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Metabolic interventions for acute coronary syndromes?

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Acute coronary syndromes (ACS) represent a major cause of morbidity and mortality for patients with cardiovascular disease. Indeed, nowadays more patients are admitted to the coronary care unit with an acute coronary syndrome than with acute myocardial infarction or heart failure. It is not a benign disease: in the main clinical article of this issue of *Heart and Metabolism*, Malhotra et al demonstrate that early mortality (14 days) may range between 0.36% and 5.8%, 1-year mortality between 6% and 11%, and 4-year mortality may be as high as 47%. Moreover, having patients with an acute coronary syndrome has also economic consequences as over the years there is a clear tendency for a more aggressive therapeutic approach with PCI and bypass surgery. Also, the increasing use of expensive glycoprotein IIb/IIIa receptor inhibitors adds to the costs. Finally, it is more and more common to dismiss 'low-risk', complaint-free patients with aspirin, clopidogrel, β -blockers, statins, and angiotensin converting enzyme (ACE)-inhibitors, some of which may be given life-long.

Management of the acute coronary syndrome patient is getting to be a complicated business, both from the diagnostic and from the therapeutic point of view. For medical therapy the use of heparin, low-molecular weight-heparin, clopidogrel, glycoprotein IIb/IIIa receptor inhibitors, iv nitrates, β -blockers, calcium antagonists, statins, and ACE-inhibitors has to be considered in an individual patient. On top of that, quite a few patients require bypass surgery or PCI. Clearly, risk stratification is needed on how to treat patients with which drug, for how long or which intervention is warranted. However in risk stratifica-

tion, things are also getting complicated. We now have risk factors such as age, gender, diabetes mellitus, and previous coronary events/known coronary artery disease, and current use of antithrombotics to take into consideration. Moreover, there are powerful diagnostic techniques like the ECG, troponin, classical cardiac enzymes, BNP levels, creatinine clearance, inflammation markers, LV function data by echocardiography, SPECT and MRI, perfusion and metabolic imaging data, and coronary angiograms to consider.

In this wilderness of diagnostic and therapeutic possibilities for patients presenting with an ACS, this issue of *Heart and Metabolism* is extremely helpful. In the 'main clinical article' and in the 'new therapeutic approaches' sections Malhotra et al and Eberli discuss how patients may be treated. The central theme of the authors is risk stratification, and patients should be treated accordingly. Both articles offer simple and easy-to-use schemes, based on the American and European guidelines on how to approach these kinds of patients, both from a diagnostic and therapeutic point of view. I would recommend that every reader study these articles thoroughly and advise them to pass on this issue after reading to fellows-in-training. Of course, simplified schemes do not tell the whole story: every patient deserves an individual approach in which all the available clinical data need to be taken into account. Nevertheless, these articles are a good starting point.

Another interesting point that is highlighted in this issue of *Heart and Metabolism* is the 'metabolic therapeutic approach' to patients with an acute coronary syndrome. In the 'basic article' by Noga et

al and in the 'refresher corner' by Stanley the metabolic changes in ACS are discussed. At the end of the articles the potential pharmacological strategies are summarized, aiming to reduce fatty acid oxidation and increasing glucose oxidation. The major role of glucose and fatty acid changes in patients (and not only in animal experiments), is highlighted in the 'imaging' article of Hambye and Franken. They also advocate the use of metabolic imaging for further risk stratification. Eberli in the 'new therapeutic approaches' section pleads for the use of metabolic interventions with glucose-insulin-potassium (GIK) and fatty acid oxidation inhibitors in ACS. The case report by Szwed shows that the fatty acid oxidation inhibitor trimetazidine reduces the frequency of ischemic episodes in a patient with previous unstable angina. Finally, the beneficial clinical effects of trimetazidine in patients undergoing revasculariza-

tion are discussed in the 'Focus on Vastarel' article by Meurin and Henane. After all, bypass surgery is a global acute coronary event.

It is clear that all authors are enthusiastic about the concept of a metabolic intervention in acute coronary syndromes, as there is a sound rationale. But in this world of evidence-based medicine we are lacking solid clinical data. There are limited data about the use of GIK in acute myocardial infarction, there are no data in ACS. The same applies to the use of fatty acid oxidation inhibitors. We do not know if these pharmacological agents reduce hard and soft end points during follow-up, or lower the risk profile of a patient. Therefore, we are not yet ready to apply these agents into clinical practice. Nevertheless, the concept of metabolic interventions in ACS is very challenging and clinical trials should be designed to prove this. Enjoy reading. ■

Alterations in energy metabolism in acute coronary syndromes

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Abstract

The substantial energy demands of the heart are met by a balanced usage of fatty acids and glucose as energy substrates. During an acute coronary event, plasma fatty acid concentrations increase dramatically, and myocardial control of fatty acid use is altered. These changes initiate a disruption of the metabolic balance in the heart such that, during reperfusion of the ischemic myocardium, fatty acids dominate as a source of energy for the heart. Consequently, glucose oxidation is inhibited. This disruption in energy metabolism is detrimental and contributes to myocardial injury. Therapeutic strategies that promote glucose oxidation or inhibit fatty acid oxidation can increase contractile recovery after ischemia, enhance cardiac efficiency (cardiac work/oxygen consumed), and diminish ischemic injury. This novel therapeutic approach, termed metabolic modulation, is already used clinically to treat angina pectoris. Both experimental and clinical studies have suggested that this approach can also be used to treat acute coronary syndromes. Trimetazidine is an example of a metabolic modulator currently used extensively in the clinical setting to treat angina. It specifically inhibits long chain 3-ketoacyl coenzyme A thiolase, the final enzyme in the mitochondrial β -oxidation of fatty acids. By directly inhibiting fatty acid oxidation, this agent indirectly accelerates glucose oxidation. Trimetazidine has also shown benefit in patients after myocardial infarction. This review will also discuss other approaches to improving the balance between glucose and fatty acid metabolism in the ischemic heart. It is anticipated that, as other promising agents undergo additional analysis, metabolic modulation will be confirmed as a valuable therapeutic approach to the treatment of acute coronary syndromes.

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Keywords: Acute coronary syndromes, energy metabolism, fatty acid oxidation, glucose oxidation, metabolic modulation, trimetazidine

Introduction

The heart needs to produce very large amounts of energy in order to meet the very high energy demands of the contracting myocardium. As the heart has little energy reserves, highly regulated metabolic pathways exist in order to match energy production with energy demand. These energy yielding pathways require large amounts of oxygen so that mitochondrial oxidative phosphorylation can synthesize ATP, the energy currency of the heart. During an acute coronary event, a myocardial supply–demand mis-

match occurs with respect to the oxygen necessary to produce this ATP. This can occur as a result of either an interruption in the blood flow and oxygen supply to the heart, or an increase in oxygen demand that exceeds the oxygen supply to the heart.

Despite major attempts to develop new therapeutic interventions, ischemic heart disease continues to be the primary cause of mortality worldwide. At present, most therapeutic approaches aim either to increase oxygen supply to the heart or to decrease oxygen demand (ie, by decreasing heart rate or contractility, or both) [1]. However, more recently a promising

alternate therapeutic approach, termed metabolic modulation, which involves the optimization of energy substrate utilization by the heart, has been introduced for the treatment of angina pectoris [2]. This new approach may also be beneficial in reducing the damage to the heart that is caused by an acute coronary event.

The heart is an omnivore and can use a variety of energy substrates to maintain ATP production, including glucose, lactate, and long-chain fatty acids (LCFAs). Normally, the metabolism of fatty acids contributes 60% to 80% of the heart's energy needs [3,4]. On a per molecule basis, LCFAs produce more ATP than do carbohydrates. However, in terms of oxygen consumption, fatty acid oxidation is less efficient and, compared with glucose, requires more oxygen to produce an equivalent amount of ATP [4]. This can be highly detrimental during an ischemic episode, when oxygen concentrations are low [4]. Therefore, therapeutic strategies that switch myocar-

dial substrate preference from LCFAs to glucose have proven to be beneficial to the ischemic heart. This paper will review the pathways by which energy is produced in the heart, in addition to the alterations in energy metabolism that occur during acute coronary syndromes. It will also discuss some of the therapeutic approaches to optimizing energy metabolism in the ischemic heart.

Energy metabolism in the normal heart

Carbohydrate metabolism

Although LCFAs are the major fuel in the heart, carbohydrate metabolism is also essential for normal myocardial function. Carbohydrate metabolism can be divided into three processes: glucose uptake, glycolysis, and glucose oxidation (*Figure 1*). In the heart,

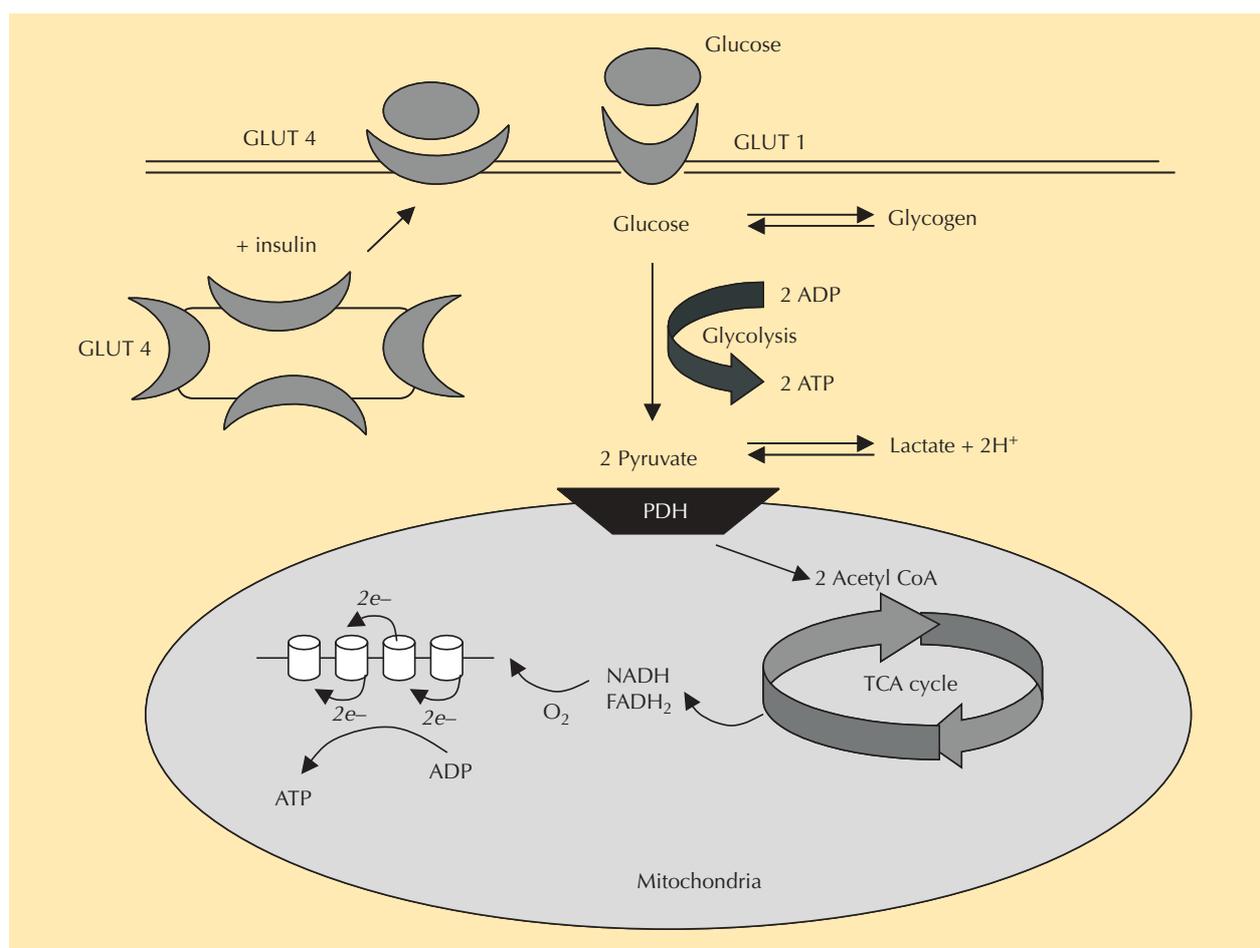


Figure 1. Glucose metabolism in the aerobic heart. Plasma-derived glucose enters the cardiac myocyte via glucose transporters (GLUT) 1 and 4. GLUT 4 is normally sequestered in intracellular stores that are mobilized in response to insulin. Upon entry into the cell, glucose primarily enters the glycolytic pathway to form pyruvate. Pyruvate is then transported into the mitochondria and converted to acetyl coenzyme A (CoA) via the pyruvate dehydrogenase (PDH) complex. ATP is produced as the acetyl CoA is further metabolized via the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. In the absence of adequate PDH activity, the pyruvate is reversibly converted to lactate.

glucose uptake is facilitated by the glucose transporters, GLUT 1 and GLUT 4. The GLUT 1 transporter maintains basal glucose uptake whereas, in response to insulin or contraction, GLUT 4 is mobilized from an intracellular storage pool to the sarcolemma, where it is available for glucose uptake from the bloodstream [5]. Once glucose is within the cell, glycolysis initiates its breakdown to pyruvate. In the normally functioning myocardium, this pathway contributes less than 10% of the total myocardial ATP. However, glycolysis is an anaerobic process and therefore its percent contribution to ATP production becomes more pronounced in conditions in which oxygen concentrations are depleted, such as hypoxia or ischemia [6].

The subsequent metabolism of glycolytically derived pyruvate is referred to as glucose oxidation. This step in the pathway occurs within the mitochondria and releases the majority of ATP that is derived from carbohydrate. Cytosolic pyruvate is converted to acetyl coenzyme A (CoA) by enzymes of the pyruvate dehydrogenase (PDH) complex. This glucose derived acetyl CoA then enters the tricarboxylic acid (TCA) cycle to produce electron donors for the production of ATP by oxidative phosphorylation in the electron transport chain.

Fatty acid metabolism

Fatty acids are taken up into the myocyte either by facilitated diffusion, or by fatty acid transporters such as FAT/CD36 and FATP6 (*Figure 2*). Upon entry of LCFAs into the cell, their subsequent metabolism requires their conversion to long chain fatty acyl CoAs. These fatty acyl CoAs must traverse the inner mitochondrial membrane in order to reach the β -oxidation machinery. The transport of these esters into the mitochondria is mediated by the carnitine shuttle, and occurs in a three-step process, involving carnitine palmitoyltransferase-1 (CPT-1), carnitine-acylcarnitine translocase, and CPT-2 (*Figure 2*). This process is controlled by malonyl CoA, a potent inhibitor of CPT-1, the production of which is under the control of acetyl CoA carboxylase and malonyl CoA decarboxylase. The fatty acyl CoA in the mitochondria then enters the β -oxidation pathway, to produce primarily acetyl CoA, which then enters the TCA cycle to produce electron donors for oxidative phosphorylation.

The Randle cycle

As described above, the PDH complex catalyzes the first step of glucose oxidation, and is considered the rate limiting step in glucose oxidation. PDH is tightly regulated in a feedback fashion, so an accumulation

of acetyl CoA, or TCA cycle end products results in its inhibition (*Figure 2*) [7]. The β -oxidation of LCFAs also contributes acetyl CoA for the TCA cycle. Hence, when fatty acid oxidation is taking place, glucose oxidation is inhibited. This balance of substrate utilization is termed the "Randle cycle." On the basis of this phenomenon, inhibition of LCFA oxidation will result in increased glucose oxidation [2]. It is probable that this mechanism developed to prevent unnecessary loss of energy substrate; however, it becomes detrimental in the setting of ischemia-reperfusion, as outlined in the next section.

Energy metabolism in the ischemic and the reperfused ischemic heart

Deprivation of an adequate oxygen supply during acute coronary syndromes results in a decrease in the oxidative metabolism of glucose and fatty acids, and a significant stimulation of glycolysis [2]. The degree to which these metabolic changes occur is dependent on the severity of the ischemic episode. During severe ischemia, glycolysis can become the primary source of ATP (*Figure 3*). However, the pyruvate produced by glycolysis is unable to enter the oxidative pathway and as a result it is converted to lactate. This imbalance between glycolysis and glucose oxidation also results in the production of deleterious protons, and is a major cause of the intracellular acidosis that occurs during severe ischemia. A consequence of this is that cardiac efficiency decreases as ATP is directed towards re-establishing ionic homeostasis rather than to contractile function [8].

Normal return of contractile function after an acute coronary event requires that the heart accelerate energy production quickly. However, myocardial recovery also depends on the energy substrate used by the heart. During an ischemic episode, circulating concentrations of free fatty acids increase as triglyceride stores in the adipose tissue are mobilized [9–11]. LCFA oxidation recovers rapidly as the heart is exposed to the high concentration of plasma fatty acids. As a result, glucose oxidation does not recover because the metabolites of fatty acid β -oxidation inhibit the PDH complex (via the Randle cycle).

The rapid recovery of LCFA oxidation is also enhanced by the activation of a kinase called AMP-activated protein kinase (AMPK). AMPK activation results in the phosphorylation of acetyl CoA carboxylase, a decrease in malonyl CoA concentrations and a dramatic increase in fatty acid oxidation (*Figure 3*) [12,13]. As a result, glucose oxidation is further inhibited. AMPK activation also results in an acceleration of glycolysis and glucose uptake as GLUT 4 is stimulated to translocate to the plasma membrane in an insulin independent manner [14,15]. Therefore

Basic article

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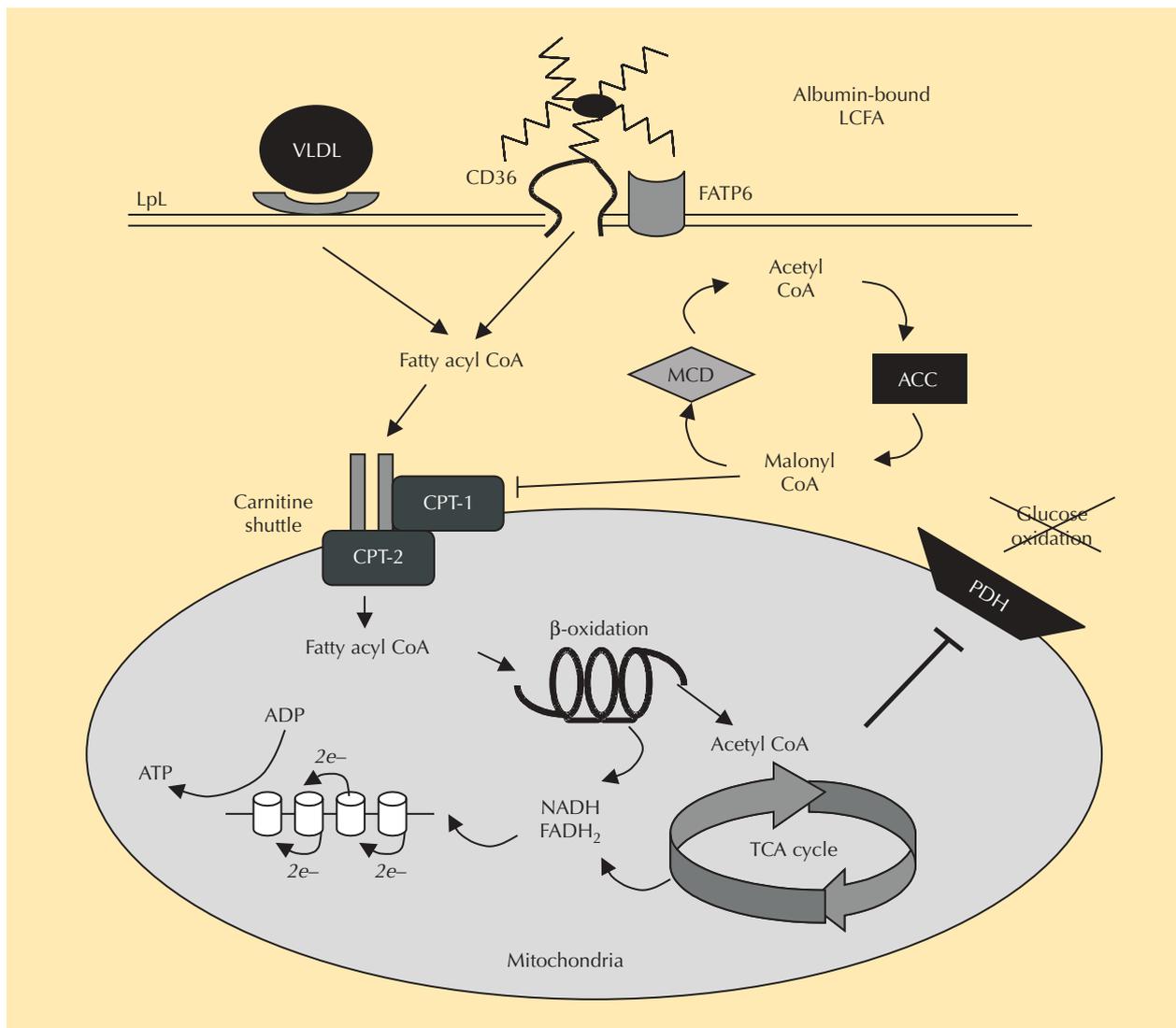


Figure 2. Long chain fatty acid (LCFA) metabolism in the aerobic heart. LCFAs enter the cardiac myocyte through a number of routes, including diffusion or facilitated by fatty acid transporter (FAT)/CD36 and FATP6. Within the cell, fatty acyl coenzyme A (CoA) synthase converts the LCFA to a long chain fatty acyl CoA. Carnitine palmitoyltransferase (CPT)-1 exchanges the CoA for carnitine and the long chain fatty acyl carnitine is transported into the mitochondria. CPT-2 catalyzes another CoA–carnitine exchange and the long chain fatty acyl CoA enters the β -oxidation pathway. The number of ATP and acetyl CoA molecules produced depends on the length of the LCFA. During active synthesis of acetyl CoA through the β -oxidation pathway, the pyruvate dehydrogenase (PDH) complex is inhibited, decreasing glucose oxidation. This phenomenon is termed the “Randle cycle”. ACC, acetyl coenzyme A (CoA) carboxylase; LpL, lipoprotein L; MCD, malonyl CoA decarboxylase; TCA, tricarboxylic acid; VLDL, very low density lipoprotein.

AMPK activation results in a more pronounced uncoupling of glycolysis from glucose oxidation [16]. Until coronary flow is returned to normal, lactate and protons continue to accumulate in the cardiac myocyte, contributing to poor cardiac efficiency during reperfusion.

During and after ischemia there can be a large increase in the intracellular concentration of Na^+ in the cardiac cells as the Na^+-H^+ exchanger facilitates the removal of intracellular protons [8]. The $\text{Na}^+-\text{Ca}^{2+}$ exchanger responds to the increase in Na^+ by exchanging the Na^+ for Ca^{2+} . This results in a rapid increase in intracellular Ca^{2+} , which can lead to

myocyte damage or cell death. Ironically, although the protons that accumulate during an ischemic insult are damaging, their rapid removal is more detrimental to the heart. This event is termed the “pH paradox” [17].

The preference for LCFA oxidation over glucose oxidation in the postischemic heart contributes to ischemic injury. Compared with glucose oxidation, LCFA oxidation utilizes considerably more oxygen for each molecule of ATP produced, therefore cardiac efficiency is decreased. This is a direct result of the imbalance between glycolysis and glucose oxidation, resulting in an increase in accumulation of lactate and protons within the cardiac myocyte [8,18].

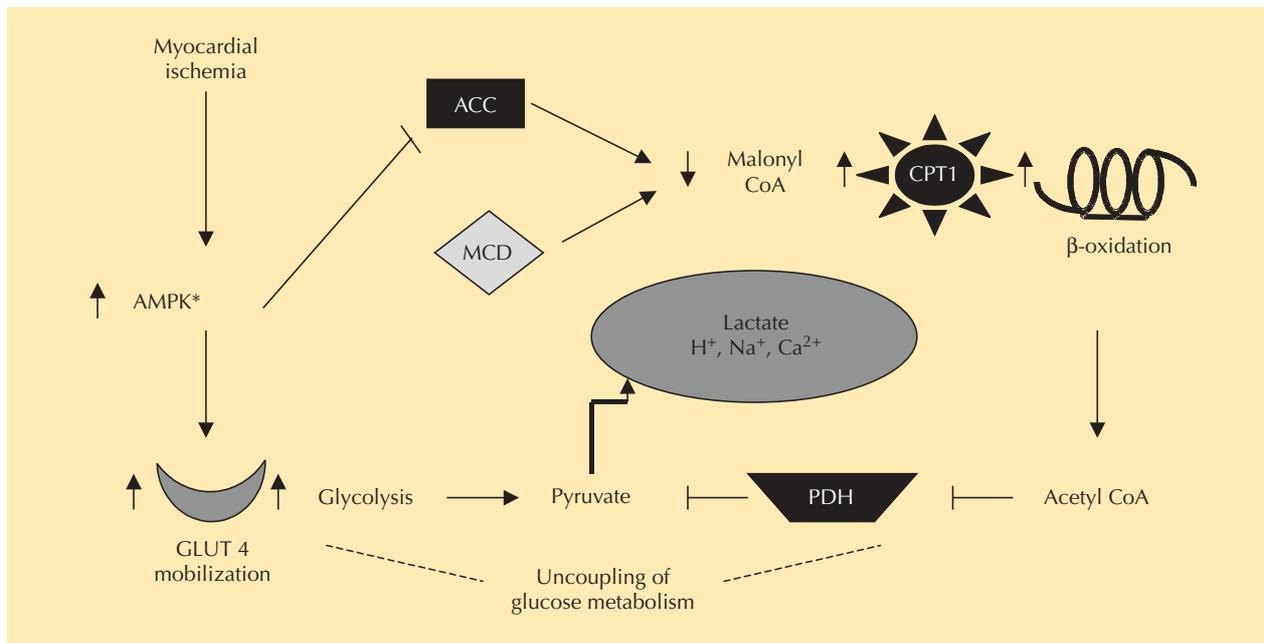


Figure 3. Deleterious effects of 5'-AMP-activated kinase (AMPK) activation in the ischemic heart. Activation of AMPK is stress-induced in the ischemic myocardium. It phosphorylates acetyl coenzyme A (CoA) carboxylase (ACC), which interrupts its activity. It is also hypothesized that AMPK activates malonyl CoA decarboxylase (MCD), although this has not been confirmed. As a result, malonyl CoA is depleted and carnitine palmitoyltransferase (CPT)-1 is activated, leading to excessive amounts of LCFA entering the β -oxidation pathway. Because of the excessive production of acetyl CoA via LCFA oxidation, the pyruvate dehydrogenase (PDH) complex is inhibited. In addition, AMPK initiates the mobilization of glucose transporter (GLUT) 4 and the acceleration of glycolysis. As a result, a large amount of pyruvate is produced, but is unable to enter glucose oxidation. Therefore lactate and H^+ accumulate in the cardiac myocyte, causing damage.

Finally, the intracellular accumulation of protons may also indirectly damage the myocardium when they are removed from the cell and this potentially leads to Ca^{2+} overload. The summation of all these effects of accelerated LCFA oxidation proves detrimental to the ischemic heart.

Potential pharmacological metabolic modulation

As discussed, metabolic changes in the myocardium during and after an acute coronary event contribute to ischemic injury. One potential metabolic treatment for ischemia is to develop pharmacological agents that can manipulate these metabolic changes. A desired effect would be to decrease LCFA oxidation and increase glucose oxidation, in order to increase glycolysis–glucose oxidation coupling and decrease the accumulation of lactate and H^+ . This can be achieved by either directly inhibiting fatty acid oxidation or directly stimulating glucose oxidation (Figure 4).

Modulation of fatty acid oxidation

The potential for increasing the rate of glucose oxidation by directly inhibiting β -oxidation of LCFAs

is already seeing clinical application in the treatment of angina pectoris. This pharmacological approach has been proven efficacious and is now beginning to have widespread usage in the clinical setting. Specifically, the antianginal agent trimetazidine has been shown to have beneficial effects secondary to the inhibition of fatty acid oxidation [19,20].

Initially described as a cytoprotective agent, trimetazidine was later shown specifically to inhibit the last step of the β -oxidation machinery catalyzed by long-chain 3-ketoacyl CoA thiolase [19,20]. Inhibition of this enzyme decreases fatty acid oxidation, resulting in a parallel increase in glucose oxidation both during [19] and after ischemia [20]. This metabolic action of trimetazidine is associated with a decrease in acidosis and accumulation of Na^+ during ischemia [21], and an improved functional recovery after ischemia [20,22]. Clinical studies have consistently shown that trimetazidine has significant antianginal effects [23–29] and has beneficial effects on cardiac function in patients with ischemic cardiomyopathies [29]. There are also clinical data suggesting that trimetazidine has beneficial effects in acute coronary syndromes. Treatment of patients undergoing coronary angioplasty procedures with trimetazidine attenuated the acute ischemic changes that normally occur [30]. Trimetazidine has also been shown to have beneficial effects on cardiac function

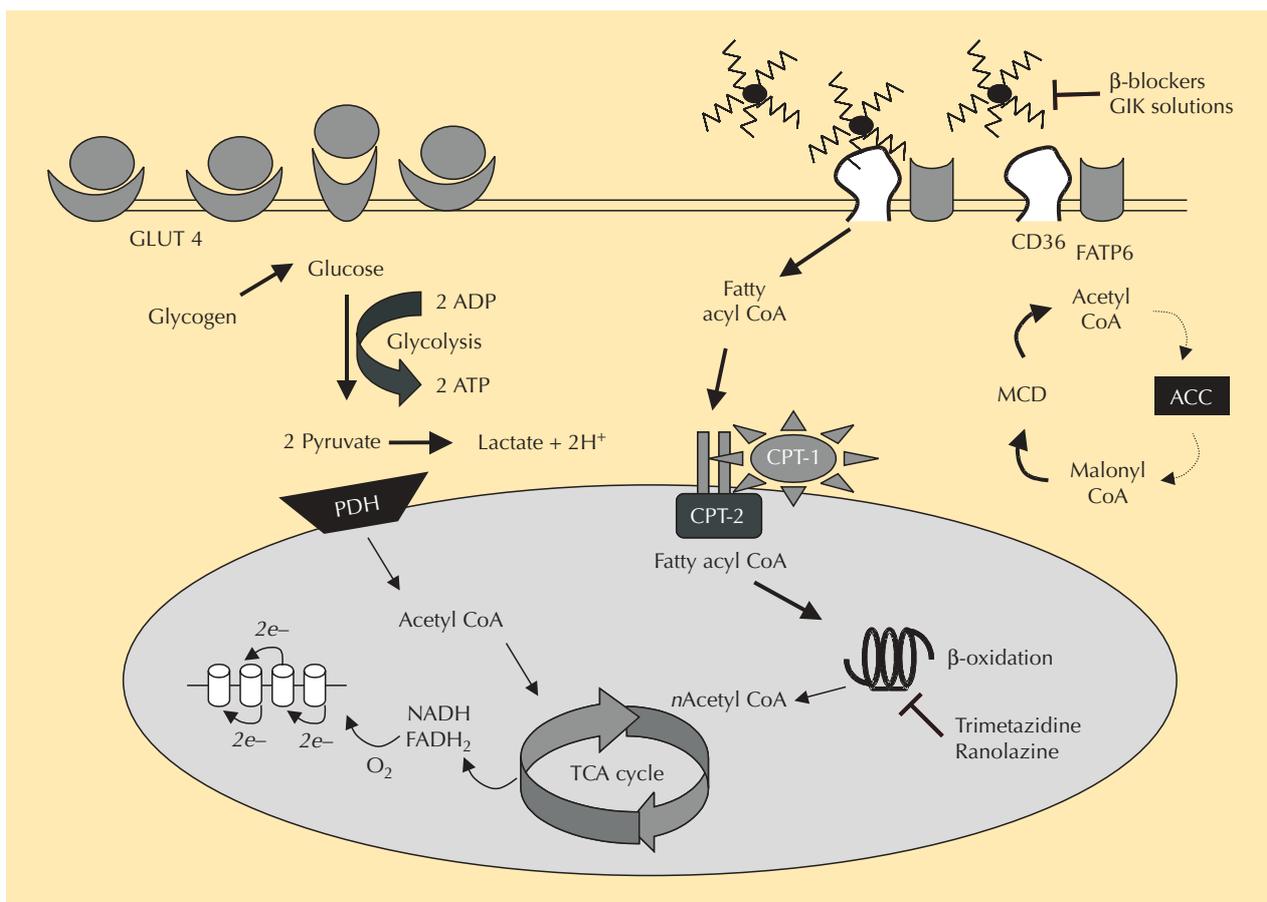


Figure 4. Pharmacological metabolic modulation of the ischemic heart. A number of pharmacological agents that change energy metabolism in the ischemic heart are outlined. β -Blockers and glucose–insulin–potassium (GIK) solutions block the increase in plasma long chain fatty acids during an ischemic episode. Trimetazidine and ranolazine are direct inhibitors of β -oxidation. Trimetazidine has been approved for clinical use in more than 80 nations. Ranolazine is as yet to be approved for clinical use. ACC, acetyl coenzyme A (CoA) carboxylase; CPT, carnitine palmitoyltransferase; FAT, fatty acid transporter; GLUT 4, glucose transporter 4; MCD, malonyl CoA decarboxylase; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid.

after cardiopulmonary bypass surgery [31]. A large trial in patients receiving trimetazidine after myocardial infarction showed a decrease in mortality rates in patients who had not undergone thrombolysis compared with those receiving placebo [32].

Other approaches to inhibition of fatty acid oxidation

Ranolazine, like trimetazidine, is an inhibitor of fatty acid oxidation that has antianginal efficacy. To date, there is no clinical experience with ranolazine in acute coronary syndromes. However, in experimental studies, ranolazine did improve functional recovery of the heart after a severe ischemic episode [33,34]. In clinically relevant concentrations, ranolazine also partially inhibits β -oxidation [34,35]. In response to the decrease in LCFA oxidation, PDH activity increases, in addition to the rate of oxidation of glucose [35]. Unlike trimetazidine, ranolazine has not

yet been approved for clinical use. However, clinical trials confirm that it is an effective treatment in patients with reproducible angina-limited exercise [36,37].

During ischemia, catecholamines stimulate the release of free fatty acids from the adipose tissue in a normal “flight/fight” response [9–11]. This excessive availability of LCFA to the heart contributes to the preference of the heart for LCFA as a substrate, rather than glucose, during the ischemia-reperfusion period [18]. One means of decreasing the oxidation of LCFA and increasing that of glucose is to inhibit this surge in plasma free fatty acids.

β -Blockers are commonly used in patients with ischemic heart disease, and they effectively increase long-term survival. The beneficial effects of β -blockers have always been attributed to an increase in oxygen supply to the myocardium. However, these agents also partially block the catecholamine-induced release of fatty acids from adipose depots [38]. Therefore, β -blockers may be a valuable

treatment option, not only for hemodynamic reasons, but also for their ability to decrease plasma LCFA and alter cardiac energy metabolism. This possibility remains to be assessed in the clinical setting.

Glucose–insulin–potassium solutions have been in use as a treatment for acute coronary syndromes for more than 40 years, yet only recently have the beneficial effects of this treatment become more apparent [39]. The South American Estudios Cardiológicos LatinoAmerica trial showed that the use of glucose–insulin–potassium treatment in patients after a myocardial infarction is associated with a decrease in mortality [40]. Further large-scale clinical trials are in progress to assess the actions of glucose–insulin–potassium in patients suffering a myocardial infarction. On the basis of the known metabolic effects of insulin, it is easy to hypothesize what may be occurring. Insulin is known to inhibit hormonal lipase in adipose tissues [41]; this should, in essence, result in a decrease in the mobilization of free fatty acids to the plasma. In addition, insulin is a known inhibitor of the secretion of very-low-density lipoprotein from the liver, which is another potential source of LCFAs [42]. The benefit of glucose–insulin–potassium in the setting of acute coronary syndromes has usually been associated with direct effects on myocardial glucose uptake and metabolism, but the possibility cannot be ruled out that insulin may also act to decrease fatty acid oxidation, secondary to a decrease in circulating fatty acid concentrations. Although further investigations are required, the clinical benefits of glucose–insulin–potassium treatment may be severalfold with regards to metabolic modulation in the ischemic heart.

Summary

After a severe ischemic episode, the heart obtains an excessive amount of its ATP from fatty acid oxidation. This imbalance in substrate utilization contributes to a number of deleterious effects in the postischemic heart, including reduced cardiac efficiency, increased acidosis and the potential for Ca^{2+} overload. The summation of these problems contributes to ischemic injury and prevents the heart from recovering full contractile function. In terms of potential treatment, pharmacological strategies focusing on decreasing the rate of oxidation of LCFA and increasing that of glucose have considerable potential in treating ischemic heart disease. The successful use of trimetazidine in treating chronic angina and the ischemia induced by cardiopulmonary bypass suggests that metabolic modulation may also be an important strategy for the treatment of acute coronary syndromes. ■

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Risk stratification and outcome in non-ST-segment elevation in acute coronary syndromes

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Abstract

Non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) are heterogeneous both in outcome as well as response to therapy, carrying significant morbidity and mortality. In this paper, we review a variety of risk factors for adverse outcomes, including clinical characteristics, metabolic parameters, ECG indicators, and cardiac biomarkers. The development of assays for biomarkers reflecting various axes of cardiac pathophysiology including myocyte necrosis, inflammation, hemodynamic stress, and vascular damage have led to multimarker approaches for the assessment of risk. Combining factors into a single risk score has been shown not only to enhance prognostic ability, but also to enable identification of subsets of patients that derive greater benefit from intense therapies. Overall, a multifactorial, multimarker approach to risk stratification will likely prove effective in optimizing therapeutic benefit in this heterogeneous population of patients.

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Keywords: Acute coronary syndrome, unstable angina, myocardial infarction, risk factor, cardiac biomarkers, electrocardiography

Non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) include unstable angina and NSTEMI myocardial infarction (NSTEMI) and occur as a result of coronary plaque rupture followed by partially occlusive thrombus formation. Both unstable angina and NSTEMI can present with angina and may have ST-segment depression T-wave inversions, or both, on the ECG. The diagnosis of NSTEMI is made if an increase in cardiac markers of necrosis accompanies these symptoms. Because the syndromes are heterogeneous and carry a mortality rate of 5% and a (re)infarction rate of 10% within 30 days [1], it is helpful to risk stratify patients (*Table 1*).

The patient's history and initial presentation provide important prognostic information in NSTEMI ACS. Every decade of age increases the relative risk for death or myocardial infarction by a factor of 1.43 ($P < 0.001$), with an inflection point occurring at approximately 65 years of age [2, 3]. The prognostic

value of sex remains unclear, with conflicting data from different studies [3–5].

The prevalence of diabetes is roughly 15% in patients with NSTEMI ACS [14]. In terms of pathophysiology, diabetes leads to formation of advanced glycosylation end products, which are proatherogenic, in addition to increased platelet aggregation, which may affect hemostasis [15–17]. Diabetes is a major risk factor for and a powerful prognostic indicator in ACS. One study showed the risk of first-time myocardial infarction in patients with diabetes to be equivalent to the risk of recurrent myocardial infarction in nondiabetic individuals [14]. Among patients with unstable angina/NSTEMI, those with diabetes were found to have a 1.7 (95% confidence interval [CI] 1.2 to 2.4) greater risk of long term mortality than those without diabetes [7]. Glycated hemoglobin (HbA_{1c}) and blood glucose concentrations are biomarkers for diabetes, and one study

Table 1. Risk factors in NSTEMI ACS.

Category	Risk factor	Comment	Reference
Clinical	Age	Risk of death or MI at 1 year increases by 1.43 for every decade (95% CI 1.26 to 1.61)	[2]
	Sex	Ambiguous, some studies showing female sex to be protective	[3–5]
	≥ 3 CAD risk factors	Odds ratio for death, MI, or urgent revascularization by 14 days is 1.54 (95% CI 1.16 to 2.06)	[6]
	Severe anginal symptoms	Odds ratio for death, MI, or urgent revascularization by 14 days is 1.53 (95% CI 1.20 to 1.96)	[6]
	Prior ASA use	Odds ratio for death, MI, or urgent revascularization by 14 days is 1.74 (95% CI 1.17 to 2.59)	[6]
Metabolic	Diabetes (HbA _{1c})	Risk of long-term mortality increases by 1.7 (95% CI 1.2 to 2.4)	[7]
	Renal insufficiency	Risk of death at 1 year if CrCl < 51 mL/min increases by 1.8 (95% CI 1.3 to 2.3)	[8]
ECG	ST-segment depression	Risk of death or MI at 1 year increases by 2.45 if depression > 0.05 mV (95% CI 1.74 to 3.45)	[2]
	T-wave inversion	Poses no significant risk	[2]
	LBBB	Risk of death or MI at 1 year increases by 2.80 (95% CI 1.81 to 4.32)	[2]
Biomarkers	Necrosis (Tn, CK-MB)	Risk of death or MI at 30 days and 6 months is 2–4-fold greater for increased Tn or CK-MB	[9, 10]
	Inflammation (CRP)	Risk of 14-day mortality increases for CRP > 15 mg/L and long term mortality increases by 2.5 (<i>P</i> =0.001) for CRP > 10 mg/L	[11, 12]
	Hemodynamics (BNP)	Odds ratio of death at 6 months for BNP > 80 pg/mL is 3.3 (95% CI 1.7 to 6.3)	[13]

ASA, acetylsalicylic acid; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CI, confidence interval; CK-MB, creatine kinase-myocardial band; CrCl, creatinine clearance; CRP, C-reactive protein; HbA_{1c}, glycated hemoglobin; LBBB, left bundle branch block; MI, myocardial infarction; Tn, troponin.

demonstrated an increasing risk of death, adverse cardiovascular events, and need for revascularization, with increasing HbA_{1c} concentrations. Hazard ratios of 1.40, 1.81, and 2.36 for increasing quartiles of HbA_{1c} concentrations were obtained when compared with the lowest quartile (*P* values of 0.26, 0.059, and 0.023, respectively) [18].

Impaired renal function is associated with greater mortality in patients with ACS, even in the setting of aggressive management [19, 20]. The prevalence of renal insufficiency in patients with NSTEMI ACS is as high as 40% [19, 20]. A creatinine clearance of less than 51 mL/min in patients with NSTEMI ACS was shown to be an independent predictor of increased mortality at 1 year [odds ratio (OR) 1.8, 95% CI 1.3 to 2.3] and risk of myocardial infarction at 30 days (OR 1.4, 95% CI 1.0 to 2.0) [8]. The inverse creatinine clearance value may serve as an integrated measure of vascular damage resulting from several processes,

including hypertension, diabetes, increased homocystine, and dyslipidemia [21, 22].

ST-segment depression on the presenting ECG is associated with a worse prognosis [23, 24], with data from one study indicating that, among patients with unstable angina/NSTEMI, those with ST-segment depression greater than 0.1 mV had 1-year rates of death or recurrent myocardial infarction of 11%, compared with 6.1% for those without ST-segment changes (*P* < 0.001) [2]. The same study did not find an increased risk among those patients with new, isolated T-wave inversions. Data from the Thrombolysis In Myocardial Infarction (TIMI) III Registry indicate that patients with ST-segment depression as little as 0.05 mV are also at increased risk [2], and that the magnitude of the depression is proportional to the degree of risk. Among patients with unstable angina/NSTEMI, the 4-year survival rates were 82%, 77%, and 53% for those with 0.05, 0.10, or more

than 0.20 mV ST-segment depression, respectively ($P < 0.0001$) [25].

Markers of myocardial necrosis are powerful predictors of outcome in ACS. Mortality rates in patients with non-ST-segment elevation ACS increase with creatine kinase-myocardial band (CK-MB) concentrations, with one study demonstrating 6-month mortalities of 4.0%, 6.2%, and 7.5%, corresponding to normal, 1–2 times, and 3–5 times normal CK-MB concentrations [9]. With better sensitivity and specificity [26], the cardiac troponins have become the test of choice for myocardial necrosis. Patients with increased troponin concentrations are at an approximately 4-fold increased risk of death or recurrent myocardial infarction [10]. Moreover, as with CK-MB, the magnitude of the increase in troponin correlates with the mortality rate [27]. Myoglobin, a cytosolic protein of cardiac and skeletal muscle, is the first biomarker to become increased, detectable 2 h after myocardial infarction, and provides additional prognostic information [28]. In TIMI 11B and TACTICS-TIMI 18, an increased baseline myoglobin in patients with NSTEMI ACS was associated with a 3-fold increase in mortality, independent of ST-segment changes or CK-MB and troponin concentrations [29].

Newer cardiac biomarkers have been discovered that provide significant prognostic information independent of the markers of necrosis. The strong inflammatory component of atherosclerosis and thrombogenesis may explain why increased concentrations of the acute-phase molecule C-reactive protein (CRP) are associated with poorer outcomes in ACS [30]. In TIMI 11A, the mortality rate at 14 days was significantly greater among those in whom CRP concentration was more than 1.55 mg/dL (5.80% compared with 0.36%, $P = 0.006$) [11]. The effects of troponin and CRP concentrations on mortality were shown to be additive and independent of one another. B-type natriuretic peptide (BNP) is released by the myocardium in response to increases in atrial and ventricular stretch during hemodynamic stress and has been proven useful in the diagnosis and monitoring of heart failure [31, 32]. Hypoxia also acts as a stimulus for BNP release, suggesting that this molecule may be an important marker for myocardial ischemia [33, 34]. Increased concentrations of BNP are associated with greater mortality rates across the spectrum of ACS [35]. In patients with NSTEMI ACS, both 7-day (2.5% compared with 0.7%, $P = 0.006$) and 6-month mortality (8.4% compared with 1.8%, $P < 0.0001$) are greater among those with BNP concentrations more than 80 pg/mL [13]. The increase in BNP concentrations may reflect not only the extent of left ventricular systolic dysfunction, often from a previous myo-

cardial infarction, but also the severity of the current ischemic episode and the concomitant diastolic dysfunction. Given the multifactorial pathophysiology of ACS – including myocyte necrosis (troponin), inflammation (CRP), hemodynamic stress (BNP), accelerated atherosclerosis (HbA_{1c}), and vascular damage (creatinine clearance) – a multimarker approach offers simultaneous insight into all these different axes and independent prognostic utility (*Figure 1*) [22, 36].

In order to take several risk factors into account simultaneously, the TIMI risk score for unstable angina/NSTEMI was developed. This risk score provides a quantitative yet easily applicable approach to the assessment of risk using seven independent criteria: age ≥ 65 years; at least three risk factors for coronary artery disease; previous coronary artery stenosis of at least 50%; severe anginal symptoms (at least two events in the previous 24 h); use of aspirin in the past 7 days; ST-segment deviation of at least 0.05 mV; and an increased serum cardiac marker of necrosis (CK-MB or troponin) [6]. Higher TIMI risk scores are associated with greater rates of death and ischemic events, including myocardial infarction, and a need for urgent revascularization. Moreover, there is a significant interaction between the TIMI risk score and the efficacy of several therapeutic options, including low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, and early invasive strategies [37–39]. As can be seen, patients in higher TIMI risk categories experience greater benefit with these therapies (*Figure 2*).

As the number of therapeutic options for ACS continues to grow, it is increasingly important for clinicians to be able to risk stratify their patients rapidly and effectively, in order to choose the appropriate intensity of treatment. ■

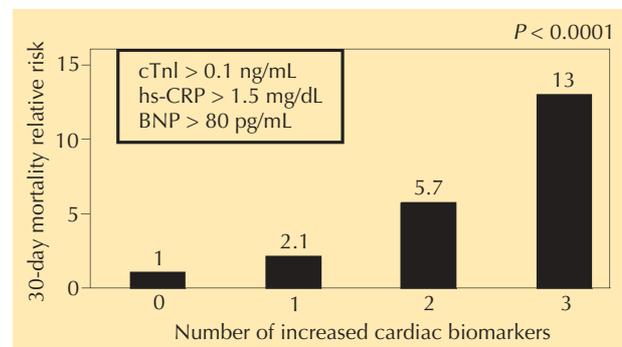


Figure 1. Multimarker approach for risk stratification in non-ST-segment elevation acute coronary syndromes. Relative risks of mortality over 30 days in patients stratified by the number of increased cardiac biomarkers in TACTICS-TIMI 18. cTnI, cardiac-specific troponin I; hs-CRP, high sensitivity C-reactive protein; BNP, B-type natriuretic peptide. (Adapted from Sabatine et al [36], with permission).

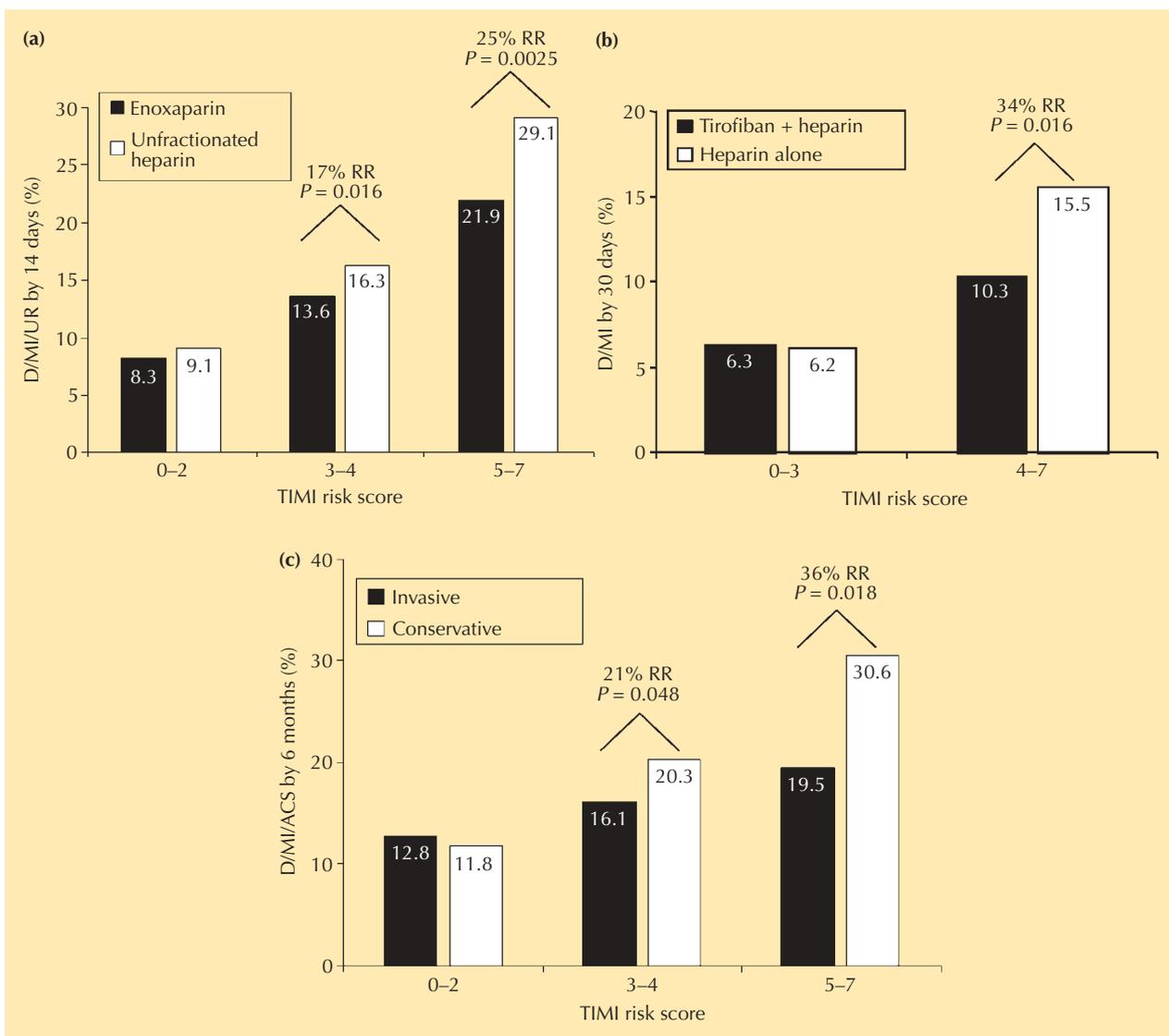


Figure 2. The TIMI risk score and interaction with therapy. (a) Rates of all-cause mortality (D), myocardial infarction (MI), or severe recurrent ischemia leading to urgent revascularization (UR) over 14 days in the unfractionated heparin and enoxaparin treatment groups. Patients were pooled from the TIMI 11B and ESSENCE trial populations and stratified by TIMI risk score. (b) Rates of D/MI over 30 days in the heparin alone and tirofiban plus heparin treatment groups in PRISM-PLUS, with patients stratified by TIMI risk score. (c) Rates of D/MI or readmission for acute coronary syndrome over 6 months in the invasive and conservative treatment arms in TACTICS-TIMI 18, with patients stratified by TIMI risk score. RR, risk reduction. (Adapted from Sabatine & Antman [40], with permission).

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Glucose and fatty acid changes in acute coronary syndromes

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Abstract

During an acute coronary syndrome, the abrupt reduction in blood and oxygen supply is accompanied by a shift from β -oxidation of fatty acids to anaerobic glycolysis to maintain some production of high energy phosphates. These metabolic modifications can be visualized noninvasively using nuclear medicine techniques. Impaired β -oxidation, the most reliable hallmark of acute ischemia, is best imaged by carbon-11 labeled fatty acids, particularly [^{11}C]acetate. However, because of technical limitations, [^{11}C]fatty acid imaging is restricted to experimental studies. Alternatively, iodine-123 labeled fatty acids can be used to visualize cardiac oxidative metabolism. Among them, ^{123}I -15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP) is the most widely used. Decreased uptake of BMIPP acts as a memory image of the ischemic injury, persisting long after normalization of flow. A negative mismatch (decreased BMIPP uptake relative to regional perfusion), mirroring the FDG/flow mismatch, is predictive of reversible myocardial damage. Widespread use of BMIPP is, however, precluded by a lack of commercial availability. With fluorine-18 labeled fluorodeoxyglucose (FDG), imaging of glucose utilization is also possible. This method currently constitutes a gold standard for myocardial viability assessment in ischemic heart disease and is a tool to guide treatment strategies. Typically, enhanced FDG uptake relative to regional perfusion (FDG/flow mismatch) is highly predictive of reversible myocardial damage after ischemia, and a matched decrease in FDG/flow of irreversible lesions.

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Keywords: [^{11}C]Fatty acid, ^{18}F -fluorodeoxyglucose, 15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid, acute coronary syndrome, ischemia

Introduction

The heart is a ceaselessly working organ, requiring abundant supplies of oxygen, nutrients and energy to maintain adequate contractile function. Although a healthy heart can use various substrates to produce energy rich phosphates, most production of ATP comes from the oxidation of fatty acids (β -oxidation) and glucose (glycolysis). Determination of which fuel will be preferably broken down is based mainly upon availability: predominantly (60% to 70%) fatty acids during fasting, and glucose after a carbohydrate rich meal [1].

The product of β -oxidation enters the tricarboxylic acid cycle as acetyl-coenzyme A and is oxidized to produce ATP, provided that the regional oxygen supply is adequate. In contrast, glucose is phosphorylated to glucose-6-phosphate before being catabolized to pyruvate. Unlike the highly oxygen-consuming oxidation of fatty acids, glycolysis can occur in either an aerobic or an anaerobic environment [1]: in aerobic conditions, the pyruvate enters the tricarboxylic acid cycle and the entire oxidation process produces 38 molecules of ATP; in an anaerobic environment, pyruvate is converted to lactate, with production of only two molecules of ATP.

Acute coronary syndromes (ACS) are characterized by a more or less complete and abrupt reduction in blood flow [2]. Depending upon the severity and acuteness of vessel obstruction, the presence and efficacy of acutely recruitable collaterals, and perhaps the myocardial oxygen demand, these syndromes range from unstable angina to transmural myocardial infarction [3].

From a metabolic viewpoint, the reduction in blood and oxygen supply results in a rapid shift from β -oxidation of fatty acids to anaerobic glycolysis, regardless of availability of the nutrients [1,4]. This shift is initially aimed at preserving a certain degree of production of ATP despite the decreased oxygenation but, if ischemia continues, the glycolytically produced ATP is broken down, with release of protons, intracellular acidosis, and, ultimately, irreversible damage and cell death [1].

The different pathways of intracellular cardiac energy metabolism, its physiological or pathological modifications, and its changes (spontaneous or after treatment) over time in ischemia can be traced noninvasively in humans by means of nuclear medicine techniques, using either positron- or photon-emitting radiopharmaceuticals.

Imaging free fatty acid metabolism by positron emission tomography (PET)

Myocardial β -oxidation can be imaged visually or quantified by means of clearance curves.

The short chain fatty acid acetate can be labeled with carbon-11, a positron-emitting isotope with a 20-min half-life. Its uptake is not substrate-dependent and is quite homogeneous in a normal heart. After extraction, it is immediately oxidized and its turnover closely follows myocardial oxygen consumption [5,6]). Typically, its clearance curve is monoexponential at rest and biexponential after increased oxygen demand such as exercise [7].

The metabolism of the long-chain fatty acid, [^{11}C]palmitate, is somewhat different. After a substrate dependent extraction, only a fraction is immediately oxidized, whereas the rest enters the endogenous lipid pool [8–10]. Its clearance thus only partly reflects cardiac oxidative metabolism, and the clearance curve is at least biexponential, with a rapid phase corresponding to the immediate oxidation and a slower phase reflecting deposition in the intracellular lipid pool [8,9].

Technical limitations have precluded widespread use of ^{11}C -labeled fatty acid imaging for the evaluation of cardiac oxidative metabolism in daily routine.

Imaging free fatty acid metabolism by single photon emission computed tomography (SPECT)

To overcome the technical problems, several fatty acids labeled with iodine-123 have been developed, among which the most widely used is 15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP), a long chain fatty acid analog [10–13].

BMIPP is an interesting tracer because it reflects both regional myocardial perfusion, because of its flow-dependent uptake [14], and intracellular fatty acid metabolism. Its uptake is significantly correlated with the kinetics of [^{11}C]palmitate [15] and changes dynamically according to various pathophysiological conditions such as exercise or ischemia [16,17]. In a normal heart, about 74% of the injected BMIPP is extracted, of which the vast majority (65%) is incorporated into the endogenous lipid pool. The presence of a methyl group in the β position precludes direct β -oxidation, and so only 6% of the injected dose is metabolized, and less than 3% is passively backdiffused [18]. Initial metabolism of BMIPP, namely its activation to BMIPP-coenzyme A, is closely correlated to the intracellular ATP concentration [19] and increases with exercise, probably as a result of greater utilization [16].

Imaging glucose metabolism

2-Deoxyglucose is a glucose analogue that undergoes only the first metabolic steps of glycolysis. Its 18-fluorinated derivative (^{18}F -fluorodeoxyglucose, FDG), a positron-emitting isotope with a 110-min half-life, can be visualized by PET or using a SPECT gamma-camera equipped with high energy collimators. Despite somewhat limited availability and a rather high price, myocardial FDG imaging nowadays constitutes one of the gold standards for the evaluation of cardiac metabolism and viability in patients with ischemic heart disease [20].

In a normal heart, glucose uptake is heterogeneous [21], although less so after a carbohydrate meal than during fasting [22]. Therefore, cardiac FDG imaging is usually performed after an oral or intravenous glucose load [23], or alternatively after administration of acipimox, a nicotinic acid derivative [24].

Cardiac metabolic imaging in acute coronary syndromes

Carbon-11 labeled fatty acids

Although changes in fatty acid metabolism over time seem to be the most reliable hallmark of acute

coronary events [25–27], only a limited number of patients have been studied, because of the technical limitations mentioned above.

By using repeated [^{11}C]acetate studies, the evolution of oxidative metabolism, considered to be the only significant predictor for functional recovery after reperfusion of an acute infarction [25], can be followed over time. In irreversibly damaged myocardium, the clearance is severely depressed and does not change over time. In contrast, in successfully reperfused regions, improvement or normalization of the clearance curve parallels the evolution of regional wall motion, but can be significantly delayed compared with the normalization of blood flow [26].

Using [^{11}C]palmitate, absolute uptake is significantly lower in ischemic than in remote myocardium, resulting in a heterogeneous pattern of uptake [28]. Analysis of the clearance curve shows a smaller and flatter rapid phase and a larger slow phase, indicating a shift toward greater incorporation in the intracellular lipid pool and less immediate β -oxidation [29]. The time course of evolution of [^{11}C]palmitate metabolism after successful reperfusion follows very closely that of [^{11}C]acetate, and parallels the recovery of contractile function [30].

Iodine-123 labeled BMIPP

Combining the advantages of being a (modified) fatty acid, probably more reliable than FDG in ACS [27], and having better availability than the ^{11}C -labeled fatty acids, BMIPP might be an interesting alternative tool for the evaluation of cardiac oxidative metabolism and, ultimately, viability in these syndromes.

Taking into account the increased backdiffusion of BMIPP in ischemic compared with normal conditions [31], analysis of its washout rate has been proposed as an approach to evaluate the presence of ischemia [16]. However, most studies rely on a comparison between BMIPP uptake and that of a perfusion tracer such as thallium-201 or technetium-99m labeled sestamibi or tetrofosmin.

In hypoperfused myocardium, two major BMIPP/flow patterns are observed: a negative mismatch, with BMIPP uptake at rest lower than the uptake of flow tracer (*Figure 1*), or a matched decreased BMIPP/flow. The former, significantly correlated with [32,33] and mirroring the (positive) FDG/flow mismatch, is highly predictive of residual viability and functional recovery after restoration of perfusion [11,34]. The latter is usually associated with absent viable myocardium and no functional recovery even after revascularization. Rarely, a third pattern of uptake has been reported, with enhanced BMIPP uptake relative to flow (positive mismatch), in both acute [35] and chronic ischemia [36].

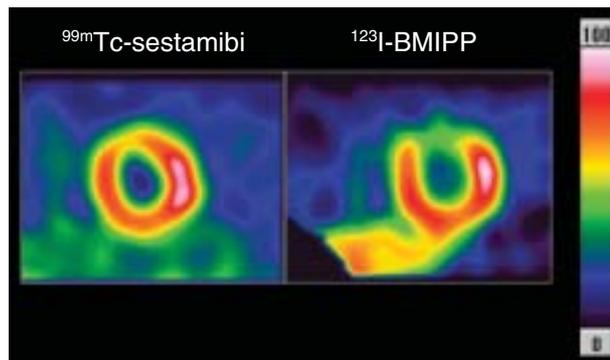


Figure 1. Midventricular short axis images of myocardial perfusion at rest ($^{99\text{m}}\text{Tc}$ -sestamibi) and free fatty acid metabolism (^{123}I -BMIPP) 5 days after successful reperfusion of an acute myocardial infarction. Perfusion is only moderately decreased in the anterior wall, whereas BMIPP uptake is severely impaired. This pattern of reverse or negative mismatch with lower BMIPP uptake relative to perfusion constitutes a “memory image” of the acute ischemic injury and is strongly suggestive of the presence of reversibly damaged myocardium, susceptible to functional recovery at follow-up. ^{123}I -BMIPP, iodine-123-iodophenyl-methylpentadecanoic acid.

In ACS, decreased BMIPP uptake, sometimes referred to as the “ischemic memory image,” is assumed to reflect myocardial stunning. It can endure for several days to weeks after myocardial blood flow and wall motion have returned to normal [10,37], and might indicate the functional severity of a coronary stenosis, suggesting that BMIPP imaging could be used as a guide for interventional treatment [38,39]. A decreased uptake correlates with the severity of coronary artery disease both in stable and in unstable angina, but is significantly more frequent in unstable conditions (79% compared with 38% [40]). In patients with acute chest pain, it detects the presence of coronary stenosis or spasm with a much greater sensitivity (74% compared with 38%), but a similar specificity (92% compared with 96%), than a perfusion study [41].

After an acute infarction, a decreased uptake, a negative BMIPP/flow mismatch, or both, helps to evaluate the area at risk [42] or the success of a reperfusion, to predict functional recovery at follow-up [10,34,43] or to tailor second-line revascularization [39,40].

Despite its promising properties, BMIPP is not in wide routine use, because of a lack of commercial registration in all countries except Japan.

Fluorine-18 labeled FDG

Despite its rather high price, FDG imaging has progressively emerged as the most sensitive tool for the detection of tissue viability in ischemic heart

disease, and currently constitutes the reference method for cardiac metabolic imaging in ACS and in the chronic phase.

Usually, uptake of FDG is compared with that of a perfusion tracer (either by SPECT [mainly ^{99m}Tc -sestamibi or ^{99m}Tc -tetrofosmin] or by PET [mostly nitrogen-13 labeled ammonia]). Typically, "FDG/flow (positive) mismatch" of enhanced FDG uptake in hypoperfused myocardium (Figure 2), indicating a metabolic shift from β -oxidation to glycolysis, is associated with functional recovery after successful restoration of flow in as much as 85% of the region [44,45], whereas a matched decreased FDG/flow uptake has a low likelihood of functional recovery after revascularization.

In ACS, however, contradictory changes in regional glucose metabolism have been reported, from a prolonged decreased utilization (with a "reversed" or negative mismatch [46]), to an increased uptake [47], or no changes [48]. The reversed mismatch, with FDG uptake lower than perfusion, seems to be predictive of absent functional recovery [49], but in addition a significant number of FDG/flow mismatched segments do not recover functionally after reperfusion [27], possibly because of insufficient coupling of chemical to mechanical energy [50].

Despite these small inconsistencies, FDG imaging is useful in the evaluation of ACS. More particularly, the presence of a FDG/flow mismatch is associated with unstable, but not stable, angina [51], delineates the jeopardized myocardium in

exercise induced ischemia [47], and identifies patients at high risk for future cardiac events after an acute infarction [52].

Summary

Acute coronary syndromes are associated with a metabolic shift from aerobic fatty acid oxidation to anaerobic glycolysis to maintain cellular function. This shift can be visualized noninvasively by nuclear medicine techniques.

In clinical practice, cardiac energy metabolism imaging relies mostly on ^{18}F -FDG for glucose utilization, and to a lesser degree on ^{123}I -BMIPP for fatty acid metabolism. Enhanced glucose or decreased fatty acid uptake relative to regional blood flow are highly predictive of reversibly damaged ischemic myocardium and can be used to guide further treatment strategies. ■

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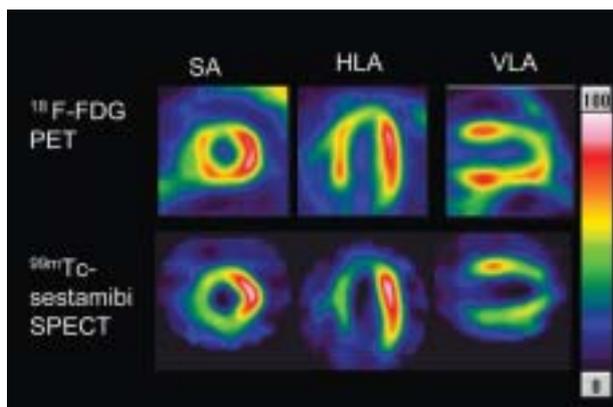


Figure 2. Midventricular short and long axis images of glucose utilization (^{18}F -fluorodeoxyglucose positron emission tomography, ^{18}F -FDG PET) and perfusion at rest (^{99m}Tc -sestamibi single photon emission computed tomography [SPECT]) in a patient with residual angina after acute myocardial infarction. A large anteroseptal and a moderate posterior perfusion defect are observed, both showing significantly greater FDG uptake relative to perfusion (FDG/blood flow mismatch), indicating preserved glucose uptake in areas of reduced blood flow. This pattern is strongly suggestive of the presence of jeopardized but viable myocardium. SA, short axis; VLA, vertical long axis; HLA, horizontal long axis.

Metabolic imaging

Glucose and fatty acid changes in ACS

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Guidelines and metabolic approach to acute coronary syndrome

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Abstract

Within recent years, considerable new evidence has resulted in a paradigm shift in the approach to patients with acute coronary syndromes. Guidelines now recommend primary percutaneous intervention as the best reperfusion strategy in patients with acute ST-segment elevation myocardial infarction and early invasive evaluation in patients with non-ST-segment elevation myocardial infarction. Metabolic support of the ischemic myocardium aims at increasing glycolysis and residual oxidative phosphorylation of glucose, and at decreasing fatty acid oxidation, which potentially uncouples mitochondria and further decreases ATP production. The infusion of glucose–insulin–potassium accelerates glycolysis and is now being tested, with promising results, in acute myocardial infarction. Similarly, metabolic agents such as 3-ketoacyl coenzyme A thiolase inhibitors, which partially reduce fatty acid oxidation, have the potential for beneficial influence on the balance between residual fatty acid and glucose oxidation.

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Keywords: Ischemia, glycolysis, glucose, insulin, free fatty acid, 3-ketoacyl coenzyme A thiolase inhibitors, oxidative phosphorylation

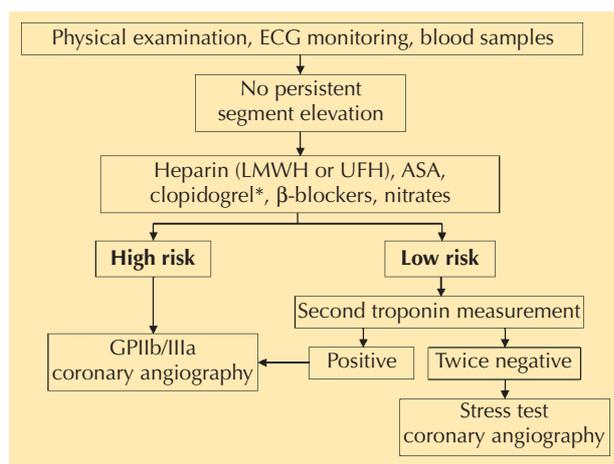
Guidelines for acute coronary syndrome

The pathophysiology of acute coronary syndrome is a plaque rupture with consequent exposure of subintimal tissue and activation of thrombosis. Depending on the degree of vessel occlusion, the patient experiences unstable angina, a non-ST-segment elevation myocardial infarction, or an ST-segment elevation myocardial infarction with transmural ischemia. Current treatment of acute ST-segment elevation myocardial infarction mandates timely reperfusion of the occluded vessel by primary percutaneous intervention (PCI) or fibrinolytic therapy; overwhelming evidence has established primary PCI as the preferred reperfusion strategy [1]. Guidelines of the European Society of Cardiology now recommend primary PCI in all patients with ST-segment elevation myocardial infarction, in whom it can be performed within 90 min by an experienced team. Fibrinolytic treatment should be performed if primary PCI within 90 min is not available [2]. Since newer

studies demonstrated a favorable outcome in patients transferred from community hospitals to a tertiary center for primary PCI compared with those given fibrinolytic treatment in the local hospital [3], there has been continuing debate whether such an approach should be recommended in all patients with acute myocardial infarction. The recommendation for adjunctive medical treatment for both reperfusion strategies (fibrinolysis or primary PCI) includes an antithrombotic agent (acetylsalicylic acid), an antithrombin (unfractionated heparin or low molecular weight heparin), and anti-ischemic agents as needed (nitrates, morphine, and β -blockers). Patients transferred from other hospitals and also hospital inpatients undergoing primary PCI seem ideal candidates for adjunctive metabolic support because, in general, 60 to 90 min elapses before flow can be restored in the infarct related artery. European guidelines mention infusion of glucose–insulin–potassium as a potential intervention, without giving any recommendation for its use [2].

The treatment guidelines for patients presenting with unstable angina are depicted in *Figure 1*. Risk stratification is central to patient management in unstable angina [4–6]. Patients at high risk should undergo early invasive evaluation [7–9]. The following findings constitute a high risk: (i) recurrent ischemia or chest pain; (ii) dynamic ST-segment changes; (iii) increased concentrations of troponin; (iv) early postinfarction angina; (v) hemodynamic or electric instability; (vi) diabetes. If coronary angiography reveals critical coronary stenoses, the patient will undergo immediate revascularization by PCI or will be referred for early bypass surgery; otherwise, medical treatment is continued. Adjunctive medical therapy includes clopidogrel, which should be given early. Because of the risk of bleeding, it is recommended to withhold clopidogrel if bypass surgery is planned within 5 days. As this decision can be made only after coronary angiography, controversy exists as to whether clopidogrel should be given in the emergency room or in the catheterization laboratory after establishment of coronary anatomy [6].

If, during a period of monitoring of at least 6 h, the patient shows no high-risk features – ie, exhibits no recurrent chest pain, no ST-segment changes, no increases in concentrations of troponin or other biochemical markers at second measurement – they have a low risk and can be prescribed acetylsalicylic acid and be discharged from hospital, with further evaluation by stress test. If the stress test reveals myocardial ischemia, they should undergo coronary angiography [4].



*Figure 1. Strategy in patients presenting with non-ST-segment elevation acute coronary syndrome. The diagram represents the current treatment algorithm as recommended by the European Society of Cardiology for patients presenting with non-ST-segment elevation myocardial infarction. *Omit clopidogrel if the patient is likely to undergo coronary artery bypass operation within 5 days. ASA, acetylsalicylic acid; ECG, electrocardiogram; GP IIb/IIIa, glycoprotein IIb/IIIa receptor inhibitors; LMWH, low molecular weight heparin; UFH, unfractionated heparin.*

Rationale for metabolic interventions in acute coronary syndromes

In acute coronary syndrome, myocardial ischemia results from partial or total occlusion of coronary flow. However, even in the center of the ischemic region, residual blood flow of at least 10% of initial flow usually persists via collateral blood flow [10,11], such that some residual oxidative metabolism also persists. This residual blood flow is also sufficient to allow a pharmacologic intervention to reach the ischemic region.

Hearts are able to use several substrates as energy sources. In normoxia, free fatty acids are the main fuel source for the production of ATP; the oxidation of glucose and lactate balances any additional need for energy. During ischemia, this balance changes. Glycolysis is accelerated by activation of phosphofructokinase, the key glycolytic enzyme [12,13], and becomes the main source of fuel for the production of energy [14]. Anaerobic glycolysis also contributes to energy production [12,15,16]. However, residual oxidative metabolism continues and remains the main source of ATP production [17–20]. Nevertheless, in severe ischemia, pyruvate can no longer be funneled into the tricarboxylic acid cycle and is reduced to lactate. Thus glycolysis may become uncoupled from glucose oxidation [20]. Furthermore, glycolysis might eventually decrease as a result of inhibition by acidosis and a lack of glycolytic substrate from glycogen [21,22].

During myocardial infarction, increased catecholamine concentrations and heparin treatment lead to an increase in plasma free fatty acid concentration [23,24]. Free fatty acids cross the sarcolemma and, after conversion into carnitine, are transferred into the mitochondria by carnitine palmitoyltransferase-1 (CPT-1), via the so-called carnitine shuttle. The key enzyme in the control of fatty acid oxidation is malonyl coenzyme A (CoA). In ischemia, malonyl CoA is decreased, resulting in a dramatic increase in fatty acid oxidation. This results in a further decrease in glucose oxidation and uncoupling of glycolysis from glucose oxidation [20]. During reperfusion, fatty acid oxidation becomes the main fuel source [21], and this results in an increase in reduced moieties, which inhibit the pyruvate dehydrogenase complex. This further uncouples glycolysis from glucose oxidation [20]. The uncoupling of glycolysis from residual oxidation is undesirable for several reasons. First, because fatty acid oxidation yields less ATP per molecule of oxygen than does glucose oxidation, oxygen is wasted. Secondly, although the amount of ATP produced by anaerobic glycolysis remains relatively small, it preserves high energy phosphates, maintains favorable energetics, and thus preserves cell viability and improves impaired systolic and

diastolic function [15,18]. Furthermore, glycolytically derived ATP has, probably via compartmentation, a protective effect on the functions of Na–K-ATPase and SR–Ca²⁺-ATPase, two important cellular ion pumps, and thus preserves membrane function [17].

Interventions that result in increased glycolysis and glucose oxidation and at the same time diminish fatty acid oxidation during ischemia and reperfusion have, therefore, the potential to preserve cell viability and function [17]. Infusion of glucose–insulin–potassium exerts such a beneficial effect. Metabolic modulators that inhibit fatty acid oxidation (trimetazidine and ranolazine) have the potential for a similar effect.

Evidence for beneficial effect of high glucose and insulin in clinical trials

Glucose–insulin–potassium was initially proposed as an antiarrhythmic (“membrane stabilizing”) agent in myocardial infarction [25]. In the 1970s, its potential as a metabolic intervention was recognized [23] and,

since then, several additional beneficial effects of glucose–insulin–potassium treatment in acute myocardial ischemia have been identified (*Table I*). Initially, several small trials individually failed to show a mortality benefit for glucose–insulin–potassium in the treatment of acute myocardial infarction. However, when the findings of the first trials in the prethrombolytic era were combined, an overall reduction in mortality of 28%, translating to 49 lives saved per 1000 patients treated, was revealed (*Table II*) [26]. The first large trial of glucose–insulin–potassium in the field of reperfusion was the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial [27]. In this trial, glucose–insulin–potassium treatment was extended to follow-up with tight control of glucose by subcutaneous infusion of insulin for 3 months, which resulted in a clear survival benefit at 1 and 3 years [27,28]. Although the DIGAMI-trial enrolled only patients with diabetes, the most striking results were obtained in patients who did not require insulin treatment before their myocardial infarction. In this prespecified subgroup, infusion of

Table I. Potential beneficial effects of high glucose–insulin–potassium infusion in ischemic myocardium.

- Increased production of ATP by anaerobic glycolysis
 - Preservation of high-energy phosphates (ATP, PCr, ADP)
 - Normalization of increased ADP/ATP ratio
 - Increased delta free energy from ATP hydrolysis
 - Prevention of loss of purines (eg, adenosine)
 - Compartmentation of ATP (cellular ion pump functions supported by anaerobic glycolytic ATP)
- Preservation/restoration of intracellular glycogen stores
- Improved coupling of glycolysis to glucose oxidation
- Decrease of FFA oxidation by decreasing transfer of fatty acids into mitochondria
- Esterification of intracellular FFAs by increased supply of α -glycerophosphate
- Antiapoptotic effects of insulin
- Replenishment of potassium
- Scavenging of free radicals
- Vasodilatory effect

ADP, adenosine diphosphate; ATP, adenosine triphosphate; FFA, free fatty acid; PCr, phosphocreatine.

Table II. Mortality in trials with glucose–insulin–potassium in acute myocardial infarction.

Study	Mortality	No. of patients		Deaths (%)		RRR	95% CI	P
		GIK	Control	GIK	Control			
Meta-analysis: 9 trials 1971–1987 DIGAMI trial	Overall	956	976	16.1	21	0.72	0.57 to 0.90	0.004
	In-hospital	306	314	9.1	11.1	0.82	NA	NS
	1 year	306	314	18.6	26.1	0.71	0.49 to 0.96	0.0273
ECLA trial	In-hospital							
	Overall	268	139	6.7	11.5	0.58	0.30 to 1.10	NS
GIPS	Reperfused	173	79	5.2	15.2	0.34	0.15 to 0.77	0.01
	30 days							
	All	476	464	4.8	5.8	0.82	0.46 to 1.46	NS
	Killip I	426	430	1.2	4.2	0.27	0.10 to 0.74	0.01
	Killip II–IV	50	34	36	26.5	1.44	0.65 to 3.22	NS

CI, confidence interval; DIGAMI, Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction; ECLA, Estudios Cardiológicos LatinoAmerica; GIK, glucose–insulin–potassium; GIPS, Glucose–Insulin–Potassium Study; Killip I, II–IV, Killip classes; RRR, relative risk reduction.

glucose–insulin–potassium reduced in-hospital mortality by 58% ($P < 0.05$) and 1-year mortality by 52% ($P < 0.02$). In the Estudios Cardiológicos Latinoamericana trial, overall mortality was not significantly different between the glucose–insulin–potassium and control groups [29]. However, in the patients who received reperfusion treatment, relative in-hospital mortality was reduced by 66%. The first trial to combine glucose–insulin–potassium with primary PCI was the Glucose–Insulin–Potassium Study (GIPS) [30]. In the 91% patients presenting without heart failure, glucose–insulin–potassium reduced 30-day mortality from 4.2% to an astonishing 1.2% (Table II). However, in the small number of patients presenting with heart failure and cardiogenic shock, glucose–insulin–potassium was not beneficial. It was hypothesized that this was attributable to the large volume load that patients received in GIPS [31].

The findings of these trials are promising; in addition, we might learn something about the mechanisms of glucose–insulin–potassium that are important in clinical practice. In all trials, administration of glucose–insulin–potassium was started relatively late in the ischemic period and was continued into the reperfusion period. Therefore, in patients with acute myocardial infarction, the metabolic effects of glucose–insulin–potassium during ischemia might be less important than the effects during reperfusion [32,33]. Glucose–insulin–potassium may also provide metabolic support for the nonischemic region, which is metabolically limited to adapt to mechanical overload [31,33]. Furthermore, the antiapoptotic effect of insulin might contribute to the favorable effect during reperfusion [34,35].

3-Ketoacyl CoA thiolase inhibitors as alternative metabolic intervention

An alternative metabolic approach to the support of ischemic myocardium is to restore coupling of glycolysis to oxidative phosphorylation by inhibiting fatty acid oxidation (Figure 2). Several agents that interfere with fatty acid oxidation have been tested experimentally: dichloroacetate, an activator of the pyruvate dehydrogenase complex [36], carnitine, a modifier of the mitochondrial acetyl CoA : CoA ratio [37], and etomoxir, an inhibitor of CPT-1 [38]. Clinically, some of these agents cannot be used, or their value has not been tested. Interestingly, β -blockers, which are crucial in the treatment of acute coronary syndromes, might inhibit CPT-1 and thus decrease fatty acid oxidation to a certain extent [39].

Of particular interest are the so-called 3-KAT inhibitors, trimetazidine and ranolazine, which reduce fatty acid oxidation secondary to selective inhibition of 3-ketoacyl CoA thiolase [40,41]. Trimetazidine is the

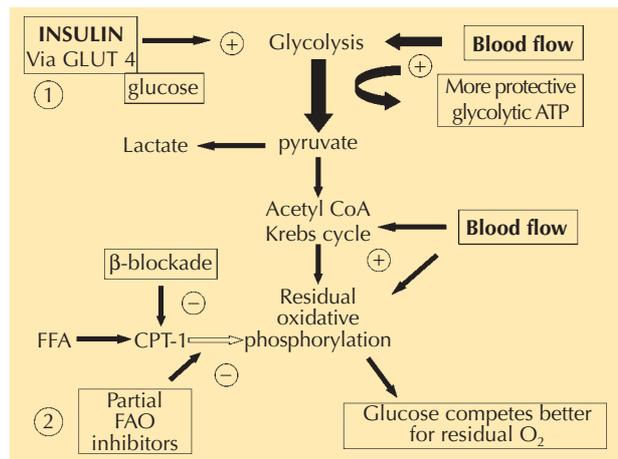


Figure 2. Potential metabolic interventions in ischemic myocardium. During ischemia and reperfusion, glucose and free fatty acids (FFA) compete for residual oxidative phosphorylation. During ischemia, ATP derived from glycolysis and glucose oxidation results in better energetics and maintains better mechanical and membrane function than ATP from residual fatty acid oxidation (FAO). Thus glycolytically derived ATP is beneficial for the ischemic myocardium. FAO results in uncoupling of the mitochondria and in oxygen waste. The goal of metabolic interventions is to increase glycolysis and prevent an uncoupling of glycolysis from residual oxidation in the mitochondria. Glucose–insulin–potassium infusion (1) accelerates glycolysis and sustains entry of pyruvate into the Krebs citrate cycle. Potentially, partial FAO inhibitors (2) can beneficially increase glycolytic flux. CPT-1, Carnitine palmitoyltransferase-1; GLUT 4, glucose transporter 4. (Adapted from Opie & Sack MN [17], with permission.)

only one that is available for clinical use worldwide, but these drugs have repeatedly been shown to be protective against ischemia-reperfusion injury in experimental conditions [41,42]. Clinically, both drugs have been tested in chronic stable angina, in which they exhibited good antianginal effects [43–46]. Therefore, they have the potential to exert a favorable influence on energetics during ischemia and reperfusion, through optimization of cardiac metabolism.

Summary

Metabolic modulators, such as the new class of 3-KAT inhibitors, have the potential for a beneficial metabolic effect in acute coronary syndrome. Glucose–insulin–potassium has beneficial effects in acute myocardial infarction with and without reperfusion therapy, and in both diabetic and nondiabetic individuals. Taken together, the findings of recent trials have not conclusively answered the question whether glucose–insulin–potassium is beneficial to all patients with myocardial infarction. Larger trials, which are currently in progress, are necessary to resolve this issue. ■

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Metabolic cardioprotection in patients undergoing revascularization

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Abstract

Trimetazidine (Vastarel MR), the first twice-daily 3-ketoacyl coenzyme A thiolase inhibitor, is a well known metabolically active agent that is widely used for the treatment of stable angina. In this review, new evidence is presented for the cardioprotective value of trimetazidine in patients who are referred for a revascularization procedure. Various clinical trials have shown trimetazidine to limit ischemia-reperfusion damage during percutaneous transluminal coronary angioplasty or coronary artery bypass grafting.

■ *Heart Metab.* 2004;23:31–33.

Keywords: Myocardial ischemia, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, trimetazidine

Introduction

The rationale of the manipulation of cardiac metabolism for the effective treatment of ischemic heart disease is now well demonstrated [1]. Trimetazidine (Vastarel MR) is the first twice-daily 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitor to become available for clinical use worldwide. It acts by switching cardiac metabolism away from fatty acids to glucose oxidation, secondary to the selective inhibition of the mitochondrial enzyme, 3-KAT [2]. This novel and innovative approach proved efficient in relieving the symptoms of angina and improving exercise performance in various subsets of patients with coronary disease [3], while being free of any hemodynamic impact [4].

In patients undergoing a revascularization procedure, myocardial damage during the intervention is an important determinant of clinical outcome [5]. This article aims to show how the metabolic effect of trimetazidine can translate into cardioprotective benefits for patients who are referred for a revascularization procedure and in whom it is crucial to limit reperfusion damage.

Cardioprotective effect of trimetazidine during percutaneous transluminal coronary angioplasty

As a result of its experimentally demonstrated anti-ischemic properties [6], the efficacy and acceptability of trimetazidine were tested in clinical settings in patients with coronary disease who were undergoing percutaneous transluminal coronary angioplasty (PTCA). Trimetazidine was given before or after PTCA. The main clinical findings are summarized in *Table 1*.

Kober et al [7] carried out a double-blind, placebo-controlled trial to assess the efficacy of injectable trimetazidine (6-mg intravenous bolus after the first balloon inflation) in patients with angina refractory to intensive medical treatment. The clinical findings confirmed that trimetazidine was able to decrease the maximum ST-segment shift at the second dilatation in comparison with the first dilatation ($P=0.02$), and to delay the onset of the shift ($P=0.02$). Maximum T-wave changes were also reduced with trimetazidine ($P=0.001$).

The Limitation of Infarct Size by Trimetazidine (LIST) study was a double-blind, randomized trial that included 94 patients who presented with a first episode of myocardial infarction with ST-segment elevation. Patients undergoing a primary angioplasty received

trimetazidine (40-mg iv bolus before the procedure, followed by 60 mg daily iv for 2 days) [8]. The results showed an earlier and more marked return to baseline of the ST-segment within the first 6 h in the trimetazidine group than in the placebo group ($P=0.01$).

In another controlled study carried out in Poland, 44 patients with one-vessel coronary artery stenosis received 4-day pretreatment with oral trimetazidine before PTCA [9]. The ability of trimetazidine to protect the myocardium against the consequences of an acute ischemic episode was confirmed. This was reflected by a lower mean ST-segment elevation

during balloon inflations. A significantly greater time from balloon inflation to onset of angina was observed ($P=0.03$), along with a smaller time to pain relief after deflation in the trimetazidine group ($P=0.001$) (Figure 1).

Cardioprotective effect of trimetazidine during coronary artery bypass grafting surgery

A double-blind, randomized, placebo-controlled study was carried out in Turkey to evaluate the anti-ischemic benefits of trimetazidine in 30 patients [10]. Vastarel was given orally for 3 weeks before a coronary artery bypass grafting (CABG) procedure. Plasma concentrations of the highly sensitive cardiac marker, troponin T, were measured 5 min after the bypass operation, at 12, 24, and 48 h postoperatively. As shown in Figure 2, troponin T concentrations in the trimetazidine group were significantly reduced in comparison with those in the placebo group, reflecting the cardioprotection triggered by the metabolic effect of trimetazidine. These results confirm previous data obtained in patients undergoing elective CABG in two or three vessels [11]. They were given a 3-week pretreatment with oral trimetazidine, then trimetazidine was added to the cardioplegic solution. Ventricular function was improved by the drug as shown by the stroke work index. Metabolic measurements showed a less important increase in malondialdehyde concentrations after trimetazidine ($P=0.01$).

In another double-blind, placebo-controlled study, the preventive effect of trimetazidine against ischemia-reperfusion injury was assessed in patients with coronary disease after bypass surgery [12]. Ischemia-reperfusion damage was monitored with measurement of creatine kinase-myocardial band concentrations, which were found to be significantly lower in the trimetazidine group ($P<0.05$ compared with placebo 12 h after operation).

Table 1. Clinical trials of trimetazidine in percutaneous transluminal coronary angioplasty: (Adapted from Marzilli [6], with permission.)

Kober et al 1993 [7]	Trimetazidine 6-mg bolus after first balloon inflation was compared with placebo in patients undergoing angioplasty. Trimetazidine significantly increased maximum ST-segment shift and maximum T-wave changes and decreased time to maximum ST-segment shift
Steg et al 2001 [8]	Patients undergoing a primary angioplasty received trimetazidine (40-mg iv bolus before the procedure, followed by 60 mg daily iv for 2 days). ST-segment deviation returned to baseline significantly earlier (within 6 h) with trimetazidine
Polonski et al 2002 [9]	Patients with one-vessel coronary artery stenosis received 4-day pretreatment with oral trimetazidine before PTCA. Mean and maximal ST-segment elevations during balloon inflation and mean and maximal amplitudes of the T-wave alteration were significantly lower with trimetazidine

PTCA, Percutaneous transluminal coronary angioplasty.

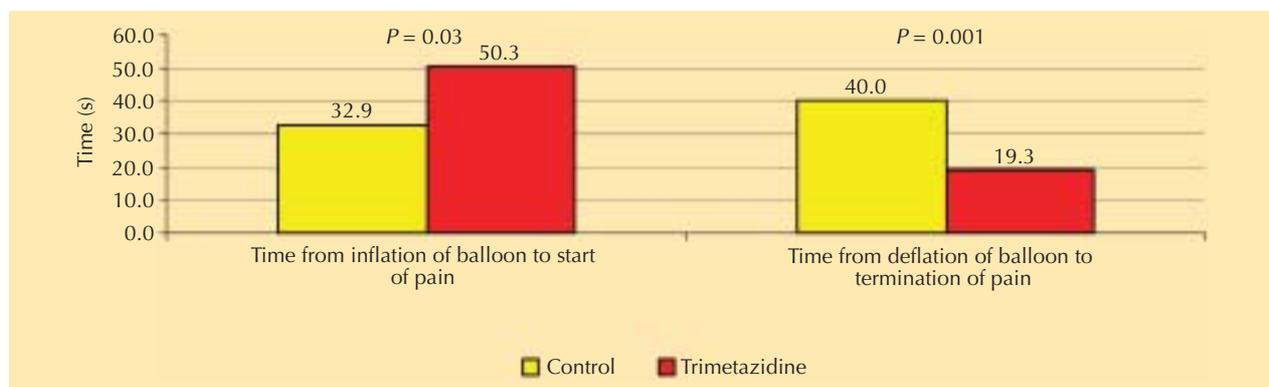


Figure 1. Anti-ischemic effect of a 4-day treatment with trimetazidine before percutaneous transluminal coronary angioplasty [9].

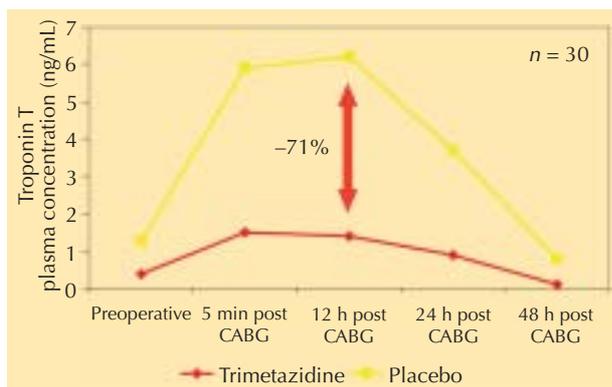


Figure 2. Cardioprotective effect of trimetazidine given for 3 weeks before coronary artery bypass grafting (CABG), judged by changes in concentrations of the cardiac marker, troponin T [10].

Conclusion

Optimizing the energy metabolism of the heart under ischemic conditions such as those encountered during a revascularization procedure (PTCA or CABG surgery) is a novel and effective approach to protect the myocardium from the deleterious consequences of ischemia-reperfusion injury. The use of metabolically active agents, such as trimetazidine (Vastarel MR), to switch energy substrate preference from fatty acid oxidation to glucose oxidation, secondary to the inhibition of the 3-KAT enzyme, improves the production and utilization of energy at the cellular level. This metabolic effect translates into clinical benefits that are reflected by a delayed ischemic threshold or an improved ventricular function in patients undergoing bypass surgery or angioplasty. Promising clinical findings suggest that trimetazidine, the first 3-KAT inhibitor, is a treatment of choice before any intervention. ■

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Beneficial role of metabolic treatment in a patient with refractory angina after an acute coronary syndrome

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Abstract

The case is reported of a 68-year-old man with a history of myocardial infarction who presented to our hospital with unstable angina. Coronary angiography showed severe three-vessel disease with diffuse lesions, not suitable for coronary artery bypass grafting. After coronary angiography, the patient had severe chest pain, with pulmonary edema and increased troponin T concentrations. Exercise treadmill testing and a single photon emission computed tomography perfusion study demonstrated extremely low coronary flow reserve. The patient was referred for heart transplantation, but refused. Three months after discharge, he was still experiencing an average of 30 angina attacks per week, despite treatment with metoprolol 200 mg/day and isosorbide mononitrate 100 mg/day. Trimetazidine MR 35 mg twice daily was added. After 2 months of trimetazidine treatment, the number of angina attacks decreased to an average 8 to 10 per week, which persisted at 2-year follow-up. This case demonstrates the efficacy of metabolic therapy as an adjunctive treatment of refractory angina.

■ *Heart Metab.* 2004;23:34–38.

Keywords: Acute coronary syndrome, refractory angina, trimetazidine

Case report

A 68-year-old man was admitted to our hospital in June 2002 with unstable angina pectoris. He had a history of anterior myocardial infarction (1986), which was the first symptom of coronary artery disease (CAD), and several CAD risk factors: hypercholesterolemia, arterial hypertension, cigarette smoking (20/day). In 1987, on the basis of coronary angiography, he was referred for coronary surgery (three coronary bypass grafts), but he refused. In 1999 he had coronary angiography repeated because of increased frequency of chest pain. He was in functional Canadian Cardiac Society (CCS) class II/III, despite antianginal treatment with a β -blocking adrenergic agent, a calcium channel blocker, aspirin, and simvastatin. Coronary angiography revealed diffuse three-vessel disease with peripheral lesions not amenable to coronary surgery. The patient was discharged from hospital receiving

isosorbide mononitrate 60 mg, metoprolol 100 mg/day, aspirin 75 mg, and simvastatin 40 mg.

Until May 2002, the patient remained stable in New York Heart Association (NYHA) functional class II, and CCS class III. He was then readmitted to the regional hospital with unstable angina, experiencing 20 angina attacks daily, including pain at rest and at night. The troponin T concentration was not increased. Physical examination showed no signs of heart failure, an arterial blood pressure of 100/60 mm Hg, and a weight of 90 kg (height 170 cm). The electrocardiogram showed sinus bradycardia of 55 beats/min, left ventricular hypertrophy with repolarization abnormality, and signs of old anteroseptal infarction. Echocardiography demonstrated a left ventricular ejection fraction of 0.3, a 60 mm end-diastolic left ventricular diameter with anterior, septal, and apical akinesia. The septum was thin and hyperechogenic (scar). There was grade 2 functional mitral regurgitation; systolic

Case Report

Benefits of metabolic treatment in refractory angina

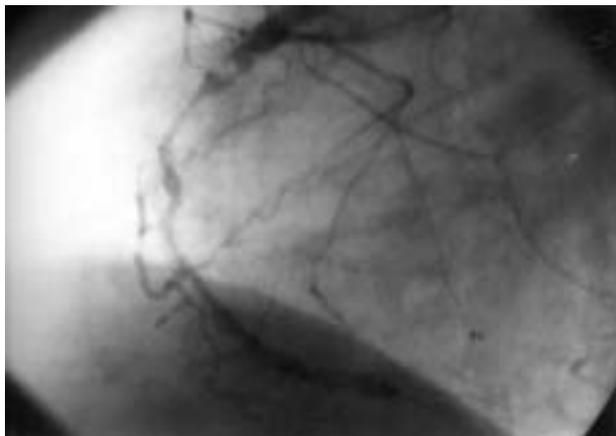
pulmonary pressure was normal. Coronary angiography showed three-vessel disease. The coronary arteries had several stenoses: left main coronary artery, 20%; left anterior descending artery, 50% in segment 6, 80% in segment 7, 80% in segment 8, and then long peripheral stenosis. The left circumflex artery was occluded, the first marginal branch presented a peripheral stenosis of 80%, and the second marginal branch was hypoplastic. The right coronary artery was stenosed in the first and second segments by 90%, and in segment 3 by 50%. The posterolateral artery was occluded in segment 4 and the posterior descending artery presented a 75% long stenosis (*Figure 1*). During angiography, the patient had experienced several angina attacks and after the procedure he had prolonged chest pain with lateral ST-segment depression and pulmonary edema. The troponin T concentration was increased to 2.8 ng/ml.

The patient was not suitable for coronary artery surgery because of diffuse, peripheral lesions. After the clinical course had stabilized, an exercise treadmill test was performed (*Figure 2*). The total workload

was 2.2 metabolic equivalent of task units (MET), and the duration of exercise was 2 min 50 s. The patient had angina pain, with ST-segment depression of 2 mm in the inferior and lateral leads. A single photon emission computed tomography (SPECT) perfusion study demonstrated diffuse fixed perfusion defects (apex and distal anteroseptal wall). Stress (2 MET)-induced severe perfusion defects of the inferior and lateral wall were observed (*Figure 3*).

In view of his angina, CCS class IV status, left ventricular failure, and the results of the stress test and SPECT study, heart transplantation was proposed for the patient, whose coronary arteries were not suitable for coronary artery bypass grafting. He did not agree to this treatment option. Drug therapy was therefore optimized as follows: the dose of isosorbide mononitrate was increased to 100 mg/day (given at 07.00 h) in combination with molsidomine 8 mg (at 22.00 h) and metoprolol 200 mg/day. He also received aspirin 75 mg, atorvastatin 40 mg, perindopril 2 mg, furosemide 40 mg, and potassium. After 3 months of combined treatment with full doses of hemodynamically acting antianginal agents, the patient still experienced episodes of chest pain, on average 30 per week, with daily activity restricted to bed and armchair. Because of refractory angina pectoris despite optimal treatment with two coronary agents, trimetazidine MR 35 mg twice daily was added to the previous drug regimen. In 2 weeks, the patient's quality of life improved. After 2 months of trimetazidine treatment, the average number of angina attacks decreased from 30 per week to 9 per week. At 2-year follow-up, the medical treatment remained unchanged. The patient remains in functional class CCS II, NYHA class II, and experiences an average 8–10 chest pains weekly.

(a)



(b)

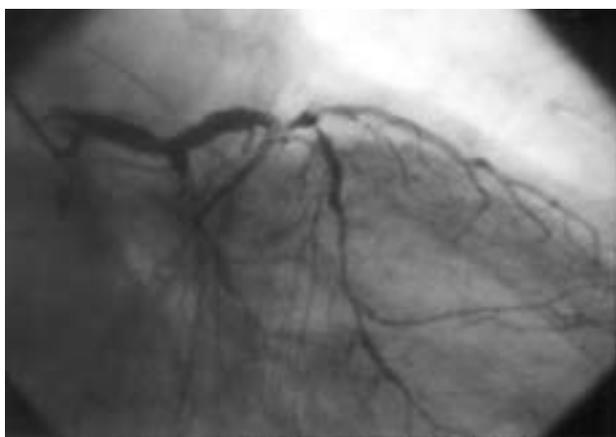


Figure 1. Coronary angiography. (a) Left coronary artery. (b) Right coronary artery.

Discussion

For this patient with dramatic angina pectoris, impaired left ventricular function, and no possibility of myocardial revascularization, it was a major problem to provide optimal medical treatment. In patients with stable coronary artery disease, relief of angina attacks may be achieved with conventional hemodynamic treatments such as nitrates, β -blockers and calcium channel antagonists. Some studies have demonstrated additional beneficial antianginal effects of the combination of a β -blocker with a calcium channel blocker or nitrate, but large multicenter trials such as the Total Ischemic Burden European Trial or CESAR showed no significant differences between monotherapy and combined therapy for mild chronic stable angina [1,2]. In our present patient, the combination of long acting nitrate and a β -blocker was ineffective. Combined

Case Report

Hanna Szwed

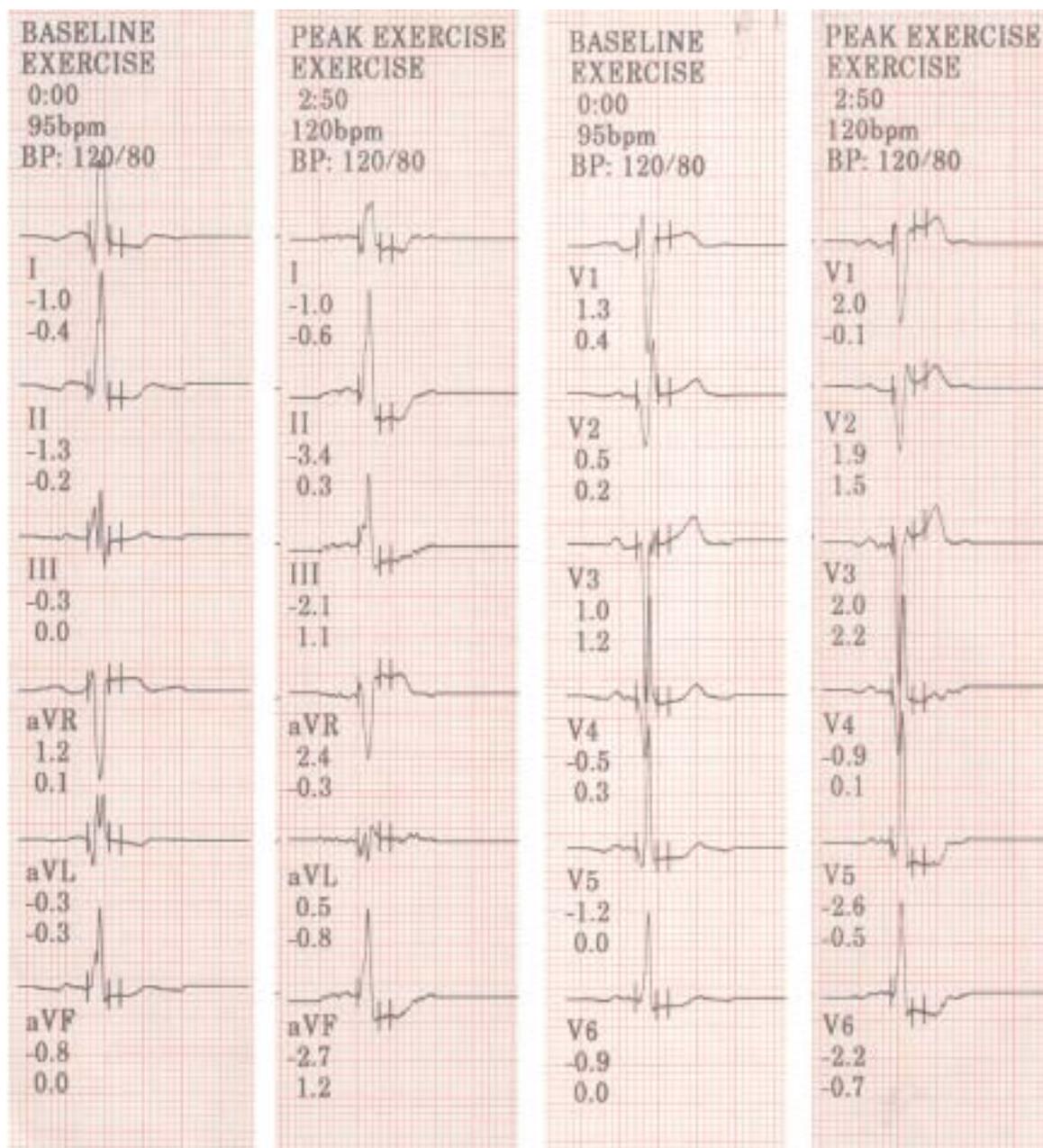


Figure 2. Exercise treadmill test.

treatment with a β -blocker and calcium antagonism was not recommended because of a tendency to bradycardia, hypotonia and impaired left ventricular function. In patients with angina refractory to treatment with hemodynamically acting agents, the addition of a metabolic agent such a trimetazidine, which is devoid of any hemodynamic effect and acts at the cellular level, would be expected to have an additive effect.

It has been demonstrated in experimental studies that trimetazidine, the first 3-ketoacyl coenzyme A thiolase inhibitor, is an effective cytoprotective agent that shifts cardiac energy metabolism from fatty acid

oxidation to glucose oxidation [3]. The antianginal activity of trimetazidine has been demonstrated in various double-blind studies. In comparative studies, trimetazidine has been demonstrated to be as effective as calcium channel antagonists or β -blockers [4,5]. Its anti-ischemic efficacy has been established in numerous studies, in which it was added to the drug regimen of patients whose angina was uncontrolled by one conventional hemodynamic agent [6–9]. The further rationale for the use of trimetazidine in the patient whose case we report here was poor left ventricular function, resulting in pulmonary edema in the course of acute coronary

Case Report

Benefits of metabolic treatment in refractory angina

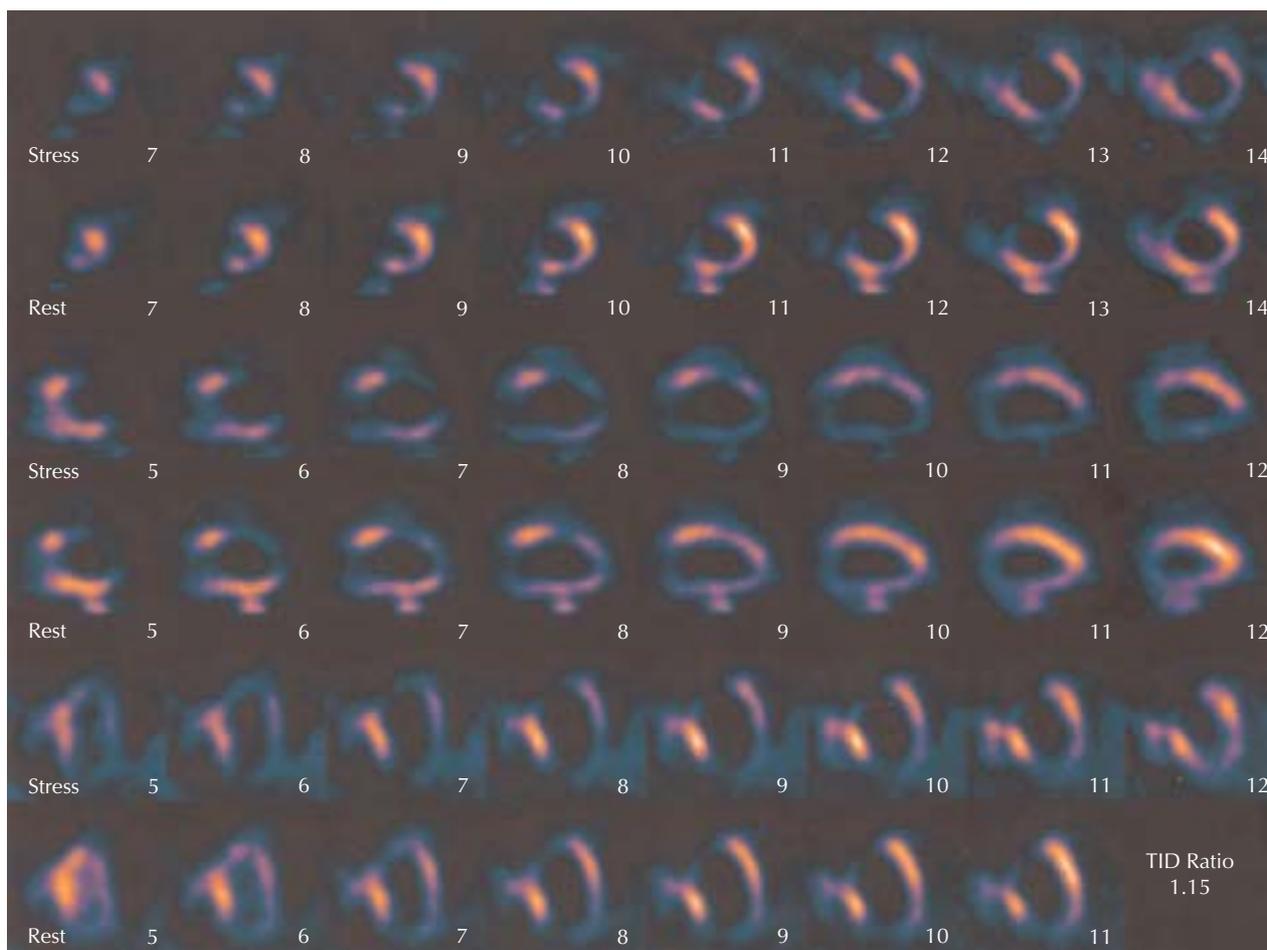


Figure 3. Single photon emission computed tomography perfusion study.

syndrome. It has been shown that treatment with trimetazidine is cytoprotective and exerts a beneficial role in patients with ischemic cardiomyopathy [10]. The reported case shows the value of cytoprotective treatment added to hemodynamically acting anti-anginal agents for treatment of the patient with advanced coronary artery disease and poor left ventricular function. ■

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Case Report

Hanna Szwed

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Metabolic changes in ischemia and myocardial infarction

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Abstract

The primary effect of ischemia is reduced myocardial oxygen consumption and impaired formation of ATP in the mitochondria. This triggers an acceleration of glycolysis, and production of lactate and H⁺. During demand-induced ischemia, the myocardium continues to have a relatively high residual oxygen consumption, which is fueled largely by fatty acid oxidation. Fatty acid oxidation inhibits glucose oxidation, and drives the conversion of pyruvate to lactate, which has detrimental effects on cell function. Traditional medical therapies for stable angina are aimed at reducing the need for ATP for contractile work by suppressing heart rate, blood pressure, and cardiac contractility. An alternative or adjunct approach is with the 3-ketoacyl coenzyme A thiolase inhibitor, trimetazidine, which partially suppresses myocardial fatty acid oxidation and further reduces the symptoms of demand-induced ischemia by removing fatty acid inhibition of glucose oxidation.

■ *Heart Metab.* 2004;23:39–43.

Keywords: Ischemia, myocardial infarction, metabolic changes, trimetazidine

Introduction

Ischemia is a metabolic problem. Myocardial ischemia can be generally defined as coronary blood flow insufficient to support the normal rate of myocardial oxygen consumption required to generate the normal external power. The primary effect of ischemia is impaired mitochondrial oxygen consumption; this results in a decrease in aerobic energy transfer from carbon fuels to formation of ATP by oxidative phosphorylation, and decreased generation of contractile power and calcium pump function [1, 2]. In the normal healthy heart, the concentrations of ATP and ADP remain relatively constant, even when the work of the heart is dramatically increased [3]. This is attributable to very tight matching of oxidative phosphorylation to ATP hydrolysis, and an abundant supply of carbon fuel and oxygen [4, 5]. During myocardial ischemia, the rate of oxidative phosphorylation is reduced, and the concentration of ATP decreases, triggering an

acceleration of glycolysis, lactate accumulation, and a decrease in contractile function [1, 2].

As shown in *Figure 1*, the healthy heart aerobically oxidizes fatty acids, glucose, and lactate to provide the energy for the contractile power that is necessary to maintain the required cardiac output. During myocardial ischemia, there is reduced oxygen consumption and the heart switches to lactate production. Myocardial substrate metabolism during ischemia is highly dependent upon the degree of reduction in coronary flow [1, 6–8]. Complete elimination of flow evolves into tissue necrosis and myocardial infarction over time. In contrast, a more modest reduction in flow (20 to 60%) causes a decrease in myocardial oxygen consumption (approximately 10 to 50%), a transient increased dependence on anaerobic glycolysis (glycogen depletion and lactate production), oxidation of fatty acids at a reduced rate, and modest to more severe contractile dysfunction [9–12]; depending on the metabolic demand, these modest

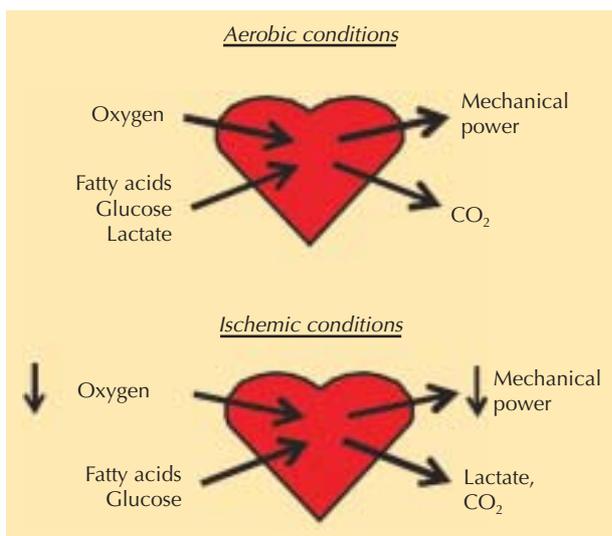


Figure 1. The healthy heart extracts fatty acid, glucose and lactate from the blood and oxidizes them to carbon dioxide (CO₂) to provide energy for the generation of external mechanical power. Myocardial ischemia results in a reduction in myocardial oxygen consumption, a switch from lactate uptake to lactate production, and a decrease in cardiac mechanical function.

reductions in flow do not necessarily lead to irreversible tissue damage.

Studies in large animals (dogs and pigs) have shown that an approximately 20 to 30% reduction in coronary blood flow results in a rapid reduction in mechanical work, a decrease in ATP and creatine phosphate concentrations, and a transient net output of lactate by the myocardium [1, 12, 13]. Over the course of 30 to 90 min, lactate output decreases and there is a partial restoration of myocardial ATP concentrations, but contractile work does not return to normal as long as the flow is reduced [11]. Restoration of flow back to normal in these mildly ischemic hearts results in a return to normal contractile function [14].

More severe ischemia (more than 70% reduction in flow) results in greater rates of accumulation of lactate and breakdown of glycogen, and severe or complete contractile dysfunction [1, 8]. Glycogen depletion and lactate accumulation increase as a function of the severity of ischemia. Complete elimination of flow differs from partial reductions in flow in that there is no residual resynthesis of ATP by oxidative phosphorylation, but complete dependence on endogenous substrate. The sole source of glycolytic substrate under these conditions becomes glycogen, because there is no blood flow to deliver glucose to the tissue. With complete elimination of blood flow, there is no washout of lactate or H⁺, and intracellular pH decreases to extremely low values [15]. If the ischemia is of sufficient duration, there is myocardial necrosis and infarction.

Residual oxidative metabolism during myocardial ischemia

Despite the contractile dysfunction and transient lactate production during moderate ischemia, the primary oxidative fuel is fatty acids. Studies in pigs and dogs with a 30 to 60% reduction in flow have shown that oxidation of exogenous free fatty acids supplies most (50 to 60%) of the energy for ATP synthesis during ischemia, even under conditions of severe contractile dysfunction, reduced myocardial oxygen consumption, and net lactate production [1, 8, 9]. Recent studies in the isolated rat heart have shown that, even during very severe ischemia (2% of normal myocardial oxygen consumption), the relative contribution of fatty acids to oxidative metabolism is unchanged from that under aerobic conditions [16]. Thus nonoxidative glycolysis and net lactate production occur during ischemia, even though the acetyl coenzyme A (CoA) is largely derived from fatty acid oxidation (Figure 2).

The production of lactate during ischemia is the result of accelerated glycolysis and pyruvate formation, and from reduced oxidation of pyruvate in the mitochondria (Figure 2). Pyruvate dehydrogenase converts pyruvate to acetyl-CoA in the mitochondria, which generates NADH. As noted in Figure 2, fatty acid oxidation also generates NADH and acetyl-CoA, exerts potent feedback inhibition on pyruvate dehydrogenase activity, and drives the conversion of pyruvate to lactate under conditions of accelerated glycolysis. Thus, during myocardial ischemia, high residual rates of fatty acid oxidation contribute to the production of lactate.

Cardiac metabolism during demand-induced ischemia

Clinically, myocardial ischemia is most frequently induced by an insufficient increase in myocardial blood flow in response to an increase in demand for cardiac power, as occurs with increases in heart rate, afterload, and cardiac contractility. This type of ischemia is referred to as "demand-induced ischemia." The healthy heart responds to exercise or sympathetic stimulation by increasing coronary blood flow, the uptake of carbon substrates, and myocardial oxygen consumption, in proportion to the increase in the rate–pressure product (heart rate × systolic blood pressure) [17, 18]. If coronary arteries are narrowed, then the capacity to increase coronary blood flow in response to a greater demand will be reduced, and there will be a failure to increase myocardial blood flow and oxygen consumption in response to the greater cardiac work demand. Thus there may be normal myocardial blood flow and oxygen consump-

Refresher corner

Metabolic changes in ischemia and myocardial infarction

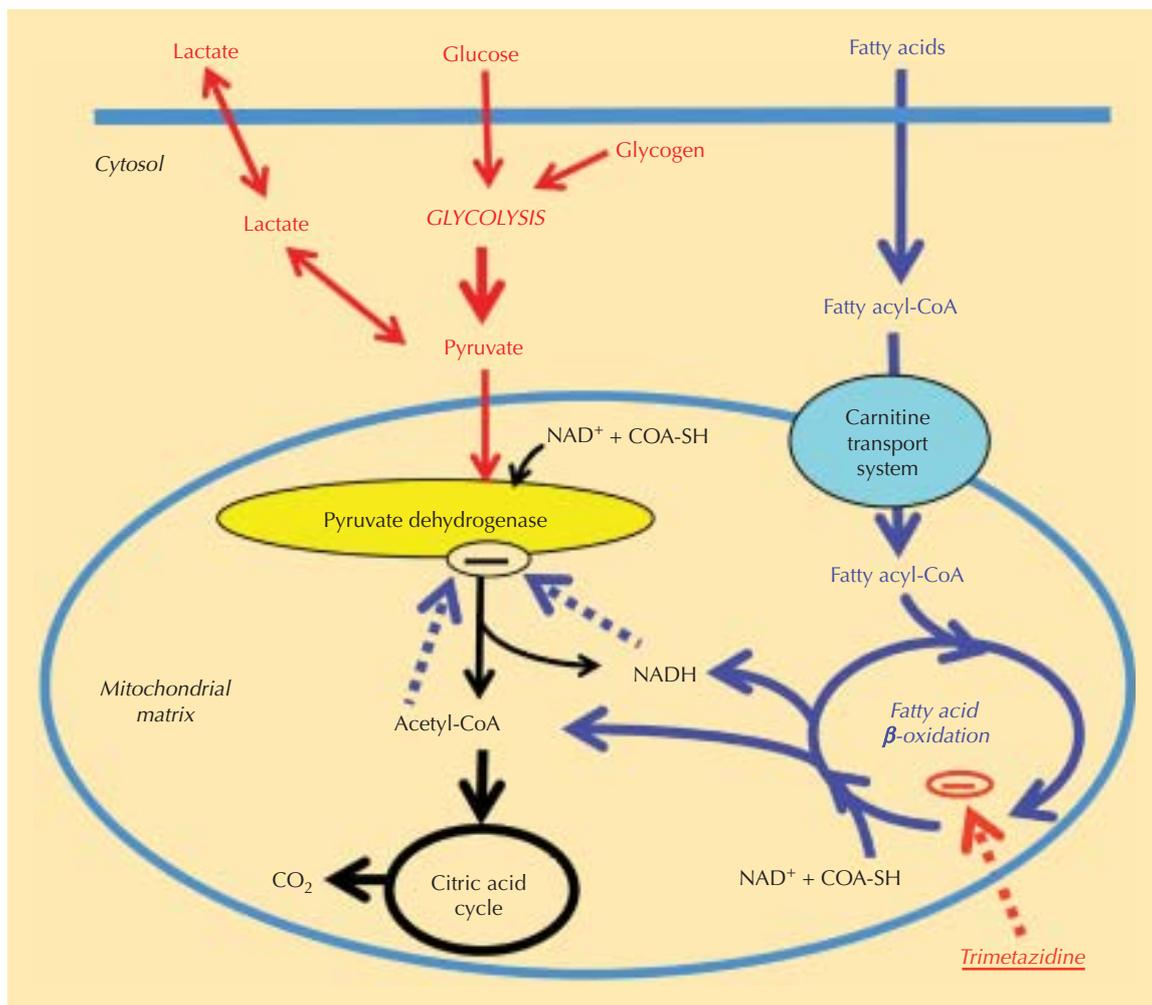


Figure 2. Schematic depiction of myocardial substrate metabolism. Fatty acid oxidation exerts potent inhibition on pyruvate dehydrogenase activity through increases in $NADH/NAD^+$ and acetyl-coenzyme A (CoA) : free coenzyme A (CoA-SH) ratios.

tion at rest, but severe myocardial ischemia during exercise or catecholamine stress, as a result of reduced coronary flow reserve. This is why exercise stress testing is performed to diagnose coronary artery disease.

Demand-induced ischemia activates glycogen breakdown, accelerates glycolysis, and causes a switch from lactate uptake to lactate output by the myocardium [19–21]. The metabolic abnormalities with demand-induced ischemia coincide with changes in the ECG, specifically a depression in the ST-segment and angina pectoris [20]. Figure 3 is from a classic 1969 study by Parker et al [20], and depicts the metabolic and electrocardiographic responses to demand-induced ischemia. A patient with coronary artery disease had arterial and coronary sinus catheters placed for determination of the release of lactate from the myocardium, and was subjected to graded atrial pacing to induce ST-segment depression and angina pectoris. Note that, at rest, the ECG is normal and the arterial lactate concentration exceeds the

coronary sinus concentration, reflecting net lactate consumption by the myocardium. Numerous studies have shown that the healthy heart continues to take up lactate when the work of the heart is increased by pacing or exercise. When the myocardial oxygen demand is progressively increased by pacing, the patient with stable angina responds with a rapid increase in coronary sinus lactate concentration and a switch to myocardial production of lactate, which coincides with a decrease in the ST-segment of the ECG and chest pain. When pacing is stopped, there is a rapid decrease in coronary sinus lactate concentration and a return to a normal ECG. Clearly, there is a link between accelerated anaerobic glycolysis and classic clinical symptoms of demand-induced ischemia (ST-segment depression and angina).

Stress-induced angina is medically treated by reducing the work demand on the heart and the oxygen requirement of the myocardium through the reduction of heart rate, contractility, and afterload with β -adrenergic receptor antagonists, calcium

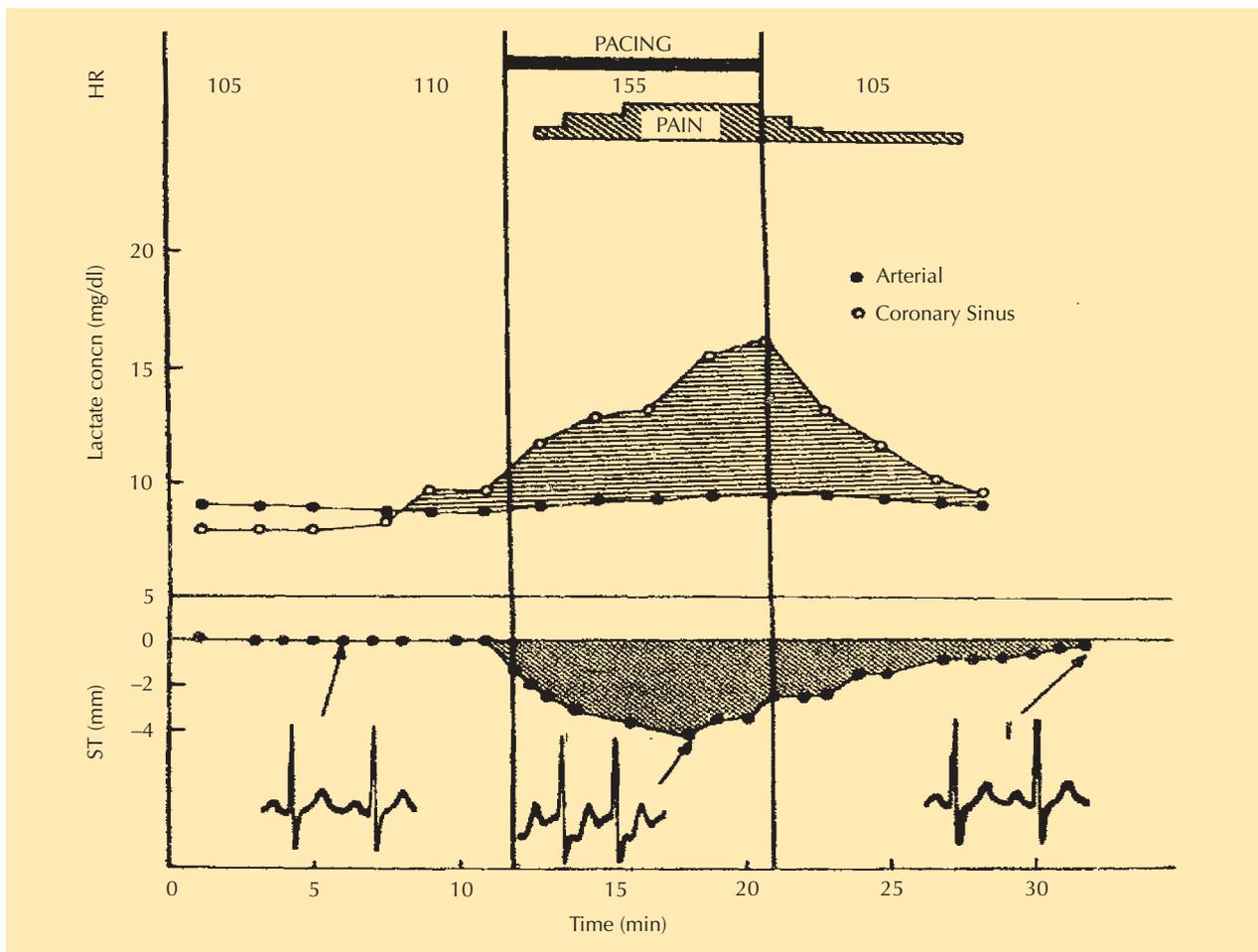


Figure 3. The effects of increasing heart rate (HR, beats/min) by atrial pacing in a patient with stable angina. Pacing stress caused a rapid switch from lactate uptake to lactate production, and a decrease in the ST-segment (ST) of the ECG. Cessation of pacing resulted in a rapid reversal from lactate production back to net uptake, and a return to a normal ST-segment. Lactate: ●, arterial; ○, coronary sinus; concn, concentration. (From Parker et al [20], with permission.)

antagonists, and nitrates [22]. These agents reduce the need for ATP and thus partially normalize the imbalance between mitochondrial generation of ATP and the normal requirement for ATP breakdown. Myocardial blood flow can be modestly increased with a calcium antagonist and nitrates; however, this effect appears to play only a small part in the mechanism of action of these agents in the treatment of angina. In addition there is metabolic treatment for stable angina is also through partial inhibition of myocardial lipid oxidation by means of inhibition of the fatty acid β -oxidation enzyme, long chain 3-ketoacyl coenzyme A thiolase (3-KAT), using trimetazidine (Figure 2) [23, 24]. During demand-induced ischemia, there is a relatively high rate of fatty acid oxidation, which inhibits the oxidation of glucose and drives the conversion of pyruvate to lactate, resulting in higher pH and improved contractile function during ischemia. Partial inhibition of myocardial fatty acid oxidation increases glucose and pyruvate oxidation and decreases lactate pro-

duction during demand-induced ischemia [25]. In clinical trials this agent does not affect heart rate, or arterial blood pressure at rest or during exercise, but is as effective as calcium channel antagonists or β -adrenergic antagonists at improving times to the onset of angina or to 1 mm depression in the ST-segment during exercise [23]. Moreover, partial inhibitors of fatty acid oxidation have an additive effect in reducing symptoms of exercise-induced angina when used in combination with either a calcium channel antagonist or a β -adrenergic receptor antagonist [23]. ■

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Featured research

Abstracts and commentaries

Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study

Sastry BK, Narasimhan C, Reddy NK, Raju BS. *J Am Coll Cardiol.* 2004; 43(7):1149–53.

Objectives: In a randomized, double-blind, crossover design, we compared the efficacy of sildenafil with placebo in patients with primary pulmonary hypertension (PPH). The primary end point was the change in exercise time on treadmill using the Naughton protocol. Secondary end points were change in cardiac index and pulmonary artery systolic pressure as assessed by Doppler echocardiography and quality of life (QOL) as assessed by a questionnaire.

Background: Primary pulmonary hypertension is a disorder with limited treatment options. Uncontrolled studies had shown sildenafil to be beneficial in the treatment of PPH.

Methods: After initial clinical evaluation, including Doppler echocardiography and treadmill exercise test, patients were randomized to placebo or sildenafil with dosages ranging from 25 to 100 mg thrice daily on the basis of body weight. The evaluation was repeated after six weeks. Then patients were crossed over to alternate therapy. Final evaluation was performed after another six weeks of treatment.

Results: Twenty-two patients completed the study. Exercise time increased by 44% from 475 ± 168 s at the end of placebo phase to 686 ± 224 s at the end of sildenafil phase ($P < 0.0001$). With sildenafil, cardiac index improved from 2.80 ± 0.9 l/m² to 3.45 ± 1.1 l/m² ($P < 0.0001$), whereas pulmonary artery systolic pressure decreased insignificantly from 105.23 ± 17.82 mm Hg to 98.50 ± 24.38 mm Hg. There was significant improvement in the dyspnea and fatigue components of the QOL questionnaire. During the placebo phase, one patient died and another had syncope. There were no serious side effects with sildenafil.

Conclusion: Sildenafil significantly improves exercise tolerance, cardiac index, and QOL in patients with PPH.

Clinical and haemodynamic effects of sildenafil in pulmonary hypertension: acute and mid-term effects.

Mikhail GW, Prasad SK, Li W, et al. *Eur Heart J.* 2004; 25(5):431–6.

Aim: The treatment of patients with pulmonary arterial hypertension remains a challenge. We set out to investigate the use of sildenafil, a selective inhibitor of phosphodiesterase type 5, in patients with this disease.

Methods and results: Ten patients (8 females, mean age 34.5 ± 3.3 years) with pulmonary hypertension underwent right heart catheterisation with vasodilator testing using incremental doses of intravenous sildenafil without adverse events. All patients were subsequently commenced on oral sildenafil 50 mg t.d.s. Nine patients had repeat right heart catheterisation 3 months after the commencement of oral therapy. There was a significant reduction in mean pulmonary artery pressure (from 55.8 ± 5.9 to 50.4 ± 6.1 mmHg, $P = 0.038$) and pulmonary vascular resistance (from 10.1 ± 1.7 to 8.6 ± 1.5 Wood units, $P = 0.009$), and an increase in cardiac output (from 4.7 ± 0.3 to 5.0 ± 0.4 l/min, $P = 0.15$). Furthermore, there was a significant increase in the 6-minute walk test, a mean of 112 m. In response to a quality-of-life questionnaire, patients indicated marked clinical improvement on sildenafil. Sildenafil was discontinued in 1 patient due to a transient visual disturbance. The only patient previously awaiting transplantation was removed from the active transplantation list.

Conclusion: Sildenafil is well tolerated in its intravenous and oral forms and appears to improve both pulmonary hemodynamics and the clinical status of patients with pulmonary hypertension after 3 months of oral therapy.

Commentary

Issue 22 of *Heart and Metabolism* focused on endothelial dysfunction and mentioned in the editorial Phosphodiesterase type 5 (PDE5) inhibitors and their role, not just in treating erectile dysfunction but also their effect throughout the vascular tree. Primary pulmonary hypertension is a disorder of unknown aetiology, which is invariably fatal over approximately 3 years, as a result of progressive elevation of pulmonary vascular resistance and right heart failure. Quality of life becomes progressively impaired with a poor exercise ability due to *dyspnea*. Case reports of the benefits from PDE5 inhibitors have been impressive and now we have two formal studies showing that sildenafil (Viagra) is well tolerated in a thrice daily dosing regime, improving pulmonary hemodynamics exercise tolerance, cardiac index and quality of life. To date there is no evidence of tolerance but long term follow up is clearly necessary. PDE5 inhibitors possess important effects on the endothelium and enhance smooth muscle relaxation. Their role in diabetes, hypertension, cardiac failure and Raynauds phenomena is just being realized. By acting within the cell to prevent the degradation of cyclic guanosine mono phosphate they have potentially important metabolic and hemodynamic effects. These two studies represent the beginning of a new therapeutic entity, which could be prognostically, as well as symptomatically, important.

Graham Jackson

Paradoxical downregulation of the glucose oxidation pathway despite enhanced flux in severe heart failure

Lei B, Lionetti V, Young ME, et al. *J Mol Cell Cardiol.* 2004; 36:567–576

An altered utilization of metabolic substrates is recognized as one of the biochemical hallmarks of the failing heart. It has been hypothesized that profound changes in the rate of free fatty acids (FFA) and carbohydrate oxidation might play a role in the complex pathophysiological mechanisms leading to decompensated heart failure. The aim of this work was to quantify changes in FFA and glucose oxidation in vivo, in dogs with normal and failing hearts. At the end of the in vivo experiment, clamp-frozen biopsies were harvested from the left ventricle. The results show that, in failing hearts, the capacity of the carbohydrate oxidative pathway is not enhanced. Rather it is moderately down-regulated, despite a marked enhancement in glucose oxidation flux. In light of recent data in

the same model demonstrating a downregulation of the fatty acid oxidation pathway [1], the results of the present investigation suggest that (1) the increase in glucose oxidation observed in the failing heart in vivo is principally due to impaired oxidation of the competing substrate fatty acid, and (2) that the capacity for both fatty acid and carbohydrate oxidation are suppressed in heart failure.

Commentary

Studies performed over the past forty years have provided solid evidence that in experimental heart failure, cardiac FFA oxidation rates are depressed during decompensation. Clinical studies on this topic are still limited and, in part, in conflict with experimental studies, probably due to indirect methods of measurement, heterogeneous groups of heart failure patients, and sometimes the absence of a control group. However, the only clinical investigation that has employed three cardiac substrates labelled with positron emitting isotopes showed decreased FFA consumption in patients with idiopathic dilated cardiomyopathy, with an increase in the utilization of the competing substrate glucose [2]. Taken together, the findings in both patients and animal models have led the authors to hypothesize that the failing heart reverts to a fetal metabolic phenotype, characterized by prevalent utilization of carbohydrate as a source of energy. Fewer studies, however, have explored possible changes in the myocardial carbohydrate oxidative pathway to determine whether this is potentiated in heart failure. In the present study, direct measurements of FFA and glucose oxidation were performed in vivo, followed by measurements of the expression (both gene and protein) and activity of key regulatory enzymes ex vivo. The authors observed the anticipated depression of fatty acid oxidation, and concomitant increase in glucose oxidation, in the failing heart. However, the report also indicates that the expression of all genes encoding for proteins involved in carbohydrate metabolism were downregulated in the failing dog heart. This is consistent with previous observations in failing human hearts [3]. Therefore, the previous study by Razeghi et al. [3] and the present one, lead to a similar conclusion that the failing heart represses the expression of all metabolic enzymes, rather than selectively potentiating the carbohydrate pathway. It remains to be demonstrated whether glucose oxidation can be pharmacologically enhanced in end stage heart failure when the capacity for carbohydrate metabolism appears to be impaired.

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Danielle Feuvray

Angina Pectoris Prior to Myocardial Infarction Protects Against Subsequent Left Ventricular Remodeling

Solomon SD, Anavekar NS, Greaves S, et al. *Journal of the American College of Cardiology* 2004; 43(9):1511–1514

Objectives: To investigate the hypothesis that prior angina pectoris confers protection from remodelling occurring after myocardial infarction (MI), we analysed echocardiograms from the Healing and Early Afterload Reducing Therapy (HEART) trial.

Background: Ischemia occurring before MI has been shown to reduce infarct size in experimental models and to improve outcomes in patients. The extent to which ischemia occurring before MI influences subsequent changes in ventricular size and function is unclear.

Methods: We studied 283 patients enrolled in the HEART trial who had echocardiograms at days 1 and 90 after MI. Left ventricular (LV) dilation from days 1 to 90 was used as a measure of LV remodelling. We explored the relationship between symptomatic angina occurring before infarction and subsequent remodelling.

Results: In patients who reported angina ($n=111$) during the three months preceding MI, LV volume change was -0.73 ± 2.6 ml over the 90-day post-MI period, compared with 6.8 ± 2.6 ml for patients ($n=172$) without angina ($P=0.017$). In contrast there were no differences in changes in ejection fraction based on prior angina. Maximal creatine kinase was significantly lower in patients with prior angina ($2,119 \pm 1,729$ vs $2,701 \pm 2,088$, $P=0.016$). In a multivariate model, prior angina remained protective for ventricular remodelling after adjusting for age, gender, baseline ejection fraction, Killip class, baseline and end-diastolic volume, and drug treatment group ($P=0.042$). However, the protective effect of pre-infarction angina appeared to be attenuated in diabetic patients.

Conclusion: Ischemic symptoms occurring before MI may protect against LV remodelling. These protective effects may be secondary to recruitment of collaterals or ischemic preconditioning of the myocardium and they appear to be attenuated in diabetic patients.

Commentary

Ischemic preconditioning is the term used to describe the phenomenon where a short period of myocardial ischemia reduces the infarction that results from subsequent more prolonged ischemia. Ischemic preconditioning was initially described, and subsequently extensively studied, in animal hearts. Since first being described 18 years ago there have been a number of clinical studies designed to detect its presence in patients. By necessity these studies have had to be observational, making use of the varying patterns of myocardial ischemia that may presage ST elevation MI. There is now a substantial literature that demonstrates patients with ST elevation MI that have preceding angina, have a more benign in-hospital course and smaller myocardial infarcts than those patients with unheralded infarction. However the interpretation of such observational studies are always clouded by differences in use of aspirin, β -blockers, ACE-I and door to needle/balloon times that are likely to exist in patients that do, or do not, have angina prior to MI. Furthermore, there is evidence to suggest that patients with prior angina more rapidly achieve TIMI 3 flow in their infarct related arteries than those that do not. In addition, it is also likely that patients with pre-infarction angina have better developed collateral flow beyond the unstable atherosclerotic plaque. Despite these caveats, which are difficult to control, there seems little doubt that myocardial infarction is reduced in patients with pre-infarction angina whatever the exact underlying mechanism. However what has not so far been demonstrated is whether this reduction in infarction is reflected by indices of more benign LV remodelling.

The above study adds further to this already extensive literature. Solomon et al enrolled almost 300 patients presenting with ST elevation MI in the anterior territory. Infarcts in this territory are most prone to cause adverse LV remodelling. Echocardiography was performed within 24 hours of MI and at 90 days. Patients were categorised as having antecedent angina or an unheralded myocardial infarction on the basis of an admission questionnaire. In keeping with other investigators a history of angina was associated with a reduction in CK-derived infarct size. However, Solomon et al were also able to show that preinfarction angina was associated with blunted LV remodelling since there was no change in LV end

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diastolic volume between day one and 90 in patients with prior MI, whilst in those without angina this parameter increased by approximately 7ml ($p=0.017$). In a multivariate model prior angina remained predictive of less remodelling after adjusting for age, gender, baseline ejection fraction and enddiastolic volume, Killip class, diabetes, and drug treatment. Unfortunately the study did not measure collateral support to the infarct related artery but there

were no differences in pain to presentation time between groups. Yet again this study supports the counterintuitive hypothesis that preinfarction angina is beneficial and demonstrates an additional benefit in terms of post-MI remodelling. It seems angina is a cloud with a silver lining.

Michael Marber

Glossary

Gary D. Lopaschuk

Acetyl CoA carboxylase (ACC) and malonyl CoA decarboxylase (MCD)

ACC and MCD are two enzymes that control malonyl CoA levels in a number of different types of cells, particularly heart and skeletal muscle. ACC synthesizes malonyl CoA from acetyl CoA, while MCD degrades malonyl CoA back to acetyl CoA. These are important reactions, since malonyl CoA is a potent inhibitor of mitochondrial fatty acid uptake, and therefore an important regulator of muscle fatty acid oxidation.

AMP-activated protein kinase (AMPK)

AMPK is a kinase that is activated in cells during times of metabolic stress. As the name implies, it is activated by AMP. AMPK phosphorylates many enzymes and, in general, inhibit enzymes involved in energy consuming anabolic process, while activating enzymes involved in catabolic energy-producing processes.

CrCl level

CrCl is the abbreviation for creatinine clearance. Measurement of creatinine clearance rates is used to assess kidney function.

Glut1 and Glut4

Glut1 and Glut4 are glucose transporters that facilitate the transport of glucose across the cell membrane. They are the two main glucose transporters found in heart and skeletal muscle. In the presence of insulin, Glut4 is translocated from the interior of the cell to the cell membrane, thereby resulting in an increase in muscle glucose uptake.

Glycosylation end products

Glycosylation is the process of adding oligosaccharide moieties to proteins or other molecules. In diabetes, chronically high glucose levels will increase the level of protein glycosylation. Therefore, by measuring glycosylation end products, the longer term degree of glucose control can be determined.

Glycolysis

Glycolysis is the first part of the pathway by which glucose is metabolized in cells. It is a highly regulated pathway that converts glucose to pyruvate. In the process of doing this, two ATP molecules are produced. This occurs without the requirement for oxygen.

Kinase

A kinase is an enzyme that phosphorylates (i.e. adds a phosphate group) to other proteins and/or itself. Kinases are very important enzymes involved in numerous cell signalling processes.

Long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT)

LC 3-KAT is the last enzyme in the fatty acid β -oxidation pathway. It functions to produce acetyl CoA from long chain fatty acids, which results in the two carbon shortening of the fatty acids. LC 3-KAT is the enzyme that is inhibited by the anti-anginal agent, trimetazidine. Inhibition of LC 3KAT results in a decrease in fatty acid oxidation and a concomitant increase in glucose oxidation in the heart.

Myoglobin

Myoglobin is an important intracellular oxygen binding hemoprotein found in abundance in heart and skeletal muscle. Myoglobin not only provides oxygen for mitochondrial oxidative metabolism, it also buffers intracellular oxygen during changes in mitochondrial oxygen demand.

Na/K-ATPase and the SR-Ca⁺⁺-ATPase

Na/K-ATPase and the SR-Ca⁺⁺-ATPase are two ion pumps that are involved in the transport of ions across membranes. They usually pump these ions against a concentration gradient, and therefore energy is required, which is provided by the hydrolysis of ATP, the main energy currency in cells (hence the name ATPases). Na/K-ATPase pumps Na⁺ out of cells, while simultaneously pumping K⁺ into cells. The SR -Ca⁺⁺-ATPase pumps Ca⁺⁺ from the