# Modification of myocardial substrate utilisation: a new therapeutic paradigm in cardiovascular disease

Roger M Beadle and Michael Frenneaux

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Roger M Beadle, Michael Frenneaux

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University of Aberdeen, School of Medicine and Dentistry, Foresterhill, Aberdeen, UK

**Correspondence to**
Dr Roger M Beadle, University of Aberdeen, School of Medicine and Dentistry, Foresterhill, Aberdeen, UK; rogerbeadle@hotmail.com

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## ABSTRACT

Therapies that aim to modify cardiac substrate utilisation are designed to increase metabolic efficiency. Although the main energy supply for the heart is generally provided by the oxidation of fatty acids, the heart is a metabolic omnivore and able to consume glucose as well as lactate and amino acids in varying proportions. A shift from fatty acid oxidation to glucose oxidation leads to lower oxygen consumption per unit of ATP produced. This concept of reduced oxygen utilisation underlies the use of metabolic modulating agents to treat chronic stable angina. Furthermore, the model of an energy-starved heart now forms the basis for our understanding of both ischaemic and non-ischaemic heart failure. Potential alterations in substrate utilisation and thus myocardial efficiency underlie the use of metabolic agents in heart failure. This is achieved by either promoting glucose or reducing the utilisation of fatty acids. Such a shift results in a relatively greater production of ATP per unit of oxygen consumed. With an ongoing demand for treatment options in ischaemic heart disease and a growing epidemic of heart failure, new treatment modalities beyond contemporary therapy need consideration.

## INTRODUCTION

Despite the advances in the treatment of both heart failure and ischaemic heart disease, including both pharmacological and interventional measures that improve symptoms and outcome, many patients continue to experience refractory symptoms. In some patients with ischaemic heart disease and stable angina conventional therapy is limited by side effects such as hypotension, and contraindications to surgical or percutaneous revascularisation. Furthermore, in heart failure, many patients remain symptomatic despite optimal medical therapy aimed particularly at neurohormonal antagonism, and the advances made with cardiac resynchronisation therapy. There is thus a need for additional therapies for both angina and heart failure.

The heart can metabolise numerous substrates for energy generation, including free fatty acids (FFA), glucose and, to a lesser extent, lactate.[1] While the fetal heart primarily uses glucose for its energy requirements, the rise of serum levels of FFA after birth is associated with a metabolic switch within the cardiomyocyte to the preferential metabolism of FFA[2] which contrasts with most other cells that preferentially metabolise glucose. In both heart failure and ischaemic heart disease there are changes in substrate utilisation and energy metabolism, including a decline in high-energy-phosphate content and mitochondrial dysfunction. There is typically a downregulation of fatty acid metabolism with preserved or increased glucose uptake, but often a relative block of the entry of pyruvate into the tricarboxylic acid cycle (TCA cycle). These metabolic changes contribute to the energy starvation.

The aim of this review is to briefly overview cardiac metabolism and the rationale behind metabolic manipulation in cardiovascular disease with particular attention to those agents with evidence from human studies.

## CARDIAC ENERGY METABOLISM

Cardiac energy metabolism can be broadly divided into three components. The first is the production of fuel for the TCA cycle via glycolysis of carbohydrates and β-oxidation of FFA. The second is the process of oxidative phosphorylation within the mitochondrion to yield ATP, the high-energy phosphate that acts as the cell's energy source. The third component involves the transport of this newly formed energy to its destination at the myofibrils, which is facilitated by the phosphocreatine shuttle.[3] It is the first of these components that appears to be the target for metabolic modulating drugs and that warrants discussion in detail. Figure 1 gives a schematic representation of these processes.

The TCA cycle provides reducing equivalents for mitochondrial oxidative phosphorylation, resulting in the regeneration of ATP from ADP and inorganic phosphate. Myocytes oxidise fatty acids derived from both the plasma and the breakdown of intracellular triacylglyerol stores, while pyruvate is derived from either glycolysis or from lactate via lactate dehydrogenase. These two main sources of energy are inter-regulated and linked to maintain an appropriate balance between substrate availability and the energy demands placed upon the heart, mediated by complex changes in gene expression and activation of various enzymes involved in FFA and glucose metabolism. Randle *et al*[4] demonstrated that FFA impair basal and insulin-stimulated glucose uptake and oxidation, an event that has been named the 'Randle Cycle'. The normal heart derives approximately 60–100% of its energy from FFA and the remainder from glucose and lactate (0–20% from each).[5]

The uptake of extracellular glucose is regulated by the transmembrane glucose gradient and the concentration and activity of glucose transporters (GLUT) in the plasma membrane. Both insulin and ischaemia lead to the relocation of GLUT transporters to the plasma membrane with a subsequent



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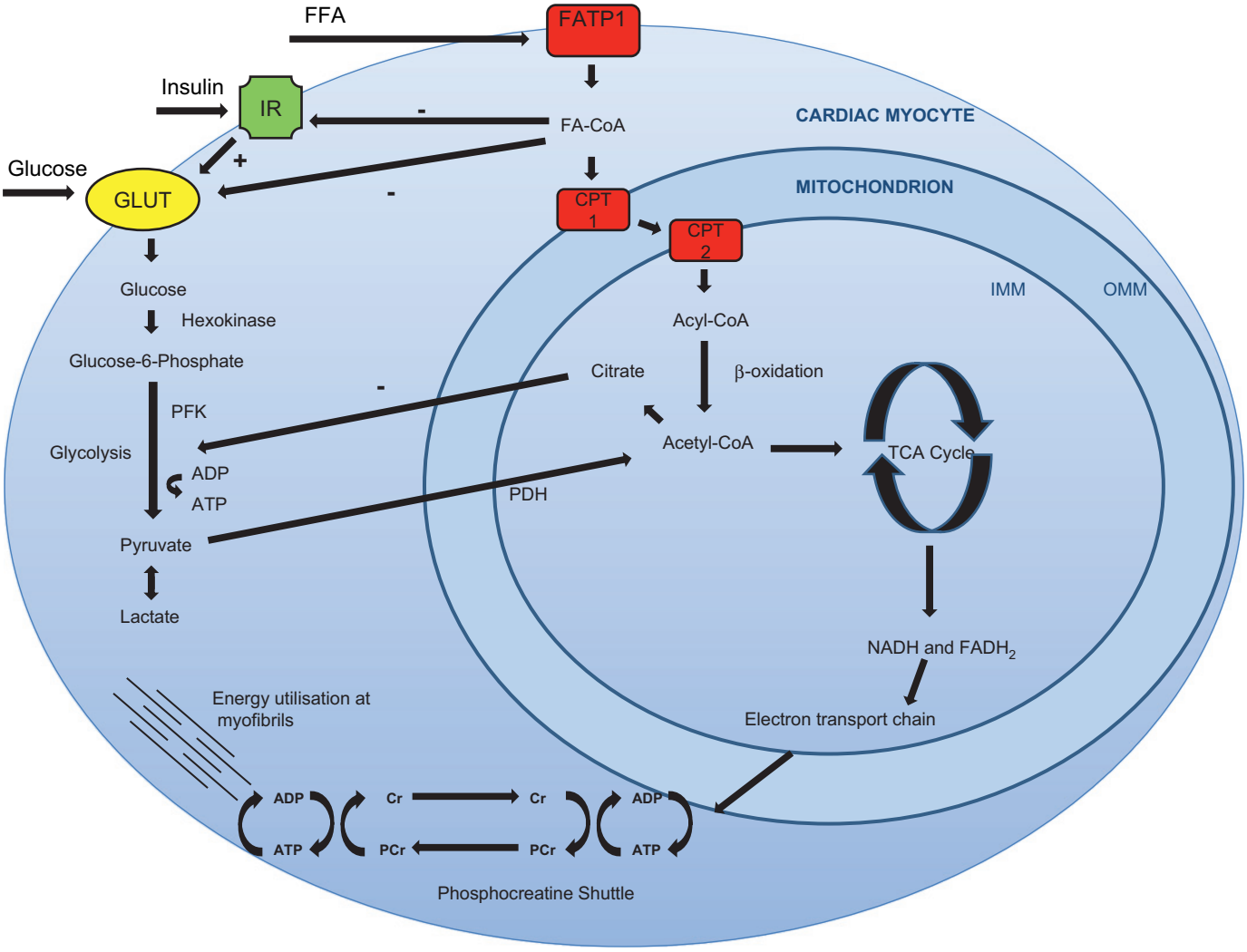


**Figure 1** Illustration of the flow and regulation of substrates through the oxidation of glucose and β-oxidation of fatty acids as described in the text. CoA, coenzyme A; CPT, carnitine palmitoyltransferase; FA-CoA, fatty acid coenzyme A; FATP1, fatty acid transport protein 1; GLUT4, glucose transporter 4; IMM, inner mitochondrial membrane; IR, insulin receptor; LDH, lactate dehydrogenase; OMM, outer mitochondrial membrane; PDH, pyruvate dehydrogenase; PFK, phosphofructokinase.

increase in capacity for glucose transport.[6 7] Once in the cell, free glucose is rapidly phophorylated by hexokinase to form glucose-6-phosphate (G6P) which is impermeable to the cell membrane. G6P is used for glycogen synthesis or may undergo glycolysis to pyruvate. Given a constant supply of G6P, the primary regulators of glycolytic rate are the activity of phosphofructokinase (PFK), and the ability to form reduced NADH.[8] NAD+ is reduced to NADH by the conversion of glyceraldehyde-3-phosphate to 3-phosphoglycerol phosphate by the enzyme glyceraldehyde-3-phoshate dehydrogenase. It has been suggested that glycolytically derived ATP is preferentially used for $Ca^{2+}$ re-uptake into the sarcoplasmic reticulum.[9] Glycolysis is also important for optimal function of the $Na^+/K^+$ ATPase and prevention of intracellular $Na^+$ accumulation during ischaemia.[10]

Lactate is a major source of pyruvate formation under well-perfused conditions in vivo, and under some conditions lactate uptake can exceed glycolysis as a source of pyruvate.[11] Studies with carbon-labelled lactate traces in humans show that 80–100% of lactate taken up by the human heart is immediately released as labelled $CO_2$ into the coronary sinus,[12] suggesting the extracted lactate is rapidly oxidised by lactate dehydrogenase, decarboxylated by pyruvate dehydrogenase (PDH) and oxidised to $CO_2$ by the TCA cycle. Pyruvate decarboxylation to acetyl-CoA is the key irreversible step in carbohydrate oxidation and is catalysed by pyruvate dehydrogenase (PDH).[13] PDH is subject to complex regulation by multiple factors acting via an inhibitor (PDH kinase) and an activator (PDH phosphatase). Acetyl-CoA derived from fatty acid β-oxidation inhibits PDH activity. During acute ischaemia, there is also block at the level of PDH, resulting in lactate generation from pyruvate.

The control enzymes of these key metabolic steps (hexokinase, phosphofructokinase, PDH) and glucose transporters represent possible therapeutic targets to modulate substrate utilisation. Indeed, augmenting glucose metabolism directly, through various means, has experimentally been shown to increase contractile function and cause haemodynamic improvements in human heart failure.[14 15]

β-Oxidation is the process by which fatty acids, in the form of acyl-CoA molecules, are broken down in the mitochondria and/or peroxisomes to generate acetyl-CoA. The TCA cycle is a four-step recurring process of dehydrogenation, hydration, oxidation and thiolysis, which liberates one molecule of acetyl-CoA and one molecule each of NASH and $FADH_2$.

While fatty acids provide the most ATP per unit of substrate consumed, the oxygen cost is greater than with carbohydrate oxidation. This amount of oxygen predicted by stoichiometry is

approximately 12% greater with FFA versus carbohydrate metabolism.[16] In vivo experiments in animal models have demonstrated even greater differences in efficiency (of approximately 40%) that are too large to be explained by the different ATP-to-oxygen ratios of these two substrates.[17] This disparity may be explained by an increase in the expression of mitochondrial uncoupling proteins.[18] The mitochondrial electron transport chain generates a proton gradient across the inner mitochondrial membrane that powers ATP production. Under normal circumstances little leakage of protons across the membrane occurs. Uncoupling proteins allow protons to leak into the mitochondrion and fatty acids and lipid peroxides to pass out. The purpose of uncoupling may be to reduce oxidative stress, which damages mitochondrial DNA. These uncoupling proteins are under the regulatory control of PPARα, which is activated by increased FFA levels. PPARs are a group of ligand-activated transcription factors. Once activated, PPARs form complexes with retinoid X receptors and bind to the promoter regions of a number of target genes that encode the proteins involved in controlling fatty acid metabolism.[19]

Transport proteins are involved in the entry of fatty acids into the cell. Fatty acid transport is decreased when the transport proteins are blocked using general transport inhibitors[20] and overexpression of CD36 or fatty acid transport protein (FATP) has been found to increase FA metabolism,[21] despite the fact that fatty acids are free to cross the cell membrane, and thus offer a potential therapeutic target. Subsequently, fatty acids require a shuttle system to enter the mitochondria. CPT-1 transports long-chain fatty acyl carnitine across the outer mitochondrial membrane (and is the rate-limiting step in FA oxidation) while CPT-2 is the enzyme involved on the matrical side. CPT inhibitors reduce FFA metabolism and consequently, swing the balance toward carbohydrate metabolism. Second, β-oxidation can be arrested by interference with enzymes directly involved in the process.

Physiological, pathological or therapeutic suppression of FFA uptake and/or oxidation by any means stimulates and increases myocardial glucose substrate utilisation,[22] probably in part by increasing the activity of PDH. Therapeutic interventions aimed at a shift in myocardial substrate utilisation towards glucose may thus be expected to offer significant benefit to patients with ischaemic heart disease. Most of the currently available agents act via a suppression of FFA oxidation. It has been debated as to whether pharmacologically altering the balance is beneficial or potentially detrimental. Genetic abnormalities in fatty acid oxidation, particularly involving acyl-CoA dehydrogenase, have been implicated in causing dilated cardiomyopathy and arrhythmias in children.[23–25] The mechanism appears to be due to accumulation of intermediary metabolites of FFA metabolism such as long-chain acyl carnitines.[23]

## CARDIAC SUBSTRATE USE IN ISCHAEMIA AND HEART FAILURE

Cardiac myocytes respond metabolically to ischaemia and heart failure similarly. In acute low-flow ischaemia, glucose uptake is augmented via translocation of GLUT receptors to the cell surface.[26] In the setting of chronic myocardial hypoperfusion, glucose uptake is stable, but there is an increase in lactate production associated with a decrease in ATP production.[27] These changes trigger upregulation of GLUT and the enzymes of glucose oxidation. Acute no-flow ischaemia similarly increases glucose uptake owing to translocation of GLUT-4 receptors.[7] Nevertheless, FFAs continue to be the predominant substrate in ischaemic heart disease,[28] and there is potential benefit to be gained by promoting glucose metabolism.

In mild to moderate heart failure there is a reduction in fatty acid oxidation. Glucose uptake is typically preserved or increased, but this fails to compensate for the loss of energy production from FFAs because there is typically relative block of the entry of pyruvate into the TCA cycle (at the level of PDH) with inadequate compensation by anapleurotic mechanisms.[29 30] The concomitant reduction of both PPARα, the oxidative enzymes and shift in substrate use have been grouped together as the likely control mechanism of metabolic adaptation in heart failure. In advanced heart failure, insulin resistance develops within the myocardium, and studies have shown a decline in glucose uptake.[31]

Changes are also found in the process of oxidative phosphorylation and the creatine kinase shuttle. The mitochondria are increased in number yet are structurally abnormal[32]; the activity of electron transport-chain complexes are reduced[33]; and the number of uncoupling proteins are increased.[18] The enzymes involved in the creatine kinase shuttle are reduced, resulting in a decline in ATP delivery to the myofibrils by up to 71%.[34]

## METABOLIC MODULATION OF STABLE ANGINA

Most prophylactic anti-anginal agents act via an alteration in haemodynamics such as a reduction in systemic vascular resistance, coronary vasodilation or negative inotropism, to improve the disparity in myocardial oxygen supply and demand. Drugs that merely alter substrate utilisation are dissimilar in that they have little effect on coronary haemodynamics, yet have been shown to be potent anti-anginal agents, especially as adjuncts to contemporary therapy. This factor alone can be useful in patients whose treatment doses are limited by symptoms of

**Table 1** Overview of the actions and utility of metabolic agents

| Agent | Action | Effect | Angina | ACS | Cardioprotection | HF |
|---|---|---|---|---|---|---|
| Perhexiline | CPT inhibition | Partial FFA inhibition leading to ↓FFA and ↑glucose metabolism | Effective anti-anginal and proved safety with level monitoring | Unclear, may have effects other than metabolic modulation | — | ↑ LVEF, ↑$VO_2$ |
| Trimetazidine | Debated—likely inhibitor of 3KAT | Partial FFA inhibition leading to ↓FFA and ↑glucose metabolism | Effective anti-anginal with proved safety record | Limit ischaemia—reperfusion injury after primary PCI | Reduction in troponin release following surgery. Limit reperfusion injury in PCI | ↑LVEF, ↓ in cardiac dimensions (remodelling), ↓NYHA class |
| Etomoxir | CPT inhibition PPARα activation | Potent irreversible FFA inhibition leading to ↓FFA and ↑glucose metabolism | — | — | — | Effective yet side effects prohibitive |
| GIK | Direct action on glucose uptake | Increase GLUT receptor activation to ↑glucose and ↓FFA metabolism | — | Debated—unlikely beneficial | Improve postop recovery and decrease arrhythmias | Chronic treatment impractical |

CPT, carnitine palmitoyltransferase; LVEF, left ventricular ejection fraction; 3KAT, 3-ketoacyl-CoA; PCI, percutaneous coronary intervention; PPARα, peroxisome proliferator-activated receptor α.

hypotension or bradycardia. A list of these medications and mechanisms of action are outlined in table 1.

β-Blockers, a common angina treatment, may alter substrate utilisation in addition to their other mechanisms of action. Using radioactive trace FFA and glucose tracers, Wallhaus *et al*[35] demonstrated a 57% reduction in myocardial FFA uptake following treatment with carvedilol in patients with heart failure, suggesting a shift in substrate utilisation towards carbohydrates. We will limit our discussion to primary metabolic manipulating drugs to those that have been investigated in humans. Both perhexiline and trimetazidine are available in the UK on a named patient basis. Trimetazidine is licensed for use in chronic angina in a number of European countries while perhexiline is licensed in Australia and New Zealand.

### Perhexiline

Perhexiline maleate is a metabolic modulating drug that gained popularity in the 1970s until it was linked to both peripheral neuropathy[36] and hepatoxicity.[37] These effects have since been demonstrated to occur in patients bearing a genetic variant of the hepatic enzyme CYP2D6, so called 'slow hydroxylators'. These patients do not metabolise the perhexiline as effectively and the drug accumulates, leading to its toxicity. However, it has since been shown that the risk of toxicity can be dramatically reduced by maintaining plasma concentrations in an established normal range of between 0.15 mg/l and 0.6 mg/l by adhering to the protocol shown in table 2.[38] There is wide variation in the dose required to achieve these levels, with patients being started on 100 mg twice daily. Early randomised controlled trials in patients with coronary artery disease demonstrated that it markedly relieved symptoms of angina, improved exercise tolerance and increased the workload needed to induce ischaemia when used as monotherapy.[39] Cole *et al*[40] used perhexiline in a small randomised, double-blind, crossover study of 17 patients with titration of drug dose according to plasma levels. None of the patients developed a major adverse event and the clinical efficacy of perhexiline as an anti-anginal drug was re-established. In this study, 65% of perhexiline-treated patients (as opposed to 18% on placebo) experienced an improvement in their angina symptoms even in those patients already on contemporary anti-anginal therapy. In the isolated rat heart perhexiline acts, at least in part, by shifting myocardial substrate utilisation from fatty acid to carbohydrate through inhibition of CPT-1 and, to a lesser extent, CPT-2, resulting in increased glucose and lactate utilisation.[41]

### Trimetazidine

Trimetazidine 1-(2,3,4-trimethoxybenzyl) piperzine dihydrochloride is a metabolic modulating agent that is likely to act by inhibition of the enzyme long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT), which is a crucial enzyme in the β-oxidation pathway.[42] Trimetazidine is prescribed as a modified release preparation at a dose of 35 mg twice daily and has the advantage of not requiring plasma level monitoring.

**Table 2** Suggested dosing adjustments for perhexiline

| Perhexiline concentration (mg/l) | Recommended new daily dosage |
|---|---|
| <0.15 | Double daily dose |
| 0.15–0.59 | No change |
| 0.6–0.89 | Reduce by 25% |
| 0.9–1.19 | Halve daily dose |
| >1.2 | Cease for 1 week, then reduce daily dose to 25% of previous dose |

Several studies have shown that trimetazidine is as effective as classic haemodynamic agents in improving myocardial ischaemia and is better tolerated. In stable exertional angina, trimetazidine improves exercise tolerance and elevates ischaemic threshold as much as β-blockers or calcium channel blockers.[43 44] Detry *et al* studied 149 men with stable angina in a double-blind parallel group study using exercise testing to measure anti-ischaemic effect on exercise capacity and time to ST-segment depression with patients on either propranolol or trimetazidine. There was no significant difference in the improvement seen in both groups. The heart rate and rate × pressure product at rest and at peak exercise remained unchanged in the trimetazidine group but was significantly depressed in the propranolol group.[43]

### Ranolazine

Ranolazine is similar to trimetazidine in that it is another piperazine substitution compound. It is an effective anti-anginal, and owing to its ability to inhibit 3-KAT in pharmacological studies, this was initially thought to be its likely mechanism of action.[45] It is likely that it never reaches sufficient tissue levels in humans to achieve this and the most established alternative mechanism is inhibition of the late sodium current.[46]

### Etomoxir

Etomoxir is an inhibitor of CPT-1. An initial small, non-randomised study showed improvement in symptoms in heart failure.[47] Following this, the drug was withdrawn from the market because of side effects on the liver, which were detected in a larger, randomised study.[48]

## METABOLIC MODULATION IN ACS

Glucose-insulin-potassium (GIK) has been used in the setting of myocardial infarction in the hope of improving infarct size and outcome. The mechanism of benefit of the GIK infusion is thought to be due to increased glycolysis and reduction in FFA uptake and metabolism by myocardial cells.[49] This has been professed to lead to lower myocardial oxygen requirement, a reduction in proton and free radical accumulation, and improved myocardial energetics.[49 50] A meta-analysis of 16 trials of GIK infusion versus control involving almost 5000 patients indicated a reduction in mortality risk with GIK infusion therapy of 18%, with wide CIs (HR, 0.82; 95% CI 0.68 to 0.98; p=0.03). CREATE-ELCA[51] was a randomised controlled trial of 20201 patients with STEMI who presented within 12 hours of symptom onset. High-dose GIK infusion had a neutral effect on mortality, cardiac arrest and cardiogenic shock.

The use of insulin in the presence of diabetes has been well established since the DIGAMI (Diabetes Insulin-Glucose in Acute Myocardial Infarction) trial, which demonstrated improved glucose control and a reduction in long-term mortality by 30%–50% for people not previously receiving insulin, with decreased mortality of subsequent myocardial infarction.[52] The use of insulin in this setting has since been brought into question with the results of the DIGAMI 2 study,[53] which failed to replicate the results of DIGAMI 1. The study design was similar but it seems that blood glucose in the control group was as well controlled as in the aggressive management arms. Despite this, glucose level was a strong, independent predictor of long-term mortality in this patient category.

Trimetazidine has also been studied in small clinical trial of ACS patients undergoing percutaneous coronary intervention (PCI) and showed reduced post PCI troponin I and an improvement in cardiac function as assessed by

echocardiography.[54] In one small study, perhexiline appeared to reduce recurrence of ischaemia in patients with ACS, an effect that appeared, at least partly, attributable to increased platelet nitric oxide sensitivities.[55]

## METABOLIC MODULATION IN HEART FAILURE

Despite continuing advances in the treatment of heart failure, with neurohormonal blockade, device therapy, revascularisation and transplantation, there is an urgent need for new therapies with novel modes of action to treat the heart failure epidemic.[56] The concept of any energy-starved heart is not new and it is firmly established that energy deficiency has a pivotal role in heart failure.[57] Theoretically, this could be due to a diminished ATP-generating capacity or an increased energy demand, related to changes in wall stress, or a combination of the two. The heart requires energy for cell preservation, maintenance of ionic gradients (important in ischaemia) and, most importantly, for myofibrillar contraction. The heart consumes more energy than any other organ and failure to produce an adequate amount of energy causes mechanical failure of the heart.[3]

Recent advances in imaging technology now allow non-invasive estimations of the energy status of the human heart, principally by using phosphorus-31 magnetic resonance spectroscopy to estimate ATP and phosphocreatine concentration and the PCr/ATP ratio. Phosphocreatine is an important short-term energy store that maintains a high phosphorylation potential under conditions of increased energy demand such as exercise. This first allows the transport of energy from its source at the mitochondrion to the point of utilisation at the myofibrils quickly and, second, it can generate ATP from ADP 10 times faster than via oxidative phosphorylation. Myocardial PCr/ATP ratios are reduced in heart failure and correlate with NHYA class[58] as well as risk of death.[59] MRS studies have failed to provide a compelling causal relation between such energy deficiency and HF.

Furthermore, the metabolic concept of heart failure is supported by the finding of reduced insulin sensitivity in idiopathic dilated cardiomyopathy and diabetic cardiomyopathy (cardiomyopathy in diabetes in the absence of ischaemic heart disease). There is a higher than expected incidence of heart failure in diabetes than cannot be accounted for by ischaemic heart disease alone. Both patients with diabetic cardiomyopathy and the idiopathic DCM population are significantly more insulin resistant and have a higher prevalence of frank glucose dysmetabolism when challenged with an oral glucose load.[60] Epidemiological evidence suggests more than simply a correlation between insulin resistance and heart failure, demonstrating that insulin resistance precedes HF rather than occurring because of it. Furthermore, insulin resistance and diabetes portend a worse prognosis in heart failure.[61] The mechanism underlying this is complicated and results from both changes in energy metabolism as well as other effects of insulin on the cell. Insulin receptor activation indirectly inhibits FFA metabolism by promoting glucose metabolism. In insulin resistance there is an increased reliance of FFA metabolism which leads to increased oxygen consumption, decreased cardiac efficiency and the potential for lipotoxicity,[19 62] which could lead to overt cardiac failure with the addition of another stressor such as hypertension. Moreover, many established therapies in heart failure improve insulin resistance such as ACE inhibitors, angiotensin receptor blockers and statins that all exert favourable effects of glucose metabolism[63–65] and medications that work primarily by improving insulin sensitivity such as metformin or thiazolidinediones offer potential new treatments. Unfortunately metformin carries a theoretical risk of lactic acidosis and recent controversy has arisen over rosiglitazone (a thiazolidinedione) and congestive cardiac failure.[66] This effect is likely to be due to fluid accumulation, which is a class side effect, and this outweighs possible salutary metabolic effects.

A series of studies have demonstrated that the use of agents that alter substrate use might be useful in heart failure. Some of these agents, such as perhexiline, are currently used in highly symptomatic patients with heart failure who are already receiving optimum medical therapy.[67] Perhexiline has been used as an anti-anginal agent as outlined above and has since been used in a relatively small clinical trial of 56 patients with chronic heart failure who exhibited a substantial improvement in LVEF, $VO_{2max}$, and quality of life (QOL).[68] This double-blind, randomised trial also demonstrated improvements in skeletal muscle energetics by measuring PCr recovery after exercise using magnetic resonance spectroscopy.

Cardiac magnetic resonance spectroscopy has been used to assess another promising agent, trimetazidine, which improves myocardial energy stores as measured by PCr/ATP ratio.[69] Trimetazidine has been investigated in small numbers of patients with heart failure and also proved beneficial with improvement in ventricular function (both systolic and diastolic) and dimensions in elderly patients with ischaemic cardiomyopathy,[70] as well as patients with diabetes.[71] Trimetazidine was also used for one of the longer trials of metabolic modulation in heart failure. Napoli *et al*[72] studied 61 patients for 18 months and demonstrated improvement in LVEF and dimensions leading to the hypothesis that metabolic modulation in heart failure can lead to beneficial remodelling. A recent small study using PET has investigated the effects of trimetazidine on FFA metabolism. Cardiac FFA oxidation modestly decreased and myocardial oxidative rate was unchanged, implying increased oxidation of glucose and thus supporting its mechanism of action.[73]

Insulin increases glucose utilisation yet the complications of long-term parenteral therapy and the risks of hypoglycaemia mean that insulin is an unattractive therapeutic option. Despite this, its utility in chronic ischaemic cardiomyopathy has been demonstrated by the application of glucose-insulin-potassium to improve left ventricular dysfunction.[14]

## FUTURE DIRECTIONS

Two further classes of metabolic modulating agents warrant discussion, as these are likely to have a role in the development of new clinical agents for potential use in angina and heart failure.

The first of these agents are the malonyl-CoA decarboxylase inhibitors. Malonyl-CoA is a potent endogenous inhibitor of CPT-1 and is formed from carboxylation of acetyl-CoA by aceyl-CoA carboxylase. Malonyl CoA is broken down by malonyl-CoA decarboxylase. Inhibitors of malonyl-CoA decarboxylase (MCD) increase malonyl CoA, resulting in inhibition of CPT-1 and a subsequent reduction in fatty acid metabolism and increase in carbohydrate metabolism. Cardiac MCD is now recognised as a central regulator of fatty acid oxidation via control of intracellular malonyl-CoA levels.[74] These agents are yet to be tested in humans; however, very promising results have been achieved in animal models of ischaemia. When administered during ischaemia in the pig model, Stanley *et al*[75] demonstrated a four-fold increase in malonyl-CoA content, reduced FFA oxidation rate by 87% and a 50% decrease in lactate production, indicating a strong shift in substrate utilisation. Furthermore, in a rat model of MCD deficiency, Dyck *et al*[76] showed improvement of cardiac functional recovery following ischaemia. Further work is

required to test the long-term effect of these agents and their tolerability in the clinical setting.

The second group of agents are glucagon like peptide-1 (GLP-1) receptor agonists. GLP-1 is an insulinotropic hormone released from the intestinal L cells in response to nutrient ingestion. This insulinotropic action has meant these agents have received a great deal of interest as therapies in diabetes mellitus. Previous studies have shown that exanatide (a GLP-1 receptor agonist) treatment resulted in lowering fasting and postprandial glucose concentrations in patients with type 2 diabetes mellitus.[77] GLP-1 acts on the heart both by improving levels of glucose and insulin, much like GIK, and also by an effect on GLP-1 receptors that have been identified in cardiac tissue.[78] A clinical study has shown that GLP-1 improves left ventricular ejection fraction and functional status in patients with congestive cardiac failure.[79] Further research is required to elucidate the exact mechanism of these salutary cardiac effects. Dipeptidyl peptidase IV inhibitors are a new class of hypoglycaemic agents that work by increasing intrinsic incretin levels (GLP-1 and GIP), which inhibit glucagon release, the effect of which in turn, reduces blood glucose and increases insulin secretion. It is possible that these agents will confer similar benefits.

## CONCLUSION

Irrespective of their method of action, metabolic modulating agents all induce a switch in substrate use from FFA towards glucose. This improves cardiac efficiency as the metabolism of carbohydrate produces more ATP per molecule of oxygen. Metabolic modulation has a clear role in the treatment of refractory angina, but its role in ACS is less clear. There are small clinical trials supporting the use of these agents in the treatment of heart failure and this holds great promise for the future.

**Competing interests** MF has applied for a method of use patent for perhexiline. RB declares no competing interests.

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