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Heart failure in diabetes

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All of us are now aware that type 2 (noninsulin-dependent) diabetes is pandemic in the developed world. Furthermore, even conservative estimates suggest further significant growth in its prevalence, with an approximate twofold increase, over the next two decades. Amongst patients with coronary artery disease, abnormal glucose regulation is extremely common. For example, in the recent EURO Heart Survey on Diabetes presented at the annual meeting of ESC in 2004, more than 50% of the 4196 patients with ischemic heart disease had abnormal glucose metabolism. In addition, many of the patients with newly diagnosed diabetes that was detected during a formal glucose tolerance test would have been missed on the basis of a random glucose test. Given the high prevalence of diabetes in the general population and the fact that most of our patients with coronary artery disease have diabetes or prediabetes, this issue of *Heart and Metabolism* is timely and topical.

In the Basic Article, Danielle Feuvray explains the actions of insulin through its effects on known glucose transporters and signaling intermediates. Although the influences of insulin on glycolysis and β -oxidation in the heart have been known for decades, our increased understanding of the underlying biology have added further layers of complexity. As Dr Feuvray explains, insulin resistance, increased circulating insulin concentrations, or dysregulation of glucose *per se* injure the myocardium. In its most extreme form, this injury manifests as true diabetic cardiomyopathy, with severe contractile dysfunction in the absence of angiographically visible obstructions within the epicardial coronary arteries. The hope is that an increased understanding of the actions of insulin, especially

through mouse models, will reveal novel therapeutic targets for this invidious disease.

In the Main Clinical Article, Vivienne Ezzat and Mark Kearney explain that the treatment of patients with heart failure and diabetes is similar to the treatment of patients with heart failure without diabetes, only more so! As the presence of diabetes further increases the risk of events, the absolute benefit of proven pharmacological interventions is likely to be even greater. Furthermore, tight glycaemic control may reduce injury to the heart through the mechanisms explained in the Basic Article. Interestingly, agents that target the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) not only reduce the complications seen with diabetes, but also reduce the incidence of new cases of diabetes. The mechanism for this robust observation, seen in the Heart Outcomes Prevention Evaluation, European Trial on Reduction of Cardiac Events with Perindopril in stable coronary Artery Disease (EUROPA) and Valsartan Antihypertensive Long-term Use Evaluation trials, is not known, but presumably would reduce the incidence of prediabetes in addition to the conversion of prediabetes to overt diabetes. Drs Ezzat and Kearney emphasize the need for treatments individually tailored to a patient's needs – a refreshing physicianly philosophy in practices increasingly moulded by evidence-base, care pathways, and quality of care measures. What is without doubt is that diabetic patients merit the most meticulous management and control of all modifiable risk factors.

The Metabolic Imaging article emphasizes the complexity of measuring substrate utilization in the hearts of patients with diabetes. Juhani Knutti

Editorial

Heart failure in diabetes

explains that, once the abnormalities in circulating glucose, insulin, and free fatty acid concentrations are controlled, quantitative positron emission tomography can no longer reliably demonstrate impaired glucose uptake/oxidation. In other words, there is no intrinsic cardiac abnormality but, rather, disordered substrate preference is the result of disordered substrate availability, and in particular the increases in free fatty acids.

Romualdo Belardinelli provides a very balanced perspective of new treatments available for diabetes, with an emphasis on the multifactorial benefits of exercise and lifestyle intervention. In addition, findings from his own research suggest that there may be some benefits from therapeutic agents that address the metabolic imbalance in diabetes and improve glucose oxidation at the expense of free fatty acids. Similar hope is offered in the Refresher Corner, in which Lazaros Nikolaidis and Barry Levine discuss

the transcriptional changes that accompany diabetes and the benefits that may accrue from peroxisome proliferator-activated receptor- α or - γ agonists such as the thiazolidinediones. These insulin-sensitizing agents have the potential to reverse many of the derangements that accompany diabetic heart disease but, as pointed out by various authors within this issue of *Heart and Metabolism*, their use is complicated by fluid retention apparently worsening heart failure. In essence, we await further guidance from clinical trials as to how to use these disease-modifying drugs in patients with diabetes and coincident left ventricular dysfunction.

I hope you enjoy this issue of *Heart and Metabolism*, and I trust that its reading does not accompany an energy-dense meal! I'm sure you will find the content educational and that, in response to the question, "Do you want that supersized?", the response will now always be, "No!". ■

Metabolic derangements in insulin resistance

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Abstract

Insulin resistance is an early event in the development of type 2 diabetes, in which insulin production is normal but there are deficient responses to insulin. Because of the importance of insulin in the control of myocardial glucose uptake and utilization, the heart relies more on fatty acid oxidation for its energy requirements. Our understanding of derangements in the insulin signaling pathway in myocardial cells is far from being complete. Future studies should help dissect the complex pathophysiology of the action of insulin on the heart and contribute to the establishment of pharmacological interventions to improve cardiac metabolism and reduce the cardiac dysfunction that is induced by insulin resistance.

■ *Heart Metab.* 2004;25:4–9.

Keywords: insulin signaling pathway, myocardial cell metabolism

Introduction

The action of insulin on the heart, as in other tissues, is initiated by the binding of insulin to its specific cell-surface receptor. Insulin binds to its receptor in the major insulin-responsive tissues of the body, namely skeletal muscle, adipose tissue, liver, and myocardium. This triggers the activation of a signaling pathway the function of which is first to stimulate the transport of nutrients, such as glucose, from the blood supply to these tissues and, secondly, to promote the conversion of these nutrients into storage macromolecules such as glycogen. Failure to regulate the uptake and storage of nutrients efficiently after feeding results in diabetes. Type 1 (insulin-dependent) diabetes is characterized by the failure to synthesize insulin and is the underlying abnormality in approximately 10% of patients with diabetes; it normally occurs in childhood. In contrast, type 2 (non-insulin-dependent) diabetes accounts for about 90% of patients with diabetes and usually occurs in adults. In this form of diabetes, the target tissues become *resistant to the effects of insulin*, presumably because the insulin signaling pathway is impaired. Insulin resistance is an early event in the development of type 2 diabetes, in which insulin production is normal but there are deficient cellular responses to insulin. Patients

suffering from both forms of diabetes suffer long-term complications, including heart disease that occurs independently of obstructive coronary artery disease [1–4] and is therefore termed diabetic cardiomyopathy. Although little is known about the pathogenesis of diabetic cardiomyopathy, evidence has emerged that it may be related to derangements in myocardial energy metabolism [5,6].

Derangements in myocardial metabolism

Under normal conditions, myocardial energy substrate preference varies in a dynamic manner to fulfill the tremendous energy needs of the postnatal mammalian heart. Whereas the fetal heart relies primarily on glucose and lactate, after birth the capacity for mitochondrial fatty acid oxidation increases markedly, affording the adult heart the option of using glucose or fatty acids to meet energy demands, depending on dietary and physiologic conditions (for review, see [7]). In diabetes, this capacity for switches in cardiac energy substrate becomes constrained because of the importance of insulin in the control of myocardial glucose uptake and utilization (*Figure 1*).

The glucose undergoing glycolysis within the heart originates from both the breakdown of

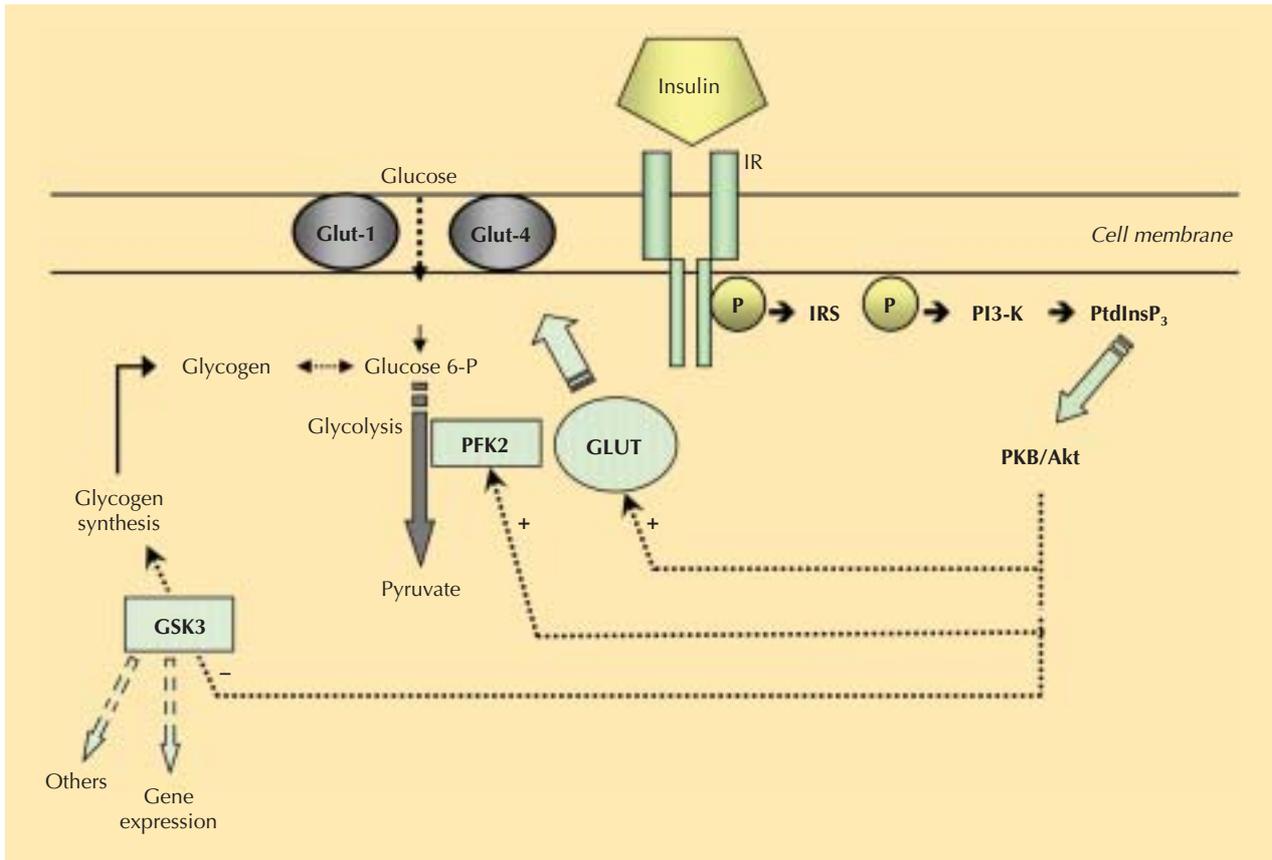


Figure 1. Schematic representation of the regulation of glucose metabolism by insulin in myocardial cells. GLUT, glucose transporter; GSK3, glycogen synthase kinase-3; IR, insulin receptor; IRS, insulin receptor substrate; P, phosphate; PFK2, 6-phosphofructose-2-kinase; PI3-K: phosphatidylinositol 3-kinase; PKB, protein kinase B (also known as Akt); PtdInsP₃, phosphatidylinositol triphosphate.

myocardial glycogen stores and the uptake of glucose from the blood. A family of glucose transporters (GLUTs) has only recently been cloned and characterized, with GLUT 1 and GLUT 4 being responsible for glucose transport in the heart (for review, see [8]). GLUT 4, the “insulin-regulatable” isoform, is the major glucose transporter in all insulin-responsive tissues. GLUT 1 is known mostly as the basal glucose transporter, although insulin might also stimulate translocation of GLUT 1 from intracellular storage vesicles to the plasma membrane [9,10].

Insulin signaling and glucose metabolism

Insulin signaling is mediated by complex multiple cascade pathways characterized both spatially and temporally [11] (for reviews, see [12,13]). Insulin signaling is initiated by the binding of insulin to the insulin receptor. This activates the tyrosine kinase activity of the insulin receptor, leading to insulin receptor autophosphorylation and to the subsequent phosphorylation of insulin receptor substrate (IRS). Insulin signaling downstream of IRS is mediated by at

least two pathways. The first leads to the activation of the mitogen-activated protein kinase (MAPK) cascade, which in turn activates MAPK-activated protein kinase-1 (also known as p90 ribosomal S6 kinase, p90rsk). There is no convincing evidence that this pathway is activated by insulin in the heart. The other pathway that is present in heart is specific for the short-term effects of insulin. It involves activation of a lipid kinase termed phosphatidylinositol 3-kinase (PI3-K). PI3-K phosphorylates its physiological substrate phosphatidylinositol (4,5) bisphosphate [PtdIns(4,5)-P₂] to generate phosphatidylinositol (3,4,5) triphosphate [PtdIns(3,4,5)-P₃]. It was the finding that inhibitors of PI3-kinase, or the over-expression of dominant negative mutants of this enzyme, inhibit most of the cellular responses to insulin that established PtdIns(3,4,5)-P₃ as a key second messenger in the insulin-signaling pathway. PtdIns(3,4,5)-P₃ binds in turn to the pleckstrin homology domain of at least two different serine/threonine protein kinases, namely phosphoinositide-dependent protein kinase-1 (PDK-1) and PKB (protein kinase B, also known as Akt). PDK-1 participates in the phosphorylation and activation of several down-

stream protein kinases, including PKB (for review, see [14]). It is now generally accepted that PKB mediates most short-term effects of insulin and can regulate glucose metabolism at several levels (*Figure 1*), which include, among others, the stimulation of glycogen synthesis by phosphorylation and inactivation of glycogen synthase kinase 3 (GSK3), and the stimulation of glucose uptake.

Increased knowledge has shown that GSK3 is a broadly influential enzyme that is a crucial regulator of many cellular functions (for review, see [15]). Insulin-induced inactivation of GSK3 normally contributes to cellular responses to insulin, such as stimulation of glycogen synthesis (*Figure 1*). The mechanisms contributing to insulin resistance and type 2 diabetes are multifactorial, but one factor is inadequate inhibitory control of GSK3 [16]. As a result, GSK3 activity is above normal in diabetic rodents [16], and in skeletal muscle from patients with type 2 diabetes [17]. GSK3 generally opposes the actions of insulin. Thus GSK3 inhibits glycogen synthesis and alters the expression of genes regulated by insulin [18]. GSK3 was also shown to phosphorylate the insulin receptor coupled protein, IRS, which, in turn attenuates insulin signaling [16]. Evidence that GSK3 is an important regulator in insulin resistance comes from studies in which inhibitors of GSK3 enhanced responses to insulin in a variety of model systems [19–21]. For example, GSK3 inhibitors decreased blood glucose concentrations and stimulated glucose transport and glycogen synthesis in skeletal muscle from insulin-resistant Zucker rats [22,23], and increased IRS expression and glucose uptake in human skeletal muscle [24]. These findings indicate that deficient inhibitory control of GSK3 is an important factor in type 2 diabetes and that inhibitors of GSK3 could be therapeutically beneficial.

PKB/Akt, the key effector of PtdIns(3,4,5)-P₃, participates in the stimulation of glucose uptake through the recruitment of GLUT 4 transporters to the plasma membrane, although the exact targets for the various protein kinases have not been identified. Moreover, recent findings have shown that the stimulation of glucose transport by insulin also implicates a pathway that is independent of PI3-K. This pathway involves the tyrosine phosphorylation of the proto-oncogene Cbl, which activates the TC10 family of Rho GTP-binding proteins. These proteins then interact with unknown effector proteins to allow insulin-stimulated GLUT 4 translocation [11]. The stimulation of heart glycolysis by insulin involves not only the recruitment of the glucose transporter GLUT 4 to the plasma membrane, but also the activation of 6-phosphofructo-2-kinase, which in turn increases the concentration of fructose 2,6-biphosphate, a well known stimulator of glycolysis. Therefore insulin forces the heart to consume glucose.

Insulin signaling and fatty acid oxidation

An additional effect of insulin that has emerged from recent studies is that it also inhibits fatty acid oxidation. This effect of insulin occurs through inhibition of AMP-activated protein kinase (AMPK), a heterotrimeric enzyme (for review, see [25]) that acts as a key “metabolic switch” in the heart in the control of fatty oxidation (*Figure 2*). AMPK phosphorylates and inactivates key enzymes involved in ATP-consuming pathways. In the heart, AMPK stimulates fatty acid oxidation by inactivating acetyl coenzyme (CoA) carboxylase and so decreasing the concentration of malonyl CoA, which inhibits the entry of long-chain fatty acids into the mitochondria and their subsequent oxidation [26,27]. It has been shown that AMPK activation is antagonized in hearts treated with insulin [28]. The anti-AMPK effect of insulin was wortmannin-sensitive, like most short-term effects of insulin, suggesting that it is mediated by PI3-K. The metabolic consequences of the interaction between insulin and AMPK would be to increase malonyl CoA concentration and consequently to limit fatty acid oxidation. Therefore, the resistance of target tissues to the effects of insulin in type 2 diabetes presumably results in the impairment in the insulin signaling pathway. As a consequence, in the uncontrolled diabetic state, because of the importance of insulin in the control of myocardial glucose uptake and utilization, the heart relies almost exclusively on fatty acid oxidation for its ATP requirements (for reviews, see [6,29]).

Fatty acid utilization or glucose utilization?

Cardiac fatty acid utilization pathways are controlled, in part, at the gene regulatory level. Recent studies have demonstrated an important role for the nuclear receptor peroxisome proliferator-activated receptor α (PPAR α) in the transcriptional control of genes involved in cardiac fatty acid uptake and oxidation (for review, see [30]). In an attempt to model the metabolic derangements of the diabetic heart, mice with cardiac-specific overexpression of the nuclear receptor PPAR α (MHC-PPAR) were produced and characterized [31]. The expression of PPAR α target genes involved in cardiac fatty acid uptake and oxidation pathways was increased in MHC-PPAR mice. Surprisingly, the expression of genes involved in glucose transport and utilization was reciprocally repressed in MHC-PPAR hearts. Consistent with the gene expression profile, myocardial fatty acid oxidation rates were increased and glucose uptake and oxidation decreased in MHC-PPAR mice – a metabolic phenotype strikingly similar to that of the

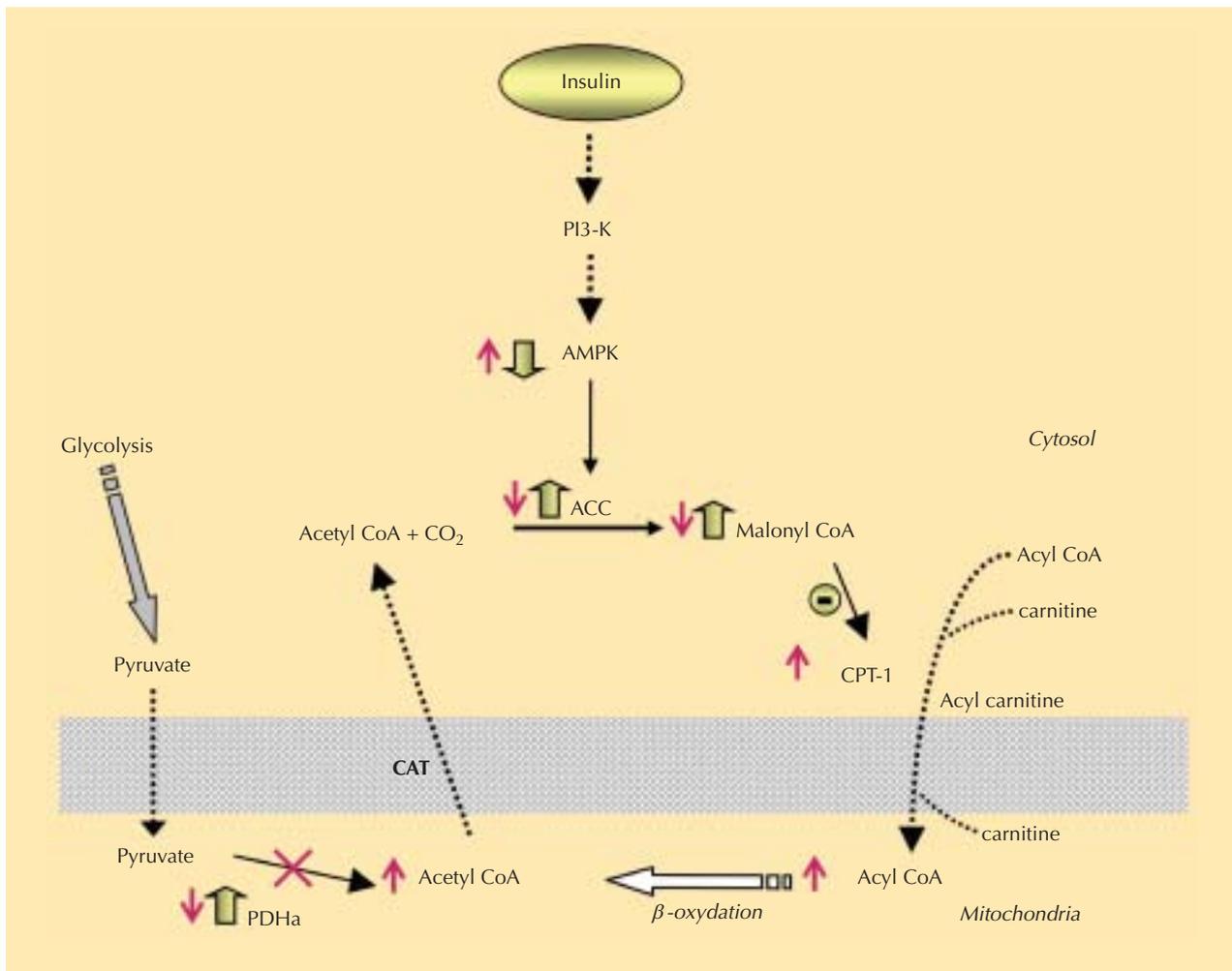


Figure 2. Insulin inhibits fatty acid oxidation through inhibition of AMP-activated protein kinase (AMPK). This results in an increase in malonyl coenzyme A (CoA) concentration, which inhibits the entry of long-chain fatty acids into the mitochondria and their subsequent oxidation. As a consequence, in insulin resistance/diabetes, the heart relies more on fatty acid oxidation for its energy requirements. $\uparrow\downarrow$, Effects of insulin; \uparrow , changes associated with diabetes; ACC, acetyl-CoA carboxylase; CAT, carnitine acetyl transferase; CPT, carnitine palmitoyl transferase; PDH, pyruvate dehydrogenase; PI3-K, phosphatidylinositol 3-kinase.

diabetic heart. In addition, MHC-PPAR hearts exhibited signatures of diabetic cardiomyopathy, including ventricular hypertrophy in association with activated expression of hypertrophic gene markers, and alterations in systolic ventricular function that were dependent on the expression of transgenes.

An important question raised by these results relates to the mechanistic link between altered myocardial energy metabolism and cardiac dysfunction in the diabetic heart. It is possible that, in the context of high-level fatty acid uptake and mitochondrial β -oxidation, toxic lipid intermediates accumulate within cardiac myocytes [5]. Reliance on fatty acid oxidation for ATP production, which results in greater mitochondrial oxygen consumption costs compared with glycolysis and glucose oxidation, could also contribute to ventricular dysfunction.

Reduced myocardial utilization of glucose may also account for the observed cardiac dysfunction in the MHC-PPAR mice. Previous studies of the ischemic and reperfused heart have indeed indicated that reductions in glycolysis and glucose oxidation are associated with diminished ventricular function [32,33]. In addition, fatty acid-induced insulin resistance has been well described and has been proposed to play a part in the development of type 2 diabetes [34,35]. In this respect, recent evidence indicates that fatty acid-induced insulin resistance involves alterations at the level of glucose transport secondary to derangements in insulin signaling [36,37]. The observation that glucose uptake and utilization can be altered in the heart secondary to PPAR α -mediated increases in fatty acid utilization suggests the intriguing possibility that some forms of

insulin resistance or type 2 diabetes could be caused by alterations in components of the PPAR α regulatory complex or downstream genes involved in cellular fatty acid utilization.

Conclusions

Taken together, these findings highlight the complexity of alterations in myocardial cell metabolism associated with diabetes or insulin resistance, or both. Obviously, insulin signaling represents an important link between cardiac energy substrate utilization and the expression of genes that determine energy generation and energy consumption. Furthermore, it is worth mentioning that insulin resistance may also account for electrophysiological abnormalities of the diabetic heart. Very recent studies have investigated changes in cardiac potassium currents in the *db/db* mouse, a model of type 2 diabetes that exhibits obesity and insulin resistance. These K⁺ currents, both transient and sustained, control repolarization of the action potential and their attenuation prolongs the action potential and the Q–T interval of the electrocardiogram. Their magnitude was attenuated over time in *db/db* mice [38]. Interestingly, the age-dependent pattern of attenuation of K⁺ currents was similar to changes in glucose oxidation [39].

Understanding the nature of repolarizing current attenuation and its underlying mechanisms is of vital importance. These results in mouse models may apply to humans, as a prolongation of the Q–T interval, measured in the electrocardiogram of diabetic patients [40,41] reflects a longer action potential, as would occur if repolarizing currents were attenuated. In addition, Shimoni et al [38] used cells isolated from cardiomyocyte-specific insulin receptor knockout mice. This allowed the direct demonstration that insulin regulated the magnitude of the K⁺ current, in the absence of other confounding factors.

In type 2 diabetes, the target tissues become resistant to the effects of insulin, presumably because the insulin signaling pathway is impaired. However, our understanding of derangements in this pathway and in other transduction pathway(s) [42] in myocardial cells is far from being complete. Future studies in genetically engineered animal models, such as mice with cardiomyocyte-selective ablation of the insulin receptor or transgenic mice overexpressing the human insulin-regulatable glucose transporter (hGLUT 4) [43,44] should help to dissect the complex pathophysiology of the action of insulin on the heart and contribute to the establishment of pharmacological interventions to improve cardiac metabolism and reduce the cardiac dysfunction that is induced by insulin resistance. ■

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Management of chronic heart failure in patients with type 2 diabetes: the importance of an integrated approach

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Abstract

Chronic heart failure (CHF) and type 2 (noninsulin-dependent) diabetes are major public health problems; both disorders have an extremely poor prognosis. CHF and diabetes share a number of pathophysiological similarities, so it is no surprise that 25% of patients with CHF are diabetic. As a result, patients with CHF and diabetes represent a unique challenge, as each disease adds to the complexity of the other. Contemporary treatments for CHF are based on pharmacological blockade of the sympathetic nervous and renin–angiotensin systems, and there are good data to support the use of these agents in diabetic patients with CHF. Other pathophysiological targets potentially include insulin resistance, hyperglycemia, hypertension, inflammation, and lipid abnormalities. An integrated, tailored approach to treatment is therefore crucial to improving outcome in CHF patients with diabetes, many of whom have a prognosis worse than that associated with many soft tissue tumors.

■ *Heart Metab.* 2004;25:10–13.

Keywords: Chronic heart failure, type 2 diabetes, sympathetic nervous system, renin–angiotensin system

Introduction

Chronic heart failure (CHF) is a complex disorder that has a prognosis worse than that of many soft tissue tumors [1]. The most frequent modes of death in patients with CHF are sudden (predominantly arrhythmic) death and a progressive decline in left ventricular function leading to decompensated heart failure [2]. A range of disorders can lead to CHF, the most frequent being ischemic heart disease and hypertension [3]. CHF is characterized by abnormalities of cardiac size [4], electrical activation [5], and renal function [2], increased activity of the sympathetic and renin–angiotensin systems [6], inflammation [7], endothelial dysfunction [8], and oxidative stress [9]. These abnormalities are believed to contribute to the poor prognosis seen in patients with CHF. More recently, it has emerged that CHF is also associated with substantial abnormalities of glucose homeostasis,

including cardiac [10] and whole-body insulin resistance [11].

It is now well established that up to 25% of patients with CHF are diabetic [12]. This is not surprising, as type 2 (noninsulin-dependent) diabetes is characterized by accelerated coronary artery disease and hypertension, and is also associated with systemic inflammation [13], increased activity of the sympathetic nervous and renin–angiotensin systems [14], endothelial dysfunction [15], and oxidative stress [16]. The association between diabetes and CHF was reported almost 30 years ago. Data from the Framingham study demonstrated that the increased risk of CHF in patients with diabetes persisted after adjustment for other risk factors, including coronary artery disease, age, and hypertension [17]. Subsequently, it has been demonstrated that not only is CHF more common in patients with diabetes, but morbidity and mortality associated with CHF are worse in diabetic than in nondiabetic patients [18].

Chronic heart failure in diabetes

The management of the diabetic patient with CHF requires an understanding of the pathophysiological mechanisms underlying the association between the two disorders (Table 1). The coexistence of myocardial ischemia, hypertension, and a specific diabetic cardiomyopathy has been termed the “cardiotoxic triad” [19]; each process is believed to contribute independently and cumulatively to the biochemical, anatomical, and functional alterations in cardiac cells and tissues that impair overall cardiac function. The factors leading to diabetic cardiomyopathy are unclear, but a number of pathophysiological processes, including those mentioned above, may contribute. The prevention and treatment of CHF in diabetes should be directed towards these abnormal mechanisms and their stimuli, principally by the improvement of glycemic control, aggressive management of coronary artery disease and its risk factors, including hypertension, and neurohumoral blockade.

Contemporary treatments for chronic heart failure in patients with diabetes

The use of angiotensin-converting enzyme inhibitors (ACEIs) and β -adrenoceptor blockers is now clearly established as appropriate for all patients with symptomatic CHF [20], and the same large meta-analysis [20] also demonstrated the benefits of ACEIs and β -blockers in the management of CHF in patients with diabetes. This meta-analysis analyzed data from the 12 largest randomized clinical trials of ACEIs and β -blockers in CHF in order to ensure sufficient statistical power to detect differences in effects of treatment. This included more than 80% of all patients enrolled in any randomized controlled trial of ACEIs or β -blockers that was of at least 12 weeks duration. Both the treatment and prevention arms of the Studies Of Left Ventricular Dysfunction (SOLVD) [12,21] were included in the analysis – that is, symptomatic and asymptomatic patients with an ejection fraction no greater than 0.35. Between them, these trials used five different ACEIs and three different β -blockers. The results demonstrated the

Table 1. Pathophysiological similarities between diabetes and chronic heart failure.

Insulin resistance and hyperinsulinemia
Endothelial dysfunction
Proinflammatory state
Sympathovagal imbalance
Disturbance of the renin–angiotensin–aldosterone axis
Oxidative stress

benefits of the use of both classes of drug in diabetic patients with CHF. In the case of ACEIs, identical reductions in mortality were achieved in patients with diabetes and those without; in contrast, although the relative risk reduction in patients treated with β -blockers was less in those with diabetes than in those without, because the absolute risk of mortality is greater in diabetic patients, it was estimated that the absolute risk reduction in diabetic patients was at least equal to, if not greater than, that in nondiabetic patients [20].

These results were confirmed in another recent meta-analysis, which also assessed the prognostic benefit of β -blockers in both diabetic and nondiabetic patients [22]. Unless there is a contraindication or inability to tolerate treatment, standard care for all patients with CHF, regardless of its severity or etiology, should include an ACEI and a β -blocker [23]. Combination therapy of ACEIs and β -blockers is now well established as standard practice in the major guidelines [24]. Because of the compelling body of evidence that exists supporting their use, if tolerated, combination therapies should be given to all diabetic patients with CHF. If combination treatment is not tolerated, candesartan is a useful alternative, according to the recent Candesartan in Heart failure – Assessment of Reduction in Mortality and Morbidity (CHARM) study [25].

Adjuvant treatment with the aldosterone antagonist, spironolactone, has also been shown to be prognostically beneficial in patients with severe CHF [26], although the original Randomized Aldactone Evaluation Study (RALES) trial did not report separate data for patients with diabetes. A more recent study, the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) evaluated a subgroup of patients with diabetes and found them to have a mortality benefit from aldosterone blockade similar to that of their nondiabetic counterparts [27].

Prevention of chronic heart failure in diabetes

Successful treatment of established CHF is a pressing concern, but the advantages of preventative strategies are also clear. The prevention of CHF in diabetes relies on the aggressive management of coronary artery disease and its risk factors, particularly hypertension. Several trials have demonstrated that the drugs used for the treatment of these conditions, especially ACEIs, not only attenuate these disease processes and the microvascular complications of diabetes, but also decrease the incidence of CHF in previously asymptomatic individuals [22,28].

In addition, there are now many studies that promote the tight control of diabetes itself as means

of directly affecting the progression of CHF. The results of the UK Prospective Diabetes Study (UKPDS) 35 suggested that the incidence of CHF was associated with poor glycemic control [29]. Further studies have confirmed that increased glycated hemoglobin is an independent predictor of CHF risk, with no apparent threshold value and no differences observed in relation to CHF pathogenesis or hypertension status [30,31]. Although it is possible that poor glycemic control may reflect inadequately focused physician care or poor compliance with treatment (extending to blood pressure and lipid-decreasing treatments), in view of the emergence of the phenomenon of diabetic cardiomyopathy it now seems likely that prolonged periods of hyperglycemia inflict direct myocardial damage that may be avoided by more strenuous glycemic control [31].

Treatment and prevention of diabetes in chronic heart failure

Diabetes mellitus is a multisystem disorder. Aggressive management of this condition through lifestyle modifications and pharmaceutical intervention is essential to prevent its consequences, regardless of duration of illness or comorbidities. The prevention of microvascular and other complications through tight glycemic control is well established; prevention of the development of diabetes itself may also be possible. Trials assessing the effects of ACEIs [32,33], angiotensin II receptor blockers [34], and some β -blockers [35] have all shown a decreased incidence of diabetes in patients with CHF, in keeping with the concept of diabetes as a cardiovascular disease. The thiazolidinediones are another group of drugs with antidiabetic and insulin-sensitizing properties, which may also have beneficial cardiovascular effects [36]; however, their use has been hampered by associated liver toxicity, weight gain, and a significantly increased risk of edema [37,38]. In view of the fact that clinical trials assessing the safety and efficacy of thiazolidinediones have excluded patients with moderate to severe limitation of physical activity from CHF, the American Heart and Diabetes Associations have issued a consensus statement asserting that, for the time being at least, their use is contraindicated in individuals with New York Heart Association (NYHA) class III or IV symptoms [38]. Thiazolidinediones may, however, be initiated in patients with diabetes who are known to have a depressed ejection fraction (eg, less than 0.40) but do not have symptoms or signs of CHF, and with caution in patients with NYHA class I or II symptoms. These patients should be monitored closely for weight gain and edema and if, after investigation into other possible causes, the thiazolidinedione is believed to have precipitated these effects, it should be discontinued [38].

Conclusion

The presence of diabetes makes the treatment of CHF even more complex, and a focused, individualized treatment package is therefore important. The tenets of practice remain the same: evidence-based treatments for CHF include ACEIs, β -blockers, and aldosterone antagonists; tight glycemic control is essential to minimize the risks of diabetic complications; aggressive management of hypertension and coronary artery disease is paramount to alleviate the potential burden of CHF to both the individual and the wider community. Evidence for the use of angiotensin II receptor blockers as an alternative to ACEIs is gathering, and another promising avenue appears to be the development of drugs aimed at increasing insulin sensitivity. Health care professionals are under an obligation on an individual level to personalize patient care in order to ensure optimal compliance and benefit, and on a national and international level to implement strategies allowing adequate care and access to all. ■

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Main clinical article

Integrated management of CHF in type 2 diabetes

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Metabolic imaging and diabetes

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Abstract

Metabolic imaging studies have been able to increase our knowledge about the physiology and pathophysiology of cardiac disease in diabetes. Noninvasive quantification of myocardial perfusion, oxygen consumption, glucose utilization, and fatty acid metabolism are possible using positron emission tomography. These studies have shown that, with normal insulin, glucose, and free fatty acid concentrations, there does not seem to be a major defect in substrate metabolism in the diabetic heart. However, very limited data are available concerning myocardial substrate metabolism under different metabolic conditions, such as ischemia, hyperlipidemia, or hyperglycemia. These conditions, although fluctuating over time, commonly accompany diabetes. Further studies are needed to clarify these issues.

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Keywords: Diabetes, heart, metabolism, positron emission tomography

Introduction

It has long been known that patients with diabetes have myocardial dysfunction and heart failure not necessarily attributable to any known cardiac disease [1]. Abnormal intracellular calcium metabolism and coronary regulation, autonomic neuropathy, and defective glucose and fatty acid metabolism have been proposed to contribute to the pathogenic mechanism [2,3].

Diabetes is a major risk factor for atherosclerotic vascular disease and individuals with diabetes have a 2- to 4-fold increased risk of developing coronary artery disease [4]. Metabolic alterations may be involved in the pathogenesis of diabetic cardiomyopathy. Glucose is an important substrate for the myocardial cells, especially during ischemia, and preserved myocardial glucose uptake appears to be crucial to the viability of the jeopardized myocardium. This is supported also by the finding that, in high-risk patients, intense insulin therapy improves prognosis in those with type 2 (noninsulin-dependent) diabetes with acute myocardial infarction [5].

Metabolic imaging studies have been able to increase our knowledge of the physiology and pathophysiology of cardiac disease in diabetes. Until now, most studies have focused on the charac-

terization of metabolic abnormalities in the diabetic heart.

Myocardial substrate metabolism

Free fatty acids (FFAs), glucose, and lactate are the main fuels of the heart [6]. Under normal resting conditions, metabolism is mainly oxidative, with FFA being the major source, whereas glycolysis contributes only about 30% of substrate to the tricarboxylic acid cycle.

Ischemia is associated with increased glycolysis, with glucose transporters translocated to the cell membrane. During states of mild ischemia, lactate continues to be removed from the myocardium by the residual blood flow, but accumulates in tissue when blood flow decreases further during more severe states of ischemia. Increased tissue concentrations of lactate and hydrogen ions impair glycolysis, leading to loss of transmembrane ion concentration gradients, disruption of cell membranes and, ultimately, to cell death [6].

As diabetes has significant effects on the concentrations of circulating substrate, it can be assumed that cardiac substrate metabolism is directly altered in diabetes (*Table 1*). In addition to potential changes

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Table 1. Is diabetes associated with changes in myocardial substrate metabolism? Summary of myocardial energy metabolism in diabetes during different physiological and pathophysiological conditions.

	Type 1 diabetes				IGT/type 2 diabetes			
	GU	FFA	FFAox	Lact	GU	FFA	FFAox	Lact
Euglycemic hyperinsulinemia	↔	?	?	↔	↔	?	?	?
Fasting with similar FFA	?	?	?	?	?	↔	↔	?
Hyperlipidemia	?↓	↑	?	↓	?	?	?	?
Hyperglycemia	?	?	?	↓	?	?	?	?
Exercise	↔	↔	?	↔	?	?	?	?

FFA, FFA uptake; FFAox, FFA oxidation; GU, glucose uptake; IGT, impaired glucose uptake; Lact, lactate uptake; ↔, no change; ↑, increased uptake; ↓, decreased uptake; ?, not known.

in glucose and FFA metabolism, there are changes in concentrations of lactate and ketone bodies, leading to their increased uptake in uncontrolled diabetes [6].

Application of metabolic imaging

Noninvasive quantification of perfusion, oxygen consumption, glucose utilization, and fatty acid metabolism are possible using positron emission tomography (PET). The most commonly applied metabolic imaging has been measurement of glucose uptake using fluorine-18 (^{18}F)-labeled deoxyglucose [7]. Recently, the use of carbon-11 (^{11}C)-labeled glucose has been reintroduced and has been shown to provide accurate quantification of glucose uptake [8].

Two PET tracers have been used to measure free fatty acid metabolism: ^{11}C palmitic acid has been traditionally used, allowing both FFA uptake and oxidative metabolism to be quantified [6,7], and ^{18}F -6-thia-heptadecanoic acid has also been used recently to study fatty acid metabolism in humans [9]. The tracers ^{11}C acetate and ^{15}O oxygen have been used to measure myocardial oxygen consumption with PET in humans [10]. Lactate also has been labeled with ^{11}C , and human studies have been successfully performed.

Myocardial scintigraphy using γ -emitting tracers has also been applied to the investigation of myocardial FFA metabolism. The limitation of this technique is that it does not allow absolute quantification of metabolic processes.

Cardiac metabolic imaging in diabetes

Most cardiac metabolic studies in diabetes have focused on the characterization of metabolic abnormalities in the diabetic heart [11–19]. It is well known that resistance to the action of insulin in peripheral tissues characterizes diabetic patients and,

thus, an apparent question is whether similar insulin resistance exists in the diabetic heart.

In patients with type 1 (insulin-dependent) diabetes, two studies have reported preserved myocardial glucose uptake despite peripheral insulin resistance and reduced glucose uptake in skeletal muscle [11,12]. These studies were performed during euglycemia and controlled infusion of insulin.

In patients with type 2 diabetes, the results are more controversial. In some studies reduced myocardial glucose uptake was observed [13–15], whereas in others no such difference was found [16–19]. As several factors affect myocardial substrate metabolism, the metabolic imaging should be performed under standardized metabolic conditions. Most of those studies that were performed during euglycemic hyperinsulinemic clamps with comparable insulin, glucose and FFA concentrations revealed myocardial glucose uptakes that were similar in those with type 2 diabetes and in nondiabetic individuals. In the study by Utriainen et al [17], concentrations of insulin were used that were 5-fold greater than in the physiological range, but in the other studies insulin concentrations were within the physiological range. In patients with type 2 diabetes, other diseases such as coronary heart disease, renal disease, and obesity are common and may also confound the findings.

Serum FFA concentrations are usually increased in patients with type 2 diabetes, as a result of enhanced rates of lipolysis, impaired suppression of lipolysis by insulin, and defective clearance of FFA [20]. An attractive hypothesis has been that increased availability and oxidation of FFAs leads to impaired insulin-mediated glucose uptake and causes insulin resistance in type 2 diabetes. In one previous study, myocardial fatty acid uptake and indices of β -oxidation (measured with scintigraphy and iodine-123-labeled heptadecanoic acid) were reduced in individuals with impaired glucose tolerance.

A recent study applying a PET technique demonstrated that FFA uptake in the femoral muscle was decreased by about 25% in a glucose-intolerant group,

whereas no differences were observed with respect to myocardial uptake of FFA [21] (Figure 1). Thus, in individuals with disturbed glucose tolerance, heart and skeletal muscle may differ with respect to substrate utilization. The findings of this study also argued against the hypothesis that excessive FFA utilization per se is the key explanation for impaired glucose utilization. This idea was also supported by another PET study using [^{11}C]palmitate, which demonstrated that, in the presence of comparable FFA concentrations, myocardial FFA uptake and oxidation are similar in diabetic and nondiabetic individuals [22].

As to the effects of treatment of diabetes on myocardial substrate metabolism, very limited data are available. Oral treatments for patients with type 2 diabetes have historically been based on sulphonylureas and metformin. Recently, the availability of glinidines and glitazones has increased the armamentarium of antidiabetic regimens. All these regimens have different mechanisms of action, but their efficacies are similar [23]. Glitazones have been shown to increase concentrations of the glucose transporter (GLUT 1 and GLUT 4) and to normalize myocardial glucose uptake in rat heart. In a recent PET study in humans, rosiglitazone increased insulin-stimulated myocardial uptake of glucose by 38%, whereas metformin had no significant effect [23]. FFA concentrations were suppressed to a greater extent by rosiglitazone, and the enhanced myocardial uptake of glucose is probably attributable to this phenomenon. In any event, this effect of rosiglitazone may counteract the metabolic alterations in the diabetic heart.

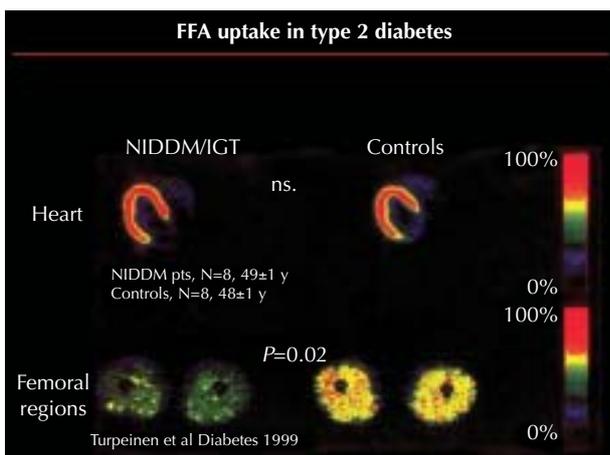


Figure 1. Positron emission tomography images of free fatty acid (FFA) uptake, using [^{18}F]labeled 6-thia-heptadecanoic acid, in the heart and femoral regions in a patient with type 2 (noninsulin-dependent) diabetes mellitus (NIDDM)/impaired glucose uptake (IGT) and a nondiabetic individual, in the fasting state with similar circulating FFA concentrations. Cardiac FFA uptake is comparable in the two individuals, but skeletal muscle uptake is decreased in the patient with diabetes.

Despite the limitations in the studies mentioned above, one may surmise that, with normal circulating insulin, glucose, and FFA concentrations, there seems to be no demonstrable major defect in myocardial substrate metabolism in the hearts of patients with diabetes. However, there are no data concerning myocardial glucose uptake during the perturbed conditions accompanying diabetes, and in particular during ischemia or exercise. Thus these studies do not exclude the possibility that, under conditions in which circulating FFA concentrations are increased, FFA utilization could be enhanced and glucose metabolism inhibited. Limited information is also available as to myocardial substrate metabolism during hyperlipidemia or hyperglycemia, conditions that commonly accompany the diabetic patient during their daily life. ■

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Novel approaches in the treatment of diabetes mellitus diabetic cardiomyopathy

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Abstract

The body of scientific evidence shows that diabetes mellitus is one of the most important coronary risk factors and causes cardiac and vascular complications with an adverse clinical outcome. Recent studies have shown that lifestyle modifications are crucial in order to delay the onset of cardiac sequelae and to prevent the progression of atherosclerosis. Glycemic control is more efficiently maintained with a combination of drugs, diet, and aerobic exercise. Trimetazidine, through its particular effect on cellular metabolism, has been shown to improve left ventricular contractility and function in chronically ischemic myocardium in patients with diabetes, without side effects. These preliminary results should be confirmed in larger controlled clinical trials.

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Keywords: Diabetes, metabolic dysfunction, therapy, metabolic modulator, trimetazidine, myocardial function

Introduction

Diabetes is a chronic, progressively worsening disease associated with a variety of complications [1]. Patients with diabetes have a greater incidence of coronary artery disease, which is in part related to concomitant cardiovascular risk factors, such as hypertension, blood lipid abnormalities, obesity, and physical inactivity. A cardiovascular event is responsible for 75% of deaths in individuals with type 2 (non insulin-dependent) diabetes, and more than 50% of medical expenditures related to diabetes result from admissions to hospital as a result of cardiovascular disease.

Metabolic dysfunction in the diabetic heart

Diabetes mellitus impairs glucose uptake and glycolysis of myocardial cells, depending in part on downregulation of the expression of glucose transporter (GLUT). Studies in animals have shown that diabetes decreases both GLUT 1 and GLUT 4 isoforms, which translocate from the intracellular pool into the plasma membrane in response to

chemical and physical stimuli such as insulin or ischemia [2,3]. This decrease is prevented by chronic treatment with insulin and is improved by aerobic exercise, such as running or cycling [4].

A common metabolic dysfunction in diabetes is a decrease in the rate of carbohydrate oxidation as a result of a decrease in mitochondrial pyruvate oxidation. Pyruvate decarboxylation – the key reaction in glucose oxidation – is catalyzed by pyruvate dehydrogenase (PDH), and the rate of pyruvate oxidation is dependent on the degree of phosphorylation of PDH, and also on the concentration of its substrates and products in the mitochondria. Diabetes is typically associated with a decrease in total PDH activity, as the dephosphorylated active form is proportionally reduced [5]. In the case of myocardial ischemia – a condition that frequently occurs without symptoms in individuals with diabetes – glucose oxidation is reduced, and this reduction is more pronounced in diabetic hearts in which PDH inhibition is more marked, along with a more accelerated rate of fatty acid oxidation [6]. The decreased ability to oxidize pyruvate appears to be a major contributor to the poor outcome in patients with diabetes who have coronary artery disease [7].

New therapeutic approaches

Treatment of diabetes mellitus diabetic cardiomyopathy

In contrast, activation of PDH with dichloroacetate results in improved contractility in both nondiabetic and diabetic hearts [8], suggesting that the addition of a metabolic modulator can improve the metabolic dysfunction and myocardial contractility.

The treatment of diabetes is aimed at two goals: elimination of symptoms of hyperglycemia, and prevention of vascular complications, both micro- and macrovascular. Given that the leading cause of morbidity and mortality in patients with diabetes is atherosclerotic vascular disease, the therapeutic approach should be targeted towards improving the blood supply and preventing the progression of atherosclerosis (Table I).

Lifestyle changes and control of cardiovascular risk factors

The American Heart Association designated diabetes as a "coronary risk equivalent", and indicated that patients with diabetes belong in the same risk category as those with known cardiovascular disease [9]. Patients with diabetes frequently have concomitant coronary risk factors such as hypertension, dyslipidemia, and obesity, which contribute to worsening their coronary artery disease and to accelerating the progression of atherosclerosis. Thus, in the clinical management of patients with diabetes, attention must be given both to major cardiovascular risk factors, such as cigarette smoking, hypertension, hypercholesterolemia, and hypertriglyceridemia, and to underlying risk factors (overweight/obesity, physical inactivity, and adverse nutrition) [9]. All these risk factors generate similar common abnormalities, such as endothelial dysfunction, prothrombotic state, inflammation, and excessive oxidation, which are involved in the pathogenesis of the atherosclerotic process. As the majority of coronary risk factors are potentially reversible, the first line of treatment of patients with diabetes should be based on modification of lifestyle and correction of concomitant risk factors.

Aerobic exercise is considered a treatment of choice in diabetes, because it reduces blood pressure and improves the lipoprotein profile and glycemic control. In addition, exercise reduces the prothrombotic state [10]. In a recent study, moderate physical activity, such as brisk walking for at least 150 minutes per week, combined with a low caloric, low-fat diet, reduced the incidence of diabetes by 58% in 3234 nondiabetic persons with increased fasting and post-load plasma glucose concentrations. The lifestyle intervention was significantly more effective than metformin, which was associated with a 31% decrease in the incidence of diabetes [11]. To prevent one case of diabetes during a period of 3 years, 6.9 persons would have to participate in the lifestyle intervention program, and 13.9 would have to receive metformin. Physical inactivity impairs insulin sensitivity, contributes importantly to development of obesity, and increases blood pressure. In contrast, aerobic exercise of moderate intensity improves endothelial function and induces a series of beneficial adaptations that improve vasomotor function and delay the progression of atherosclerosis (Figure 1).

It is now well established that hypocaloric diets and body weight reduction improve insulin resistance. Insulin sensitivity may improve by up to 60% with equivalent diet or exercise-induced weight loss among obese middle-aged men [12]. These improvements are in part related to changes in body fat distribution, with decreased visceral obesity. Ross [13] reported that a 3-month exercise training program without weight loss in obese males was associated with a 30% improvement in insulin sensitivity compared with inactivity. However, a long-term moderate exercise intervention combined with an isocaloric diet low in saturated fat has been shown to reduce total abdominal obesity among overweight adults with type 2 diabetes [13].

Results from a meta-analysis of 20 studies on the effects of exercise training in patients with diabetes and metabolic syndrome showed that functional capacity, expressed as maximum oxygen consump-

Table I. Therapeutic goals in patients with diabetes mellitus. (Data from the American Diabetes Association [15].)

Parameter	Goal	Suggested value for intervention
HbA _{1c} (%)	<7	>8
Fasting capillary glucose (mg/dL)	80–120	<80/>140
Bedtime capillary glucose (mg/dL)	100–140	<100/>160
LDL cholesterol (mg/dL)	<100	
HDL cholesterol (mg/dL)	>45 (men)/>55 (women)	
Triglycerides (mg/dL)	<150	
Blood pressure (mm Hg)	<130/<80	

HbA_{1c}, glycated hemoglobin; HDL, LDL, high-density and low-density lipoproteins.

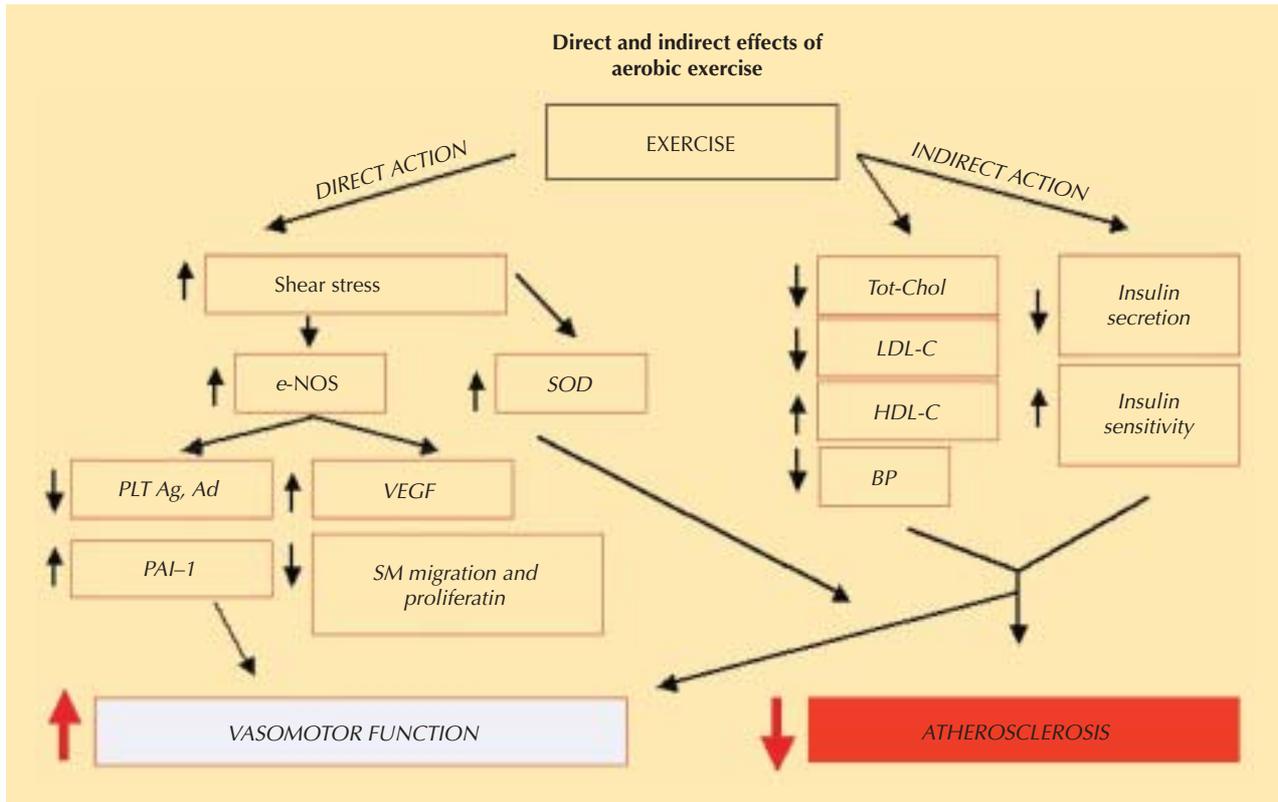


Figure 1. Main cardiovascular adaptations induced by aerobic exercise training of moderate intensity. Exercise determines direct and indirect effects on the vascular tree. A direct action is the result of increased shear stress, determining expression and activity of endothelial nitric oxide synthase (eNOS) and the release of nitric oxide. Exercise improves the prothrombotic state of patients with diabetes by inhibiting platelet aggregability and adhesivity (PLT ag, ad) and by increasing concentrations of plasminogen activator inhibitor 1 (PAI-1) in the plasma. Exercise also reduces the rate of inactivation of nitric oxide by increasing superoxide dismutase (SOD) activity. Concentrations of vascular endothelial growth factor (VEGF) are increased, and migration and proliferation of smooth muscle cells (SM) are decreased. As a result, vasomotor reactivity is improved. An indirect action of aerobic exercise is improvement in cardiovascular risk profile, which prevents or delays the progression of atherosclerosis. BP, blood pressure; HDL-C, LDL-C, high-density and low-density lipoprotein cholesterol; Tot-cholesterol.

tion (VO_2 max), improved by 11% (range 1% to 25%), body mass index was modestly reduced as compared with controls ($-0.60 \pm 0.32 \text{ kg/m}^2$ compared with $-0.30 \pm 0.69 \text{ kg/m}^2$, respectively; $P=0.03$), high-density lipoprotein cholesterol increased by 0.046 mmol/L ($P < 0.0001$), and triglycerides were decreased by 15% ($P < 0.0001$). No significant changes were observed in total cholesterol and low-density lipoprotein cholesterol. The Obesity Expert Panel reported that three meta-analyses of 68 randomized controlled studies of physical training among hypertensive patients showed significant blood pressure reductions independent of weight loss [15]. Thus, among other interventions, aerobic exercise of moderate intensity (50% to 80% of VO_2 max) induces several effects on different risk factors, and has the greatest potential to control coronary risk profile in diabetic patients. The effects are similar in type 1 (insulin-dependent) and type 2 diabetes.

Metabolic modulators

Cardiovascular disease in patients with diabetes has several components, including cardiac, macrovascular, and microvascular diseases, which create a vicious cycle of progressive and worsening abnormalities. A typical condition in patients with diabetes is multiple coronary artery stenoses with dysfunctional myocardium, the so-called diabetic cardiomyopathy. Coronary lesions are typically multiple and at different maturative states in the same vessels. Furthermore, lesions frequently extend to the distal end of the coronary tree. After years, the disease spreads to all major coronary vessels, causing functional and structural abnormalities in the myocardial cells. Chronic ischemia generates hibernating myocardium with depressed contractility and consequent regional left ventricular dysfunction. When dysfunction is sufficiently severe, heart failure will develop, causing clinical deterioration.

New therapeutic approaches

Treatment of diabetes mellitus diabetic cardiomyopathy

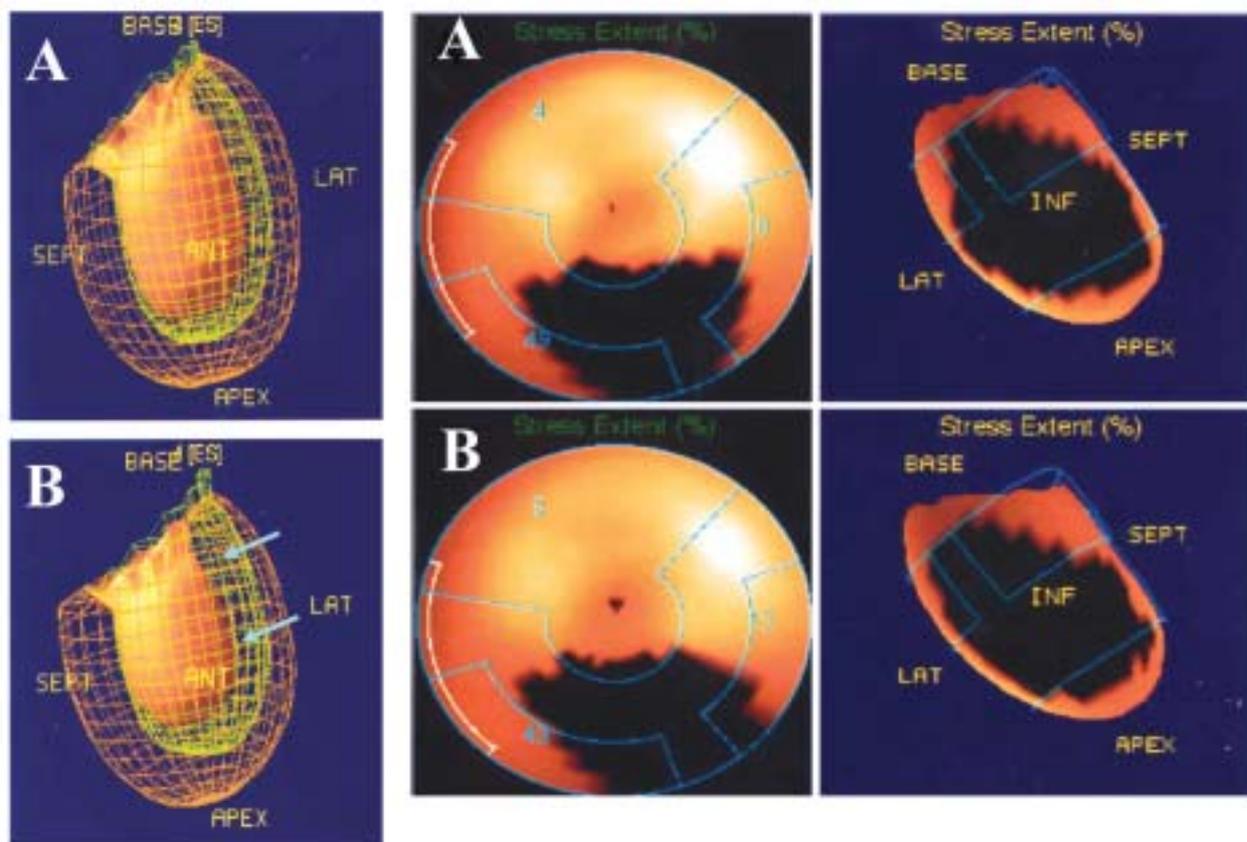


Figure 2. Example of the effects of trimetazidine in a 55-year-old man with type 2 diabetes and ischemic cardiomyopathy. Images are from single photon emission computed tomography myocardial scintigraphy (dual head-gated SPECT, ADAC Vertex, CA, USA) with a dual-day stress (Bruce)–rest procedure after 500 + 500 MBq intravenous tetrofosmin. A 3-dimensional algorithm was used for perfusion quantification, using a semiquantitative scoring system (from 0=normal to 4=absent uptake). Quantitative measurements of left ventricular volumes from gated perfusion SPECT images were obtained, from which ejection fraction was automatically calculated. (a, c, e) Initial study; (b, d, f) after trimetazidine 20 mg three times daily for 3 months. Regional myocardial contractility improved in the anterolateral wall (b, arrows), and left ventricular ejection fraction increased from 41% (baseline) to 51% at 3 months. Despite the improved contractility, no change in myocardial perfusion was observed. SPECT stress imaging after 3 months was unchanged from baseline (sum of the stress scores 15 and 14, respectively). Trimetazidine improved left ventricular regional and global function without changes in perfusion, as a result of its cytoprotective effect.

As previously mentioned, activation of PDH with dichloroacetate results in improved contractility in both nondiabetic and diabetic hearts, suggesting that the addition of a metabolic modulator can improve the metabolic dysfunction and myocardial contractility [8]. Trimetazidine – a piperazine derivative – is used as antianginal agent for its particular properties: it selectively inhibits mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, resulting in inhibition of fatty acid oxidation and increased glucose oxidation. Under conditions of chronic reduction in coronary blood flow, free fatty acid concentrations are increased as a result of the lipolytic action of sympathetic activation, causing a reduction in myocardial contractility and increases in cAMP concentrations and oxygen consumption, with no concomitant increase in myocardial work. A shift toward glucose oxidation, requiring less oxygen than

β -oxidation, is likely to benefit hypoperfused myocardium, because ATP production per mole of oxygen consumed is about 12% greater when glucose, rather than fatty acid, is the preferred energy substrate. In patients with ischemic cardiomyopathy and depressed left ventricular function, trimetazidine (20 mg three times daily) produced significant improvements in systolic wall thickening score index (SWTI) and left ventricular ejection fraction (LVEF) (19% and 14%, respectively; $P < 0.001$ compared with placebo) after 2 months [16]. These benefits were obtained without changes in heart rate and blood pressure, suggesting that the cytoprotective effect induced by trimetazidine was unrelated to hemodynamic modifications. The improvement in contractility was more evident in territories chronically hypoperfused, suggesting that the presence of hibernating myocardium is essential

to obtain a beneficial effect with trimetazidine. As left ventricular dysfunction that results from macro- and microvascular coronary alterations is frequent in patients with diabetes, it has been suggested that trimetazidine may help to improve contractility and left ventricular function in combination with standard medications.

Recently, we studied 34 clinically stable patients with diabetes mellitus and documented multivessel coronary artery disease (29 men, five women; mean age 54 ± 9 years, ejection fraction 0.38 ± 0.6) [17]. Twenty-four patients had type 2 (noninsulin-dependent) diabetes mellitus, and 10 had type 1 (insulin-dependent) diabetes mellitus. Patients were allocated randomly to two groups: one group received trimetazidine (20 mg three times daily) for 3 months (group T, $n=19$), and the other received a placebo for the same period (group C, $n=15$). Medications were unchanged during the study. On study entry and at 3 months, all patients underwent gated single photon emission computed tomography (SPECT) myocardial scintigraphy with a 2-day stress (Bruce)–rest procedure (500 MBq tetrofosmin). Quantitative measurements of left ventricular volumes were obtained from the gated perfusion SPECT images and from these the ejection fraction was automatically calculated. All patients completed the procedure and no side effects were reported. On initial evaluation, there were no differences between the two groups with respect to the severity of perfusion defects (summed difference score [SDS] 8.9 ± 2.2 in group T and 8.6 ± 2 in group C), SWTI (2.2 ± 0.8 in group T and 2.3 ± 0.9 in group C), and LVEF ($37 \pm 6\%$ in group T and $38 \pm 6\%$ in group C). At 3 months, however, as compared with control patients, those treated with trimetazidine had a significant improvement in SWTI (1.7 ± 0.9 compared with 2.3 ± 0.9 ; $P < 0.05$) and LVEF ($43 \pm 6\%$ compared with $38 \pm 6\%$, $P=0.007$). These results were similar in patients with type 1 or type 2 diabetes. No changes were observed in myocardial perfusion defects (SDS 8.2 ± 2.4 in group T and 8.9 ± 2.1 in group C; $P=0.38$). Total exercise time was also improved in trimetazidine-treated patients (from 440 ± 140 s to 530 ± 145 s; $P < 0.05$), whereas no change was observed in controls. One example of changes in myocardial performance after trimetazidine is shown in Figure 2. We conclude that, in patients with diabetic cardiomyopathy, trimetazidine improves left ventricular systolic function and functional capacity without significant changes in myocardial defects, suggesting that a direct cytoprotective effect on myocardial cells may translate into improvements in the contractility of dysfunctional myocardium and functional capacity. We need to confirm these preliminary results in larger clinical trials. ■

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Ischemic heart disease and diabetes: rationale for a metabolic approach, and clinical evidence

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Abstract

The increased incidence of cardiovascular disease in patients with diabetes exposes them to a greater risk of mortality. Ischemic heart disease, which is often found in patients with diabetes, is a metabolic disease that relies on changes in cardiac metabolism. Because of this, manipulation of the energy metabolism of the diabetic heart has been investigated with the aim of relieving symptoms and improving exercise capacity and left ventricular contractile work. Trimetazidine (Vastarel MR), the first twice-daily 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitor, is a well known metabolically active agent that is widely used for the treatment of stable angina. This review highlights recent publications that demonstrate the anti-ischemic and cardioprotective value of trimetazidine in patients with diabetes and coronary heart disease.

■ *Heart Metab.* 2004;25:23–25.

Keywords: Diabetes, ischemic heart disease, trimetazidine, cardiac metabolism

Introduction

It is now well established that patients with diabetes present with a greater incidence and severity of cardiovascular events such as angina, myocardial infarction, and heart failure than do those without diabetes. For example, the risk of an event is as high in patients with diabetes as in those without diabetes who have suffered a previous myocardial infarction (*Figure 1*) [1]. This increased risk can be explained by the existence of a diabetic cardiomyopathy that is associated with the following signs: reduction in diastolic relaxation and left ventricular end-diastolic diameter; prolongation of maximal filling velocity and isovolumetric filling time. The left ventricular diastolic dysfunction is likely to appear at an early stage. The severity of this diabetic cardiomyopathy is strongly related to changes in energy metabolism of the myocytes. It has been demonstrated that ischemic damage is exacerbated by the excessive use of fatty acids by the diabetic heart. These observations have

led to consideration of pharmacological manipulation of the cardiac metabolism as a promising approach to counteracting the deleterious consequences of myocardial ischemia, particularly in patients with diabetes who have coronary heart disease.

Trimetazidine (Vastarel MR): a unique metabolic mechanism of action

The rationale of optimizing myocardial energy production through a reduction in fatty acid oxidation to relieve symptoms and improve contractile work is now well demonstrated [2]. Trimetazidine (Vastarel MR) opens up a new class of metabolic anti-ischemic agents known as 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors. When the diabetic heart is under ischemic conditions, trimetazidine shifts cardiac metabolism away from fatty acids to glucose oxidation, secondary to selective inhibition of the 3-KAT [3] (*Figure 2*). This metabolic anti-ischemic agent

Focus on Vastarel MR

P. Meurin and T. Hénane

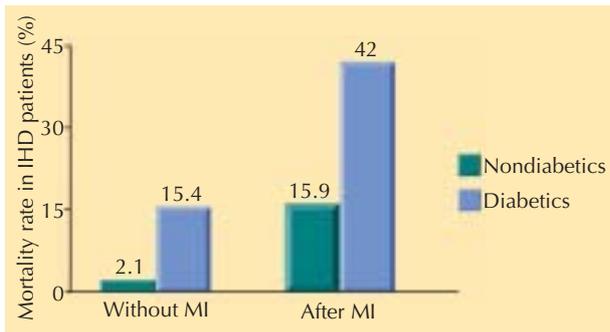


Figure 1. Cardiovascular mortality in diabetic and nondiabetic individuals with coronary artery disease. IHD, ischemic heart disease; MI, myocardial infarction.

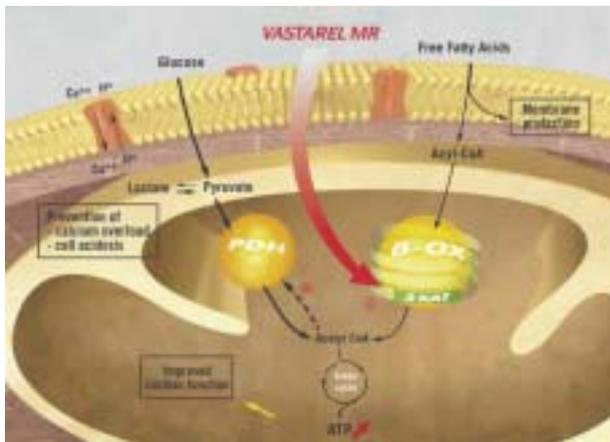


Figure 2. Trimetazidine (Vastarel MR), the first twice-daily 3-ketoacyl coenzyme A (CoA) thiolase (3 KAT) inhibitor, optimizes cardiac metabolism. β -ox, β -oxidation; PDH, pyruvate dehydrogenase.

effectively reduces the incidence of angina attacks and improves exercise performance in various subsets of patients with coronary heart disease [4], and these benefits are unrelated to changes in hemodynamic variables such as heart rate or blood pressure [5]. As both diabetes and coronary artery disease can be considered as metabolic diseases, the clinical benefits of trimetazidine are most likely to be operative in patients with diabetes who have ischemic cardiomyopathy.

Trimetazidine (Vastarel MR): evidence-based efficacy in patients with diabetes and coronary heart disease

Several publications have demonstrated the value of trimetazidine in patients with diabetes and

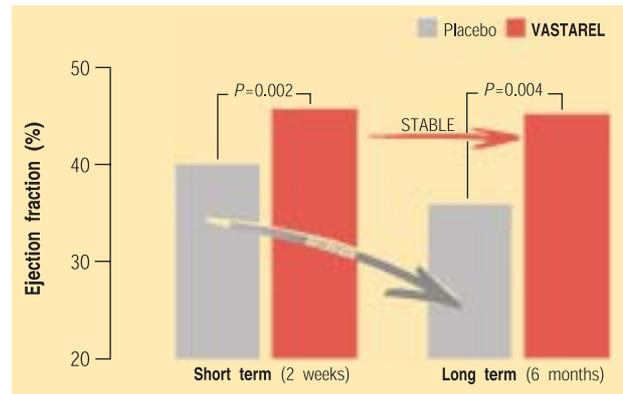


Figure 3. Improvement in left ventricular contractile function in response to short- and long-term treatment with trimetazidine (Vastarel MR) in patients with diabetes and dilated ischemic cardiomyopathy.

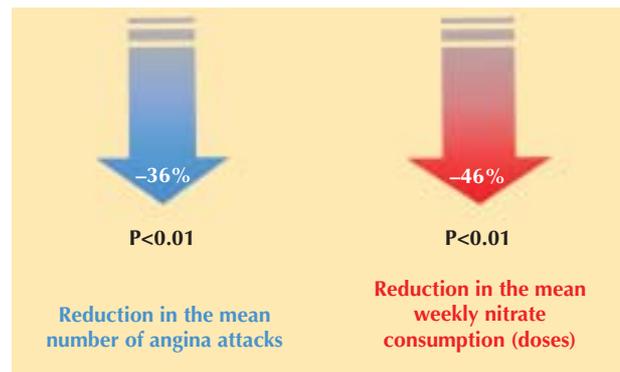


Figure 4. Effective relief of symptoms with trimetazidine (Vastarel MR) in patients with diabetes and stable angina (substudy of Trimetazidine in Poland I).

coronary heart disease. In a pilot study, Fragasso et al [6] showed that short-term (2 weeks) and long-term (6 months) treatment with trimetazidine was able to produce a significant increase in the left ventricular ejection fraction ($P < 0.001$) of patients with diabetes and ischemic cardiomyopathy (Figure 3). Plasma concentrations of endothelin-1 were also significantly reduced, reflecting an improvement in endothelial function, along with glycated hemoglobin concentrations. Another double-blind, parallel-group, placebo-controlled study also produced evidence of the beneficial effect of trimetazidine on left ventricular function in patients with diabetes who had coronary artery disease [7].

In patients with coronary artery disease and type 2 (non-insulin-dependent) diabetes, 6 months of treatment with trimetazidine in addition to standard

therapy was associated with significant improvement in left ventricular ejection fraction and wall motion score index in comparison with placebo. These studies confirmed previous findings that established the cardioprotective effect of trimetazidine in patients with chronically dysfunctioning myocardium [8]. Finally, in another study, in 50 patients with diabetes and stable angina whose condition remained uncontrolled with conventional treatment (long-acting nitrates, β -blockers, or calcium antagonists), 4 weeks of treatment with trimetazidine resulted in improved exercise capacity and exercise duration, and a significant reduction in the mean number of angina attacks per week (*Figure 4*), independently of any change in hemodynamic parameters [9]. This study of daily practice also demonstrated the excellent tolerance profile of trimetazidine in these at-risk patients, in whom no specific adverse event was reported and biological variables remain unchanged.

Conclusion

Modulation of cardiac energy metabolism has proved to be an attractive option for the treatment of ischemic heart disease in patients with diabetes, as reflected by the significant improvements obtained in exercise capacity, symptom relief, and left ventricular function. In these fragile populations, at high risk of cardiovascular events, twice-daily trimetazidine should be considered seriously as a treatment of choice to provide efficient protection of the diabetic heart against the deleterious consequences of chronic myocardial ischemia. ■

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Diabetes and heart failure

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Abstract

Diabetes is a major risk factor for the development of heart failure. This is partly explained by the association of diabetes with coronary heart disease and hypertension. However, diabetes-specific biochemical, structural, and functional abnormalities may exacerbate adverse remodeling and lead to progressive cardiac dysfunction. This case demonstrates the presentation and clinical management of heart failure in a patient with type 2 (non-insulin-dependent) diabetes.

■ *Heart Metab.* 2004;25:26–29.

Keywords: Heart failure, diabetes, cardiomyopathy, pharmacotherapy, neurohumoral blockade

Case report

A 56-year-old man presented to hospital with an 8-hour history of lower chest and epigastric discomfort. He had a background of type 2 (noninsulin-dependent) diabetes, diagnosed 12 years earlier, and had been receiving treatment for hypertension for 8 years. His electrocardiogram on admission revealed ST-segment elevation in leads II, III, and aVF (*Figure 1*), consistent with an inferior ST-segment elevation myocardial infarction.

On assessment, the patient had a sinus tachycardia of 100 beats/min and an increased blood pressure of 170/80 mm Hg. There were no cardiac murmurs, but inspiratory crackles were audible in both lung fields. He was taking an oral hypoglycemic agent and a thiazide diuretic before his admission to hospital.

The patient had never smoked; he consumed about 6 units of alcohol weekly. His mother and brother had diabetes, but there was no family history of premature cardiovascular disease.

The initial management comprised aspirin, oxygen, intravenous diuretics, and a nitrate infusion. Strepto-kinase was administered as a thrombolytic agent. The patient was transferred to the coronary care unit, where a sliding-scale insulin infusion was commenced in the short term, before being changed to a twice-daily subcutaneous regimen after 48 hours. His progress in hospital was uneventful, with no further chest discomfort and no arrhythmias. Echocardiography revealed infer-

opical akinesis with mural thrombus, prompting anticoagulation with warfarin. Coronary arteriography demonstrated diffuse left coronary artery disease. The right coronary artery was patent, with a severe stenosis at the crux and diffuse distal atheroma (*Figure 2*). An exercise electrocardiogram was satisfactory, with no inducible ischemia at a moderate workload, and the patient was discharged taking insulin, aspirin, a statin, an angiotensin-converting enzyme (ACE) inhibitor, a β -blocker, and warfarin.

Over the next 18 months, the patient developed symptomatic heart failure, with progressive exertional breathlessness culminating in New York Heart Association class III symptoms. Repeat echocardiography demonstrated progressive left ventricular dilatation, significant impairment of systolic function, and dyssynchronous contraction. His functional status improved after optimization of pharmacotherapy with titration of the doses of β -blocker and ACE inhibitor and the initiation of spironolactone. The patient is currently under regular review in a dedicated heart failure clinic and, if limiting symptoms persist despite maximal medical treatment, he will be evaluated for cardiac resynchronization therapy with biventricular pacing.

Discussion

Diabetes is a potent risk factor for the development of heart failure. The Framingham study revealed that

Case Report

Diabetes and heart failure

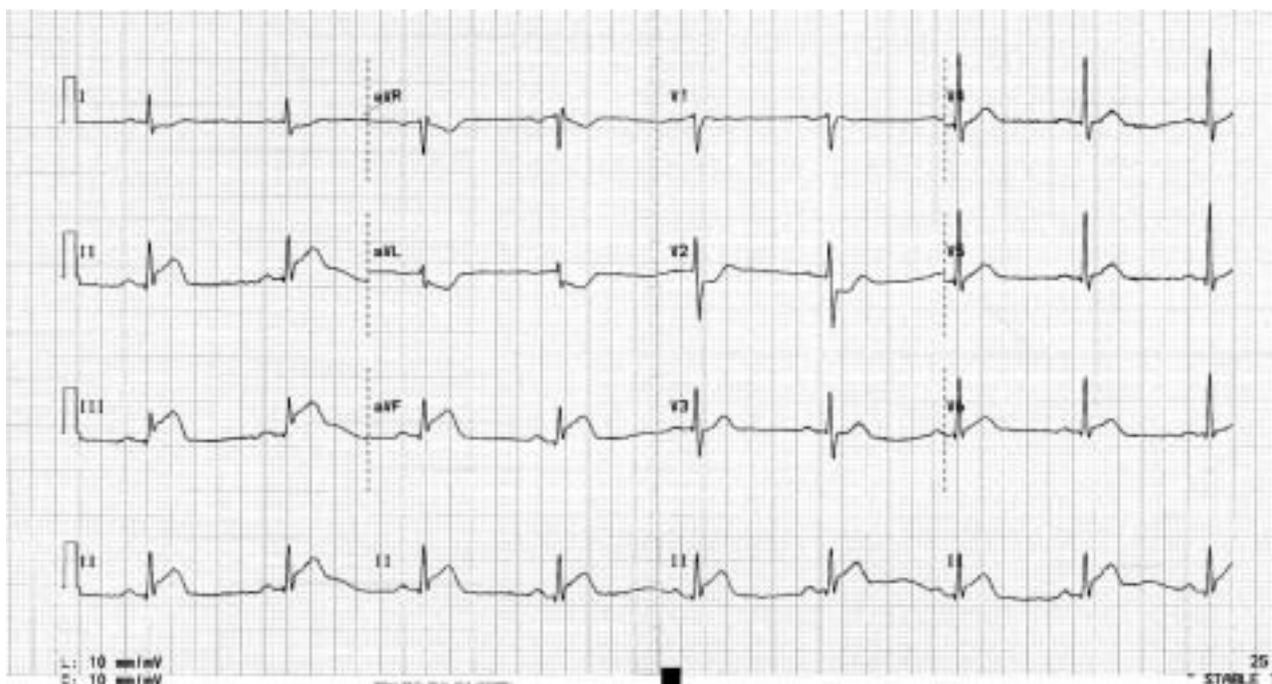


Figure 1. Electrocardiogram showing inferior ST-segment elevation myocardial infarction.



Figure 2. Angiographic appearance of right coronary artery.

heart failure is twice as common in diabetic men, and five times as common in diabetic women, than in age-matched nondiabetic controls [1]. This is largely explained by the close association between diabetes and coronary heart disease or hypertension, as illustrated by the present case. However, heart failure may develop in the absence of these factors, when complex diabetes-specific biochemical, morphological, and functional changes in cardiac cells lead ultimately to the development of diabetic cardiomyopathy.

The presence of diabetes substantially increases the risk of development of cardiac failure in individuals presenting with acute coronary syndromes [2], and diabetic individuals who do develop heart failure have a significantly increased mortality [3]. Angiographic studies confirm more diffuse, extensive coronary disease, with poor collateral development. Despite this, infarct size is not consistently greater in diabetic than in nondiabetic individuals, suggesting that cellular metabolic derangement, autonomic dysfunction, increased neurohumoral activation, and the presence of microvascular disease may collectively contribute to adverse cardiac remodeling.

Patients with diabetes who suffer acute myocardial infarction derive more benefit from thrombolysis or primary angioplasty than do nondiabetic patients, emphasizing the importance of early delivery of reperfusion strategies to this group. The findings of the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study highlighted the beneficial effects of tight glycemic control, with postinfarction administration of glucose/insulin and subsequent intensive insulin treatment leading to a 30% reduction in mortality at 1 year [4]. Subgroup analysis of other postmyocardial infarction trials confirmed that, compared with patients without diabetes, those with the condition derive similar, if not more, benefit from the introduction of aspirin, ACE inhibitors, statins, and β -blockers [5].

Despite optimal peri-infarction care, however, the patient presented here illustrates the increased risk of adverse cardiac remodeling in diabetes, characterized by left ventricular dilatation, myocardial fibrosis,

neurohumoral activation, and eventual progression to overt heart failure.

Table 1 summarizes the factors contributing to the progression of heart failure in diabetes. Although metabolic derangements, including hyperglycemia, hyperinsulinemia, and increased free fatty acids, may contribute to cardiac dysfunction, the effects of optimal metabolic control on chronic heart failure have not been tested in a large clinical trial. Instead, modern drug therapy focuses on achieving complete neurohumoral blockade.

Abundant evidence supports the beneficial effects of ACE inhibition in patients with symptomatic heart failure. A recent meta-analysis confirmed that ACE inhibitors confer a reduction in mortality in patients with diabetes and heart failure similar to that in their nondiabetic counterparts [6]. ACE inhibition can also reduce the risk of development of heart failure in at-risk diabetic individuals without heart failure at the outset [7,8].

The findings of recent trials suggest that angiotensin II receptor blockers (ARBs) exert a benefit similar to that of ACE inhibitors in postinfarction and chronic heart failure, supporting the use of ARBs when ACE inhibitors are not tolerated. Whether ARBs should be used in combination with an ACE inhibitor and β -blocker in the treatment of heart failure remains controversial. However, the recent Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM)-Added study, in which almost a 33% of those studied had diabetes, showed that the addition of an ARB to an ACE inhibitor and, in most cases, a β -blocker, led to a significant reduction in cardiovascular death or admission to hospital with heart failure [9]. Interestingly, treatment of diabetic individuals without overt heart failure with an ARB may prevent the subsequent development of heart failure [10,11].

Aldosterone contributes to cardiac dysfunction in heart failure, largely by promoting myocardial fibrosis. In the Randomized Aldactone Evaluation Study (RALES) of patients with severe heart failure, aldosterone blockade with spironolactone reduced mortality by 30% [12]. Subgroup analysis of the more recent Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), in which mortality was reduced by 15% by the

aldosterone antagonist, eplerenone, confirmed the benefit of aldosterone blockade in diabetic individuals with postinfarction heart failure [13].

Insulin resistance and hyperinsulinemia exacerbate the deleterious effects of the sympathetic nervous system in heart failure. β -Blockers improve left ventricular function and partially reverse the remodeling process, reducing left ventricular mass and favorably altering ventricular geometry. Although β -blockers may potentially promote glucose intolerance, inhibit insulin release, and adversely effect the lipid profile, these concerns should not limit the use of these drugs in diabetic individuals in clinical practice. Several large-scale trials have confirmed significant reductions of mortality by β -blockade in chronic heart failure and this effect is consistent in subgroups with diabetes [14].

Summary

Patients with diabetes are at high risk of developing heart failure. The cellular, metabolic, and neurohumoral abnormalities associated with diabetes contribute to the progression of heart failure and ultimately lead to impaired long-term survival. Pharmacological intervention, with effective antagonism of the renin-angiotensin system, sympathetic nervous system, and aldosterone, has been shown to decrease the morbidity and mortality associated with heart failure, particularly in those with diabetes. Dedicated heart failure clinics enhance the focused delivery of care to such patients. However, despite optimal pharmacotherapy, the prognosis of chronic heart failure remains impaired in patients with diabetes, emphasizing the importance of continued research in this area. ■

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Table 1. Factors contributing to heart failure progression in diabetes.

Sympathetic nervous system activation
Renin-angiotensin system activation
Hyperglycemia
Hyperinsulinemia
Increased circulating free fatty acids
Endothelial dysfunction
Inflammation
Oxidative stress

Case Report

Diabetes and heart failure

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Peroxisome proliferator-activated receptors and the cardiovascular system

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Abstract

Beyond the association of diabetes with ischemia, clinical and experimental evidence suggests that congestive heart failure (CHF) begets insulin resistance, resulting from neurohormone- and cytokine-mediated metabolic perturbations. Peroxisome proliferator-activated receptor-gamma (PPAR- γ) agonists alleviate insulin resistance, ameliorate lipid metabolism, and inhibit nuclear factor kappa B, implicated in detrimental cellular pathways activated in CHF. Experimental studies confirm the pleiotropic cardiovascular benefits of these compounds. Nevertheless, their clinical application is thwarted because of fluid retention and a few incidents of exacerbation of CHF in patients with diabetes. Despite plausible benefits from long-term treatment, these agents should not be initiated in acutely decompensated CHF. Whether combined PPAR- γ /PPAR- α activation provides a promising metabolic approach, sparing peripheral edema, remains under investigation.

■ *Heart Metab.* 2004;25:30–35.

Keywords: Heart, heart failure, insulin resistance, peroxisome proliferator activated receptors, thiazolidinediones

Introduction

Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors of the hormone receptor family, predominantly regulating the expression of metabolic enzymes [1,2]. Three known isoforms (PPARs α , γ , and β/δ), which have discrete tissue distribution and metabolic properties, become activated after binding to either natural (physiologic) or synthetic (pharmacologic) ligands (*Table 1*).

Peroxisome proliferator-activated receptor- α

PPARs- α regulate lipid metabolism and are expressed in tissues with active lipid turnover, where they promote mitochondrial transport and β -oxidation of free fatty acids (FFAs) and decrease FFA esterification into triglycerides. PPARs- α also upregulate apolipoproteins A-I and A-II genes and increase high-density

lipoprotein concentrations. The antilipemic effect of fibrates involves activation of PPAR- α [3].

Peroxisome proliferator-activated receptor- γ

Metabolic effects

PPARs- γ are predominantly expressed in adipocytes, but also in skeletal muscle, liver, macrophages, T cells, myocardium, and vascular endothelium. When activated by ligands, PPARs- γ modulate lipid storage and redistribution away from visceral organs and into adipose tissue [4] by promoting catabolic over anabolic utilization of FFA in the liver and skeletal muscle, and modulating adipokines (adiponectin upregulation, leptin downregulation). PPARs- γ also enhance insulin signaling [5] by upregulating proteins necessary for insulin action (insulin receptor substrate-1, the regulatory kinase Akt, and glucose

Refresher corner

PPARs and the cardiovascular system

Table I. Tissue distribution and cardinal action of the three known peroxisome proliferator-activated receptor (PPAR) isoforms.

	PPAR- α	PPAR- β/δ	PPAR- γ
Tissue expression	Liver Skeletal muscle Heart Kidneys Intestines Vascular cells Immune cells	Ubiquitous	Adipose tissue Intestines Vascular cells Immune cells Heart Skeletal muscle Liver
Physiologic ligands	FFA Eicosanoids Leukotrienes	?	FFA Eicosanoids Prostaglandins
Pharmacologic ligands (activators)	Fibrates	? Prostacyclin	Thiazolidinediones
Target metabolic functions	Lipid transport and oxidation (liver, muscle) Lipoprotein metabolism	Brain lipid metabolism	Adipogenesis, lipid storage and distribution Modulation of insulin signaling Increased glucose uptake (muscle), FFA and glucose uptake (adipocytes) Anti-inflammatory activities Inhibition of NF κ B Adipokine modulation
Target protein modulation	\uparrow CPT-I (mitochondrial transport) \uparrow Enzymes implicated in β -oxidation of FFA ApoA-I, A-II (\uparrow HDL, reverse cholesterol transport)		\downarrow Leptin \uparrow Adiponectin \uparrow Insulin signaling (IRS-1, PI3-K, Akt) and glucose transport (GLUT 4) proteins \downarrow TNF- α , interleukins-1, -2, -6, and -8, adhesion molecules (VCAM, ICAM, E-selectin)

Akt, protein kinase B; ApoA-I, A-II, apolipoproteins A-I, A-II; CPT-1, carnitine palmityltransferase; FFA, free fatty acid; GLUT 4, glucose transporter 4; HDL, high-density lipoprotein; ICAM, intercellular adhesion molecule; IRS-1, insulin receptor substrate-1; NF κ B, nuclear factor kappa B; PI3-K, phosphatidylinositol 3-kinase; TNF- α , tumor necrosis factor- α ; VCAM, vascular cell adhesion molecule; \uparrow , increased; \downarrow , decreased.

transporter 4), accounting for the antidiabetic effects of PPAR- γ agonists (thiazolidinediones [TZDs]).

Cardiovascular effects

Beyond affecting lipid and carbohydrate metabolism, PPARs- γ inhibit nuclear transcription factor kappa B (NF κ B), which is implicated in atherogenesis, endothelial dysfunction, vascular growth and proliferation, expression of adhesion molecules (vascular cell adhesion molecule, intercellular adhesion molecule-1, E-selectin), and oxidation of low-density lipoprotein in atherosclerotic plaques [6]. Activation of NF κ B by endothelin, catecholamines, and angiotensin II is involved in hypertrophic, proinflammatory, and cytotoxic pathways [7], promoting myocardial remodeling, cardiac hypertrophy, and CHF. Expression of PPAR- γ by T cells reduces the proinflammatory cytokines tumor necrosis factor (TNF)- α and interleukins-1, -2, -6, and -8 [8].

Thiazolidinediones

Cardiovascular effects of thiazolidinediones

As activators of PPAR- γ , TZDs exert insulinotropic and insulin-sensitizing cellular effects and improve the lipid profile. In addition, they exhibit pleiotropic cardiovascular effects independent of metabolism (Table II), via inhibition of NF κ B at tissues expressing PPAR- γ [9]. TZDs promote regression of left ventricular hypertrophy [10,11] and improve systemic hemodynamics [12], left ventricular systolic and diastolic function, and experimental mitral regurgitation, inhibit myocardial collagen synthesis in experimental models [13], and exert antioxidant and anti-inflammatory effects via downregulation of TNF- α , transforming growth factor- β , adhesion molecules, and proinflammatory interleukins [8]. They have cardioprotective effects in ischemia-reperfusion in diabetic [14] and nondiabetic [15] animals, decrease infarct size, and attenuate postinfarct ventricular

Refresher corner

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Table II. Cardiovascular effects of thiazolidinedione (TZD) treatment.

	Salutary	Detrimental
Metabolism	Improves insulin sensitivity, glycemic control	
Atherogenesis	Improves lipid profile (↑ HDL, LDL particle size; ↓ TG, circulating FFA) ↓ Adhesion molecules ↓ Macrophage migration and lipid content	
Thrombogenesis	Prevents progression of atheroma in animals fed high-fat diets ↓ PAI-1, fibrinogen	
Inflammation	↓ TNF- α , interleukins-1, -2, -6, -8	
Hypertension	↓ MAP (modest)	
LVH	Regression (experimental)	In one rat study, LV mass increased with supratherapeutic doses
LV function	? Neutral (one human study) Positively inotropic, lusitropic, improves LV systolic function, improves LV diastolic function Decreases MR (experimental model) Neutral in one human study (1 year ECHO follow-up)	
Myocardial ischemia	Cardioprotective in I/R models in diabetic or nondiabetic animals	
Myocardial infarction	Decreases size of infarct (experimental MI)	One study in which TZD "neutral" compared with ACEI (favorable)
Myocardial remodeling	Attenuates post-MI remodeling	
Coronary circulation	Coronary vasodilatation Improves vascular remodeling after angioplasty injury Better clinical restenosis rates in TZD-treated diabetics	
Systemic circulation	Vasodilatation	? Vasodilatory edema
Endothelial function	Increases NO production Endothelial function improves also by non-NO (? prostaglandin)-mediated mechanisms	"Reflex" RAS activation
Capillary vascular permeability	In one study, lung capillary permeability decreased by 50%	Worse at renal glomerulus; implicated in increased Na ⁺ retention and edema
Transplant allograft disease	Favorable effect on T cells Decreases cyclosporine concentrations Anti-NF κ B: improved immune tolerance	

ACEI, angiotensin-converting enzyme inhibitor; ECHO, echocardiography; FFA, free fatty acid; HDL, LDL, high-density and low-density lipoproteins; I/R, ischemia–reperfusion; LV, left ventricular; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; MI, myocardial infarction; MR, mitral regurgitation; NF κ B, nuclear factor kappa B; NO, nitric oxide; PAI-1, plasminogen activator inhibitor 1; RAS, renin–angiotensin system; TG, triglycerides; TNF- α , tumor necrosis factor- α ; ↑, increased; ↓, decreased.

remodeling [16]. Vascular effects include systemic and coronary vasodilatation, improvement of endothelial function [17], prevention of atherosclerosis [18], attenuation of vascular remodeling and restenosis after angioplasty [19], and mitigation of posttransplant arteriosclerosis [20].

Congestive heart failure as insulin resistant state

Diabetes or the metabolic syndrome frequently accompanies ischemic cardiomyopathy. Diabetic cardiomyopathy develops in the absence of epicardial coronary stenosis, as a result of impaired coronary microcirculation and flow reserve or myocardial autonomic dysfunction [21]. The potential

applicability of TZDs in CHF is intriguing, even in the absence of diabetes, in the light of emerging evidence of progressive insulin resistance developing as a result of cardiomyopathy. Glucose intolerance develops in nondiabetic patients with CHF, irrespective of the etiology, and signifies a poor prognosis [22,23]. Clinical studies have demonstrated impaired systemic and myocardial glucose uptake in CHF [24], in contrast to intact myocardial glucose uptake in patients with diabetes who have coronary artery disease but a preserved left ventricular ejection fraction [25].

CHF is characterized by myocardial energetic dysequilibrium with high myocardial oxygen demands, benefiting from utilization of glucose rather than FFA as preferred metabolic substrate. Although the expression of metabolic enzymes shifts to an

“embryonic pattern” favoring glucose oxidation in chronic CHF [26], this “new equilibrium” can be jeopardized by excess catecholamine- and cytokine-mediated overproduction of FFA (“lipotoxicity”) and cellular events impeding glucose uptake and oxidation in endstage, decompensated CHF. Such mechanisms extend beyond competitive substrate inhibition and involve the deleterious effects of metabolic intermediaries [27] such as diacyl glycerol, ceramides, inactivation of insulin receptors by angiotensin II or endothelin, and distal cellular deficits in glucose transporter 4 transporters or key regulatory proteins of insulin signaling, such as impaired phosphorylation of Akt [28], a survival kinase also implicated in apoptosis.

Limitations of the clinical use of thiazolidinediones in congestive heart failure

In spite of potential benefits and salutary experimental studies, utilization of TZDs is restricted even in patients with diabetes who have CHF [29,30]. The first-generation TZD, troglitazone, has been withdrawn because of hepatotoxicity. Currently, two second-generation, nonhepatotoxic TZDs (rosiglitazone, pioglitazone) are used clinically. The main limitations restricting the use of TZDs in patients with diabetes who have CHF relate primarily to an

increased incidence of peripheral edema, and secondarily to a less well defined risk of exacerbation of CHF, attributable to volume expansion [30]. These side effects are more frequent (*Table III*) when TZDs are combined with insulin [31]. Although peripheral edema is a frequent adverse event, it is unlikely to be mediated by detrimental effects of TZDs on central hemodynamics [32,33]; indeed, the findings of a retrospective study [33] suggested that TZDs improved central hemodynamics in patients with CHF who were diabetic. Peripheral edema is usually reversible, dose-dependent and responsive to diuretics or angiotensin-converting enzyme inhibitors [30]. Suggested mechanisms (*Table IV*) include calcium channel blockade [34], effects on renal microcirculation and permeability, and increased renal reabsorption of sodium [35], attributed to compensatory activation of the renin–angiotensin–aldosterone system in response to a vasodilatory effect. In contrast, TZDs may improve pulmonary capillary function [36]. True exacerbation of CHF is rare (33 incidents reported up to July 2004), and is not causally or exclusively attributable to TZDs per se, with all fatal cases involving plausible comorbid etiologies [37]. Because of these concerns, American College of Cardiology/American Heart Association/American Diabetes Association guidelines advocate against treatment with TZDs in patients with diabetes who have New York Heart Association III–IV CHF, and

Table III. Incidence of edema associated with thiazolidinedione (TZD) monotherapy and combination therapy with other antidiabetic modalities in patients with diabetes. (From Nesto et al [30], with permission.)

	Incidence (%)	
	Pioglitazone (15–45 mg daily)	Rosiglitazone (2–8 mg daily)
TZD vs placebo	4.8 (vs 1.2)	4.8 (vs 1.3)
TZD + sulfanylurea vs sulfanylurea	7.5 (vs 2.1)	4 (vs 2.2)
TZD + metformin vs metformin	6 (vs 2.5)	4 (vs 1.1)
TZD + insulin vs insulin	11–15 (vs 7) ^a	13–16 (vs 4.7) ^b

^a15–30 mg, 16 weeks follow-up; ^b4–8 mg, 26 weeks follow-up.

Table IV. Plausible mechanisms associated with thiazolidinedione (TZD)-mediated peripheral edema.

Evidence in favor	Evidence against
Plasma volume expansion Calcium channel blockade “Vasodilatory” Reflex RAAS activation Comparable to amlodipine, hydralazine Effects of TZD in renal microcirculation, increased renal permeability Upregulation of renal Na ⁺ transporters ? Angioedema effect	Increased central venous pressure Adverse systemic hemodynamic effects Increased pulmonary vascular permeability
RAAS, renin–angiotensin–aldosterone system.	

against the use of TZD–insulin combinations in patients with diabetes who have known left ventricular dysfunction or risk factors for CHF [30].

Future directions

The safety and efficacy of TZDs in patients with diabetes at different stages of left ventricular dysfunction require further investigation to define the risk–benefit ratio for every subgroup of patient. Evidence-based therapeutic algorithms may allow patients with CHF to derive benefit from treatment with TZDs. However, these drugs should not be initiated or administered during acutely decompensated, fluid-overloaded states (akin to the β -blocker paradigm). Precise delineation of mechanisms of TZD-mediated edema will have a positive influence on the design of safer alternatives for this population of patients. Such drugs may exploit combined PPAR- γ /PPAR- α strategies, yet be devoid of adverse effects. Whether the benefits of TZDs represent class effects, are more pronounced in ischemic than in nonischemic cardiomyopathy, or persist in combination with oral hypoglycemic agents, in spite of greater rates of edema, remain to be investigated. Most intriguing is the concept of potential salutary effects of TZDs in patients with CHF who do not have diabetes but who are at risk of developing insulin resistance as a result of cardiomyopathy. ■

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Abstracts and commentaries

Gender differences in hypertrophy, insulin resistance and ischemic injury in the aging type 2 diabetic rat heart

Desrois M, Sidell RJ, Gauguier D, Davey CL, et al. *J Mol Cell Cardiol.* 2004; 37:547–555.

Patients with type 2 (noninsulin-dependent) diabetes mellitus have greater mortality after myocardial infarction and increased risk of congestive heart failure [1]. Type 2 diabetes also abolishes sex differences in premenopausal women, and women with diabetes have significantly greater mortality after myocardial infarction than men with diabetes [2]. As relationships among sex, diabetes, and susceptibility to ischemic injury have not been well documented, the aim of this study was to determine whether sex differences in cardiac insulin resistance and tolerance to ischemic injury occur in the aging type 2 diabetic rat heart. The results show that the aging hearts of female type 2 diabetic rats [Goto-Kakizaki or GK, a highly inbred strain derived from an outbred Wistar rat colony that spontaneously develops diabetes] has greater insulin resistance and greater susceptibility to ischemic injury compared with nondiabetic or male type 2 diabetic rat hearts.

Commentary

These results indicate that sex has a significant role in the development of the diabetic phenotype. Systolic blood pressure was the same in type 2 diabetic GK rats as in their sex-matched controls, suggesting that the insulin resistance was not attributable to hypertension. Decreased insulin-stimulated glucose uptake appears to be associated with cardiac hypertrophy in the type 2 diabetic GK rat heart, and the greater insulin resistance in the female GK rat hearts may be related to their increased hypertrophy, as has been suggested by

others [3]. A decreased content of glucose transporter 4 protein may have contributed to the insulin resistance, but it did not explain the differences between the male and female GK rat hearts, because concentrations were decreased to the same extent in all GK rat hearts. Consequently, other mechanism(s) may be involved, such as greater abnormalities in insulin signaling in the female, compared with the male, GK rat hearts. Moreover, it was also observed that the female GK rat hearts had significantly reduced recovery of contractile function after ischemia. This may have been a result of the lower cardiac glycogen concentrations before ischemia, plus the decreased glucose uptake during ischemia, resulting in less glycolytic production of ATP in female GK rat hearts, which has been shown to underlie contracture [4]. Future studies will certainly address the important issue of possible mechanism(s) underlying the influence of sex in insulin resistance and their consequences on the development of postinfarction heart failure.

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Danielle Feuvray

The Association of fasting glucose levels with congestive heart failure in diabetic adults ≥ 65 years

The Cardiovascular Health Study

Barzilay, JI, Kronmal RA, Gottdiener JS, et al. *J Am Coll Cardiol.* 2004;43:2236–41.

Objectives: The purpose of this study was to determine if fasting glucose levels are an independent risk factor for congestive heart failure (CHF) in elderly individuals with diabetes mellitus (DM) with or without coronary heart disease (CHD).

Background: Diabetes mellitus and CHF frequently coexist in the elderly. It is not clear whether fasting glucose levels in the setting of DM are a risk factor for incident CHF in the elderly.

Methods: A cohort of 829 diabetic participants, age ≥ 65 years, without prevalent CHF, was followed for 5–8 years. The Cox proportional hazards modelling was used to determine the risk of CHF by fasting glucose levels. The cohort was categorised by the presence or absence of prevalent CHD.

Results: For a 1 standard deviation (60.6 mg/dL) increase in fasting glucose, the adjusted hazard ratios for incident CHF among participants without CHD at baseline with or without an incident myocardial infarction (MI) or CHD event on follow-up, was 1.41 (95% confidence interval 1.24 to 1.61; $P < 0.0001$). Among those with prevalent CHD at baseline with or without another incident MI or CHD event on follow-up, the corresponding adjusted hazard ratio was 1.27 (95% confidence interval 1.02 to 1.58; $P < 0.05$).

Conclusions: Among older adults with DM, elevated fasting glucose levels are a risk factor for incident CHF. The relationship of fasting glucose to

CHF differs somewhat by the presence or absence or prevalent CHD

Commentary

In this study elevated fasting glucose levels in older adults were associated with an increased risk of cardiac failure. This may reflect poor adherence to therapy but the authors did not detect any difference in the use of diabetic therapy so the alternate mechanisms of impaired endothelial function and increased myocardial fibrosis and stiffness are postulated (diastolic dysfunction is a recognised problem in diabetes). In those without documented coronary heart disease (CHD) a 40% increased risk was recorded and in those with CHD it was increased by 16%.

The patients were the relatively healthy elderly and not the very ill which is of importance when considering the need for early diagnosis and treatment of diabetes. Fasting glucose was recorded and not glycated hemoglobin as an indication of diabetic control perhaps reflecting a 'real world' approach but it would be of interest to know the glycated hemoglobin relationship to cardiac failure.

Given that elevated fasting glucose levels in subjects over 65 years of age are associated with an increased risk of cardiac failure it is important to know if better glucose control can reduce the risk and whether metabolic drug therapy early in the diagnosis may also be of benefit.

Graham Jackson

Glossary

Gary D. Lopaschuk

AMP-activated protein kinase (AMPK)

AMPK is a widely distributed cellular kinase that is activated during times of metabolic stress. It has been termed a cellular “fuel gauge”, and primarily functions to turn off energy consuming pathways and turn on energy producing pathways during metabolic stress.

Acetyl-CoA carboxylase (ACC)

ACC is a key enzyme involved in both synthesis and metabolism of fatty acids. ACC produces malonyl CoA, which is both a substrate for fatty acid biosynthesis, and is a potent inhibitor of mitochondrial fatty acid uptake. In lipogenic tissues like the liver, ACC is the rate-limiting enzyme for fatty acid biosynthesis. In muscle, ACC is a key regulator of fatty acid oxidation, secondary to the production of malonyl CoA.

Adipokines

Adipokines is a term that is used to collectively describe a variety of signalling molecules that are released from adipose tissue. Examples of adipokines include adiponectin, and cytokines such as TNF-1 α .

Adiponectin

Adiponectin is an adipokine that is released from adipose tissue. It is an important signalling molecule that acts centrally at the level of the hypothalamus to decrease food intake, and peripherally to modify fatty acid and glucose metabolism. Low levels of adiponectin are associated with obesity and insulin resistance.

Ceramides

Ceramides are specialized lipids that are derived from sphingomyelin and glycosphingolipids present in plasma membrane of cells. Various cytokines can release ceramide, which then act as important intracellular signalling molecules. Considerable in-

terest has focused on ceramide as a signalling molecule in apoptosis (programmed cell death).

Dichloroacetate

Dichloroacetate is a molecule that activates pyruvate dehydrogenase (PDH). PDH is the rate-limiting enzyme involved in glucose oxidation. In muscle cells, dichloroacetate activation of PDH results in an increase in glucose oxidation. In the heart, this activation of glucose oxidation has cardioprotective effects during and following ischemia.

¹⁸F-labeled 6-thia-hepta-decanoic acid

¹⁸F-labeled 6-thia-hepta-decanoic acid is an ¹⁸F-labeled fatty acid. It can be used to measure fatty acid metabolism in tissue, by following the myocardial fate of ¹⁸F with positron emission tomography (PET) imaging. This tracer has been used for measuring fatty acid metabolism in vivo, including the identification of defects in fatty acid metabolism in subjects with medium- and short-chain fatty acid oxidation defects.

Glycogen synthase kinase 3 (GSK3)

GSK3 is an unusual protein serine/threonine kinase that, as the name implies phosphorylates glycogen synthase. The two mammalian isoforms, GSK-3 α and β , play largely overlapping roles and have been implicated in a variety of human pathologies, including type 2 diabetes, Alzheimer’s disease, bipolar disorder and cancer. Inhibition of glycogen synthase kinase-3 has been shown to prevent caspase-dependent apoptosis.

Lipid kinase termed PI3-kinase (phosphatidylinositol 3-kinase, PI3-K)

PI3-K is an intracellular kinase involved in a number of important cellular pathways, including glucose metabolism. PI3-K produces PtdIns(3,4,5)-P₃, which is part a signalling cascade initiated by a number of different hormones, including insulin.

Leptin

Leptin is a peptide hormone synthesized by adipocytes that plays a key role in the regulation of appetite and energy expenditure. This can occur through direct actions of leptin on the hypothalamus or via direct actions of leptin on peripheral lipid and glucose metabolism.

Mitogen-activated protein kinase (MAPK) cascade

The MAPK cascade involves a number of kinases that have diverse functions in cells. The inflammatory effects of tumor necrosis factor (TNF)- α in cells is mediated by signaling pathways involving MAPK's pathways. MAP-KAPK-1 (also known as p90 ribosomal S6 kinase, p90rsk).

The mitogen-activated protein kinase (MAPK)-activated kinase, p90 ribosomal S6 kinase is a kinase in the MAPK cascade. p90 ribosomal S6 kinase is activated by phosphorylation, whereby it then participates in many cellular processes, including the regulation of protein synthesis.

Malonyl-CoA

Malonyl CoA is a small molecule synthesized in cells by acetyl CoA carboxylase. Malonyl CoA has an important role in regulating muscle fatty acid oxidation, secondary to inhibiting mitochondrial fatty acid uptake. It also is an important substrate for fatty acid biosynthesis.

Nuclear transcription factor kappa-B (NFk-B)

NFk-B is a ubiquitous transcription factor that plays an important integrating role in the intracellular regulation of immune response, inflammation and cell cycle regulation. NFk-B is activated by various stimuli, such as those that are implicated in the progression of chronic heart failure. Signaling by NFk-B involves its release from inhibitor kappa B (IkappaB) in the cytosol, followed by translocation into the nucleus, where it affects gene transcription.

Peroxisome proliferator-activated receptor γ (PPAR γ)

Peroxisomal proliferators-activated receptors are nuclear receptors involved in the transcriptional regula-

tion of proteins. One of these nuclear receptors is PPAR γ , which modifies the expression of a number of proteins, including those involved in insulin sensitivity and lipid metabolism. Activation of PPAR γ is a therapeutic approach to treating diabetes, which may in part be due lowering blood fatty acid levels, secondary to decreasing fatty acid release from adipose tissue.

Phosphorylation

Phosphorylation refers to the process of adding a phosphate group to proteins, usually a tyrosine, serine or threonine residue. This occurs via the action of numerous kinases. Phosphorylation is a very important mechanism that regulates enzyme activity, and is a component of most cellular signaling pathways.

Phosphatidylinositol (4,5) biphosphate (PtdIns(4,5)-P₂)

Phosphoinositol-4,5-bisphosphate (PIP₂) is an intracellular signalling molecule produced by phosphoinositol-4-phosphate-5-kinase. PIP₂ is produced by various stimuli, including activation of the insulin receptor. PIP₂ then acts as a substrate for phosphoinositol 3-kinase (PI 3-K) to produce PtdIns(3,4,5)-P₃ (see below).

PtdIns(3,4,5)-P₃

PtdIns(3,4,5)-P₃ is released from membrane phosphatidylinositol as part of a signaling cascade initiated by a number of different hormones, including insulin. PtdIns(3,4,5)-P₃ activates downstream targets, such as 3-phosphoinositide-dependent kinase-1 (PDK-1). This kinase then acts on downstream kinases such as PKB and protein kinase C to mediate numerous cellular events.

Pleckstrin homology domain

Pleckstrin homology (PH) domains are the 11th most common domain in the human genome, and are best known as domains in an enzyme that have the ability to target cellular membranes by binding specifically to phosphoinositides. Most PH domains are not capable of independent membrane targeting and usually require both phosphoinositide and non-phosphoinositide determinants for their subcellular localization.

Phosphoinositide-dependent protein kinase-1 (PDK-1) and PKB (protein kinase B also known as Akt)

3-phosphoinositide-dependent kinase-1 (PDK-1) is a signaling kinase activated by PtdIns(3,4,5)-P₃. This kinase then acts on downstream kinases such as PKB and protein kinase C to mediate numerous cellular events. Protein kinase B is an intracellular kinase that is important in regulating glucose metabolism. It is a kinase downstream of PDK-1, and insulin activation of PKB will result in GLUT-4 translocation to the cell membrane, thereby stimulating glucose uptake.

Proto-oncogene Cbl

Cbl is a protooncogene product that was initially identified as part of a murine retrovirus transforming protein. Cbl is ubiquitously expressed protein containing a set of sequences providing interactions with a wide range of receptor and nonreceptor tyrosine kinases and signaling proteins. These properties permit Cbl to take part in many protein-protein interactions as an adaptor, which forms multimolecular signaling complexes, and coordinates the activity of its components.

Peroxisome proliferator-activated receptor α (PPAR α)

PPAR α is a nuclear receptor involved in the transcriptional regulation of proteins. PPAR α has many functions, including regulating the expression of many enzymes involved in the control of fatty acid oxidation in muscle.

Pyruvate dehydrogenase (PDH)

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

6-phosphofructo-2-kinase (PFK-2)

PFK-2 is an enzyme that converts fructose 6-phosphate to fructose 2,6-bisphosphate. Fructose

2,6-bisphosphate is a potent stimulator of 6-phosphofructo-1-kinase (PFK-1), the rate-limiting enzyme of glycolysis. As a result, increasing fructose 2,6-bisphosphate is an important mechanism by which glycolysis is regulated.

Thiazolidinediones (TZDs)

TZDs are a class of drugs that act as ligands for PPAR γ . An example of a TZD is rosiglitazone. Activation of PPAR γ by TZDs can improve muscle insulin sensitivity. They also can have beneficial effects on blood lipids and vascular smooth muscle lipid accumulation.

Tyrosine kinase

Tyrosine kinase is a kinase that phosphorylates tyrosine residues on proteins. Many different tyrosine kinases exist, with an important one being the insulin receptor. Insulin binding to the receptor stimulates a tyrosine kinase to initiate the downstream insulin-signalling pathway.

TC10 family of Rho GTP-binding proteins

The Rho GTPases are related to the Ras proto-oncogenes and consist of 22 family members. These proteins have important roles in regulating the organization of the actin filament system, and thereby the morphogenesis of vertebrate cells as well as their ability to migrate. Signal initiation from the insulin receptor and a series of adapter proteins result in the activation of the G protein TC10. TC10 can influence a number of cellular processes, including changes in the actin cytoskeleton, recruitment of adapter proteins CIP4, and assembly of the exocyst complex. These events play crucial roles in the trafficking, docking and fusion of vesicles containing the insulin-responsive glucose transporter Glut4 at the plasma membrane.

VCAM, ICAM, E-selectin

Vascular cell adhesion molecule (VCAM)-1, intracellular adhesion molecule-1 (ICAM-1) and E-Selectin play a central role in the recruitment of inflammatory cells, and its expression is rapidly induced by proinflammatory cytokines such as TNF α . VCAM-1, ICAM-1 and E-Selection also play critical roles in many other processes, such as early atherogenesis.