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# Metabolic approach in heart failure

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Heart failure occurs when the heart is unable to maintain cardiac output to accommodate metabolic requirements and the venous return [1]. It is important because it is common (1–2% of the population and 10–20% in the very elderly), disabling symptomatically, and deadly, with a mortality rate worse than that of cancer (24% 3-year survival, compared with: breast cancer 72%, prostate cancer 55% and colon cancer 42%) [2]. The classical sequence of events of failure begetting failure reflects the neurohormonal response to a reduction in ventricular function [3] (Figure 1).

Treatment focuses on reducing symptoms, increasing exercise capacity and quality of life, and improving survival. Diuretics address volume overload and relieve symptoms, and angiotensin-converting enzyme inhibitors, angiotensin II antagonists and  $\beta$ -blockers target the neurohormonal responses, both improving symptoms and reducing mortality [4]. Despite the use of all evidence-based therapies, cardiac resynchronization therapy, and implantable cardiac defibrillators, the outlook remains grim [5]. An additional symptomatic and prognostic treatment is needed, in addition to a more aggressive approach to prevention.

As long ago as 1990, Brottier et al [6] reported improved left ventricular function in patients with severe ischemic cardiomyopathy after 6 months of treatment with trimetazidine. Since then, this metabolic strategy has repeatedly been shown to improve clinical status and left ventricular ejection fraction [7]. In the most recently reported study, trimetazidine was added to up-to-date usual treatment for up to 18 months, resulting in a significant improvement in functional ability, left ventricular function, and the remodeling process in 61 patients with dilated

ischemic cardiomyopathy [8]. The beneficial pharmacological intervention with trimetazidine, which shifts metabolism from free fatty acid to glucose oxidation, suggests a cytoprotective affect on the myocardium, with enhancement of carbohydrate oxidation increasing cardiac contractility – the heart prefers glucose as its energy source.

In this issue of *Heart and Metabolism*, we explain, expand, and build on the metabolic story – moving from the basic concepts of a metabolic approach to the clinical context. The efficacy of metabolic agents is reviewed, and the role of trimetazidine expanded on with a clinical example.

The failing heart needs help and addressing the metabolic aspects of cardiac failure offers it assistance in addition to the other established strategies. A survival benefit from metabolic treatment needs long-term outcome studies, and these appear to be justified on the basis of accumulating evidence to date with trimetazidine. ■

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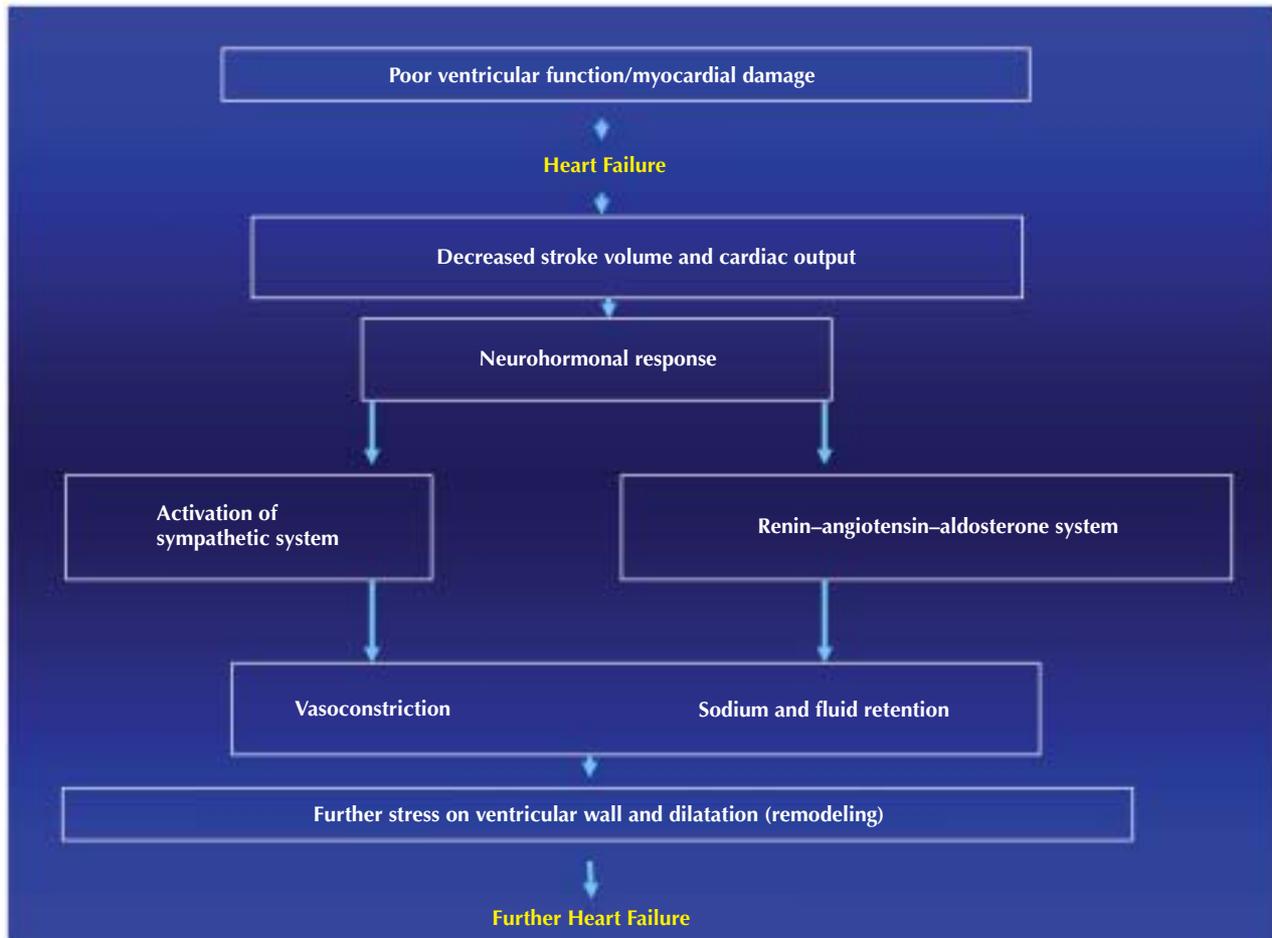


Figure 1. Sequence of events leading to heart failure.

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# Metabolic approach in heart failure: the rationale for metabolic interventions

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## Abstract

Alterations in myocardial energy substrate metabolism in patients with heart failure can contribute to contractile dysfunction and to the progression of left ventricular remodeling. Recent evidence has emerged that myocardial energy metabolism is relatively normal during the early stages of heart failure; however, in the advanced stages there is reduced mitochondrial oxidative metabolism, an increase in glycolysis, and a downregulation of glucose and fatty acid oxidation. This paper discusses the metabolic changes that occur in chronic heart failure, the consequences of these metabolic changes for cardiac function, and the therapeutic potential of acute and long-term manipulation of cardiac substrate metabolism in heart failure.

■ *Heart Metab.* 2005;27:5–10.

**Keywords:** Cardiac function, chronic heart failure, energy metabolism, metabolic intervention, fatty acid oxidation, glucose metabolism

## Introduction

Modern health care has brought us to a point at which we are living much longer and with a better quality of life. However, cardiovascular disease remains the primary cause of death and disability in the industrialized world. Advancements in acute cardiac care have improved survival after acute myocardial infarctions, but alongside this there has been an increase in mortality as a result of heart failure [1].

The term 'heart failure' encompasses a number of clinical variations and differing etiologies. Heart failure is defined as 'a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood' [2]. Treatment of heart failure currently targets fluid overload and neurohormonal activation. Diuretics, digoxin, and inotropes treat fluid overload and improve hemodynamics; while angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists,  $\beta$ -receptor antagonists, and aldosterone antagonists suppress neurohormonal acti-

vation. In spite of these treatments, there is still progression of contractile dysfunction and continuing left ventricular enlargement [3–5]. Furthermore, recent evidence has shown that more aggressive treatment with aldosterone antagonists does not provide any better outcome [6–8]. Therefore, there is a need for new treatments for heart failure that work independently of mechanisms already targeted.

Emerging evidence suggests that the failure of the myocardium in heart failure is caused by alterations in substrate metabolism (reviewed in Stanley et al [9]). In particular, there is now evidence that in the failing heart, shifting metabolism away from a preference for fatty acids towards more carbohydrate oxidation can improve contractile function and slow the progression of pump failure [10–17].

## Energy metabolism in the normal heart

In the normal, healthy heart, the large amounts of adenosine triphosphate (ATP) necessary to sustain

contractile function and basal metabolism are generated primarily by mitochondrial oxidative metabolism, with a small proportion derived from glycolysis (*Figure 1*). The heart is an omnivore and can use many different energy substrates (fatty acids, glucose, lactate, ketones, amino acids), but mitochondrial ATP is primarily produced by the oxidation of fatty acids and of pyruvate (derived from either glycolysis or lactate) (*Figure 1*). The rate of metabolism along these different pathways is determined by arterial substrate concentration, hormones, coronary flow, inotropic state, and nutritional status [9]. These effects are mediated by various enzymes and substrate–product relationships. In the normal heart, approximately 10–40% of the ATP is produced via pyruvate oxidation, whereas the remaining 60–90% is derived from the oxidation of fatty acids. An important enzyme at the interface between carbohydrate oxidation and fatty acid metabolism is pyruvate dehydrogenase (PDH), which decarboxylates pyruvate to acetyl coenzyme A (CoA) (*Figure 1*). PDH activity is influenced not only by glycolysis, but also by an inhibitory effect exerted through fatty acid oxidation. In situations in which the circulating free fatty acid concentrations are high, the oxidation of glucose and pyruvate and the activity of PDH are decreased. As a result of this, pyruvate is redirected towards lactate production and released from the heart. This produces protons, which the heart must also clear – a process that often requires energy, and results in redirecting ATP away from contractile function, which can decrease cardiac efficiency [18]. Conversely, decreasing plasma free fatty acid concentrations, or directly inhibiting fatty acid oxidation, increases PDH activity and, hence, pyruvate oxidation and cardiac efficiency [18,19].

The rate at which fatty acids are taken up and oxidized by the heart is dependent on both their plasma concentration and their intracellular control. In addition, a number of membrane transporters and enzymes are involved in transferring the substrates from the cytosol into the mitochondrial matrix (*Figure 2*). It is also worth noting here the enzyme malonyl CoA, which has an inhibitory effect on the enzyme carnitine palmitoyl transferase (CPT-1) and is thus a key physiological regulator of fatty acid oxidation in the heart, acts to suppress fatty acid oxidation (*Figure 2*). Increases in malonyl CoA decrease the rate of fatty acid oxidation and, conversely, reductions in malonyl CoA activity will increase the rates of fatty acid uptake and oxidation [9,18].

### Energy metabolism in the failing heart

Because of the difficulty of obtaining myocardial tissue samples and assessing cardiac energy metabolism in humans, direct measurements of energy

metabolism in the failing heart are few. However, studies both in patients with heart failure and in animal models of heart failure show that there is a decrease in tissue ATP content, an increase in ADP, and a decrease in the phosphorylation potential (reviewed in Stanley et al [9]), thus impairing the kinetics for the utilization of ATP for cell contraction. In addition, heart failure impairs the capacity for the creatine kinase system to transfer mitochondrial ATP to the myofibril, and decreases mitochondrial oxidative capacity, in part as a result of a decrease in electron transport chain activity [9]. The electron transport chain defects in heart failure are consistent with the concept that, in heart failure, there is a major lesion in oxidative metabolism at the level of the chain. It appears that impairment in the electron transport chain reduces the in-vivo capacity for myocardial generation of ATP and thus limits cardiac contractile function during high-level work, such as exercise or acute adrenergic stress. This is supported by the studies in dogs with pacing-induced heart failure, that reduced myocardial oxygen consumption in response to increased cardiac work was the result of a limitation of oxygen extraction, not of myocardial blood flow [20,21]. These findings are consistent with the concept of impaired mitochondrial respiratory capacity in heart failure, resulting in reduced ability to generate ATP in response to increased demand for cardiac power. In support, of this, recent studies have demonstrated that downregulation of the enzymes of fatty acid oxidation can be triggered by a defect in the electron transport chain in the mouse heart [22].

Numerous studies, in patients and in animal models, have shown that heart failure reduces the capacity to transduce the energy from foodstuffs into ATP, but less is known about the effects of heart failure on myocardial substrate metabolism and fuel selection. In the early stages of heart failure, there is a normal (or slightly increased) rate of fatty acid oxidation, and in advanced or endstage heart failure there is downregulation of fatty acid oxidation. Paolisso et al [23] found increased extraction and uptake of plasma free fatty acids and decreased glucose uptake in patients with congestive heart failure Classes II and III compared with age-matched healthy individuals. In these patients there was a corresponding 60% decrease in cardiac carbohydrate oxidation compared with the healthy controls. Using positron emission tomography (PET), Taylor et al [24] found greater myocardial uptake of a radiolabeled fatty acid analog and less uptake of a radiolabeled deoxyglucose in patients with Class III heart failure compared with those in healthy individuals. In contrast, patients with idiopathic dilated cardiomyopathy appear to exhibit the reverse: a greater myocardial glucose uptake and less fatty acid uptake compared with normal people. Yazaki et al [25] and

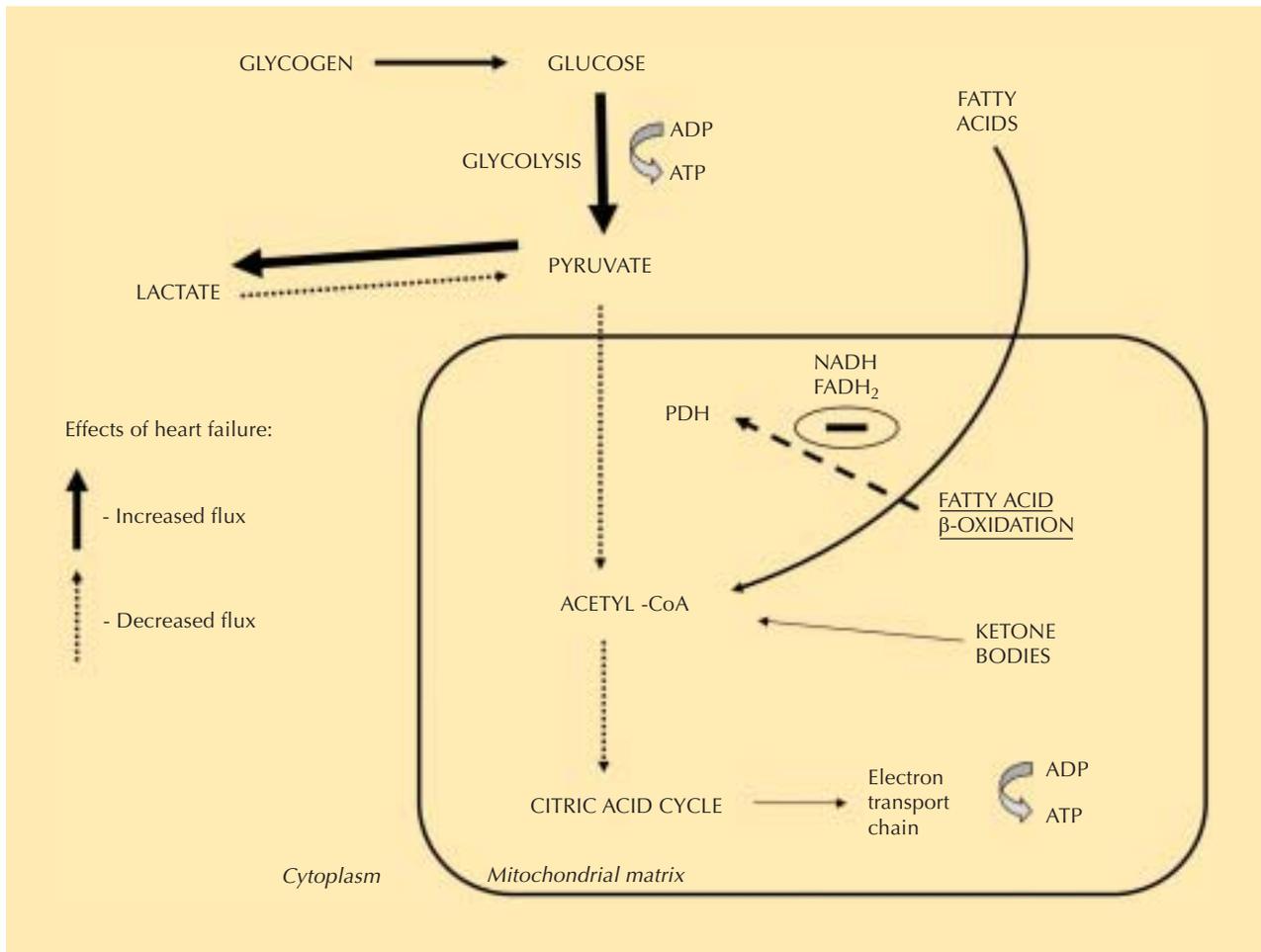


Figure 1. Alterations in cardiac energy metabolism in heart failure. In early heart failure, fatty acid oxidation rates in the heart are either normal or increased. Glucose uptake and glycolysis can be accelerated, with a normal or decreased influx through pyruvate dehydrogenase. In severe heart failure, the overall mitochondrial oxidative capacity decreases, as does fatty acid oxidation. ATP, adenosine triphosphate; CoA, coenzyme A; FADH<sub>2</sub>, reduced flavine adenine dinucleotide; PDH, pyruvate dehydrogenase.

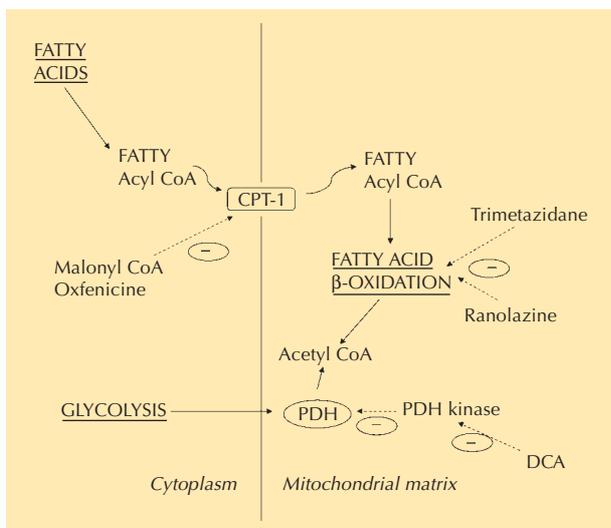


Figure 2. Potential sites of inhibition of fatty acid oxidation in heart failure. CoA, coenzyme A; CPT-1, carnitine palmitoyl transferase; DCA, dichloroacetate; PDH, pyruvate dehydrogenase.

Dávila-Román et al [26] found impaired utilization of fatty acids in patients with severe idiopathic dilated cardiomyopathy. It is important to note that, with PET, although one can estimate glucose uptake, it is not possible to make a direct measurement of the rate of glucose oxidation. It is therefore not clear from these studies whether flux through PDH is altered in these patients. To date, the limited availability of data on clinical investigations may be attributable to the severity of heart failure, supporting the idea that, in the early stages of heart failure, there is a normal (or slightly increased) rate of fatty acid oxidation, with a dramatic downregulation of fatty acid oxidation in advanced or endstage heart failure.

Studies in animal models of heart failure parallel human studies that suggest increased or normal fatty acid oxidation in early heart failure and impaired fatty acid oxidation in severe heart failure. Chandler et al [27] measured myocardial substrate oxidation in dogs with well compensated microembolization-induced

heart failure using isotopic tracers, and found no differences in myocardial glucose, lactate, or fatty acid metabolism compared with those in normal dogs. In a canine rapid-pacing model of heart failure, Recchi et al [28] showed a relatively normal myocardial substrate metabolism in the early and middle stages of heart failure, and a decrease in fatty acid oxidation in severe heart failure. In general, measurements of the level of expression of key enzymes in fatty acid oxidation support these direct measurements of energy metabolism (reviewed in Stanley et al [9]).

### Therapeutic options in the metabolic treatment of heart failure

Because heart failure can decrease cardiac energy reserve, and utilization of fatty acid oxidation is less efficient than glucose oxidation, it may be possible to improve myocardial contractile function by reducing fatty acid oxidation and increasing the flux through PDH. There are already limited clinical data to support this concept. For instance, patients with Classes II and III heart failure were infused with dichloroacetate [29,30], a compound that inhibits PDH kinase and thereby activates PDH and increases glucose oxidation. This resulted in an increase in stroke volume and ejection fraction, in addition to an improvement in cardiac efficiency. Increasing the plasma insulin concentration will also increase glucose oxidation and inhibit fatty acid oxidation. Patients with ischemic heart disease and left ventricular dysfunction were treated with an infusion of insulin and showed an improvement in their wall motion scores and left ventricular ejection fraction [31]. Thus, in the short term, left ventricular function and mechanical efficiency are improved by the acute stimulation of myocardial carbohydrate metabolism and inhibition of fatty acid oxidation. This can be achieved by increasing activity at the level of PDH.

In long-term studies, patients with New York Heart Association (NYHA) Classes II and III heart failure have been followed while receiving trimetazidine [15,32,33], a fatty acid oxidation inhibitor. Two months of treatment resulted in significant improvement in left ventricular ejection fraction at rest and in left ventricular wall motion during a dobutamine stress test as compared with placebo. Six months of treatment with trimetazidine improved diastolic function, whereas no change was seen in patients receiving placebo. A recent study by Di Napoli et al [34] also showed that, in patients with NYHA Classes II and III heart failure with ischemic dilated cardiomyopathy, chronic treatment (up to 18 months) with trimetazidine can increase ejection fraction in the patients by 26–38%. Large-scale clinical trials are still needed.

Another way of suppressing fatty acid oxidation is to inhibit CPT-1 (*Figure 2*). It has now been shown that inhibiting CPT-1 with oxfenicine can prevent ventricular remodeling and slow the progression of heart failure in dogs [35,36]. Other pharmacological agents available for long-term treatment include  $\beta$  blockers, ACE inhibitors, and angiotensin receptor antagonists. The clinical improvement in heart failure seen with these agents is associated with a switch in myocardial metabolism away from fatty acid oxidation towards more glucose uptake and carbohydrate oxidation [37–39]. The mechanism for this is unknown.

### Conclusions

Newly emerging evidence suggests that the mechanism of myocardial injury that leads to failing heart function is based on a switch in metabolic substrate preference by the heart. Improvements in heart function, in both the short and the long term, have been achieved by enhancing carbohydrate metabolism and inhibiting fatty acid metabolism. To date, the most promising results have come from increasing activity at the level of PDH in the mitochondria.

Current medical treatments for heart failure will improve heart function for a time, but act only to slow, not prevent, the progression of disease or reverse the damage to the myocardium. New treatments, through a metabolic approach, can be used to achieve further enhancement of performance in the failing heart. Much more research needs to be done in this exciting and potentially highly therapeutic area. ■

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# The place of metabolic treatment

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## Abstract

The metabolic manipulation of the myocardium is a novel method of treatment in heart failure. Several drugs shift cardiac energy metabolism from oxidation of free fatty acids to the energetically more efficient oxidation of glucose and lactate. These metabolically acting agents include trimetazidine, ranolazine, etomoxir, and perhexiline, directly modifying substrate utilization by the heart. Trimetazidine and ranolazine, partial inhibitors of fatty acid  $\beta$ -oxidation, are potent anti-ischemic drugs. It has been shown in several studies that trimetazidine improves impaired left ventricular function in patients with ischemic cardiomyopathy, elderly patients with heart failure, and diabetic patients with ischemic myocardial dysfunction. Drugs for the treatment of heart failure that alter cardiac metabolism by mechanisms unrelated to their pharmacological target include  $\beta$ -blockers and glucose–insulin–potassium.

■ *Heart Metab.* 2005;27:11–15.

**Keywords:** Metabolic treatment, trimetazidine, ranolazine, heart failure, ischemic heart disease

## Introduction

Coronary artery disease is the most common cause of heart failure. The metabolic manipulation of the myocardium is an innovative approach to the treatment of patients with heart failure, a hyperadrenergic state in which the concentrations of circulating free fatty acids (FFAs) are increased [1]. The normal heart derives approximately 60–80% of the energy it consumes from FFAs and the remainder from glucose and lactate (*Figure 1*). FFA metabolism yields more adenosine triphosphate (ATP) per gram of substrate, but requires greater oxygen consumption. In an ischemic cardiomyocyte, FFA metabolism leads to a decrease in glucose oxidation and an increase in the production of lactate and hydrogen ion, leading in turn to intracellular acidosis; under these conditions, sodium and calcium overload exacerbate myocardial dysfunction. Under conditions of energy demand in the ischemic heart, however, the utilization of glucose can increase markedly [2], although FFA metabolism still predominates.

A number of different agents have been used to manipulate energy metabolism in cardiac myocytes (*Figure 2*). In experimental models of ischemia, several drugs have been shown to possess the ability to shift cardiac energy metabolism from oxidation of FFAs to the energetically more efficient oxidation of glucose and lactate, indicating a potential use of

partial inhibitors of fatty acid oxidation for therapeutic purposes [3]. The manipulative techniques include increasing glucose oxidation and decreasing FFA metabolism by the administration of glucose–insulin solutions [4] and the use of  $\beta$ -adrenergic blocking drugs [5]. Another approach consists of the direct modification of substrate utilization by the heart. This can be achieved by inhibiting fatty acid oxidation at various levels, by activating the pyruvate dehydrogenase complex or by restoring the insulin sensitivity of the heart.

## Inhibitors of free fatty acid $\beta$ -oxidation

Trimetazidine and ranolazine (a substituted piperazine compound) act as partial inhibitors of fatty acid oxidation and stimulate glucose oxidation.

### Trimetazidine

Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride) is used as an antianginal drug. Recent evidence indicates that its metabolic effect is achieved mainly through the inhibition of long-chain 3-ketoacyl coenzyme A thiolase [6], the last enzyme involved in  $\beta$ -oxidation, leading to increased glucose oxidation and production of membrane-protective

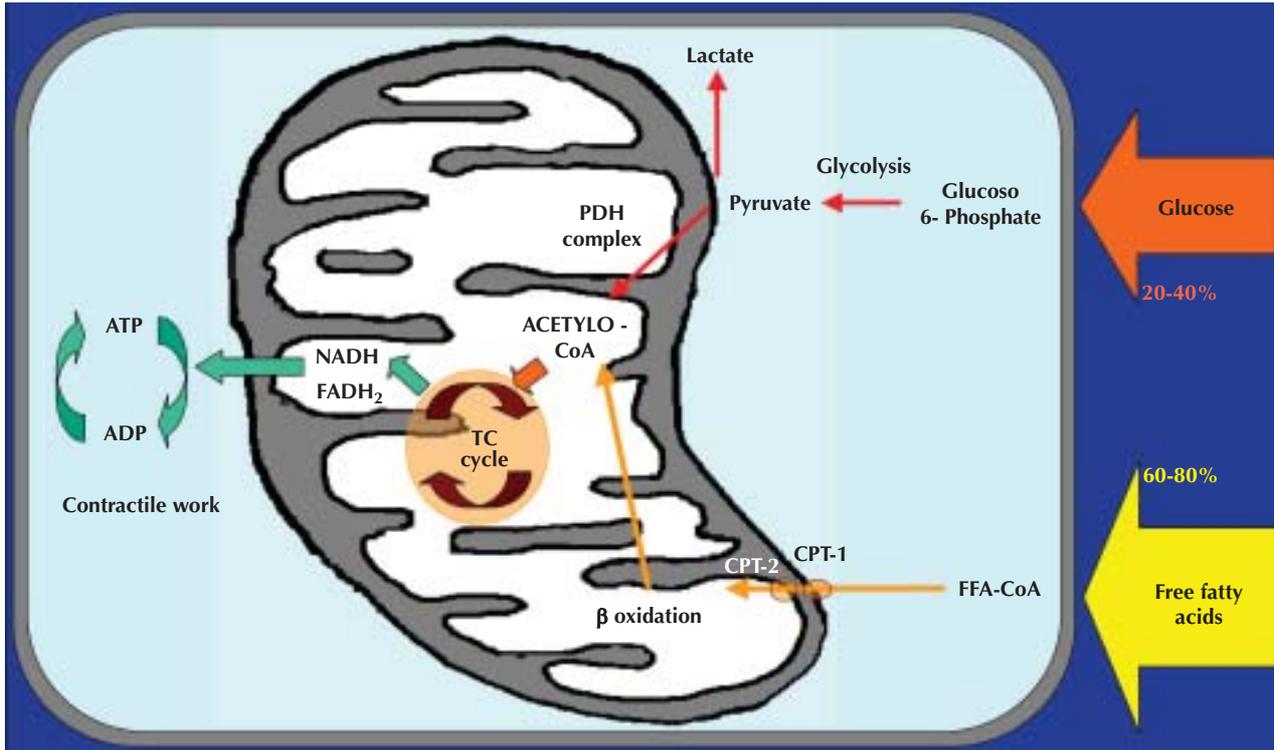


Figure 1. The metabolic pathways in cardiomyocyte. ADP, adenosine diphosphate; ATP, adenosine triphosphate; FFA, free fatty acids; CPT-1, carnitine palmitoyl transferase-1.

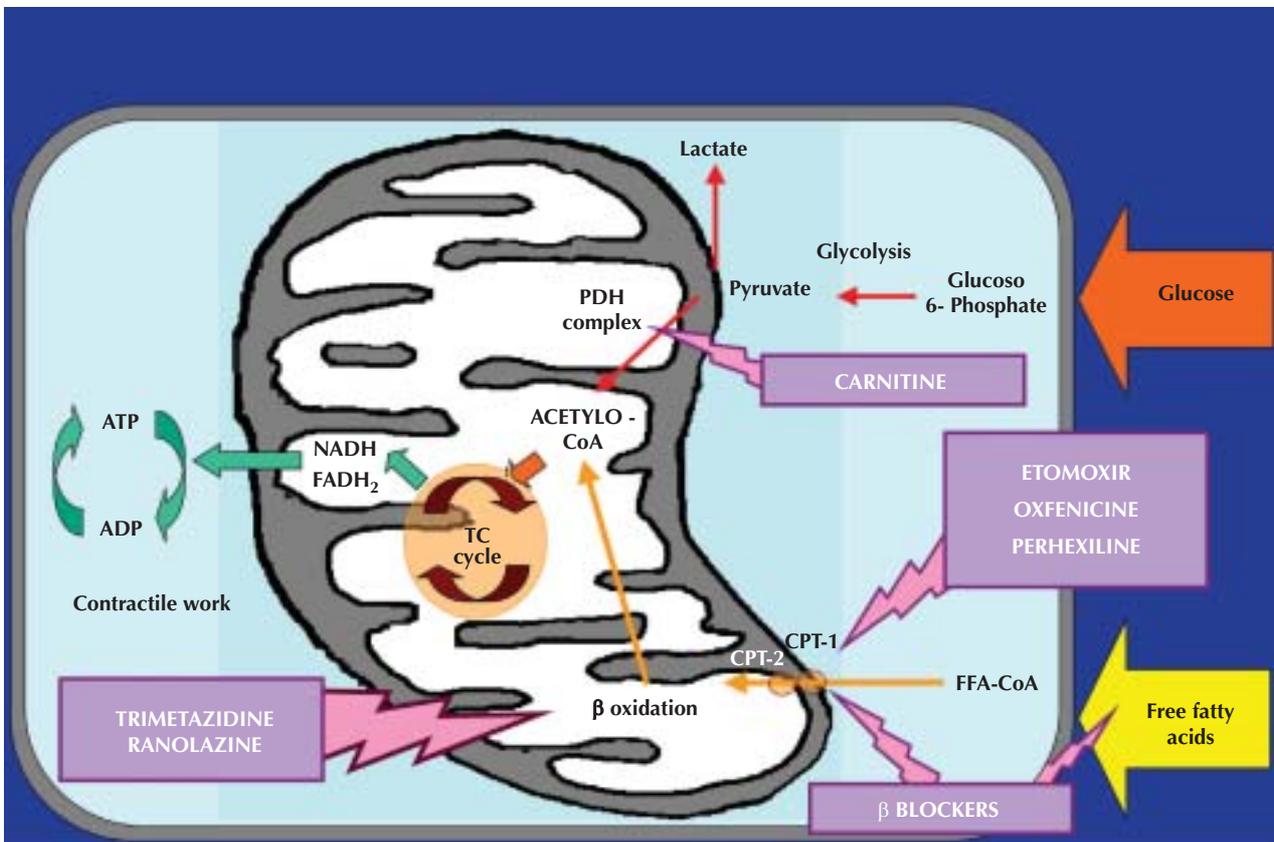


Figure 2. The modification and substrate utilization by the cardiac myocyte by different agents. ADP, adenosine diphosphate; ATP, adenosine triphosphate; CPT-1, carnitine palmitoyl transferase-1; FFA, free fatty acids.

## Main clinical article

### The place of metabolic treatment

glycolytic ATP, a potential source of energy for the sodium pump. Trimetazidine not only improves energy metabolism, but also exerts a cytoprotective action by decreasing the intracellular accumulation of sodium and calcium ions and protecting cell membranes against the accumulation of hydrogen ions.

Several studies have shown the beneficial role of trimetazidine in the treatment of patients with stable angina [7]; it improves exercise test parameters and reduces the number of anginal attacks without any hemodynamic changes. Other studies have demonstrated the usefulness of trimetazidine in heart failure. In an experimental study, long-term treatment with trimetazidine prolonged the life of cardiomyopathic Syrian hamsters by 57% [8]. The drug has also been shown to improve recovery of postischemic left ventricular dysfunction of the isolated arrested rat heart [9]. Clinical studies of patients with chronic congestive heart failure have focused on ischemic cardiomyopathy. In a double-blind, randomized, crossover study by Lu et al [10], patients received trimetazidine 20 mg three times daily, or placebo, for 15 days. Trimetazidine improved both resting and dobutamine-induced ischemic dysfunction in patients with impaired left ventricular function. Bellardinelli and Purcaro [11] demonstrated the effects of trimetazidine on the contractile function of chronically dysfunctional myocardium. They studied 38 patients

with postinfarction left ventricular dysfunction (mean ejection fraction 33%) who were allocated randomly to groups to receive either trimetazidine 20 mg three times daily or placebo, for 2 months. Low-dose dobutamine echocardiography and cardiopulmonary exercise testing were performed at study baseline and after 2 months of treatment. At 2 months, significant improvements in the at-rest and peak systolic wall thickening score index and ejection fraction were observed in the group of patients treated with trimetazidine; peak  $\text{VO}_2$  also increased significantly [11]. Due to decrease of insulin sensitivity and elevation of FFA metabolism in the diabetes (Figure 3) pharmacologic agents that inhibit fatty acid oxidation may be especially useful in diabetic patients. In a study by Fragasso et al [12], in 16 patients with diabetes and ischemic cardiomyopathy, both short- (15 days) and long-term periods of treatment with trimetazidine (60 mg daily) improved left ventricular ejection fraction, clinical symptoms, glucose metabolism, and endothelial function. Beneficial effects of trimetazidine in diabetic patients with ischemic left ventricular dysfunction were also observed in an earlier study by Rosano et al [13].

Heart failure is a major problem in the elderly population. Treatment of this group of patients can be associated with problems as a result of adverse events of commonly used drugs and difficulties in maintaining therapeutic doses. Recently, in a double-blind,

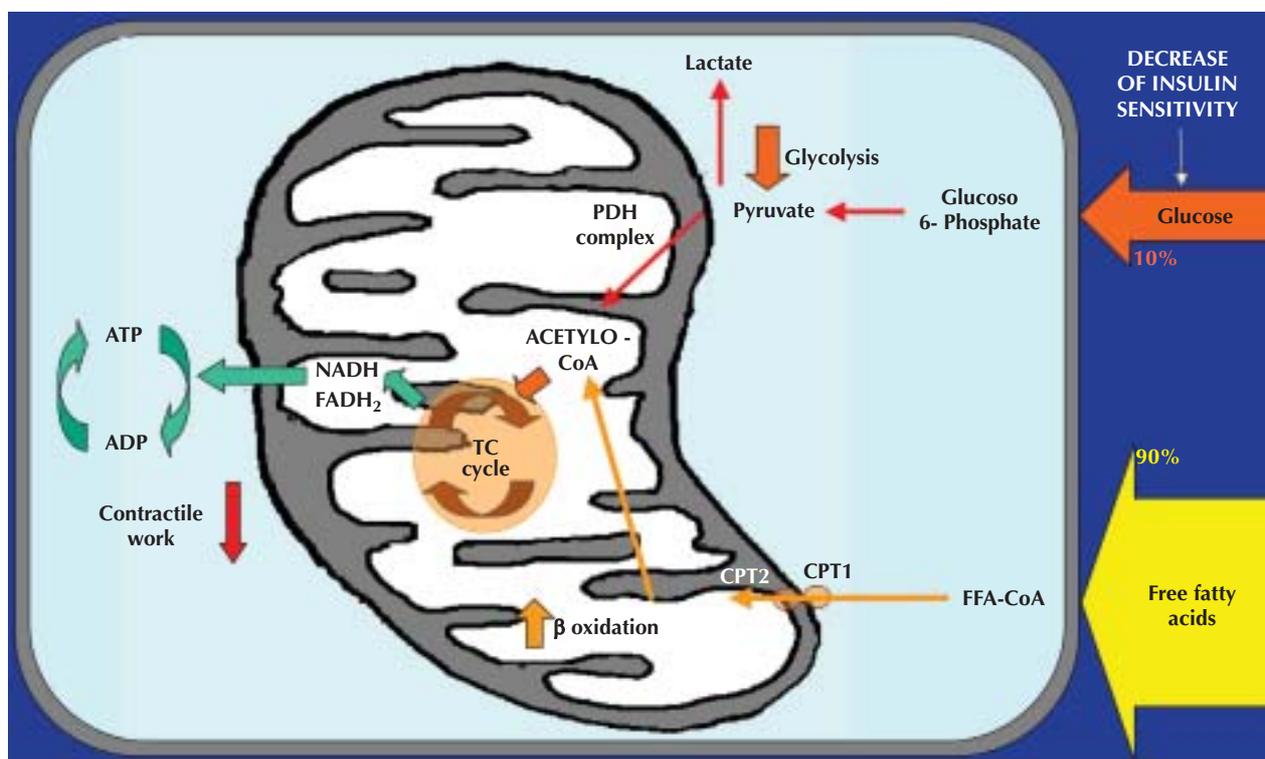


Figure 3. Changing of metabolism in diabetic heart – would you accept them? ADP, adenosine diphosphate; ATP, adenosine triphosphate; CPT-1, carnitine palmitoyl transferase-1; FFA, free fatty acids.

placebo-controlled study of 47 elderly patients (mean age 78 years) with congestive heart failure caused by ischemic heart disease (impaired left ventricular function: ejection fraction <50%), Vitale et al [14] demonstrated the effectiveness of trimetazidine in improving both left ventricular function and quality of life. After 6 months, the trimetazidine-treated group demonstrated a significant improvement in ejection fraction (from 27% to 34%), a reduction in left ventricular diameters, and better diastolic function. Trimetazidine also reduced the clinical symptoms of angina and heart failure.

A very recent study by Napoli et al [15] revealed that 18 months of treatment with trimetazidine improved left ventricular function and the remodeling process in patients with ischemic cardiomyopathy. It also limited the inflammatory response measured as the C reactive protein concentration.

## Ranolazine

Ranolazine [(+/-)-N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine acetamide] is another piperazine derivative. It decreases FFA  $\beta$ -oxidation, promotes glucose oxidation, and acts indirectly by activation of pyruvate dehydrogenase [16]. The anti-ischemic effect of ranolazine has been demonstrated in experimental and clinical studies. In the Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) study [17], a therapeutic effect of monotherapy with ranolazine (500 mg twice daily, 1000 mg twice daily, or 1500 mg twice daily) was demonstrated in 191 patients. In a double-blind randomized trial (Combination Assessment of Ranolazine in Stable Angina [CARISA]), ranolazine 750 mg or 1000 mg given twice daily, added to other antianginal drugs, prolonged exercise duration and reduced clinical symptoms. Small dose-related increases in QTc (<10 ms compared with placebo, on average) were not associated with persistent prolongation of the QT interval in any patient, or with the occurrence of torsade de pointes; however, five patients taking ranolazine 1000 mg twice daily experienced syncope for unknown reasons [18] – a finding that prompted discussion as to the safety of ranolazine. It was postulated that the syncopes may have been caused by postural hypotension in patients treated actively with other drugs such as diltiazem (four of the five patients) and angiotensin-converting enzyme inhibitors (all five patients). It remains an important issue whether high doses of ranolazine would be well tolerated when given to patients treated with maximal doses of other antianginal medications. Since the CARISA trial has been completed, only small studies of ranolazine have been performed, and less is

known about its effectiveness in patients with heart failure than is known about trimetazidine.

## Carnitine palmitoyl transferase-1 inhibitors

Carnitine palmitoyl transferase-1 (CPT-1) inhibitors inhibit long-chain fatty acid oxidation by inhibiting the entry of long-chain fatty acids into the mitochondria at the level of CPT-1. There is major interest concerning the value of CPT-1 in pharmacological intervention in postischemic, reperfused heart.

## Etomoxir

Etomoxir (ethyl-2-tetradecyl glycidate) has been developed for treating non-insulin dependent diabetes mellitus. There has been only one open-label, non-controlled pilot study performed to examine the potential benefits of etomoxir in heart failure. The drug was given to 15 patients with chronic congestive heart failure, in a dose of 80 mg daily. After 3 months, improvements in left ventricular function and clinical symptoms were observed [19]. However, the clinical value of this drug is limited by a narrow therapeutic window resulting from its potential to cause phospholipidosis [20].

## Perhexiline

Perhexiline, a calcium-channel blocker, was introduced as an effective antianginal agent. It acts by switching myocardial substrate utilization from FFA to carbohydrates through inhibition of CPT-1 and CPT-2, resulting in increased glucose and lactate oxidation [21]. The use of perhexiline is limited because of its side effects, such as hepatotoxicity and peripheral neuropathy.

## Drugs with additional metabolic action

Various drugs used in cardiology appear to treat cardiac dysfunction by mechanisms that are not related to their primary pharmacological target. The list of such drugs with additional metabolic activity includes  $\beta$ -blockers and glucose-insulin-potassium.

$\beta$ -Blockers are active antianginal agents. For some, such as bisoprolol, metoprolol and carvedilol, an improvement in left ventricular function in heart failure has been established in major clinical trials. It is postulated that this improved function observed with  $\beta$ -blockers in heart failure could be, in part, a result of reduced CPT-1 activity and decreased FFA oxidation [22].

The findings of a meta-analysis by Fath-Ordoubadi and Beatt [23] suggested that infusion of glucose–insulin–potassium improves outcome after myocardial infarction. However, the most recent studies have failed to demonstrate a significant improvement in mortality in response to this treatment [24].

Another metabolic agent, carnitine, stimulates the oxidation of pyruvate. In a study of 80 patients with dilated cardiomyopathy and heart failure, administration of L-carnitine 2 g daily for 3 years was associated with reduced mortality [25].

## Conclusion

Several studies of agents that decrease FFA concentrations or inhibit myocardial oxidation of FFAs have demonstrated that metabolic manipulation is an important new approach to the treatment of heart failure. ■

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# Glucose–insulin–potassium infusion enhances myocardial wall motion in patients with chronic ischemic heart failure

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### Abstract

A growing body of evidence suggests that administration of glucose–insulin–potassium (GIK) improves segmental myocardial function in patients with (chronic) left ventricular dysfunction. We performed low-dose dobutamine (LDD) echocardiography and echocardiography during infusion of GIK in 75 patients with chronic ischemic cardiomyopathy and observed a similar improvement in segmental wall motion during both interventions. Wall motion score index decreased by  $0.25 \pm 0.16$  (from  $0.87 \pm 0.35$  to  $0.62 \pm 0.35$   $P < 0.0001$ ) during LDD and by  $0.23 \pm 0.17$  (from  $0.86 \pm 0.34$  to  $0.63 \pm 0.35$ ;  $P < 0.0001$ ) during the infusion of GIK. The possible mechanisms and literature are reviewed.

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**Keywords:** Chronic ischemic cardiomyopathy, glucose–insulin–potassium, low-dose dobutamine, segmental wall motion, echocardiography

### Introduction

Hyperinsulinemic euglycemic clamping is a procedure that is frequently used in combination with [<sup>18</sup>F]2-fluoro-2-deoxyglucose (FDG) positron emission tomography scanning to determine viability in patients with heart failure caused by ischemic heart disease. The procedure was first described by DeFronzo et al [1] as a method to determine insulin secretion and resistance, but was adapted to enhance the uptake of glucose and FDG in myocardial tissue. The method closely resembles the metabolic modulation by infusion of glucose–insulin–potassium (GIK) that has been used in several studies in patients with acute myocardial infarction. Fath-Ordoubadi and Beatt [2] performed a meta-analysis of studies using GIK before the era of thrombolysis or percutaneous coronary intervention. Other trials using GIK in myocardial infarction were the Diabetes Mellitus and Insulin Glucose Infusion in Acute Myocardial Infarc-

tion (DIGAMI) study [3] and the pilot Estudios Cardiológicos LatinoAmerica (ECLA) trial [4]. The meta-analysis and both the DIGAMI study and the ECLA trial showed a benefit (reduction in mortality) from GIK in patients with myocardial infarction. However, the mechanism responsible for this reduction in mortality is unclear.

Several authors have observed that administration of insulin to the (ischemic) heart increases systolic function and results in an increased relaxation [5–9]. Dobutamine, a synthetic catecholamine, increases myocardial systolic function and is frequently used in dysfunctional myocardium in ischemic heart disease to determine contractile reserve, which is a predictor of recovery of function after revascularization [10]. Because insulin enhances myocardial systolic function in dysfunctional myocardium after ischemia, it may be possible that it enhances segmental myocardial wall motion to an extent similar to that achieved with the infusion of low-dose dobutamine (LDD).

## Patients and methods

In total, 75 patients, referred to either the VU University Medical Center or Princess Alexandra Hospital for evaluation of viability, were included in the study. Patients were eligible for inclusion if they had ischemic heart disease with left ventricular dysfunction. Exclusion criteria were left bundle branch block, pacemaker rhythm, presence of serious ventricular tachyarrhythmias, atrial fibrillation, and the presence of a poor acoustic window. Patients gave informed consent before inclusion in the study and the Ethics Committees of both hospitals approved the study. Patients underwent standard LDD echocardiography and GIK echocardiography on two separate occasions.

## Echocardiography

Standard echocardiograms were obtained with standard parasternal long-axis and short-axis views, in addition to apical four-, three- and two-chamber views. Echocardiograms were obtained at baseline and after LDD and GIK infusions.

**Dobutamine procedure** Patients underwent LDD echocardiography according to a standardized procedure, starting with 5  $\mu\text{g}/\text{kg}$  per min for 5 min, and then increasing to 10  $\mu\text{g}/\text{kg}$  per min. Further evaluation for ischemia followed the standard of the Princess Alexandra Hospital.

**Glucose–insulin–potassium procedure** Patients received an infusion of insulin 100 mU/kg per h plus glucose 20% with KCl 40 mmol/L at a target rate of 1.8 mL/kg per h (6 mg/kg per min; rate adjusted for instantaneously determined blood glucose concentrations) during a period of 1 h (VU University Medical Center) or 30 mL/h of a solution of 10% glucose, 80 units of insulin and potassium 40 mmol/L for 4 h (Princess Alexandra Hospital; for a 75 kg individual: insulin 32 mU/kg per h and glucose 0.67 mg/kg per min).

## Echocardiographic analysis

Echocardiograms were judged by experienced observers according to a 13-segment (6 basal, 6 mid, 1 apical) model [11] on a 3-point scale: 0 = normokinesia, 1 = hypokinesia, 2 = a/dyskinesia. For each dyssynergic segment, the response to LDD or GIK was determined. Wall motion score (WMS) was calculated as the sum score of visualised segments in each patient; a higher score implies a worse CV function. Wall motion score index (WMSI) was calculated as WMS divided by the number of

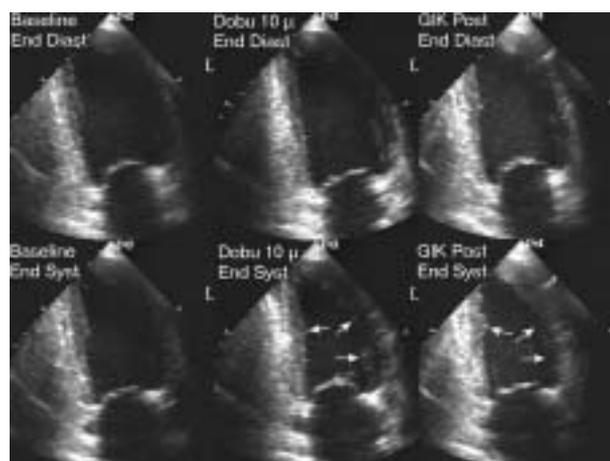
segments visualized and is less dependent on acoustic window.

Comparisons were made between baseline and each intervention, and between the results of the interventions. Total agreement and Cohen's kappa coefficient [12] were calculated.

## Results

A sample image of the response to dobutamine and insulin is shown in *Figure 1*. In all, 973 segments were suitable for analysis. *Figure 2a* shows the improvement (decrease) in WMS achieved with each intervention:  $3.1 \pm 2.1$  (from  $11.4 \pm 4.4$  to  $8.0 \pm 4.5$ ;  $P < 0.0001$ ) during LDD and  $3.1 \pm 2.2$  (from  $11.4 \pm 4.4$  to  $8.2 \pm 4.3$ ;  $P < 0.0001$ ) during GIK. Likewise, WMSI decreased, by  $0.25 \pm 0.16$  (from  $0.87 \pm 0.35$  to  $0.62 \pm 0.35$ ;  $P < 0.0001$ ) during LDD and by  $0.23 \pm 0.17$  (from  $0.86 \pm 0.34$  to  $0.63 \pm 0.35$ ;  $P < 0.0001$ ) during GIK. The number of segments exhibiting an improvement in response to LDD and GIK was also significant (*Figure 2b*): with LDD, at baseline  $7.2 \pm 2.6$  segments were dysfunctional and improvement was found in  $3.0 \pm 1.9$ ; in concert, with GIK, at baseline  $7.4 \pm 2.6$  segments were dysfunctional and there was improvement in  $2.8 \pm 2.1$  ( $P = \text{NS}$  for the number of improving segments).

A total of 593 segments were dyssynergic at baseline with both interventions. Of these dyssynergic segments, 185 showed increased wall motion with both interventions, and 307 did not improve with respect to wall motion. In 47 segments (8.4%), the findings from LDD echocardiography and GIK



*Figure 1. Example of echocardiographic end-diastolic (End Diast; top row) and end-systolic (End Syst; bottom row) apical two-chamber views at baseline (left), during low-dose (10  $\mu\text{g}/\text{kg}$  per min) dobutamine (Dobu; middle) and during infusion of glucose–insulin–potassium (GIK; right). Improvement is seen (arrows) in the distal inferior wall and in both the distal and mid anterior segments, during low-dose dobutamine and during GIK infusion.*

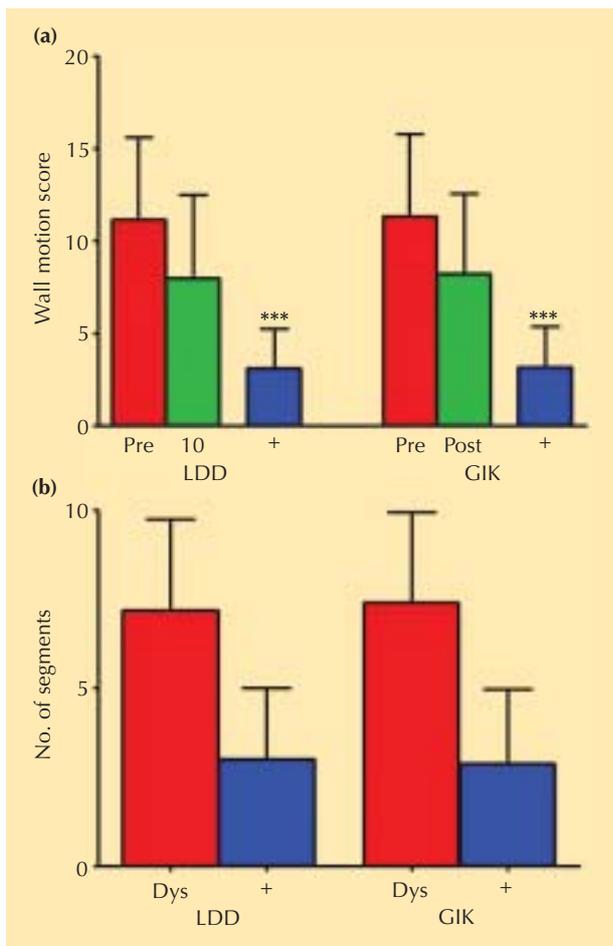


Figure 2. (a) Improvement (decrease) in wall motion score during the intervention with low-dose dobutamine (LDD) and with glucose–insulin–potassium (GIK). Pre, before; 10, LDD 10  $\mu\text{g}/\text{kg}$  per min; +, improvement. (b) Number of dysfunctional segments (Dys) and the number of segments improving (+) during the interventions with LDD and with GIK.

echocardiography were not in agreement: in 29 segments, wall motion increased with GIK and not with LDD, whereas the opposite was observed in 18 segments. Most of these segments (31) were hypokinetic at baseline in the case of both GIK and LDD, whereas 12 were a/dyskinetic by both techniques. This resulted in an agreement between the two interventions of 0.91, and a kappa value of 0.82.

## Discussion

This study of patients with chronic left ventricular dysfunction and coronary artery disease has shown that infusion of GIK leads to increased segmental myocardial wall motion (decreased WMS and WMSI). It provided an opportunity to study contractile reserve by means of metabolic modulation similar to that which occurs in myocardial infarction. There

was a high agreement with the contractile reserve determined by LDD infusion.

Other authors also have observed an effect of GIK on myocardial wall motion [13–16]. In a study of patients from a category similar to that in our present study, Cottin et al [13] observed improvement in systolic myocardial function (determined by echocardiography) after 20 min of infusion of GIK at a rate of insulin 300 mU/kg per h. Twenty and forty minutes after discontinuation of the infusion, improvement in wall motion was still present. No comparison was made with LDD. Also using echocardiography, Yetkin et al observed an improvement in wall motion in patients with chronic left ventricular dysfunction, in patients with recent myocardial infarction [14], and in patients with chronic coronary artery disease and left ventricular dysfunction [15], using insulin 100  $\mu\text{U}/\text{kg}$  per h. Alan et al [16] observed a significant increase in ejection fraction, prolongation of diastolic filling period, decrease in wedge pressure and decrease in defect score by resting technetium-99m ( $^{99\text{m}}\text{Tc}$ )-sestamibi scintigraphy after administration of GIK at a rate of insulin 300 mU/kg per h over 24 h.

In the studies using GIK to enhance myocardial wall motion, many different procedures have been used, varying from that of the DIGAMI study (also used in the Princess Alexandra Hospital patients in this study: for a 75 kg man, insulin 32 mU/kg per h) to a high-dose insulin regimen (300 mU/kg per h) for shorter (20 min) or longer (24 h) periods. In the studies under discussion here, no changes in heart rate or blood pressure were observed, which may be of advantage in patients who have suffered myocardial infarction. In canine papillary muscle preparations, incubation with insulin led to an increased contractile force that counteracted the addition of propranolol – an effect that could be reproduced by coronary injection of insulin [6]. Future studies will be needed to demonstrate whether echocardiographic assessment of the response to short-duration infusion of high-dose GIK can predict recovery of function. The benefit of GIK in patients with myocardial infarction remains to be demonstrated in one or more large, prospective trials, especially because treatment of myocardial infarction has been changed dramatically by the introduction of thrombolysis and primary percutaneous intervention, and a number of these studies were performed in the prethrombolytic era.

## Mechanism of action

Infusion of GIK results in a reduction in circulating free fatty acids [17–22], often to less than the myocardial uptake threshold concentration, which has been determined to be between 100 and 200  $\mu\text{mol}/\text{L}$  [17]. Myocardial uptake of free fatty

acids is therefore minimized [17–22], uptake of glucose and lactate increases [17–22], and the myocardial respiratory quotient changes towards 1.0 [18,19] (in the fasting state, when free fatty acids are the predominant fuel, the myocardial respiratory quotient is around 0.7). In most studies, a change in oxygen consumption was not observed [18,19,21], and only one study has related oxygen consumption to a clinical determinant of oxygen consumption (pressure–volume–area [PVA] loops) and observed a reduced “normalized” oxygen consumption, especially in the unloaded heart [23].

Altered availability of substrate is exploited in anaerobic glycolysis, providing ATP to improve intracellular calcium homeostasis [24,25]. Although a direct effect of insulin on calcium metabolism in human myocardium has not yet been established, circumstantial evidence suggests that there will be an effect, as insulin-like growth factor seems to improve contractile function in cardiomyocytes isolated from failing human hearts [26,27]. Furthermore, the transition from free fatty acid to glucose metabolism will result in a more efficient use of oxygen, providing more ATP per molecule of oxygen used [28].

In this study, the concentration of glucose was kept greater than 4.0 mmol/L (preferably more than 5.0 mmol/L), and thus a catecholamine-induced increase in myocardial wall motion as a result of hypoglycemia was unlikely to be present. Furthermore, catecholamine concentrations measured in patients at the Princess Alexandra Hospital did not exhibit such an increase (data not shown).

The mechanism of action of LDD on myocardium with decreased wall motion in coronary artery disease is believed to be partly attributable to the increase in myocardial blood flow, which provides more oxygen and energy supply to the middle and outer layer of the myocardium and enables them to increase contractility. After the infusion of GIK,  $^{99m}\text{Tc}$ -sestamibi or  $^{99m}\text{Tc}$ -tetrofosmin scintigraphy show decreased defect scores, suggesting increased myocardial perfusion [6,29]. This was confirmed by a study in which insulin was injected directly into the coronary arteries in patients with coronary artery disease, with a significant 10% increase in myocardial blood flow and a transition from free fatty acid metabolism to glucose metabolism without an increase in myocardial oxygen consumption [30]. In another study, myocardial blood flow increased and oxygen extraction decreased, together with a decrease in coronary vascular resistance [18].

## Conclusion

Infusion of GIK enhances segmental wall motion and can be used to detect myocardial contractile reserve

in patients with chronic coronary artery disease, with the potential advantage over low-dose dobutamine echocardiography that it does not cause an increase in blood pressure or heart rate during the infusion. ■

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# Evidence of efficacy of metabolic agents

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### Abstract

Abnormalities of cardiac energy metabolism may contribute to progressive worsening of left ventricular function. In failing hearts a reduced ATP content, dysfunctional mitochondria, increased fatty acid oxidation, and decreased carbohydrate oxidation have been found. Therefore, metabolic agents, able to shift substrate utilization from fatty acid to glucose, may be useful. Trimetazidine improves ventricular function in patients with coronary artery disease and contractile dysfunction, preventing or delaying regional myocardial dysfunction during ischemia, and improving the contractile response to inotropic stimulation. Several clinical trials have confirmed the efficacy of trimetazidine in various subgroups of heart failure patients.

■ *Heart Metab.* 2005;27:21–23.

**Keywords:** Efficacy, free fatty acids, left ventricular contractile function, metabolic agents, trimetazidine

### Cardiac energy metabolism in heart failure

Abnormalities of cardiac energy metabolism may contribute to the progressive worsening of left ventricular contractile function. Many investigators have reported a reduced ATP content and dysfunctional mitochondria, increased fatty acid oxidation, and decreased carbohydrate oxidation in failing hearts as compared with normal hearts [1–3]. Reduced rates of carbohydrate oxidation and increased rates of fatty acid oxidation contribute to the progression of myocardial dysfunction in heart failure: the contractile performance of the heart is improved when the heart uses more glucose and lactate rather than fatty acids [4,5]. Furthermore, increased plasma concentrations of free fatty acids can be harmful to the ischemic myocardium, especially in the presence of increased catecholamine concentrations [6]. The rate of fatty acid oxidation is regulated by the plasma concentration of free fatty acids, by the activity of carnitine palmitoyl transferase-1 and by a series of enzymes that catalyze the several steps of fatty acid oxidation [7]. In individuals with failing hearts, the utilization of noncarbohydrate substrates for energy production is increased. In fact, blood concentrations of ketone bodies [8], in addition to fat oxidation during exercise [9] are increased in these patients. Insulin resistance

has been found in this condition [10], and the consequent impaired suppression of lipolysis could contribute to the development of ketosis.

Many different approaches have been proposed to manipulate energy metabolism in the ischemic heart [11], including increasing glucose oxidation and decreasing fatty acid metabolism by glucose–insulin solutions or nicotinic acid, by  $\beta$ -adrenergic blockade, or by drugs that inhibit key enzymes in the fatty acid oxidation chain. Agents such as trimetazidine shift substrate utilization from fatty acid to glucose, by inhibiting a key enzyme in the  $\beta$ -oxidation chain, 3-ketoacyl coenzyme A thiolase (“3-KAT”).

Trimetazidine improves ventricular function in patients with coronary artery disease and various degrees of contractile dysfunction, preventing or delaying regional myocardial dysfunction during ischemia, and improving the contractile response to inotropic stimulation.

### Metabolic approach to heart failure

The first evidence of the efficacy of trimetazidine in heart failure was reported by Brottier et al in 1990 [12]. In patients with ischemic cardiomyopathy and severely depressed ventricular ejection fraction, these investigators completed a double-blind placebo-con-

trolled study assessing the effect of trimetazidine 60 mg in addition to standard treatment. After 6 months of treatment, patients receiving trimetazidine were more free from angina, dyspnea was improved, the ejection fraction increased, and cardiac volume decreased.

## Ischemic cardiomyopathy

In 1998, Lu et al [13] demonstrated that trimetazidine can delay the onset of ischemic myocardial dysfunction and reduce its severity. In a double-blind, randomized placebo-controlled study, they applied dobutamine testing in patients with coronary artery disease to demonstrate that trimetazidine improved resting left ventricular function and reduced the severity of dobutamine-induced dysfunction.

Belardinelli and Purcaro [14], in a more recent study, showed that trimetazidine improves the mechanical efficiency of chronically dysfunctional myocardium. Low-dose dobutamine echocardiographic testing was performed in a double-blind, randomized placebo-controlled fashion in 38 patients with ischemic cardiomyopathy treated with trimetazidine for 2 months. Trimetazidine improved the contractile response of chronically dysfunctional myocardium to dobutamine without associated hemodynamic changes. This effect was associated with an improvement of left ventricular function and peak oxygen consumption ( $VO_2$ ).

The importance of fatty acid inhibition in the improvement of left ventricular function has been confirmed recently by Sabbah's group [15,16], who found that ranolazine, a drug with a mechanism of action similar to that of trimetazidine, also increased the ejection fraction without increasing myocardial oxygen demand in a dog model of chronic ischemia. The absence of any hemodynamic effects of either ranolazine or trimetazidine confirms that these drugs have no direct inotropic effect and act primarily by optimizing cardiac metabolism.

## Diabetes and the metabolic approach

Fragasso et al [17] have reported findings similar to the above in patients with diabetes and postischemic cardiomyopathy: trimetazidine consistently improved patients' tolerance to exercise, and their left ventricular function. In addition, for the first time, the beneficial effects of trimetazidine have been associated with improved endothelial function. These results support the hypothesis that shifting energy substrate preference from fatty acid toward glucose utilization is an effective treatment in patients with diabetes and postischemic cardiomyopathy.

Rosano et al [18] confirmed the beneficial effects of trimetazidine in diabetes: the addition of trimetazidine to standard treatment in 32 patients with type 2 diabetes mellitus and ischemic cardiomyopathy was associated with a significant reduction in left ventricular diameter and volume index. An improvement in ejection fraction and a significant decrease in wall motion score index were also reported.

## Metabolic treatment in elderly patients

Vitale et al [19] confirmed the beneficial effects of trimetazidine on left ventricular function in elderly patients with ischemic heart disease and reduced left ventricular function. Forty-seven elderly patients were allocated randomly to groups to receive, in addition to standard treatment, either trimetazidine or placebo, and were evaluated by echocardiography at baseline and after 6 months. The adjunct of trimetazidine to standard treatment prevented or limited reverse remodeling of chronically dysfunctional myocardium, attenuated cardiac symptoms, and improved the quality of life in these elderly patients with coronary artery disease.

## Anti-inflammatory effect

The cardioprotective action of trimetazidine has recently been associated with a possible anti-inflammatory effect in patients with ischemic dilated cardiomyopathy [20]. Sixty-one patients were randomly assigned to receive trimetazidine in addition to their conventional treatment for 18 months. Trimetazidine improved the patients' functional class, increased the ejection fraction, with a significant effect on ventricular remodeling, and limited the inflammatory response.

## Metabolic treatment in nonischemic cardiomyopathy

The findings of several studies suggest that an effect on cellular lipid metabolism may contribute to the cytoprotective properties of trimetazidine. Sentex et al [21] demonstrated that a significant increase in membrane phospholipid synthesis was a major effect of the administration of trimetazidine. This beneficial effect on membrane homeostasis induced a significant increase in the incorporation of long-chain polyunsaturated fatty acids into membrane structures.

More recently, this effect on lipid metabolism was reported to occur *in vitro* in addition to *in vivo*. Tabbi-Annenni et al [22] tested the hypothesis that, through the acceleration of phospholipid turnover, treatment with

trimetazidine would result in a delayed development of heart failure in the rat. In that species, chronic pressure overload secondary to aortic banding results in physiological and morphological signs of heart failure, including acceleration of breathing, hydrothorax and ascites, liver congestion, renal hypotrophy, and possible renal failure. In this model of heart failure, trimetazidine treatment results in a significant decrease in cardiac hypertrophy and an increase in plasma concentrations of brain natriuretic peptide. The morphological alterations associated with heart failure were also less severe in the trimetazidine-treated rats. In addition,  $\beta$ -adrenergic receptor density was also significantly limited by the trimetazidine treatment during the progression from hypertrophy to failure.

## Conclusion

Agents, such as trimetazidine, that decrease free fatty acid concentrations or inhibit myocardial oxidation of free fatty acids improve the contractile performance of failing hearts and offer a promising alternative to the clinical management of heart failure. ■

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# Vastarel MR: an innovative metabolic approach to ischemic heart failure

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## Abstract

Heart failure can be regarded as the final outcome of many cardiovascular disorders, among which cardiomyopathies related to ischemia, hypertension and valvular disorders are predominant. Current medical therapy for patients with heart failure is mainly based on conventional drugs such as angiotensin-converting enzyme (ACE) inhibitors,  $\beta$ -blockers, and aldosterone inhibitors. New treatments targeting other pathological mechanisms need to be given more consideration. Vastarel MR (modified release), the first twice-daily 3-ketoacyl coenzyme A (3-KAT) thiolase inhibitor, is a well known metabolically active agent that is widely used in the treatment of stable angina. This review discusses new evidence supporting cardioprotective action of Vastarel MR in patients with ischemic cardiomyopathy. Vastarel MR has been shown to improve New York Heart Association functional class (NYHA) and left ventricular systolic function in patients with ischemic cardiomyopathy.

■ *Heart Metab.* 2005;27:24–26.

**Keywords:** Ischemic cardiomyopathy, left ventricular systolic function, trimetazidine

## Introduction

Heart failure can be regarded as the final outcome of many cardiovascular disorders, among which cardiomyopathies related to ischemia, hypertension and valvular disorders are predominant [1].

Although substantial progress has been made over the past years in the treatment of heart failure, the quality of life and the prognosis of heart failure patients remains very poor. Current medical therapy for patients with heart failure is mainly based on conventional drugs such as angiotensin-converting enzyme (ACE) inhibitors,  $\beta$ -blockers, and aldosterone inhibitors. However new treatments targeting other pathological mechanisms need to be given more consideration.

Since metabolism and function in the heart are closely interdependent, energy substrate metabolism is a logical target when seeking to improve the function of the failing heart [2]. In heart failure, myocardial metabolism shifts toward increased oxidation of free fatty acids, which is energy-consuming compared with glucose oxidation. The metabolic

agent trimetazidine (Vastarel MR) is able to restore and optimize cardiac energy metabolism in myocardial cells by making metabolism revert from fatty acid oxidation to glucose oxidation.

Trimetazidine is a 3-ketoacyl coenzyme A (CoA) thiolase (3-KAT) inhibitor which following twice-daily administration reduces fatty acid  $\beta$ -oxidation via selective inhibition of mitochondrial long chain 3-ketoacyl coenzyme A thiolase (*Figure 1*). This results in a shift towards glucose oxidation and better use of the energy supply, thus reducing ischemia-induced metabolic damage.

This innovative metabolic approach has proven effective in relieving symptoms and improving the exercise capacity of patients with angina pectoris. Furthermore, the metabolic mode of action of Vastarel MR, added to standard therapy, enhances left ventricular function in patients with ischemic cardiomyopathy. This has been confirmed by several studies using Vastarel MR in patients with left ventricular dysfunction and ischemic cardiomyopathy [4–9].

# Focus on Vastarel MR

## Vastarel MR in ischemic heart failure

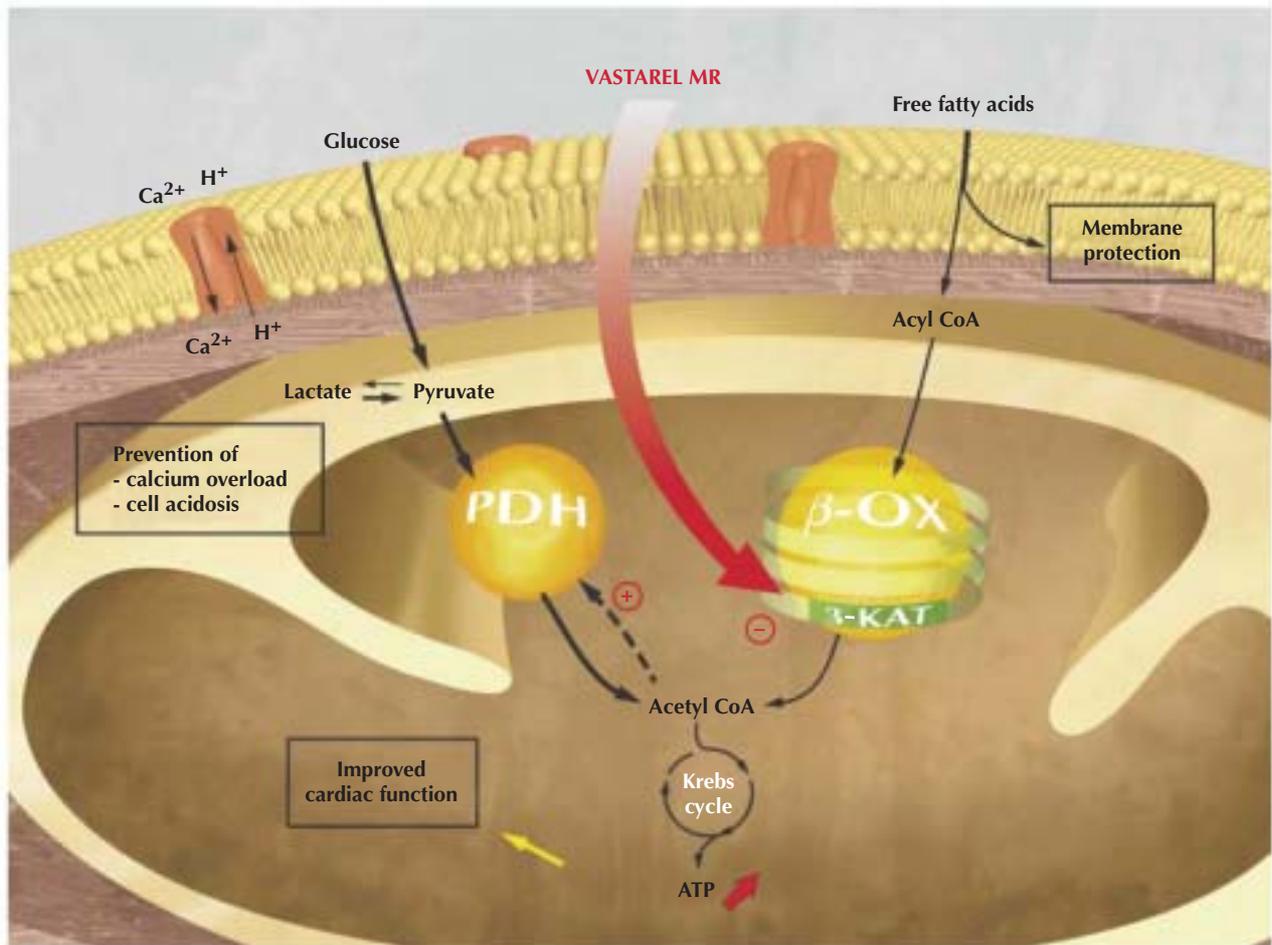


Figure 1. Trimetazidine (Vastarel MR), the first twice-daily 3-ketoacyl coenzyme A (CoA) thiolase (3-KAT) inhibitor, optimizes cardiac metabolism.  $\beta$ -ox,  $\beta$ -oxidation; PDH, pyruvate dehydrogenase.

### Trimetazidine provides major anti-ischemic efficacy and improves left ventricular function in patients with ischemic cardiomyopathy

In a recent study, Vitale et al [10] assessed the effect of Vastarel on cardiac function in elderly patients with left ventricular dysfunction after 6 months of treatment. The results showed that Vastarel resulted in a significant reduction in episodes of anginal attacks ( $P < 0.01$ ) and the consumption of nitroglycerin ( $P < 0.01$ ) (Figure 2), while simultaneously improving myocardial contractile function.

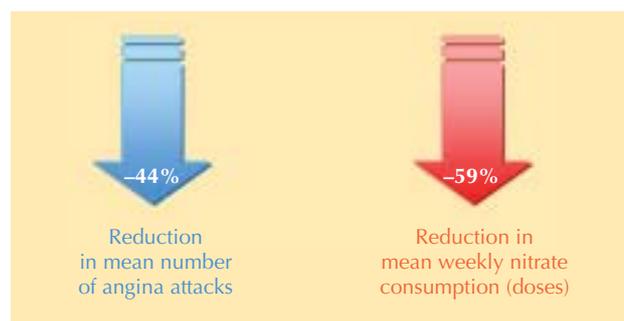


Figure 2. Effective relief of symptoms with trimetazidine (Vastarel) in elderly patients with left ventricular dysfunction.

### Trimetazidine, added to standard medical therapy, provides long-term benefits in patients with left ventricular dysfunction and ischemic cardiomyopathy

More recently, Di Napoli et al [11] have shown that long-term treatment with Vastarel provides clear

clinical benefits in patients with left ventricular dysfunction and ischemic cardiomyopathy. Sixty-one patients were allocated randomly to groups either to receive Vastarel in addition to their conventional treatment or to continue their usual therapy for 18 months. They were evaluated at baseline and at 6, 12, and 18 months. In patients in

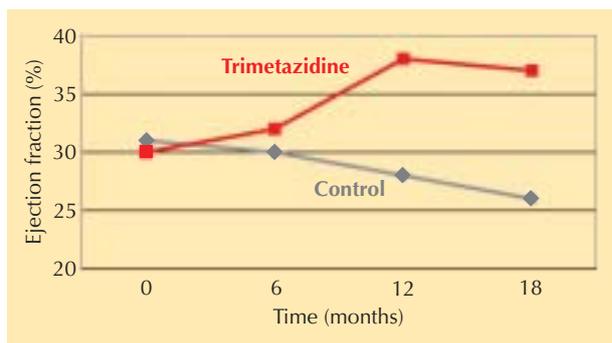


Figure 3. Improvement in left ventricular contractile function in response to long-term treatment with trimetazidine (Vastarel) in patients with dilated ischemic cardiomyopathy.

the Vastarel group, an increase in left ventricular ejection fraction (LVEF) was reported, starting at 6 months and maintained after 12 and 18 months of treatment (from 30% at baseline, 32% at 6 months, 38% at 12 months, and 37% at 18 months). In contrast, LVEF deteriorated in the control group during the same period (from 31% at baseline to 30%, 28%, and 26%, respectively) (Figure 3).

The increase in LVEF in the Vastarel group was associated with a significant reduction in the left ventricular volumes. Also, a significant improvement in functional status (assessed by the New York Heart Association [NYHA] functional class) was found in most patients receiving Vastarel as an adjunct to their usual treatment ( $P < 0.001$ ), at the 12 and 18 month visits, compared with baseline.

The study by Di Napoli et al was also the first to assess the potential anti-inflammatory effects of Vastarel through measurement of C-reactive protein levels (CRP). Their findings showed that CRP levels in the Vastarel group remained stable over the 18-month treatment, whereas a progressive and significant increase in CRP levels for the same period ( $P < 0.001$ ) was noted in the control group. These new data suggest that Vastarel may limit the inflammatory process.

## Conclusion

Modified-release trimetazidine (Vastarel MR), the first 3-KAT inhibitor which, under ischemic conditions, shifts energy production from fatty acids to glucose oxidation, benefits a wide range of coronary patients, from stable angina to ischemic cardiomyopathy. Increasing evidence supports the importance of a

metabolic treatment such as Vastarel MR, in optimizing cardiac metabolism and improving the working efficiency of the failing heart. This novel approach to the management of heart failure suggests that metabolic therapy added to conventional treatment, is an important step towards achieving “optimal treatment” and better prognosis in these severe coronary patients. ■

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# An elderly lady with angina and heart failure – successful response to trimetazidine

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### Abstract

An elderly lady with angina and left ventricular dysfunction remained symptomatic on conventional medical therapy. The addition of trimetazidine relieved her symptoms and improved her ejection fraction. Trimetazidine may have important prognostic implications in addition to its anti-anginal efficacy if the improvement in left ventricular function can be sustained.

■ *Heart Metab.* 2005;27:27–29.

**Keywords:** Angina, cardiac failure, trimetazidine, elderly

### Case report

Difficult cases often involve multiple pathology, especially in the elderly, but none more so than as exemplified by Mrs J, a 91-year-old widow who lives alone. A patient known to be ischemic, she was admitted to hospital with angina and left ventricular failure. Her pulmonary edema was brought under control with intravenous frusemide but her angina, although stable and not experienced at rest, restricted her walking the few meters along the hospital ward to the toilet. Her routine pathology tests demonstrated normal renal function and blood glucose, a hemoglobin of 13.7 g/dL, and normal thyroid function. Her chest X-ray revealed cardiomegaly and, initially, pulmonary edema, which cleared after her diuresis. Her ECG identified left bundle branch block and sinus rhythm (*Figure 1*) and, although there was no recent chest pain, silent infarction was ruled out by normal concentrations of cardiac enzymes and troponin. An echocardiogram excluded significant aortic and mitral valve disease, but confirmed global left ventricular dysfunction, with an ejection fraction of approximately 15–20%. The patient's admission medication of bisoprolol 1.25 mg daily, perindopril 4 mg daily, and atorvastatin 10 mg daily was

continued, along with aspirin 75 mg daily. After her daily oral dose of frusemide 40 mg had been changed to 80 mg, her heart failure remained controlled. Unfortunately, she remained very restricted by her angina, and we did not feel she was able to be independent in her home environment, even though she was mentally very alert and motivated.

Isosorbide mononitrate, an additional agent that was logical to try in this situation, was not tolerated, inducing severe headaches and lightheadedness. After further consideration and discussion with the patient, intervention was declined (wisely, in my opinion) and we decided on a metabolic approach, adding trimetazidine 20 mg three times daily. The patient tolerated this well and improved quickly, experiencing less angina and increased exercise ability. With the help of the cardiac rehabilitation team and community support, after 10 days of trimetazidine she was able to leave hospital continuing on trimetazidine and return to her sheltered accommodation.

I saw the patient in the outpatient clinic 6 weeks later and she was much improved, having traveled to the hospital on her own. At 3, 6 and 12 months the improvement has been sustained, with a pleasing level of mobility (she manages her housework and is

# Case report

Graham Jackson

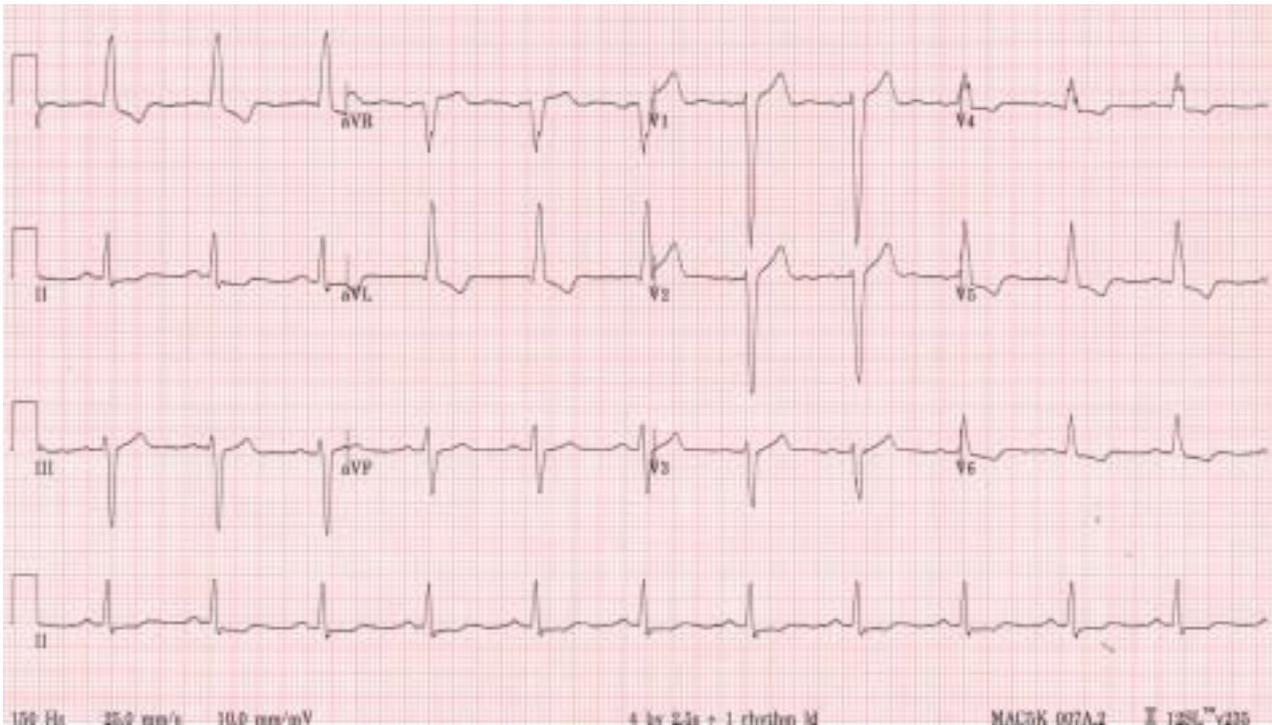


Figure 1. The patient's ECG on admission to hospital.

able to walk slowly in her local park) and good quality of life (playing Bridge with friends, and attending social gatherings). A repeat echocardiogram at 6 months suggested some improvement in left ventricular function, with the ejection fraction estimated at 20–25%.

## Comment

This lady presented a challenge at many levels. We needed to control her heart failure and improve her angina to try to maintain her independence. We were helped by her determination and the various support agencies, but it was the introduction of trimetazidine to her drug regimen that gave us the opportunity to mobilize her sufficiently to facilitate her discharge from hospital. Using echocardiography, which is an essential part of the assessment of heart failure, we ruled out a treatable valvular mechanical cause of her condition (eg, aortic stenosis), and there was no suggestion of atrial fibrillation as a precipitating arrhythmia. It was also important to exclude biochemical causes and "silent" myocardial infarction.

The importance of a nonhemodynamic metabolic approach to ischemic heart disease has been realized in relation to various clinical ischemic presentations, including diabetes and refractory angina [1]. We now have increasing evidence of the importance and safety of the metabolic agent trimetazidine in the presence of left ventricular dysfunction [2].

Vitale et al [3] studied left ventricular function and quality of life in elderly patients with coronary heart disease. Forty-seven patients with ischemic cardiomyopathy (mean age  $78 \pm 3$  years) received trimetazidine 20 mg three times daily or matching placebo, for 6 months. At the end of the study, the trimetazidine group showed significantly improved left ventricular function (systolic and diastolic). In addition, patients receiving trimetazidine showed a greater improvement in angina control and quality of life. Trimetazidine exerts its effects by increasing glucose oxidation and decreasing fatty acid oxidation, which in turn reduces fatty-acid-induced inhibition of pyruvate dehydrogenase [4]. The consequences are increased production of membrane-protective ATP, improved substrate use, and improved cardiac function; the failing heart should thereby be mechanically improved and, at the same time, ischemic pain should be decreased.

The patient described here benefited from this approach, which importantly facilitates a particularly useful noninvasive strategy in patients in an age group who in general prefer a conservative approach to their treatment.

## Conclusion

Heart failure (ischemic or nonischemic) has a poor prognosis, no matter what the evidence-based med-

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## Case report

### *Trimetazidine in angina and heart failure*

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icine that is optimally deployed. An additional metabolic approach to its management in order to establish whether there is a long-term benefit to morbidity and mortality is certainly worthy of further study [5]. ■

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# Metabolic link between ischemia and cardiac dysfunction

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## Abstract

Myocardial contractile power is dependent upon the breakdown of ATP to fuel contractile shortening and the uptake of  $\text{Ca}^{2+}$  into the sarcoplasmic reticulum at the end of systole. Energy for resynthesis of ATP comes from aerobic metabolism in the mitochondria, fueled by the combustion of fatty acids, and to a lesser extent glucose and lactate. Traditional drugs for chronic angina work through a reduction of the need for ATP by suppressing heart rate, blood pressure, and cardiac contractility. Excessive fatty acid oxidation during stress-induced ischemia has been shown to contribute to the development of angina and wall motion dysfunction, and improvement in contractile function has been documented with drugs that partially inhibit myocardial fatty acid oxidation. Trimetazidine, an inhibitor of the fatty acid oxidation enzyme, 3-ketoacyl coenzyme A thiolase, reduces the symptoms of demand-induced ischemia. Patients with ischemic heart disease and angina frequently have left ventricular dysfunction, a condition termed "ischemic cardiomyopathy", and recent studies have shown that trimetazidine not only reduces the symptoms of angina, but also improves ventricular function in patients with ischemic cardiomyopathy.

■ *Heart Metab.* 2005;27:30–33.

**Keywords:** Angina, heart failure, metabolism, mitochondrial, trimetazidine

Classically, the heart is considered a pump, generating mechanical power and heat as products. The power generated by the heart is fueled by high rates of myocardial blood flow, oxygen consumption, and carbon fuel combustion. The chemical energy for the mechanical work of the heart comes from ATP – the energy "currency" of the cell (*Figure 1*). ATP is broken down to ADP and inorganic phosphate, to drive cardiac muscle contraction and to fuel the  $\text{Ca}^{2+}$ -ATPase to pump  $\text{Ca}^{2+}$  into the sarcoplasmic reticulum and allow diastolic relaxation [1]. ADP is rapidly resynthesized to ATP in the mitochondria by oxidative phosphorylation. This is driven by the oxidation of fatty acids, glucose, and lactate, delivering reduced nicotinamide adenine dinucleotide (NADH) to the electron transport chain, consuming oxygen, and forming ATP. In the healthy heart, the breakdown of ATP is exquisitely matched to ATP synthesis, and there is never a significant decrease in myocardial

ATP concentration, even with large increases in cardiac power output, such as occurs with intense exercise [1].

Myocardial ischemia occurs when the delivery of oxygenated blood to the myocardium does not meet the requirement for the aerobic synthesis of ATP in the mitochondria to support the normal cardiac function at a given heart rate, afterload, preload, and contractility. Normally, the heart generates ATP from the oxidation of fatty acids, glucose, and lactate, with the majority (60–90%) coming from fatty acids [1]. When there is a mismatch between oxygen delivery to the myocardium and the demand for ATP, there is activation of glycolysis in an attempt to generate ATP anaerobically (*Figure 1*). Myocardial glycogen stores are broken down, the heart takes up more glucose, and the heart switches from lactate consumption to lactate production. The decrease in ATP and the accumulation of lactate reduce the pH in

## Refresher corner

### Metabolic link between ischemia and cardiac dysfunction

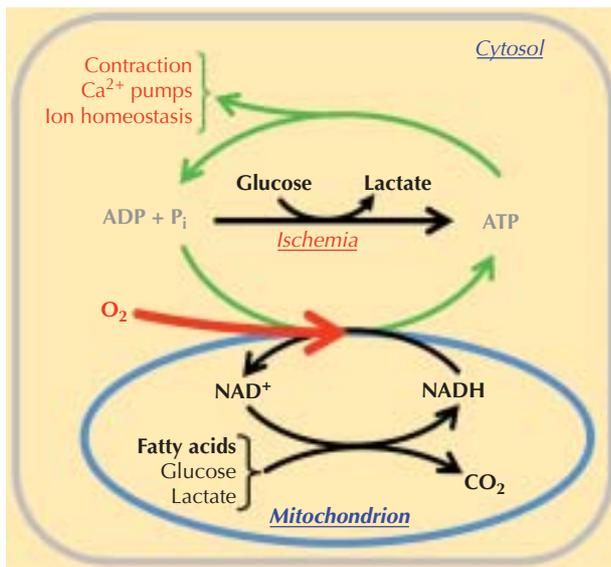


Figure 1. Cardiac function is dependent upon a constant supply of ATP to maintain contraction, relaxation, and ion homeostasis. ATP is made aerobically in the mitochondria. During ischemia, anaerobic ATP formation is activated in the cytosol from glycolysis.  $P_i$ , inorganic phosphate.

the cell and result in  $Ca^{2+}$  overload and contractile dysfunction. The breakdown of ATP generates adenosine and causes ion channel dysfunction, leading to an increase in extracellular adenosine,  $K^+$ , and  $H^+$ , which can activate cardiac afferent sensory nerve fibers, and triggers the classic symptom of myocardial ischemia: angina pectoris.

Traditional treatments for ischemia act by restoring the balance between oxygen delivery and the myocardial demand for oxygen. Most bouts of myocardial ischemia occur during stress caused by either physical exercise or emotional stress, and are the result of a reduced coronary flow reserve. This can occur either as a result of classic coronary artery disease when there is a lesion at the macrovascular level, or as a result of smaller, more diffuse lesions, or even microvessel dysfunction. In any case, these patients do not have the ability to increase myocardial blood flow to meet the normal requirement for delivery of oxygenated blood. Traditional treatments for chronic stable angina pectoris are aimed at increasing blood flow to the myocardium via coronary vasodilatation (eg, with nitrates), and at reducing the oxygen requirement of the ischemic tissue by decreasing heart rate, arterial blood pressure, and cardiac contractility (with  $\beta$ -blockers, calcium channel antagonists, or nitrates) [2]. These hemodynamic approaches are effective at reducing anginal symptoms and improving exercise tolerance, but many patients continue to suffer from angina, despite optimal treatment with these drugs [2].

During stress-induced angina (such as occurs with exercise or a dobutamine stress test) there is a failure to increase myocardial oxygen consumption and aerobic formation of ATP (Figure 1), which triggers the anaerobic formation of ATP and lactate production even though there is a relatively high residual rate of oxygen consumption by the myocardium [3–5]. Studies in large animals have shown that this residual aerobic formation of ATP is largely supported by the oxidation of fatty acids [3,4,6,7]. Importantly, the oxidation of fatty acids inhibits the oxidation of glucose in the mitochondria, and acts to drive the conversion of pyruvate to lactate in the cytosol [2,7,8]. Thus the high residual rates of fatty acid oxidation during myocardial ischemia contribute to the production of lactate.

In addition to traditional hemodynamic treatments for angina, metabolic treatment is available, through the partial inhibition of myocardial fatty acid oxidation with trimetazidine [2,9]. Inhibition of myocardial fatty acid oxidation increases glucose and pyruvate oxidation, and decreases the production of lactate during demand-induced ischemia [7]. Trimetazidine inhibits the enzyme of fatty acid  $\beta$ -oxidation, long-chain 3-ketoacyl coenzyme A thiolase (3-KAT). In clinical trials, this agent has been found not to affect heart rate, or arterial blood pressure at rest or during exercise, but to be as effective as calcium channel antagonists or  $\beta$ -adrenergic antagonists at improving exercise time to the onset of angina or 1 mm depression in the ST segment [9]. Moreover, trimetazidine has an additive effect in reducing the symptoms of exercise-induced angina when used in combination with either a calcium channel antagonist or a  $\beta$ -adrenergic receptor antagonist [9].

Patients with ischemic heart disease and angina frequently have left ventricular dysfunction and heart failure. This condition is termed “ischemic cardiomyopathy”, and is treated with suppressors of the renin–angiotensin system (angiotensin-converting enzyme inhibitors or angiotensin antagonists), and with traditional antianginal therapies. Results of recent clinical studies have demonstrated that treatment with trimetazidine significantly improves left ventricular function in this population. In a double-blind study of 38 patients with ischemic cardiomyopathy, Bellardine and Purcaro [10] showed that 12 weeks of treatment with trimetazidine improved the contractile response during a dobutamine stress test, increased peak oxygen consumption during a graded exercise test, and increased left ventricular ejection fraction at rest, compared with placebo (Figure 2) [10]. Vitale et al [11] observed a similar response in 47 elderly patients with coronary artery disease with left ventricular dysfunction. Compared with standard treatment, 6 months of treatment with trimetazidine reduced the frequency of angina attacks, reduced left

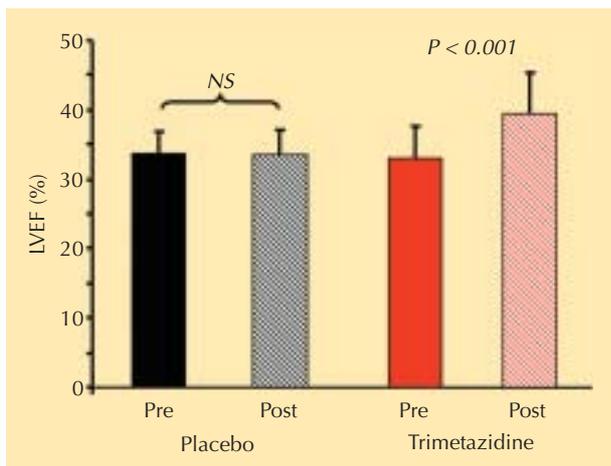


Figure 2. Treatment with trimetazidine 20 mg three times a day for 12 weeks increases left ventricular ejection fraction (LVEF) in patients with contractile dysfunction and coronary artery disease. Pre, before treatment; Post, after treatment. (Drawn from data present in Bellardinelli and Purcaro [10], with permission.)

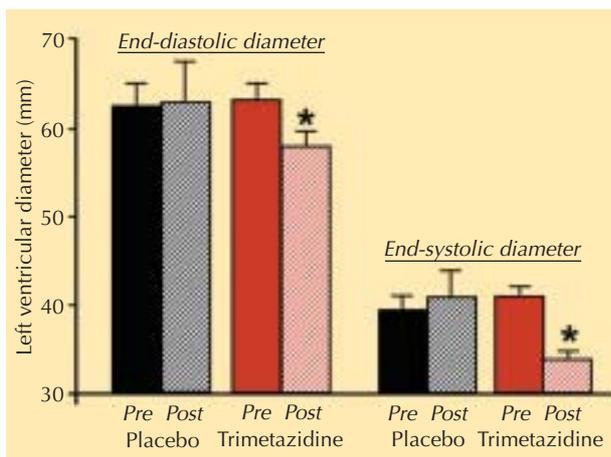


Figure 3. Treatment with trimetazidine for 6 months in patients with type 2 diabetes with coronary artery disease and left ventricular dysfunction results in a reduction in left ventricular end-diastolic and end-systolic diameters, as assessed by echocardiography. Pre, before treatment; Post, after treatment. (Modified from Rosano et al [12], with permission.)

ventricular end-diastolic and end-systolic volumes, and increased resting ejection fraction (from 29% at pretreatment to 34% after treatment with trimetazidine, compared with values of 29% and 27% with placebo). In addition, there was an improvement in the quality of life score with trimetazidine compared with placebo.

Approximately 20–30% of European and North American patients with angina or heart failure are also diagnosed with diabetes. Diabetes is a major risk factor for heart disease, and is associated with

diastolic left ventricular dysfunction, accelerated myocardial fatty acid oxidation, and impaired oxidation of glucose by the heart. One would speculate that metabolic treatments for angina and ischemic cardiomyopathy would be particularly effective in this population. Rosano et al [12] studied 32 patients with type 2 diabetes and ischemic cardiomyopathy who were allocated randomly to groups to receive either treatment with trimetazidine or placebo, for 6 months [12]. Unlike those who received placebo, the trimetazidine-treated group achieved a reduction in left ventricular end-diastolic and end-systolic diameters (Figure 3) and increased ejection fraction.

Taken together, these findings support the concept that, in these patient populations, cardiac dysfunction is caused by high rates of myocardial fatty acid oxidation, and that partial inhibition of this fatty acid oxidation with trimetazidine results in improved cardiac function.

## Summary

Patients with ischemic heart disease and angina frequently have left ventricular dysfunction and heart failure – a condition termed “ischemic cardiomyopathy”. 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 that is fueled largely by fatty acid oxidation which, in turn, inhibits glucose oxidation, and drives the conversion of pyruvate to lactate, which has detrimental effects on cell function. Results of recent clinical studies demonstrate that treatment with trimetazidine significantly improves left ventricular function in this population of patients. ■

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# Featured research

### Abstracts and commentaries

#### Mechanisms of creatine depletion in chronically failing rat heart

Ten Hove M, Chan S, Lygate C, et al. *J Mol Cell Cardiol.* 2005;38:309–313.

Clinical heart failure trials have uniformly shown that any energy-costly chronic pharmacologic treatment increases mortality, while energy-sparing treatment improves survival. The failing myocardium is characterized by deranged energetics: in addition to decreased concentrations of ATP and reduced creatine kinase activity and flux, a consistent finding has been a substantial reduction in phosphocreatine and creatine contents, resulting in a reduced energy reserve of the failing heart. It has thus been speculated that maintenance of creatine/phosphocreatine concentrations may be a potential mechanism for therapeutic intervention in heart failure. However, for the implementation of such a therapeutic approach, the regulation of creatine content in normal and failing heart needs to be fully understood. The aim of this study was to investigate the mechanisms of creatine regulation in chronically failing myocardium. This was induced in rats by left coronary artery ligation. The results show that depletion of creatine/phosphocreatine content in the failing heart is the result of reduced sarcolemmal uptake of creatine.

#### Commentary

This study has directly demonstrated that a major mechanism responsible for creatine depletion in the failing myocardium is reduced creatine uptake. Creatine is not synthesized in muscle, and thus the cardiomyocyte content depends on the creatine transporter accumulating creatine intracellularly against a large concentration gradient, opposed by a passive back-leak of creatine out of the cell. Creatine transport is sodium-dependent, with a stoichiometry of either 1 or 2 Na<sup>+</sup> and not near equilibrium, and is thus a potential site for the control of intracellular

creatine content. This study describes that heart failure led to a significant (30%) decrease in intracellular creatine content and to a significant (26%) reduction in creatine uptake.

The signaling pathways involved in downregulation of creatine uptake in heart failure are currently unknown. Among others, factors that regulate the Na<sup>+</sup> gradient across the cell membrane, thus influencing the thermodynamic driving force of the cell, have been suggested to play a part in the regulation of creatine transporter activity. It has previously been shown that the strategy of chronically providing high dosages of creatine to the failing heart is ineffective in preventing the decrease in creatine content [1]. The results presented here demonstrate that a possible explanation for the inefficiency of oral creatine in chronic heart failure is the fact that the rate of uptake of creatine is reduced in the failing myocardium.

Whether this reduction in the creatine uptake capacity constitutes a pathophysiological or an adaptive mechanism in heart failure remains to be determined. A pathophysiological mechanism would be mediated by a reduction in total creatine content, thereby decreasing the rate and extent of intracellular ATP transfer via the creatine kinase reaction, and limiting energy availability at the myofibrils. In contrast, an adaptive mechanism leading to a reduction in free creatine as a response to decreasing phosphocreatine concentrations would prevent a decrease in the free-energy change of ATP hydrolysis, and maintaining a high free-energy change is essential for maintenance of contractile function.

If reductions in creatine content do have a causal role in heart failure, then understanding the regulation of creatine concentrations and the factors that govern down- and upregulation of the rates of uptake of creatine may be clinically relevant in the search for new treatment strategies specifically targeted at maintaining cardiac energetics.

*D. Feuvray*

### Sildenafil prevents endothelial dysfunction induced by ischemia and reperfusion via opening of adenosine triphosphate-sensitive potassium channels: a human in vivo study

Gori T, Sicuro S, Dragoni S, Donati G, Forconi S, Parker JD. *Circulation*. 2005;111:742–746.

Animal studies have demonstrated that administration of sildenafil can limit myocardial damage induced by prolonged ischemia, an effect that appears to be mediated by opening of ATP-sensitive potassium ( $K_{ATP}$ ) channels. No study has investigated whether sildenafil can also prevent the impairment in endothelium-dependent vasodilatation induced by ischemia-reperfusion in humans. In a double-blind, placebo-controlled, crossover design, 10 healthy male volunteers (25–45 years old) were allocated randomly to groups to receive oral sildenafil (50 mg) or placebo. Two hours later, endothelium-dependent, flow-mediated dilatation (FMD) of the radial artery was measured before and after ischemia-reperfusion (15 min of ischemia at the level of the brachial artery, followed by 15 min of reperfusion). Seven days later, the volunteers received the other treatment (ie, placebo or sildenafil) and underwent the same procedure.

Radial artery diameter and FMD before ischemia-reperfusion, and baseline radial artery diameter after ischemia-reperfusion, were similar between visits ( $P=NS$ ). After administration of placebo, ischemia-reperfusion significantly blunted FMD (before ischemia-reperfusion:  $7.9 \pm 1.1\%$ ; after ischemia-reperfusion:  $1.2 \pm 0.7\%$ ;  $P < 0.01$ ). Importantly, sildenafil limited this impairment in endothelium-dependent vasodilatation (before ischemia-reperfusion:  $7.0 \pm 0.9\%$ ; after ischemia-reperfusion:  $6.2 \pm 1.1\%$ ;  $P=NS$ ;  $P < 0.01$  compared with placebo). In a separate procedure, this protective effect was completely prevented by previous administration of the sulfonyleurea, glibenclamide (5 mg), a blocker of  $K_{ATP}$  channels ( $n=7$ ; FMD before ischemia-reperfusion:  $10.3 \pm 1.5\%$ ; after ischemia-reperfusion:  $1.3 \pm 1.4\%$ ;  $P < 0.05$ ).

We conclude that, in humans, oral sildenafil induces potent protection against ischemia-reperfusion-induced endothelial dysfunction through opening of  $K_{ATP}$  channels. Further studies are needed to test the potential clinical implications of this finding.

#### Commentary

Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, has been shown to improve endothelial function in acute and chronic dosing studies in diabetic and nondiabetic individuals. Tadalafil has also been shown to improve endothelial function in men at increased cardiovascular risk. In mice,

sildenafil reversed pre-established ventricular hypertrophy induced by pressure overload and restored chamber function to normal. Similar studies in humans (men and women) are awaited, but in this paper Gori et al have shown, in healthy male volunteers, that sildenafil can induce potent endothelial protection as a result of opening  $K_{ATP}$  channels.

Animal and human studies suggest that PDE5 inhibitors may have important effects in addition to their use in treating erectile dysfunction. These important vascular and potential myocardial protective actions have already been demonstrated in the treatment of pulmonary hypertension, with minimal adverse effects. With no interaction with metabolic agents, the concept of an additive or synergistic action from combination therapy is one of the many important clinical areas to warrant further study.

G. Jackson

### Uncoupling proteins in human heart

Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K. *Lancet*. 2004;364:1786–1788.

Abnormal energetic activity in heart failure correlates inversely with plasma free fatty acid concentrations. However, the link between energetic and metabolic abnormalities is unknown. To investigate this association, we obtained blood samples from 39 patients undergoing coronary artery bypass graft surgery. Patients fasted overnight before samples were taken. When plasma free fatty acid concentrations were increased, concentrations of cardiac mitochondrial uncoupling protein (UCP) increased (isoform UCP2,  $P < 0.0001$ ; isoform UCP3,  $P=0.0036$ ) and those of glucose transporter 4 (GLUT 4) protein decreased (cardiac,  $P=0.0001$ ; skeletal muscle,  $P=0.0006$ ). Consequently, energy deficiency in heart failure might result from increased concentrations of mitochondrial UCPs (ie, less efficient ATP synthesis) and depleted GLUT 4 (ie, reduced glucose uptake). New treatments to correct these energy defects would be to achieve a simultaneous decrease in plasma free fatty acids and provision of an alternative energy source.

#### Commentary

Cardiac energetics and energy reserve can be decreased in patients with heart failure. Alterations in mitochondrial function and ATP production have been implicated in this decreased capacity for energy production in the failing myocardium. Direct assessments of mitochondrial function in the heart have

shown that a number of defects can occur in the failing heart, including a decrease in electron transport chain activity. Another metabolic alteration that can occur in patients with heart failure is an increase in plasma fatty acid concentrations. This study by Murray et al shows that, in patients with low ejection fraction undergoing elective cardiac surgery, increased plasma fatty acid concentrations correlated with an increase in mitochondrial UCP2. UCP2 can decrease the proton gradient in the inner mitochondrial matrix, thereby uncoupling electron transport chain activity from ATP production. This study provides a possible alternative mechanism by which energy depletion can occur in heart failure – uncoupling of mitochondrial respiration and a decrease in ATP production. High plasma concentrations of fatty acids seen in patients with heart failure may exacerbate this mitochondrial dysfunction. The authors propose that a reduction in concentrations of circulating fatty acids or provision of an alternative substrate (such as glucose) may reduce the expression of UCP2 and thereby improve the efficiency of mitochondrial energy production. This possibility remains to be explored.

*G. Lopaschuk*

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### **Cardiovascular risk factors emerge after artificial selection for low aerobic capacity**

Wisløff U, Najjar SM, Ellingsen O, et al. *Science*. 2005;307:418–420.

In humans, the strong statistical association between fitness and survival suggests a link between impaired oxygen metabolism and disease. We hypothesized that artificial selection of rats based on low and high intrinsic exercise capacity would yield models that also contrasted for disease risk. After 11 generations, rats with low aerobic capacity scored high on cardiovascular risk factors that constitute the metabolic syndrome. The decrease in aerobic capacity was associated with decreases in the amounts of transcription factors required for mitochondrial biogenesis and in the amounts of oxidative enzymes in skeletal muscle. Impairment of mitochondrial function may link reduced fitness to cardiovascular and metabolic disease.

### **Commentary**

An individual's aerobic/exercise capacity is probably determined by the interaction of numerous biochemical and physiological characteristics that are both genetically and environmentally influenced. However, studies in twins confirm a substantial

genetic component that may determine both aerobic capacity in the untrained state and the additional performance gained by training. There is also a wealth of evidence that shows an individual's aerobic capacity relates to risk of cardiovascular events and to the presence of features of the metabolic syndrome such as insulin resistance and adiposity. The difficulty lies in establishing how these factors interrelate and which is chicken and which is egg.

This fascinating and far-reaching study by Wisløff et al is based on the detailed phenotyping of rats bred for aerobic capacity. The study started with 192 genetically heterogenous rats. Through a structured and regimented training program, the 13 males and females with the greatest exercise capacity were selected and bred. Their offspring were similarly selected and bred; inbreeding was avoided by maintaining at least 13 families throughout the study. Exactly the same graded treadmill exercise test was used to select rats with low aerobic capacity. After 11 generations of selective breeding, offspring of families bred for high exercise performance were capable of running 3.5 times as far as offspring of families bred for low exercise performance. The question is, what other differences existed between the low capacity runners (LCRs) and high capacity runners (HCRs)?

Despite being selected only for traits relating to exercise capacity, the HCR rats were healthier than the LCR rats, even in their sedentary state. For example, their mean daytime blood pressure was 17 mm Hg lower (although differences at night were less marked), endothelial function (as assessed by *in vitro* responses to acetylcholine) was 48% better, fasting glucose 20% lower, insulin concentrations 131% lower, triglycerides 168% lower, and intra-abdominal fat 63% lower. In their untrained state, the HCRs' greater  $\text{VO}_2\text{max}$  was associated with hearts that were slighter heavier and comprised of myocytes with better contractile performance when isolated. Thus it seems that the genes that determine low exercise performance also determine features of the metabolic syndrome. The authors hypothesized that the two may be interrelated through compromised mitochondrial oxidative function.

Comparing soleus muscle harvested from the LCRs with that obtained from the HCRs, the authors found evidence of markedly reduced mitochondrial biogenesis and function, including reduced amounts of peroxisome proliferative activated receptor gamma (PPAR- $\gamma$ ) and PPAR- $\gamma$  coactivator 1 $\alpha$ .

The above analyses were performed in rats aged 16–24 weeks, equivalent to young adulthood. At this age, the HCRs were already leaner than the LCRs. It is possible, therefore, that the changes described are secondary to body weight rather than directly

genetically determined. To address this, further analyses were performed in 5-week-old HCR and LCR pups that had identical weights and visceral fat. Despite identical adiposity, there were already significant differences in circulating glucose and triglycerides, suggesting that, in this model, genetically determined metabolic derangements may precede, and even contribute to, obesity, rather than vice versa.

This study provides an excellent example of the bidirectional nature of translational research. The notion that impaired regulation of oxidative pathways in mitochondria may be a common factor linking reduced aerobic capacity to cardiovascular and metabolic disease had originally been suggested by epidemiological and clinical studies. The authors have reinforced this interrelationship by showing that the genetic selection of reduced aerobic capacity results in coincident mitochondrial dysfunction and cardiovascular risk. Before using this information to influence choice of partner I, for one, would like to know the answer to the following question: Are the LCRs more intelligent than the HCRs?

M. Marber

### Endothelial dysfunction and damage in congestive heart failure: relation of flow-mediated dilation to circulating endothelial cells, plasma indexes of endothelial damage, and brain natriuretic peptide

Chong AY, Blann AD, Patel J, Freestone B, Hughes E, Lip GY. *Circulation*. 2004;110:1794–1798.

Congestive heart failure (CHF) is associated with endothelial perturbation (as defined by flow-mediated endothelial-dependent vasodilatation [FMD, an index of endothelial dysfunction], circulating endothelial cells [CECs, an index of endothelial damage], or plasma indexes of endothelial damage/dysfunction [eg, von Willebrand factor (vWF) and soluble thrombomodulin (sTM)]) and increased plasma concentrations of brain natriuretic peptide (BNP, a peptide hormone associated with left ventricular systolic dysfunction and prognosis). However, the relationships between these parameters are unclear.

To test the hypothesis that there is a relationship between endothelial perturbation (defined by FMD, CECs, vWF, and sTM) and BNP in CHF, we studied these indexes in 30 patients with CHF who were compared with 20 age-matched control individuals. FMD, CECs, plasma vWF, and BNP concentrations (but not sTM) were all abnormal in patients with CHF. There were significant inverse correlations between

FMD and vWF ( $P=0.001$ ), CECs ( $P=0.002$ ), and BNP ( $P=0.006$ ), and a positive correlation between CECs and vWF ( $P=0.032$ ). In multivariate analysis, BNP ( $P<0.001$ ) and FMD ( $P<0.001$ ) were both independently associated with CHF.

We conclude that ample evidence of endothelial cell damage/dysfunction in CHF cannot be fully explained by the variance in plasma BNP per se. Therefore, the routes by which these indexes influence the pathophysiology of CHF and predict adverse outcomes may be independent.

### Commentary

A generalized endothelial damage has been suggested to contribute to CHF. Cellular, biochemical, and hemodynamic markers of endothelial dysfunction have been consistently found to be abnormal in patients with heart failure. In the present study, an inverse correlation between FMD of the brachial artery and increased concentrations of vWF is reported. Impaired endothelium-dependent vasodilatation may explain the abnormal vasoconstriction that is a hallmark of CHF. Increased vWF is an established marker of endothelial damage that facilitates platelet adhesion and activation. The presence of increased numbers of circulating endothelial cells in heart failure is proposed as evidence that CECs are desquamated, damaged endothelial cells, raising the possibility that some part of the vascular wall may be denuded. Endothelial denudation exposes the underlying collagen, activating the coagulation system that, coupled with increased vWF, may explain the excess risk of thromboembolism associated with heart failure.

An inverse relationship is also reported between FMD and plasma BNP, neither being apparently related with left ventricular ejection fraction or New York Heart Association class.

Interestingly enough, both increased BNP and endothelial function may be improved in heart failure by the administration of trimetazidine. The mechanism linking the cardiac energy metabolism switch associated with the inhibition of 3-ketoacyl coenzyme A thiolase to the improvement in endothelial function and the reduction in BNP, in addition to reductions in inflammatory markers, is not clear at present. The possibility of a direct protective and anti-inflammatory effect of trimetazidine on the endothelium appears worthy of direct investigation, both into its possible use as a therapeutic alternative in heart failure, and to gain a better understanding of the pathogenetic mechanisms of progressive heart failure.

M. Marzilli

## Evaluation of 18F-FDG uptake and arterial wall calcifications using 18F-FDG PET/CT

Ben-Haim S, Kupzov E, Tamir A, Israel O. [Abstract] *J Nucl Med.* 2004;45:1816–1821.

Glucose metabolic activity expressed as uptake of [<sup>18</sup>F]2-fluoro-2-deoxyglucose (18F-FDG) may be increased in active atherosclerotic plaque. Calcium depositions are often increased in mature atherosclerotic plaque. The purpose of the present study was to assess the patterns of vascular wall uptake of 18F-FDG and computed tomography (CT) calcifications, using combined positron emission tomography (PET)/CT.

We evaluated retrospectively 122 consecutive patients older than 50 years (47 women and 75 men; mean age 66 ± 9 years) undergoing whole-body 18F-FDG PET/CT for tumor assessment. PET, CT, and PET/CT slices were generated for review. Abnormal vascular findings in major arteries in the chest and abdomen were categorized as PET positive (PET+), PET negative (PET-), CT positive (CT+), or CT negative (CT-). The topographic relationship between increased vascular wall uptake of 18F-FDG on PET and the presence of calcifications on CT was assessed on PET/CT fused images, with abnormal sites further classified as PET+/CT+, PET+/CT-, or PET-/CT+. The presence of CT calcifications and increased vascular wall uptake of 18F-FDG was correlated with age, sex, presence of cardiovascular risk factors, and cardiovascular disease.

Abnormal findings were identified at 349 sites. CT calcifications (CT+) were observed at 320 sites (92%) in 100 patients (82%), more commonly in men ( $P < 0.03$ ), in older patients ( $P < 0.0001$ ), in patients with hypertension ( $P < 0.003$ ) or hyperlipidemia ( $P < 0.04$ ), and in smokers ( $P < 0.008$ ). Increased vascular wall uptake of 18F-FDG (PET+) was observed at 52 sites (15%) in 38 patients (31%), more commonly in men ( $P < 0.02$ ), in older patients ( $P < 0.0001$ ), and in patients with hypertension ( $P < 0.02$ ), and was borderline in patients with cardiovascular disease ( $P = 0.057$ ). PET+ and CT+ findings correlated in 12 patients, a PET+/CT- pattern was found in 18 patients, and eight patients exhibited increased vascular wall uptake of 18F-FDG in sites with and without calcifications (PET+/CT+, CT-). Twenty-two patients (18%) had a PET-/CT- pattern.

We conclude that hybrid PET/CT can be used to identify and correctly localize vascular wall 18F-FDG activity. Increased vascular wall 18F-FDG activity was found in 15% of sites and CT calcifications were noted in 92% of sites, with congruent findings in 7%.

The clinical significance of the relationship between vascular wall uptake of 18F-FDG and CT calcifications needs to be assessed by further prospective studies with long-term follow-up.

## Commentary

Electron-beam CT can diagnose atherosclerosis in the arterial wall by detecting the presence of calcium. This is a well established technique and several studies and reviews have indicated its use as a screening tool for atherosclerosis. Moreover, the technique may provide prognostic information. A relatively new technique with which to visualize atherosclerosis is the use of [<sup>18</sup>F]2-fluoro-2-deoxyglucose (FDG) in combination with PET. Earlier studies have shown that, in the normal vessel wall, there is no measurable uptake of FDG, whereas in the atherosclerotic plaque FDG is taken up predominantly by macrophages. In the present study by Ben-Haim et al, the authors compared the uptake of FDG and electron-beam CT calcification in patients, using a novel technique of combined PET and CT scanning. Interestingly, the authors found a high prevalence of CT calcifications and a low prevalence of FDG uptake. Moreover, there was a low coincidence of CT-positive and FDG-positive findings.

In an excellent editorial in the same issue of *Journal of Nuclear Medicine*, Peter Weissberg offers a plausible explanation for these findings. He states that calcification and FDG uptake measure different features of the atherosclerotic plaque. FDG uptake is related to active metabolism of macrophages, and is therefore closely related to inflammation. Inflammation may lead to plaque rupture and coronary events. In contrast, calcification is a long-lasting, cumulative phenomenon, and may be the result of repeated episodes of inflammation. It is therefore a very frequent finding of atherosclerosis, but may have a limited prognostic effect.

Thus combined CT and metabolic imaging of the arterial wall is a new and exciting technique, which may give further insight into the dynamics of the atherosclerotic process.

Frans Visser

## REFERENCE

1. Horn M, Frantz S, Remkes H, et al. Effects of chronic dietary creatine feeding on cardiac energy metabolism and on creatine content in heart, skeletal muscle, brain, liver and kidney. *J Mol Cell Cardiol.* 1998;30:277–284.

# Glossary

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### Creatine/phosphocreatine

Phosphocreatine is a chemical storage form of energy in cells. In times of increased energy demand, the high energy phosphate on phosphocreatine can be transferred to adenosine diphosphate (ADP) to form adenosine triphosphate (ATP) and creatine. ATP is then used by enzymes in energy requiring cellular processes. In times of low energy demand, the reverse reaction occurs, with creatine kinase catalyzing the formation of phosphocreatine and ADP from ATP and creatine. A creatine and phosphocreatine shuttle system is important in the transfer of high energy phosphates from mitochondria to the cytoplasm.

### Peroxisome proliferative activated receptor gamma (PPAR- $\gamma$ ) and PPAR- $\gamma$ coactivator 1 $\alpha$

Peroxisomal proliferators-activated receptors are nuclear receptors involved in the transcriptional regulation of proteins. One of these nuclear receptors is PPAR- $\gamma$ , which modifies the expression of a number of proteins, including those involved in insulin sensitivity and lipid metabolism. Activation of PPAR- $\gamma$  is a therapeutic approach to treating diabetes, which may in part be due lowering blood fatty acid levels, secondary to decreasing fatty acid release from adipose tissue. In the nucleus, a complex of proteins is involved in the regulation of PPAR mediated transcription. One of these proteins is peroxisome proliferator-activated receptor gamma coactivator 1

alpha (PGC-1alpha). PGC-1-alpha is a transcriptional coactivator that plays a role in mitochondrial biogenesis and energy metabolism, and has been implicated in insulin release by beta cells and in insulin resistance. It is predominantly expressed in the kidney, heart, liver and skeletal muscle tissues.

### Uncoupling protein

Uncoupling proteins (UCP) are proteins that are present in the inner mitochondrial membrane of cells that dissipate the proton gradient across this membrane. As a result of this action, mitochondrial respiration produces heat instead of ATP. Heart and skeletal muscle contain two isoforms of UCPs, UCP2 and UCP3. The exact function of these UCP's is not clear, but they may be involved in decreasing reactive oxygen species production by the mitochondria or transporting excess fatty acids out of the mitochondria. The expression of UCPs in the mitochondria is increased in muscle exposed to high fats.

### GLUT-4

GLUT-4 is a protein that transports glucose across cell membranes. In insulin-responsive tissues (such as the heart), insulin will cause GLUT-4 to be translocated from inside the cell to the plasma membrane, thereby stimulating glucose uptake.

