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Stable angina – taking time

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''Time is the great physician''
Disraeli [1804–1881]

Stable angina that is chronic is, by definition, chronic and stable. This may seem obvious, but stability may often be overlooked by interventional cardiologists whose mind-sets are catheter-based rather than clinically based in the broadest context of the term. The real question is whether we can improve a patient's quality of life with the minimum risk. We recognize certain prognostically important anatomical subsets, such as left main-stem disease or triple-vessel disease with reduced left ventricular function, which benefit from surgical intervention but, to date, percutaneous coronary intervention (PCI) has not been shown to improve or reduce life expectancy. It follows that, once a patient at high prognostic risk has been identified (usually by exercise testing and subsequent angiography), we have time to optimize the management of those at lower risk. Time taken to address lifestyle issues and utilize drug therapy to its evidence-based best is time well spent.

The Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) randomized trial addressed the question of whether, in patients with stable coronary artery disease, PCI as the *initial* management, followed by aggressive risk reduction, lifestyle advice, and drug treatment was superior to optimal medical treatment alone in reducing cardiovascular events over a median of 4.6 years of follow-up [1]. PCI as the initial strategy did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when combined with optimal medical treatment. Optimal medical therapy was impressive in both groups with more than 70% taking an angiotensin-converting enzyme inhibitor or angiotensin II antagonist, 90% a statin, 95% aspirin and 85% a β-blocker.

The Medicine, Angioplasty or Surgery Study (MASS II) compared coronary artery bypass grafting (CABG) with PCI and medical treatment in patients with stable multivessel disease over a 5-year period [2]. All three treatments were associated with similar low rates of death, and medical treatment was similar to PCI with regard to the long-term incidence of events and the need for revascularization.

Medical treatment has made a substantial impact on cardiac events in both the acute and chronic coronary settings, with the evidence base for, in particular, high-dose statin therapy being particularly strong [3]. In stable patients, the coronary atheroma is usually obstructive to flow and symptomatic, with plaque that, in turn, is usually stable (thick fibrous cap, lipid-poor, smooth muscle cells present), giving us time to optimize medical treatment. In the acute situation, a lipid-rich plaque that is usually non obstructive ruptures through its thin fibrous cap, often in the presence of evidence of inflammation – giving us little time to take action [4]. Both pathologies may coexist, and we know, from the Pravastatin or Atorvastatin Evaluation and Infection Treatment (PROVE-IT) trial in patients with acute coronary syndrome, that an aggressive lipid-decreasing approach with atorvastatin complemented intervention when used in addition to good evidence-based standard medical treatment, with a significant benefit occurring by 30 days (probably as a result of anti-inflammatory actions) and continuing beyond 2 years (plaque stability) [5]. Of importance is the need to continue medical treatment as optimally as possible into the long term [6].

In stable angina, the key is the stability of the clinical situation, and therefore the *time* to optimize overall treatment – not forgetting medical treatment continues after PCI or CABG. Given the evidence for a symptom-driven strategy, additional symptom-relieving treatment has a potentially important part to play.

Trimetazidine acts metabolically and is a very effective agent when used in addition to conventional hemodynamic therapy in stable angina, so its role is

likely to increase as part of the evolving paradigm [7]. In view of the findings of the COURAGE and MASS II trials, trimetazidine should be considered in patients whose condition is stable and who are receiving medical treatment if their symptoms are troublesome, and before angiography that is undertaken with a view to PCI or CABG. Medical treatment using trimetazidine in addition to conventional hemodynamic antianginal agents can be further optimized, which is good news for patients with stable coronary artery disease.

In this issue of *Heart and Metabolism*, we look at stable angina from all aspects, trying to find a balanced approach to both symptoms and prognosis. Whilst I am not obsessed with time, it is time that we have on our side, allowing us to optimize care with minimum risk, so we need to make the most of it.

"The physician's best remedy is 'Tincture of Time!'" Shick [1872–1967]

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Optimizing cardiac energy substrate metabolism: a novel therapeutic intervention for ischemic heart disease

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Abstract

Ischemic heart diseases, encompassing and ranging from angina pectoris to acute myocardial infarction, have a major impact on both cardiac energy metabolism and cardiac function. In the normal heart, energy metabolism and function are exquisitely matched. However, during and after ischemia there are both a decrease in energy production and disturbances in the balance between use of fatty acid and of glucose by the heart. The dominance of fatty acid oxidation as a source for the generation of ATP at the expense of glucose oxidation during and after ischemia has a negative impact on both cardiac efficiency and cardiac contractile function. Thus optimizing energy substrate metabolism, such that the efficiency of both generating and utilizing ATP is maximized has emerged as a novel therapeutic intervention in various manifestations of ischemic heart disease. For example, the antianginal benefit of trimetazidine can be attributed to the partial inhibition of fatty acid oxidation and the reciprocal increase in glucose oxidation. This optimization of the balance between fatty acid and glucose metabolism results in an improvement in the efficiency of both the generation and utilization of ATP. Other pharmacological agents also exploit this plasticity and interdependence between the pathways of fatty acid and glucose oxidation. This is achieved either by altering flux through these metabolic pathways, or by altering the availability of circulating energy substrates. Thus the multitude of targets available to optimize myocardial energy metabolism may significantly increase the armamentarium of therapeutic interventions for preserving cardiac contractile function and limit the untoward effects of ischemic heart disease.

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Introduction

Alterations in myocardial energy substrate metabolism contribute significantly to ischemic heart disease. Angina pectoris is a common form of ischemic heart disease, and has an impact on both the amount of energy produced by the heart and the type of fuel it metabolizes. In this context, a growing body of evidence indicates that the modulation and optimizing of myocardial energy substrate metabolism are useful therapeutic interventions for the treatment of various forms of ischemic heart disease, including angina pectoris.

The heart is an omnivorous organ. It uses fatty acids, glucose, lactate, and ketone bodies as fuels to sustain contractile function. The contribution of each substrate to the overall production of ATP is tightly regulated, with each pathway possessing a considerable

degree of plasticity and interdependence. Under normal aerobic conditions, the heart relies primarily on fatty acids as substrates for oxidative metabolism. Fatty acid β-oxidation normally contributes 60–70% of total ATP production in the healthy adult heart; the remainder is provided mainly by carbohydrate oxidation (glucose oxidation and lactate oxidation), and also (at a very low percentage) by the oxidation of ketone bodies [1,2]. With respect to the major ATP-producing processes in the heart, fatty acid oxidation produces more ATP per molecule oxidized than does glucose oxidation; however, fatty acid oxidation requires a greater amount of oxygen per molecule of ATP produced. Thus fatty acid oxidation is less efficient than glucose oxidation with regards to ATP production per molecule of oxygen consumed.

Disease states and other conditions (eg, elective cardiac surgical procedures) that result in a serious insult to the heart can perturb the tightly regulated energetic balance in the heart, which can contribute to myocardial damage. An example of this is ischemic heart disease, which dramatically alters both the rate of energy production and the source of energy supply. During ischemia, oxygen availability is reduced as a result of deficient tissue perfusion, resulting in a mismatch between oxygen demand and oxygen supply. A decrease in oxygen supply results in a concomitant decline in the rates of mitochondrial oxidative metabolism. During ischemia, glycolysis becomes increasingly important because of its ability to generate ATP in the absence of oxygen. Unfortunately, this can lead to the intracellular accumulation of lactate and protons (H^+), which in itself can decrease cardiac efficiency. Furthermore, during ischemia, plasma free fatty acid concentrations increase dramatically, and result in the rapid recovery of fatty acid oxidation during subsequent reperfusion of the ischemic myocardium. These increased rates of fatty acid oxidation uncouple glycolysis and glucose oxidation, and so increase H^+ production. The dramatic increase in rates of fatty acid oxidation in early reperfusion can impair the recovery of cardiac function.

As knowledge of how cardiac energy metabolism is regulated increases, the potential application of metabolic modulation to the treatment of ischemic heart disease has become the subject of extensive research and review. The aim of this article is to present the mechanistic basis for the use of pharmacological agents to optimize myocardial energy substrate metabolism in order to limit the deleterious consequences of ischemia.

Myocardial energy metabolism

Under aerobic conditions, more than 50% of the ATP produced in the heart is derived from mitochondrial oxidative phosphorylation (*Figure 1*) [1,2]. Reducing equivalents (H^+ and electrons) are transferred from substrates to the mitochondria by the reduced forms of flavine adenine dinucleotide ($FADH_2$) and nicotinamide adenine dinucleotide (NADH), generated by dehydrogenase reactions occurring during β-oxidation, the Krebs (tricarboxylic acid [TCA]) cycle and pyruvate oxidation (glucose oxidation). The extents to which the various metabolic pathways contribute to the production of ATP are dependent on energetic demand, which itself is determined by contractile work.

In the presence of a normal oxygen supply, glucose and fatty acids both undergo oxidation through different processes that link at the level of the TCA cycle

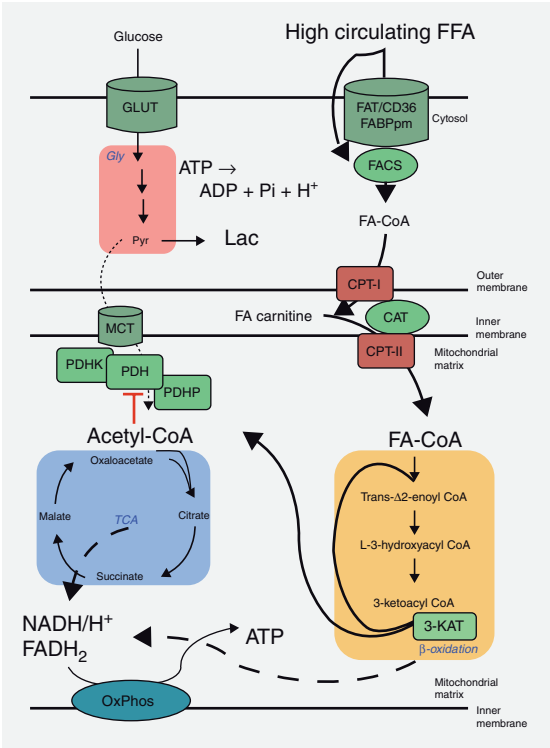

Figure 1. Glucose/fatty acid cycle. In the presence of high concentrations of circulating free fatty acids, fatty acid uptake and oxidation increase considerably, resulting in an accumulation of acetyl coenzyme A (CoA), which in turn inhibits the pyruvate dehydrogenase (PDH) complex, uncoupling glycolysis from subsequent oxidation. This further results in the hydrolysis of glycolytic ATP uncoupled from oxidative metabolism and concomitantly increased production of cytosolic protons, which can result in intracellular acidosis. CAT, carnitine acyl translocase; CPT, carnitine palmitoyl transferase; FABPpm, fatty acid binding protein of the plasma membrane; FACS, fatty acyl CoA synthase; FA CoA, fatty acyl CoA; FAT/CD36, fatty acid transporter; FFA, free fatty acid; GLUT, glucose transporter; Gly, glycolysis; 3-KAT, 3-ketoacyl CoA thiolase; Lac, lactate; MCT, monocarboxylic transporter; OxPhos, oxidative phosphorylation; PDHK, pyruvate dehydrogenase kinase; PDHP, pyruvate dehydrogenase phosphatase; Pi, inorganic phosphate; Pyr, pyruvate; TCA, tricarboxylic acid cycle.

(*Figure 1*). The presence of this common pathway is central both to the mechanisms regulating flux through these pathways and to the interdependence of these processes for ATP production.

Glucose used for the generation of ATP originates from the blood stream, or is liberated from endogenous glucose stores (ie, glycogen). Glucose enters the cardiac myocyte via glucose transporters (GLUTs) [3]. GLUT 4 is the main myocardial glucose transporter, and is sensitive to insulin stimulation, whereas a small percentage of glucose transport occurs via the insulin-insensitive transporter, GLUT 1. By the glycolytic pathway, glucose is converted into pyruvate with the net production of two molecules of ATP and two molecules of NADH. In the presence of oxygen, pyruvate is oxidized (glucose oxidation) by the pyruvate dehydrogenase (PDH) complex to form acetyl coenzyme A (CoA), which then feeds into the TCA cycle. Alternatively, in the absence of adequate oxygen, pyruvate can be converted to lactate by the enzyme lactate dehydrogenase (LDH), to regenerate the NAD^+ required to maintain glycolysis. The PDH complex is rate-limiting for glucose oxidation, and is highly sensitive to product inhibition by acetyl CoA. When high rates of fatty acid oxidation are present, there is an increase in the concentration of acetyl CoA, which in turn can inhibit glucose oxidation [4–6]. This reciprocal inter-regulatory relationship between glucose oxidation and fatty acid oxidation was originally described by Philip Randle, and is known as the glucose/fatty acid cycle or Randle cycle [7].

On the other side of oxidative metabolism lies fatty acid oxidation. Fatty acid oxidation occurs mainly in the mitochondrial matrix and is highly dependent on the delivery of fatty acids, first from the plasma to the cytoplasm, and subsequently from the cytoplasm to the mitochondrial matrix. Fatty acids enter the cardiac myocyte either by passive diffusion or via protein-mediated uptake. The key transporters involved in fatty acid uptake are fatty acyl translocase (FAT/CD36) and the plasma membrane isoform of fatty acid binding protein (FABPpm) [3,8]. Fatty acids are then esterified to fatty acyl CoA, which is mediated by a family of fatty acyl CoA synthase (FACS) enzymes. The mitochondrial uptake of fatty acyl CoAs is mediated by carnitine palmitoyl transferases (CPT) I and II and carnitine acyl translocase (CAT) [1,9]. CPT-I is present on the outer mitochondrial membrane. It binds to fatty acyl CoAs and catalyzes the formation of fatty acyl carnitines which are transported to the mitochondrial inter-membrane space. There, CAT translocates fatty acyl carnitines into the matrix (in exchange for carnitine), where CPT-II re-esterifies acyl carnitines into acyl CoAs (*Figure 1*). Matrix acyl CoAs can then be progressively metabolized by fatty acid oxidation. Four main enzyme classes are involved in the mitochondrial fatty acid oxidation: acyl CoA dehydrogenase, 2-enoyl CoA hydratase, 3-hydroxyacyl CoA dehydrogenase and 3-ketoacyl CoA thiolase (3-KAT). In the fatty acid oxidation spiral, fatty acyl CoAs are broken down to acetyl CoA, which feeds into the TCA cycle for the production of ATP. Both acyl CoA dehydrogenase and 3-hydroxyacyl CoA dehydrogenase are sensitive to the redox state of the matrix (FAD/$FADH_2$ and NAD^+/NADH ratios). In the presence of high rates of glucose oxidation, the concentration of NADH is increased, and the redox state of the mitochondria favors an inhibition of fatty acid oxidation. Fatty acid oxidation is also regulated at the level of 3-KAT, which is sensitive to the acetyl CoA/CoA ratio, and in the presence of high glucose oxidation rates acetyl CoA accumulates and inhibits 3-KAT.

On the basis of the enzymes involved in fatty acid oxidation, there are numerous targets available that can be exploited to optimize and modulate myocardial energy metabolism in order to limit the untoward effects of ischemic heart disease. Several pharmacological approaches to the optimization of energy substrate metabolism at the level of the balance between fatty acid and glucose metabolism (*Figure 2*) are considered below.

Carnitine palmitoyl transferase I inhibitors

Carnitine palmitoyl transferase-I is considered to be the rate-limiting enzyme for mitochondrial uptake of fatty acids. As a result, pharmacological agents exerting their anti-ischemic effects by inhibiting CPT-I have potential for therapeutic use in the treatment of ischemic heart disease (*Figure 2*). CPT-I inhibitors that have been developed for this purpose include oxfenicine, etomoxir, and perhexiline. Several experimental studies have demonstrated that the protective effects of oxfenicine [10,11], etomoxir [12,13], and perhexiline [11,14] are associated with a shift in energy substrate metabolism from fatty acid oxidation towards glucose oxidation. Of these compounds, perhexiline has received the most clinical attention.

Perhexiline was frequently prescribed as an anti-anginal agent in the 1970s; however, its use declined in the 1980s because of adverse effects, including hepatic toxicity (steatosis and necrosis), and peripheral neuropathy [15]. The mechanism responsible for these adverse effects of perhexiline is believed to be accumulation of phospholipid, secondary to the inhibition of CPT-I, and these adverse effects can therefore be presumed to be shared by CPT-I inhibitors as a class of drugs. It is of importance to note that the hepatotoxic effects of perhexiline arise as a result of the inhibition of hepatic CPT-I [16]; however, in-vitro studies indicate that the cardiac isoform of CPT-I is more sensitive to inhibition by perhexiline than is the hepatic CPT-I isoform [17]. Furthermore, monitoring

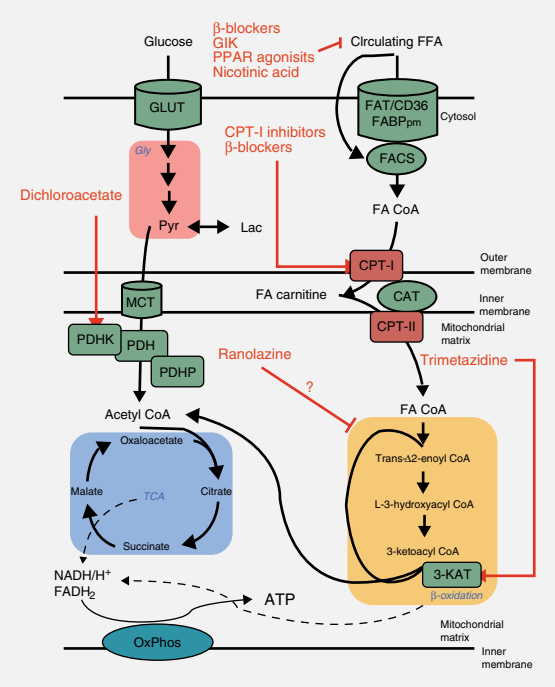

Figure 2. Pharmacological optimization of fatty acid and glucose metabolism. Three major metabolic pathways provide the necessary energy for heart function: fatty acid β-oxidation, glycolysis (Gly), and glucose oxidation (glycolysis + pyruvate [Pyr] oxidation by the tricarboxylic acid [TCA] cycle). Pharmacological compounds (shown in red) can modify energy substrate metabolism by modulating circulating concentrations of free fatty acids (FFA) and enzymatic activity at the levels of glucose oxidation, carnitine palmitoyl transferase (CPT)-I, and fatty acid oxidation. CAT, carnitine acyl translocase; CoA, coenzyme A; FABPpm, fatty acid binding protein of the plasma membrane; FA CoA, fatty acyl CoA; FACS, fatty acyl CoA synthase; FAT/CD36, fatty acid transporter; FFA, free fatty acid; GLUT, glucose transporter; Gly, glycolysis; 3-KAT, 3-ketoacyl CoA thiolase; Lac, lactate; MCT, monocarboxylic transporter; OxPhos, oxidative phosphorylation; PDH, pyruvate dehydrogenase (complex); PDHK, pyruvate dehydrogenase kinase; PDHP, pyruvate dehydrogenase phosphatase.

the plasma concentration of perhexiline and maintaining it in the therapeutic range of 150–600 μg/L markedly limits the serious adverse effects of the drug while preserving its anti-ischemic efficacy [18]. Accordingly, the potential of targeting myocardial energy substrate metabolism to limit the consequences of ischemia has led to a resurgence in the use of perhexiline.

With the biochemical mechanisms responsible for both its therapeutic and its adverse effects being elucidated, perhexiline is used as antianginal agent in New Zealand, Australia, and most European countries, on a named-patient basis. Furthermore, clinical trials have demonstrated the utility of perhexiline in refractory angina pectoris [18], aortic stenosis [19], and chronic heart failure (of ischemic and non ischemic origin) [20], in which it improves symptomatic status, left ventricular ejection fraction, and quality of life. Therefore, inhibition of CPT-I and fatty acid oxidation, with the resultant reciprocal increase in glucose oxidation, is a cardioprotective strategy that is effectively utilized in diverse forms of ischemic heart disease.

β-Adrenoceptor antagonists and myocardial energy substrate metabolism

The anti-ischemic properties of β-adrenoceptor antagonists (β-blockers) are classically attributed to an oxygen-sparing effect elicited by negative inotropic and chronotropic actions. In addition to effects on cardiac contractility, β-blockers also possess additional anti-ischemic mechanisms related to energy substrate metabolism. They reduce neurohormonal activation, and thereby can reduce catecholamine-induced lipolysis, and hence circulating plasma fatty acid concentrations (*Figure 2*) – a major determinant of the rates of fatty acid oxidation. Furthermore, several clinical studies have indicated that β-blockers decrease fatty acid uptake [21,22] and increase left ventricular function, independently of decreased oxygen consumption [23,24] – effects indicative of increased cardiac efficiency (work/oxygen consumed). These effects are probably related to the ability of β-blockers to inhibit the activity of CPT-I (*Figure 2*) [25], and induce a shift in energy substrate metabolism from fatty acid oxidation towards glucose oxidation [26].

3-Ketoacyl-coenzyme A thiolase inhibitors

Being a key enzyme in fatty acid oxidation, 3-KAT has emerged as a target for modifying fatty acid oxidation. Trimetazidine is the first of a class of partial fatty acid oxidation inhibitors that competitively inhibit the terminal enzyme of fatty acid oxidation, long-chain 3-ketoacyl CoA thiolase (*Figure 2*) [27,28]. It is clinically utilized as an antianginal agent throughout Europe and more than 90 countries worldwide [29]. The protective effects of trimetazidine are demonstrable in experimental models of ischemia-reperfusion. It decreases ischemic contracture, and lessens the increase in diastolic pressure during reperfusion after ischemia [30], and inhibits cardiac myocyte apoptosis to preserve cardiac function during reperfusion [31]. With regards to the mechanism of its anti-ischemic action, trimetazidine also protects hearts from the deleterious effects of fatty acids on the recovery of cardiac function [32]. By virtue of inhibiting fatty acid oxidation, it reciprocally stimulates glucose oxidation [27,28], and thus improves the

coupling between glycolysis and glucose oxidation, thereby decreasing the rate of H^+ production attributable to the hydrolysis of glycolytically derived ATP. These effects of trimetazidine on the pathways of fatty acid and glucose metabolism can prevent deleterious alterations in intracellular ionic homeostasis by diminishing the potential for intracellular acidosis during ischemia, in addition to intracellular Na^+ and Ca^{2+} overload during reperfusion [33,34]. Therefore, the metabolic effects of trimetazidine increase cardiac efficiency by sparing ATP hydrolysis from being utilized for correcting ionic homeostasis, thus increasing the amount of ATP hydrolysis available to drive meaningful contractile work.

Numerous clinical trials have demonstrated the efficacy of trimetazidine in various forms of ischemic heart disease, ranging from angina pectoris to acute myocardial infarction, ischemic cardiomyopathy, and heart failure. With respect to angina, the beneficial effects of trimetazidine include an increased time to 1 mm ST-segment depression, a reduction in weekly consumption of nitrates, and a reduction in the number of weekly angina attacks both in patients who have not undergone revascularization and in those undergoing revascularization via coronary artery bypass grafting procedures or percutaneous coronary intervention [35]. Trimetazidine also has cardioprotective effects in the setting of acute myocardial infarction, where it reduces reperfusion arrhythmias [36] and reduces the time to resolution of ST-segment elevation [37]. Furthermore, trimetazidine added to existing treatment has been shown to improve New York Heart Association (NYHA) functional class, decrease left ventricular end-systolic volume, and increase left ventricular ejection fraction in patients with ischemic cardiomyopathy and heart failure [38,39]. Therefore, the partial inhibition of fatty acid β-oxidation with trimetazidine limits the deleterious consequences of myocardial ischemia in varied manifestations of ischemic heart disease.

Ranolazine, similar to trimetazidine, is a partial inhibitor of fatty acid oxidation, although the molecular target responsible for this effect remains to be identified (*Figure 2*). It is now approved for use as an antianginal agent in the USA [40], and, in addition to its metabolic effects, appears to have antiarrhythmic activity. Experimental studies have demonstrated that ranolazine preserves mitochondrial ultrastructure, decreases tissue Ca^{2+} content, and improves the recovery of ventricular function during reperfusion after ischemia [41], in addition to decreasing the incidence of ventricular fibrillation during reperfusion [42]. It has also been reported to reduce the magnitude of myocardial stunning [43] and to reduce infarct size [44]. Furthermore, in canine models of heart failure, ranolazine improves ejection fraction and stroke volume without increasing oxygen consumption, and hence increases myocardial efficiency [45,46].

Several of the beneficial actions of ranolazine are most probably attributable to either a greater amount of ATP synthesized at a given level of oxygen consumption or a more effective use of the energy released from ATP hydrolysis – effects that can be explained by a shifting of myocardial energy substrate preference from fatty acid oxidation to glucose oxidation (described above) [47–49].

Clinical trials have demonstrated the antianginal efficacy of ranolazine. Both as monotherapy and in combination therapy with standard antianginal regimens, it has been shown to increase exercise duration, increase time to 1 mm ST-segment depression, reduce the weekly number of angina attacks, and reduce weekly consumption of nitroglyerin [50–53]. Furthermore, the antianginal efficacy of ranolazine is similar in both non diabetic and diabetic patients [54].

Recent clinical trials have also indicated that ranolazine decreases the incidence of ventricular tachycardia, supraventricular tachycardia, and ventricular pauses, and has no adverse effect on survival, thus confirming its long-term safety and efficacy [55,56]. The antiarrhythmic effects of the drug may be attributable to its effects on various cardiac ionic currents, particularly the late Na^+ current (for review see [57]). Interestingly, the antianginal and antiarrhythmic effects of ranolazine occur at similar therapeutic concentrations (10–20 μmol/L), and thus are probably not mutually exclusive. The effects on ranolazine on the pathways of fatty acid and glucose oxidation probably underlie its antianginal activity by improving the efficiency of ATP production.

Dichloroacetate

Dichloroacetate, like trimetazidine and ranolazine, also facilitates the shift in the balance of myocardial energy substrate metabolism away from fatty acid oxidation towards glucose oxidation; however, unlike trimetazidine and ranolazine, dichloroacetate exerts direct effects on the mitochondrial PDH complex. It inhibits the activity of PDH kinase, and thus stimulates glucose oxidation (*Figure 2*). Experimental studies have demonstrated the efficacy of dichloroacetate in enhancing the recovery of cardiac function during reperfusion after ischemia both in vitro and in vivo [58–60]. The protective effects of dichloroacetate are accompanied by a stimulation of the rate of glucose oxidation, and a resultant improved coupling between glycolysis and glucose oxidation (which reduces the production of H^+ attributable to glucose metabolism), and an increase in myocardial efficiency (work per molecule of oxygen consumed) [61,62].

Although clinical experience with dichloroacetate is limited, its metabolic mechanism of action appears to persist in the setting of heart failure. In a small clinical trial, dichloroacetate increased left ventricular stroke volume and myocardial efficiency, effects accompanied by increased utilization of lactate [63], which itself is probably the result of an increased rate of pyruvate oxidation (ie, glucose oxidation). These metabolic effects of dichloroacetate may be of therapeutic relevance in angina pectoris; however, they remain to be assessed in this setting.

Glucose–insulin–potassium for acute coronary syndromes

The concept of using glucose–insulin–potassium (GIK) solutions to protect the ischemic myocardium in acute coronary syndromes encompassing clinical conditions ranging from myocardial infarction to unstable angina was initially introduced by Sodi-Pollares et al [64]. The beneficial effects of GIK on cardiac energy metabolism that underlie the protection it affords were originally proposed by L.H. Opie as promotion of glycolysis and reduction in circulating fatty acids (*Figure 2*), with a resultant decrease in cardiac fatty acid metabolism [65]. Indeed, experimental studies have demonstrated the ability of GIK to suppress circulating fatty acid concentrations, while maintaining circulating glucose concentration [66]. These effects on circulating energy substrate concentrations are effective in inducing a shift in myocardial substrate preference from fatty acid to glucose utilization [67], and in improving post-ischemic recovery of contractile function, reducing the release of creatine kinase and lactate dehydrogenase, and reducing infarct size [66,67]. However, the protective effects of GIK are not unambiguous, as previous reports also indicate a lack of reduction in infarct size [68]. This ambiguity of GIK in experimental studies may be related to the complex nature of its effects on myocardial energy substrate metabolism – specifically, its ability to accelerate the rate of glycolysis disproportionately to that of glucose oxidation, and thus to increase the rate of H^+ production attributable to myocardial glucose metabolism, which can impair postischemic recovery of function [69].

The ambiguous effects of GIK on myocardial protection are transferred to the clinical setting, where GIK has been shown to be beneficial, neutral, and detrimental. A meta-analysis of GIK in the 'prethrombolytic' era demonstrated the ability of GIK to reduce the mortality associated with acute myocardial infarction [70], which was also evident in the thrombolytic era, as demonstrated by the Diabetic Patients with Acute Myocardial Infarction (DIGAMI) study [71] and the Estudios Cardiologicos Latinoamerica (ECLA) Collaborative Group [72]. However, a Polish GIK study (Pol-GIK) failed to demonstrate any benefit of GIK on cardiovascular mortality [73]. Furthermore, in contrast to the Dutch Glucose–Insulin–Potassium Study 1 (GIPS 1), which demonstrated a survival benefit of GIK in a subset of patients [74], the Dutch GIPS 2 study, which assessed the effects of GIK on mortality and infarct size had to be stopped early because of a potentially greater mortality in the GIK group [75]. These differences in clinical outcomes may be related to the differing doses used, the timing of administration, and the functional NYHA classes of the patient populations. As there remains no clear consensus with regards to the beneficial, neutral, or detrimental clinical effects of GIK in acute coronary syndromes, further study is warranted.

Peroxisome proliferator-activated receptor agonists

Peroxisome proliferator-activated receptors (PPARs) are members of the ligand-activated nuclear hormone receptor superfamily. PPARs exert major influences on lipid metabolism at the whole-body level (*Figure 2*); specifically, they have a central role in regulating the balance between fatty acid oxidation and fatty acid storage, by regulating the expression of enzymes involved in both fatty acid oxidation and lipogenesis [76]. Three distinct PPAR isoforms, with overlapping yet differing/preferential tissue distributions, have been identified in mammals: PPARα, PPARγ, and PPARδ. Expression of PPARα is greatest in tissues with a high capacity for fatty acid oxidation, including the liver, skeletal muscle, and heart [76,77]. PPARγ is expressed to the greatest extent in adipose tissue, with only low concentrations detected in the skeletal and cardiac muscle. PPARδ is the predominant isoform expressed in skeletal muscle, white adipose tissue, and brown adipose tissue (in rodents) [78]. Importantly, PPARs are the molecular targets of several clinically useful pharmacological agents that alter whole-body lipid metabolism.

PPARα is the molecular target of the antihyperlipidemic fibrate class of drugs (clofibrate, fenobibrate, gemfibrozil). Fibrates differentially affect the fatty acid binding capacity of cytosolic proteins from different tissues. They increase the fatty acid binding capacity of liver and kidney while not affecting that of skeletal muscle and decreasing that of cardiac cytosolic proteins [79]. This may be associated with the ability of fibrates to increase the expression and activity of long-chain acyl CoA synthetase in extracardiac tissue [80]. Furthermore, fibrates have been shown to increase the expression of the enzymes involved in fatty acid

oxidation preferentially in the liver [81]. Taken together, these effects increase extracardiac fatty acid utilization, decreasing both circulating plasma and myocardial fatty acid concentrations, and thus myocardial fatty acid oxidation. Experimental studies have demonstrated that fibrates can improve the recovery of cardiac function after ischemia [82], and reduce infarct size [83] – protective effects that may arise as a result of the partitioning of fatty acids away from the heart.

PPARγ is the molecular target of the oral antidiabetic thiazolidinedione class of drugs (rosiglitazone, pioglitazone, troglitazone). Thiazolidinediones prevent the spillover of lipids from adipose tissue into non adipocytes (eg, cardiac myocytes), thereby increasing adiposity, an effect attributed to a reduction in the ectopic deposition of fatty acids in tissues not suited for the storage of excess lipid. Experimental studies have demonstrated that thiazolidinediones can decrease circulating plasma triglyceride [84] and fatty acid [84,85] concentrations, while increasing both myocardial glucose uptake [86] and net lactate uptake [85] (indicative of increased glucose oxidation) and glucose oxidation [84]. These alterations in energy substrate selection and metabolism translate into improvements in the recovery of cardiac function after ischemia [84,85,87].

Interestingly, there exists discordance between the protective effects of thiazolidinediones in experimental studies and the potential to exacerbate the symptoms of heart failure in some diabetic patients treated with these compounds. Specifically, thiazolidinediones can cause fluid retention and peripheral edema, effects that are of concern in patients with heart failure [88]. Furthermore, the findings of a recent meta-analysis indicated that the use of thiazolidinediones in patients with type 2 diabetes mellitus is associated with an increase in the risk of myocardial infarction and an increased risk of death from cardiovascular causes [89]. Therefore, despite the potentially beneficial effects of thiazolidinediones on circulating plasma fatty acid concentrations and cardiac fatty acid and glucose metabolism, the use of thiazolidinediones in any cardiovascular disease state requires additional research and trials of safety.

PPARδ is not as well characterized as PPARα and PPARγ; however, experimental studies do implicate it in the regulation of fatty acid metabolism in skeletal muscle and adipose tissue. The activation of PPARδ in both skeletal muscle [90] and adipose tissue [91] increases fatty acid β-oxidation, and thus has the potential to reduce the circulating concentration of free fatty acids to which the heart is exposed, and thereby decreases cardiac fatty acid oxidation, which has protective effects in cardiac ischemia.

Nicotinic acid

Nicotinic acid is a broad-spectrum lipid-modifying agent that possesses antiatherogenic properties, including the ability to decrease the circulating concentrations of very-low density lipoproteins and low-density lipoproteins while increasing those of high-density lipoproteins. With regards to ischemic heart disease, nicotinic acid (both as monotherapy and in combination with other lipid-decreasing drugs) has been shown to decrease the progression of atherosclerotic lesions, and to increase plaque regression [92], effects shown to decrease cardiovascular mortality (for review see [93]). In addition to its antiatherogenic properties, nicotinic acid also has the ability to modify energy substrate metabolism.

A high-affinity G-protein-coupled receptor for nicotinic acid is highly expressed in adipose tissue [94] and is most probably responsible for the unique distribution of nicotinic acid to this tissue after administration. Nicotinic acid inhibits adipose tissue lipolysis and thus decreases circulating fatty acid concentrations (*Figure 2*). These effects alter both whole-body and cardiac energy metabolism by reducing the availability of fatty acids to peripheral tissues (eg, skeletal and cardiac muscle). Human studies have demonstrated that nicotinic acid increases the cardiac respiratory quotient while not affecting the oxygen extraction ratio – effects indicative of a shift in myocardial energy substrate preference from fatty acid to carbohydrate [95,96], which may contribute to potential anti-ischemic properties in the myocardium.

Summary

The modulation of myocardial energy substrate metabolism, particularly by shifting energy substrate preference from the use of fatty acids towards the use of glucose as an oxidative fuel, is a novel therapeutic intervention, not only for angina, but also for various other manifestations of ischemic heart disease. The shift in energy substrate preference can be achieved through the use of pharmacological agents that act at several levels of the pathways of fatty acid and glucose metabolism, altering the balance and contribution of these pathways to overall cardiac energetics and thereby increasing the efficiency of both the production and utilization of ATP. Such effects can be attained by regulating the rates of flux through the pathways of fatty acid oxidation and glucose oxidation, both by manipulating the activities of key enzymes and by altering the availability of circulating substrates. The efficacy of, for example, trimetazidine in the widespread treatment of angina is of particular relevance to the feasibility of modulating and optimizing energy substrate metabolism to limit

cardiac dysfunction in the setting of ischemic heart disease. ■

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Stable angina: a balanced approach

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Abstract

Coronary artery disease is a chronic medical condition associated with high mortality and morbidity. Among individuals with coronary artery disease, more than 50% have chronic stable angina. Recent evidence supports initial treatment with medical therapy, followed by revascularization, if indicated, in patients with chronic stable angina. The successful management of patients with chronic stable angina involves a combination of proven secondary preventative strategies, conventional medications for symptom relief, and, in some selected suitable patients, revascularization therapy.
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Keywords: coronary artery disease, angina, management strategies

Introduction

Diseases caused by atherosclerosis are widespread chronic conditions, among which coronary artery disease (CAD), in particular, is associated with high mortality and morbidity, and is the leading cause of death worldwide [1]. It is very prevalent in Western industrialized countries. For example, approximately 13 million Americans have CAD, with more than 50% having angina pectoris [2].

Angina is a clinical manifestation of CAD resulting from transient myocardial ischemia secondary to flow-limiting coronary atherosclerosis. Individuals may present with effort or stable angina, unstable angina, or acute coronary syndromes. Data on outcomes from randomized clinical trials for treatment of these clinical syndromes vary greatly and the evidence is much clearer in the treatment of the more acute and severe coronary syndromes. Conversely, there are much fewer trial data on management of patients with chronic stable angina, who form the majority of individuals with CAD. The three commonly used classes of anti-ischemic drugs – β-blockers, calcium channel blockers, and nitrates – are known to be effective in reducing the severity and frequency of stable effort angina, but there are no data on the effectiveness of these agents on outcomes such as death or myocardial infarction in the treatment of these patients. Patients with chronic stable angina commonly receive a combination of conventional anti-ischemic medications for symptom relief, proven secondary prevention drugs, and, in selected suitable patients, revascularization therapy. These treatment strategies are based on extrapolation of trial data from patients after myocardial infarction and with acute coronary syndromes. Although secondary prevention strategies with β-blockers, antiplatelet agents, lipid-decreasing agents, and angiotensin converting enzyme inhibitors are recommended in high-risk individuals with a previous history of myocardial infarction and other vascular diseases, irrespective of whether or not they have current angina, the role of and contributions from other strategies such as routine revascularization or use of some of the newer antianginal medications are still being evaluated. A balanced approach to the appropriate stepwise management of patients with stable angina would be helpful for clinicians.

Case presentation

A 55-year-old man is referred to a community cardiologist with symptoms consistent with stable Canadian Cardiovascular Society (CCS) class II/III angina that he has experienced for the previous 12 months without changes in severity and frequency. His only cardiac risk factor is hypertension. He has

had no history of myocardial infarction or congestive heart failure. His current medications include enteric-coated aspirin 81 mg daily, atorvastatin 10 mg daily, and bisoprolol 2.5 mg daily. His resting heart rate is 84 beats/min, his blood pressure is 150/70 mm Hg, and his body mass index is 30 kg/m^2; otherwise, his examination findings are within normal limits. His baseline electrocardiogram demonstrates voltage criteria for left ventricular hypertrophy with strain pattern.

Because the baseline electrocardiogram is abnormal, an exercise sestamibi nuclear perfusion scan is performed. He achieves a target heart rate of 85% and the exercise is stopped because of limiting chest pain. The nuclear imaging reveals a normal ejection fraction without transient ischemic dilatation. A reversible perfusion defect of moderate size in the distribution of the distal left anterior descending artery is noted.

Clinical questions

Given that this patient's angina is limiting his day-to-day activities, and that there is no evidence of proximal flow-limiting coronary artery disease on exercise perfusion imaging, what is the next appropriate step in his management? Are further investigations required? What does the evidence suggest?

Discussion

The treatment of angina is multifaceted. Secondary prevention strategies are crucial in the management of CAD, but some of the drugs used often offer limited relief of anginal symptoms. Angiotensin-converting enzyme inhibitors and statins do not directly reduce angina, but have beneficial indirect anti-ischemic effects. Lifestyle modification counseling should be provided; however, although cessation of smoking, weight loss, balanced healthy-heart diet, and regular exercise are important in reducing the mortality and morbidity associated with CAD [3], poor uptake and compliance with lifestyle counseling are major issues. In patients with established CAD, strong evidence supports the use of medications aimed at platelet inhibition with aspirin, decreasing cholesterol by means of a statin, and blood pressure control, particularly with a β-blocker, and an angiotensin converting enzyme inhibitor [4,5].

Conventional anti-ischemic medical therapies with β-blockers, calcium channel blockers, and nitrates improve symptoms by easing the balance between myocardial oxygen demand and supply in stable angina. Many studies have demonstrated the effectiveness of these agents. A meta-analysis of 90 randomized controlled trials comparing nitrates, β-blockers, and calcium channel blockers demonstrated no significant difference between them, with respect to cardiac death or myocardial infarction, in the treatment of stable angina [6]. β-Blockers tended to be better tolerated and to reduce the frequency of angina [6], and as β-blockers are also indicated for secondary prevention in patients who have suffered myocardial infarction, the use of these agents is particularly appropriate. The choice of which of these agents to use as initial treatment is usually made by considering the patient's other associated comorbidities. The choice for β-blockers can be made if the patient has suffered myocardial infarction, or has heart failure or hypertension; however, β-blockers are contraindicated if the patient has reactive bronchospastic airway disease. Calcium channel blockers may be used in situations in which β-blockers are not effective when used as sole therapy or are contraindicated. Nitrate monotherapy is usually inadequate, and there is concern about development of nitrate tolerance associated with long-term use. Often, a combination of nitrates, β-blockers, or calcium channel blockers is required for better control of symptoms compared with monotherapy [7].

Coronary revascularization, usually reserved for angina that is intractable to medical therapy, has made numerous advances in the past decade. With improving surgical techniques, rates of in-hospital mortality less than 1.8% for all patients undergoing coronary artery bypass grafting have been reported [8]. However, in the absence of high-risk features on the coronary angiogram (left main or multivessel disease, including stenosis of the proximal left anterior descending artery combined with left ventricular dysfunction), surgical revascularization fails to offer a prognostic benefit [9].

Percutaneous coronary intervention (PCI) has also been shown to be effective in reducing angina. With the advent of drug-eluting stents, PCI offers significantly reduced rates of target lesion revascularization up to 4 years of follow-up when compared with bare-metal stents (20% compared with less than 8%, depending on the type of drug-eluting stent, $P < 0.001$) [10] and, presumably, this advance will prevent recurrence of angina as a result of restenosis of the treated lesions. However, the procedure does not affect other lesions in the coronary tree. Clinicians and patients are often under the impression, from extrapolation of the trial data on PCI in acute coronary syndromes and myocardial infarction, that PCI will similarly improve the prognosis for myocardial infarction or death in patients with stable angina. There are no data to support this belief. The role of routine PCI as an initial strategy as a background to optimal medical therapy for the treatment of chronic stable angina in patients has been evaluated by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug

Evaluation (COURAGE) trial, which allocated 2287 patients with stable CAD and angina randomly to groups to receive either PCI and optimal medical therapy or optimal medical therapy alone, in order to determine whether PCI would have the additional advantage of conferring a better prognosis [11]. At a median follow-up of 4.6 years, the cumulative primary event rates of death and non fatal myocardial infarction were 19.0% for the PCI group and 18.5% for the optimal medical therapy group (hazard ratio 1.05, 95% confidence interval [CI] 0.87 to 1.27, $P = 0.61$). Rates for the combined endpoint of death, myocardial infarction and stroke were 20.0% and 19.5%, respectively (hazard ratio 1.05, 95% CI 0.87 to 1.27, $P = 0.62$). There were no significant differences between the groups with respect to other clinical outcomes. Patients from both groups had substantial improvements in angina control from the start of the trial although the proportion of angina free patients in the PCI group were significantly higher than the optimal medical therapy group during the early phase of follow-up. At year one of follow-up, the proportion of patients who were free of angina in the group given PCI plus optimal medical therapy was 66%, compared with 58% in the group receiving optimal medical therapy alone ($P < 0.001$), compared with 12% and 13%, respectively, who were free of angina at baseline. Such between-group differences in angina were not observed after the first 2 years. At 5 years of follow-up, approximately 73% of patients were free of angina in both groups, without a difference between the groups. Given these findings, an initial approach with medical therapy for the treatment of chronic stable angina for all patients should be undertaken. In patients with persisting symptoms of angina, PCI can be considered for treatment of the angina, in the knowledge that there is no added benefit in reducing the risk of death or myocardial infarction.

A proportion of patients with angina do not respond adequately to conventional antianginal treatments and are not amendable to revascularization, but may still experience limiting chest pain. A number of new antianginal treatments and interventions are currently being investigated.

Metabolically acting agents such as trimetazidine and ranolazine have protective anti-ischemic effects by increasing glucose metabolism relative to that of fatty acids. They both act through inhibition of fatty acid oxidation to increase cardiac metabolic efficiency and, more importantly, by preventing calcium overload in ischemic myocytes resulting in decreased diastolic tension [12,13]. For the past 20 years, trimetazidine has been used throughout Europe and over 90 countries worldwide for the treatment of stable angina. In stable effort angina, it affords improvements in exercise tolerance and increases ischemic threshold at least as great as those obtained with β-blockers or calcium antagonists [14,15]. A meta-analysis of 12 randomized, controlled, clinical trials confirmed that trimetazidine is an effective antianginal agent when used alone or in combination with traditional hemodynamic agents [16].

In placebo-controlled clinical trials involving more than 1500 patients, ranolazine has been demonstrated clinically to increase exercise duration and reduce the frequency of angina when used alone or in combination with other antianginal drugs [17–19]. However, in a large randomized controlled trial in more than 6500 patients with non ST-elevation acute coronary syndromes, ranolazine did not offer a benefit over placebo in the primary endpoint of cardiovascular death, myocardial infarction, or recurrent ischemia [20]. Despite this finding, its effectiveness in angina relief is a welcome addition in management of angina.

Ivabradine, recently licensed by the European Medicines Agency (EMEA), offers an innovative approach to the management of stable angina thanks to its selective and specific inhibition of the I_f current of the myocardial sinus node, thus providing pure reduction in heart rate and antianginal efficacy [21,22]. The efficacy of ivabradine in improving prognosis is currently being evaluated in a large morbidity–mortality trial (The Morbidity–Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction [BEAUTIFUL] Study) [23].

Non pharmaceutical strategies that have demonstrated interesting trends toward symptom improvement, increased exercise duration, and reduced admissions to hospital in a few small trials and registries include transmyocardial laser revascularization, enhanced external counterpulsation, and spinal cord stimulation [24–26]. However, the only blinded, placebo-controlled trial evaluating the benefits of transmyocardial laser revascularization did not demonstrate improvements in anginal class, survival, and quality of life [27]. Such interventions are not standard practice, and further studies are required [28].

Back to the case study

The next appropriate step in the management of this patient involves three components.

First, aggressive secondary preventative strategies need to be introduced. Lifestyle modifications, including counseling on weight loss, nutrition, and regular exercise, while difficult to implement and maintain, are essential for the comprehensive care of patients with CAD. Medical treatments, including continued antiplatelet therapy with aspirin, decreasing

cholesterol by means of a statin, and control of blood pressure with an angiotensin converting enzyme inhibitor, β-blocker, or both, are important for conferring long-term clinical benefit. The doses of these medications should be adjusted to achieve maximal benefits.

Secondly, antianginal treatments can be maximized to improve quality of life. A stepwise approach, first with a β-blocker (giving mortality and antianginal benefits), then with calcium channel blockers, nitrates, or both, should be uptitrated to obtain relief of symptoms.

Finally, should the patient still experience limiting angina despite maximal medical treatment, revascularization therapy with either coronary artery bypass grafting or PCI should be considered. This approach follows the current standard guidelines [28].

In the very unlikely event that the patient develops intractable angina despite these interventions, alternative and newer antianginal treatment modalities may be considered. ■

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Magnetic resonance perfusion imaging for detection of ischemic heart disease

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Abstract

In recent years, magnetic resonance first-pass perfusion imaging (MRPI) has developed from a research technique to a mature clinical application. Sufficient evidence has been presented to demonstrate that a high-quality MRPI scan is at least as good as a single photon emission computed tomography scan for the diagnosis of significant coronary artery disease. The ability of this new technique to assess the hemodynamic relevance of a stenosis has been shown by its close correlation with invasive coronary flow and pressure measurements. Initial data demonstrate that patients with a negative MRPI scan have an excellent prognosis.

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Keywords: Diagnosis, ischemic heart disease, magnetic resonance perfusion imaging

Introduction

The non invasive assessment of myocardial perfusion is one of the most attractive methods for detecting coronary artery disease (CAD), because a decrease in myocardial blood flow is the first event after induction of myocardial ischemia (ischemic cascade) [1]. Currently, single photon emission computed tomography (SPECT) is the technique most widely used to prove or exclude significant CAD. However, several limitations of SPECT, such as attenuation artifacts and its relatively low spatial resolution, make the introduction of a new technique attractive. The techniques used for magnetic resonance first-pass perfusion imaging (MRPI) have been improved considerably in recent years, are sufficiently robust, and yield high-quality images if used with some experience and a state-of-the art scanner. Several single-center and initial multicenter trials [2,3] have demonstrated the high accuracy of the technique in comparison with invasive coronary angiography. In addition, a close correlation has been shown between the findings of MRPI and the assessment of coronary artery flow reserve or fractional flow reserve. The main limitations of the new technique are the needs to understand potential artifacts and to have sufficient practice to obtain high-quality imaging and image interpretation.

Pathophysiology

Myocardial perfusion depends on the driving pressure gradient and the resistance of the coronary vascular bed. Coronary autoregulation makes it possible to keep myocardial perfusion stable for a wide range of coronary perfusion pressures, even in the presence of a stenosis that narrows the coronary artery diameter by up to 90% [4]. During exercise or pharmacological stress, autoregulation becomes exhausted, leading to a relative reduction in blood flow distal to a coronary artery stenosis. With perfusion imaging, these relative changes in blood flow can be visualized and the hemodynamic significance of a coronary artery

stenosis demonstrated. It is important to remember that there is no direct correlation between alterations in blood flow and the degree of a coronary artery stenosis. Consequently, there is a limited agreement between MRPI measurements and invasive angiography, but a closer agreement with invasive measurements of fractional flow reserve.

Imaging technique

Usually a T1-weighted sequence is used to visualize the first passage of a gadolinium contrast agent through the myocardium. Three to five short-axis views with an in-plane resolution less than 3 mm × 3 mm are acquired at each heart beat (*Figure 1*). Images are first acquired during adenosine stress, and then imaging is repeated approximately 10 min later with the patient at rest. At some stage during the procedure, cine wall-motion images are acquired with the patient at rest; finally, delayed enhancement imaging, as described elsewhere [5], is performed.

Image analysis

For clinical purposes, a rapid visual assessment is performed by comparing the contrast enhancement in different myocardial regions. Importantly, the speed of the increase in signal (contrast agent wash-in), rather than the absolute maximum signal, is the most important parameter for visual assessment [6]. Patients with suspected CAD may be considered to be positive for CAD based on a positive late gadolinium enhancement scan, independent of the perfusion results [7]. However, in patients whose condition is complex (known myocardial infarction, previous revascularization), the approach is less straightforward. In these patients, the stress perfusion images need to be compared carefully with the scar images, and only those patients with perfusion defects that are larger than the scar territory are regarded as positive for ischemia.

For a more precise analysis, and for research purposes, semiquantitative or quantitative analyses are available [8].

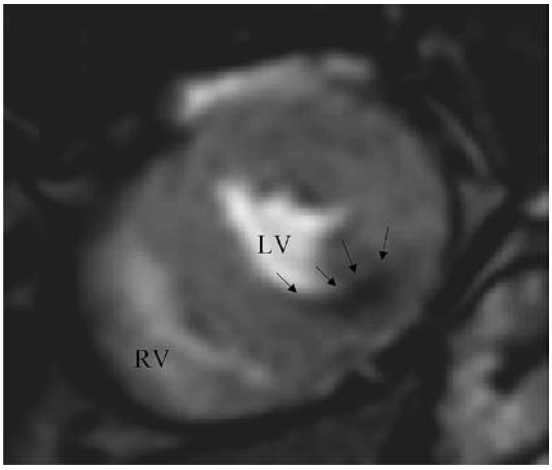

Figure 1. Equatorial short axis view of a first pass perfusion scan. An image during peak myocardial enhancement was chosen. The arrows indicate a subendocardial perfusion defect in the inferior wall, most likely due to a significant stenosis of the right coronary artery. Spatial resolution is app. 3 mm x 3 mm which allows visualization of subendocardial defects.

Accuracy and prognostic value

The overall accuracy of MRPI is about 90% sensitivity and 70–80% specificity compared with invasive angiography. The main reasons for false-positive results are artifacts in patients in whom image quality is suboptimal (a problem that has lessened significantly in recent years) and the physiologic differences between measuring ischemia and coronary artery stenoses (as outlined above). The correlation between MRPI and functional measurements of the severity of stenosis (coronary flow reserve, fractional flow reserve) is good [9] and Kühl et al [10] have reported a sensitivity of 92% with a specificity of 92% for MRPI compared with fractional flow reserve. These findings demonstrate the high accuracy of MRPI. In addition, patients with a negative MRPI scan have an excellent prognosis, with an event rate of only 0.7% for major cardiac events within the next 2 years [11]. Thus this technique can be safely applied in patients referred for invasive angiography without proven evidence of ischemia or who demonstrate an intermediate pretest likelihood of CAD. Recently, MRPI was regarded as an appropriate indication in a variety of situations, most importantly in patients with chest pain, who have an intermediate risk for CAD and are unable to exercise, or in whom the electrocardiogram cannot be interpreted, and in patients who have an intermediate stenosis of unclear hemodynamic significance found by coronary artery imaging (either cardiac computed tomography or invasive angiography) [12].

Summary

Despite the lack of large multicenter trials for the assessment of MRPI, the technique can be regarded at least as not inferior to SPECT. A negative study has an excellent negative predictive value for the occurrence of major cardiac events. The test has several accepted indications, mainly in patients with chest pain, who have an intermediate risk for coronary artery disease and are unable to exercise, or in whom the electrocardiogram cannot be interpreted, and in patients who have an intermediate stenosis of unclear

hemodynamic significance found by coronary artery imaging (either cardiac computed tomography or invasive angiography). ■

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Coronary microcirculation: the new frontier in coronary artery disease

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A large body of evidence challenges the common view which attributes myocardial ischemia entirely and exclusively to atherosclerotic obstructions of large epicardial coronary vessels. In animal model as well in man, altered vasomotor control at the microvascular level may aggravate the effects of epicardial obstructions and/or hinder myocardial perfusion even in the absence of a proximal obstruction.
However, based on the assumption that atherosclerotic obstructions of the coronary vessels are the only cause of myocardial ischemia, thousands of surgical and percutaneous revascularization procedures are performed worldwide. Unfortunately, these procedures do not reduce the risk of death or myocardial infarction and even the symptomatic benefit has been limited. Randomized trials comparing revascularization with medical therapy have consistently shown that one third of patients remained symptomatic for angina after a successful procedure.
The prevalence and relevance of angina persisting after PCI need to be assessed in prospective trials, and the pathogenetic mechanims clarified. Microvascular dysfunction is likely to play a major role in persisting angina and the development of therapeutic strategies directed to restoring microvascular function appear of paramount importance in order to consistently improve symptoms and prognosis in patient with IHD.
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Keywords: Persisting angina, microvascular dysfunction, ischemic heart disease, percutaneous coronary revascularization, angina pectoris

Introduction

Over the past 3–4 decades, the view has evolved that coronary syndromes are caused by epicardial coronary plaques that can undergo rupture, with subsequent thrombus formation. The pathophysiology of ST-segment elevation myocardial infarction (STEMI) is believed to differ from the pathophysiology of unstable angina or non STEMI in the presence of a more stable and occlusive platelet-rich thrombus, less collateral circulation, and, generally, a more severe and prolonged imbalance between myocardial oxygen supply and demand in the culprit vessel territory, causing more prolonged and severe ischemia [1].

However, autopsy studies do not support the concept that the extent of intimal vessel injury determines the magnitude and stability of the intraluminal thrombus [2], and the findings of prospective clinical trials do not support a relevant role for platelet-rich thrombi in unstable angina and non Q-wave infarction [3].

The behavior of the entire coronary vascular tree in relation to the pathogenesis of ischemic syndromes deserves further investigation. Classical concepts, often derived from animal models, do not fit with clinical observations. Focal increases in resistance at the coronary epicardial level, regardless of the causative mechanism, are expected to result in compensatory vasodilatation at the microcirculatory level [4]. Conversely, several studies have shown that this is not the case, and that a paradoxical microvascular vasoconstriction may be associated with stable or unstable angina [5,6].

Coronary microvascular dysfunction in the pathogenesis of myocardial ischemia

We have measured trans-stenotic and microvascular coronary resistances to flow in patients with tight left anterior descending (LAD) coronary artery stenosis, at baseline, after the intracoronary administration of adenosine, and during ischemia [6]. The major finding of that study was the recognition of an increased coronary microvascular resistance at a time when the traditional view would predict maximal vasodilatation of the coronary vascular bed. This observation strongly supports the hypothesis that abnormalities in coronary vasomotion can contribute to the precipitation and maintenance of ischemia in man. Endothelial dysfunction may impair microvascular adaptation to ischemia, and constrictor response to reduced intraluminal pressure has been described in isolated microvessels [7].

A large body of evidence challenges the common view that attributes myocardial ischemia entirely and exclusively to atherosclerotic obstruction of large epicardial coronary vessels. Altered control of distal coronary tone may aggravate the effects of epicardial obstructions or hinder myocardial perfusion, or both, even in the absence of a proximal obstruction.

Evidence of a prominent role of the coronary microcirculation in ischemic heart disease

Thousands of surgical and percutaneous revascularization procedures are performed every year, on the assumption that removal of coronary obstructions may improve symptoms and prolong survival. Unfortunately, available evidence does not support this popular opinion. In the Randomised Intervention Treatment of Angina (RITA)-2 trial, after a median 7 years of follow-up, death or myocardial infarction occurred in 14.5% of patients who underwent percutaneous transluminal coronary angioplasty (PTCA) and in 12.3% of patients treated medically. In addition, the prevalence of angina remained increased in both groups, with 70% of patients undergoing PTCA and 83% of those treated medically receiving at least one antianginal drug at 5 years [8].

The findings of a meta-analysis [9] confirmed that PTCA may lead to a reduction in angina, although the magnitude of the effects varies considerably, but it is unlikely to reduce non fatal myocardial infarction and death. In a critical review of the literature, it was concluded that PTCA of flow-limiting stenosis in chronic coronary artery disease does not reduce the rate of subsequent myocardial infarction or mortality. PTCA results in superior symptomatic relief of angina and improved exercise tolerance compared with medical therapy, but the difference narrows with time; however, only a minority of patients are free from angina and antianginal medication after a revascularization procedure [10].

The recently published Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial has demonstrated conclusively that percutaneous coronary intervention does not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical treatment [11].

Pathogenetic mechanisms for ''persistent'' angina

On the basis of current pathogenetic concepts, it is not easy to understand the limited prognostic benefit deriving from removal of obstructive coronary lesions – and even more puzzling is the persistence of ischemia in the absence of visible obstructions in the large epicardial coronary branches. Several hypotheses may be considered, including incomplete revascularization, graft/PTCA failure, and disease progression, but none of these provides a satisfactory explanation.

Incomplete revascularization may be a planned choice in patients with acute coronary syndromes and multivessel coronary disease. In several circumstances, operators may find it appropriate to limit treatment to the culprit lesion. Incomplete revascularization may be inevitable in patients with chronic disease who have obstructions that are not amenable to dilatation, such as lesions in small vessels or in the distal portion of larger vessels. Nevertheless, it appears unlikely that incomplete revascularization has contributed, to any significant extent, to the findings of studies in which patients were carefully selected for being amenable to multivessel revascularization.

Failure of a graft or PTCA is certainly possible, but is today a rare occurrence, all techniques claiming success rates close to 100%.

Disease progression in native coronary arteries has been observed during the time interval between the diagnostic angiogram and the PTCA procedure, and following bypass operations. Reported rates of disease progression, however, are far too low to explain persistent angina early after the procedure, which can be estimated as being present in close to one-third of patients who have undergone revascularization.

Thus, even accounting for the additive effects of several pathogenetic mechanisms, it remains difficult to understand why so many patients suffer from persistent angina after ''successful'' revascularization procedures, unless we take into consideration another mechanism, namely persisting microvascular dysfunction.

It has long been known that removal of coronary obstructions is not consistently followed by recovery of coronary blood flow reserve. Several investigators, using different techniques, have reported that coronary blood flow reserve remains markedly impaired in

a large proportion of patients after balloon angioplasty or stent implantation.

Conclusions

Microcirculatory dysfunction is emerging as a relevant pathogenetic mechanism for ischemic heart disease. It manifests as a paradoxical increase in resistance to flow in response to reduced perfusion pressure, and contributes to the precipitation of ischemic attacks in both stable angina and acute coronary syndromes. The limited impact of revascularization procedures on patients' prognosis, and the persistence of angina in a large number of patients after removal of coronary obstructions strongly support this hypothesis. A better understanding of the role of microvascular dysfunction and the development of therapeutic strategies directed to restoring microvascular function appear to be of paramount importance in the improvement of symptoms and prognosis in patients with ischemic heart disease. ■

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Efficacy of Vastarel MR on silent and symptomatic myocardial ischemia

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Abstract

Despite advances in the medical treatment of myocardial ischemia, a large proportion of patients with coronary artery disease suffer from angina and have silent episodes of myocardial ischemia. Chronic repetitive ischemic episodes may lead to ischemic cardiomyopathy. Trimetazidine, the 3-ketoacyl coenzyme A thiolase inhibitor, is a metabolically active agent that is effective, whether alone or in combination with standard therapy, in reducing myocardial ischemia. It has been shown to reduce daily episodes of both silent and symptomatic myocardial ischemia. These effects, together with those of trimetazidine on myocardial energy production, are likely to reduce the progression of ventricular dysfunction in patients with ischemic cardiomyopathy.
Heart Metab. 2008;38:27–29.

Keywords: Ischemic cardiomyopathy, myocardial energy, silent myocardial ischemia, symptomatic myocardial ischemia, trimetazidine

Introduction

Despite treatment with hemodynamic drugs, angina remains a significant health problem for many patients with ischemic heart disease. It has long been known that hemodynamic anti-ischemic drugs do not have a significant additive effect, whereas the combination of hemodynamic agents with drugs that improve cardiac metabolism is an effective treatment for myocardial ischemia. The ''metabolic'' antianginal drugs that partially inhibit fatty acid metabolism induce a shift from utilization of free fatty acids towards utilization of glucose, thereby increasing energy production for a given amount of oxygen. Trimetazidine, the most effective among the cardiometabolic drugs, has been shown to have significant anti-ischemic effect without any influence on hemodynamic parameters.

The mechanism of action of trimetazidine has been well established experimentally and is related to the inhibition of the enzyme, long-chain 3-ketoacyl coenzyme A thiolase, which is a crucial enzyme in the β-oxidation pathway [1]. This inhibition decreases the utilization of free fatty acids as a source of energy for the myocardium. It has been shown that inhibition of free fatty acid oxidation with trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation and increases the oxidation of pyruvate formed from glucose, glycogen, and lactate, restoring coupling between glycolysis and carbohydrate oxidation, and leading to the production of ATP with the consumption of less oxygen [2].

Effect of trimetazidine on symptomatic ischemia

Several clinical trials have demonstrated the potential benefits of trimetazidine in ischemic heart disease.

In stable effort angina, trimetazidine improves exercise tolerance and increases the ischemic threshold to the same extent as β-blockers or calcium antagonists [3,4]. When given in combination with β-blockers,

trimetazidine has a greater anti-ischemic effect than nitrates and calcium antagonists [5]. The Trimetazidine in Poland (TRIMPOL) II trial [6], a large, randomized, controlled trial, enrolled 426 patients with stable angina who were allocated randomly to groups receiving either trimetazidine or placebo in addition to metoprolol. This study demonstrated an improvement in time to ST-segment depression in exercise tolerance tests, total exercise workload, mean nitrate consumption, and frequency of angina in patients who received trimetazidine.

A meta-analysis of 12 double-blind, randomized, controlled clinical trials of trimetazidine in the treatment of stable angina [7] showed that trimetazidine was associated with significant reductions in the number of weekly angina attacks, and improved the time to 1 mm ST-segment depression and the total work at peak exercise. Overall, this meta-analysis confirmed that trimetazidine is an effective antianginal agent when used alone or in combination with traditional hemodynamic agents.

A Cochrane Review of trimetazidine in stable angina [8] included 23 studies involving 1378 patients. Compared with placebo, trimetazidine significantly reduced the number of weekly angina attacks and the weekly consumption of glyceryl trinitrate tablets. There was also an improvement in the exercise time to 1 mm ST-segment depression.

In a multinational, randomized, double-blind, placebo-controlled study [9], a new slow-release (modified-release [MR]) formulation of trimetazidine has been shown to improve both symptoms and myocardial ischemia significantly. Patients with stable angina received atenolol 50 mg per day and trimetazidine MR 35 mg or placebo. The primary endpoint, time to 1 mm ST-segment depression, was increased significantly with trimetazidine compared with placebo.

A larger open clinical trial enrolled 906 patients with stable angina. All patients were required to have experienced at least three angina attacks per week for more than 6 months despite traditional angina treatment with long-lasting nitrates, β-blockers, or calcium antagonists. After 2 months of treatment with trimetazidine MR 35 mg twice a day, there was a significant ($P < 0.0001$) decrease (67%) in the number of angina attacks per week and a significant decrease (71%) in the number of short-acting nitrates taken per week ($P < 0.0001$) in the treated group [10].

Recent findings suggest that the modified-release formulation of trimetazidine could be more effective than immediate-release with respect to relief of angina. In an Indian multicenter prospective study of 279 patients with uncontrolled stable angina, the immediate-release trimetazidine formulation was substituted with twice-daily trimetazidine MR, which reduced the mean frequency of angina by four attacks per week and the consumption of glyceryl trinitrate by 3.6 tablets per week [11].

Effect of trimetazidine on silent ischemia

Silent myocardial ischemia, defined as objective documentation of myocardial ischemia in the absence of angina or anginal equivalents, is often diagnosed in patients with known or unknown ischemic heart disease, with prevalence rates ranging from 9 to 57% [12] and with considerable differences in specific subgroups of patients such as those with diabetes or the elderly [2].

Treatment of repetitive episodes of silent myocardial ischemia in patients with coronary artery disease is a primary goal because these episodes may cause the progression of coronary artery disease to ischemic cardiomyopathy. Trimetazidine has been demonstrated to be an effective option for reducing the incidence of symptomatic ischemia and silent myocardial ischemia in diabetic individuals with coronary artery disease. In a study by Marazzi et al [13], 6 months of administration of trimetazidine to 15 diabetic patients receiving standard antianginal therapy, in addition to significantly reducing the number of episodes of transient myocardial ischemia, also (*Figure 1*) significantly reduced the number of episodes of silent myocardial ischemia with respect to placebo, and the total silent ischemic burden compared with placebo.

Silent myocardial ischemia after infarction is associated with stunned or hibernating myocardium, left ventricular dysfunction, and an adverse prognosis. Surgical revascularization is the optimal treatment for dysfunctional but viable myocardium; however, it is not always feasible. Trimetazidine acts on chronically hibernating myocardium by diminishing the effects of ischemia and thus improving contractile

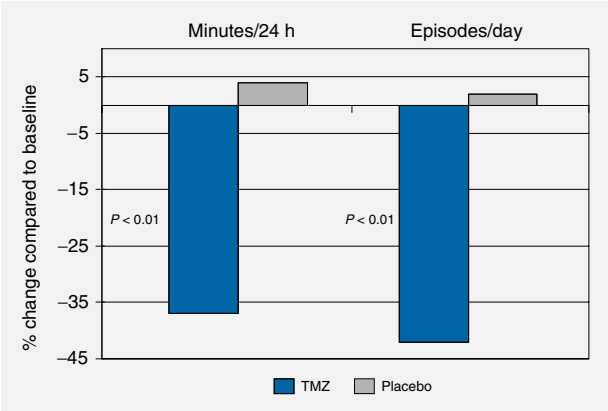

Figure 1. Effect of trimetazidine added to standard antianginal therapy on total silent ischemic burden and episodes of silent myocardial ischemia in patients with coronary artery disease.

function by correcting the imbalance between energy and function. Belardinelli and Purcaro [14], using low-dose dobutamine echocardiography, demonstrated a significant improvement in the rest and peak systolic wall thickening score index and ejection fraction in 38 patients with left ventricular dysfunction and multivessel left coronary artery disease who were treated with trimetazidine for 2 months. Similar results have been observed when the contractile response of the left ventricle was evaluated by means of gated single photon emission computed tomography. El-Kadi et al [15] demonstrated improvements in stress and rest perfusion scores, and in systolic wall thickness, in patients who received 24 months of treatment with trimetazidine.

More recently, our group demonstrated that the adjunct of trimetazidine to standard treatment in patients with type 2 diabetes, coronary artery disease, and reduced left ventricular function improved the left ventricular systolic and diastolic function of chronically dysfunctional myocardium [16].

Summary

Trimetazidine is an effective drug in the metabolic management of both symptomatic and silent ischemia. It shifts metabolism away from a preference for fatty acids toward more carbohydrate oxidation, ameliorating the energy–function imbalance of the myocardial cells. This can lead to a reduction in the number of episodes of refractory angina and improve contractile function of the hibernating myocardium, slowing the progression of cardiac failure. ■

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Trimetazidine in the management of ischemic heart disease in a patient with diabetes mellitus and recurrent angina

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Acute coronary syndromes in diabetic patients often pose therapeutic challenges. Both percutaneous and surgical revascularization procedures have a lower success rate and a greater complication rate in diabetics compared to non diabetic patients. Here we discuss the case of an old diabetic patient with angina recurring 15 year after a CABG operation. Based on coronary anatomy and clinical presentation, several options were considered, including re-do operation, percutaneous revascularization, and medical therapy alone. A combination of PCI and trimetazidine addition to standard medical therapy was eventually chosen. This approach has been very effective and has so far protected the patient from angina.
Heart Metab. 2008;38:31–33.

Keywords: Angina, CABG, diabetes mellitus, ischemic heart disease, management, PCI, trimetazidine

Case report

An 82-year-old man with a family history of ischemic heart disease was referred to our Coronary Care Unit because of recurrent angina. He had been diagnosed with type 2 diabetes mellitus 16 years previously, and 1 year later had presented with an episode of prolonged chest pain followed by fainting. On that occasion, he was admitted to our Coronary Care Unit, where an acute inferior myocardial infarction was diagnosed. Coronary angiography, performed a few days later, revealed multivessel coronary disease, and the patient underwent coronary artery bypass grafting, with a left internal mammary artery implanted on the obtuse marginal branch of the left circumflex coronary artery and a saphenous graft implanted on the distal right coronary artery. After discharge he was followed regularly by a cardiologist, and had been treated with antiplatelet agents, angiotensin-converting enzyme inhibitors, calcium channel blockers, nitrates, diuretics, statins, and oral antidiabetic drugs. He had been asymptomatic, with a normal lifestyle, until 1 week before the present referral, when he began to complain of chest discomfort that was triggered by exercise but promptly relieved by rest.

At the time of his current admission, an electrocardiogram showed complete left bundle branch block, chest radiographs were unremarkable, and an echocardiogram showed left ventricular dilatation, moderate systolic dysfunction (ejection fraction 42%), and inferobasal akinesis.

A dipyridamole echo stress test was performed. With the high dose, the patient complained of chest discomfort, and anterolateral wall dysfunction (akinesis) was observed. Symptoms and regional left ventricular dysfunction were quickly corrected by intravenous aminophylline.

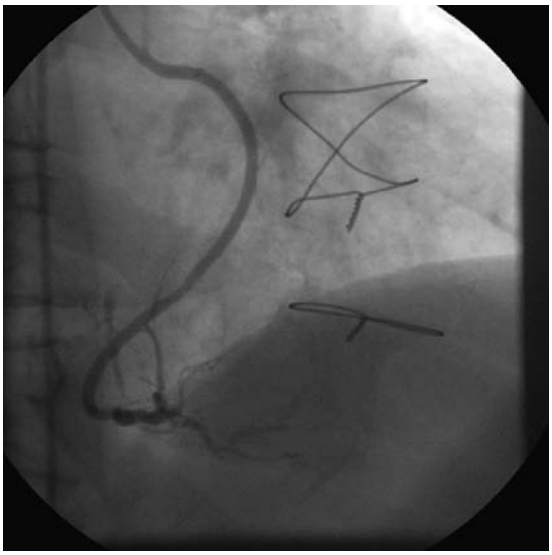

Figure 1. Angiogram showing patency of the venous graft on the distal right coronary artery.

Trimetazidine 20 mg (two tablets three times a day; total 120 mg/day) was added to standard medical treatment and the patient was scheduled to undergo coronary angiography, which was performed 2 days later.

Angiography demonstrated patency of the venous graft on the distal right coronary artery (*Figure 1*), patency of the left internal mammary artery (LIMA) implant on the marginal branch (*Figure 2*), and progression of the atherosclerotic disease on the left main/left anterior descending (LAD) arteries, with a tight stenosis in the proximal segment of the LAD artery (*Figure 3*).

After several options had been considered, given the ''protection'' offered by the patent mammary artery on the marginal branch, the left main/LAD artery segment was dilated with a balloon and implanted with a 3.5 × 23 mm stent (*Figure 4*).

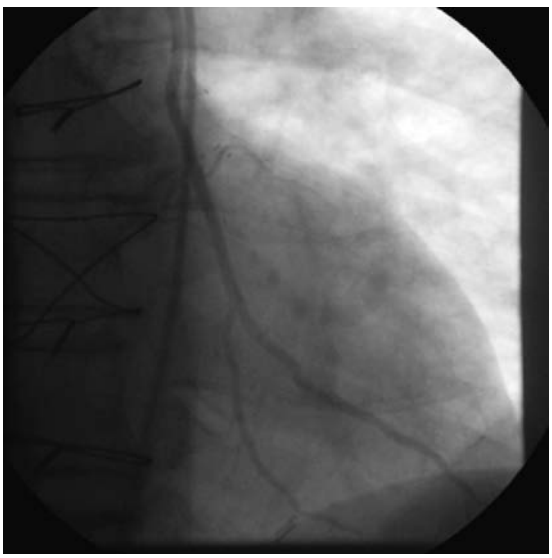

Figure 2. Angiogram showing patency of the left mammary artery implant on the obtuse marginal branch of the circumflex coronary artery.

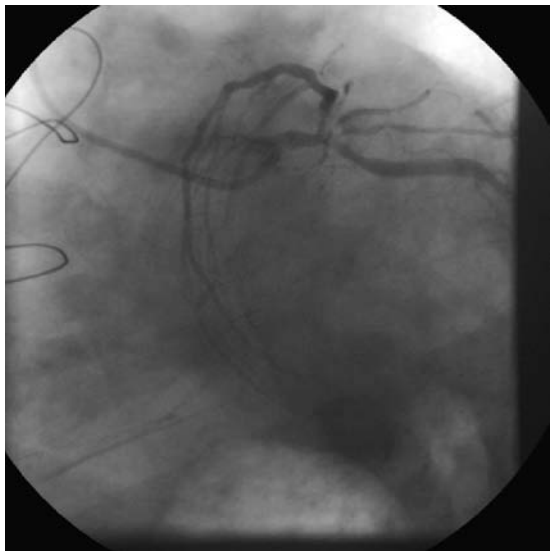

Figure 3. Angiogram showing progression of the atherosclerotic disease on the left main/left anterior descending (LAD) arteries, with a tight stenosis in the proximal segment of the LAD artery.

The postprocedural course was uneventful, with a minor increase in the serum creatinine concentration that reverted quickly to normal, with no other side effect.

At the 4-week follow-up visit, the patient was fully asymptomatic and enjoying a normal life; results of an echo-dipyridamole test were negative.

Discussion

This Case Report is of an elderly patient with diabetes and severe coronary artery disease who had undergone CABG 15 years previously after an acute coronary syndrome. That revascularization procedure, combined with aggressive medical treatment, assured the patient of prolonged survival and a good quality of life. Progression of his coronary atherosclerosis on native vessels eventually precipitated recurrent angina, with inducible ischemia in the LAD artery territory.

Several therapeutic options were considered for the management of this patient, including re-operation, percutaneous revascularization, and medical treatment.

- The surgical option was initially considered for the presence of a left main obstruction in this diabetic patient, but was discarded after evaluating the risk of a repeat operation for only one graft.
- Medical treatment alone was felt not to be adequate to provide optimal treatment of an acute coronary

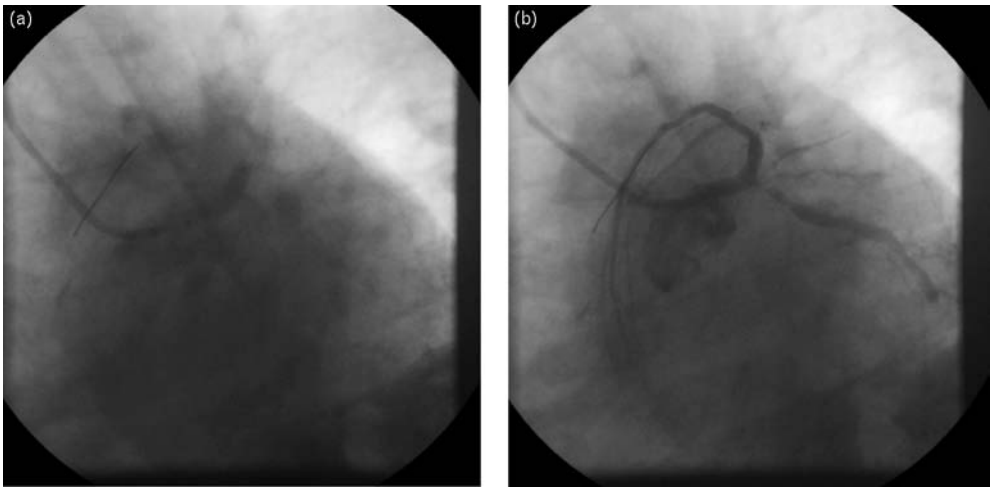

Figure 4. Angiograms showing (a) balloon dilatation of the left main/LAD artery segment and (b) implanted 3.5 × 23 mm stent.

syndrome in a patient in whom recanalization of the culprit lesion was technically feasible.
- Percutaneous coronary intervention alone was not deemed adequate because of the diffusion of the atherosclerotic lesions to distal coronary segments, which prevented a complete myocardial reperfusion.

In the event, a strategy of medical treatment based on a metabolic agent, trimetazidine, followed by percutaneous revascularization of the left main/LAD artery lesion was applied. The revascularization procedure was well tolerated by the patient, who was sent home 2 days later.

Follow-up at 1 month confirmed the success of the treatment strategy, with complete remission of symptoms.

Comment

Diabetes mellitus is closely associated with coronary heart disease. The prevalence of coronary artery disease increases from 2–4% in the general population to a figure as high as 55% among adult patients with diabetes [1]. The management of ischemic heart disease in diabetic patients remains a challenge. Macrovascular and microvascular disease limit the efficacy of revascularization procedures and increase the risk of early and late complications. Correction of the alterations in cardiac metabolism that are associated with diabetes mellitus may represent an innovative and effective therapeutic approach in the management of this group of patients.

The mechanism of action of trimetazidine, which is based on a switch from utilization of fatty acids to that of glucose, makes this drug the ideal treatment for angina pectoris in patients with diabetes [2,3]. Furthermore, pretreatment with trimetazidine has been shown to limit myocardial damage associated with revascularization procedures [4].

In the patient described here, a strategy of trimetazidine administration followed by PCI, in addition to standard medical therapy, was safe and effective in controlling his symptoms of recurrent angina. ■

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The place of exercise in the patient with chronic stable angina

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Abstract

Exercise is an often overlooked but highly valuable non pharmacological treatment for patients with chronic stable angina. Regular exercise is associated with several cardioprotective effects, including improving endothelial function and reducing systemic inflammation. In addition, regular exercise leads to better control of major coronary risk factors. On a symptomatic level, exercise training reduces myocardial ischemia and the frequency of anginal attacks while also improving functional capacity and long-term outcomes. Patients with angina pectoris should be encouraged to engage in regular physical activity as part of a comprehensive lifestyle intervention for the secondary prevention of coronary heart disease.

Heart Metab. 2008;38:34–37.

Keywords: Angina, exercise, heart rate, lifestyle, myocardial ischemia

Introduction

The past few decades have led to a major increase in the understanding of the pathogenic mechanisms underlying atherosclerosis, and the beneficial role that regular exercise can play in the treatment of coronary heart disease (CHD) and angina pectoris. The benefits of regular exercise in patients with chronic stable angina are multifaceted. Exercise training leads to better control of risk factors for CHD. In addition, chronic exercise leads to reductions in endothelial dysfunction and systemic inflammation, both of which are known to be paramount in the development and progression of atherosclerosis. On a more practical level, regular exercise has been shown to improve functional capacity and increase the anginal threshold, leading to a reduction in the frequency of anginal attacks. This article will review the cardioprotective mechanisms of exercise training and the effects of physical activity and physical fitness on symptoms and prognosis, and provide recommendations regarding initiation of an exercise program in the patient with chronic stable angina.

Cardioprotective mechanisms of exercise

Endothelial dysfunction is known to be the precursor of atherosclerosis [1,2]. Both acute and chronic exercise have been shown to improve endothelial function by increasing shear stress-induced flow-mediated arterial vasodilatation [3,4]. Increased shear stress on the arterial wall during exercise leads to increased production and release of nitric oxide from endothelial cells [5]; nitric oxide is responsible for endothelium-dependent vasodilatation of the coronary arteries [6]. This vasoactive substance also has numerous antiatherosclerotic and antithrombotic effects [7].

A single bout of vigorous exercise was recently shown to improve endothelial function in the rat, with regular exercise for 6 weeks further improving endothelial function [3]. In humans, 4 weeks of intense physical training was shown to improve coronary endothelial function and coronary blood flow in patients with stable CHD [4].

Inflammation has a major role in the pathogenesis of atherosclerosis and CHD [8]. A very sensitive marker of inflammation, and one of the most studied biomarkers in patients with CHD, is the acute-phase reactant, C-reactive protein [9]. Increased concentrations of C-reactive protein are associated with a significantly greater risk of morbidity and mortality in otherwise healthy men and women [10,11]. A 12-week aerobic exercise training program has been shown to produce a significant reduction in concentrations of several markers of inflammation, including C-reactive protein, in patients with stable CHD [10]. Exercise training and high physical fitness are also associated with lower concentrations of markers of inflammation in individuals without known CHD [12,13].

Chronic exercise is also believed to improve the health of patients with angina pectoris by improving the control of risk factors. Regular exercise may result in weight loss, or the prevention of weight gain, although the dose–response effect between exercise and body weight may vary from individual to individual and between patient populations [14]. Similarly, long-term exercise training reduces body weight, the prevalence of insulin resistance, and the metabolic syndrome in patients with CHD who have this condition [15]. A comprehensive lifestyle intervention with regular exercise was shown to reduce the incidence of new-onset diabetes by 50% in individuals with impaired glucose tolerance [16]. Aerobic exercise training has also been shown to improve the lipid profile, primarily by increasing high-density lipoprotein cholesterol concentrations and decreasing those of triglycerides [14,17]. In a meta-analysis of 54 randomized trials, aerobic exercise training was shown to decrease both systolic and diastolic blood pressure by 3–4 mm Hg, with a greater blood pressure-decreasing effect noted in hypertensive patients [18]. Exercise training has also been shown to have antithrombotic effects, leading to decreased platelet aggregation and increased fibrinolytic activity [19].

Regular exercise may also provide benefit to the individual with chronic angina by increasing the tolerance of the myocardium to prolonged ischemia, thereby reducing the degree of myocardial injury, a phenomenon known as ischemic preconditioning [20]. Ischemic preconditioning may not only prevent or reduce myocardial damage during an episode of prolonged ischemia, but may also reduce the risk of fatal ventricular arrhythmias that may occur during reperfusion when blood flow is restored to the injured myocardium [20].

Table I. Cardioprotective effects of exercise training.

1. Improved endothelial function
2. Reduction in systemic inflammation
3. Improvement in risk factor control
   a. Reduction in body weight
   b. Improved glucose metabolism
   c. Reduction in blood pressure
   d. Increase in HDL-cholesterol concentrations
   e. Reduction in triglyceride concentrations
4. Antithrombotic effects
   a. Decreased platelet aggregation
   b. Increased fibrinolytic activity
5. Ischemic preconditioning
   a. Reduced myocardial damage during prolonged ischemia
   b. Prevention of reperfusion-induced ventricular arrhythmias

HDL = high-density lipoprotein

The cardioprotective effects of exercise training are summarized in Table I.

Effects of exercise on symptoms and prognosis

It is well recognized that exercise training improves functional capacity and reduces myocardial ischemia and anginal symptoms in patients with stable CHD [21]. In addition to improving symptoms, regular exercise has also been shown to improve long-term prognosis. In a meta-analysis of 48 randomized trials of up to 6 months duration, which included 8940 patients with stable CHD, exercise training was associated with a 20% reduction in total mortality and a 26% reduction in cardiac mortality relative to a usual-care strategy [22]. In a clinical trial in which 100 patients with stable angina were allocated randomly to groups to receive percutaneous coronary intervention or exercise training for 12 months, exercise training was associated with better functional capacity and a greater event-free survival at the end of the follow-up period [23].

Exercise recommendations for patients with angina pectoris

Although the benefits of regular exercise outweigh its potential risks in patient with stable angina pectoris, it is also recognized that habitually sedentary patients with CHD who engage in strenuous physically activity are at increased risk of myocardial infarction and sudden cardiac death [24]. For this reason, patients with angina who are not routinely active should initially engage in low-intensity activities before engaging in more vigorous physical activity. In addition, patients with CHD who are initiating an exercise

program should avoid physical exertion in very cold or hot, humid conditions that might increase the risk of an acute coronary event. Studies performed in supervised exercise programs suggest the risk of major cardiovascular events during exercise training to be between 1/50 000 and 1/120 000 patient-hours of exercise in patients with CHD [25].

Patients with stable angina pectoris should undergo a medical evaluation, including an exercise stress test, for exercise prescription before embarking on an exercise program. General recommendations include low-intensity aerobic training (<40% of maximum aerobic capacity; 50–70% of maximum heart rate) three times per week at the outset. Exercise intensity may progressively be increased as tolerated. Should ischemia or anginal symptoms occur during exercise testing, the target heart rate should generally be fixed at 10 beats/min below the observed ischemic threshold. Each exercise session should consist of three components: (i) a 10 min warm-up period consisting of stretching and low-level calisthenics, (ii) a 20–30 min period of aerobic exercise, and (iii) a 10 min cool-down period also involving low-level calisthenics and walking. Aerobic exercise (for example, fast walking, jogging, swimming) should be the mainstay of exercise training in patients with CHD. Supervised exercise training programs are also beneficial, especially during the initiation period. They ensure that patients are exercising safely, and permit one to assess progress. The reader is invited to consult exercise training guidelines for more complete details regarding exercise prescription in patients with angina pectoris [25].

Conclusions

Exercise training is beneficial in patients with chronic stable angina and is associated with an improvement in exercise tolerance, a reduction in anginal symptoms, and improved long-term survival. Regular exercise is associated with numerous cardioprotective mechanisms, including effects on endothelial function, inflammation, and improved risk factor control. Patients with angina pectoris should be encouraged to engage in regular physical activity as part of a comprehensive lifestyle intervention for the secondary prevention of CHD. ■

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Featured research

Abstracts and commentaries

The cardiovascular risk factor, left ventricular hypertrophy, is highly prevalent in stable, treated angina pectoris

Ang DSC, Pringle SD, Struthers AD. *Am J Hypertens*. 2007;20:1029–1035.

Recent evidence suggests that left ventricular hypertrophy (LVH) is an important cause of cardiac death in patients with coronary artery disease (CAD). Not only is LVH common in patients with CAD, it also confers an added independent risk of cardiac death. Furthermore, a recent analysis suggests that identifying and regressing LVH in patients with angina should be worthwhile and cost effective. Despite this, the role of LVH in CAD is underappreciated and little studied. In fact, the only previous prevalence study was carried out in Chicago in 1992, where 70–80% of the patients with CAD were black and had hypertension [1]. Clearly, the treatments for both CAD and hypertension are considerably different 15 years later, which means that currently we lack up-to-date information on the prevalence of LVH in CAD. Therefore, this study assessed the current prevalence of LVH in stable, treated patients with CAD. The investigators deliberately chose stable, treated patients, as they were mainly interested in the prevalence of LVH that remained after the CAD had been optimally treated, to determine whether LVH was a possible residual therapeutic target.

Commentary

Three hundred and twenty-two consecutive patients with angiographically confirmed coronary artery disease were recruited. It is worth noting that the majority of patients had been stable on their antianginal treatments for a prolonged period of time. Echocardiographic left ventricular mass was measured and correlated with both office and 24 h ambulatory blood pressure. The inclusion criteria were a history of ischemic chest pain and the presence of angiographically proven CAD (more than 50% reduction in the cross-sectional diameter of a major coronary artery). The majority of the patients had been treated with stable antianginal medication for approximately 1 year and the majority had no current symptoms of angina pectoris. Of the 267 patients in whom left ventricular mass measurements were obtained, 195 (73%) had LVH. The mean 24 h ambulatory blood pressure reading was systolic 125 ± 12 mm Hg and diastolic 68 ± 8 mm Hg in the group with LVH. Of the LVH patients, 62% had a non hypertensive 24 h blood pressure reading. On multivariate logistic regression analysis, factors independently related to LVH were history of hypertension (odds ratio [OR] 1.848, 95% confidence interval [CI] 1.051 to 3.248), body mass index (OR 1.085, 95% CI 1.011 to 1.165), and age (OR 1.039, 95% CI 1.004 to 1.076). The predominant left ventricular geometry pattern in this study population was concentric LVH (39% when indexed to body surface area). The results of this study suggest a high prevalence of echo LVH in patients with stable, treated CAD. The other main finding of practical clinical relevance is that LVH is common even in the presence of a normal office or 24 h ambulatory blood pressure (68%, 113/165 mm Hg; 75%, 78/104 mm Hg, respectively) in patients with stable, treated angina. In summary, this is the first study to demonstrate that the prevalence of LVH in stable, optimally treated patients with angina is high. Future studies should now examine whether detecting and fully regressing LVH in normotensive, stable patients with CAD and with LVH would improve the prognosis in patients with CAD.

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Danielle Feuvray

Gender differences in the management and clinical outcome of stable angina

Daly C, Clemens F, Lopez Sendon JL et al, for the Euro Heart Survey Investigators. *Circulation*. 2006;113:490–498.

The Euro Heart Survey of Stable Angina examined the impact of gender on the investigation and subsequent management of stable angina and assessed gender differences in clinical outcome at 1 year. A total of 3779 patients (42% women) with a clinical diagnosis of stable angina on initial assessment by a cardiologist were enrolled in the survey. Baseline clinical details and cardiac investigations planned or performed within a 4-week period of the assessment were recorded, and follow-up data were collected at 1 year. Women were less likely to undergo an exercise ECG (odds ratio 0.81; 95% confidence interval [CI] 0.69 to 0.95), and less likely to be referred for coronary angiography (odds ratio 0.59; 95% CI 0.48 to 0.72). Antiplatelet and statin therapies were used significantly less in women than in men, both at initial assessment and at 1 year, even in those in whom coronary disease had been confirmed. Women with confirmed coronary disease were less likely to undergo revascularization than were their male counterparts, and were twice as likely to suffer death or non fatal myocardial infarction during the 1-year follow-up period (hazard ratio 2.09; 95% CI 1.13 to 3.85), even after multivariable adjustment for age, abnormal ventricular function, severity of coronary disease, and diabetes. It was concluded that significant gender bias exists in the use of investigations and evidence-based medical therapy in stable angina. Women were also less likely to undergo revascularization. The observed bias is of particular concern in light of the adverse prognosis observed among women with stable angina and confirmed coronary disease.

Commentary

This large survey of patients with stable angina pectoris revealed a substantial undertreatment of the female patients compared with the male patients, at least according to European standards. This conclusion is based on fewer referrals for invasive and non invasive investigations, fewer revascularization procedures, and fewer female patients receiving ''optimal'' medical treatment. According to the investigators, this trend is all the more worrying in view of the worse prognosis for angina in women who have confirmed coronary disease.

Several factors must be taken into account when evaluating the clinical relevance of these conclusions.

- The Euro Heart Survey program includes a small number of patients, on a voluntary basis, and they may not be representative of the entire population. Moreover, major differences in the practice of medicine among European countries may affect the overall results, depending on the geographical origin of the patients who are included.
- Angina in women with coronary artery disease certainly has a worse prognosis than that in men. The Survey investigators seem to imply that a more liberal access to investigations and procedures could modify this situation. However, this suggestion does not appear to be supported by scientific evidence; if anything, we know that revascularization procedures in stable angina have a very limited impact on prognosis. No trial comparing percutaneous coronary intervention with medical treatment has been able to demonstrate a significant reduction in the rates of death, myocardial infarction, or both, in patients with stable angina. Given the fact that such percutaneous coronary intervention is less effective and more complicated in women than in men, it appears difficult to imagine that a wider use of revascularization procedures could improve prognosis among women.
- The relationship between angina and age in women is more complex than in men. Angina in younger women is often associated with absence of obstructive coronary lesions whereas, in older women, coronary atherosclerosis is more severe and diffuse than in men. Among men, the relationship between age and coronary atherosclerosis is more uniform and progressive. The fact that men and women studied in the Euro Heart Survey had a similar mean age, does not, therefore, provide sufficient information as to the likelihood of significant coronary atherosclerosis.

Mario Marzilli

Glossary

Gary D. Lopaschuk

Cytokines

Cytokines refer to a group of compounds that are produced under a variety of conditions, including the immune response and inflammatory reactions. Tumor necrosis factor-α and interleukin-1 are examples of two cytokines.

Free fatty acids

The majority of fatty acids in the blood are esterified to glycerol in the form of triacylglycerols or phospholipids in lipoproteins such as very low density lipoproteins or chylomicrons. However, some circulate as unesterified fatty acids. Because of the low solubility of fatty acids, these ''free fatty acids'' are bound to albumin, which facilitate the passage of the free fatty acids throughout the circulation.

Glucose oxidation

The metabolism of glucose in muscle first involves the uptake of glucose into the cell, following which most of the glucose is metabolized by the glycolytic pathway, with pyruvate being one of the metabolic byproducts of glycolysis. This pyruvate can taken up into the mitochondria where it is used as a substrate of pyruvate dehydrogenase or pyruvate carboxylase, which provides carbons for the citric acid cycle. If glucose both passes through glycolysis and the pyruvate is subsequently oxidized by the mitochondria the process is called glucose oxidation.

Insulin resistance

Insulin resistance refers to a situation where the amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in hydrolysis of stored triacylglycerol, which blood free fatty acids in the levels. Insulin resistance in muscle decreases glucose uptake, whereas insulin resistance in liver reduces glucose storage. Both of these actions increases blood glucose levels. Insulin-resistance is often characetized by high plasma levels of insulin, since higher insulin levels are needed to evoke similar responses in adipocytes, muscle, and liver.

Lactate metabolism

Lactate is a carbohydrate used by various tissues, including muscle. Lactate can be taken up by muscle and converted to pyruvate (by lactate dehydrogenase), where the pyruvate is subsequently oxidized in the mitochondria. Lactate is also a product of muscle glycolysis, and if the pyruvate from glycolysis is not oxidized it is converted to lactate (also by lactate dehydrogenase), and the lactate is subsequently released from the muscle.

Pyruvate dehydrogenase

Pyruvate dehydrogenase (PDH) is an intramitochondrial complex that converts pyruvate (which primarily originates from glucose or lactate) into acetyl CoA. PDH is the rat-limiting enzyme for the mitochondrial metabolism of carbohydrates. Maintaining mitochondrial glucose metabolism is an important therapeutic strategy to protect the ischemic heart. Therefore, activating PDH is a potential therapeutic approach to treating heart disease.

Slow sodium current

During rhythmic firing, the action potential of cardiac cells involves different phases, all involving different ion fluxes across the membrane. In Phase 4 of the action potential there is a slow inward flow of sodium, called the funny current, as well as an inward flow of calcium. This all serves to make the cell more positive, and involves a relatively slow depolarization of the cell until a threshold potential is reached and the cells enter phase 0 of depolarization.

3 KAT

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 ß-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.