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In 1996, a triumphant editorial in Science by Brown and Goldstein, Nobel Prize winners for their brilliant work on the role of low-density lipoprotein (LDL) receptor in cholesterol regulation, proclaimed the possible “end of coronary disease… early in the next century”. Yet, nearly 16 million people are living with coronary heart disease and nearly half a million die from it each year, in the United States of America alone.

It is time to stop giving the message that “we are winning the war on heart disease”; in fact, we are now starting to lose the battle against heart disease. All recent trials and meta-analyses in ischemic heart disease (IHD) consistently conclude that available treatments, including coronary revascularization procedures, have a limited impact, if any, on morbidity and mortality.

The 30 November 2009 issue of the Forbes Asia finance magazine published an article entitled “Useless Medicine”, listing treatments that are of no help, increase costs, and may even cause harm. Coronary angioplasty and stents, high-tech cardiac imaging, and investigation of fainting spells topped the list.

Indeed, there is extensive evidence that the gains against mortality from IHD that were observed in many countries from 1965 to 2000 were overwhelmingly the result of improvements in population levels of risk factors, rather than being attributable to invasive procedures or new medications.

These rather bitter-tasting considerations would deserve an in-depth analysis that is beyond the scope of this Editorial. Nevertheless, I cannot but remark how excessive appears the emphasis in current medical literature on coronary artery disease, as opposed to ischemic heart disease.

Many Cardiologists seem to use these terms as if they were synonymous, dramatically underestimating the complexity and multiplicity of factors that can precipitate IHD, and forgetting that coronary artery disease is but one of these factors, because coronary artery disease per se is not necessary or sufficient to cause IHD.

This Special Anniversary Issue of Heart and Metabolism, fully consistent with the editorial strategy of the Journal since its foundation, focuses on the “heart” of the matter: the cardiac cell, its survival, and its performance.

It is my privilege to introduce readers to a remarkable collection of papers reporting on key aspects of cardiac cell function and metabolism in a variety of clinical conditions, including acute coronary syndromes, cardiomyopathy, and diabetes. They are the product of the combined effort of the Editorial Board of the Journal.

I do not wish to summarize here the content of each article, but I can assure you, the reader, that they all represent a state-of-the art paper and merit your full attention…and I do happen to share the concepts they express.

Enjoy your reading!
Evolution of the metabolic approach to heart disease

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Abstract
Cardiovascular disease is a broad term that describes a host of conditions affecting both the heart and the vasculature, ischemic heart disease being the most prevalent. Ischemic heart disease is often accompanied by a drastic change in myocardial energy metabolism that favors fatty acid oxidation at the expense of glucose oxidation. This form of energy production is both inefficient and detrimental to the myocardium. However, both the glucose and fatty acid oxidative pathways can be targeted to improve cardiac efficiency. In particular, decreasing fatty acid oxidation and increasing glucose metabolism can improve cardiac efficiency in the ischemic heart. Optimizing energy metabolism in the diseased heart is an exciting approach, with tremendous therapeutic potential. Although the concept of modulating cardiac metabolism has existed for decades, it has only recently gained momentum with the introduction of new and effective pharmacological agents targeting key components in the metabolic pathways. This review will examine the use of metabolic therapies in heart disease and provide an update on current research and potential new therapies.

Keywords: Cardiac efficiency, fatty acid oxidation, glucose oxidation, ischemic heart disease

Introduction
Ischemic heart disease is the most common form of cardiovascular disease (CVD) and is often the underlying cause of angina, acute myocardial infarction (AMI) and heart failure [1–3]. Traditionally, ischemic heart disease is treated by pharmacological or mechanical means that act primarily either to increase oxygen supply to the heart or to decrease oxygen demand of the heart muscle [1]. Recently, a number of studies of cardiac metabolism have suggested that an additional approach to treating ischemic heart disease is by means of metabolic modulation, whereby optimizing energetics in the myocardium can improve cardiac efficiency of the heart muscle (i.e., increase the contractile work achieved per molecule of oxygen consumed). This emerging approach holds the promise of providing added benefit when used alongside existing therapies.

Energy metabolism in the diseased heart
The relative contribution of glucose and fatty acid oxidation to myocardial energy production dictates cardiac function in addition to efficiency. Therefore, any disruption to the metabolic homeostasis can adversely affect the heart and contribute to cardiac pathologies. In the ischemic myocardium, fatty acid oxidation dominates as the residual source of oxidative phosphorylation as a result both of an increase in fatty acid concentrations in the coronary circulation...
and of subcellular changes that result in a dysregulation of fatty acid oxidation [4,5]. This increased dependence on fatty acids is both inefficient and undesirable at a time of oxygen shortage [1]. Furthermore, high rates of fatty acid oxidation inhibit glucose oxidation via the Randle Cycle phenomenon, thereby uncoupling glucose oxidation from glycolysis [1,6]. This uncoupling eventually leads to proton overload and intracellular acidosis that not only further decreases cardiac efficiency, but also increases the risk for ischemic injury while compromising cardiac contractility [5].

**Metabolic approach to heart disease**

The premise for a metabolic intervention is to switch the energy substrate preference from fatty acid oxidation to glucose oxidation. By increasing glucose oxidation, the ischemic heart will produce less lactate and protons, thereby increasing cardiac efficiency. The energetics of the heart can be altered to favor this shift by the direct inhibition of fatty acid β-oxidation (which results in a secondary increase in glucose oxidation) or by the direct stimulation of glucose oxidation (Figure 1) [7]. A number of pharmacological agents have been developed that act at different levels in the fatty acid and glucose metabolic pathways (Table I). These agents modulate fatty acid metabolism by decreasing the supply of fatty acids to the heart, inhibiting fatty acid uptake and β-oxidation, or stimulating glucose oxidation.

**Therapies targeting fatty acid and glucose supplies to the heart**

One of the earliest strategies to modulate fatty acid metabolism was regulation of the supply of fatty acids and glucose to the heart. Introduced in the 1960s for treating acute myocardial infarctions, glucose–insulin–potassium (GIK) solution was one of the first pharmacological agents used to improve the efficiency of cardiac energy production [8]. Initially, the cardioprotective effects of GIK were attributed to its ability to increase glucose uptake and stimulate glycolysis while reducing the concentrations of free fatty acids (by suppressing lipolysis) and their subsequent oxidation [8,9]. Indeed, early studies in animal models of myocardial infarction demonstrated a favorable switch in energy substrate, in addition to a reduction in infarct size and improved post-ischemic recovery after an infusion of GIK [10,11]. However, there is considerable discrepancy among the findings of recent clinical studies, in which GIK therapy has failed to improve ischemic recovery and mortality. Although both the Estudios Cardiológicos

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**Figure 1. Summary of myocardial energy metabolism and therapeutic targets.** ACC, acetyl coenzyme A carboxylase; CoA, coenzyme A; CPT-1, CPT-2, carnitine palmitoyl transferases-1 and -2; 3-KAT, 3-ketoacyl CoA thiase; MCD, malonyl CoA decarboxylase; P, inorganic phosphate; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase.
Latinoamerica (ECLA) and the Dutch Glucose–Insulin–Potassium Study 1 (GIPS 1) studies found that GIK treatment significantly reduced mortality with reperfusion, the GIPS 2 study did not demonstrate a benefit in terms of mortality or infarct size [8,12]. Even the largest study to assess the effect of GIK on mortality in patients with acute ST-segment elevation myocardial infarction, the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latinoamerica (CREATE-ECLA), produced findings leading the investigators to conclude that such treatment afforded no benefit [13]. Furthermore, a combined analysis of the Organization for the Assessment of Strategies for Ischemic Syndromes-6 (OASIS-6) and CREATE-ECLA found a greater mortality in the GIK group after early treatment [14].

The lack of identified benefit, or even adverse effects, of GIK may possibly be related to a situation in which glycolysis becomes uncoupled from glucose oxidation, leading to intracellular acidosis and ischemic injury [15]. Hyperglycemia is another potential untoward effect of GIK therapy, whereby a glucose overload can exacerbate ischemic injury [8,12]. Differences in patient populations studied, in addition to the dose and timing of GIK therapy, could also account for some of the ambiguity in these clinical studies. Thus further studies are warranted to validate the use of GIK in heart disease, especially for altering myocardial fatty acid oxidation to minimize ischemic injury.

β-Blockers and nicotinic acid are drugs that are commonly prescribed in heart disease. β-Blockers are used to reduce cardiac workload and improve contractility [12,15], whereas nicotinic acid is used mainly for its antiatherogenic effects [16]. However, both have the added benefit of decreasing circulating concentrations of fatty acids. They exert their anti-ischemic effects by decreasing lipolysis, and therefore indirectly reduce myocardial fatty acid oxidation and promote glucose utilization [16–18]. In clinical studies, both agents have been shown to improve cardiac function without increasing oxygen consumption [19–21], an effect desirable for patients with ischemic heart disease or heart failure, or both.

### Therapies targeting the import of fatty acids

In addition to regulation of the supply of substrates to the heart, a more direct approach to the modulation of fatty acid metabolism is to regulate the import of long-chain fatty acids into the mitochondria. Carnitine palmitoyl transferase-1 (CPT-1) catalyzes the rate-limiting step in the mitochondrial uptake of long-chain fatty acids [7]. This enzyme has become the target of several pharmacological agents known as CPT-1 inhibitors, including etomoxir, oxfenicine, and perhexiline [3,12]. All three decrease CPT-1 activity and thus limit fatty acid oxidation while favoring glucose oxidation (via the Randle Cycle) [3]. In animal studies, etomoxir has demonstrated favorable outcomes. Lopaschuk et al [22] showed that etomoxir improved glucose oxidation and cardiac function while protecting the heart from injury after ischemia-reperfusion.
In a separate study, etomoxir was found to reduce myocardial oxygen consumption while sustaining contractile function in ischemic rat hearts [12,23]. Although studies using etomoxir in animals are extensive, epidemiological studies have been limited to a few clinical trials. In one open-label and uncontrolled study, etomoxir was found to improve left ventricular ejection fraction, cardiac output at peak exercise, and clinical status in patients with New York Heart Association Class II–III heart failure [12,24], but the Etomoxir for the Recovery of Glucose Oxidation (ERGO) study was terminated prematurely because of toxicities resulting from irreversible effects on fatty acid oxidation [25]. Although etomoxir has been investigated as a treatment for heart failure, its antianginal properties remain to be evaluated. In contrast, perhexiline was introduced in the 1970s as an antianginal agent effective in improving anginal symptoms and increasing exercise tolerance [3,26]. Furthermore, the findings of recent studies have supported its suitability for the treatment of angina pectoris and heart failure, in addition to short-term therapy for ischemia [12]. A randomized control trial consisting of 56 patients with heart failure receiving 8 weeks of treatment led to the conclusion that perhexiline was associated with an improved left ventricular ejection fraction and peak oxygen uptake (VO₂max) [27]. Although perhexiline may have clinical benefit, its use in treating CVD is limited.

Another approach to inhibiting CPT-1 and decreasing mitochondrial fatty acid uptake is via inhibition of malonyl coenzyme A (CoA) decarboxylase (MCD). MCD is responsible for degrading malonyl CoA, a potent endogenous reversible inhibitor of CPT-1 [7]. Several experimental studies have found that pharmacological MCD inhibitors increase malonyl CoA concentrations in the heart, thereby indirectly inhibiting CPT-1 and decreasing fatty acid oxidation [28,29]. Stanley et al [30] reported that inhibition of MCD by CBM-301940 was associated with a 4-fold increase in malonyl CoA concentration, an 87% decrease in the rate of fatty acid oxidation, and a 50% decrease in lactate production. In a study by Dyck et al [28], MCD knockout mice demonstrated a lower rate of fatty acid oxidation, greater glucose oxidation, and overall improved cardiac function during and after ischemia. These findings suggest that the inhibition of MCD may be a feasible approach to optimizing energy metabolism and have potential in the treatment of heart disease. However, clinical studies using this approach have yet to be performed.

**Therapies targeting fatty acid β-oxidation**

Direct inhibition of fatty acid oxidation can be achieved by targeting enzymes in the β-oxidative pathway, particularly long-chain 3-ketoacyl CoA thiolase (3-KAT). Trimetazidine is a 3-KAT inhibitor that reduces fatty acid oxidation while promoting glucose oxidation via the Randle Cycle [31]. The Trimetazidine in Angina Combination Therapy (TACT) study showed that trimetazidine, in conjunction with either long-acting nitrates or β-blockers, improved exercise test duration and anginal symptoms [32]. Recently, the Cochrane Collaboration conducted a review of randomized studies comparing trimetazidine with placebo or other antiangina drugs in adults with stable angina [33]. This meta-analysis led to the conclusion that trimetazidine is effective in the treatment of stable angina when compared with placebo, alone or combined with conventional antianginal agents, and that trimetazidine may result in fewer failures to continue treatment as a result of adverse events. Furthermore, in the Second Trimetazidine in Poland (TRIMPOL II) study, trimetazidine improved workload, time to 1 mm ST-segment depression, and anginal symptoms in patients already receiving metoprolol, and was beneficial even after percutaneous coronary intervention [34]. A number of studies have shown that trimetazidine can also improve the symptoms of heart failure (for review see [35]). Currently, trimetazidine is the metabolic agent most commonly prescribed worldwide to treat CVD, and is available in Europe and more than 80 countries worldwide [15].

Ranolazine is an antianginal agent recently approved in the USA for treating chronic stable angina [3]. It is structurally similar to trimetazidine and, although substantially less potent than trimetazidine, at clinically relevant concentrations ranolazine partially inhibits fatty acid oxidation while stimulating glucose oxidation, under normoxic and ischemic conditions [36]. Although the mechanism of action remains under investigation, the therapeutic effect of ranolazine on metabolism may be mediated via inhibition of 3-KAT [12]. However, the findings of recent studies suggest that its cardioprotective effects may also be attributable to inhibition of the late sodium current, thereby preventing the sodium-dependent calcium overload that is characteristic of ischemic injury [37]. Support for a metabolic mechanism of action comes from a recent study in which it was shown that ranolazine significantly improved glycated hemoglobin A (HbA₁c) concentrations and recurrent ischemia in patients with diabetes mellitus, and reduced the incidence of increased HbA₁c in those without evidence of previous hyperglycemia [38].

The anti-ischemic effects of ranolazine have been established in numerous experimental studies [39,40]. In an animal model of heart failure, for example, ranolazine increased both ejection fraction and mechanical function without increasing oxygen consumption [41]. In clinical settings, ranolazine has
demonstrated favorable cardiac outcomes in patients with angina. The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) study revealed a significant increase in exercise duration and time to 1 mm ST-segment depression with ranolazine [42]. The Efficacy of Ranolazine in Chronic Angina (ERICA) trial also found that, compared with placebo, ranolazine significantly reduced the frequency of angina episodes and consumption of glyceryl trinitrate in patients already receiving the maximum recommended dose of amlodipine [43]. In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes (MERLIN-TIMI) trial, ranolazine was effective in reducing recurrent ischemic episodes and angina, but not AMI and death, in patients with ischemic heart disease [44]. Ranolazine is an effective antiagulant agent, yet it remains to be clarified whether its cardioprotective effects against ischemia are mediated by metabolic or electrophysiological changes, or both.

**Therapies targeting glucose oxidation**

Glucose oxidation can be directly stimulated with dichloroacetate by inhibiting pyruvate dehydrogenase kinase (PDK), an enzyme that inactivates mitochondrial pyruvate dehydrogenase (PDH) [1,45]. Numerous in-vitro and in-vivo studies have documented that activation of PDH improves glucose oxidation, shifting the energy metabolism to an efficient fuel source. Furthermore, it improves coupling between glycolysis and glucose oxidation, minimizing intracellular acidosis and contractile dysfunction [1,45,46]. In a small clinical study, dichloroacetate increased myocardial efficiency, left ventricular stroke volume, and lactate disposal; however, its use is limited by a short half-life and need for high doses and intravenous administration [47]. Novel PDK inhibitors are currently being investigated.

**Summary**

Over the past decade, considerable progress has been made in the development of new treatments to combat cardiovascular disease. The metabolic approach to treating heart disease has evolved from a broad concept of minimizing circulating plasma fatty acid concentrations to a more refined approach focusing on the enzymatic machinery in the metabolic pathway. Recent advances have led to the development of pharmacological agents targeting specific enzymes such as CPT-1, MCD, 3-KAT, and PDK. Currently, several metabolic therapies are used as adjunct treatments in heart disease, and the findings of recent studies suggest that metabolic modulation could become a mainstay in the treatment of cardiovascular disease.

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Cardiac metabolism in the diabetic patient

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Abstract

Both clinical and experimental studies have pointed to a diabetic cardiomyopathy in humans that produces abnormalities in ventricular structure and function, independent of coronary artery disease or hypertension. A large body of evidence now indicates that metabolic perturbations and development of a cardiomyopathic phenotype are intimately related. In the diabetic heart, glucose oxidation is decreased and fatty acid oxidation is increased. This arises from the interplay of depressed insulin signaling with associated consequences in the control of myocardial glucose uptake and utilization, and increased circulating free fatty acids. Excessive reliance on fatty acid oxidation for ATP production results in greater costs in mitochondrial oxygen consumption. Fatty acids can also induce uncoupling of mitochondria, probably by upregulation of uncoupling proteins. Activity of uncoupling proteins decreases the mitochondrial proton gradient without the generation of ATP, and thereby decreases myocardial energy production. Defects in energy metabolism in the heart are likely to impair energy-requiring processes and therefore myocardial function, cardiac contractile performance, and diastolic function, the latter being a hallmark phenotype of diabetic cardiomyopathy at the earlier stages. This may also limit the ability of the myocardium in patients with type 2 diabetes to withstand ischemia, and may contribute to the increased cardiovascular morbidity and mortality in such patients. 

Keywords: Cardiac energy metabolism, diabetes, fatty acid utilization, mitochondrial uncoupling, ventricular dysfunction

Introduction

Cardiovascular disease largely accounts for the 2-fold increase in mortality associated with type 2 diabetes. Since Rubler and colleagues [1] first suggested the existence of diabetic cardiomyopathy on the basis of postmortem findings in only four adult patients, general agreement has emerged on the type of heart disease that is associated with diabetes mellitus. Both clinical and experimental studies [2–4] have indeed pointed to a diabetic cardiomyopathy in humans that produces abnormalities in ventricular structure and function, independent of coronary artery disease or hypertension. In particular, diabetes is now well recognized as a risk factor for the development of heart failure. Men with diabetes are more than twice as likely to have heart failure than those without the disease, and diabetic women have an even greater risk [5]. Heart failure can affect diastolic function or systolic function, or both. Although little is known about the pathogenesis of diabetic cardiomyopathy, a large body of evidence indicates that it is related to derangements in myocardial energy metabolism [6,7].

The aim of this short review is to summarize our current understanding of the complexity of
cardiac abnormalities that accompany diabetes, with a special emphasis on the relationship between metabolic perturbations and the development of a cardiomyopathic phenotype. An understanding of the effects of these metabolic disturbances on cardiac myocytes should be useful in optimizing therapeutic strategies to influence myocardial function favorably.

Cardiac energy metabolism in diabetes

In the normal adult heart, myocardial energy substrate preference varies in a dynamic manner to fulfill the tremendous energy needs. Whereas mitochondrial fatty acid oxidation is the chief source of energy, the relative contribution of glucose utilization pathways is significant, allowing the plasticity necessary for permanent cellular energy (ATP) production in the mitochondria in the context of diverse physiologic and dietary conditions. However, in the diabetic heart, utilization of carbohydrates is decreased and fatty acid oxidation is increased (Figure 1). The increased reliance on fatty acid oxidation arises from the interplay of depressed insulin signaling with associated consequences in the control of myocardial glucose uptake and utilization, and increased circulating free fatty acids. Few studies have assessed insulin-stimulated glucose metabolism in the myocardium of patients with diabetes. Those studies that have used positron emission tomography to determine insulin-stimulated fluorine-18-labeled fluorodeoxyglucose uptake have clearly shown that type 2 diabetes is specifically associated with severe insulin resistance, regardless of coronary artery disease and despite normal basal blood flow [8,9].

Compared with glucose oxidation, reliance on fatty acid oxidation for ATP production results in higher costs in mitochondrial oxygen consumption, and calculations of the yield of ATP per oxygen atom consumed (P/O ratios) show that fatty acids are a less efficient fuel when compared with glucose. Therefore, more oxygen is required for ATP production when hearts are metabolizing fatty acids than when they utilize glucose. However, the theoretical difference in

Figure 1. Schematic diagram showing cardiac myocyte energy metabolism. Fatty acids and glucose oxidation are the main ATP-producing pathways. In the uncontrolled diabetic state, because of the combined effects of insulin resistance and high circulating concentrations of fatty acids, glucose oxidation is decreased and fatty acid oxidation is increased. ACC, acetyl coenzyme A (CoA) carboxylase; Acyl carnitine, long-chain acyl carnitine; Acyl CoA, long-chain acyl CoA esters; Akt, also known as protein kinase B; AMPK, 5'-AMP-activated protein kinase; CPT-1, carnitine palmitoyl transferase-1; FA, fatty acid; IR, insulin receptor; PI3-K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle; TG, triglycerides; UCPs, uncoupling proteins.
cardiac efficiency based on calculations of P/O ratios for fat and glucose metabolism still appears greater than expected when the utilization of lipid is increased [10]. This observation feeds the argument that fatty acids can induce uncoupling of mitochondria, perhaps by upregulation of the expression and activity of uncoupling proteins. Uncoupling proteins are mitochondrial transporters present in the inner membrane of mitochondria. They belong to the family of anion mitochondrial carriers including adenine nucleotide transporters. The term “uncoupling protein” (UCP) was originally used for UCP1, which is uniquely present in mitochondria of brown adipocytes [11]. UCP1 catalyzes a highly regulated proton leak, converting energy stored within the mitochondrial proton electrochemical potential gradient to heat. This uncouples fuel oxidation from conversion of ADP to ATP, resulting in decreased synthesis of ATP [12]. Two uncoupling protein isoforms, UCP2 and UCP3, are located in the heart [13]. The expression of mitochondrial UCP2 and UCP3 that are present in human hearts correlates positively with fasting concentrations of plasma free fatty acids [13]. In parallel, there is a decrease in the concentrations of insulin-responsive glucose transporter (GLUT-4) protein.

It is also worth noting that fatty acids reduce insulin action by inhibiting insulin signaling pathways [14], leading to a decrease in glucose transporter function and further reduction in glucose oxidation. Work from a number of sources [15,16] supports the notion that fatty acids play a critical role in triggering the development of cellular insulin resistance through derangements in the insulin signaling cascade. Insulin signaling is mediated by complex multiple pathways characterized by spatial and temporal factors [17,18]. Binding of insulin to the insulin receptor stimulates the tyrosine kinase activity of the insulin receptor, leading to its autophosphorylation and to the subsequent phosphorylation of insulin receptor substrate. Studies have suggested that local accumulation of fat metabolites inside skeletal muscle, such as accumulation of fatty acyl coenzyme A (CoA), induces the activation of atypical protein kinase C (PKC-theta), a serine/threonine kinase that phosphorylates and subsequently activates another kinase, IκB kinase [14], which in turn phosphorylates serine residues on insulin receptor substrate, inhibiting its ability to bind SH2 domains of the p85 regulatory subunit of the lipid kinase, phosphatidylinositol 3-kinase (PI3-K). This results in impaired insulin signal transduction. As a consequence, the recruitment of GLUT-4 transporters to the plasma membrane, and therefore glucose uptake, is compromised. Although this mechanism is active in skeletal muscle and adipose tissue, it has been less clear whether similar mechanisms are apparent in cardiac muscle. This appears likely, since cellular accumulation of long-chain fatty acyl derivatives such as long-chain acyl CoA has been shown to occur [19]. Another role for increased fatty acid concentrations is the attenuation of insulin regulation of 5'-AMP-activated protein kinase (AMPK) [20]. AMPK is a heterotrimeric enzyme that acts as a key ‘‘metabolic switch’’ in the heart in the control of glucose and fatty acid oxidation. AMPK also phosphorylates and inactivates key enzymes involved in ATP-consuming pathways. In the heart, AMPK stimulates fatty acid oxidation by inactivating acetyl CoA carboxylase and so decreasing the concentration of malonyl CoA, which inhibits the entry into, and the subsequent oxidation of long-chain fatty acids in, the mitochondria [21]. Interestingly, it has been shown that AMPK activation is antagonized by insulin [20]. The anti-AMPK effect of insulin is wortmannin-sensitive, like most short-term effects of insulin, suggesting that it is mediated by PI3-K. Therefore, the metabolic consequence of the interaction between insulin and AMPK is normally to increase the concentration of malonyl CoA, and consequently to limit fatty acid oxidation while facilitating glucose oxidation. This may be blunted by the presence of high plasma concentrations of fatty acids in diabetes [22].

**Metabolic disturbances and left ventricular dysfunction in hearts of diabetic patients**

An important question that arises relates to the mechanistic link(s) between altered myocardial energy metabolism and cardiac dysfunction in the diabetic heart. In the context of high-level fatty acid uptake, lipid intermediates accumulate within cardiac myocytes [19]. Experimental data indicate that increases in long-chain acyl CoA esters and fatty acids directly link metabolism to ATP-dependent potassium (KATP) channels in the heart [23]. Long-chain acyl CoA esters facilitate opening of KATP channels by reducing ATP sensitivity. The effects of the acyl CoA esters on KATP channels in cardiac myocytes may be functionally important, because long-chain fatty acids, particularly C16 and C18 fatty acids, serve as the main metabolic substrates of the heart, especially for the diabetic heart. The metabolizable form of these fatty acids is that of acyl CoA esters, which are synthesized at the outer mitochondrial membrane via acyl CoA synthetase, imported into the mitochondria, and subsequently metabolized via β-oxidation. However, as excessive concentrations of long-chain acyl CoA ester are present in the diabetic heart [19], it is tempting to speculate that this may favor opening of cell membrane KATP channels. The resulting shortening of the action potential would lead to a reduction in transsarcolemmal Ca2+ influx [23]. This, together with a deficiency of cardiomyocyte Ca2+ handling, in particular an increased Ca2+ leakage from the
sarcolemmal Na$^+$–H$^+$ exchanger (NHE isoform 1) activity, which is involved in molecular mechanisms of hypertrophy, has been examined. This exchanger contributes significantly to the integrated control of intracellular pH in myocardial cells [26], and therefore directly links the cardiac metabolic state to ionic homeostasis. Recent data on a type 2 diabetic animal model have contributed to shedding light on the central role that NHE1 may play in favoring left ventricular hypertrophy in patients with type 2 diabetes, particularly under conditions of impaired myocardial perfusion and therefore myocardial ischemia in some circumstances [27,28].

Reliance on fatty acid oxidation for the production of ATP, which results in higher costs in mitochondrial oxygen consumption compared with glucose oxidation, may also contribute to ventricular dysfunction [29]. In this context, the activity of UCP2 and UCP3 proteins lowers the mitochondrial proton gradient without the generation of ATP and thereby decreases myocardial energy production. This process could explain why human phosphocreatine to ATP ratios correlate negatively with plasma free fatty acid concentrations [13]. It should be noted here that patients with heart failure also have increased plasma free fatty acid concentrations, high whole-body insulin resistance, and low insulin-stimulated fluorodeoxyglucose uptake in the heart [13,30,31]. A study of mitochondrial energetics in hearts of leptin-receptor-mutant (db/db) type 2 diabetic obese mice has demonstrated that mitochondrial uncoupling is indeed mediated by activation of uncoupling proteins [32]. This probably occurs on the basis of increased delivery of the reducing equivalents FADH$_2$ and NADH from fatty acid oxidation, coupled with a reduced ability for complete oxidation of these equivalents. This might contribute to increased generation of mitochondrial reactive oxygen species, which, in turn, activates uncoupling proteins. Mitochondrial uncoupling may initially represent an adaptive response to increased fatty acid oxidation and fatty-acid-mediated generation of reactive oxygen species. However, it does not completely normalize the overproduction of mitochondrial reactive oxygen species, as demonstrated by the accumulation of products of lipid peroxidation [32]. Therefore, the negative impact of mitochondrial uncoupling is to reduce the mitochondrial supply of ATP. Altered myocardial energetics characterizes these hearts, and clearly precedes measurable alterations in in-vivo cardiac function, as assessed by echocardiography [32,33]. Cardiac high-energy phosphate metabolites, measured at rest in patients with type 2 diabetes using phosphorus-31 nuclear magnetic resonance spectroscopy, have revealed a decrease in phosphocreatine to ATP ratios [33]. Furthermore, data have underlined that, not only do alterations in cardiac energetics occur early in the pathophysiology of type 2 diabetes, but these alterations are correlated negatively with the fasting plasma free fatty acid concentrations.

**Conclusion**

Defects in energy metabolism in the heart are likely to impair energy-requiring processes and therefore myocardial function, cardiac contractile performance, and diastolic function [7], the latter being a hallmark phenotype of diabetic cardiomyopathy at the earlier stages. This may also limit the ability of the myocardium in patients with type 2 diabetes to withstand ischemia, and may contribute to the increased cardiovascular morbidity and mortality in such patients [34]. Manipulation of the myocardial metabolic substrate, aimed at shifting energy substrate preference from the use of fatty acids towards the use of glucose, as can be achieved with trimetazidine treatment [35,36], or at improving the coupling between fatty acid delivery and oxidation in cardiomyocytes to limit the production of reactive oxygen species, could be of benefit to the heart of diabetic patients. Interestingly, and of particular note, is the recent observation that part of the positive effects of trimetazidine on cardiac function might also be related to improved glucose homeostasis and insulin sensitivity [37].

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Metabolism of the diabetic heart


Cardiomyopathies and heart failure

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Abstract

Primary heart failure in cardiomyopathy occurs in (1) hypertrophic cardiomyopathy, a genetic disease of
the sarcomere; and (2) in dilated cardiomyopathy. The latter is often regarded as idiopathic in origin, but
requires exclusion of all possible etiologies which are becoming easier to identify with modern
investigative techniques. Tachycardia-induced cardiomyopathy is now increasingly recognized
especially in uncontrolled atrial fibrillation. Pharmacological treatment of cardiomyopathic heart
failure includes diuretics, renin-angiotensin-aldosterone inhibition (RAAS), β-blockade, vasodilators
and metabolic therapy. Agents that modify fatty acid metabolism such as trimetazidine and perhexiline
and ranolazine can have beneficial effects. In addition, in one study trimetazidine unexpectedly
increased high-density lipoprotein-cholesterol (HDL-C).

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Keywords: Cardiomyopathic heart failure, therapy, metabolic, trimetazidine

“"A big heart is bad heart." Interpretation of the
Egyptian Book of the Dead

Introduction

The term “cardiomyopathy” literally means “disease of the heart muscle” (myopathy, muscle degeneration). In practice, this term specifically means a primary disease of the heart muscle of unknown causation, which may present as heart failure. Of particular interest are two groups of such diseases: those that are genetically determined, such as hypertrophic cardiomyopathy, and those that are of unknown origin, the idiopathic dilated cardiomyopathy (DCM) group. These two extremes are morphologically very different (Figure 1). In the cardiomyopathy group, of specific therapeutic interest is the use of metabolically active agents such as trimetazidine that favorably influence muscle metabolism and lead to clinical improvements.

Primary myocardial failure in cardiomyopathy

In primary myocardial failure, there is no initial defect in the loading conditions of the left ventricle, so that both volume and pressure load are initially normal. For a given end-diastolic volume (and, therefore, sarcomere length), tension generation is inadequate as a result of the primary myocardial disease or cardiomyopathy. Sometimes the cause of the disease is known (secondary cardiomyopathy), and sometimes it is unknown (primary cardiomyopathy). For practical purposes, whenever the origin of the myocardial disease is obscure, it is useful to think of a state of primary cardiomyopathy.

Hypertrophic cardiomyopathy

In hypertrophic cardiomyopathy, the ventricular wall is abnormally thick and the cavity size small (Figure 1b). There are some similarities between the early stages of compensated concentric hypertrophy of this type of
cardiomyopathy and the first phase of hypertrophy in response to a pressure load. The state of marked concentric hypertrophy found in primary hypertrophic cardiomyopathy causes a high systolic ejection fraction, and diastolic dysfunction predominates. Here the major problem lies in the small size of the left ventricular cavity, which is virtually obliterated by the hypertrophy, with consequent inability to fill normally during diastole. The obstructive subvariety of hypertrophic cardiomyopathy, hypertrophic obstructive cardiomyopathy, is characterized by an excessively thick interventricular septum that, during systole, actually obstructs the left ventricular outflow, causing a pressure gradient between the left ventricular cavity and the aorta, thereby increasing the pressure that has to be generated within the left ventricle [1]. Thus the systolic wall stress increases, theoretically to exaggerate the degree of hypertrophy.

Genetic defects are believed to underlie hypertrophic cardiomyopathy, which is now called a “disease of the sarcomere”. The muscle cells undergo excess growth in size in response to a genetic abnormality of the contractile proteins. The growth factors concerned may be similar to those evoked in aortic stenosis. Many abnormal genes have now been found, encoding for different contractile proteins such as β-myosin heavy chain, α-tropomyosin, or cardiac troponin T [2]. However, there is no clear correlation between the myofilament mutation and the clinical phenotype [3]. In the familial disease, there are links to mutations in the genes for AMP-activated protein kinase (AMP kinase), a key enzyme in the control of ATP concentrations in the heart. Thus the suggestion is that energy depletion may underlie the myocardial dysfunction [2]. Of interest, some of the affected patients also suffer from an inborn conduction defect called pre-excitation – that is, the Wolff–Parkinson–White syndrome. The latter may account for the high incidence of sudden death.

Figure 1. Patterns of cardiomyopathy. A normal heart (a) compared with the typical contrasting differences in the phenotypes of the two major types of cardiomyopathy: hypertrophic cardiomyopathy (b) and dilated cardiomyopathy (c).
Dilated cardiomyopathy

The hallmarks of DCM are left ventricular enlargement with wall thinning (Figure 1c), poor systolic function, decreased ejection fraction and cardiac output, and increased end-systolic and end-diastolic volumes. Poor systolic pressure generation causes the ejection fraction to decrease, leading to a self-induced volume overload that is accompanied by a marked increase in wall stress. There is usually a certain degree of compensatory hypertrophy, inadequate to normalize wall stress. DCM can also develop as a secondary phenomenon, whenever a large mass of myocardium is damaged, as in alcoholic damage, after a large myocardial infarct, or with severe generalized coronary artery disease (Table I).

Paradoxically, suspected preceding virus infection of the myocardium is still sometimes included in the category of idiopathic DCM, because it can act on the same cytoskeletal protein as the genetic variety, namely dystrophin. Thus a virus infection that might be occult could elicit a macrophage response that produces cytokines, which then initiate an immune response that damages the cytoskeleton [4]. There might be lymphocytic infiltrates betraying the infective origin, but if the inflammatory response is muted, the patient could present with an apparently “idiopathic” cardiomyopathy.

**Dilated cardiomyopathy**

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**Idiopathic dilated cardiomyopathy**

In idiopathic DCM, the initial event is myocardial failure of unknown cause. That means that a primary cause must be excluded, which is not a simple matter. As investigations become increasingly more sophisticated and molecular in nature, the prophesy is that an exact diagnosis will be made in about 75% of cases (Table II). Increasingly, abnormalities of the cytoskeleton are regarded as basic in DCM. For example, dystrophin defects are common. Similar dystrophin defects are found in Duchenne’s genetically caused cardiomyopathy. Closely related is dystroglycan, an extracellular matrix protein. In animal models, defects in dystroglycan do not directly cause a cardiomyopathy, but can promote the spread of muscle damage – for example, that caused by severe exercise or by excessive β-adrenergic stimulation [5].

**Cardiomyopathy of the elderly**

Cardiomyopathy of the elderly is essentially the result of a decrease in the complement of myocytes (sarcopenia). From a starting point of about 10^9 cells in the heart of a young adult, the number of cells diminishes at the rate of 38 × 10^9 per year [6]. In compensation,
Tachycardia-induced cardiomyopathy

Tachycardia-induced cardiomyopathy is the type of heart failure that is induced in animals by prolonged pacing-precipitated tachycardia. In a dog model of chronic heart failure by rapid pacing-induced tachycardia, as the plasma norepinephrine (noradrenaline) concentration increased, so did that of plasma free fatty acids (FFAs), insulin, and glucose, indicating the adrenergically induced development of insulin resistance [7]. Furthermore, in the same model, treatment by combined α- and β-blockade (carvedilol) was superior to pure β-blockade (metoprolol), showing that metabolic control, for example by β-blockade, was not enough to provide complete therapeutic relief [8]. Interestingly, in this model, a role for decreasing the concentrations of fatty acids – for example by insulin therapy – has not yet been reported.

The human counterpart is a failing heart resulting from incessant ventricular tachycardia or persistent fast atrial fibrillation. For example, in patients with atrial fibrillation without overt failure resulting from mitral valve disease in whom tachycardia-induced heart failure was suspected, the size of the left ventricle was smaller than those in the dilated hearts of patients with idiopathic cardiomyopathy and heart failure [9]. The mechanisms of the heart failure are not fully understood, but include calcium overload, ultrastructural changes such as a decreased myocyte volume, and impaired contraction of isolated myocytes.

Restrictive cardiomyopathy

Restrictive cardiomyopathy is characterized by a “stiff” myocardium, which impairs diastolic relaxation and ventricular filling. The genotype is still under study. Unexpectedly, a single mutation of troponin I could, among members of the same family, cause either restrictive or hypertrophic cardiomyopathy, providing another example of overlap of clinical phenotypes associated with the same molecular genotype.

Cardiomyopathies of Africa

Heart failure of unknown origin is common in Africa, and is under intense investigation [10,11]. Two specific types are peripartum cardiomyopathy [12] and endomyocardial fibrosis [11]. Unfortunately, cardiomyopathies secondary to nutritional deficiency and alcohol abuse remain common [10].

Principles of treatment for congestive heart failure

The same principles apply to the treatment of heart failure caused by DCM as apply to that caused by other conditions.

Pharmacological treatment

Pharmacological treatment of congestive heart failure comprises five major principles.

1. Diuretic treatment, by increasing the output of urine and sodium, relieves the fluid retention and pulmonary congestion, thereby reducing the preload on the heart. Unfortunately, diuretic therapy promotes the secretion of renin, which helps to cause angiotensin-induced vasoconstriction. Diuretics are therefore not given indiscriminately, but are given specifically to reduce symptoms. There are no good data to show that they alter the course of events in heart failure.

2. Inhibition of the overactive renin–angiotensin–aldosterone-system is required. Angiotensin-converting enzyme (ACE) inhibition has several benefits. Most obviously, it relieves the vasoconstriction and excess afterload resulting from excess activation of the renin–angiotensin system. More hidden benefits might lie in the inhibition of the myocardial renin–angiotensin system and lessening of fibrosis, with improvement of diastolic function. These compounds improve exercise capacity,
probably in part through improving diastolic properties. In patients with severe congestive heart failure, added treatment with ACE inhibition decreases mortality. Treatment with angiotensin receptor blockers has generally been less successful in reducing mortality, perhaps because of underdosing, as shown by the much improved endpoint benefits in the HEAAL study that compared losartan 150 mg daily with 50 mg daily [13].

3. **β-Blockade**, cautiously introduced to those already treated as above, lessens mortality. The mechanism may be in part antiarrhythmic, in part reversed remodeling, and in part improved internal calcium cycling. Which β-blocker should be chosen? As enhanced adrenergic activity increases both α- and β-adrenergic outflow, a combined receptor blocker such as carvedilol is usually chosen, especially because, in its favor, it has better outcome data than the pure β-blockers.

4. **Vasodilators** other than ACE inhibitors, such as nitrate–hydralazine were shown to reduce mortality from heart failure when added to pre-existing treatment in patients with heart failure [14]. To date, the only convincing data have been for African-Americans; however, these drugs may be effective when added to treatment given to other patients judged to require a decrease in preload (by dilating the venous system) and a decrease in afterload (by acting as arterial dilators).

5. **Metabolic therapy** (considered below) is coming to the fore as an increasingly well documented concept.

### Less used treatments

**Inotropic agents**

The chronic use of positive inotropic agents, including digoxin, in the treatment of congestive failure is associated with short-term stimulation of the myocardiun, moving it to a higher Frank–Starling curve [15]. The use of such agents has not led to a decrease in mortality; rather, in general, they have lessened survival, perhaps because of the adverse effects of an increased cytosolic concentration of calcium. Note that there has been no well controlled study on digoxin in the modern era, whereas excellent current evidence exists for non inotropic therapy. In practice, the prescription of digoxin is declining; positive inotropes tend instead to be reserved largely for acute heart failure, for the treatment of which levosimendan is a calcium-sensitizing agent that compares well with dobutamine [16].

**Gene therapy**

Gene therapy is rapidly being developed. For example, fibroblasts made “human” by reprogramming with human “stemness” factors improve cytostructure and contractile function when given experimentally to infarcted hearts [17]. The drawback is that these cells must be given intramyocardially.

### Cardiac resynchronization therapy

The benefits of cardiac resynchronization therapy (CRT) for patients with heart failure and with a wide QRS complex are well established, including decreased mortality. Surprisingly, there are also short-term hemodynamic effects of CRT in patients with heart failure and a narrow QRS duration, and without ventricular dysynchrony [18]. One proposed mechanism might be through resensitization of the downregulated β-adrenergic receptor in response to chronic β-adrenergic stimulation, as found in advanced heart failure (Figure 3) [19].

### Surgical procedures

Surgical procedures have expanded the possibilities of survival in severe heart failure. The first and best known major advance was the initial cardiac transplantation in Cape Town by Christiaan Barnard in 1967. This technique is still limited by problems of immune-based rejection of the donor heart, and currently by lack of donors. Left ventricular assist devices unload the dilated ventricle by pumping blood from the ventricle to the aorta; myocyte function and size improve, there is better uptake of calcium by the sarcoplasmic reticulum, and left ventricular remodeling is reversed. Collagen crosslinking improves,
sugest decreased destruction of the extracellular matrix by matrix metalloproteinases. Thus mechanical assistance to the ailing left ventricle allows it to recover towards normal as the load is lessened, thereby providing a bridge to recovery.

Metabolic therapy for cardiomyopathy with heart failure

It is widely accepted that chronic heart failure invokes increased activity of the adrenergic system, with enhanced circulating concentrations of both epinephrine (adrenaline) and norepinephrine (noradrenaline), thus stimulating both α- and β-adrenergic receptors, with the risk of β-receptor downregulation and decreased, rather than increased, inotropic activity (for review see [20]).

Less widely, heart failure is considered to be an abnormal and adverse metabolic state in which increased FFA concentrations inhibit glucose oxidation, with the risk of insulin resistance [21,22]. Chronic inhibition of glucose oxidation by FFAs was first described in the isolated rat heart in 1961 by a Harvard group [23], and has since been confirmed in human studies. Opie and Knuuti [24] have proposed that the FFA-induced damage is widespread, and includes mitochondrial uncoupling associated with the generation of excess reactive oxygen species. The subsequent degree of oxygen wastage varies with the experimental conditions, but can be substantial, including values greater than 50% in some experiments. In this context, the therapeutic aims of metabolic therapy are: (1) to inhibit lipotoxicity and glucotoxicity, and (2) to increase glucose uptake by muscle.

Trimetazidine for heart failure

Trimetazidine is best known as an antianginal agent that is very well tolerated and is widely used in Europe. The major proposed site of action is partial inhibition of fatty acid oxidation in the heart, but many other metabolic effects have been reported. We noted that all previous studies in which trimetazidine had been evaluated as an established anti-ischemic agent in heart failure had either focused on patients with ischemic heart failure or included a majority of patients with that disease [24,25]. Thus the effects mitigating against heart failure, such as an increased ejection fraction, could have been the result of relief of ischemia, with a subsequent improvement in the glucose metabolism of the heart. We noted that decreased fatty acid oxidation of the heart was often held to be the explanation for the beneficial effects of trimetazidine in heart failure, and that the drug was effective in seven studies of heart failure, but that there had been no studies in which the rate of myocardial fatty acid oxidation had actually been measured. To date, our study has been the only one to undertake direct measurement of FFA oxidation by the heart, and the first to study chronic DCM heart failure in patients who had tested negative for myocardial ischemia [24,25].

Extracardiac effects of trimetazidine

We gave trimetazidine orally, 35 mg twice daily, and found a modest increase in the ejection fraction, from 30.9 to 34.8% (P = 0.027) – with, however, an unchanged myocardial fatty acid uptake and a small decrease (10%) in the rate of myocardial oxidation of FFA. We proposed that the myocardium was probably not the major site of action of trimetazidine, especially as work efficiency remained unchanged and therefore there was no effect on any FFA-induced wastage of oxygen. Trimetazidine decreased insulin resistance (glucose decreased from 5.9 ± 0.7 mmol/L to 5.5 ± 0.6 mmol/L, P = 0.047; insulin decreased from 10 ± 6.9 mU/L to 7.6 ± 3.6 mU/L, P = 0.031; homeostasis model assessment index decreased from 2.75 ± 2.28 to 1.89 ± 1.06, P = 0.027). Unexpectedly, plasma concentrations of high-density lipoprotein increased by 11%, presumably reflecting decreased insulin resistance. The decrease in insulin resistance confirmed previous findings in patients with diabetic heart failure; of importance, it is an independent risk factor for mortality in heart failure. We speculated that these extracardiac effects could be related, at least in part, to decreased FFA oxidation and increased glucose oxidation in skeletal muscle, as has been documented in patients with type 2 diabetes and heart failure [26].

We also noted that the change in ejection fraction induced by trimetazidine was highly correlated with β1-receptor occupancy, suggesting a synergistic interaction between the general metabolic changes achieved by trimetazidine and the degree of β1-receptor blockade that was already part of the existing optimal treatment of heart failure in our study. We noted that both β-blockade and trimetazidine improved insulin resistance in heart failure, and postulated that different mechanisms were operative. Hypothetically, decreased FFA oxidation and insulin resistance should increase glucose oxidation in the failing human heart and skeletal muscle, and could decrease FFA- and hyperglycemia-associated oxidative stress. Of note, normalizing excess concentrations of reactive oxygen species counters pathways of hyperglycemic damage [27]. However, no trimetazidine-induced effect on diabetic glucose oxidation in human heart failure has yet been measured.

In summary, the major points in favor of the use of trimetazidine for heart failure are its simplicity of use, the benefit added to existing β-blockade, the
decreased insulin resistance, and the absence of any major adverse side effects.

**Perhexiline for heart failure**

Perhexiline is a partial inhibitor of fatty acid oxidation, inhibiting the mitochondrial uptake of FFAs that is catalyzed by the enzyme carnitine palmitoyltransferase-1 – which differs from the proposed site of action of trimetazidine. It requires monitoring of blood concentrations to avoid liver or neural toxicity. In the only study of perhexiline in heart failure, when the drug was added to the existing therapy, peak exercise-induced oxygen uptake, quality of life, and left ventricular ejection fraction were all improved [28]. Perhexiline also normalized the post-exercise recovery of phosphocreatine in skeletal muscle. Although, to date, that remains the only detailed study of this drug in heart failure, the concordance of the findings with basic science studies and the unique mechanism of action of perhexiline on one mitochondrial enzyme are in contrast to the many diverse effects reported for trimetazidine. Note, however, that there is, as yet, no proof that perhexiline inhibits cardiac FFA oxidation in human heart failure, which remains an inferential mechanism of action.

**Ranolazine for heart failure**

Ranolazine, an agent that structurally resembles trimetazidine, is registered for use in angina of effort in the USA. It was originally regarded as having metabolic effects consonant with the benefits of a shift from fatty acid to glucose metabolism, as found in ischemic rat hearts. In patients with chronic angina and diabetes [29] or with acute coronary syndrome [30], there is improved glycemic control, with a persistent decrease in glycated hemoglobin concentrations, which would agree with the decreased insulin resistance found in the trimetazidine studies. The current suggestion is that ranolazine inhibits the late sodium inward current. Sodium overload may be responsible for a secondary calcium overload by subsequent sodium–calcium exchange, a hypothesis that requires further testing and studies in humans.

**Summary**

In DCM, the diseased myocardium causes the size of the myocardial cavity to enlarge, thereby increasing wall tension. In hypertrophic cardiomyopathy, the cause of the hypertrophy is genetic. The extreme degree of hypertrophy sensitizes the myocardium to a series of abnormalities that eventually cause myocardial fibrosis and, thereby, myocardial failure. The most common cause of cardiomyopathy secondary to pre-existing disease is that resulting from coronary artery disease complicated by myocardial infarction. Before diagnosing primary cardiomyopathy, which is myocardial disease of truly unknown cause, other diseases that must also be excluded are endocrine disorders, antineoplastic drugs, alcohol, and nutritional disorders; latent virus infection may be difficult to exclude. As investigations become more and more sophisticated, the diagnosis of primary idiopathic cardiomyopathy of unknown cause becomes less and less frequent.

From the point of view of treatment of heart failure caused by cardiomyopathy, any underlying cause must be addressed, while the heart failure is managed by standard therapy with diuretics as needed, chronic ACE inhibition (often with aldosterone blockade), and titrated doses of β-blockade. This paper has argued for the addition of metabolic therapy, the best tested example of which in humans is trimetazidine, with its ultimate extracardiac effect being on insulin resistance; perhexiline has only one study in human heart failure in its favor, and ranolazine none to date. Theoretically, each of these agents works on a different molecular site; ultimately, their use in combination should be possible, in order to achieve maximal metabolic benefits.

**REFERENCES**


The winding road to cardioprotection

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Abstract

Over the past two decades, the mortality from acute myocardial infarction (AMI) has been reduced dramatically. Timely reperfusion is the most powerful intervention for limiting infarct size, alongside antiplatelet, antithrombotic and anti-ischemic therapies. Paradoxically, reperfusion itself can also exacerbate myocardial injury, so called “reperfusion injury”, which can cause additional cardiomyocyte death or microvascular obstruction. This may partially explain why the rate of death after an AMI still approaches 10%, despite optimal reperfusion. “Postconditioning” describes the exciting phenomenon whereby a pharmacological agent or a repeated brief ischemic stimulus can provide cardioprotection, despite administration after the lethal ischemic event. Furthermore, cardioprotection has also been demonstrated when ischemic stimuli are applied in a distant organ, so called “remote” postconditioning. Basic laboratory and animal studies have demonstrated significant reductions in infarct size with both pharmacological and ischemic postconditioning. Despite further promising results from proof of concept clinical studies, subsequent larger randomised controlled trials (RCTs) have failed to confirm beneficial effects with pharmacological agents. However, ongoing clinical trials using novel pharmacological agents, alongside RCTs investigating ischemic postconditioning and additional trials investigating “remote” postconditioning, all hold promise.

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Keywords: Acute myocardial infarction, reperfusion injury, ischemic preconditioning, postconditioning, pharmacological cardioprotection

Introduction

After an acute myocardial infarction (AMI), reperfusion is paramount, and is the most powerful intervention for limiting infarct size. Minimizing infarct size is essential to preserve left ventricular systolic function, which is the critical determinant of clinical outcome. With the widespread use of reperfusion strategies alongside ancillary anti-ischemic, antithrombotic, and antiplatelet therapies, the overall 1-month mortality from AMI has been reduced from 18% in the mid-1980s [1] to 6–7% [2] currently. However, despite such advances from these established therapies, the morbidity and mortality from AMI remains significant, with 5–6% of patients having a subsequent cardiovascular event by 30 days [3]. It is therefore necessary to develop novel cardioprotective strategies that can further reduce infarct size, preserve left ventricular function, and improve clinical outcome.

Over the past two decades, the focus on primary percutaneous coronary intervention (PCI) as the gold-standard reperfusion therapy in acute ST-segment elevation myocardial infarction (STEMI) provides a
unique opportunity for adjunctive pharmacological agents, given just before or simultaneously with reperfusion, to attenuate reperfusion injury. This concept defines the pathophysiological process via which myocardium that is viable at the onset of reperfusion subsequently dies – not as an indirect result of predetermined events that occurred during ischemia, but as a direct result of the reperfusion process itself. Such pharmacological manipulation also has great potential for improving clinical outcome in other forms of ischemia-reperfusion injury outside acute STEMI; for example, during coronary artery bypass graft surgery, or in PCI for unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI). It seems appropriate, therefore, to dedicate this Special Anniversary Issue of Heart and Metabolism to summarizing established therapies in the treatment of AMI, and to focus on novel treatments that specifically target reperfusion injury.

Established therapies

Reperfusion therapies

The landmark studies Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto MIocardico (GISSI)-1 [4] and International Study of Infarct Survival (ISIS)-2 [5] demonstrated a 23% reduction in 30-day mortality with fibrinolytic treatment compared with placebo after STEM1. Nine subsequent phase III trials confirmed a similar benefit, and reinforced the time-dependent loss of benefit. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I [6] trial subsequently demonstrated a further 15% mortality reduction with “accelerated” alteplase compared with streptokinase, albeit associated with a greater risk of intracranial hemorrhage. The role of primary PCI as compared with thrombolysis in STEMI was debated for a considerable period; however, 22 randomized trials (involving 7437 patients) undertaken between 1990 and 2003 demonstrated a 19% mortality benefit with PCI when compared with accelerated alteplase, alongside a reduced incidence of myocardial re-infarction, stroke, and intracranial hemorrhage [7].

Antiplatelet and antithrombotic therapies

The role of antiplatelet therapy in AMI is also very well established: four clinical trials encompassing 3096 patients with NSTEMI were the first to demonstrate a 53% reduction in relative risk with aspirin against the incidence of death or myocardial infarction, albeit with dosing varying between 324 and 1300 mg [8–11]. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial [12] highlighted a further 20% reduction in cardiovascular death, myocardial infarction, or stroke with the use of clopidogrel, a prodrug causing irreversible inhibition of the ADP receptor P2Y12, in dual antiplatelet therapy. Prasugrel and ticagrelor are more novel ADP inhibitors, ticagrelor having the advantage of reversible inhibition without any need for metabolic activation [13]. With regard to efficacy, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38 trial [14], involving 13 608 high-risk patients with acute coronary syndrome undergoing PCI, demonstrated a 19% reduction in relative risk of cardiovascular death with prasugrel compared with clopidogrel, but with an adverse significant increase in major and lifethreatening bleeds. Wallentin et al [15] have recently published impressive data from the Platelet Inhibition and Patient Outcomes (PLATO) trial (involving 18 624 patients with AMI), demonstrating a 17% reduction in relative risk of composite vascular deaths achieved with ticagrelor as compared with clopidogrel, and without an increase in the rate of overall major bleeding.

Glycoprotein IIb/IIIa inhibitors are potent antiplatelet agents, blocking the final common pathway in platelet aggregation. A meta-analysis [16] of the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) [17], Chimeric 7E3 Antiplatelet in Unstable Angina Refractory to Standard Treatment (CAPTURE) [18], and Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM PLUS) [19] trials demonstrated a 41% reduction in relative risk in periprocedural complications with glycoprotein IIb/IIIa inhibitors in patients with NSTEMI undergoing early PCI. However, prolonged treatment after PCI actually showed a significant adverse effect on mortality [20].

With regard to antithrombotic therapy, six randomized trials involving 1353 patients with NSTEMI demonstrated a 34% reduction in relative risk in the composite endpoint of death and myocardial infarction with unfractionated heparin [10,11,21–24]. Subsequently, the low-molecular-weight heparin enoxaparin was shown to afford a marginally significant advantage over unfractionated heparin in the same composite endpoint [25]. More recent research has been targeted towards the use of direct thrombin inhibitors, which may be administered orally, although they are not currently licensed for use in AMI.

Anti-ischemic therapies

Anti-ischemic treatments in AMI include β-blockers, nitrates, and calcium-channel antagonists. However
Pathogenesis of reperfusion injury

In order to discuss targets for pharmacological manipulation of reperfusion injury, it is first necessary to understand the proposed mechanisms via which such injury occurs. The term “reperfusion injury” encompasses stunning, the no-reflow phenomenon, and reperfusion arrhythmias (which all occur in the absence of irreversible damage), and irreversible or lethal reperfusion injury. This distinction is very important, as the latter implies reperfusion as an independent mediator of cell death, as opposed to an exacerbator of cellular stress initiated during ischemia. Some controversy remains as to whether reperfusion injury provokes such independent pathology, although consistent basic laboratory data demonstrating reduction in infarct size with pharmacological agents added to the reperfusate have provided striking evidence, which has been taken very seriously.

During ischemia of cardiomyocytes, mitochondrial production of ATP is compromised as a result of inadequate supply of substrates and oxygen. This results in derangement of the mitochondrial electron transport chain, causing further incapacitation of aerobic glycolysis and adverse generation of reactive oxygen species (ROS). Reduced ATP results in the failure of the sarcolemmal Na+/K+-ATPase and the sarcoplasmic reticulum Ca²⁺-ATPase pumps. Anaerobic glycolysis compensates in an attempt to meet energy demands, and results in increased accumulation of H⁺ ions, leading in turn to intracellular acidosis. Overactivity of the Na⁺–H⁺ exchanger occurs to attempt to correct this acidosis. However this, in combination with ATPase pump failure, results in intracellular Na⁺ overload, which can reverse the Na⁺–Ca²⁺ exchanger, leading to intracellular Ca²⁺ overload. The degree of Ca²⁺ overload is also influenced by the extent of generation of ROS, and both are dependent upon the duration of ischemia (Figure 1).

Upon reperfusion, the cardiomyocytes are subject to several abrupt biochemical changes, which include a substantial increase in the production of ROS, further exacerbation of intracellular Ca²⁺ overload, rapid restoration of intracellular pH, mitochondrial re-energization of the electron transport chain, and inflammation [30]. These processes integrate to create an intracellular environment that causes synergistic detrimental effects, and subsequently all processes converge to mediate the opening of the mitochondrial permeability transition pore (mPTP); this initiates cell death by inducing mitochondrial swelling, the uncoupling of oxidative phosphorylation, and the release of death effector proteins, including cytochrome C [31]. Intracellular Ca²⁺ overload also directly mediates both cell death via activation of proteases and hypercontracture with cytoskeletal fragility, leading to membrane rupture [30]. In addition, reperfusion subsequently causes the migration of neutrophils to infarcted tissue, which may mediate further cardiomyocyte death through vascular plugging, enzymatic degradation, and oxidative stress.

In view of the above mechanisms, the principal targets for manipulating reperfusion injury include: reduction of ROS, inhibition of the Na⁺–H⁺ exchanger, inhibition of opening of the mPTP, and attenuation of the delayed inflammatory response [30]. In addition to the above, basic laboratory studies have demonstrated that there are prosurvival antiapoptotic protein kinases (Akt, Erk 1/2) that are specifically activated at the time of reperfusion and may confer significant cardioprotection [32], as well as apoposing kinases that aggravate injury (p38, JNK). Pharmacological agents that have shown great promise in animal studies include erythropoetin [33], adenosine [34], insulin [35], and statins [36] that, when administered specifically at the time of myocardial

Figure 1. Pathophysiology of ischemia in the cardiomyocyte. NO, nitric oxide; SR, sarcoplasmic reticulum.

Figure 1. Pathophysiology of ischemia in the cardiomyocyte. NO, nitric oxide; SR, sarcoplasmic reticulum.
reperfusion, activate survival kinases converging on the mPTP to inhibit its opening [31]. Further studies have also demonstrated the critical time window for blockade of the mPTP, as mPTP inhibitors given a few minutes after the onset of reperfusion have failed to provide any protection against reperfusion injury [37]. The key clinical studies specifically targeting the mechanisms outlined above are explained in the later section, ‘Pharmacological manipulation of reperfusion injury’.

Can ischemia be protective?

The term “ischemic preconditioning” describes the phenomenon whereby brief periods of sublethal ischemia and reperfusion protect against a subsequent lethal “index” ischemia; this was first demonstrated by Murry et al [38]. Unfortunately, clinical application of ischemic preconditioning is limited because the cardioprotective stimulus must be applied before the index ischemic event. As AMI is often unheralded, the use of ischemic preconditioning is therefore restricted to elective procedures inducing ischemia-reperfusion injury, such as coronary artery bypass grafting or heart transplant surgery. Before the concept of ischemic preconditioning, Jaffe and Quinn [39] illustrated a form of innate cardioprotection in patients with coronary artery disease whereby exertional angina induced by initial exercise was greatly attenuated on second exercise if interrupted by a brief rest period; this was termed the ‘‘warm-up phenomenon’’. However, to this day, the mechanisms involved in this cardioprotective mechanism remain uncharacterized.

It has subsequently been found that brief periods of ischemia and reperfusion also protect against infarct size when applied simultaneously with the onset of reperfusion – so-called ‘‘postconditioning’’ [40]. This is an area of intensive research at present; current clinical trials [41–48] are summarized in Table I. Basic research data suggest that the protective mechanisms initiated by both ischemic preconditioning and postconditioning converge to target inhibition of opening of the mPTP [49]. However, postconditioning is also limited by its invasive nature, and therefore is restricted to patients with AMI undergoing PCI. Interestingly, more recent data have demonstrated cardioprotection with brief remote ischemic stimuli, which can be applied before, during, or immediately after the index ischemia; these are termed ‘‘remote ischemic preconditioning’’, ‘‘remote preconditioning’’, and ‘‘remote postconditioning’’, respectively, and they offer the opportunity for protection in all patients with AMI. Some animal studies

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<td>Canada, 2009</td>
<td>?</td>
<td>STEMI &lt;12 h</td>
<td>4 × 1 min balloon I + R</td>
</tr>
<tr>
<td>Remote PostC [48]</td>
<td>Italy, 2009</td>
<td>60</td>
<td>STEMI &lt;6 h</td>
<td>3 × 5 min I + R of lower limb (200 mm Hg)</td>
</tr>
</tbody>
</table>

n, Number of individuals enrolled; ↑, increased; ↓, decreased; AMI, acute myocardial infarction; AUC, area under curve; CK-MB, creatine kinase-myocardial band; I, ischemia (balloon inflation); MR perfusion, magnetic resonance perfusion imaging; MACE, major adverse cardiovascular events; MRI–LGE, magnetic resonance imaging late gadolinium enhancement; R, reperfusion (balloon deflation); STEMI, ST-segment elevation myocardial infarction.
Table II. Pharmacological manipulation of reperfusion injury [29,50–75].

<table>
<thead>
<tr>
<th>Trial [ref]</th>
<th>Location / year</th>
<th>n</th>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Magnesium</strong> (hypothesized to reduce Ca(^{2+}) overload, enhance membrane stabilization, and conserve ATP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIMIT2 [50]</td>
<td>England, 1992</td>
<td>2316</td>
<td>AMI &lt;12 h</td>
<td>8 mmol bolus, then 65 mmol infusion over 24 h Not specified when started</td>
<td>24% RRR in 28-day mortality</td>
</tr>
<tr>
<td>ISS-4 [29]</td>
<td>Multicentre, 1995</td>
<td>58050</td>
<td>AMI &lt;24 h</td>
<td>8 mmol bolus, then 65 mmol infusion over 24 h Started &lt;2 h post STK</td>
<td>No diff in S-5 week mortality; † Incidence hypotension, bradycardia, heart failure</td>
</tr>
<tr>
<td>MAGIC [51]</td>
<td>Multicentre, 2002</td>
<td>6213</td>
<td>STEMI &lt;6 h</td>
<td>2 g bolus, then 17 g infusion over 24 h; 95% received bolus at onset of reperfusion</td>
<td>No diff in 30-day mortality; No harmful effects noted</td>
</tr>
<tr>
<td><strong>Adenosine</strong> (believed to mimic ischemic preconditioning and postconditioning, and prevent neutrophil migration and downstream inflammation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMISTAD [52]</td>
<td>Multicentre, 1999</td>
<td>236</td>
<td>STEMI &lt;6 h</td>
<td>3 h infusion given at start of reperfusion ± 10 min (dose 70 µg/kg per min)</td>
<td>33% RRR infarct size assessed by SPECT 6 days post STEMI, and greater effect in anterior MI</td>
</tr>
<tr>
<td>AMISTAD-2 [53]</td>
<td>Multicentre, 2005</td>
<td>2118</td>
<td>STEMI &lt;6 h</td>
<td>3 h infusion just before thrombolysis or PCI (dose 50 or 70 µg/kg per min)</td>
<td>No diff in composite 1st endpoint (new CHF, death at 6 months); † Infarct size (SPECT) in subgroup</td>
</tr>
<tr>
<td>PROMISE [54]</td>
<td>Spain, 2009</td>
<td>200</td>
<td>STEMI &lt;6 h, undergoing PCI</td>
<td>Intracoronary adenosine given distal to culprit lesion just after TIMI 2 flow</td>
<td>Currently recruiting; 1st endpoint = MRI–LGE 2 weeks and 6 months post STEMI</td>
</tr>
<tr>
<td><strong>Na(^{-}–)H(^{+}) Exchange inhibitor</strong> (attenuation of Na(^{+}) accumulation and subsequent inhibition of Ca(^{2+}) overload)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rupprecht et al [55]</td>
<td>Germany, 2000</td>
<td>100</td>
<td>STEMI &lt;6 h</td>
<td>Cariporide 40 mg bolus over 10 min just before reperfusion</td>
<td>Significant † in LVEF and RWMA with cariporide; CK-MB, CK and LDH release significantly ↓</td>
</tr>
<tr>
<td>GUARDIAN [56]</td>
<td>Multicentre, 2000</td>
<td>11590</td>
<td>NSTEMI, unstable angina PCI or CABG</td>
<td>Cariporide 20, 80, or 120 mg as a 60 min infusion, before PCI or CABG</td>
<td>No diff in death or MI at 30 days, except in CABG patients with cariporide 120 mg, in whom 10% RRR noted</td>
</tr>
<tr>
<td>ESCAMI [57]</td>
<td>Multicentre, 2001</td>
<td>978</td>
<td>STEMI &lt;6 h</td>
<td>10 min infusion of enpizlipase just before reperfusion (thrombolysis or PCI)</td>
<td>No diff in infarct size (HDBH AUC)</td>
</tr>
<tr>
<td>EXPEDITION [58]</td>
<td>Multicentre, 2008</td>
<td>5761</td>
<td>High-risk CABG patients</td>
<td>Cariporide: 180 mg loading dose before operation, then 20 mg/h for 24 h</td>
<td>† Death or MI at 5 days; † MI alone, while mortality † (secondary to † cerebrovascular events)</td>
</tr>
<tr>
<td><strong>C5 complement inhibitor</strong> (potential to modulate inflammatory response during reperfusion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMMA [59]</td>
<td>Multicentre, 2003</td>
<td>960</td>
<td>STEMI &lt;6 h, undergoing PCI</td>
<td>Pexelizumab 2 mg/kg bolus just before PCI, ± 0.05 mg/kg per h for 24 h</td>
<td>No diff in composite (OKMB AUC), or MACE at 90 days; † Mortality at 90 days</td>
</tr>
<tr>
<td>APEX–AMI [60]</td>
<td>Multicentre, 2007</td>
<td>5745</td>
<td>STEMI &lt;6 h, undergoing PCI</td>
<td>Pexelizumab 2 mg/kg bolus just before PCI, ± 0.05 mg/kg per h for 24 h</td>
<td>No diff in all-cause mortality at 30 days; No diff in composite clinical outcome at 30 and 90 days</td>
</tr>
<tr>
<td>RheoRx (surfactant with antithrombotic, anti-inflammatory actions; potential to enhance fibrinolysis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORE [61]</td>
<td>Multicentre, 1997</td>
<td>2948</td>
<td>STEMI &lt;12 h</td>
<td>1 h bolus poloxamer 188, ± followed by 11 h or 23 h infusion</td>
<td>No diff in mortality at 35 days, or composite clinical outcome; † Significant increase in renal dysfunction</td>
</tr>
</tbody>
</table>
### Anti-inflammatory fibrin

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lesion undergoing PCI</td>
<td>2 x 200 mg boluses of FX06 given just before guidewire crossed occlusion</td>
<td>No diff in infarct size assessed by MRI–LGE at 5 days and troponin I at 4 months. No diff in clinical outcome</td>
</tr>
</tbody>
</table>

### GIK infusion

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ECG criteria</td>
<td>GIK (25% / 50 U / 80 mmol/L or 10% / 20 U / 40 mmol/L started before reperfusion</td>
<td>No diff in 30-day mortality or cardiac arrest or cardiogenic shock</td>
</tr>
</tbody>
</table>

### Creat-ECLA

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary or rescue PCI</td>
<td>GIK 25% / 50 U / 80 mmol/L started before reperfusion</td>
<td>No diff in 30-day mortality or cardiac arrest or cardiogenic shock</td>
</tr>
</tbody>
</table>

### Hyperoxemic reperfusion

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diff in infarct size or RWMA index at 14 days, but RWMA improved in patients with anterior MI</td>
<td>Aqueous oxygen perfused for 90 min with onset of reperfusion</td>
<td>No diff in infarct size or RWMA index at 14 days, but RWMA improved in patients with anterior MI</td>
</tr>
</tbody>
</table>

### Selected clinical trials currently in progress / recruiting patients

#### VITAL-1

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSTEMI or STEMI with PCI</td>
<td>ARC1779 (vWF antagonist)</td>
<td>Timeframe 48 h post PCI bleeding Infarct size assessed by MRI–LGE at 3 months (Cardiac death 1 and 15 months)</td>
</tr>
</tbody>
</table>

#### POSTCONII

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI &lt;24 h</td>
<td>Intensive insulin regimen targeting normoglycemia</td>
<td>24 h diff in mean glucose (Mortality, non-recurrent MI)</td>
</tr>
</tbody>
</table>

#### RECREATE

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI &lt;24 h</td>
<td>Intensive insulin regimen targeting normoglycemia</td>
<td>24 h diff in mean glucose (Mortality, non-recurrent MI)</td>
</tr>
</tbody>
</table>

#### SOLSTICE

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI &lt;24 h</td>
<td>Intensive insulin regimen targeting normoglycemia</td>
<td>24 h diff in mean glucose (Mortality, non-recurrent MI)</td>
</tr>
</tbody>
</table>

#### Erythropoetin

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus intravenous EPO just before PCI, followed by infusion</td>
<td>No diff in infarct size or RWMA index at 14 days, but RWMA improved in patients with anterior MI</td>
<td>No diff in infarct size or RWMA index at 14 days, but RWMA improved in patients with anterior MI</td>
</tr>
</tbody>
</table>

#### KAI-9803

<table>
<thead>
<tr>
<th>Setting</th>
<th>Protocol</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety: no 1st endpoint specified</td>
<td>Bolus intravenous EPO just before PCI, followed by infusion</td>
<td>No diff in infarct size or RWMA index at 14 days, but RWMA improved in patients with anterior MI</td>
</tr>
</tbody>
</table>

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Route of administration of drugs is intravenous unless otherwise stated. \( n \), Number of individuals enrolled; \( \uparrow \), increased; \( \downarrow \), decreased; AMI, acute myocardial infarction; AUC, area under curve; BM, blood glucose; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; diff, difference; ECG, electrocardiogram; EPO, erythropoetin; GIK, glucose-insulin-potassium; GLP-1, glucagon-like peptide-1; a-HDBH, alpha-hydroxybutyrate dehydrogenase; hsCRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; LVEF–MRI, left ventricular ejection fraction–magnetic resonance imaging; MACE, major adverse cardiovascular events; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MRI–LGE, magnetic resonance imaging–late gadolinium enhancement; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PKC, protein kinase C; RRR, relative risk reduction; RWMA, regional wall motion abnormality; STEMI, ST-segment elevation myocardial infarction; STK, streptokinase; vWF, von Willebrand factor.
have failed to demonstrate cardioprotection with these remote phenomena, but this may reflect an insufficient remote ischemic stimulus.

**Pharmacological manipulation of reperfusion injury**

Improvement in clinical outcome with pharmacological intervention at the onset of reperfusion defines the very concept of reperfusion injury. Several mechanisms highlighted in the section above on ischemia-reperfusion have been specifically targeted, with several more potential targets yet to be tested. Space constraints prevent us, in this review, from expanding on each treatment tried to date, therefore we have produced a Table (Table II), which summarizes the most important clinical studies [52–75], grouped into categories based on the pharmacological intervention used. In particular, note that, despite a substantial number of adjuncts to reperfusion initially showing great promise, subsequent larger multicenter studies were unable to confirm efficacy (for examples, see [29,50,51]).

In addition to the studies outlined above, studies have also focused on other anti-inflammatory agents such as anti-CD18 and -CD11 antibodies, P-selectin antagonists, antioxidants, intravenous nicorandil (a K<sub>ATP</sub> channel opener) and therapeutic hypothermia, although the larger clinical trials in these categories have also failed to show consistent benefit. With regard to the glucose–insulin–potassium debate, it remains unclear whether metabolic modulation at the moment of reperfusion can afford benefit in clinical outcome. Previous studies may have masked therapeutic potential through inadvertent hypoglycemia; further studies are needed with more intensive monitoring and maintenance of normoglycemia, and in this regard we await the results of the Researching Coronary Reduction by Appropriately Targeting Euglycemia (RECREATE) trial with anticipation.

**Conclusions**

To determine the efficacy of adjunctive treatments given at the onset of reperfusion, meticulous attention to study design and careful selection of end points are paramount. From the two Tables in this article alone, one can see the great variety in both of these parameters, which makes interpretation of a small but potentially invaluable effect on clinical outcome very difficult. Furthermore, established treatments have greatly reduced the morbidity and mortality from AML, reducing the potential absolute benefit from novel therapies. A notable strength of more recent studies is the use of magnetic resonance imaging to assess infarct size with late gadolinium enhancement. This technique is particularly accurate at quantifying the region of ischemia-reperfusion injury and therefore identifying a potential therapeutic benefit. Furthermore, MRI-LGE has been shown to have a significantly higher correlation with prognosis, compared with SPECT. Hence, with an increased awareness of the importance of scrupulous study design that incorporates the use of novel techniques such as MRI–LGE as well as relevant clinical end points, we will be better able to assess the effects of new therapies, thus enabling progression along the winding road to cardioprotection.

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The winding road to cardioprotection


68. Pharmacological Postconditioning to Reduce Infarct Size Follow-


70. Effect of Atorvastatin Administration before Primary Percuta-


72. EPOMI Study: Erythropoietin in Myocardial Infarction. Cli-


Cardioprotective therapy in reperfusion injury: lessons from the European Myocardial Infarction Project – Free Radicals (EMIP-FR)

Mario Marzilli and Alda Huqi
Cardiac and Thoracic Department, University of Pisa, Pisa, Italy

Abstract

Early and successful myocardial reperfusion improves clinical outcomes of patients presenting with acute myocardial infarction (AMI). However, reperfusion itself can exacerbate myocardial injury beyond that caused by ischemia. The European Myocardial Infarction Project – Free Radicals trial (EMIP-FR) was one of the first studies that tested the hypothesis that a cardioprotective agent, such as trimetazidine, could reduce mortality from reperfusion injury in AMI. Compared with placebo, no benefit of such cardioprotection was observed for the population as a whole with respect to mortality. However, a significant benefit was observed in patients who had not undergone thrombolysis and were receiving trimetazidine, confirming the powerful anti-ischemic properties of trimetazidine, even in the setting of AMI.

Keywords: EMIP-FR, free radicals, myocardial infarction, reperfusion injury, trimetazidine

Introduction

It is now well established that early and successful myocardial reperfusion by either thrombolysis or primary percutaneous coronary intervention (PCI) represents the most effective strategy for improving clinical outcomes in patients presenting with acute myocardial infarction (AMI) [1–3]. However, soon after recognition of the crucial role of early coronary reperfusion in AMI [4–7], it became evident that reperfusion itself could potentially exacerbate myocardial damage above that produced by the initial ischemic insult – the so-called “reperfusion injury” [8–10]. Several strategies are currently under scrutiny to limit the ischemia-reperfusion injury that is associated with coronary recanalization in AMI, including administration of cardioprotective agents, mechanical prevention of distal coronary embolization, intermittent reperfusion, and thrombus aspiration.

The European Myocardial Infarction Project – Free Radicals (EMIP-FR)

The clinical relevance of protecting the ischemic myocardium from ischemia-reperfusion injury had been anticipated many years ago by a group of European investigators who, in the early 1990’s, designed the European Myocardial Infarction Project – Free Radicals (EMIP-FR) trial [11]. At that time, reactive oxygen species (ROS) were considered the major factors in ischemia-reperfusion injury, and benefits
observed in animal models were mostly attributed to a reduction in ROS [12]. Furthermore, in the setting of coronary revascularization, an anti-ischemic agent, trimetazidine, had been shown to have anti-ischemic and potentially cardioprotective effects that had been attributed to its antioxidant effects on membrane activity [13–15].

In this context, the EMIP-FR trial, recognizing reperfusion injury as an important determinant of the outcome of myocardial perfusion therapy, was designed to test the hypothesis that trimetazidine could reduce mortality resulting from reperfusion injury in patients with AMI. It was a double-blind, multicenter study, conducted from 1992 to 1996, that included a total of 19,725 patients presenting with AMI, undergoing either thrombolysis or conservative therapy in cases of contraindication to reperfusion. Patients were allocated randomly to groups to receive either trimetazidine or placebo therapy with either the thrombolysis or the conservative therapy. Treatment comprised an intravenous bolus injection of 40 mg of trimetazidine followed by a continuous infusion of 60 mg/24 h for 48 h and was started before or simultaneously with the thrombolysis, and as soon as possible for those not undergoing thrombolysis. The primary endpoint was total mortality at 35 days. Secondary endpoints were death while in hospital, long-term mortality, cardiovascular mortality, and a combined endpoint of major adverse cardiovascular events. The results showed that, compared with placebo, trimetazidine did not confer any benefit on 35-day, hospital, or long-term mortality for the population as a whole. However, in those patients not undergoing thrombolysis, a non significant reduction in mortality was observed in those receiving trimetazidine in the intention-to-treat analysis, which became significant in the per-protocol population analysis.

EMIP-FR was therefore considered a disappointing clinical trial, adding to the list of other such trials with drugs that were very effective in animal models, but ineffective in humans. Although several years have past since the termination of EMIP-FR, we are still left with an unresolved conundrum: why have clinical studies failed to confirm the beneficial effects of pharmacological interventions that were observed in experimental models?

To reconsider the EMIP-FR study, although the investigators are to be congratulated for having promptly addressed the role of reperfusion injury in the clinical outcome of patients undergoing reperfusion therapy in STEMI, it has to be recognized that they committed a common mistake observed in the design of this kind of trials: the choice of the intravenous route of administration. Cardioprotective agents have been shown to prevent reperfusion injury if delivered by the intracoronary route or administered before reperfusion, but to be ineffective when given intravenously or after reperfusion. Besides permitting the drug to reach the ischemic area, intracoronary delivery also makes it possible to achieve a dosage of the drug that is optimal to carry out the specific action. This may be one of the reasons for the negative results of EMIP-FR and similar trials. However, there are other differences in methodology and biology between experimental and clinical studies, including: comorbid conditions, concomitant medication, preconditioning, severity and duration of ischemia, mode of occlusion and reperfusion, treatment-related factors, timing of drug administration, and choice of endpoint. A detailed analysis of these factors goes beyond the aims of this paper, but they should be kept in mind.

What needs to be emphasized is the clear demonstration of the anti-ischemic properties of trimetazidine. In the study design for EMIP-FR, trimetazidine was presumed to improve patient outcomes mostly on the basis of its anti-oxidant effects. However, although the anti-ischemic properties of trimetazidine had been noted previously, its mechanism of action was elucidated only later. Trimetazidine inhibits the enzyme 3-ketoacyl coenzyme A thiolase (3-KAT), and thus reduces fatty acid oxidation and stimulates glucose oxidation [16]. In this way it directly modulates the use of energy substrates in the heart, increases the production of ATP, limits ischemic injury, and thus improves cardiac performance. Moreover, during ischemia, it limits the increase in blood concentrations of free fatty acids, which augment lactate and proton accumulation, decrease cellular pH, and impair calcium handling [17].

In the EMIP-FR study, trimetazidine was tested in two distinct groups of patients: one undergoing reperfusion therapy (thrombolysis) and one not reperfused. As mentioned before, the final infarct size is determined by ischemic necrosis and reperfusion injury (Figure 1). The angiographic equivalent of reperfusion injury is the no-reflow phenomenon, and is observed in up to 35% of patients undergoing successful PCI [18].

To redraw the calcium hypothesis, it is important to understand that calcium homeostasis is a delicate balance between calcium influx and calcium removal. Calcium influx is primarily mediated by the sodium-calcium exchanger, which exchanges extracellular calcium for intracellular sodium. Calcium removal is primarily mediated by the sarcolemmal calcium ATPase, which uses ATP to pump calcium out of the cell. When calcium influx exceeds calcium removal, calcium accumulates in the cytoplasm, leading to calcium overload and cell death.

In addition to calcium overload, excess oxygen-derived free radicals (FRs) can contribute to myocardial injury during reperfusion. FRs are generated as a byproduct of metabolic activity and can damage cellular structures, leading to cell death.

Understanding the mechanisms of reperfusion injury is crucial for developing effective therapeutic strategies. The use of pharmacological agents with anti-ischemic and cardioprotective properties, such as trimetazidine, can mitigate the effects of reperfusion injury and improve patient outcomes. However, further research is needed to fully understand the underlying mechanisms and optimize therapeutic strategies.
Even though, in animal models, reperfusion injury accounts for up to 50% of the final infarct size [19], the burden of each major determinant (ischemia and reperfusion injury) is hard to determine in clinical practice, and this was so in the case of the thrombolysis group in EMIP-FR. In contrast, except for cases of spontaneous reperfusion, the non-reperfused group experienced only the ischemia-related injury and, thus, any benefit obtained in this group of patients can be attributed to the anti-ischemic properties of the drug under investigation. Long-term mortality was greater in the non-reperfused group (25.5%) than in the thrombolysis group (17.1%), and this is consistent with other findings that support prompt revascularization [20]. In addition, patients in the non-reperfused group tended to have more previous myocardial infarction, and to have histories of angina, atherosclerotic disease, or diabetes mellitus. However, despite being at greater risk, patients in this group who received trimetazidine experienced a significant reduction in mortality in the per-protocol population analysis.

**Summary**

The EMIP-FR trial highlights the powerful anti-ischemic properties of trimetazidine in the setting of AMI. However, the study design for the trial prevented demonstration of the postulated cardioprotective effects of trimetazidine compared with reperfusion injury. Other factors may also have contributed to the lack of benefit in this context. Paradoxically, reperfusion injury is relevant in patients who undergo very early reperfusion, when a sizeable part of salvageable myocardium is present. The efficacy of cardioprotective agents is barely evident when the total ischemic time exceeds 2h and the ischemic damage is complete and irreversible [21]. Given the negative results of subsequent clinical trials testing other cardioprotective agents (adenosine, cariporide, calcium channel blockers), it must be admitted that we are still far from correctly translating the findings from animal studies into clinical practice. In fact, even within acceptable time intervals for reperfusion therapy, the incidence of cardiac failure in AMI survivors is increasing progressively, reaching almost 25% [22].

**REFERENCES**


Stable angina: treatment selection

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Conflicts of interest: None.

Abstract

In the management of stable angina, there is time to optimize medical treatment while using stress testing to stratify long-term risk. Percutaneous coronary intervention does not decrease mortality or risk of myocardial infarction when compared with rigorously applied optimal medical treatment and should not be considered as part of a secondary prevention strategy. Whereas all patients should receive long-term medical therapy combined with advice on lifestyle, carefully selected patients will benefit from percutaneous coronary intervention and coronary surgery in addition. As in many areas of medicine, a balanced multidisciplinary approach based on evidence will offer the right treatment to the right patient at the right time.

Heart Metab. 2010;46:39–41.

Keywords: Stable angina, optimal medical therapy, percutaneous and surgical intervention

Introduction

In the UK each year, 320,000 people consult a physician because of angina. In both sexes, the prevalence increases with age. Between the ages of 45 and 54 years, 2–5% of the population have angina; this increases to 10–20% in those aged 65–74 years, and in those older than 75 years the prevalence is 1 in 3. In Europe, approximately 20,000 to 40,000 per 1 million of the population (both sexes) have angina, and the lives of 50% are significantly limited as a consequence [1]. As the population ages, although the death rates from coronary artery disease (CAD) are declining, the overall burden will not decrease, giving rise to increasing management challenges [2].

Treatment objectives

The aims of treatment can be summarized as:

- To reduce or abolish symptoms, resulting in an improvement in the quality of life.
- To improve prognosis by preventing myocardial infarction and death – quantity of life.

It may seem logical to aim for both objectives, but it needs to be remembered that, unfortunately, prolonging life does not always imply improved quality of life, and a shorter life of good quality may be preferable to many. That is to say, we are dealing with individuals, not statistics, although statistics and guidelines are fundamental to the advice we give [3].

Treatment strategies

There are three treatment modalities: medical treatment (which includes lifestyle issues), percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). Often depicted as competitors, they are in fact complementary, and the challenge is to select the right treatment at the right time for the right individual (male or female).

Surgery remains the treatment of choice for those with severe coronary artery disease, in particular severe stenosis of the left main stem coronary artery and when there is triple-vessel disease with reduced left ventricular function [4]. Recent studies have reinforced the PCI guidelines so that, in the context
of stable angina, PCI is primarily an option when medical treatment fails to relieve symptoms and restrictions to a satisfactory degree [5].

**COURAGE study**

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study evaluated patients with stable angina who had objective evidence of myocardial ischemia and significant CAD [6]. After more than 35,000 patients had been screened, only 6.4% (2,287) fulfilled the entry criteria: stenosis of at least 70% in at least one proximal coronary artery and evidence of ischemia on the resting electrocardiogram or after stress testing, or a lesion of more than 80% and symptomatic angina. In the former category, 25% were asymptomatic at entry. Enrolled patients (85% men, 86% white) were allocated randomly to receive PCI plus optimal medical therapy (n = 1,149) or optimal medical therapy alone (n = 1,138). The primary outcome was the composite of death from any cause and non-fatal myocardial infarction during a mean follow-up of 4.6 years.

One of the remarkable features of COURAGE was the adherence to strictly defined optimal medical therapy for both arms of the study. Lifestyle issues were addressed, including diet, exercise, and smoking cessation, and there was an intensive approach to decreasing low-density lipoprotein cholesterol and triglyceride concentrations and blood pressure. Compliance with guideline-driven medical therapy was impressive, with 95% taking aspirin, 93% a statin, 85% a β-blocker with additional medication with amlodipine or isosorbide mononitrate alone or in combination. Lisinopril or losartan were prescribed if the left ventricular ejection fraction was <40%. In the PCI group, drug-eluting stents were approved only towards the end of the study, so that only 2.7% of patients received them. Although this has been a focus of criticism, a recent analysis comparing bare-metal with drug-eluting stents in patients with stable angina revealed no difference in recurrent myocardial infarction or mortality [7]. Whether drug-eluting stents might have reduced the rates of revascularization – and therefore subsequent angina – is debated, but these are not the primary endpoints.

The study found that an initial strategy of PCI in patients with stable CAD did not reduce the cumulative rates of myocardial infarction and death (19.0% compared with 18.5%) or all-cause death (7.6% compared with 8.3%) when compared with optimal medical treatment alone. In addition, it was not cost effective [8]. PCI decreased the rate of anginal attacks initially, but by 5 years there was no difference. Crossovers did occur, and in the first year 16% of the medical group underwent interventions; this increased to 33% by the end of the study. However, 21% of the PCI group needed re-intervention in the first year.

In the COURAGE study, PCI did not emerge as a significant contributor to secondary prevention when the established evidence base included lifestyle modification, lipid-decreasing treatment (statins), aspirin, β-blockade, and angiotensin-converting enzyme inhibitors. COURAGE participants all underwent an initial coronary angiogram, which is not routine practice, but we can deduce from this study that we have time to evaluate risk while initiating optimal medical therapy [9]. This will lead to a symptom-driven (failed medical therapy) or high-risk-driven (abnormal stress testing) approach to invasive evaluation (Figure 1) [10]. As multidetector computed tomography becomes more readily accessible, with reduced X-ray exposure, it may be expected to form an important part of the risk evaluation, complementing or replacing current stress-testing procedures.

**Preceding studies**

The Atorvastatin Versus Revascularization Treatment (AVERT) trial looked at the impact of intensive lipid decreasing (atorvastatin 80 mg) or PCI (no stents) in 341 patients [11]. In the medication group, 95% adhered to high-dose statin, but only 73% of those in the PCI group received statin therapy during the study (compare with COURAGE). In the medical group at the end of the 18-month study, there was a 38% reduction in ischemic events when compared with PCI (21% in the PCI group and 13% in the medical group).

The Second Randomized Intervention Treatment of Angina (RITA-2) study enrolled 1018 patients, with a 7-year follow-up [12,13]. The use of stents was introduced as the study progressed from its initiation in 1992, and PCI was compared with medical treatment. There was an initial symptomatic benefit in the PCI group, but this had disappeared by 7 years, and in the first 2 years the PCI group had experienced more adverse events (6.3% compared with 3.3%; P = 0.02). The primary endpoint at 5 and 7 years – of death or myocardial infarction – was not different between the groups.

In the Medicine, Angioplasty or Surgery Study (MASS-II), CABG, PCI, and medical therapy were compared in 611 patients [14]. At 5 years there was no significant difference in overall mortality, although the secondary endpoint of angina was less frequent in the intervention group. However, medical therapy was suboptimal compared with that in the COURAGE study.
Summary

In stable CAD, PCI has not been shown to decrease mortality or myocardial infarction when compared with optimal medical therapy rigorously applied. An initial conservative medical approach to relieve symptoms and reduce risk factors allows time for the prognostic risk to be assessed. Optimal medical treatment combined with lifestyle advice should be initiated in all patients with stable angina. It will not be the answer for everyone, but it will continue to be essential for those who need PCI or CABG in addition.

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Vastarel MR: from decades of clinical experience in stable angina to new perspectives

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Abstract

Trimetazidine has been known for years as being an effective, “patient-friendly”, anti-anginal agent. Recent studies using the modified release formulation (Vastarel MR) have confirmed the efficacy of trimetazidine in stable ischemic heart disease and suggested that it can be beneficial in a number of cardiac conditions. Trimetazidine has been reported to have a favourable impact on the prognosis of patients surviving an ST-elevation myocardial infarction and to exert a cardioprotective effect in patients undergoing an ischemia-reperfusion sequence, such as patients submitted to PCI or CABG procedures. However, the most exciting perspectives come from the heart failure area, where a beneficial effect has been reported on quality of life and prognosis.

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Introduction

Cardiovascular disease and chronic congestive heart failure represent major public health concerns that continue to have a poor prognosis [1]. The need to improve the management of myocardial ischemia and heart failure is therefore widely recognized, even though many advances have been made over the past decade.

In recent years, strong evidence has been accumulated implicating altered cardiac energy metabolism in the pathogenesis and progression of ischemic heart disease and of heart failure, and this has focused attention on new pharmacological targets for the better management of these diseases [2].

In myocardial ischemia, most patients are initially prescribed drugs (such as β-blockers, calcium antagonists, and nitrates) that address the hemodynamic imbalance between oxygen supply and demand. However, besides hemodynamic imbalance, ischemia has harmful metabolic consequences that also should be addressed from the outset. These are approached through anti-ischemic metabolic therapy, which acts directly on cardiomyocytes and optimizes energy production, enhancing cardiac efficiency and counteracting the metabolic disturbances caused by ischemia.

The use of metabolic therapies for treating myocardial ischemia began to attract attention in the late 1960s and the 1970s. In 1999 it was clearly
recognized that “fundamentally, myocardial ischaemia is a metabolic disorder and thus should ideally be treated by metabolic therapy” [3].

Trimetazidine (Vastarel MR), inhibits 3-ketoacyl coenzyme A thiolase within the cardiomyocytes, which reallocates energy generation from fatty acids to the more efficient oxidation of glucose [4]. By its unique mode of action, trimetazidine increases the amount of energy available for the heart under ischemic conditions by one-third [5]. Today, trimetazidine is the most studied and widely used metabolic anti-ischemic agent.

**Trimetazidine in stable angina**

The therapeutic effect of trimetazidine in patients with stable angina has been extensively investigated in monotherapy and in association with β-blockers, calcium antagonists, or nitrates [6–8]. The clinical benefits include a reduced number of anginal attacks, increased exercise capacity, and a prolonged ischemic threshold and time to 1-mm ST-segment depression.

A recent meta-analysis, performed on the same methodological basis as that published in the Cochrane library, gathered 2786 patients from 22 randomized, placebo-controlled, simple or double-blind, parallel or crossover design trials conducted with trimetazidine in patients with stable angina [9]. It evaluated the effect on symptoms and exercise response achieved by treatment with trimetazidine, in monotherapy and in combination, in comparison with placebo or classic agents. The results of this meta-analysis showed that the overall treatment effect was statistically significant in favor of trimetazidine for all efficacy criteria, with the following differences between the trimetazidine and placebo groups at the end of treatment:

- a reduction of 1.44 (95% confidence interval [CI] 0.82 to 2.06) in the number of weekly episodes of angina.
- a decrease of 1.29 (95% CI 0.71 to 1.88) in the frequency of use of glyceryl trinitrate per week.
- an increase of 23.31 s (95% CI 2.65 to 43.97 s) in total exercise duration.
- a delay of 33.88 s (95% CI 15.94 to 51.83 s) in the time to 1-mm ST-segment depression.

Trimetazidine, therefore, has today an extensive clinical evidence base demonstrating its efficacy in treating patients with stable angina when it is used either as monotherapy or in combination with other antianginal drugs. Moreover, unlike the hemodynamically acting agents, trimetazidine does not suppress heart rate or blood pressure and is very well tolerated, providing a particularly well suited solution for fragile coronary patients such as those with diabetes or who are elderly.

The findings of a recent original research paper, furthermore, revealed that the inclusion of the metabolic agent trimetazidine early in the treatment of patients with stable angina may confer a survival benefit [10]. These were the data from a multicenter study that assessed the independent effects, on 6-month predicted mortality risk, of different antianginal agents used in patients with stable angina who went on to survive a myocardial infarction. The study included 353 relatively young (mean age 55 years) patients with stable angina, most of whom (91.5%) had not had a prior myocardial infarction and had previously been receiving at least one antianginal drug (β-blockers, calcium antagonists, nitrates, nicorandil, or trimetazidine) for an average of 2 years.

The 6-month postdischarge mortality risk was calculated using a GRACE (Global Registry of Acute Coronary Events) prediction score card and nomogram for each patient. For treatments that included the agents listed, the odds ratios (95% CI) of 6-month all-cause mortality after surviving a myocardial infarction were:

- β-adrenoceptor antagonist: 0.63 (0.26 to 1.52; \( P = 0.309 \))
- calcium channel antagonist: 0.76 (0.12 to 2.89; \( P = 0.638 \))
- nitrate: 0.52 (0.26 to 1.05; \( P = 0.070 \))
- nicorandil: 0.62 (0.29 to 1.33; \( P = 0.221 \))
- trimetazidine: 0.36 (0.15 to 0.86; \( P = 0.022 \)).

The results (Figure 1) indicated that only those patients receiving antianginal treatment that included trimetazidine before they had a myocardial infarction experienced a significant reduction in mortality risk.

![Figure 1](image-url)
Trimetazidine in acute ischemic conditions

Various mechanisms are involved in the development and the progression of ischemia-reperfusion injury, such as increased oxidative stress, endothelial dysfunction, and metabolic disturbances. A better understanding of the changes associated with ischemia and reperfusion is now translating into new cardioprotective strategies that might provide benefits over and above those derived from myocardial reperfusion alone [11]. A strategy involving trimetazidine has also been shown to confer important benefits in patients experiencing acute periods of ischemia when undergoing revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]). The effect of pretreatment with, or concomitantly administered, trimetazidine on ischemic reperfusion injury was first studied some time ago. Trimetazidine was reported to protect the myocardium and improve cardiac function during percutaneous transluminal coronary angioplasty (PTCA), without altering heart rate or systemic or intracoronary pressures [12,13].

More recently, it has been shown that trimetazidine prevents contrast-induced nephropathy in patients undergoing coronary procedures, even in those who are at high risk (patients with chronic renal insufficiency) [14]. An accompanying paper [15] reported the beneficial effects of pretreatment with an acute loading dose of trimetazidine before PTCA. Before intervention, 266 patients with coronary artery disease were randomly assigned to a trimetazidine group or a control group. Troponin Ic concentrations were measured before and 6, 12, 18, and 24 h after PTCA. Post procedural cTnl concentrations were significantly reduced in the trimetazidine-treated group compared with the control group, at all time points: 6 h (4.2 ± 0.8 ng/mL compared with 1.7 ± 0.2 ng/mL; \( P < 0.0001 \)), 12 h (5.5 ± 1.5 ng/mL compared with 2.3 ± 0.4 ng/mL; \( P < 0.0001 \)), 18 h (9 ± 2.3 ng/mL compared with 3 ± 0.5 ng/mL; \( P < 0.0001 \)), and 24 h (3.2 ± 1.2 ng/mL compared with 1 ± 0.5 ng/mL; \( P < 0.0001 \)).

Labrou et al [16] have demonstrated that the administration of trimetazidine to patients before and after PCI minimizes PCI-induced myocardial damage and improves left ventricular function 1 and 3 months after the procedure.

The cardioprotective effect of trimetazidine during coronary artery graft surgery was assessed by treating patients with the drug for 3 weeks before surgery and by including trimetazidine in the cardioplegic solution. Patients pretreated with trimetazidine had better ventricular function (\( P = 0.01 \)) than patients treated with placebo [17]. In another study, patients received trimetazidine 3 weeks before CABG and troponin T concentrations were measured before and at 12, 24, and 48 h after the procedure, to evaluate myocardial injury. The patients pretreated with trimetazidine exhibited significantly lower troponin T concentrations after completion of surgery and at each postoperative time point (Figure 2) [18].

The findings of a very recent double-blind, parallel-controlled, randomized trial confirmed the previous demonstration of the beneficial effects of trimetazidine in protecting the myocardium during cardioplegic arrest in open heart surgery [19]. Treatment with trimetazidine was started 2 weeks before the operation. Several biochemical markers – creatine kinase (CK), CK isoenzyme MB (CK-MB), troponin T, myoglobin, and calculation of lactate extraction – were used to detect myocardial injury and hence the degree of myocardial protection afforded by trimetazidine. The results showed that postoperative concentrations of all these markers of myocardial injury were significantly lower in the trimetazidine group than in the control group (\( P < 0.05 \)).

In all the above studies, whether given before, during, or after intervention, trimetazidine consistently showed marked anti-ischemic properties, which translate into important cardioprotective benefits.

Trimetazidine: therapeutic potential for the treatment of ischemic heart failure

Available evidence suggests that heart failure represents a state of cardiac energy starvation – “an engine out of fuel” [20]. This is why the optimization of cardiac energetics by selective inhibition of myocardial fatty acid oxidation may be effective in the early stages of heart failure and might slow down the progression of heart failure and improve cardiac function [21].

Trimetazidine, as an anti-ischemic agent, has also been studied in the more severe stages of ischemic heart disease such as heart failure, predominantly of
ischemic origin. The first report of the beneficial effect of trimetazidine on left ventricular function and of a reduction in the symptoms of patients with ischemic heart failure was published as early as 1989 [22], and other clinical trials confirming these beneficial effects have been completed since then [23,24].

The addition of trimetazidine to conventional medication in long-term treatment has been shown to preserve left ventricular ejection fraction (LVEF) in patients with ischemic dilated cardiomyopathy [25]. The results from a 48-month follow-up of these patients were subsequently reported [26]. The distribution of patients in the New York Heart Association functional classification and their exercise capacity (6-min walk test) significantly improved with trimetazidine. Furthermore, two studies conducted with trimetazidine have provided preliminary findings on its potential beneficial prognostic effects in patients with coronary heart disease presenting with severe conditions such as altered cardiac function. More particularly, in 2005, El Kady et al [27] showed that trimetazidine substantially increased the survival rate (92%, compared with 62% in the placebo group) in 200 patients with left ventricular dysfunction and severe multivessel coronary disease at 2-year follow-up. Later on, Di Napoli et al [26] also showed, in 62 similar patients, that trimetazidine significantly reduced all-cause mortality (by 56%) and admission to hospital for heart failure by (47%).

The positive effects of trimetazidine treatment on cardiac function have also been evaluated in patients with non ischemic cardiomyopathy. A paper published in 2008 [28] reported that trimetazidine was found to improve left ventricular function in patients with chronic heart failure caused by non ischemic dilated cardiomyopathy, and a new study published in 2009 assessed the effects of trimetazidine on cardiac function using myocardial tissue Doppler imaging in patients with heart failure of ischemic or non ischemic origin [29]. In this latter study, trimetazidine or placebo was given to 87 patients with heart failure who were receiving “optimal” heart failure therapy for 3 months. In those treated with trimetazidine, the increase in LVEF was significantly greater than that in the placebo group (9.1 ± 4.2% compared with 2.5 ± 1.4%; P < 0.001). Similar results were observed with the increase in left ventricular and right ventricular myocardial velocities (P < 0.001).

Conclusion

Most pharmacological treatments of myocardial ischemia act on hemodynamic parameters of myocardial ischemia, by increasing oxygen supply (calcium antagonists, nitrates) or decreasing oxygen demand (β-adrenergic receptor antagonists), or both. However, it is now obvious that there is still a need for other antianginal and anti-ischemic drugs as new options for both initial and subsequent management of these diseases. Scrutinizing the altered energy metabolism during myocardial ischemia helps toward better understanding of a more comprehensive anti-ischemic approach, including metabolic optimization, which seems to be “the missing component of the optimal treatment strategy”.

Improvement in cardiac energy metabolism during cardiac ischemia, confirmed as achievable with trimetazidine, is an established therapeutic option for relieving the symptoms of stable angina, but also shows beneficial effects on cardiac function and a possible positive influence on prognosis.

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