# Contents

## Editorial
Diabetes and cardiovascular disease  
*Gary D. Lopaschuk* .................................................. 3

## Basic Article
Non ischemic heart failure in diabetes mellitus: still incompletely understood  
*Romain Harmancey and Heinrich Taegtmeyer* ........................................ 5

## Main Clinical Article
Clinical manifestations of diabetic cardiomyopathy  
*Sihem Boudina* .......................................................... 10

## Metabolic Imaging
Nuclear magnetic resonance for the study of cardiac metabolism in diabetes  
*Giancarlo Todiere and Mario Marzilli* ........................................... 15

## New Therapeutic Approaches
Cardiac considerations in the treatment of the metabolic syndrome  
*David S. H. Bell* ........................................................... 20

## Focus on Trimetazidine (Vastarel MR)
Clinical benefits of trimetazidine in patients with coronary artery disease and diabetes mellitus  
*Luis Rodríguez Padial* .................................................... 26

## Case Report
Reduction of coronary flow reserve in a patient with type 2 diabetes mellitus without epicardial coronary stenosis  
*Maurizio Galderisi and Rosa Raia* ............................................. 30

## Refresh Corner
Energy metabolism in the heart of the diabetic patient  
*Danielle Feuvray* ........................................................ 35

## Featured Research
Abstracts and commentaries .................................................. 38

## Glossary
*Gary D. Lopaschuk* ...................................................... 40
Diabetes mellitus and obesity are major health concerns, and the worldwide incidence of these problems is growing at an alarming rate. This growth is disconcerting, because diabetes is associated with a high incidence of morbidity and mortality, and heart diseases are the major cause of death in the diabetic patient. This high risk for heart disease results from both a high incidence of coronary artery disease and hypertension in the diabetic, and the development of cardiomyopathies that occur independent of these risk factors. This leads to a high incidence of heart failure in the diabetic population. Although the mechanisms responsible for the high incidence of coronary artery disease and hypertension in patients with diabetes, insulin resistance, obesity, or combinations thereof, are reasonably well defined, the important mechanisms responsible for the non-ischemic cardiac dysfunction induced in these individuals are less clear. It is well documented that diabetes can lead to a progressive cardiomyocyte dysfunction that can result in both diastolic and systolic dysfunction. A considerable research effort has focused on trying to understand what is responsible for the alterations in cardiomyocyte function in patients with diabetes.

Diabetes-induced alterations in cardiac energy metabolism are increasingly being recognized as important contributors to abnormal cardiac function in those with diabetes. High circulating concentrations of fatty acids in diabetes, and an increased reliance of the heart on fatty acids as a source of energy, not only inhibit myocardial glucose utilization, but also result in excessive accumulation of lipids in muscle. This lipid accumulation can further exacerbate insulin resistance in the heart muscle. High rates of fatty acid oxidation in the heart of the diabetic patient also contribute to the severity of ischemic injury, primarily by inhibiting glucose oxidation. Because of this, the aim of decreasing cardiac fatty acid metabolism is becoming an important therapeutic approach to the treatment of diabetes and its complications.

This issue of Heart and Metabolism addresses a number of key issues related to the effects of diabetes on cardiac function and cardiac metabolism. Articles by Sihem Boudina and by David Bell nicely define the cardiac clinical manifestations that occur in diabetes and insulin resistance, in addition to some of the potential therapeutic approaches to treating cardiac dysfunction in affected individuals. The article by Danielle Feuvray and that by Romain Harmancey and Heinrich Taegtmeyer define some of the energy metabolic changes that occur in diabetes that can lead to the development of cardiomyopathy and heart failure. Both articles highlight an excessive supply of fatty acid to the heart and the excessive use of fatty acids by the heart as potentially important factors contributing to the development of heart failure. This raises the possibility of altering fatty acid metabolism as an approach to treating diabetes-induced cardiac dysfunction. This can be achieved either by altering the supply of fatty acid to the heart or by directly modifying cardiac fatty acid oxidation. With regard to the latter, the article by Luis Rodríguez Padial describes some of the clinical benefit that can be achieved with trimetazidine, an inhibitor of fatty acid oxidation, in diabetic patients. It is interesting that this metabolic approach to the treatment of heart disease is particularly useful in the patient with diabetes, which may be attributable to the underlying metabolic abnormalities in fatty acid metabolism in this population of patients. G. Todiere and Mario Marzilli nicely describe some of the imaging approaches that can be used to assess the severity of metabolic abnormalities in diabetic individuals.
In addition to metabolic changes, abnormalities in the coronary microcirculation may also be an important contributor to the development of diabetic cardiomyopathy. To enable a better definition of this phenomenon, Maurizio Galderisi and Rosa Raia describe the usefulness of Doppler-derived coronary flow reserve measurements in assessing the severity of abnormalities of the coronary microcirculation.

The importance of diabetic cardiomyopathy in contributing to contractile dysfunction and heart failure in diabetes has now been well established. The importance of alterations in cardiac fatty acid metabolism in contributing to these cardiomyopathies is also becoming more evident. This raises the possibility that optimizing cardiac energy metabolism may become a more widely used therapeutic approach to treating heart failure in the diabetic.
Non ischemic heart failure in diabetes mellitus: still incompletely understood

Romain Harmancey and Heinrich Taegtmeyer
Department of Internal Medicine, Division of Cardiology, University of Texas Medical School at Houston, University of Texas Health Science Center at Houston, Houston, Texas, USA

Correspondence: Dr Romain Harmancey, University of Texas Medical School at Houston, 6431 Fannin, MSB 1.246, Houston, TX 77030, USA.
Tel: +1 713 500 6569; fax: +1 713 500 0637; e-mail: romain.harmancey@uth.tmc.edu

Sponsorship: This work was supported by a grant from the National Heart, Lung and Blood Institute (R01-HL073162). Dr Harmancey is supported by a post doctoral fellowship from the American Heart Association (09POST2060155).

Abstract
Independently of conventional factors for coronary artery disease, the risk of death from heart disease is several-fold greater in diabetic patients than in those without diabetes. Although the term “diabetic cardiomyopathy” probably describes a heterogeneous disease for which a clear definition is still lacking, we propose that heart failure in diabetes can be traced to alterations in whole-body energy homeostasis and myocardial metabolism. Here we review some of the mechanisms that have been proposed to cause the disease.

Keywords: Apoptosis, calcium homeostasis, contractile dysfunction, diabetic cardiomyopathy, heart failure, myocardial metabolism

Introduction
The increased incidence of vascular disease in patients with diabetes only partially explains the greater incidence of heart failure that they exhibit. Depending on age, the prevalence of heart failure in diabetic individuals is as high as 12–22%, whereas it is only 1–4% in the general population [1]. We present the concept that non ischemic heart failure in diabetes is the result of synergy among several pathophysiological mechanisms (Figure 1). These derangements contribute to progressive myocyte dysfunction, cell loss, fibrosis, and hypertrophy, with the clinical consequence of diastolic – and often also systolic – dysfunction. Although different investigators have given different definitions to the term “diabetic cardiomyopathy”, its origin can be traced to a dysregulation of both whole-body energy homeostasis and myocardial metabolism (Table I) [2–7].

In diabetes the heart is exposed to an increased supply of fatty acids and of glucose. The increase in substrate supply is accompanied by systemic and myocardial insulin resistance. This extreme metabolic environment influences energy substrate metabolism and directly affects myocyte survival, together with cardiac structure and contractility. Other postulated causes for non ischemic heart failure in diabetes, not developed in this review, include microangiopathy related to endothelial dysfunction and the development of autonomic neuropathy.

Changes in myocardial metabolism
We have termed the mammalian heart a “metabolic omnivore”, because it uses fatty acids, glucose, lactate, and several other substrates for the production of ATP [8]. Although the heart preferentially oxidizes
fatty acids, it readily oxidizes more efficient fuels in response to stress or injury [9]. The metabolic “flexibility” of the heart is impaired in diabetes mellitus. Increased reliance of the heart on fatty acid oxidation is induced by the enhanced availability and uptake of free fatty acids and the simultaneous inhibition of glucose oxidation, glycolysis, and glucose uptake, a phenomenon explained by the glucose–fatty acid cycle [10]. Cardiac efficiency is decreased, because complete oxidation of fatty acids yields less ATP per molecule of oxygen consumed than does oxidation of glucose, and because fatty acids promote mitochondrial uncoupling [11]. Changes in mitochondrial dynamics and function and their relation to contractile dysfunction in diabetes are therefore of particular interest and the subject of extensive investigation. High rates of uptake of long-chain fatty acid by mitochondria enhance the production of reducing equivalents in the mitochondrial electron transport chain, and cause an overproduction of reactive oxygen species [5,12]. In addition, mitochondrial dysfunction in diabetes is characterized by reduced

Table 1. Metabolic concepts concerning the pathophysiology of diabetic cardiomyopathy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Authors</th>
<th>Year</th>
<th>Metabolic concepts</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2]</td>
<td>Rubler et al</td>
<td>1972</td>
<td>The myocardial disease might be produced by the metabolic derangements associated with diabetes, ie, limited glucose utilization and increased extraction of fatty acids and ketone bodies</td>
</tr>
<tr>
<td>[3]</td>
<td>Kannel et al</td>
<td>1974</td>
<td>The major metabolic disturbances could provide a metabolic basis for eventual myocardial failure: an energy crisis originating from faulty utilization of both fatty acids and glucose</td>
</tr>
<tr>
<td>[4]</td>
<td>Taegtmeyer et al</td>
<td>2002</td>
<td>Altered metabolism and impaired insulin action in heart and skeletal muscle are both cause and consequence of altered cardiac function</td>
</tr>
<tr>
<td>[5]</td>
<td>Boudina and Abel</td>
<td>2007</td>
<td>The potential contributors to the development of diabetic cardiomyopathy include altered substrate metabolism, increased oxidative stress, and mitochondrial dysfunction</td>
</tr>
<tr>
<td>[6]</td>
<td>Witteles and Fowler</td>
<td>2008</td>
<td>Insulin resistance probably creates an environment in which the addition of another stressor (eg, pressure/volume overload, drugs/toxins, tachycardia) is poorly tolerated and enough to “tip the balance” in favor of developing a cardiomyopathy</td>
</tr>
<tr>
<td>[7]</td>
<td>Harmancey and Taegtmeyer</td>
<td>2008</td>
<td>Diabetic cardiomyopathy may originate from the failure of the heart to adapt to chronic changes in systemic metabolism. Insulin resistance may be a short-term protective mechanism that becomes maladaptive in the long term</td>
</tr>
</tbody>
</table>
Insulin resistance and hyperglycemia activate the to diminish the survival of cardiomyocytes [23]. Resistance to insulin-like growth factor 1 is likely for a causal link between diabetes mellitus, premature cardiac aging, and heart failure [22]. Increased cardiac progenitor cell function provides evidence that naturally occurring with aging. The impairment of phenomena that are caused by the neurohumoral and metabolic changes that accelerate processes naturally occurring with aging. The impairment of cardiac progenitor cell function provides evidence for a causal link between diabetes mellitus, premature myocardial aging, and heart failure [22]. Increased resistance to insulin-like growth factor 1 is likely to diminish the survival of cardiomyocytes [23]. Insulin resistance and hyperglycemia activate the local renin–angiotensin–aldosterone system, which increases oxidative damage and stimulates hypertrophy and fibrosis in the heart [24]. Hyperglycemia also promotes the formation of reactive intracellular dicarbonyls, which react with amino groups of intracellular and extracellular proteins to form advanced glycation end products (AGEs)'. AGEs increase myocardial chamber stiffness by inducing irreversible crosslinks in long-living matrix structural proteins such as collagen, laminin, and fibronectin [25]. Lastly, excess availability of glucose and fatty acids can induce cell death through oxidative stress generated by mitochondrial hyperpolarization or increased flux of glucose to the pentose phosphate and polyol pathways [12], and by the generation of proapoptotic molecules such as ceramide [26]. All these metabolic signals are likely candidates for driving cardiac remodeling in diabetes.

Impaired calcium homeostasis

Diabetes also causes abnormal intracellular calcium ion cycling, resulting in slowed myocyte contraction and relaxation. Calcium derangements are caused by both transcriptional and post-translational modifications (for review see [27]). Hyperglycemia promotes the phosphorylation of cardiac troponin I through angiotensin II-mediated activation of protein kinase C, resulting in reduced calcium sensitivity and reduced rates of crossbridge cycling of the contractile machinery [27,28]. Ryanodine receptors and sarcoplasmic reticulum calcium ATPase (SERCA2a) are inactivated by AGEs [29,30]. In diabetes and in failing hearts, ryanodine receptors are hyperphosphorylated and become leaky to Ca^2+ during diastole [31,32]. Excess protein glycosylation reduces SERCA2a expression, possibly through the regulation of the transcription factor, Sp1 [33]. The reduction in SERCA2a function seems also to be the result of increased inhibition of the protein by phosphorylamban [34]. In this context, it is of interest that diabetic patients with non ischemic heart failure present with lower levels of expression of the transcription factor MEF2C and its target genes, including SERCA2a [20]. Depressed ß-adrenergic receptor signaling in the heart and autonomic neuropathy further impair excitation–contraction coupling. Lastly, mitochondria constitute a calcium sink, and reduced mitochondrial uptake of Ca^2+, which is related to an enhanced susceptibility to permeability transition, may contribute to impaired cardiac relaxation [35].

Summary and conclusions

It can be concluded that cardiac metabolism has a key role in diabetes-induced contractile dysfunction. Although diabetic cardiomyopathy is multifactorial, metabolic derangements probably have a central role.
in the disease (Figure 2). There is evidence that non ischemic heart failure in diabetes can develop independently of other comorbidities. High concentrations of substrates, and the development of insulin resistance, have pro-aging effects on cardiac structure and function. Most of the above has, however, been determined in genetic models of cardiomyopathy, and in animal models of untreated insulin- and non-insulin-dependent diabetes. The demonstration of a causal link between heart failure and diabetic cardiomyopathy in humans is hampered by a lack of consensus on how to diagnose and treat this entity at the subclinical level. Recent clinical trials aiming at tight glycemic control in patients with diabetes have ended with disappointing results, because the pathophysiology of heart failure in diabetes is still not understood.

*See glossary for definition of these terms.*

## Acknowledgements

The authors thank Roxy A. Tate for editorial assistance.

## REFERENCES

Clinical manifestations of diabetic cardiomyopathy

Sihem Boudina
Division of Endocrinology Metabolism and Diabetes, Program in Molecular Medicine,
University of Utah School of Medicine, Salt Lake City, Utah, USA

Correspondence: Dr Sihem Boudina, HMBG, 15N 2030E bldg 533 rm 3145, Salt Lake City, UT 84112, USA.
Tel: +1 (801) 585 6833; e-mail: Sihem.boudina@hmbg.utah.edu
Conflict of interest: None.

Abstract
Patients with diabetes have an increased incidence of heart failure, even after analyses have controlled for coronary artery disease and hypertension. Thus, as diabetic cardiomyopathy (DCM) has become a well recognized entity among clinicians, a better understanding of its development is necessary for the early diagnosis and the future treatment of diabetes-associated cardiovascular disease. In this article, the latest clinical research on the diagnosis and manifestations of DCM will be outlined. The discussion will be focused on the structural, functional, and metabolic changes that occur in the diabetic myocardium and how these changes contribute to the development of DCM in humans.

Keywords: Diabetic cardiomyopathy, diastolic dysfunction, fibrosis, mitochondrial dysfunction, substrate utilization

Introduction
About three decades ago, Rubler et al [1] first introduced the concept of “diabetic cardiomyopathy” (DCM), which has since been extensively used by epidemiologists and clinicians. DCM is defined as a disease that directly affects the structure and the function of the myocardium, in the absence of other confounding factors such as coronary artery disease (CAD) or hypertension. These early alterations that progress with other diabetes-associated complications lead to the development of more clinically recognized conditions such as left ventricular hypertrophy and heart failure [2].

Structural changes
Left ventricular hypertrophy
Increased left ventricular mass is an independent marker of cardiovascular risk that often occurs independently of arterial blood pressure in type 2 diabetes. Thus diabetes is an independent contributor to left ventricular hypertrophy (LVH) and myocardial stiffness [3]. The Framingham study investigators used echocardiography and reported a significant increase in left ventricular wall thickness in women with diabetes [4]. This was further confirmed in a follow-up study on the Framingham offspring, which also showed that women with diabetes experienced a steeper increase in left ventricular mass with advancing age compared with men and those without diabetes [5]. In contrast, the Strong Heart Study, conducted in a population of American Indians, found that both men and women with diabetes had greater left ventricular mass and wall thickness [6]. Furthermore, in a multi-ethnic population, the likelihood of having left ventricular mass above the 75th percentile of the distribution was 1.5-fold greater in patients with type 2 diabetes, independently of various covariates, including hypertension [7]. In this same population, it was shown that increased left ventricular mass can be
seen only in patients with diabetes, as compared with patients with impaired or normal fasting glucose concentrations [8], suggesting that alterations in the geometry of the heart in diabetic individuals are not an early defect but, rather, a consequence of changes associated with diabetes such as hyperglycemia or obesity. Indeed, Eguchi et al [7] found a significant interaction between diabetes and central obesity and the risk for LVH. Although associations between type 2 diabetes and LVH have been well studied, the influence of type 1 diabetes on left ventricular mass is not well characterized. For example, increased left ventricular wall stiffness was detected in women with type 1 diabetes [9], but 50% of these patients had microvascular complications and some exhibited abnormalities in autonomic function tests; furthermore, in a small cohort of patients with long-standing type 1 diabetes, improved glycemic control significantly reduced septal thickness and left ventricular mass when compared with those in patients who did not achieve improvement of glycemic control [10]. However, in this study, diabetic patients had other complications that may have affected left ventricular mass independently of diabetes. Indeed, it is known that retinopathy and nephropathy, associated with type 1 diabetes, can also affect myocardial remodeling [11]. In this regard, studies conducted in individuals with uncomplicated type 1 diabetes did not detect LVH [12,13].

**Interstitial fibrosis**

Diabetic cardiomyopathy is characterized by interstitial fibrosis, mainly composed of collagen, and perivascular fibrosis. Regan et al [14] found a significant increase in deposition of collagen around the vessel and between the myofibers in heart biopsies from diabetic patients. In addition, a significant increase in collagen type III, but not type I or VI, was found in endomyocardial biopsies obtained from patients with type 2 diabetes, free of CAD and hypertension [15]. Furthermore, diastolic dysfunction detected in a population of patients with uncomplicated type 2 diabetes correlated with pro-collagen type I carboxy-terminal peptide [16], suggesting a mechanistic involvement of myocardial fibrosis in the myocardial dysfunction that occurs in diabetes.

**Increased cell death and oxidative stress**

Diabetes is associated with myocyte cell death; however, it is unclear whether diabetes can directly activate cell death or, rather, it activates pathways known to induce this process. Indeed, activation of the renin–angiotensin system (RAS) was associated with increased oxidative stress and cardiomyocyte and endothelial cell death in hearts of patients with diabetes [17,18]. Thus inhibition of the RAS reduced the rate of first admission to hospital from heart failure and improved echocardiographic indices of left ventricular diastolic function in patients with type 2 diabetes [19,20]. The mechanisms by which cell death occurs in the human myocardium are still not well understood. Thus, where both forms of cell death (necrosis and apoptosis) were identified in myocardium biopsies of patients with diabetes, apoptosis was maximally induced in the diabetic myocardium, whereas necrosis was exaggerated by hyperglycemia [17]. Recently, Chowdhry et al [21] showed that apoptosis and necrosis were increased in the right atrial appendage of patients with type 1 and type 2 diabetes, and that inhibition of caspase-3 reduced apoptosis without influencing necrosis, whereas inhibition of poly-adenosine diphosphate-ribose polymerase reduced necrosis and apoptosis. Although the findings of previous studies have implied that oxidative stress may have a critical role in the development of DCM, this issue has not been properly and fully addressed in humans. The majority of reactive oxygen species (ROS) are generated in the mitochondria. However, enzymatic systems capable of generating ROS in the cytosol – such as NADPH oxidase – can be modulated by hyperglycemia [22]. ROS can also interact with nitric oxide to form nitrotyrosine, which was found to be increased in myocardial biopsies of humans with type 2 diabetes [17]. Finally, studies of the role of antioxidants in preventing cardiac dysfunction in humans have been disappointing. Indeed, in a randomized controlled trial in patients receiving vitamin E, the risk of heart failure was greater in patients receiving the antioxidant treatment [23].

**Myocardial lipotoxicity**

Myocardial diabetic myocardium is also characterized by increased deposition of intramyocardial lipids, which can contribute to cell death and thus to cardiac dysfunction. Regan et al [14] identified deposits of lipofuscin, which are brown pigment granules composed of lipid-containing residues, in left ventricular transmural biopsies obtained from diabetic patients. Furthermore, they measured myocardial triglyceride and cholesterol content in these biopsies and found a significant increase. Similarly, Oil Red O staining of heart sections of non ischemic failing hearts revealed an increased deposition of lipid that was exacerbated by diabetes [24]. More importantly, increased myocardial triglyceride in patients with type 2 diabetes was associated with diastolic, but not systolic, dysfunction [25].

**Functional changes**

In the course of DCM, several functional changes develop and progress (Figure 1). It is therefore incumbent upon clinicians to identify these abnormalities,
because early detection and appropriate treatment can prevent worsening of this condition to overt heart failure.

**Diastolic dysfunction**

Diabetic cardiomyopathy in humans is characterized by diastolic dysfunction, which may precede the development of systolic dysfunction. Indeed, echocardiography performed in 87 patients with type 1 diabetes mellitus without known CAD revealed diastolic dysfunction as indicated by reduced early diastolic filling, increased atrial filling, extended isovolumetric relaxation, and increased supraventricular premature beats [26]. Similarly, in individuals with uncomplicated type 1 diabetes without clinically apparent macrovascular or microvascular complications, Carugo et al [27] reported an age-related increase in diastolic diameter. Similar approaches in patients with well controlled type 2 diabetes revealed a prevalence of diastolic dysfunction in up to 30% [28,29]. The use of flow and tissue Doppler techniques suggests an even greater prevalence of diastolic dysfunction (as much as 40–75%) in individuals with type 1 and type 2 diabetes without overt CAD [30,31]. Indeed, indices for diastolic dysfunction such as E/E' and E/A' ratios (where E is the flow related to early ventricular filling and E' and A' are early and late diastolic velocities, respectively) were impaired in patients with type 2 diabetes [32,33].

**Systolic dysfunction**

In the context of DCM, systolic dysfunction occurs late, often when patients have already developed significant diastolic dysfunction. Thus, in a population of patients with type 1 diabetes with several degree of complications, systolic dysfunction was observed in 39% of those with complications and in only 6% of those free from complications [34]. In addition, a subtle systolic dysfunction, which is usually charac-
In contrast to skeletal muscle, studies examining mitochondrial function in cardiac muscle of diabetic patients have been challenging. Our contribution to the understanding of mitochondrial bioenergetics comes mainly from animal studies of obesity and diabetes [47]. Reagan et al [14] first reported increased numbers of mitochondria with pleomorphism, but no swelling or evident distortion of cristae in the myocardium of patients with diabetes. Using phosphorus-31 nuclear resonance spectroscopy, Clarke’s group provided evidence for decreased cardiac energetics in patients with type 2 diabetic who were free from CAD [48]. Although no direct measure of mitochondrial capacity was provided in this study, mitochondrial generation of ATP was reduced with diabetes, as indicated by the reduction in phosphocreatine/ATP ratios. Finally, studies related to the response of the diabetic heart to ischemic preconditioning have suggested that a defect in the mitochondrial ATP-sensitive potassium channel could explain the inability of the diabetic myocardium to respond to ischemic preconditioning and increase the risk for myocardial infarction [49].

Conclusion

The belief is widely held that the increase in cardiovascular mortality is a consequence of accelerated atherosclerosis. However, compelling epidemiological and clinical data indicate that diabetes mellitus increases the risk for cardiac dysfunction and heart failure independently of other risk factors such as CAD and hypertension. Thus DCM has become a well characterized clinical disease that is manifested by structural, functional, and metabolic changes. It is hoped that, as the mechanisms responsible for DCM continue to be elucidated, they will provide the impetus for generating novel therapies tailored to reduce the risk of heart failure in individuals with diabetes mellitus.

See glossary for definition of this terms.

REFERENCES

Main clinical article

Sihem Boudina


Nuclear magnetic resonance spectroscopy

Nuclear magnetic resonance (NMR) [1] is an imaging technique that uses the nuclear spin of protons in water and fat to provide anatomical and functional information, for example on the myocardium. Magnetic resonance spectroscopy (MRS) [2] is the only non invasive method, not involving exposure to radiation, that allows study of the metabolic components of the myocardium without the use of a tracer [3].

Proton (1H) NMR is performed immediately before spectroscopy to enable selection of the anatomically most suitable “voxel” (the smallest distinguishable box-shaped part of a 3-dimensional space) for the subsequent metabolic study. This aim is achieved by analyzing signals from other nuclei possessing a nuclear spin [sodium-23 (23Na), carbon-13 (13C), phosphorus-31 (31P)], providing information on the chemical and physical state of the tissue.

A current limitation of the technique, confining it to the field of research, is the low sensitivity of the signals acquired from these non proton nuclei. That low sensitivity is secondary to the lower polarization of the nuclei at thermal equilibrium. The level of polarization ($P$) is defined as:

$$P = \frac{(N^+ - N^-)}{(N^+ + N^-)}$$

where $N^+$ and $N^-$ are the number of spins in the (parallel) “up” and the (antiparallel) “down” directions, respectively; the net magnetization, and thus the available NMR signal, is proportional to the ratio of nuclei showing “up” spins to that of nuclei showing “down” spins. However, despite of the use of a high magnetic field [greater than 3 Tesla (T)] to increase the thermal equilibrium polarization (the energy difference between the two spin states), which contributes to the genesis of a useful signal, the polarization is very low.
In ¹H-MRS, the limit of low sensitivity is overcome by the high concentration of protons in organic tissues, but suboptimal spatial and temporal resolutions limit more widespread use of the technique in the clinical setting: using magnetic fields of 1.5 T, the voxels achieved are large (20–70 ml), compared with 8 ml obtained with 7 T, and acquisition takes about 30–40 min, these lengthy scans being associated with a corresponding increase in motion artifacts. In addition, MRS is technically demanding, and requires specialist expertise and additional magnetic resonance hardware and software [2].

Cardiac metabolism

In the past, most studies of cardiac metabolism were performed with ³¹P-MRS [4]. This technique mainly examines the ratio between phosphocreatine (PCr) and ATP, which represents a reliable index of the cardiac energy state. During myocardial ischemia, ATP demand exceeds its production, resulting in a decrease in PCr concentrations and, consequently, a decrease in the PCr/ATP ratio [5]. Using ¹H-MRS in 10 patients with a history of myocardial infarction, Bottomley and Weiss [6] measured the content of creatine in infarct zones with respect to those in control areas, and found it to be reduced in infarcted areas. With ²³Na-MRS it was also possible to show high levels of ²³Na signal both in areas of acute necrosis and in chronic myocardial scar tissue. In theory, combination of these three spectroscopic measurements could enable the identification of ischemic, non viable, and hibernating myocardial tissue.

Among these techniques, ¹H-MRS is now the easiest to use in the clinical setting because of its higher sensitivity compared with other MRS techniques. A large number of metabolites – including creatine, lactate, carnitine, and lipids – have indeed been studied. The major limitation of ¹H-MRS remains the need to suppress the signal deriving from water.

NMR and the diabetic heart

In the research setting, NMR (²³Na, ¹³C, ³¹P) has provided data on the metabolic changes associated with coronary artery disease, heart failure and its treatment (metabolic therapy with trimetazidine [7]), valvular disease (on a possible future role in the optimal timing for surgical treatment [8]), hypertrophic cardiomyopathy [9], and diabetes mellitus.

Given that diabetic patients surviving a myocardial infarction have higher mortality and higher prevalence of heart failure than non diabetic patients, it would be very useful to evaluate and monitor cardiac energy metabolism in diabetic individuals [10]. Indeed, the cardiac metabolic state has been identified as a major predictor of cardiovascular morbidity and mortality (stronger than left ventricular ejection fraction and New York Heart Association class [11]) in patients with heart failure.

The pathways of myocardial metabolism are summarized in Figure 1 [12]. In the diabetic heart, glucose and lactate oxidation decrease [13] and fatty acid oxidation is increased [14], increasing the oxygen requirement for ATP production. Studies with MRS in patients with type 1 and with type 2 diabetes have confirmed these observations. For example,
21 patients with type 2 diabetes and normal systolic left ventricular function (normal left ventricular ejection fraction [LVEF]) and normal myocardial left ventricular mass, free from other major cardiovascular risk factors, were studied with $^{31}$P-MRS [15]. The PCr/ATP ratio in the diabetes group (1.35) was decreased by 35% relative to that in the control group (2.35), and these figures correlated positively with fasting plasma glucose concentrations and negatively with plasma free fatty acid concentrations (Figures 2 and 3). Similar observations (a lower PCr/ATP ratio) were reported in patients with type 1 diabetes and a normal LVEF [16]. These findings are consistent with those from positron emission tomography (PET) studies demonstrating lower rates of uptake of $[^{18}$F]$^{2}$-fluoro-2-deoxyglucose [17] and decreased myocardial blood flow [18] in patients with diabetes compared with those in healthy volunteers.

A shift to glycolysis would be more favorable during myocardial ischemia, but this metabolic pathway is less accessible in patients with diabetes. Changes in cardiac substrate metabolism have been identified in the early stage of diabetes, when left ventricular systolic function is fully preserved. Diamant et al [19] suggested that altered energy metabolism (PCr/ATP ratio) could contribute to the left ventricular diastolic dysfunction [evaluated by E/A ratio with magnetic resonance imaging (MRI)] that may occur in patients with type 2 diabetes with normal LVEF.

Previous studies, using Oil Red O staining of explanted hearts at the time of cardiac transplantation, demonstrated cardiac steatosis in diabetic patients with endstage heart failure [20]. Before the publication of the paper by McGavock et al [21], it was unknown if this phenomenon was a cause or a consequence of heart failure. Using $^{1}$H-MRS, McGavock and colleagues found an increased myocardial triglyceride content in patients with impaired glucose tolerance and type 2 diabetes in early stage of the disease (Figure 4). This study thus demonstrated that cardiac steatosis precedes the onset of diabetes mellitus and left ventricular systolic dysfunction.

The study of myocardial energy metabolism in the diabetic population is a promising application of spectroscopy in the clinical setting. Myocardial spectroscopy could identify the various stages of diabetes and could help towards an understanding of the tight connection between diabetes and cardiovascular diseases, eventually enabling objective assessment of metabolic treatments.

![Figure 2. Positive correlation between phosphocreatine (PCr)/ATP ratio and fasting plasma glucose concentrations.](image2)

![Figure 3. Phosphorus-31 spectra in (a) a normal control individual and (b) a diabetic patient.](image3)
Technological considerations

The use of spectroscopy in the clinical arena strongly depends on technological progress. The transition from 1.5 T to 3 T MRI has already significantly improved the spatial resolution; further improvements are expected with 7 T magnetic fields, which could provide adequate coverage of the entire heart with a spatial resolution corresponding to a 17-segment model [11]. However, increasing the magnetic field gives rise to problems of cost, depth of penetration of the radiofrequency instrumentation, and the available sequences and tissue contrast.

An alternative strategy with which to improve the signal-to-noise ratio while limiting the increase in the magnetic field with all its attendant negative con-

sequences, lies in a different means of increasing the polarization – a ‘‘hyperpolarization’’ technique [22]. This method can increase the signal by several orders of magnitude, using magnetic fields of relatively low strength (up to 3 T) (Figure 5). Referring to equation (1), and bearing in mind that the signal-to-noise ratio (SNR) is proportional to the gyromagnetic ratio (γ), the concentration of nuclear spin (c) and the polarization (P) (SNR = c γ P), it is clear that creating a non equilibrium distribution of the nuclei (N'') will achieve an increase in the signal-to-noise ratio. The main advantage of this approach is that the hyperpolarized nuclei create the signal themselves, rather than moderating the signal from surrounding protons.

Carbon-13 is able to label any substance that contains carbon, including glucose, pyruvate, and proteins. Given the absence of 13C in biological tissues, the images are free from background signal, whereas the intensity of the signal is a linear function of its concentration (quantitative perfusion). Therefore, 13C-NMR could be used in studies of cardiac metabolism, playing a role similar to PET but with better spatial resolution and without exposing the

sequences, lies in a different means of increasing the polarization – a ‘‘hyperpolarization’’ technique [22]. This method can increase the signal by several orders of magnitude, using magnetic fields of relatively low strength (up to 3 T) (Figure 5). Referring to equation (1), and bearing in mind that the signal-to-noise ratio (SNR) is proportional to the gyromagnetic ratio (γ), the concentration of nuclear spin (c) and the polarization (P) (SNR = c γ P), it is clear that creating a non equilibrium distribution of the nuclei (N'') will achieve an increase in the signal-to-noise ratio. The main advantage of this approach is that the hyperpolarized nuclei create the signal themselves, rather than moderating the signal from surrounding protons.

Carbon-13 is able to label any substance that contains carbon, including glucose, pyruvate, and proteins. Given the absence of 13C in biological tissues, the images are free from background signal, whereas the intensity of the signal is a linear function of its concentration (quantitative perfusion). Therefore, 13C-NMR could be used in studies of cardiac metabolism, playing a role similar to PET but with better spatial resolution and without exposing the

sequences, lies in a different means of increasing the polarization – a ‘‘hyperpolarization’’ technique [22]. This method can increase the signal by several orders of magnitude, using magnetic fields of relatively low strength (up to 3 T) (Figure 5). Referring to equation (1), and bearing in mind that the signal-to-noise ratio (SNR) is proportional to the gyromagnetic ratio (γ), the concentration of nuclear spin (c) and the polarization (P) (SNR = c γ P), it is clear that creating a non equilibrium distribution of the nuclei (N'') will achieve an increase in the signal-to-noise ratio. The main advantage of this approach is that the hyperpolarized nuclei create the signal themselves, rather than moderating the signal from surrounding protons.

Carbon-13 is able to label any substance that contains carbon, including glucose, pyruvate, and proteins. Given the absence of 13C in biological tissues, the images are free from background signal, whereas the intensity of the signal is a linear function of its concentration (quantitative perfusion). Therefore, 13C-NMR could be used in studies of cardiac metabolism, playing a role similar to PET but with better spatial resolution and without exposing the
Metabolic imaging

Magnetic Resonance Imaging for the study of cardiac metabolism in diabetes

... patient to ionizing radiations. PET with fluordeoxyglucose makes it possible to evaluate glucose uptake by the cell, but, unlike $^{13}$C-NMR, cannot discriminate between changes to the mechanisms of cellular transport and intracellular metabolic pathways downstream. The major limitation of this technique is that the hyperpolarization is a short physical phenomenon – its half-life is only several minutes – so MRI laboratory facilities capable of performing the hyperpolarization in situ are essential.

In a recent study, Golman et al [23] combined $^{13}$C-NMR and $^{1}$H-NMR to examine metabolism in the ischemic heart. Myocardial ischemia was induced by ligation of the circumflex artery for 15 min and myocardial necrosis was induced by an occlusion lasting 45 min. The group estimated myocardial perfusion (using a paramagnetic contrast agent), regional and global function, and myocardial fibrosis (using delayed enhancement); they also quantified metabolites such as pyruvate, alanine, and bicarbonate in normal, ischemic, and necrotic tissue. They found reduced alanine and bicarbonate signal from areas with hyperenhancement (Figure 6). Production of lactate and alanine is a reliable indicator of the metabolic activity of the cell, whereas production of bicarbonate reflects mitochondrial activity.

Together, $^{1}$H-NMR and $^{13}$C-NMR show promise of becoming, in the near future, a “one-stop shop” for studying morphology, function, perfusion, and metabolic activity by means of a single imaging technique.

REFERENCES


Abstract

To treat insulin resistance and avoid type 2 diabetes the condition must first be diagnosed. When diagnosed it can be assumed that with or without type 2 diabetes the insulin resistant subject has significant cardiovascular disease. Once diagnosed, aggressive therapy of insulin resistance and its associated risk factors has the potential to avoid cardiac events in both the diabetic and non-diabetic insulin resistant subjects. Treating insulin resistance can also avoid the development of diabetes and improve glycemic control and long-term complications in the established type 2 diabetic patient.

Heart Metab. 2009;45:20–25.

Keywords: Insulin resistance, metabolic syndrome, cardiovascular events, type 2 diabetes, lifestyle modification, thiazolidinediones, metformin

Diagnosing the insulin resistance (metabolic) syndrome

To treat a patient with the insulin resistance syndrome or metabolic syndrome, the syndrome must first be identified. The gold standard for diagnosing insulin resistance in the USA is represented by the criteria of the National Cholesterol Educator Program, and three of these criteria need to be present to make the diagnosis of insulin resistance [1] (Table 1). Under most circumstances, patients never have their waist circumference measured or, if measured, it is often measured inaccurately. In addition, a normal waist circumference is dependent upon the patient’s height and a more predictive value is a waist to height ratio greater than 0.6 (ideally the waist circumference should be half of the patient’s height) [2]. As the waist circumference is the only clinical criterion that is diagnostic of excess peritoneal fat (the key factor in the insulin resistance syndrome), omission of this measurement results in the insulin resistance syndrome being greatly underdiagnosed.

The fallacy that insulin resistance is simply a manifestation of obesity is not true, because approximately 40% of those with a body mass index (BMI) greater than 35 kg/m² are not insulin resistant, and 6% of those with a BMI less than 25 kg/m² are insulin resistant [3]. This is because many overweight individuals have mainly increased subcutaneous fat, and some thin persons have excessive peritoneal fat.

In the absence of a waist circumference measurement, a more convenient and remarkably accurate test for the diagnosis of metabolic syndrome is the fasting triglyceride to high-density lipoprotein (HDL) ratio [4]. If this ratio exceeds 3.8, the presence of insulin resistance is very likely. The accuracy of the triglyceride to HDL ratio has been validated by...

Type 2 diabetes, in association with coronary artery dysfunction, which occurs in 50–60% of patients with the combination of ventricular hypertrophy and diastolic tensive patients with new-onset diabetes [9,10]. The established type 2 diabetes and in 30% of non hypertensive [12]. When acted upon by hepatic lipase, triglyceride-laden low-density lipoprotein (LDL) and HDL particles form small dense particles [13]. The small dense HDL particle is less cardioprotective than the larger HDL particles, with decreased effects on inflammation, oxidative stress, endothelial dysfunction, oxidation of LDL, and reverse cholesterol transportation. In addition, the smaller HDL particle has a shorter half-life as a result of an increased rate of hepatic breakdown, which accounts for the decrease in total HDL concentration that is typical of the metabolic syndrome [14]. The smaller LDL particle is more easily taken up by the scavenger receptor on the macrophage, which leads to increased formation of atheromatous plaque [15]. Therefore, the calculated LDL cholesterol concentration can be very misleading in patients with the metabolic syndrome because, in the presence of an increased number of very small highly atherogenic LDL particles, the total calculated LDL may be normal [16]. Because of this, measurement of apolipoprotein B (one molecule per LDL particle) or the easily calculated non HDL cholesterol (total cholesterol minus HDL cholesterol) that reflects the total number of atherogenic particles (LDL, remnant intermediate-density, and small VLDL particles) are more predictive measurements of cardiac risk in patients with metabolic syndrome. Indeed, in the diabetic patient, especially in the presence of increased triglycerides, the non HDL cholesterol has been shown to be more predictive of a cardiac event than the calculated LDL concentration [17].

Why is insulin resistance associated with more cardiac events?

Approximately 50% of hypertensive individuals are insulin resistant and have the metabolic syndrome, and 75% of patients with type 2 diabetes are hypertensive [6]. This is mainly because high concentrations of insulin stimulate both the sympathetic nervous system and the angiotensin II type 1 receptor. Furthermore, through its action on the distal tubule of the kidney, insulin is a salt- and water-retaining hormone. In addition, insulin is an anabolic growth-promoting hormone that causes proliferation of vascular smooth muscle cells and remodeling of the arterial wall. The progression of insulin resistance to the development of hyperglycemia causes an additional increase in sodium retention because, for every molecule of glucose filtered and reabsorbed in the proximal tubule of the kidney, one molecule of sodium is also absorbed [6]. An additional factor in the increased prevalence of hypertension in metabolic syndrome is the increased concentration of free fatty acid (FFA) that is associated with resistance to the action of insulin on peritoneal adipocytes. Increased FFA concentrations, experimentally induced by heparin and Intralipid infusion, worsen inflammation, oxidative stress, and endothelial function, and increase both systolic and diastolic blood pressures [7].

Hyperinsulinemia therefore results, not only in hypertension, but, as a result of a combination of hypertension with the growth-inducing anabolic effects of insulin, also in left ventricular hypertrophy (LVH) [8]. LVH is present in 71% of individuals with established type 2 diabetes and in 30% of non hypertensive patients with new-onset diabetes [9,10]. The combination of ventricular hypertrophy and diastolic dysfunction, which occurs in 50–60% of patients with type 2 diabetes, in association with coronary artery disease leads to a greater prevalence and an earlier onset of heart failure in the diabetic patient [11].

Currently, 43% of patients admitted to hospital with heart failure in the USA have diabetes.

Patients with metabolic syndrome have the characteristic dyslipidemic pattern of increased triglyceride and decreased HDL concentrations. The syndrome results, not only in an increased release of FFAs from the adipocyte, but also in decreased FFA utilization and increased serum FFA concentrations. Resistance to the hepatic action of insulin results in decreased suppression of triglyceride production and increased triglyceride concentrations [12]. When acted upon by hepatic lipase, triglyceride-laden low-density lipoprotein (LDL) and HDL particles form small dense particles [13]. The small dense HDL particle is less cardioprotective than the larger HDL particles, with decreased effects on inflammation, oxidative stress, endothelial dysfunction, oxidation of LDL, and reverse cholesterol transportation. In addition, the smaller HDL particle has a shorter half-life as a result of an increased rate of hepatic breakdown, which accounts for the decrease in total HDL concentration that is typical of the metabolic syndrome [14]. The smaller LDL particle is more easily taken up by the scavenger receptor on the macrophage, which leads to increased formation of atheromatous plaque [15]. Therefore, the calculated LDL cholesterol concentration can be very misleading in patients with the metabolic syndrome because, in the presence of an increased number of very small highly atherogenic LDL particles, the total calculated LDL may be normal [16]. Because of this, measurement of apolipoprotein B (one molecule per LDL particle) or the easily calculated non HDL cholesterol (total cholesterol minus HDL cholesterol) that reflects the total number of atherogenic particles (LDL, remnant intermediate-density, and small VLDL particles) are more predictive measurements of cardiac risk in patients with metabolic syndrome. Indeed, in the diabetic patient, especially in the presence of increased triglycerides, the non HDL cholesterol has been shown to be more predictive of a cardiac event than the calculated LDL concentration [17].

Although the fasting triglyceride concentration has been shown to be only weakly predictive for a cardiovascular event, the postprandial triglyceride concentration, which is increased in the metabolic syndrome, has been shown to be highly predictive. This is because postprandial hyperlipidemia (triglycerides and FFAs) is an inflammatory state associated with oxidative stress and endothelial dysfunction, as well as the formation of atheromatous plaque. In addition, postprandial dyslipidemia is associated with increased inflammation within the atheromatous plaque, leading to an increased risk of plaque rupture and an acute cardiac event [18]. Postprandial dyslipidemia occurs in the metabolic syndrome as a result of increased intestinal absorption of triglycerides.

### Table 1. Criteria for diagnosing the metabolic (insulin resistance) syndrome [1].

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fasting glucose concentration of at least 100 mg/dL</td>
<td></td>
</tr>
<tr>
<td>2. Fasting triglyceride concentrations of at least 150 mg/dL</td>
<td></td>
</tr>
<tr>
<td>3. High-density lipoprotein cholesterol concentration less than 50 mg/dL in women; less than 40 mg/dL in men</td>
<td></td>
</tr>
<tr>
<td>4. Blood pressure of at least 130/85 mm Hg</td>
<td></td>
</tr>
<tr>
<td>5. Central obesity: abdominal waist circumference greater than 77 cm (35 inches) in women; greater than 88 cm (40 inches) in men</td>
<td></td>
</tr>
</tbody>
</table>

euglycemic insulin clamp studies, which are the “gold standard” for measuring insulin resistance [5].
Interestingly, this increased intestinal absorption is reversed with the thiazolidinediones [19].

Even in the absence of diabetes, hyperglycemia – especially postprandial hyperglycemia – is present in the insulin resistance syndrome. In the Norfolk-EPIC study, the greater the glycated hemoglobin (HbA1c) value above 5.0%, the greater was the frequency of cardiac events. In fact for every 1% by which the HbA1c value was above 5%, the rate of cardiac events increased by 26% in men and by 28% in women [20]. At lower HbA1c values, the postprandial, rather than fasting or preprandial, glycose is responsible for the HbA1c, and therefore the most logical reason for the increase in cardiac events with increasing HbA1c is postprandial hyperglycemia [21].

Especially when accompanied by postprandial dyslipidemia (postprandial dysmetabolism), postprandial hyperglycemia is an inflammatory state associated with oxidative stress, endothelial dysfunction, a hypercoagulable state, increased formation of atheroma, and an increased risk of rupture of the atheromatous plaques [18]. Indeed, even within the normal range of postprandial glucose concentrations, the lower the postprandial glucose concentration, the lower the rate of progression of coronary artery disease over a 3 year period. Furthermore, a 2 h glucose concentration less than 90 mg/dL has been found to be associated with regression of atheromatous plaque [22].

The metabolic syndrome in itself is an inflammatory state caused by an excessive production of cytokines, such as tumor necrosis factor α and interleukin-6, by the macrophages that infiltrate peritoneal fat [23]. The increased inflammation leads to oxidative stress, endothelial dysfunction, increased atherogenesis and thrombosis, and an increased frequency of plaque rupture and cardiac events [24]. Increased urine albumin is a marker for endothelial dysfunction, and albuminuria is recognized as being a feature of the metabolic syndrome [25].

Treating the risk factors of the metabolic syndrome

Obviously, weight loss and exercise are the cornerstones of treatment of the metabolic syndrome. Although weight loss is difficult to achieve, many patients are willing to embark on a long-term program of aerobic exercise. Fortunately, exercise is a more powerful tool in decreasing insulin resistance than is weight loss. Decreasing the fat and carbohydrate content of the diet is helpful, not only to achieve weight loss, but also to decrease further the insulin resistance and postprandial dysmetabolism [26].

Decreasing blood pressure to 130/80 mm Hg or less is a goal of therapy. However, in the patient with metabolic syndrome, blockade at the various points of the renin–angiotensin system (RAS) will also decrease insulin resistance. Therefore a RAS blocker (angiotensin-converting enzyme [ACE] inhibitor, angiotensin receptor blocker [ARB]) should be the first antihypertensive agent utilized in patient with metabolic syndrome, type 2 diabetes, or both [27]. Following the use of a RAS blocker, most practitioners would recommend the addition of a thiazide diuretic [28]. Furthermore, the ACCOMPLISH trial [29] showed that the combination of the ACE inhibitor, benazepril, and the dihydropyridine calcium-channel blocker, amlodipine, resulted in 19.6% fewer cardiac events than occurred with the combination of benazepril and hydrochlorothiazide. Unlike thiazide diuretics that increase insulin resistance, amlodipine has been shown not only to improve insulin resistance, but also to decrease inflammation and oxidative stress [30]. In addition, calcium-channel blockers, through increasing the expression of ATP-binding transporter A1, mediate both cellular lipid release and the production of HDL, in addition to improving inflammation and endothelial function [31]. Therefore, in the hypertensive patient with insulin resistance, after a RAS inhibitor has been given, a calcium-channel blocker, preferably amlodipine, rather than a thiazide diuretic, should be the next addition.

Recently, β-blockers have fallen into disrepute for the treatment of hypertension, because of a small increase in the incidence of stroke [32]. However, because of the high prevalence of coronary artery disease in patients with type 2 diabetes and those with metabolic syndrome, these patients should benefit from the utilization of a β-blocker [33]. Unfortunately, vasoconstricting β-blockers increase insulin resistance, which results in the incidence of new-onset type 2 diabetes being increased by 25–30% when a vasoconstricting β-blocker is used to treat hypertension [34]. Furthermore, through increased insulin resistance, glycemic control worsens in the patient with type 2 diabetes. Fortunately, vasodilating β-blockers, such as carvedilol, which has β1- in addition to β2- and α1- blocking properties, decrease insulin resistance and improve glycemic control. In addition, carvedilol has powerful anti-inflammatory properties, which may lead to carvedilol being more cardioprotective than other β-blockers. Therefore, third-line treatment for the insulin-resistant, hypertensive patient should be a β-blocker, and β-blocker therapy must be utilized in every patient with metabolic syndrome who has coronary artery disease, heart failure, or both [35]. In all these situations, a vasodilating β-blocker should be utilized.

Treatment of hyperlipidemia in the patient with metabolic syndrome should be very aggressive,
because studies of the combined thickness of the intima and media of the carotid artery – a surrogate maker for atherosclerosis – have clearly shown that atherosclerosis is more prevalent and severe in the patient with metabolic syndrome [36]. Therefore, the patient with the syndrome should be treated with the same intensity as the patient who has already been diagnosed as having coronary artery disease. Because of this, the target total LDL concentration in the patient with metabolic syndrome, type 2 diabetes, or both, should be 70 mg/dL or less. To achieve this, a powerful statin, such as rosvastatin, which does not decrease HDL at high doses in the way that atorvastatin does, should be utilized.

Statins will increase HDL concentrations by as much as 10–15%, but achieving HDL goals in the insulin-resistant patient usually requires the addition of other lipid-decreasing therapies [37]. The use of nicotinic acid is ideal, as it increases HDL and decreases triglyceride concentrations. However, compliance is a major problem because of flushing, and nicotinic acid also increases insulin resistance and may therefore both increase the risk of new-onset diabetes and worsen glycemic control in the patient with established diabetes [38]. An alternative treatment is to add a fibrate to existing statin medication. The only fibrate that has been shown to decrease cardiac events is gemfibrozil but, unfortunately, gemfibrozil is associated with several drug–drug interactions. Particularly problematic is that the combination of gemfibrozil and a statin decelerates the hepatic breakdown of the statin, leading to toxic concentrations of statins, which causes varying degrees of myositis and the more severe myopathies [39]. An alternate fibrate is fenofibrate, which does not have adverse myopathic effects when it is combined with a statin, although its efficacy in decreasing cardiac events has never been proven [40,41]. Weight loss, a low carbohydrate diet, daily small amounts of alcohol, and thiazolidinediones can also increase HDL concentrations.

Decreasing triglyceride concentrations and insulin resistance will result in an increase in the size of both the HDL and LDL particle, which makes the LDL particle less atherogenic and the HDL particle more cardioprotective [15]. Again, the insulin-sensitizing thiazolidinediones, particularly pioglitazone, are efficacious in increasing both the LDL and the HDL particle sizes. Unfortunately, the thiazolidinedione, rosiglitazone, has been shown to increase the number of LDL particles, whereas the other available thiazolidinedione, pioglitazone, decreases the number of LDL particles [42]. This difference is a possible explanation for the better cardioprotective effect that has been shown to be achieved with pioglitazone in type 2 diabetes [43,44].

Statins, while the cornerstone of preventative therapy in the insulin-resistant patient, may increase the risk of development of diabetes, as was shown with rosvastatin in the JUPITER study [45]. This is unlikely to be as a result of increased insulin resistance, because simvastatin has been shown neither to increase nor to decrease insulin resistance. However, a meta-analysis of statin studies has shown a trend for statins, with the exception of pravastatin, to increase the risk of developing diabetes [46]. The protective effect of pravastatin was largely attributable to pravastatin decreasing the development of diabetes by 30% in the West of Scotland Study, although it did not do so in other studies [47]. The likely increase in diabetes with statins appears to be the result of increased hepatic production of glucose, which is increased more with lipophilic than with hydrophilic statins.

Antiplatelet therapy with low-dose aspirin is advisable in patients with metabolic syndrome; however, justification for its use is lacking, as there is no evidence that aspirin is effective in decreasing cardiac events in these patients. Indeed, resistance to the antiplatelet effect of aspirin is more common in patients with type 2 diabetes, and it is probable that this is also true in those with the metabolic syndrome [48,49].

Many physicians believe that early treatment of the metabolic syndrome is indicated in the non diabetic patient with the syndrome, to avoid the development of diabetes and cardiac events. Certainly, weight loss, including that achieved with bariatric surgery (gastric banding and gastric bypass), and an aerobic exercise program are recommended and acceptable therapies for this group [50]. However, the use of drugs such as metformin or thiazolidinediones in this situation is questionable, largely because of the side effects of both these drugs, making them unsuitable as preventative therapies. In the Diabetes Prevention Program, both troglitazone and metformin (especially in younger persons) decreased the incidence of new-onset diabetes [51]. Rosiglitazone in the DREAM trial, and pioglitazone in the ACT NOW trial, both decreased the progression of impaired glucose tolerance to diabetes, perhaps by decreasing insulin resistance [52]. The addition of pioglitazone to existing diabetes therapy in the PROACTIVE study significantly decreased the incidence of the combination of death, myocardial infarction, acute coronary artery syndrome, and stroke [43,53,54]. However, the potential for side effects – particularly fluid retention and weight gain – with thiazolidinediones, and especially the potential increase in cardiac events with rosiglitazone, preclude the utilization of these drugs in a non diabetic patient [44]. However, when being appropriately utilized for approved indications, drugs such as RAS inhibitors, vasodilating β-blockers,
and perhaps even dihydropyridine calcium-channel blockers, will decrease insulin resistance and help avoid diabetes and cardiac events in non-diabetic patients with metabolic syndrome [55]. In addition, avoiding, where possible, drugs such as thiazide diuretics, vasoconstricting β-blockers, and nicotinic acid derivatives will avoid an increase in insulin resistance and may decrease the risk of a cardiac event and delay, or even avoid, the development of type 2 diabetes in patients with the metabolic syndrome [55].

### Conclusion

To treat insulin resistance, the condition must first be diagnosed and, when diagnosed, treated aggressively, assuming that, like the individual with type 2 diabetes, the insulin-resistant patient has significant cardiovascular disease. Aggressive treatment, which should include choosing medication that will decrease rather than increase insulin resistance, has the potential to avoid cardiac events in both the diabetic and non-diabetic insulin-resistant patient, improve glycemic control in the patient with established type 2 diabetes, and delay or avoid the onset of diabetes in the non-diabetic insulin-resistant patient.

### REFERENCES


Clinical benefits of trimetazidine in patients with coronary artery disease and diabetes mellitus

Luis Rodríguez Padial
Cardiac Unit, Hospital Virgen de la Salud, Toledo, Spain

Correspondence: Dr Luis Rodríguez Padial, Cardiac Unit, Hospital Virgen de la Salud, Avda Barber 30, 45004 Toledo, Spain.
Tel: +34 925269134; fax: +34 925269149; e-mail: lrodriguez@sescam.org

Conflicts of interest: None.

Abstract

The heart is capable of using fatty acids and glucose as its main sources of energy, with their balance depending on many physiological and pathological situations. In the presence of ischemia, there is a switch to oxidation of fatty acids, which has deleterious effects on the function of the heart. Trimetazidine reduces fatty acid oxidation and increases glucose oxidation, which tends to normalize the metabolism and function of the heart in ischemia and diabetes. It has been shown that trimetazidine reduces angina and ischemia in patients with stable coronary artery disease – an effect that has also been observed in patients with coronary artery disease who have diabetes mellitus.

Heart Metab. 2009;45:26–29.

Keywords: Cardiac metabolism, coronary artery disease, diabetes, trimetazidine

Introduction

The prevalence of diabetes mellitus has increased dramatically over recent decades, and this trend is expected to continue in the foreseeable future. Most cases of diabetes are attributed to type 2 (non-insulin-dependent) diabetes mellitus, which carries a high cardiovascular risk. Indeed, cardiovascular disease is the leading cause of death in these patients, atherosclerosis being responsible for around 80% of deaths [1].

Many pathogenic factors can pave the road to the development and progression of atherosclerosis in diabetes mellitus; among them, hyperglycemia, hypertension, dyslipidemia, insulin resistance, hypercoagulability, impaired fibrinolysis, and endothelial dysfunction are key [2]. Furthermore, these factors can also play a part in worsening the clinical presentation and prognosis of patients with diabetes who have coronary artery disease, such as those with myocardial infarction. As the same adverse prognosis has been observed in diabetic patients with other types of heart disease, such as left ventricular hypertrophy and dilated cardiomyopathy, the cause is most probably a derangement of cardiac metabolism produced by diabetes mellitus, not a differential pathophysiology of the atherosclerotic plaque in this disease [3].

Effect of diabetes mellitus and ischemia on cardiac metabolism and function

Under normal circumstances, the heart is an “omnivorous” organ, capable of oxidizing different classes of substrates, such as carbohydrates or free fatty acids (FFAs), for the production of energy (Figure 1) [4]. The normal heart obtains 60–90% of its energy from FFA oxidation, and the remainder from glucose and lactate. FFA metabolism yields more ATP per gram,
but requires a greater oxygen consumption because it is less efficient. The ability of the heart to switch from one substrate to another allows it to adapt efficiently to many different factors, such as substrate availability, tissue perfusion, hormonal regulation, and the amount of cardiac work, and is therefore fundamental to its health.

Type 2 diabetes mellitus disturbs the capability of the heart to use different metabolic substrates and makes it dependent almost exclusively on the metabolism of fatty acids. Peripheral insulin resistance produces an increase in the delivery of fatty acids to the heart. The increased uptake of fatty acids by the heart produces a decrease in glucose oxidation by the organ as a result of the Randle phenomenon and the activation of peroxisome proliferator activated α. Fatty acids also inhibit insulin signaling pathways, which produces a further reduction in the oxidation of glucose by the heart. As a consequence of all of these changes, fatty acid oxidation increases and glucose oxidation decreases in the diabetic heart [5]. However, because of the hyperglycemia present in diabetes mellitus, glucose uptake by the heart is frequently within normal ranges in diabetes mellitus.

These metabolic changes in the hearts of patients with diabetes result in a derangement of cardiac function that can have a specific clinical expression [6]. Fatty acid oxidation is less efficient than glucose oxidation, because less ATP is produced per mole of oxygen used. Furthermore, other factors such as an increase in mitochondrial uncoupling, an overproduction of reactive oxygen species with consequent deleterious effects, and an accumulation of glucose and fatty acid metabolic intermediates in the cells also contribute to further deterioration of cardiac cellular function and survival.

Several studies in experimental models have shown that the metabolic modification of the heart in diabetes mellitus produces an improvement in cardiac function [7]. This, together with the fact that magnetic resonance spectroscopy enables study of the metabolic status of the heart [8,9], has increased interest in this type of study in humans. A recent study performed with pioglitazone and metformin failed to demonstrate that a change in cardiac metabolism translates into a change in cardiac function in men with diabetes mellitus [10], whereas other authors have found an improvement in cardiac function in patients with myocardial dysfunction and diabetes mellitus treated with a metabolic modulator such as trimetazidine [11].

Because mitochondrial oxidative metabolism is critically dependent on the supply of oxygen to the heart, any decrease in oxygen supply to the myocardium, such as is seen in myocardial ischemia, can result in a decrease in the production of ATP. There is an initial adaptive increase in glycolysis, aimed at producing ATP in the absence of oxygen, which is followed by a significant increase in the oxidation of fatty acids. Therefore, fatty acid oxidation becomes the main residual source of mitochondrial oxidative metabolism in myocardial ischemia. The high glycolysis coupled to low glucose oxidation results in the production of lactate and protons, which leads to a reduction in the pH of cell, calcium overload, and contractile dysfunction. These changes are even more marked in diabetic individuals with coronary artery disease [12].

The optimization of cardiac metabolism represents an interesting approach to the treatment of heart disease that is aimed at switching the fuel preference of the heart to glucose instead of fatty acid. This can be attained through different strategies: direct inhibition of mitochondrial fatty acid oxidation (trimetazidine and ranolazine), prevention of the mitochondrial uptake of fatty acids (etomoxir), reduction of the circulating concentrations of free fatty acids (infusion of glucose–insulin–potassium solution), or direct stimulation of glucose oxidation and improvement in its coupling to glycolysis (dichloroacetate) [13,14].

**Trimetazidine in diabetes and myocardial ischemia**

As inhibition of fatty acid oxidation and stimulation of glucose oxidation can improve cardiac efficiency and function in the heart, trimetazidine, a piperazine derivative that belongs to the family of partial fatty acid oxidation inhibitors, offers one interesting approach to the modification of the metabolic phenotype of the heart in diabetes and ischemia, switching the substrate for oxidation from fatty acid to glucose.
Trimetazidine inhibits the enzyme of fatty acid \( \beta \)-oxidation, long-chain 3-ketoacyl coenzyme A thiolyase (3-KAT). Through the inhibition of myocardial fatty acid oxidation, glucose and pyruvate oxidation are increased (pyruvate dehydrogenase activity is increased) and lactate production is decreased at the time of ischemia. As a consequence, the deleterious metabolic consequences of ischemia are corrected independently of hemodynamic factors [15].

Trimetazidine has been shown to be an effective drug for the treatment of angina pectoris and ischemia in chronic coronary artery disease. In a Cochrane review of the clinical efficacy and tolerability of trimetazidine in patients with stable angina, a total of 23 randomized trials involving 1378 patients were included. Compared with placebo, trimetazidine reduced both the weekly rate of angina attacks (by 40%; \( P < 0.0001 \)) and consumption of nitrate medication (\( P < 0.0001 \)). Objectively, trimetazidine improved exercise time to 1 mm ST-segment depression (\( P = 0.0002 \)). Furthermore, the effects of trimetazidine were found to be similar to those of hemodynamic anti-anginal agents, but with a lower incidence of adverse effects. The benefits were obtained with trimetazidine used both as monotherapy and in combination with other agents [16].

We studied a total of 580 patients with type 2 diabetes mellitus and coronary artery disease (the DIETRIC study) treated with trimetazidine in association with other anti-ischemic drugs, with the aim of analyzing the anti-ischemic effect of trimetazidine. The clinical response and results of a treadmill stress test at 6 months were assessed. The weekly number of angina crises (\( P < 0.001 \)) and the use of glyceryl trinitrate pills (\( P < 0.001 \)) were reduced by trimetazidine. Furthermore, there were increases in total exercise time (\( P < 0.001 \)) and in time to a 1 mm ST-segment depression (\( P = 0.02 \)) in the 6 months stress test, in addition to an excellent tolerance of the drug [17] (Figure 2). Similar observations in small randomized trials have been made by other authors [18,19].

Although there are no data concerning improved prognosis after treatments with trimetazidine, small trials have revealed an interesting trend. It has been demonstrated recently, in 116 patients with coronary artery disease and left ventricular dysfunction undergoing cardiac rehabilitation, that the addition of trimetazidine to exercise training produced greater improvements in functional capacity, left ventricular ejection fraction, and endothelium-dependent dilatation than were achieved with trimetazidine or exercise training alone. Some of the patients studied had diabetes, and this randomized study revealed a synergistic role of trimetazidine with exercise [20]. Furthermore, the addition of trimetazidine to the standard treatment in patients with diabetic cardiomyopathy can improve left ventricular systolic function and functional capacity despite no change in myocardial perfusion [21].

Summary

Trimetazidine is an anti-ischemic drug that modulates the metabolism of the heart and improve symptoms and quality of life in patients with angina pectoris. Its profile is especially useful in patients with diabetes mellitus, as it tends to normalize the metabolic functional changes in the heart that are induced by diabetes mellitus [22].

REFERENCES

Focus on Vastarel MR
Trimetazidine in CAD with diabetes mellitus

Reduction of coronary flow reserve in a patient with type 2 diabetes mellitus without epicardial coronary stenosis

Maurizio Galderisi and Rosa Raia
Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy

Abstract
We present a clinical case that demonstrates the usefulness of transthoracic Doppler-derived coronary flow reserve in distinguishing coronary microvascular dysfunction from epicardial coronary artery stenosis in type 2 diabetes mellitus. Our patient had signs of inducible ischemia on effort electrocardiogram and single photon emission computed tomography, but no angiographic evidence of epicardial coronary artery stenosis. On these grounds, coronary microvascular impairment was identified because the coronary flow reserve was reduced, whereas regional wall motion was completely normal, after administration of high-dose dipyridamole. These abnormalities of the coronary microcirculation were combined with concentric left ventricular hypertrophy, whereas the metabolic status (fasting blood glucose 149 mg/dL, HbA1c 7.7%) was near normal.

Keywords: Coronary flow reserve, coronary microcirculation, diabetes mellitus, transthoracic doppler echocardiography, single positron emission computed tomography

Introduction
Functional and structural alterations of the coronary microcirculation are possible in patients who have type 2 diabetes mellitus but do not present coronary artery stenosis [1–3]. Although frequently associated with myocardial perfusion defects on single photon emission computed tomography (SPECT) [4], these alterations can remain silent for several years during the time course of the disease, or contribute to the development of myocardial ischemia and angina pectoris when myocardial oxygen demand is increased [5].
Doppler flow wire [9], and is highly practicable and reproducible [7].

We present the case of a patient with asymptomatic type 2 diabetes mellitus, normal coronary angiography, and a SPECT-derived myocardial perfusion defect, in whom transthoracic Doppler-derived CFR was of additional value in achieving the correct diagnosis.

Case report

A 48-year-old woman affected by type 2 diabetes mellitus presented at the outpatient clinic of the Department of Clinical and Experimental Medicine of Federico II University Hospital. The diagnosis of diabetes mellitus was based on the American Diabetic Association guidelines [10]. Fasting blood glucose was 149 mg/dL and the glycated hemoglobin value (HbA1c) 7.7%. The duration of the patient’s type 2 diabetes mellitus was 10 years. No signs of retinopathy had been found by fundus oculi. The patient was referred to the Echocardiography Laboratory of our Department because of inducible myocardial ischaemia detected on both effort electrocardiogram (ECG) and effort myocardial SPECT (Figure 1), and after the performance of a coronary angiography that revealed evidence of absence of significant epicardial coronary artery stenosis (Figure 2). At the time of the echocardiogram, the woman was receiving anti-hypertensive therapy with an angiotensin-converting enzyme inhibitor and a β-blocker; her blood pressure was 140/80 mm Hg.

A standard Doppler echocardiographic examination was performed with a Vivid Seven ultrasound machine (GE, Northen, Norway), using a 2.5 MHz phased-array transducer with harmonic capability. Quantitative analysis of the left ventricle and Doppler-derived transmitral inflow, recorded and analyzed as previously reported [11], showed a typical picture of concentric left ventricular hypertrophy (LVH) (left ventricular mass index 48 g/m².7; relative wall thickness 0.44) and grade I diastolic dysfunction (transmitral E/A ratio 0.80; E velocity deceleration time 256 ms). Doppler assessment of the distal left anterior descending artery was performed using a 5 MHz shallow-focus phased-array transducer [12]. Coronary blood flow velocities were recorded at rest and after the administration of high-dose dipyridamole (0.84 mg/kg in a 6 min infusion). Heart rate, blood pressure, and ECG were monitored during the test. In addition, semi-simultaneous imaging of coronary flow and 2-dimensional echocardiography-derived left ventricular wall motion were performed before and after the dipyridamole infusion, according to a validated procedure [13]. Coronary diastolic peak velocities were measured at rest and
after dipyridamole vasodilatation, and CFR was defined as the ratio of hyperemic to resting diastolic peak velocities. After the dipyridamole infusion, the patient experienced neither major adverse reactions nor symptoms of angina, and did not show significant changes on the ECG or left ventricular wall motion abnormalities. The CFR was reduced as a result of a blunted hyperemic response to stimulation of the coronary flow peak velocity by high-dose dipyridamole; the velocity at rest was normal (Figure 3).

Discussion

The case presented here demonstrates the usefulness of transthoracic Doppler-derived CFR in distinguishing coronary microvascular dysfunction from epicardial coronary artery stenosis in type 2 diabetes mellitus. Our patient, in fact, had signs of inducible ischemia on effort ECG and SPECT, but no angiographic evidence of epicardial coronary artery stenosis. On these grounds, coronary microvascular impairment was identified because the CFR was reduced, whereas regional wall motion was completely normal, after high-dose dipyridamole.

Diabetes mellitus induces functional and structural abnormalities of the coronary microvascular environment, which can play a part in the development of diabetic cardiomyopathy [14,15]. Coronary microvascular function may be evaluated non invasively by the assessment of TTE-derived CFR. Reduction in CFR corresponds to coronary microvessel damage when stenosis of the epicardial coronary arteries is excluded [6]. An impairment of CFR has been documented in both type 1 and type 2 diabetes mellitus. Several factors such as hyperglycemia, insulin resistance, endothelial dysfunction, and increased cardiac sympathetic activity [16–19] can be involved in this impairment. However, the impact of concomitant cardiovascular risk factors, particularly of increased blood pressure, should also be taken into account [15].
Left ventricular hypertrophy is an independent hallmark of cardiovascular risk in the general population [20]. It develops frequently in diabetic patients, independent of the effect of concomitant risk factors [21], but can also be induced by the often coexisting increased blood pressure [20]. Worthy of note, the presence of LVH is associated with left ventricular diastolic dysfunction [22]. In agreement with previously reported observations [15,23], the CFR in our patient with type 2 diabetes mellitus was reduced, mainly as a result of a blunted hyperemic response to dipyridamole. The reduction in CFR was combined with structural changes to the left ventricle, mainly concentric LVH and left ventricular diastolic dysfunction, whereas the metabolic picture (fasting blood glucose concentration, HbA1c values) was near normal. This evidence is in agreement with the findings of previous studies indicating that impairment of the coronary microvessels in patients with type 2 diabetes mellitus and hypertension could be, at least in part, mediated by changes in left ventricular structure associated with LVH. Extravascular compressive forces and concomitant hypertrophy of the coronary microvascular walls might be mechanisms underlying the abnormalities of CFR observed in the diabetic and hypertensive heart [15].

Conclusion

The clinical case presented highlights the role of transthoracic Doppler-derived CFR in the diagnosis of isolated coronary microvascular dysfunction in type 2 diabetes mellitus, and illustrates that abnormalities of the coronary microvessels are associated more with myocardial structural changes than with metabolic status.

REFERENCES

Editorial comment to the article “Reduction of coronary flow reserve in a patient with type 2 diabetes mellitus without epicardial coronary stenosis” by Maurizio Galderisi and Rosa Raia

In this manuscript, the authors describe a 48-year-old diabetic patient referred for cardiological evaluation following a positive exercise stress test and an abnormal myocardial perfusion scan. The patient was asymptomatic and a coronary angiography excluded significant coronary obstructions. The patient was also hypertensive and a left ventricular hypertrophy was diagnosed by echocardiography. The patient underwent a transthoracic Doppler-derived Coronary Flow Velocity measurement during dipyridamole infusion.

The test did not elicit angina or EKG changes, or regional wall abnormalities. So, given the absence of any marker of ischemia, this test must be labelled as negative.

However, the ratio of peak flow velocity, measured during dipyridamole infusion, to the initial flow velocity was 1.88. This value is below the cut-off value of 2, which in most laboratories is used as the lower limit of normal, therefore must be considered abnormal.

The authors conclude that transthoracic CFR assessment was instrumental in formulating the right diagnosis for this patient. But the right diagnosis for this patient is not clear.

Effort angina? This diagnosis cannot be formulated because the patient was asymptomatic. We are all aware that myocardial ischemia may be not associated with chest pain in diabetic patients; nevertheless we cannot use the term angina in the absence of symptoms.

Syndrome X? To qualify as Syndrome X a patient must have a positive exercise stress test, angina and normal coronary angiography, but again this patient was asymptomatic, therefore this diagnosis cannot be formulated.

Silent ischemia? Silent ischemia (asymptomatic ST segment depression during exercise) is relatively frequent in diabetics, but it is usually associated with coronary obstructions and wall motion abnormalities. So, this diagnosis must also be discarded.

In summary, we have an asymptomatic diabetic patient with EKG abnormalities and myocardial perfusion defects during exercise, and a negative echo-dipyridamole stress test. Abnormal EKG changes and perfusion defects are frequently observed during stress tests in hypertensive patients and in patients with LV hypertrophy but, in the absence of coronary obstructions, they are usually labelled as “false positive” tests. Diabetes, hypertension, and hypertrophy are all associated with coronary microvascular dysfunction. Microvascular dysfunction may be severe enough to limit flow increase during exercise down to the ischemic threshold. The observation in this patient of an impaired CFR, is consistent with the hypothesis that the abnormalities in the EKG and in the perfusion scan observed during exercise may well be a “true” marker of ischemia even in the absence of an atherosclerotic coronary obstruction. The patient remains asymptomatic as many diabetics, and the negative echo-stress test is consistent with the absence of significant coronary obstructions.

Mario Marzilli
Because of the combined effects of insulin resistance and high concentrations of circulating fatty acids in the uncontrolled diabetic state, cardiac myocytes use fatty acids almost exclusively to support ATP synthesis. Reliance on fatty acid oxidation for ATP production results in greater mitochondrial oxygen consumption costs compared with glucose oxidation. Fatty acids can induce uncoupling of mitochondria, probably by upregulation of uncoupling proteins (UCPs). Two uncoupling protein isoforms, UCP2 and UCP3, are present in the human heart. The activity of these proteins decreases the mitochondrial proton gradient without the generation of ATP, and thereby decreases myocardial energy production. Their expression correlates positively with fasting plasma FFA concentrations. In parallel, there is a decrease in insulin-responsive glucose transporter function and glucose oxidation. Alterations in myocardial energetics occur early in the pathophysiology of type 2 diabetes and appear to precede measurable alterations in in-vivo cardiac function.

Heart Metab. 2009;45:35–37.

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

Introduction

It is well recognized that patients with diabetes mellitus have an increased risk of cardiac disease that is independent of the presence of secondary risk factors such as coronary artery disease [1,2]. A large body of evidence now indicates that cardiac metabolism and disease are intimately related [3,4]. In the normal adult heart, free fatty acids (FFAs) and carbohydrates (glucose and lactate) are metabolized for permanent cellular energy (ATP) production in the mitochondria. However, in the diabetic heart, glucose and lactate oxidation are decreased and fatty acid oxidation is increased. The increased reliance on fatty acid oxidation arises from the interplay of depressed insulin signaling, with associated consequences in the control of myocardial glucose uptake and utilization, and increased circulating concentrations of FFAs. Few studies have assessed insulin-stimulated glucose metabolism in the myocardium of patients with diabetes. Those studies that have used positron emission tomography to determine insulin-stimulated uptake of fluorine-18-labeled fluorodeoxyglucose have clearly shown that type 2 diabetes is specifically associated with severe insulin resistance, regardless of coronary artery disease and despite normal basal blood flow [5,6]. Because of the importance of insulin in the control of myocardial glucose uptake and utilization, the flexibility for metabolic substrate use is then lost, and cardiac myocytes use fatty acids almost exclusively to support ATP synthesis.

Metabolic disturbances in cardiac myocytes

Reliance on fatty acid oxidation for ATP production results in greater mitochondrial oxygen consumption costs compared with glucose oxidation, and
Mitochondrial energy production

As mentioned above, the activity of UCP2 and UCP3 proteins decreases the mitochondrial proton gradient without the generation of ATP, and thereby decreases myocardial energy production. This process could explain why human phosphocreatine (PCr) to ATP ratios correlate negatively with plasma FFA concentrations [10]. It should be noted in this context that patients with heart failure have also increased plasma FFA concentrations, high whole-body insulin resistance, and low insulin-stimulated uptake of fluorodeoxyglucose in the heart [10,12,13]. A recent study of mitochondrial energetics in hearts of leptin receptor-mutant (db/db) type 2 diabetic obese mice has demonstrated that mitochondrial uncoupling is indeed mediated by activation of uncoupling proteins [14]. This probably occurs on the basis of increased delivery of the reducing equivalents FADH$_2$ and NADH from fatty acid oxidation, coupled with a reduced ability for complete oxidation of these equivalents. This might contribute to increased generation of mitochondrial reactive oxygen species (ROS) which, in turn, activates uncoupling proteins. Mitochondrial uncoupling may initially represent an adaptive response to increased fatty acid oxidation and fatty-acid-mediated generation of reactive oxygen species. However, it does not completely normalize the operation of mitochondrial reactive oxygen species, as demonstrated by the accumulation of products of lipid peroxidation [14]. Therefore the negative impact of mitochondrial uncoupling is to reduce the mitochondrial supply of ATP. Altered myocardial energetics characterizes these hearts and clearly precedes measurable alterations in in-vivo cardiac function, as assessed by echocardiography [14,15]. Cardiac high-energy phosphate metabolites, measured at rest in patients with type 2 diabetes using phosphorus-31 nuclear magnetic resonance spectroscopy, have revealed a decrease in PCR to ATP ratios [15]. Furthermore, data have underlined that not only do alterations in cardiac energetics occur early in the pathophysiology of type 2 diabetes, but these alterations are correlated negatively with the fasting plasma FFA concentrations. Defective energy metabolism in the heart is likely to impair energy-requiring processes and therefore myocardial function, cardiac contractile performance, and diastolic function [4], the last of these being a hallmark phenotype of diabetic cardiomyopathy in the earlier stages. This may also limit the ability of the myocardium in patients with type 2 diabetes to withstand ischemia, and may contribute to the increased cardiovascular morbidity and mortality in such patients [16].

Conclusion

The evidence available at present highlights the complexity of alterations in myocardial cell metabolism that may be associated with a multifactorial disease such as diabetes, especially type 2 diabetes. Target tissues become resistant to the effects of insulin, and fatty acids probably have a critical role in the development of cellular insulin resistance [11]. Certainly, there are similarities in cardiac dysfunction in animal models and human type 2 diabetes or obesity, or both. For instance, obese young women showed increased cardiac utilization of fatty acid as measured by positron emission tomography, and increased myocardial oxygen consumption, with reduced cardiac efficiency [17]. Numerous detrimental effects ensue from the loss in myocardial substrate flexibility, and can lead to impaired left ventricular function.

Further supporting the metabolic–functional relation are studies in experimental models of diabetes demonstrating that reversing metabolic alterations results in improved contractile function. The metabolic improvements are paralleled by a more
favorable energetic profile and improved left ventricular function. The success of experimental studies has led to the investigation of myocardial metabolic manipulation in patients with type 2 diabetes. Recent work has investigated high-energy phosphate metabolism in a well controlled diabetic population in which only men with short duration (~3–4 years) type 2 diabetes were included [18]. In this population, in which the extent of left ventricular dysfunction was limited to subtle abnormalities in diastolic function, the PCr to ATP ratio was similar to that observed in normal controls, and no correlation was found between increased myocardial glucose uptake induced by pioglitazone and high-energy phosphate metabolism. Conversely, another study that used phosphorus nuclear magnetic resonance spectroscopy in patients with type 2 diabetes (both men and women) clearly showed significantly altered cardiac high-energy phosphate metabolism, despite still apparently normal cardiac morphologic and function [15].

These data, in accordance with those obtained in hearts of diabetic db/db mice [14], indicate that alterations in cardiac energetics occur early in the pathophysiology of type 2 diabetes and are associated with alterations in circulating metabolic substrates. These findings suggest that chronic manipulation of the myocardial metabolic substrate, aimed at reducing fatty acid oxidation, such as can be achieved with trimetazidine [19], or at improving the coupling between fatty acid delivery and oxidation in cardiac myocytes, may prevent or slow the progression of left ventricular dysfunction in hearts of diabetic patients.

REFERENCES


Metabolic profiling reveals distinct patterns of myocardial substrate use in humans with coronary artery disease or left ventricular dysfunction during surgical ischemia-reperfusion


Human myocardial metabolism has been incompletely characterized in the setting of surgical cardioplegic arrest and ischemia-reperfusion. Furthermore, the effect of the pre-existing ventricular state on ischemia-induced metabolic derangements has not been established. We used a technique based on mass spectrometry to profile 63 intermediary metabolites in serial paired peripheral arterial and coronary sinus blood effluents obtained from 37 patients undergoing cardiac surgery, stratified by presence of coronary artery disease and left ventricular dysfunction. The myocardium was a net user of a number of fuel substrates before ischemia, with significant differences between patients with and without coronary artery disease. After reperfusion, significantly lower extraction ratios were found for most substrates, in addition to significant release of two specific acylcarnitine species, acetyl carnitine and 3-hydroxybutyryl carnitine. These changes were especially evident in patients with impaired ventricular function, who exhibited profound limitations in the extraction of all forms of metabolic fuel. Principal component analysis highlighted several metabolic groupings as potentially important in the postoperative clinical course. We conclude that the pre-existing ventricular state is associated with significant differences in myocardial fuel uptake both at baseline and after ischemia-reperfusion. The dysfunctional ventricle is characterized by global suppression of the uptake of metabolic fuel and limited myocardial metabolic reserve and flexibility after global ischemia-reperfusion stress in the setting of cardiac surgery. Altered metabolic profiles after ischemia-reperfusion are associated with the postoperative hemodynamic course and suggest a role for perioperative metabolic monitoring and targeted optimization in cardiac surgical patients.

Commentary

This study by Turer et al determined which energy substrates are used in patients undergoing elective cardiac surgical procedures that included planned placement of a coronary sinus catheter for the delivery of retrograde cardioplegia. This was achieved utilizing a technique of metabolomic profiling that was based on mass spectrometry, to analyze the transmyocardial extraction of a number of important energy substrates both before aortic cross-clamping (ischemia) and during reperfusion. The study population was divided into three cohorts: control patients (valvular lesions with normal systolic function/normal coronary arteries; \( n = 17 \)), patients with coronary artery disease (CAD) (luminal stenosis >50%; \( n = 12 \)), and patients with left ventricular dysfunction (LVD) (left ventricular ejection fraction <45%; \( n = 10 \)).

Before ischemia there was no difference in the absolute extraction (\( \mu \text{mol/L} \)) of glucose, lactate, or fatty acids between control patients, those with CAD, and those with LVD. However, during reperfusion after ischemia, glucose, lactate, and fatty acid extraction persisted only in control patients. The values for glucose and fatty acid extraction were clearly suppressed during reperfusion in the control patients; however, the relative proportion of fatty acid/glucose extraction nearly doubled. During reperfusion, defects in glucose uptake (ie, net glucose elution) coupled to net lactate release were observed in patients with CAD and LVD, with continued extraction of fatty acid. Thus, although depressed compared with pre-ischemic values, fatty acid extraction did persist during reperfusion, and probably represented the major substrate contributing to myocardial ATP requirements. Importantly, during this time period, the increased reliance on fatty acids as a metabolic fuel probably uncoupled glycolysis and glucose oxidation at the level of pyruvate dehydrogenase, as indicated by transmyocardial lactate release. Furthermore, during reperfusion, the apparent relative reliance on fatty acids as a metabolic fuel was accompanied by net myocardial release of \( \beta \)-hydroxybutyryl carnitine, which has been implicated as a marker of incomplete fatty acid oxidation,
particularly when the supply of fatty-acid-derived acetyl coenzyme A exceeds the capacity of the tricarboxylic acid cycle to utilize it. An important clinical correlate of these findings was that the need for post-operative inotropic support, both immediately after cardiopulmonary bypass and during the stay in the intensive care unit, was greater in patients manifesting net lactate release compared with those who exhibited continued lactate extraction and, hence, continued myocardial carbohydrate oxidation.

This study has important implications for the utilization of metabolic modulation as a therapeutic strategy in the treatment of ischemic heart disease. It implies that incomplete fatty acid oxidation can decrease ventricular performance, and thus can necessitate the requirement for inotropic support during reperfusion in the clinical setting. Furthermore, this study supports the concepts, (1) that there is an increased relative reliance on fatty acids as a metabolic fuel during reperfusion after ischemia and (2) that shifting energy substrate preference from the use of fatty acids to the use of carbohydrates as an oxidative fuel can limit cardiac dysfunction in the setting of ischemic heart disease. These findings warrant future studies assessing the ability of partial fatty acid β-oxidation inhibitors to reduce incomplete fatty acid oxidation as a potential mechanism contributing to cardioprotection in both experimental and clinical settings.

Jagdip S. Jaswal and Gary D. Lopaschuk
Homeostasis
Homeostasis, in physiological/biological systems, refers to the processes and mechanisms involved in the maintenance of a constant internal environment, in spite of fluctuations in environmental conditions.

Diabetic microangiopathy
Diabetic microangiopathy describes the microvascular complications that are manifest in the diabetic state. These complications arise from hyperglycemia-induced damage to the microvasculature from (at least in part) the formation of advanced glycation end products; they include diabetic nephropathy, retinopathy, and neuropathy.

Cardiac efficiency
Cardiac efficiency describes the relationship between cardiac work and myocardial oxygen consumption (mVO₂) by the ventricle during the course of cardiac contraction, and is expressed as the work/mVO₂ ratio.

PPAR (peroxisome proliferator activated receptor)
The PPARs are a family of nuclear receptors that act as transcription factors controlling the expression of a number of genes involved primarily in fatty acid oxidation, fatty acid synthesis, and inflammation.

AGE (advanced glycation end products)
Advanced glycation end products are the result of a chain of chemical reactions after an initial glycation reaction. They may be formed externally, such as heating of sugars with fats or proteins, or they may be formed internally within the body through normal metabolism and aging. AGEs have also been shown to have a role as proinflammatory mediators in disease states such as gestational diabetes.

Myocardial stiffness
Myocardial stiffness is a term that often relates to diastolic function of the heart and is defined by the relationship between pressure and volume. People with heart failure with normal ejection fraction (diastolic heart failure) often have increased myocardial stiffness.