	90%	NSD		-3% ^c	0%
Aaerge et al [11]	2000	CO ₂	4%	39%	0% ^b	+8	-10	88%	92%	Not assessed		Not assessed	

NSD, no significant difference.
^aImprovement in two CCS or NYHA classes at 12 months.
^bStatistically significant difference between TMR and medical therapy ($P < 0.05$).
^cStatistically significant change compared with baseline ($P < 0.001$).

cies that have resulted in ongoing controversy about the validity of their results [12]. In both of these studies there was a high crossover rate from medical therapy to TMR and a significant loss to follow-up.

Three trials did not permit crossover and had more complete follow-up data [7, 10, 11]. All three studies demonstrated a significant improvement in angina status and quality of life, and in one, a significant improvement in exercise capacity [10]. However, none of these studies were able to show any improvement in survival, myocardial perfusion, or left ventricular ejection fraction. It is therefore difficult to exclude the possibility of a significant contribution from a placebo effect in the TMR trial results, particularly as none of the trials performed a sham procedure, eg, a thoracotomy incision, that would have enabled blinding of patient and assessor.

Finally, TMR is associated with significant procedural mortality and morbidity rates. In observational studies, the perioperative mortality was as high as 10% [5, 6], and although this was lower (1% to 5%) in trials in which patients were carefully selected [7–11], significant morbidity persisted. Combination of these perioperative mortality and morbidity data has led some observers to conclude that, despite the consistent demonstration of an improvement in anginal symptoms, the magnitude of the risks may outweigh the benefits [7].

Percutaneous myocardial laser revascularization (PMR)

PMR differs from TMR in both the site of delivery of the laser energy and the depth of the channels created. During PMR, the laser is directed against the endocardial surface of the left ventricle via a guiding catheter inserted via the femoral artery and positioned in the left ventricular cavity.

An intuitive attraction of PMR was the potential to achieve the symptomatic benefits of TMR with a lower associated mortality and morbidity. Initial observational data were promising [13] and have been supported by the results of the first randomized trial of PMR and medical therapy, the PACIFIC trial [14]. The results of this trial are presented in *Table II*. The results were similar to the TMR trials: an improvement in anginal symptoms and exercise time, but, once again, no improvement in myocardial perfusion, left ventricular function, or survival. In marked contrast to the TMR trials, however, there were no procedural deaths and morbidity was low.

Two blinded trials of PMR have been conducted: the DIRECT trial [15] and the BELIEF trial (presented at the 2001 American College of Cardiology conference). The results of these two studies have not yet been published in full, but preliminary results are conflicting, possibly as a result of different laser technolo-

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Table II. Results of a randomized trial of PMR.

Authors	Year	Laser	Procedural mortality	Change in angina status ^a		Exercise time (s)		12-Month survival		Myocardial perfusion		Left ventricular ejection fraction	
				PMR	Medical	PMR	Medical	PMR	Medical	PMR	Medical	PMR	Medical
Oesterle et al [14]	2000	Ho:YAG	0%	45%	11% ^b	+89	+12.5 ^b	84%	89%	Not assessed		+1%	0%

^aImprovement in two CCS or NYHA classes at 12 months.

^bStatistically significant difference between PMR and medical therapy ($P < 0.05$).

gies employed in each trial. The DIRECT trial did not show any significant difference in angina relief between PMR plus medical therapy and placebo PMR plus medical therapy. The BELIEF trial reported that at 6 months, 41% of the PMR-treated patients had an improvement in two angina classes compared with 13% of those who received the sham PMR (J.E. Nordrehaug, personal communication, March 2001).

Spinal cord stimulation (SCS)

SCS involves placement of a quadripolar lead into the epidural space, sited so that when activated, SCS results in paresthesia in the dermatomes corresponding to the patient's anginal symptoms.

Observational studies have shown that SCS use improves NYHA functional angina class [16], exercise duration [16–19], time to angina [17–19] on treadmill testing, angina severity (frequency, duration, and severity of episodes) [16–18, 20], medication use (nitrates and opiates) [16–19], and hospital admissions (frequency and duration of stay) [20]. Hautvast and colleagues [21] conducted a small, randomized study with 25 patients in which SCS was implanted in all subjects, but was inactivated in the control group for 6 weeks after implantation. The SCS group enjoyed significant improvements in symptoms, exercise time, and ischemic changes on a 48-h ambulatory ECG, which did not occur in the control group. In another trial, the ESBY study, 104 patients with chronic angina but no prognostic indications for surgery were randomized to either SCS or CABG [22]. Both interventions

relieved angina to a comparable and significant degree (83.7% and 79.5%, respectively), although cardiac mortality was significantly lower in the SCS group (1.9% vs. 13.7%, $P = 0.02$). However, compared with SCS, the CABG group had an increase in exercise capacity ($P = 0.02$) and less ST-segment depression on maximum workload ($P = 0.0003$).

Early concerns about the potential for adverse outcomes resulting from the masking of ischemic symptoms have not been substantiated. SCS does not conceal the symptoms of myocardial ischemia [19], including those of myocardial infarction [23], and, despite the increased activity of patients as a consequence of better symptom control, is not associated with an increase in ischemic burden or arrhythmia [24].

The possibility of a placebo effect with SCS has been suggested. Several factors argue against this as the sole mode of benefit, for, in addition to relieving symptoms of angina, SCS also improves markers of myocardial ischemia. These include a decrease in the degree of ST-segment depression during both exercise and atrial pacing [17, 18, 21], an improvement in myocardial lactate metabolism with SCS use during pacing [19], and a decrease in the frequency and duration of ischemic ECG abnormalities during 24-h ambulatory ECG monitoring [16, 21].

Conclusion

There appears to be reasonably robust clinical evidence that each of these new therapies improves anginal symptoms in patients with chronic refractory angina to a degree that is

both statistically and clinically significant. The mechanisms of action of these modalities remain unclear. TMR may be best employed during CABG for regions of the myocardium that cannot be sufficiently revascularized by grafting, as use in this setting would avoid the additional mortality and morbidity associated with thoracotomy. For other patients, both PMR and SCS are attractive options. Which of these procedures, if either, is more effective, is not known. We are currently conducting a randomized trial at our institution to address this issue. Until the results of this trial are known, practical issues including patient and physician preference and the availability of each procedure are likely strongly to influence the choice of therapy. ■

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Cardioprotection during myocardial revascularization: benefit of a metabolic intervention

Ioana Holban, MD

Abstract

Revascularization procedures such as PCI or CABG currently represent a widely used therapeutic option for treating coronary patients.

While improving the prognosis of patients, these techniques still trigger myocardial damage as they induce transient and profound ischemia.

Therefore, myocardial protection during such interventions remains an important therapeutic target. Conventional hemodynamic agents (β -blockers, calcium antagonists and long-acting nitrates) do not seem to provide patients with strong benefits in terms of cardioprotection.

A new therapeutic approach, derived from a better understanding of cardiac metabolism alterations during ischemia, has provided myocardial protection during revascularization procedures through a direct action on myocyte metabolism. Trimetazidine (Vastarel 20), the first of a new class of metabolic agents, known as 3-KAT inhibitors, acts on a critical step in cardiac metabolism: fatty acid oxidation. Through a decrease in fatty acid oxidation, secondary to the selective inhibition of an enzyme (the 3-KetoAcyl CoA Thiolase), trimetazidine significantly reduces ischemia-induced metabolic injury. Recent randomized clinical trials illustrate the anti-ischemic benefits of this agent during primary angioplasty (LIST study) or during surgery (Fabiani study). In both situations, trimetazidine was shown to prevent ischemia-reperfusion damage.

■ *Heart Metabol.* 2002;16:23–25.

Key words: Cardioprotection, PTCA, CABG, metabolic intervention, trimetazidine

In patients with stable angina, angiography and revascularization of all stenoses, irrespective of prognostic stratification, are unwarranted. Establishment of an appropriate risk profile, including noninvasive investigation of left ventricular function, reversible ischemia, exercise tolerance, and response to pharmacological therapy, is a sensitive, cost-effective, and responsible use of resources [1].

Nonetheless, cardiology entered a new era in the late 1970s when heart specialists performed the first therapeutic catheterization procedures. In September 1977, in Switzerland, Grüntzig performed the first PTCA procedure for the treatment of angina [2]. Angioplasty revolutionized cardiology, especially for the treatment of acute coronary syndromes.

Angiography plays a pivotal role in establishing the advisability and need for revascularization. If the patient is in a high-risk group, revascularization techniques should be considered. Patients with significant left main artery stenosis or triple-vessel coronary disease are best managed with CABG surgery, particularly if they are diabetic [3].

Controversy has accompanied the development of stenting procedures, which permit a significantly lower rate of restenosis, compared with PTCA, and improve clinical outcomes in acute myocardial infarction. Stenting must therefore be compared with surgery in large-scale, randomized trials in patients with three-vessel disease or left main artery stenosis.

Despite the significant improvement in prognosis due to the development of revascularization procedures, myocardial injury during PTCA and stenting is an important determinant of clinical outcome. Protection of the myocardial tissue during such procedures should therefore be an important target. Randomized studies, however, have shown limited benefits for cardioprotection using traditional hemodynamic agents (β -blockers, nitrates, and calcium antagonists). However, better understanding of the sequences of the ischemic cascade have led to the development of a metabolic approach using new pharmacologic agents. Much attention has been given to metabolic agents that are capable of acting directly on myocyte metabolism. Among these agents, trimetazidine (Vastarel 20 mg) is the first 3-KAT inhibitor to be used worldwide due to its well-documented anti-ischemic cardioprotective properties in patients with angina pectoris; while other agents, such as sodium-hydrogen exchange inhibitors, remain under evaluation.

Recent studies with trimetazidine have raised new hopes for cardioprotection during revascularization procedures due to the originality of its mechanism of action. Trimetazidine significantly reduces metabolic damage caused by ischemia, by acting on a critical step in cardiac metabolism: fatty acid β -oxidation. This is due to selective inhibition of an enzyme, the long-chain 3-ketoacyl-CoA-thiolase (3-KAT) [4]. The beneficial effects of

trimetazidine during revascularization procedures were recently illustrated in randomized clinical trials.

PTCA and stenting represent a typical model of transient profound myocardial ischemia. In a controlled, randomized trial, intracoronary trimetazidine was shown to delay ST-segment shift and reduce it by more than 40% during balloon inflation (Figure 1) [5]. These results agree with the findings of the LIST study [6]. This randomized, double-blind, placebo-controlled study assessed the value of trimetazidine in patients undergoing primary angioplasty following acute myocardial infarction [6]. Ninety-four patients with acute myocardial infarction were randomized to trimetazidine (40 mg bolus followed by 60 mg/day intravenously for 48 h) or placebo ($n = 50$), starting prior to recanalization of the infarcted vessel. Patients underwent continuous ST-segment monitoring to evaluate the return of the ST-segment deviation to baseline and the presence of ST-segment exacerbation at the time of vessel recanalization. Infarct size was measured enzymatically from serial myoglobin measurements. Left ventricular angiography was performed before treatment and repeated at day 14. The results showed an earlier and more marked return towards baseline within the first 6 h in the trimetazidine group compared with placebo ($P = 0.014$), despite higher initial ST deviation from baseline in the trimetazidine group. The clinical outcomes were similar in both groups, which

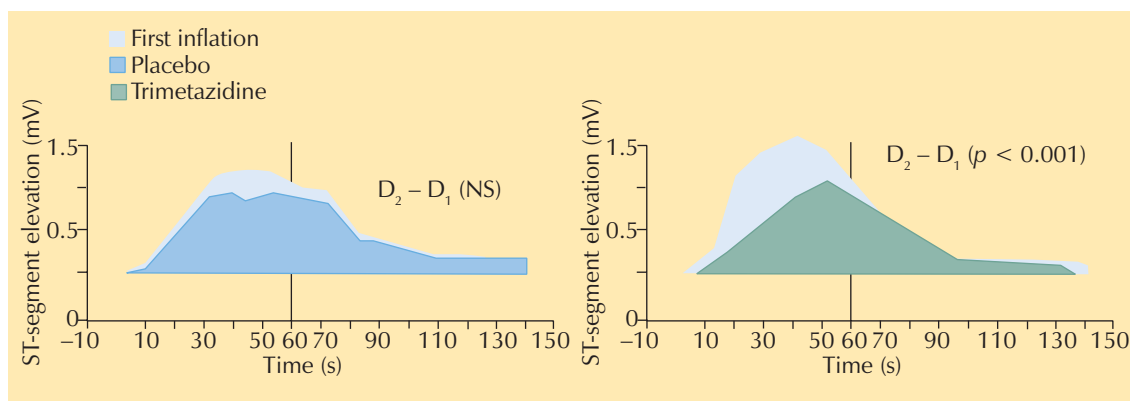


Figure 1. Change in ST-segment shift and extent with trimetazidine vs placebo during balloon inflation [5]. D_1 , first inflation 5 min after successful dilatation; D_2 , second inflation 5 min after D_1 .

may probably be related to the relatively small size of the study as well as to the selection of a low-risk patient population and the relatively short follow-up time.

In view of the LIST study, we can conclude that trimetazidine, compared with placebo, leads to earlier resolution of ST-segment elevation in patients undergoing PTCA following acute myocardial infarction. This confirms the anti-ischemic effect of the drug.

Other metabolic agents, for example cariporide used in the GUARDIAN study, failed to demonstrate any benefits in comparison with placebo on the composite end point of death and myocardial infarction in patients undergoing high-risk PTCA [7].

Trimetazidine has also been shown to possess cardioprotective benefits during CABG. In a double-blind, placebo-controlled study, 19 patients were randomized to either trimetazidine or placebo, 3 weeks before CABG [8]. Metabolic assessments showed that the increase in malondialdehyde measured in the coronary sinus after reperfusion was significantly reduced by trimetazidine compared with placebo ($P = 0.014$). Myosin level was lower with trimetazidine ($P = 0.036$), and ventricular function also improved ($P = 0.01$). Trimetazidine seems to reduce ischemia-reperfusion damage during cardiac surgery, since pretreatment with trimetazidine prior to CABG allows the patient to undergo the procedure with preserved left ventricular function.

Conclusion

Prevention of myocardial injury during revascularization procedures (PTCA, stent, CABG)

is an important goal that has important clinical consequences in the prognosis of patients with coronary artery disease. Following initial experimental data and recent randomized clinical trials using the anti-ischemic agent trimetazidine, metabolic intervention appears to be a promising means of reducing myocardial ischemia and injury. Large-scale trials will confirm the long-term clinical benefits of trimetazidine in these specific situations. ■

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Refractory angina

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Abstract

Refractory angina implies that optimal use of all treatment modalities have been rigorously applied. This case study illustrates the importance of combining a metabolic approach to treatment with conventional hemodynamic agents enabling a satisfactory quality of life to be restored. ■ *Heart Metabol.* 2002;16:26–29.

Keywords: Refractory angina, trimetazidine

A 70-year-old woman was referred because of angina on minimal activity. She had undergone CABG surgery 10 years previously and had been well until 3 months prior to her clinic visit when her angina had returned. She was being treated with aspirin 75 mg daily, simvastatin 20 mg daily, bisoprolol 10 mg daily, nifedipine retard 20 mg twice daily, isosorbide mononitrate in a long-acting preparation 40 mg daily, and glyceryl trinitrate spray.

Clinical evaluation revealed normal sinus rhythm, blood pressure 135/80 mm Hg, no evidence of anemia, and no murmurs to suggest aortic valve disease. She was a non-insulin-dependent diabetic, well controlled on gliclazide 80 mg daily. Routine blood tests ruled out anemia (Hb 12 g/dL) and her lipids were reasonably well controlled (cholesterol 5.9 mmol/L, HDL 1.18 mmol/L, LDL 3.51 mmol/L, triglycerides 1.55 mmol/L). Her fasting glucose was 5.8 mmol/L and HbA_{1c} 6%. Her ECG revealed anterolateral ischemia (Figure 1) and her echocardiogram ruled out valvular heart disease but suggested reduced left ventricular function with an ejection fraction of 35% to 40%.

Because her symptoms were severe on conventional medical therapy she underwent coronary angiography. Unfortunately, extensive coronary artery disease was documented and none of her bypass grafts were patent (Figure 2). Discussion with the surgeons and interventional cardiologists identified no possibility of further surgery or coronary angioplasty.

It was therefore decided to continue medical therapy. Simvastatin was increased to 40 mg daily to try to achieve an LDL cholesterol <3.0 mmol/L. She was continued on bisoprolol because of the evidence of both symptomatic and prognostic benefit, but, as it was in the optimum hemodynamic dose, oral nifedipine and isosorbide mononitrate were discontinued and trimetazidine 20 mg three times daily substituted [1]. The combined strategy of a hemodynamic and a metabolic agent led to symptomatic improvement. Once stable, perindopril was added to her therapy for prognostic reasons as her ejection fraction was less than 40% [2]. Though still limited by angina, her quality of life has improved and she continues to be stable, living contentedly with her restrictions. Her current LDL cholesterol is 2.6 mmol/L.

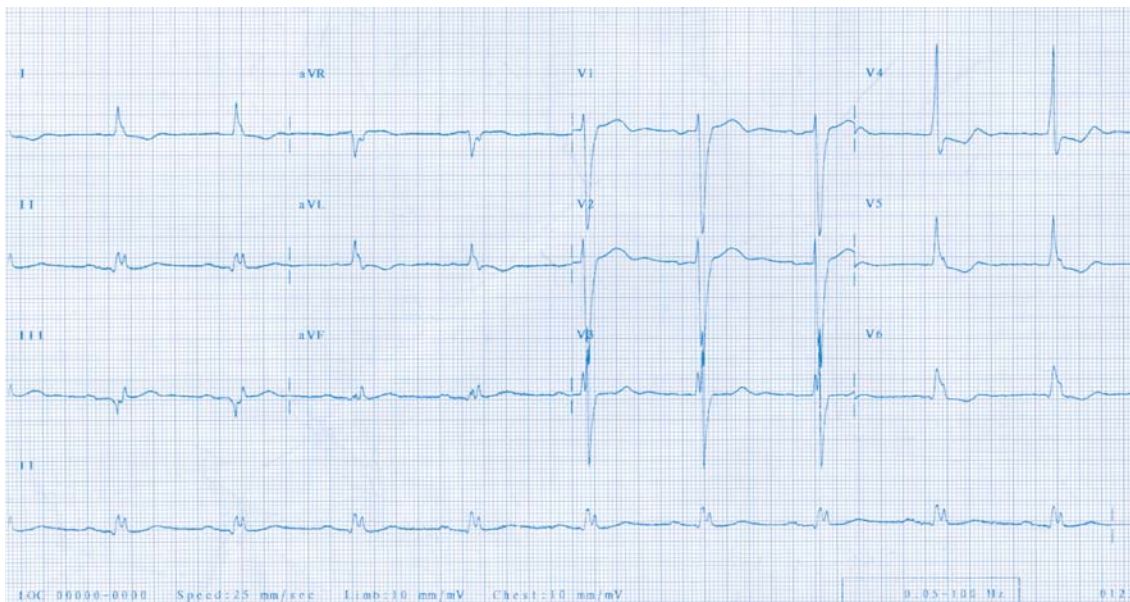


Figure 1. ECG showing extensive antero-lateral ischaemia.

Comment

The mechanism of action of conventional antianginal drugs (β -blockers, calcium antagonists, oral nitrates, nicorandil) is to reduce myocardial oxygen demand by acting hemodynamically [3]. β -Blockers slow the heart rate, lower blood pressure, and reduce the inotropic state. Calcium antagonists, nitrates,

and potassium channel activators (nicorandil), by acting as peripheral arterial and venous dilators to a variable degree, also reduce oxygen demand. Diltiazem and verapamil in addition slow the heart rate and reduce the inotropic state in a similar manner to that of β -blockers. This mechanism of benefit (reducing demand) outweighs any benefit from increasing blood supply by dilating the coronary arteries. When the maximum hemodynamic benefit has been achieved, for example by using optimal doses of β -blockers (atenolol 100 mg, not 50 mg), the addition of agents which act in a similar manner is unlikely to confer any further advantage. Judging optimal β -blockade relies on evidence from clinical trials which invariably involve peak exercise heart rate suppression as the benchmark for full β -blockade [4]. The resting heart rate is not an accurate guide. If a patient cannot tolerate full β -blockade, then combination therapy may be effective because the full hemodynamic option has not been maximized by monotherapy.

In his review of β -blockers and calcium antagonists in combination in stable angina, Packer [5] concluded:

"Evidence gathered from careful pharmacologic studies and controlled clinical trials does not

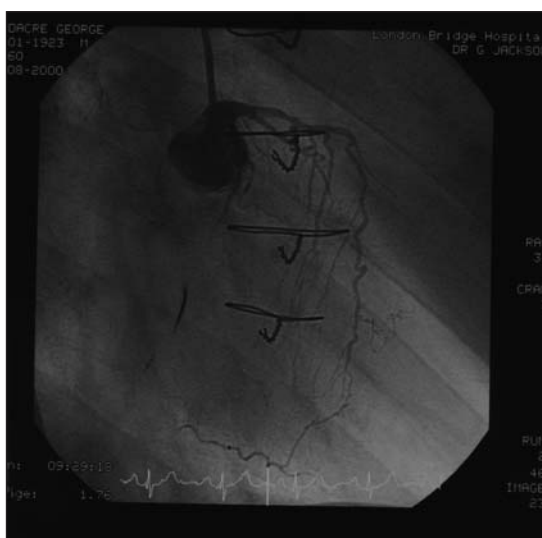


Figure 2. Extensive CAD - not suitable for percutaneous intervention or surgery.

Table 1. Trials suggesting combination hemodynamic therapy is of questionable value.

Study	Comparison	Finding
IMAGE, 1996 [8]	Metoprolol vs nifedipine vs combination of both	No evidence of additive effect in individual patients
TIBET, 1996 [9]	Atenolol vs nifedipine vs combination of both	No additive benefit from the combination
Akhras & Jackson, 1991 [4]	Atenolol alone vs: Atenolol + mononitrate, or Atenolol + nifedipine, or Atenolol + mononitrate + nifedipine (triple therapy)	Minor additive benefit for atenolol + nifedipine No additive benefit for atenolol + nifedipine or triple therapy

IMAGE, International Metoprolol/Nifedipine Angina Exercise Trial.
TIBET, Total Ischaemic Burden European Trial.

support the concept that combined therapy with a β -blocker and a calcium-entry blocker produces additive or synergistic clinical benefits in most patients with coronary artery disease.”

Ferguson and colleagues [6] found no benefit from adding either nifedipine retard 20 mg twice daily or amlodipine 5 mg once daily to bisoprolol 10 mg daily in patients with chronic stable angina. Once more, these authors used optimal-dose β -blockade, maximizing the hemodynamic approach with, as a consequence, little chance of further benefit from adding other hemodynamic-acting agents.

Reviewing the literature in 1997, Thadani [7] concluded:

“Combination therapy with two or three agents is not always superior to optimal monotherapy.”

This view is supported by the results of two major trials (IMAGE [8], comparing metoprolol with nifedipine and its combination, and TIBET [9], comparing atenolol with nifedipine and its combination) in which, again, no additional benefits were demonstrated (Table 1). Studies that have suggested a possible benefit may have underdosed the β -blocker (eg, atenolol 50 mg daily in CESAR, a trial comparing amlodipine with diltiazem in addition to atenolol [10], and atenolol 50 mg or 100 mg in a study evaluating the addition of amlodipine to atenolol [11]), because adequate β -blockade was not defined.

Metabolic agents

In contrast to the negative findings of the abovementioned hemodynamic studies are the positive findings with the use of trimetazidine in combination with conventional therapy [11]. Trimetazidine does not have any hemodynamic effects, thus it offers a unique alternative approach to conventional therapy [12]. Clinical benefit has been shown in the management of stable angina in comparison with propranolol [13] and in addition to β -blockade (which we would expect because of the different modes of action). Trimetazidine is also reported to be more effective than isosorbide dinitrate when added to propranolol [14]. In combination with diltiazem, trimetazidine favorably affects time to onset of ischemia [15].

Trimetazidine has a logical role in combination with hemodynamic agents because of its different mode of action. By using hemodynamic and metabolic agents in combination, we can optimize symptom relief for our patients with stable angina pectoris. Trimetazidine should be considered for all patients refractory to conventional hemodynamic agents.

Conclusions

- Metabolic agents combined with hemodynamic agents can significantly benefit patients with poorly controlled angina.
- A careful evaluation of other correctable exacerbating factors is essential. ■

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The physiology of pain perception in angina pectoris

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Abstract

Retrosternal chest pain with crushing, burning, or squeezing characteristics that may radiate to the left arm, the right arm, and sometimes the neck and jaw, are cardinal signs of angina pectoris. This chapter will review the neurophysiological mechanisms that may underlie these symptoms. The mechanisms providing an explanation for angina pectoris include convergence of nociceptive information from the heart, with afferent input from the overlying somatic structures, cardiac afferent input generally exciting spinothalamic tract cells that receive inputs from proximal somatic fields, and the somatic input originating predominately from muscle. Neck and jaw pain that is occasionally experienced in patients may occur because potent vagal cardiac afferent input converges on upper cervical spinothalamic tract cells that also receive somatic afferent input from the cervical and trigeminal regions. Variations in angina pectoris from patient to patient may result from modulation and processing of cardiac afferent information occurring in the hierarchy of control mechanisms that permit independent intrinsic and extrinsic cardiac and central spinal integration. ■ *Heart Metabol.* 2002;16:30–35.

Key words: Ischemic heart disease, muscle pain, spinothalamic tract, viscerosomatic convergence, vagus

Patients generally experience angina pectoris as a retrosternal chest pain with crushing, burning, or squeezing characteristics. This pain may radiate to the throat, neck, or ulnar aspect of the left arm, the right arm, sometimes reaching to the little finger. Less often, it radiates to the neck and jaw, or either the right or both arms. Intensity and pain location often vary among persons and episodes. Angina pectoris may also be expressed subjectively as a sensation of anguish and fear of impending death.

The purpose of this chapter is to review the neurophysiological basis for angina pectoris associated with ischemic heart disease. The symptoms experienced by the patients depend on how the central nervous system processes information received from the heart

and somatic structures, the state of the peripheral and central nervous system at the time these events occur, and the psychological state of the person experiencing the sensations. At present our understanding of the supraspinal mechanisms involved with angina pectoris is limited; the scope of this chapter will therefore be limited to spinal cord processing. Detailed reviews related to neurophysiological mechanisms of angina pectoris are available [1–5].

Spinal cord processing of afferent information from the heart

The heart and coronary arteries are innervated by sympathetic afferent fibers that have their

cell bodies concentrated in the dorsal root ganglia of the T2 to T6 spinal segments but can extend as far as the C8 to T9 segments [6–8]. Dorsal root ganglion cells have axons that enter the tract of Lissauer and terminate in the same segment, or the axons can ascend and descend a few segments before terminating in the spinal gray matter [7]. An important observation is that the number of sympathetic afferent fibers entering the spinal cord is much less and the afferent fibers are more diffusely distributed than is true for the somatic afferent fibers. This diffuse and extensive organization of the sympathetic afferent fibers most likely contributes to the poorly localized nature of angina pectoris.

Ascending pathways transmitting noxious cardiac information

Noxious cardiac information can be transmitted via cells of origin of ascending pathways, propriospinal neurons, and interneurons in the gray matter of the spinal cord. Of the cells in the upper thoracic gray matter, the spinothalamic tract (STT) cells are the most studied system of the ascending pathways for transmitting visceral afferent information from the heart to the brain [9–11]. The STT axons generally cross to the contralateral side within one or two segments and then ascend in the anterolateral quadrant (*Figure 1, a*) [9, 12]. These cells usually receive converging information from the heart and from somatic structures and have axons that ascend to the lateral and medial thalamus (*Figure 1, b*) [10, 11, 13, 14].

The lateral thalamus (*Figure 1, c*) that receives cardiac information via the STT incorporates the ventroposterolateral, ventroposteromedial, and ventroposteroinferior nuclei. Axons from cells of the lateral thalamus relay information to the primary somatosensory cortex and possibly to the secondary somatic cortex. Some evidence exists to suggest that visceral information projects to the somatosensory cortex [15, 16]. Information processed in this cortical area contributes to sensory discrimination [17, 18].

Cardiac and somatic information also projects via the STT to the medial thalamus (*Figure 1, d*), consisting primarily of the centralis lateralis and centrum medianum-parafascicularis nuclei [19–21]. The information generated in these nuclei is relayed to the association cortex, including the insular cortex, amygdala, and cingulate gyrus [22–24]. These nuclei may contribute to the emotional components of pain including autonomic adaptations [17, 25–27].

Common pain referral of angina pectoris: chest and arm

Angina pectoris generally has three main clinical characteristics: (1) nociceptive information from the heart is generally felt as pain referred to the overlying somatic structures [28]; (2) this pain is referred to proximal and axial body structures but generally not to distal limbs [29]; (3) the pain is generally deep and aching, and not a superficial or cutaneous pain [30].

This section will address animal studies that provide possible neurophysiological mechanisms to explain angina pectoris.

Convergence

Stimulation of cardiopulmonary afferent fibers strongly excites a majority of the STT cells in the T1 to T5 segments (*Figure 1, e*) [31] and more than half of the neurons in the C5 to C6 segments (*Figure 1, f*) [11, 14]. These same cells receive convergent somatic input from the overlying chest and arms. In contrast to thoracic and midcervical STT cells, cells in the cervical enlargement (C7 to C8) receive very little, if any, input from the activity transmitted in cardiopulmonary afferent fibers (*Figure 1, g*); their somatic innervation originates primarily from the distal forelimb and hand. This minimal activation of cells by stimulation of the cardiac afferents most likely means that pain would not be referred to the distal forelimb and head, which fits, in general, with clinical observations [32–34]. Since cardiopulmonary fibers enter the spinal cord primarily in the upper thoracic segments and they do not excite C7 to C8 STT cells, the afferent

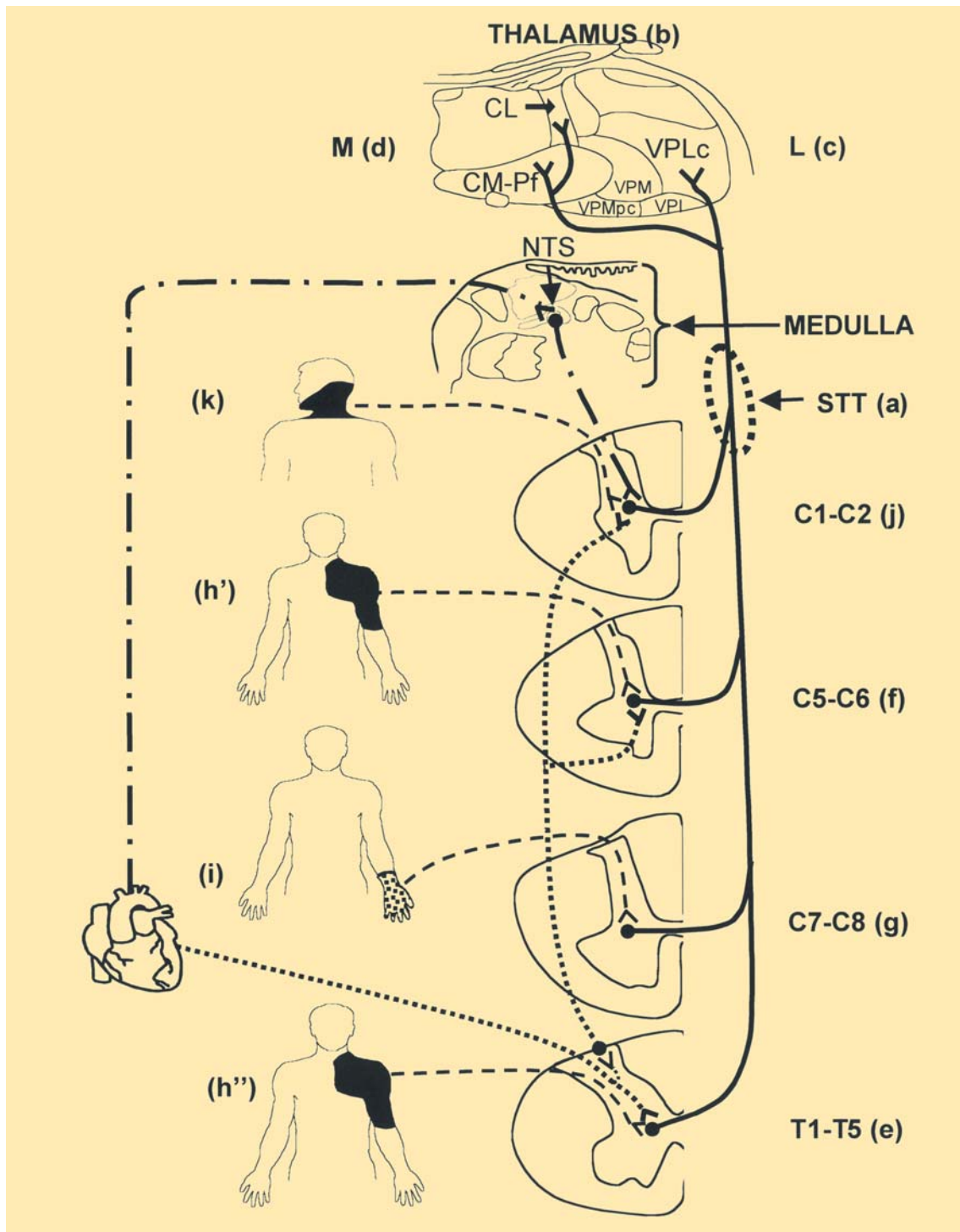


Figure 1. Schematic diagram outlining the neural organization that could explain the characteristics of referred pain associated with angina pectoris. The spinothalamic tract (STT) (a) cells in the T1 to T5 (e), C5 to C6 (f), C7 to C8 (g), and C1 to C2 (j) spinal segments are represented as a solid black line. The STT ends in the lateral (L, c) and medial (M, d) nuclei of the thalamus (b). Broken lines from figurines represent somatic afferent nerves. The dashed lines are the cardiac afferent fibers that enter the T1 to T5 spinal segments and the

input must be dependent on a propriospinal pathway that makes direct or indirect synaptic connection with upper cervical STT cells [35].

In summary, convergence of cardiac and somatic input onto a common pool of STT cells provides a substrate to explain referral of pain to somatic structures.

Proximal and axial referral

Neurophysiological observations support human studies showing that angina pectoris is most commonly felt in the proximal and axial regions of the left arm and chest, and less frequently sensed further down the arm [33, 36, 37]. In animal studies, stimulation of cardiopulmonary afferent fibers strongly excites approximately 80% of the STT cells with proximal somatic receptor fields (*Figure 1, h,h'*), but only weakly excites 35% of the cells with distal somatic input (*Figure 1, i*) [31]. Thus, a highly significant relationship exists between cells with excitatory visceral input and proximal axial fields.

Muscle-like pain

Angina pectoris often mimics muscle pain in that both of these types of pain are described as deep, diffuse, dull, and suffering. In contrast, cutaneous pain is usually sharp and localized. Similarities between muscle pain and cardiac pain are shown in patients suffering from angina pectoris [30]. Patients compared pain provoked by a hypertonic saline solution injected into the paraspinal muscles of the left eighth cervical or first thoracic spinal segment with pain that was evoked during angina pectoris. These patients observed that the onset, continuation, segmental localization, and character very closely mimicked angina pectoris [30].

Research on animal models also supports the interaction between muscle and cardiac

inputs. The STT cells excited by visceral stimulus are more likely to be excited with input from muscle than from skin [31, 38]. Muscle stimulation most powerfully excited STT cells that receive input primarily from the proximal arm and chest region (*Figure 1, h,h'*). By contrast, cutaneous stimulation alone elicited only a small response in cells with input from proximal fields. Cells with proximal somatic fields are strongly excited during cardiopulmonary afferent stimulation. However, noxious pinching of the skin alone on the hand and fingers generates the greatest responses in STT cells of C7 to C8 segments, and these responses do not increase when skin and muscle are pinched together (*Figure 1, i*). The STT cells with distal cutaneous fields were minimally excited by cardiopulmonary afferent fiber stimulation. These results provide evidence that visceral input from cardiopulmonary afferents converged most commonly with muscle afferent input onto the same STT cells, whereas the visceral stimulus has little effect on STT cells with primarily cutaneous input. Since visceral afferents converge on STT cells with afferent input from deep tissue, visceral pain, such as that resulting from myocardial ischemia, mimics muscle pain.

Uncommon pain of angina pectoris: neck and jaw pain

Pain referred to the neck and jaw region is less frequently associated with angina pectoris [33]. Interestingly, this pain sometimes remained or even appeared after surgical sympathectomy was carried out to reduce the incidence of refractory angina pectoris [4, 39]. This pain was attributed to transmission of nociceptive information in vagal afferent fibers, which commonly were thought to transmit innocuous cardiac sensory informa-

ascending pathway that bypasses the C7 to C8 segments and enters the upper cervical segments. The long dash-dot line represents the vagal afferent fibers that synapse in the nucleus tractus solitarius (NTS) of the medulla, which then sends information to the STT cells of the C1 to C2 segments. The black filled areas on the figurines represent primarily muscle input from the chest and upper arm (h,h') and neck and jaw (k). The stippled area (i) is the cutaneous input from the hand and distal arm. CL, nucleus, centralis lateralis; CMPf, centrum medianum parafascicular nucleus; VPI, ventral posteroinferior nucleus; VPLc, ventral posterolateral nucleus, caudal part; VPM, ventral posteromedial nucleus; VPMpc, ventral posteromedial nucleus, parvocellular part (Adapted from [43]).

tion. Neurophysiological studies support this supposition by showing that stimulation of vagal and sympathetic afferent fibers from the heart and chemical stimulation of the heart excite STT neurons in the C1 to C3 segments (Figure 1, j) [40, 41]. However, vagal afferent stimulation provided a much more potent activation of the STT cells than activation of cardiopulmonary afferent fibers. Somatic receptive fields for these C1 to C3 STT neurons receiving cardiac input are most commonly located on the neck, jaw, ear, and upper arm (Figure 1, k).

Summary

Afferent input from the heart excites STT cells in the thoracic and upper cervical segments of the spinal cord (Figure 1). These cells receive convergent input from the overlying somatic structures. Thus, this information forms the basis for understanding the pain resulting from ischemic heart disease. However, the huge variations in the expression of pain of overlying somatic structures and in episodes of silent ischemia raise important issues about how information is processed, modulated, and perceived. These variations could occur in the intrinsic and extrinsic cardiac ganglia, the dorsal root ganglia, spinal gray matter, and descending pathways from supraspinal nuclei. Future studies will explore the hierarchy of control mechanisms that permit independent intrinsic cardiac as well as intrathoracic, extracardiac, and central spinal integration of afferent and efferent autonomic influences involved in regional control of normal and stressed hearts [42]. ■

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Featured research

Abstracts and commentaries

Combination treatment in stable effort angina using trimetazidine and metoprolol. Results of a randomized, double-blind, multicentre study (TRIMPOL II)

Szwed H, Sadowski Z, Elikowski W, et al. *Eur Heart J*. 2001;22:2267–2274.

Commentary

Combination therapy for treating stable angina using conventional hemodynamic agents (β -blockers, calcium antagonists, and oral nitrates) confers no advantage over optimal dose of a single agent, eg, atenolol 100 mg daily. The search for an alternative strategy explored the mechanism behind ischemia at both the cellular (metabolic) and hemodynamic levels. Trimetazidine is free of any hemodynamic actions, but by partially inhibiting long-chain 3-ketoacyl-coenzyme A-thiolase it reduces fatty acid oxidation and increases myocardial glucose oxidation. These anti-ischemic properties have been confirmed both experimentally and clinically. The TRIMPOL II study was designed to assess the anti-ischemic efficacy and tolerability of trimetazidine as a form of metabolic combination therapy using the hemodynamic agent metoprolol.

TRIMPOL II was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study of patients with stable angina and documented myocardial ischemia. Metoprolol 50 mg bid was combined with trimetazidine 20 mg tid or identical placebo for a 12-week period. The primary outcome measure was time to 1-mm ST-segment depression at 12 weeks. Secondary outcome measures included exercise duration, time to angina onset, maximal ST depression, and the subjective markers of weekly anginal attack rate and nitrate consumption. In total, 347 patients

completed the study (179 taking trimetazidine and 168 taking placebo).

After 12 weeks the trimetazidine group had a significant ($P < 0.01$) improvement in time to 1-mm ST-segment depression, time to onset of angina, degree of ST depression, anginal attack rate, and nitrate consumption; total exercise duration was also significantly prolonged ($P < 0.05$). The acceptability was excellent since no drug-attributable adverse effects were reported. Of interest, the rate–pressure product was the same in both groups, suggesting a nonhemodynamic benefit of trimetazidine therapy.

This study complements other studies and confirms the validity, both theoretically and clinically, of the concept of a metabolic approach. TRIMPOL II specifically addresses the issue of combination therapy: when conventional monotherapy with a β -blocker insufficiently controls anginal symptoms, a metabolic agent such as trimetazidine is of particular value. Its fully additive benefit in combination therapy has been demonstrated both subjectively and objectively.

Graham Jackson

An evaluation of myocardial fatty acid and glucose uptake using PET with [18 F]fluoro-6-thia-heptadecanoic acid and [18 F]FDG in patients with heart failure

Taylor M, Wallhaus TR, Degradó TR, et al. *J Nucl Med*. 2001;42:55–62.

Understanding the metabolic consequences of heart failure is important in evaluating potential mechanisms for disease progression and assessing targets for therapies designed to improve myocardial metabolism in patients

with heart failure. PET is uniquely suited to noninvasively evaluate myocardial metabolism. In this study, we investigated the kinetics of 14(R,S)-[¹⁸F]fluoro-6-thia-heptadecanoic acid (FTHA) and [¹⁸F]fluoro-2-deoxy-glucose (FDG) in patients with stable NYHA functional class III congestive heart failure and a left ventricular ejection fraction of no more than 35%. Twelve fasting patients underwent dynamic PET studies using [¹⁸F]FTHA and [¹⁸F]FDG. From the dynamic image data, the fractional uptake rates (Ki) were determined for [¹⁸F]FTHA and [¹⁸F]FDG. Subsequently, serum FFA and glucose concentrations were used to calculate the myocardial FFA and glucose uptake rates, respectively. Uptake rates were compared with reported values for [¹⁸F]FTHA and [¹⁸F]FDG in subjects with normal left ventricular function. The average Ki for [¹⁸F]FTHA was 19.7 ± 9.3 mL 100 g⁻¹ min⁻¹ (range, 7.2–36.0 mL 100 g⁻¹ min⁻¹). The average myocardial fatty acid use was 19.3 ± 2.3 mmol 100 g⁻¹ min⁻¹. The average Ki for [¹⁸F]FDG was 1.5 ± 0.37 mL 100 g⁻¹ min⁻¹ (range, 0.1–3.3 mL 100 g⁻¹ min⁻¹), and the average myocardial glucose use was 12.3 ± 2.3 mmol 100 g⁻¹ min⁻¹. Myocardial FFA and glucose use in heart failure can be quantitatively assessed using PET with [¹⁸F]FTHA and [¹⁸F]FDG. Myocardial fatty acid uptake rates in heart failure are higher than expected for the normal heart, whereas myocardial glucose uptake rates are lower. This shift in myocardial substrate use may be an indication of impaired energy efficiency in the failing heart, providing a target for therapies directed at improving myocardial energy efficiency.

Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure

Wallhaus TR, Taylor M, DeGrado TR, et al. *Circulation*. 2001;103:2441–2446.

Use of β-adrenoceptor blockade in the treatment of heart failure has been associated with a reduction in myocardial oxygen consumption and an improvement in myocardial energy efficiency. One potential mechanism for

this beneficial effect is a shift in myocardial substrate use from increased FFA oxidation to increased glucose oxidation. We studied the effect of carvedilol therapy on myocardial FFA and glucose use in nine patients with stable NYHA functional class III ischemic cardiomyopathy (left ventricular ejection fraction ≤35%) using myocardial PET studies and resting echocardiograms before and 3 months after carvedilol treatment. Myocardial uptake of the novel long-chain fatty acid metabolic tracer 14(R,S)-[¹⁸F]fluoro-6-thia-heptadecanoic acid (FTHA) was used to determine myocardial FFA use, and [¹⁸F]fluoro-2-deoxy-glucose (FDG) was used to determine myocardial glucose use. After carvedilol treatment, the mean myocardial uptake rate for [¹⁸F]FTHA decreased (from 20.4 ± 8.6 to 9.7 ± 2.3 mL 100 g⁻¹ min⁻¹; $P < 0.005$), mean fatty acid use decreased (from 19.3 ± 7.0 to 8.2 ± 1.8 μmol 100 g⁻¹ min⁻¹; $P < 0.005$), mean myocardial uptake rate for [¹⁸F]FDG was unchanged (from 1.4 ± 0.4 to 2.4 ± 0.8 mL 100 g⁻¹ min⁻¹; $P = 0.14$), and mean glucose use was unchanged (from 11.1 ± 3.1 to 18.7 ± 6.0 μmol 100 g⁻¹ min⁻¹; $P = 0.12$). Serum FFA and glucose concentrations were unchanged, and mean left ventricular ejection fraction improved (from $26 \pm 2\%$ to $37 \pm 4\%$; $P < 0.05$). Carvedilol treatment in patients with heart failure results in a 57% decrease in myocardial FFA use without a significant change in glucose use. These metabolic changes could contribute to the observed improvements in energy efficiency seen in patients with heart failure.

The effects of β_1 -blockade on oxidative metabolism and the metabolic cost of ventricular work in patients with left ventricular dysfunction: a double-blind, placebo-controlled, positron-emission tomography study

Beanlands RS, Nahmias C, Gordon E, et al. *Circulation*. 2000;102:2070–2075.

The mechanism for the beneficial effect of β -blocker therapy in patients with left ventricular dysfunction is unclear, but it may relate to an energy-sparing effect that results in improved cardiac efficiency. C-11 acetate kinetics, measured using PET, are a proven noninvasive marker of oxidative metabolism and myocardial oxygen consumption (MVO_2). This approach can be used to measure the work–metabolic index, which is a noninvasive estimate of cardiac efficiency. The aim of this study was to determine the effect of metoprolol on oxidative metabolism and the work–metabolic index in patients with left ventricular dysfunction. Forty patients (29 with ischemic and 11 with nonischemic heart disease; left ventricular ejection fraction <40%) were randomized to receive metoprolol or placebo in a treatment protocol of titration plus 3 months of stable therapy. Seven patients were not included in the analysis because of withdrawal from the study, incomplete follow-up, or nonanalyzable PET data. The rate of oxidative metabolism (k) was measured using C-11 acetate PET, and stroke volume index (SVI) was measured using echocardiography. The work–metabolic index was calculated as follows: (systolic blood pressure \times SVI \times heart rate)/ k . No significant change in oxidative metabolism occurred with placebo ($k = 0.061 \pm 0.022$ to 0.054 ± 0.012 per min). Metoprolol reduced oxidative metabolism ($k = 0.062 \pm 0.024$ to 0.045 ± 0.015 per min; $P = 0.002$). The work–metabolic index did not change with placebo (from $5.29 \pm 2.46 \times 10^6$ to $5.14 \pm 2.06 \times 10^6$ mm Hg mL/m²), but it increased with metoprolol (from $5.31 \pm 2.15 \times 10^6$ to $7.08 \pm 2.36 \times 10^6$ mm Hg mL/m²; $P < 0.001$). Selective β -blocker therapy with metoprolol leads to a reduc-

tion in oxidative metabolism and an improvement in cardiac efficiency in patients with left ventricular dysfunction. It is likely that this energy-sparing effect contributes to the clinical benefits observed with β -blocker therapy in this patient population.

Commentary

The three abovementioned articles give some insight into the alterations of oxidative metabolism in patients with heart failure. The study by Taylor et al shows that in patients with heart failure, fatty acid uptake is increased and glucose uptake is decreased in comparison with normal healthy volunteers. This is surprising as it is generally assumed (from animal data) that fatty acid oxidation is decreased and glucose oxidation is increased in heart failure [1]. However, the data are in line with previous clinical studies in patients with heart failure (see the original paper for references). Importantly, the FTHA and FDG measurements were performed in myocardial segments with relatively preserved contractile function. Possibly, this remodeled tissue may have other metabolic characteristics than failing (post)ischemic tissue. Thus, further studies are needed to unravel the seemingly contradictory changes of metabolism in heart failure.

Patients with heart failure may have elevated levels of catecholamines, leading to an increased and inefficient oxygen use of the myocardium. This inefficient use of oxygen and energy substrates was studied by the same group (Wallhaus et al). These authors studied the effect of β -blocker treatment in patients with heart failure and demonstrated that carvedilol treatment reduced fatty acid (FTHA) uptake, while glucose (FDG) uptake remained unaltered. Despite the fact that fatty acid uptake was decreased, the ejection fraction and stroke volume were increased. This indicates that the heart more efficiently uses the energy substrates (glucose and fatty acids) for contraction. This may well be one of the protective mechanisms of β -blocker therapy in heart failure.

The relation between cardiac work and

metabolic efficiency was particularly studied in the third abstract by Beanlands et al using C-11 acetate. In a double-blind placebo-controlled study they clearly demonstrated that the efficiency of oxidative metabolism was increased during β -blocker treatment in patients with heart failure. Similarly to Wallhaus et al, they found that the oxidation rate of C-11 acetate was reduced after metoprolol treatment, but at the same time the efficiency (hemodynamics parameters divided by the oxidation rate of C-11 acetate) increased.

To summarize, there are clear changes in fatty acid and glucose metabolism in patients with heart failure. The exact nature of the changes in relation to the type of dysfunctional tissue needs further study. It is clear that metabolic studies need to be linked to hemodynamics. Further, the failing heart inefficiently uses metabolic substrates and this inefficiency can be improved by therapeutic interventions such as β -blockade.

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Frans C. Visser

Targeted disruption of inducible nitric oxide synthase protects against obesity-linked insulin resistance in muscle

Perreault M, Marette A. *Nat Med.* 2001;7:1138–1143.

The authors investigated whether genetic disruption of iNOS expression could protect against obesity-linked insulin resistance. iNOS expression was increased in skeletal muscle of genetic and dietary models of obesity. Moreover, mice in which the gene encoding iNOS was disrupted (*Nos2*^{-/-} mice) are protected from high-fat-induced insulin resistance.

Whereas both wild-type and *Nos2*^{-/-} mice developed obesity on the high-fat diet, obese *Nos2*^{-/-} mice exhibited improved glucose tolerance, normal insulin sensitivity *in vivo*, and normal insulin-stimulated glucose uptake in muscles. iNOS induction in obese wild-type mice was associated with impairments in phosphatidylinositol 3-kinase activation by insulin in muscle. These defects were fully prevented in obese *Nos2*^{-/-} mice. These findings provide genetic evidence that iNOS is involved in the development of muscle insulin resistance in diet-induced obesity.

Commentary

Nitric oxide (NO) has a pivotal role in the physiology and pathophysiology of the central nervous, cardiovascular, and immune systems. The reactivity of NO toward molecular oxygen and various biological targets enables it to act as a signal transduction molecule and to control diverse biological functions. However, excessive NO formation by the inducible member of the nitric oxide synthase family (iNOS) has also been shown to be a mediator of nonspecific tissue damage and is thought to be involved in the pathogenesis of inflammatory and autoimmune diseases. Recent studies also suggest that iNOS may be involved in the pathogenesis of metabolic disorders associated with a low-grade chronic inflammatory state, such as atherosclerosis and obesity-linked type 2 diabetes. These diseases are characterized by insulin resistance, as indicated by the inability of insulin to promote glucose disposal in peripheral tissues and to inhibit hepatic glucose production. It has been proposed that chronic iNOS induction may cause insulin resistance.

High-fat-mediated obesity likely causes iNOS induction by promoting the expression and secretion of TNF α * and other proinflammatory cytokine*. Because skeletal muscle is infiltrated with adipose tissue in obese subjects, enhanced production of cytokines by

*See Glossary, *Heart Metabol.* 2001;13:48–49.

adipocytes may thus contribute to the development of muscle insulin resistance in obesity. Another potential factor that may be involved in iNOS induction in muscle of obese mice is an increased availability of circulating or intramyocellular free fatty acids. As NO is a low-molecular-weight, highly lipophilic molecule, and can diffuse rapidly to adjacent cells, it is possible that iNOS induction and NO production by local adipose cells also contribute to muscle insulin resistance in obesity. Recent studies have shown that iNOS is induced in the pancreatic β -cells and hearts of Zucker diabetic fatty rats, and suggested that NO production in these tissues caused impaired insulin secretion and cardiac dysfunction by promoting programmed cell death (apoptosis) [1, 2]. Together with those findings, the present data by Perreault and Marette strongly suggest that iNOS may have a pathogenic role not only in the develop-

ment of skeletal muscle insulin resistance but also possibly in obesity-linked β -cell failure and cardiovascular dysfunction. This study also raises the possibility that agents that reduce iNOS expression or activity may have beneficial effects on obesity-linked insulin resistance and associated complications.

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J. Danielle Feuvray

* See Glossary, *Heart and Metabolism*

Glossary

Gary Lopaschuk and William Stanley

Allogenic

Is a medical term that refers to any stimulus or situation that causes pain.

Bradykinin

Bradykinin is a kinin hormone that binds to bradykinin receptors and produces various responses. Binding of bradykinin to receptors on smooth muscle cells causes vasodilatation. Bradykinin binding to neural receptors can also produce pain sensations.

Cariporide

Cariporide is a drug that inhibits an enzyme called the sodium-hydrogen exchanger. This exchanger exists in the membrane of cells, including the cardiomyocyte, and exchanges intracellular hydrogen for extracellular sodium. Inhibition of this enzyme prevents the accumulation of sodium inside the cell during ischemia. Cariporide has been tested in clinical trials for use in various forms of ischemic heart disease, and has shown some promise as a cardioprotective agent during coronary artery bypass surgery.

3-KAT inhibitor

3-KAT is the abbreviation for 3-ketoacyl-CoA thiolase. 3-KAT is the last enzyme in the intramitochondrial pathway that is involved in the metabolism of fatty acids (fatty acid β -oxidation). 3-KAT inhibitors, such as trimetazidine, inhibit the activity of this enzyme, thereby inhibiting fatty acid oxidation. Recent interest has focused on 3-KAT inhibitors as a novel therapeutic approach to protecting the ischemic heart.

Ligands

A ligand is term used to identify any molecule that binds to another molecule. Examples of ligands include hormones, peptides, or other molecules that bind to receptors or enzymes. For example, norepinephrine is a ligand for the β -receptor, and fatty acids are ligands for peroxisome proliferator-activated receptors.

Malonyldialdehyde

Malonyldialdehyde is a small molecule that is released from larger molecules, such as lipids, during oxidative stress. Measurement of the release of this compound is often used as an index of the degree of free radical oxidative stress to which a cell or organ is being exposed.

Myosin

Myosin is one of the two main proteins involved in muscle contraction. It is a large protein that interacts with actin to form the muscle striations typical of muscle fibers. Sliding of myosin by actin is an important step in muscle contraction.

Nociceptor

A nociceptor is a receptor organ that is sensitive to stimuli capable of causing harm or injury. In response to the stimuli, the receptor would provide the sensation of pain (via neural transmission of the sensory stimulus from the receptor to the brain).