Improving prognosis in ischemic heart disease: time to maximize benefit

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Focusing purely on mortality as a quantity of life issue is obviously the most precise measurement of prognosis, but for many people it is the quality of life along the journey that is as, if not more, important. In the stable angina population the estimated annual mortality is 0.9–1.4%, with an annual non-fatal myocardial infarction incidence of 0.5–2.6% [1]. Within this clinical condition the conventional risk factors of hypertension, hyperlipidemia, diabetes and cigarette smoking adversely affect prognosis. These are, however, modifiable and there is good evidence for risk intervention leading to clinical endpoint benefit so we have time to maximize benefit medically.

In Europe each year 947,420 deaths are caused by coronary heart disease in women and 943,085 in men [2]. The myth that it is predominantly a man’s disease has been dispelled by the facts; but women do develop the disease at an older age. In general, however, the same risk factors predispose to cardiovascular disease in men and women (even allowing for a degree of female hormonal protection), so management is the same with no room for sex bias.

Addressing prognosis must take into account the person’s lifestyle and perception of the problem, their personal interpretation of life’s quality and quantity, their social environment and family circumstances. An approach that leads to an active life of good quality without necessarily lengthening life must not be dismissed as scientifically invalid; living the same length of life with a preventable stroke is not a justifiable argument for avoiding risk reduction advice and therapy.

In this issue of Heart and Metabolism we start at the beginning; this sounds obvious, but often the basics are overlooked or taken for granted. From the dynamic nature of plaque progression it is logical to look at the prevention of plaque rupture; stabilizing the plaque being the primary objective. The UK National Institute for Health and Clinical Excellence has issued an excellent quick reference guide, which should be consulted in addition to our more comprehensive reviews [3]. Diabetes is a particular challenge needing comprehensive lifestyle and therapeutic intervention, not just glucose control. We look into the future with stem cells and enlarge on the growing recognition of the importance of metabolic therapy in improving prognosis as well as symptoms.

As we all get older, we may “feel our age” but age should not be a barrier to all the options available, although a more aggressive interventional approach should take into account the higher complication rate. Being old does not mean being denied a good quality of life.

Improving the prognosis for ischemic heart disease involves maximizing the evidence base we have accumulated; no risk factor should be managed in isolation, but we must not lose sight of quality of life and must tailor our approach accordingly.

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The atherosclerotic plaque was not built in a day: the dynamic nature of plaque progression and instability

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Abstract

Recent studies have determined that atherosclerosis is a dynamic disease, with both progression and regression of plaques possible, as well as marked change in composition that affect plaque stability. Plaque composition, rather than size, determines the clinical course and consequences of atherosclerosis. In particular, recent findings from models of atherosclerosis have emphasized the important contribution of both inflammatory cells and the death of smooth muscle cells. The mechanisms underlying plaque vulnerability and their implications for development of treatment for atherosclerosis are discussed in the light of this knowledge.

Keywords: Vascular smooth muscle cells, apoptosis, atherosclerosis, vascular, inflammation

Introduction

Atherosclerotic plaques consist of an accumulation of vascular smooth muscle cells (VSMCs), inflammatory cells (macrophages, T lymphocytes, dendritic cells, and mast cells) underlying a dysfunctional endothelium, together with extracellular lipid, collagen and matrix. These cellular and acellular components are arranged into defined structures within the plaque. Thus many advanced plaques comprise a VSMC-rich fibrous cap overlying a lipid- and macrophage-rich necrotic core. Most atherosclerosis is clinically silent, and the consequences of its presence rarely occur before the development of advanced lesions. This transition from silent to clinically manifest disease is a reflection of profound changes in the components and structure of the plaque, resulting in plaque erosion or plaque rupture, the major triggers to myocardial infarction [1].

Composition of atherosclerotic plaques – the key to clinical outcome

Although plaques can show similar structures, there are defining features that determine whether a plaque is more likely to undergo erosion or rupture. These features of stability are important both to predict the individual risk and as major targets for drug therapy for plaque stabilization. Thus plaques liable to undergo rupture show a thin fibrous cap, a larger necrotic core and lipid component, and a reduced VSMC component compared with plaques that are less likely to rupture [2]. The fibrous cap of advanced plaques is thinned from loss of VSMCs, and these thin-cap fibroatheromata are the most common of the lesions that rupture [3].

Until recently, the plaque has been considered to be a passive structure, caused by gradual accumulation of tissue that obstructs the vessel. In contrast, recent
research has demonstrated the dynamic nature of plaque components. The biological processes that maintain the plaque include cell migration and emigration, cell division and cell death, matrix synthesis and degradation, and accumulation or loss of lipid. The cellular changes occur in many of the different cell types within the lesion, increasing the complexity of plaque dynamics. Each of these processes would be predicted to increase or decrease the relative stability of the plaque, and are thus all targets for therapy. For example, macrophage accumulation, and activation and release of matrix-degrading proteinases would all be predicted to promote plaque rupture, and there is considerable evidence in humans to support this contention. In contrast, loss of VSMCs from the fibrous cap, for example via the process of apoptosis, would be predicted to promote plaque instability, and both human and animal data support this assertion [4,5]. Increased lipid content also promotes instability, and recent studies have shown that reducing lipid content also reduces plaque inflammation, and may in some cases cause plaque regression.

Composition of atherosclerotic plaques – the key to treatment

These observations reinforce the concept that changes in plaque composition, rather than plaque volume per se, can have profound influences on plaque instability and thus the risk to the patient. We would also predict that treatments aimed at several processes that promote plaque instability, or which result in changes in several components of the plaque, would have beneficial effects. For example, statin therapy reduces lipid content of the plaque, reduces the accumulation and activation of macrophages and lymphocytes, increases VSMC content, increases fibrous cap thickness, and improves endothelial reactivity and function [6–9]. These effects are all noted at standard therapeutic doses, and in animal models they occur without any change in serum cholesterol [9]. In contrast, VSMC apoptosis reduces fibrous cap thickness, increases necrotic cores, and increases plaque inflammation – all processes predicted to promote plaque instability [5]. This concept may also suggest why there is more limited benefit for agents that target only one process involved in plaque rupture or its consequences. In such a complex process as atherosclerosis it may be that the more “dirty” the drug, the more processes it affects, and the more benefit may be derived.

Our increasing understanding of plaque dynamics also raises the question of the stage at which a plaque is too far advanced to be altered by therapy. Results from both animal and human studies have demonstrated that atherogenesis is more easily manipulated than are established plaques [10], and the more advanced the lesion, the less likely that intervention will alter plaque components in a beneficial manner. In advanced plaques, VSMCs become senescent [11], and are thus less able to divide and repair lesions. More advanced plaques, and particularly calcified plaques, are less likely to regress after intensive lipid-decreasing regimens than are more moderate lesions [12,13]. The implications of this are that plaque modification is best achieved by prevention, or at the early stages of disease, and although therapy is hugely beneficial, plaques are less tractable once they present with symptoms.

Not only do we need to treat plaques early, we need systemic therapy to treat the systemic effects of atherosclerosis. Although local treatment with angioplasty/stenting (coronary disease), endarterectomy (carotid disease) and angioplasty/surgery (iliofemoral disease) is effective at relieving symptoms, and in some cases reduces future patient events, it is clear that unstable plaques occur throughout the arterial tree, and what is identified as the culprit lesion may not be so. In particular, recent studies have shown that there are several unstable lesions in coronary arteries both upstream and downstream of what is designated the culprit lesion (reviewed in [14]). Although some workers advocate local coronary stenting at regions most likely to result in myocardial infarcts [15], recent scares over late patency of drug elution stents means that systemic therapy is likely to be both more effective and cost-efficient for the majority of patients.

Summary

Recent studies have demonstrated the complex and dynamic nature of the atherosclerotic plaque. Plaque behavior is governed more by composition than by volume. Early plaques are tractable, although the ability to alter both plaque composition and plaque size decreases with advanced disease. Atherosclerosis is a systemic disease, and early systemic therapy to alter plaque composition is likely to be the most effective method of altering the natural history of atherosclerosis.

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Pharmacologic prevention of coronary plaque rupture – the major cause of acute coronary syndromes

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Abstract

The rupture of a vulnerable coronary atherosclerotic plaque results in coronary thrombosis, the main cause of unstable angina, acute myocardial infarction, and sudden cardiac death. Usually, a culprit plaque that ultimately ruptures does not cause significant flow-limiting stenosis, but is characterized by a typical histological structure: it contains a large necrotic lipid core and a thin fibrous cap, which separates the core from the circulating blood. The formation of such thin-cap fibroatheromata results from a reactive inflammatory response of the growing plaque to continuous accumulation of lipids derived from low-density lipoprotein. Consequently, adequate control of both lipid accumulation and inflammation in the plaque are crucial in the prevention of plaque rupture. At present, these requirements are pharmacologically best fulfilled by statins. Emerging therapies with a similar dual effect on coronary plaques include intravenous infusion of synthetic high-density lipoprotein. These therapies are likely initially to stabilize inflamed plaques and, if administered sufficiently rigorously and for a sufficiently long time, they lead to regression of lipid-laden vulnerable plaques. It is becoming increasingly evident that other cardiovascular drugs may also increase plaque stability. These agents include peroxisome proliferator activated receptor α and γ agonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, and aspirin.

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Keywords: Coronary artery disease, plaque rupture, pharmacotherapy

Introduction

Atherosclerosis of epicardial coronary arteries and their major branches is the underlying cause of ischemic coronary heart disease. Acute coronary syndrome usually results from an occluding thrombus of the culprit coronary artery and manifests clinically as unstable angina, acute myocardial infarction, or sudden cardiac death. The most common cause of acute coronary thrombosis is plaque rupture, notably the rupture of a thin-cap fibroatheroma [1]. Careful analysis of such ruptured culprit lesions has created the concept of “vulnerable plaques”. These plaques typically cause only minor stenosis of the coronary lumen and are morphologically characterized by a large lipid core and a thin cap, which contains few collagen-producing smooth muscle cells but numerous inflammatory cells, namely macrophages, T cells, and mast cells [2].

Ambrose and D’Agate recently discussed the systemic therapies that prevent acute myocardial infarction by potentially stabilizing vulnerable plaques [3]. Since then, new clinical studies, new imaging techniques, and direct analysis of excised atherosclerotic lesions after defined drug therapies have provided new insight into pharmacological plaque stabilization. Here, we briefly discuss some of these new findings and their implications for pharmacological stabilization of vulnerable coronary plaques. The findings are summarized in Table I.
Statins

There is extensive evidence to indicate that inhibition of the rate-regulating enzyme of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase, by means of statin drugs ("statins") reduces the incidence of acute coronary syndrome in the settings of both primary and secondary prevention. Experimental studies with cultured cells and animal models have provided compelling evidence that statins diminish inflammation in the arterial wall and may thereby contribute to the stabilization of vulnerable plaques. Most importantly, this conclusion also appears to apply to humans, notably to patients with advanced atherosclerosis. Thus immunohistochemical analyses of atherosclerotic coronary and carotid samples surgically removed from patients who have been treated with statins have shown that these drugs are able to decrease inflammation and to promote the transformation of vulnerable plaques into more stable plaques [4–6]. On the basis of these findings, we can conclude that any successful prevention of coronary or carotid atherothrombotic events by statin medication is likely to result from plaque stabilization.

The above conclusion is supported by the clinical findings of the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT–TIMI 22) trial, in which high-dose atorvastatin (80 mg/day) initiated early after acute coronary syndrome, compared with standard-dose pravastatin (40 mg/day), led to a rapid reduction in clinical events [7]. This effect was seen within 1 month after the initiation of the treatment. In this study, the patients who achieved the lowest low-density lipoprotein (LDL) cholesterol and C-reactive protein (CRP) concentrations at 30 days also had the lowest risk of future acute cardiac events. The early benefits of statin therapy correlated with CRP reduction, which may have been related to the intensity of the direct anti-inflammatory plaque-stabilizing or "pleiotropic" effects of the statins. Further support for such plaque-stabilizing effects of statins, which are independent of their lipid-decreasing ability, was obtained in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, which compared the effects of the above-mentioned two statin regimes on the progression of change in coronary atheroma volume [8]. Intravascular ultrasound revealed that, relative to a given reduction in LDL cholesterol concentration, the rate of progression of atheroma was slower in individuals receiving atorvastatin than in those receiving pravastatin. The notably greater reduction of CRP in the atorvastatin group (36% compared with 5%) seemed to explain at least some of this additional benefit. It must be noted, however, that high LDL cholesterol concentrations are proinflammatory per se, and that the reduction of LDL cholesterol by means other than statins, for example by physically removing LDL particles from the circulation (LDL apheresis), also exerts anti-inflammatory effects, as reflected by a decrease in C-reactive protein concentrations after such treatment [9]. Accordingly, the contribution of the direct pleiotropic effects of statins to their anti-inflammatory actions remains unknown.

Most recently, the A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) trial convincingly demonstrated that very intensive statin therapy (rosuvastatin 40 mg), which decreases LDL cholesterol to "physiological" concentrations (1.5 mmol/L or 60 mg/dL), can induce true regression of human advanced atherosclerosis — that is, it decreases the size of coronary atherosclerotic plaques in patients with angiographic evidence of coronary artery disease [10]. Obviously, such an aggressive lipid-decreasing strategy that reverses the atherosclerotic disease process at its very late stages inevitably also leads to plaque stabilization. Thus, in patients at very high risk of developing atherothrombotic complications in their coronary tree, LDL cholesterol concentrations should be decreased as much as possible in a safe manner. The observed simultaneous significant 15%
increase in HDL cholesterol may have contributed to the substantial reduction in the atheroma lesion burden in these patients.

**High-density lipoprotein infusion therapy**

High-density lipoprotein infusion therapy is a novel and emerging modality in the acute treatment of atherosclerosis. In this treatment, synthetic HDL particles containing complexes of phospholipids with either native apolipoprotein (apo) A-I or recombinant apolipoprotein (apo) A-I Milano, a variant form of native apoA-I, are repeatedly infused intravenously. Experiments with animal models have convincingly shown that induction of reverse cholesterol transport by infusion of phospholipid vesicles or either type of synthetic HDL leads to rapid mobilization of cholesterol from tissues, promotes fecal excretion of steroids, and reverses endothelial dysfunction induced by hypercholesterolemia [11]. Most importantly, after a single injection of a high dose of synthetic HDL containing apoA-I Milano, the size and macrophage content of established atherosclerotic lesions in apoE-deficient mice were significantly decreased within 48 h, reflecting regression and potential stabilization of atherosclerotic lesions [12]. Recently, two small clinical studies have evaluated the use of these compounds in patients with acute coronary syndromes. Nissen et al [13] reported that over a period of 5 weeks, weekly injections of synthetic HDL containing apoA-I Milano induced a 4.2% decrease in atheroma volume, as assessed by intravenous ultrasound. Using similar intravenous ultrasound examinations, Tardif et al [14] showed that four weekly injections of reconstituted HDL containing normal apoA-I decreased atheroma volume by 3.4%, with a concomitant change in plaque characteristics compatible with an increase in the content of dense fibrous tissue – that is, the treatment appeared to induce more stable plaque composition. Moreover, the treatment significantly decreased the mean reduction in coronary luminal diameter, as determined with quantitative coronary angiography. Overall, on the basis of experimental and clinical data, induction of reverse cholesterol transport with synthetic HDL appears a promising way to stabilize plaques. However, before this mode of treatment is ready for common use, larger studies are needed to verify the safety of these compounds and to demonstrate that the observed beneficial effect on atherosclerotic plaques will actually lead to a decrease in the incidence of adverse cardiovascular events.

**Peroxisome proliferator activated nuclear receptor agonists**

Peroxisome proliferator activated receptors α and γ are members of the superfamily of nuclear receptors that regulate both lipid and glucose homeostasis in response to fatty acids and their metabolites [15]. They are expressed by the major cell types of atherosclerotic lesions, where they have the potential for negative regulation of the transcription of proinflammatory genes. Thus their activators or agonists, notably the two classes of drugs, the fibrates and thiazolidinediones, could theoretically exert direct anti-inflammatory actions on vulnerable plaques.

Fibrates are ligands for PPARα and their major lipid-regulatory effects consist of a reduction in triglycerides and an increase in HDL cholesterol. Various fibrates have been shown to decrease the incidence of acute cardiovascular events, but to do so less consistently than statins [15]. Fibrates also decrease experimental atherogenesis and diminish the size of carotid plaques, with a concomitant decrease in the incidence of strokes in patients with essential hypertension [16]. Thus fibrates appear to have some plaque-stabilizing effects. It is obvious that these effects largely result from the ability of fibrates to regulate plasma lipids; the extent of their plaque-stabilizing potential attributed to direct effects on various cell types present in vulnerable plaques remains unknown.

Thiazolidinediones are ligands for PPARγ and they increase insulin sensitivity and have favorable effects on blood glucose concentrations and the serum lipid profile. Moreover, thiazolidinediones have anti-inflammatory effects on cultured vascular cells and slow down the development of atherosclerosis in experimental animals. In the PROactive study, pioglitazone was found to decrease cardiovascular events in patients with type 2 diabetes [17]. Moreover, both pioglitazone [18] and rosiglitazone [19] decreased carotid atherosclerosis in diabetic patients and, interestingly, rosiglitazone has been shown to inhibit inflammation and to stabilize carotid plaques in non diabetic patients [20,21]. Unfortunately, however, a recent meta-analysis of the cardiovascular effects of rosiglitazone showed that its use was associated with a significant increase in the risk of myocardial infarction, which necessitates careful reconsideration of its use in patients with cardiovascular diseases [22].

**Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists**

By reducing blood pressure, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor type 1 antagonists also reduce the physical stress exerted on vulnerable plaques and hence tend to prevent their rupture. As ACE is abundantly expressed in atherosclerotic lesions, and angiotensin II has been shown to possess potent proinflammatory effects, these compounds may also have direct effects on...
plaque biology. Both ACE inhibitors and angiotensin receptor antagonists have been shown to decrease cardiovascular events in high-risk patients without heart failure [23–25]. Importantly, ultrasound imaging analysis of carotid arteries has shown that both ACE inhibitors [26] and angiotensin receptor antagonists [27] decrease the size of carotid artery atherosclerotic lesions, and treatment with irbesartan for 4 months was shown to decrease the degree of inflammation in human carotid plaques [28]. Overall, these findings suggest that inhibition of the renin–angiotensin system, both systemically and locally in lesions, helps to stabilize plaques.

**Calcium channel blockers**

Dihydropyridine calcium channel blockers have been shown to have direct plaque-stabilizing effects beyond the decreasing of blood pressure, and some of these actions appear to be dependent on, and some others independent of, calcium channel modulation [29]. Earlier studies with short-acting dihydropyridine calcium channel blockers failed to show any effect on plaque size or to reduce coronary events, but more recent studies with the long-acting third-generation dihydropyridine calcium channel blockers, amlodipine and lacidipine, have shown some clinical benefit. Thus, in patients with coronary heart disease and normal blood pressure, amlodipine decreased cardiovascular morbidity and slowed down the progression of coronary and carotid atherosclerosis [30,31]. Similarly, lacidipine has been shown to inhibit the progression of carotid atherosclerosis in patients with hypertension [32].

**β-Blockers**

β-Blockers are indicated and widely used to prevent adverse cardiovascular events after myocardial infarction. In addition, they are used in antihypertensive drug regimens. However, recent large clinical trials have challenged the use of β-blockers, especially atenolol, as first-line antihypertensive drugs [33]. β-Blockers are likely to have beneficial effects on plaque biology by regulating hemodynamic forces exerted on the plaques, and so prevent cardiovascular events triggered by heavy physical exertion or psychosocial stress [34]. There is also some evidence that β-blockers may have antiatherogenic effects that are not mediated by their effects on hemodynamics. Thus, in experimental animals, endothelial injury caused by adrenergic stimulation can be prevented with β-blockers [35], and β-blockers have also been shown to decrease diet-induced and stress-induced atherosclerosis [36,37]. In humans, β-blockers have been shown to retard the progression of carotid atherosclerosis in patients without [38] and with [39] statin medication. Overall, β-blockers are indicated in the primary and secondary prevention of cardiovascular diseases, and some of their beneficial effects may be derived from plaque-stabilizing effects.

**Aspirin**

Aspirin, when administered in a daily single low dose (100 mg or less), is an antiplatelet agent that completely blocks the synthesis of thromboxane A₂ in platelets and therefore effectively inhibits platelet-dependent formation of arterial thrombus. On the basis of this well characterized antiplatelet effect, it is easy to appreciate that low-dose aspirin is effective not only for secondary but also for primary prevention of atherothrombotic diseases [40]. Importantly, low-dose aspirin has also been demonstrated to reduce proinflammatory cytokines in patients with chronic stable angina [41]. Moreover, among apparently healthy men, aspirin was most effective in reducing the cardiovascular risk in the individuals with the most increased concentrations of C-reactive protein [42]. These findings have provided strong suggestive evidence that aspirin, besides its antiplatelet action, may have additional anti-inflammatory effects on atherosclerotic plaques. To date, this hypothesis has been tested in genetically hyperlipidemic mice, in which low-dose aspirin was found to suppress aortic inflammation and to increase the stability of already developed atherosclerotic plaques [43]. These experimental studies call for future human investigations to evaluate whether low-dose aspirin might retard the progression and evolution of human atherosclerotic plaques and prevent their conversion into vulnerable plaques.

**Conclusion**

It is of major importance to realize that none of the currently available systemically applied pharmacotherapies specifically targets vulnerable coronary plaques prone to rupture. The pharmaceutical industry is actively developing molecules with this ability, and searching for the “magic bullet”. At present, decreasing LDL concentrations to physiological values and induction of true regression of lesions with statins appears to be the treatment modality closest to this ideal. In our present enthusiasm about modern medications, we should not forget the emergence of the concept of plaque stabilization [44,45]. Indeed, the formulation of this concept was prompted by the amazing results attained with “old drugs”, such as niacin and colestipol. Thus, in the Familial Atherosclerosis Treatment Study (FATS) study, a combination...
of these two drugs induced a remarkable 80% reduction in cardiovascular events [46]. We are now witnessing the second coming of niacin along with the discovery of its receptor, and the replacement of bile acid binding resins by molecularly targeting the absorption of cholesterol from the gut with ezetimibe. We have good reason to believe that the reduction in plasma LDL cholesterol to extremely low concentrations, which is already possible today, will stabilize vulnerable plaques sufficiently to lead to a significant decrease in acute coronary events.

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Metabolic imaging: the role of imaging in risk evaluation of ischemic heart disease

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Abstract

In ischemic heart disease (IHD), understanding the pathophysiology, and relating this to prognosis, are of prime importance. Many important physiological parameters have been shown to be closely related to patient outcome in IHD. Myocardial perfusion, myocardial cell viability, left ventricular function, response of dysfunctional myocardium to revascularization, and cardiac sympathetic innervation represent important metabolic targets in such patients. Nuclear imaging techniques utilizing radioisotopes designed to probe these processes have advanced our understanding of the underlying pathophysiology of IHD, and have provided robust markers of risk and prognosis suitable for use in routine clinical practice.

Keywords: Ischemic heart disease, metabolic tracers, myocardial perfusion imaging, nuclear cardiology, prognosis

Introduction

This issue of Heart and Metabolism addresses the important subject of prognosis in ischemic heart disease (IHD). In this review, the application of metabolic imaging techniques to this problem is discussed. Clearly, it is impossible to make a comprehensive survey of all the possible techniques available, and here the focus will be on the use of radionuclide tracers that help to define the underlying pathophysiological and metabolic processes that have an impact on patient prognosis. Other imaging techniques that describe metabolic processes such as magnetic resonance spectroscopy [1] are not included because of space constraints.

Imaging myocardial ischemia

From a clinical perspective, prognosis in IHD is dominated by left ventricular systolic function, the extent of myocardial ischemia (which is related to the extent of coronary artery disease), and the risk of fatal ventricular arrhythmias; the last is closely linked to the first two. It is not surprising, therefore, that myocardial perfusion abnormalities, which represent ischemia, are very strong prognostic markers in IHD. Radionuclide tracers such as thallium-201 (201Tl) and technetium-99m (99mTc) have been used for many years to demonstrate myocardial ischemia in man. Both tracers are extracted from the blood into the myocardium according to coronary blood flow,
their distribution is imaged using a gamma camera. The amount of tracer uptake in the heart is determined after a resting injection (representing resting perfusion) and then after either exercise or pharmacological stress (representing stress perfusion). A defect in stress perfusion that normalizes on the resting study represents myocardial ischemia. There have been several studies over many years showing this to be a very powerful prognostic discriminator, both in large populations and in defined subgroups such as men, women, patients with diabetes, and patients who have previously undergone revascularization [2–4]. The extent of ischemia in terms of the amount of left ventricle involved, and the depth of ischemia in terms of the severity of the reduction in perfusion, are, independently and in combination, powerful predictors of death and coronary events, including myocardial infarction [5]. A normal myocardial perfusion study predicts a very low likelihood of myocardial infarction or death (usually less than 1% per year), but an abnormal study predicts major events in an incremental fashion correlated with the degree of imaging abnormality [5, 6].

Imaging left ventricular systolic function

Although, strictly speaking, it is generally not interrogated in a metabolic sense by imaging techniques, left ventricular systolic function remains one of the most important determinants of prognosis in IHD [7]. Numerous studies have shown a clear link between left ventricular function and prognosis, particularly cardiac death, heart failure, and arrhythmias. For example, gated myocardial perfusion imaging with technetium agents has shown that, in IHD, prognosis in terms of cardiac death is predicted by left ventricular ejection fraction and end-systolic volume [8]. Other imaging techniques, including echocardiography, have become routine tools for assessing systolic function. Recently, cardiac magnetic resonance imaging has gained prominence because of its excellent reproducibility and accuracy in a variety of clinical settings.

Imaging myocardial viability and metabolism

In addition to perfusion and functional information, radionuclides provide information about the metabolic status of the myocardium. The resting uptake of the tracers discussed above depends, not only on the state of myocardial perfusion, but on the active metabolic processes of the myocardium. Tracer is taken up only into myocardium that is alive (“viable” or metabolically active). This is important in IHD, because the amount of viable myocardium is related to patient prognosis in two ways. First, it has been shown that patients with large myocardial infarctions and little viable remaining tissue have an adverse prognosis [9]. Secondly, there is a strong suggestion from the findings of many relatively small studies that patients with chronic ischemic left ventricular dysfunction experience a prognostic benefit when revascularization is undertaken in the setting of large amounts of viable myocardium; conversely, in the absence of viable myocardium, revascularization seems to have little benefit [10].

In general, radionuclides that reflect metabolic activity in the heart are viability tracers. Thallium-201 is an analog of potassium and exchanges across myocardial cell membranes, and thus reflects myocardial cell membrane integrity [11]. Technetium-99m is taken up into myocytes into the cytosol or mitochondria, and resting uptake therefore reflects myocardial cell membrane integrity and adequate mitochondrial function [12] (Figure 1). The positron-emitting tracer, Metabolic imaging

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Figure 1. Stress (left) and rest (right) 99mTc myocardial perfusion tomograms in selected vertical long axis (top), horizontal long axis (middle), and short axis (bottom) orientation. The images show absence of tracer uptake in the basal and mid inferior and lateral territories, with relatively normal uptake elsewhere. The lack of tracer uptake in the inferolateral territory is compatible with transmural myocardial infarction in this territory, and suggests that there is no viable myocardium in the territory. The absence of difference between the images implies that there is little residual ischemia.
18-fluorodeoxyglucose (FDG), is transported into the myocardium in the same way as glucose, and is then phosphorylated to FDG-6-PO₄, which remains fixed within the cell [13]. Cardiac uptake of FDG therefore reflects the extent of metabolically active myocardium that is capable of utilizing glucose as a substrate. Other tracers similarly evaluated in man include [11C]acetate, which reflects the extent of oxidative phosphorylation within myocytes and has also been shown to predict functional recovery after revascularization [14]. Rubidium-82, a positron-emitting tracer frequently used to assess myocardial perfusion, has in addition been shown to predict outcome on the basis of the amount of viable myocardium it demonstrates [9]. Therefore, radiotracers which show that various aspects of myocardial metabolism are still intact can identify viable myocardium and, when associated with the presence of ischemic dysfunction, can select those myocardial segments which – and thus those patients who – may gain a prognostic advantage from revascularization. Demonstrating the metabolic signature of myocardial hibernation therefore carries prognostic and therapeutic information.

Imaging cardiac neuronal function

Another aspect of metabolism in which there has been renewed interest recently is cardiac sympathetic innervation. Sympathetic nervous function is often abnormal in patients with left ventricular dysfunction and heart failure, and abnormalities in this parameter have prognostic importance. [123I]Metiodobenzylguanidine (MIBG) is a radioactively labeled norepinephrine (noradrenaline) analog that is taken up by presynaptic nerve terminals and is handled in the same way as norepinephrine. Abnormalities of the cardiac sympathetic nervous system can therefore be evaluated from the scintigraphic pattern of uptake of [123I]MIBG. In heart failure, uptake of MIBG by cardiac sympathetic nerves is reduced because of high turnover as a result of increased sympathetic tone. In addition, there may be damage to the sympathetic coverage of the heart in parallel with myocardial damage in patients with IHD. Uptake of [123I]MIBG by the heart is compared with that in a non heart area, usually the mediastinum, to give a heart--mediastinal ratio. Reduced heart--mediastinal ratio indicates poor sympathetic coverage and is an adverse prognostic factor in patients with heart failure [15–17]. There is current interest in the evaluation of this metabolic marker in assessing prognosis related to the likelihood of ventricular arrhythmias and the selection of patients for implanted defibrillator therapy.

Imaging other underlying metabolic processes

Gamma tracers for other metabolic processes in man (such as the tracer, annexin V, which images apoptotic cells, and [123I]β-methyliodophenyl pentadecanoic acid, which assesses fatty acid metabolism) have been assessed in recent years [18,19]. Many positron tracers probing a variety of underlying cardiac metabolic processes have been evaluated in small studies, and many more are currently under investigation [20]. These are all promising, but there are as yet no compelling long-term data in man to establish their place as established imaging markers of prognosis.

Conclusion

There are currently commercially available, in daily clinical practice, nuclear tracers that can accurately reflect several underlying cardiac metabolic processes, including myocardial perfusion and myocardial cell integrity, the imaging of which is closely linked to prognosis in large series of patients.

Summary

In this article, the role of imaging techniques for assessing various pathophysiological and metabolic aspects of cardiac function in ischemic heart disease is discussed. Important metabolic processes that are closely linked with patient prognosis in clinical trials may be interrogated using nuclear radioisotopes designed for specific cardiac targets. The critical predictors of patient prognosis in IHD, including myocardial perfusion, myocardial cell viability, and left ventricular function, can be assessed using gamma-emitting radiotracers such as thallium-201 or technetium-99m. Other metabolic targets linked to prognosis, such as cardiac sympathetic function (assessed with [123I]MIBG) are coming to the point of more routine clinical use, and various other tracers for different processes are currently under investigation. The role of metabolic imaging in cardiology is set to step closer to clinical application in the next few years.

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Beyond pharmacology in heart attacks: coronary stents and stem cells

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Abstract

The past two decades have been tremendously exciting for clinicians managing patients suffering myocardial infarction, as we defined our understanding of the proximate cause of the thrombotic occlusion of the infarct-related artery, triggered mostly by a ruptured or fissured coronary plaque, with downstream embolism of thrombotic material and resultant myocardial necrosis. This article summarizes developments in non pharmacological therapy with percutaneous coronary artery stenting of the culprit occlusion, and newer approaches in reparative cardiology via stem cell implantation in the infarcted zone.

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Keywords: Myocardial infarction, stem cells, stents

Introduction

The revolution in the management of myocardial infarction in the past two decades can be described by the phrase “going direct”. The approach that is considered optimal under most circumstances is to proceed as rapidly as possible to direct coronary revascularization, with angioplasty and stenting thus restoring normal coronary perfusion and limiting further damage to the myocardium. However, in many cases, even after reperfusion of the myocardium, recovery of cardiac function is incomplete. As a result, much attention is now focused on “reparative cardiology” – that is, trying to reverse myocardial damage through stem cell implantation.

The proximate cause of myocardial infarction is coronary thrombotic occlusion caused by disruption of an unstable (but not necessarily obstructive) atherosclerotic plaque [1]. Complete obstruction of blood flow to the myocardium is usually manifest as ST-segment elevation infarction. When thrombosis is not totally occlusive, or is only temporarily occlusive (ie, non ST-segment elevation acute coronary syndrome), embolization of coronary thrombotic material formed on the ruptured plaque can lead to downstream myocardial cellular damage (Figure 1) [2].

The pharmacological management of acute coronary syndromes is fairly well established, but stabilization of the ruptured or eroded plaque requires a mechanical approach. In contrast, regenerating the lost myocardium requires a biological solution.

Evidence favoring percutaneous coronary intervention

In a meta-analysis of 23 randomized trials published in 2003, percutaneous coronary intervention (PCI)
was found to be superior to fibrinolysis in treating ST-segment elevation myocardium [3]. A distinct advantage was reduction in recurrent infarction and intracranial hemorrhage. Recurrent infarction after successful fibrinolysis can be interpreted as success of initial reperfusion but failure to maintain patency in the infarct-related lesion. An exception to this paradigm may exist in patients in whom therapy can be started within the first 1 h of the onset of symptoms. In this uncommon situation, the rapidity with which thrombolysis can be started may offer an advantage [4].

The advantage of PCI with stenting is that the plaque material is scaffolded and a wide lumen restored, the latter allowing almost laminar flow, with minimal stasis and turbulence.

It must be emphasized that the symbiosis between the mechanical therapy and the fine-tuning of pharmacological treatments is critically important because, with balloon dilatation and stenting, plaque disruption and exposure of thrombogenic tissue deep within the plaque lead to activation of platelet and coagulation systems. Thus, in the past two decades, we have witnessed an explosion in the development of new medication targeting the different stages of the hemostatic pathway: the glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparins, the direct thrombin inhibitors, and the platelet P2Y12 blockers are the most prominent agents. Of interest, this fine tuning includes managing the balance of risk of bleeding and anti-ischemic efficacy [5]; doses of medications are often the critical factor [6]. Timely performance of primary PCI for ST-segment elevation myocardial infarction is mandatory [7]. The urgency of restoring blood flow to a segment of myocardium that is undergoing necrosis is not present among patients with non ST-segment elevation acute coronary syndromes, but the findings of at least one small study have suggested that earlier implementation of an invasive strategy may result in a more robust reduction in myocardial infarction [8].

Concepts in reparative cardiology

The traditional concept has been that the adult heart is a “postmitotic organ” – that is, myocardial growth is accomplished exclusively from hypertrophy of differentiated myocytes, rather than from growth of new myocytes. However, preclinical observations in the past decade have challenged the traditional view and have proposed a new paradigm in which cells in the heart are continuously replaced by newly formed younger populations of myocytes, in addition to replacement by vascular smooth muscle and endothelial cells. Moreover, circulating adult bone marrow cells are able to differentiate into non myelogenous tissue, and may create cardiomyocytes and coronary vessels [9].

Perhaps the seminal observation that challenged the old paradigm was the identification of Y-chromosome-positive myocytes and coronary vessels in female hearts transplanted into male recipients [10]. This finding suggests that circulating cells in the male transplant recipient colonized the female heart and differentiated into myocytes and vascular structures, an important finding consistent with the contention that stem-like cells can migrate to the transplanted heart and give rise to cardiac cell progeny. Subsequent work has led to the identification of a resident pool of cardiac stem cells in the adult heart [11].

Mechanisms of benefit and procedural risks of cellular therapy

Evidence from the clinical trials tends to suggest some degree of efficacy of cellular therapy, although the findings have not been universal across trials, and histologically the question of engraftment of circulating cells versus co-localization of these cells with existing myocytes has not been answered. Two potential lines of benefit from cell therapies exist: contractile capacity...
and angiogenic capacity. The latter may be most relevant in patients with severe coronary disease that is not amendable to revascularization, who develop myocardial hibernation. Quite possibly, different progenitor cell types may be better suited to different regenerative tasks, as outlined below (Figure 2) [12].

Myocyte regeneration may not be the only or the major mechanism through which contractile function is restored. Animal studies have shown that the bone marrow cells do not engraft into the heart as cardiomyocytes in large numbers, suggesting that such alternative mechanisms as paracrine effects (including secretion of growth factors by transplanted cells, which may stimulate an endogenous repair response), angiogenic effects, or antiapoptotic effects may be operative [12]. Indeed, one hypothesis, the dying stem cell hypothesis, proposed immune modulation as a possible mechanism for the benefit of therapy [13]. In this model, in the setting of cell therapy for acute myocardial infarction, the stem cells that fail to engraft undergo apoptosis and alter the innate and adaptive immunity in the infarcted area, leading to reduced scar formation and reduced myocardial apoptosis.

Recent clinical trials of cell therapies for acute myocardial infarction

Two studies, the Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction (REPAIR-AMI) trial [14,15] and the Autologous Stem-Cell Transplantation in Acute Myocardial Infarction (ASTAMI) trial [16], were reported in 2006. Both trials used bone marrow cells delivered through the infarct-related artery to the myocardium. Data from these trials are summarized in Table I, together with findings from earlier trials [17].

The discrepant findings between the REPAIR-AMI and ASTAMI trials are intriguing; among other possible explanations are the different number of cells delivered and the different methods of harvesting bone marrow cells. The sensitivity of the different methods for measuring the ejection fraction could also be relevant in explaining the different results, but the absence of a dramatic improvement in ejection fraction in all the studies should be noted.

Future perspectives

Unlike the mechanical treatment of bare-metal coronary stenting, biological stem cell therapy is considerably more complex and requires collaboration between several disciplines, from basic scientists to clinical cardiologists. In the USA, a research network has been established to conduct clinical cell therapy trials. Basic preclinical investigators will collaborate with clinical imaging specialists to measure the efficacy of the technique and to track the fate of cells. It will also be necessary to develop strategies for the application of stem cell therapy in clinical practice, as appropriate.

There remains a considerable lack of understanding about the immunogenicity of stem cells, control of their differentiation, and the best way to introduce them into the damaged heart. However, the use of stem cells has enormous potential for cardiac repair.
Table I. Randomized, controlled trials of bone marrow cells for cardiac disease. (Adapted from Rosenzweig A et al [17], with permission.)

<table>
<thead>
<tr>
<th>Trial or investigator group</th>
<th>Setting</th>
<th>Design</th>
<th>Cells administered in treatment group (No.)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOOST [18,19]</td>
<td>PCI after acute myocardial infarction</td>
<td>Randomized trial. 30 patients received BMC; 30 received no infusion. LVEF assessed by MRI</td>
<td>Approximately 2.5 x 10^9 unfractionated BMC</td>
<td>At 6 months: LVEF 6% greater in BMC group than in control group. At 18 months: no significant difference in LVEF between the two groups</td>
</tr>
<tr>
<td>Janssens et al [17,20]</td>
<td>PCI after acute myocardial infarction</td>
<td>Randomized double-blind trial. 33 patients received BMC; 34 received placebo infusion. LVEF assessed by MRI</td>
<td>Approximately 3 x 10^8 Ficoll-separated BMC</td>
<td>At 4 months: no significant difference in overall LVEF; decreased infarct size and better regional function in BMC group</td>
</tr>
<tr>
<td>TOPCARE-CHD [17,21]</td>
<td>Chronic left ventricular dysfunction</td>
<td>Randomized, crossover trial. In the second phase, 24 patients received CPC, 28 received BMC, and 23 received no infusion. LVEF assessed by left ventricular angiography</td>
<td>Approximately 2 x 10^8 Ficoll-separated BMC or approximately 2 x 10^7 Ficoll-separated, cultured CPC</td>
<td>At 3 months: greater increase in LVEF (2.9%) in BMC group than in CPC group or control group</td>
</tr>
<tr>
<td>ASTAMI [16]</td>
<td>PCI after acute myocardial infarction</td>
<td>Randomized trial. 47 patients received BMC; 50 received no infusion. LVEF assessed by SPECT, echocardiography, and MRI</td>
<td>Approximately 7 x 10^7 Ficoll-separated BMC</td>
<td>At 6 months: no significant difference in LVEF between the two groups</td>
</tr>
<tr>
<td>REPAIR-AMI [14,15]</td>
<td>PCI after acute myocardial infarction</td>
<td>Randomized double-blind trial. 101 patients received BMC; 98 received placebo infusion. LVEF assessed by left ventricular angiography</td>
<td>Approximately 2.4 x 10^8 Ficoll-separated BMC</td>
<td>At 4 months: greater absolute increase in LVEF in BMC group than in placebo group (5.5% vs 3.0%) At 1 year: reduction in combined adverse clinical events in BMC group compared with placebo group</td>
</tr>
</tbody>
</table>

ASTAMI, Autologous Stem-Cell Transplantation in Acute Myocardial Infarction; BMC, bone marrow cells; BOOST, Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration; CPC, progenitor cells derived from circulating blood; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; REPAIR-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction; SPECT, single photon emission computed tomography; TOPCARE-CHD, Transplantation of Progenitor Cells and Recovery of LV Function in Patients with Chronic Ischemic Heart Disease.
New therapeutic approaches
Stents and stem cells for myocardial infarction

and regeneration after myocardial infarction, and thus for improvement of patient outcomes.

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The Emperor has no clothes: reading between the lines of the COURAGE report

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Abstract

Large clinical trials have consistently shown that PCI has limited if any impact on prognosis in patients with chronic ischemic heart disease. Most reports suggest that a large fraction of patients with effort angina remains symptomatic after coronary recanalization. The recently released COURAGE trial has confirmed the persistence of angina in one third of the patients after a “successfull” angioplasty procedure and that a similar fraction of patients becomes asymptomatic at follow-up despite they did not undergo PCI. This data underscore the complexity of the pathogenesis of myocardial ischemia and emphasize the need for innovative approaches to the treatment of IHD.


Keywords: Angina, coronary artery disease, ischemic syndromes, percutaneous coronary intervention, percutaneous transluminal coronary angioplasty

“Many, many years ago lived an emperor, who thought so much of new clothes that he spent all his money in order to obtain them; his only ambition was to be always well dressed ...”.

This is the beginning of a tale that Hans Christian Andersen wrote back in 1837. The story was about people who denied even the most obvious evidence and pretended not to see what was in front of their eyes, just to follow the prevailing trend, and for fear of contradicting the “Emperor”.

Turning now to present-day cardiology... The obvious aesthetic benefit of re-opening obstructed arteries has fuelled great expectations in cardiologists, and in patients with ischemic heart disease. In recent decades we have witnessed an enormous increase in the use of percutaneous transluminal coronary angioplasty for the treatment of acute and chronic coronary syndromes [1,2]. Surprisingly enough, although there is evidence that percutaneous coronary intervention (PCI) reduces the incidence of death and non fatal myocardial infarction in acute coronary syndromes [3–8], similar beneficial effects have not been observed in patients with stable coronary artery disease [9–14].

The widespread use of percutaneous transluminal coronary angioplasty in chronic stable ischemic syndromes is thus not supported by conclusive evidence. However, despite official guidelines recommending limiting the use of PCI to those patients with angina refractory to medical therapy, our “Emperors” have carried on dilating arteries whenever possible.

A recent paper by Boden et al [15] reporting the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial presented further, and possibly conclusive, evidence against this approach.

Between 1999 and 2004 in the COURAGE trial, 2287 patients with objective evidence of myocardial ischemia and significant coronary artery disease were allocated randomly to groups to receive PCI plus optimal medical therapy, or optimal medical therapy alone. The primary outcomes were death from any
New therapeutic approaches

Does PCI relieve chronic stable angina?

cause, and non fatal myocardial infarction, during a follow-up period of 2.5–7.0 years. The authors reported no significant difference between the two groups in the composite of death, myocardial infarction, and stroke ($P = 0.62$), in the rate of admission to hospital for acute coronary syndrome ($P = 0.56$), and in non fatal myocardial infarction ($P = 0.33$). They concluded that, despite the presence of a high baseline prevalence of clinical coexisting illnesses, objective evidence of ischemia, and extensive coronary artery disease, PCI, when added to optimal medical therapy as an initial management strategy, is no better than medical therapy alone.

The conclusions of the COURAGE Trial are fully consistent with those of previous reports. Kastrati and Ioannidis [16] performed a meta-analysis of the findings of 11 studies (Randomised Intervention Treatment of Angina-2 [RITA-2], ACME-1, ACME-2, AVERT, Dakik, the Medicine, Angioplasty, or Surgery Study [MASS], Medicine, Angioplasty, or Surgery Study II [MASS II], ALKK, Sievers, Hambrecht, Bech). Among a total of 2950 patients (1476 of whom received PCI and 1474 of whom received conservative treatment), it was concluded that there was no difference between PCI and conservative treatment with regard to the risk of death, the rate of non fatal myocardial infarction, or the need for coronary artery bypass grafting.

One obvious objection to these conclusions is that the COURAGE Trial has included few patients treated with drug-eluting stents (they were not approved for clinical use until the final 6 months of the study), and that no trial included in the meta-analysis [16] included the use of drug-eluting stents. However, it very unlikely that a liberal use of these stents would have modified the findings. Analyzing individual data of 4958 patients enrolled in 14 randomized trials comparing sirolimus-eluting stents with bare-metal stents, Kastrati et al [17] concluded that drug-eluting stents do not have a significant effects on long-term survival and on survival free of myocardial infarction, as compared with bare-metal stents. A similar conclusion was reached by Spaulding et al, who analyzed data from four trials comparing sirolimus-eluting stents and bare-metal stents [18].

We all must therefore accept that PCI has no significant impact on prognosis in chronic ischemic syndromes, regardless of the use of stents and of the type of stent used. Indeed, most of the debate that has followed the presentation of the findings of the COURAGE trial at the American College of Cardiologists’ meeting has focused on these points.

To return to the analogy of Andersen’s tale: we must make an additional effort to dissect other relevant information from the COURAGE Trial; otherwise, we would be behaving like the citizens of the “Emperor who had no clothes”!

The most disturbing data included in the report of the COURAGE Trial [15] are those presented in its Table 2 (p. 1510) concerning the effects of optimal medical therapy, plus or minus PCI, on clinical status, risk, lifestyle factors, and the use of medications. At 1 year, 66% of the patients in the group given PCI plus optimal medical therapy were free of angina, compared with 58% in the group who received medical therapy alone. These rates have been substantially confirmed at 3 and 5 years, with minor, non significant variations.

With few and unheard exceptions, nobody to date has dared to question the superiority of PCI over medical therapy in relieving angina. This assumption is clearly challenged by the figures presented in Table 2 of the COURAGE Trial report. If we open our eyes and minds to these figures, some provocative questions arise spontaneously:

1. Which is the cause of persisting angina in the patients receiving PCI on top of optimal medical therapy?
2. Why angina disappears in 58% of the patients still carrying a coronary obstruction?
3. Which therapeutic alternative can be offered to all those patients who, despite “optimal medical therapy”, plus or minus PCI, continue to complain of angina?

These questions may sound very disturbing to many clinical and interventional cardiologists, not to mention the pharmaceutical industry and companies manufacturing interventional devices. Nevertheless, these questions deserve answers: too many patients are still waiting for a satisfactory response to their therapeutic needs.

A better understanding of the mechanism causing angina is urgently needed, innovative pharmacological agents must be actively sought, and cardiologists must fully realize the complexity of the pathogenetic and therapeutic implications of chronic ischemic syndromes. The problem is far from being solved.

REFERENCES

New therapeutic approaches
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The metabolic approach to improving prognosis in ischemic heart disease

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Abstract
Recent studies have demonstrated that alterations in cardiac metabolism can be present in ischemic heart disease and heart failure, suggesting an increased utilization of non carbohydrate substrates for energy production, with a reduction in the efficiency of myocardial oxygen consumption. A direct approach to the manipulation of cardiac energy metabolism consists in modifying substrate utilization. Trimetazidine is a pharmacological agent that shifts the preference for energy substrate away from fatty acid metabolism and towards glucose metabolism. Recent findings suggest that trimetazidine has a positive influence on ventricular function, various prognostic factors (inflammation and biochemical markers), and, probably, prognosis. Metabolic therapy offers concrete help in the management of coronary artery disease and dilated cardiomyopathy.

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Keywords: Trimetazidine, heart failure, ischemic heart disease, prognosis

Introduction
Cardiovascular diseases are the leading cause of mortality in development countries and they still represent a heavy economic burden [1]. The global number of deaths attributable to ischemic heart disease is very high and, since 1990, it has become the most frequent cause of chronic heart failure, demonstrable in about 65% of the patients [2]. Aspirin, β-blockers, angiotens converting enzyme (ACE) inhibitors, angiotensin type 1 receptor blockers, and lipid-decreasing agents are currently the milestones of pharmacologic management, supplemented by lifestyle changes [3]. However, side effects of chronic drug treatment may affect quality of life, and they are the main reason for poor patient compliance. Coronary artery bypass surgery and angioplasty are interventional procedures that are frequently used for ischemic heart disease, although they can be invasive and costly, and need to be repeated. In spite of these therapeutic options, mortality rates remain high, and many patients continue to have symptoms. An alternative strategy to improve prognosis and quality of life could be to treat the metabolic causes or consequences of ischemia [4].

The metabolic approach in ischemic heart disease and heart failure

The main problem in the management of ischemic heart disease is prevention of ventricular remodeling, the pivotal mechanism contributing to evolution from left ventricular dysfunction to irreversible heart failure in patients with the condition [5]. This progressive process is linked to neurohormonal activation. Prevention of remodeling appears to be consistent with improvement in clinical outcome. In patients with left ventricular dysfunction or heart failure, treatment by combination neurohormonal blockade with ACE
inhibition and β-blockade is the standard evidence-based recommendation [6–8]. Recent studies have investigated the possibility of increasing cardiac performance without affecting oxygen consumption and hemodynamics, using agents aimed at enhancing myocardial energy efficiency. These drugs shift energy substrate utilization away from fatty acid metabolism and towards glucose metabolism, which is more efficient in terms of production of adenosine triphosphate (ATP). A decrease in circulating free fatty acid concentrations is obtained by the administration of glucose–insulin solutions [9] or β-blockers [10,11], or, alternatively, by agents that directly inhibit fatty acid oxidation, such as inhibitors of mitochondrial uptake of free fatty acids (via suppression of carnitine palmitoyl transferase I and II), or direct inhibitors of 3-ketoacyl coenzyme A thiolase (3-KAT), the last enzyme involved in β-oxidation. Of the latter class of pharmacological agents, trimetazidine and ranolazine are the only available drugs. Trimetazidine in particular, has been shown to affect myocardial substrate utilization by inhibiting oxidative phosphorylation, and by shifting energy production from free fatty acids to glucose oxidation by selective block of long-chain 3-KAT [12]. However, recent studies have outlined the potential benefits that trimetazidine may offer in myocardial dysfunction because of its ability to increase utilization of glucose and lactate, which are more efficient fuels for aerobic respiration, improving oxygen consumption of the myocardium by 16–26% [13].

The metabolic approach: clinical relevance in patients with ischemic heart disease

Many studies have been undertaken to determine which factors increase mortality and morbidity in patients with ischemic heart disease and heart failure, across a variety of clinical settings. Factors that have been shown to be predictors of mortality are increasing age, history of diabetes mellitus or renal dysfunction, measures of higher functional disability such as New York Heart Association (NYHA) class, lower left ventricular ejection fraction (LVEF), lower sodium concentrations and lower quality-of-life scores [14–16]. Recently, intense interest has emerged in the predictive value of plasma biochemical markers such as C-reactive protein, B-type natriuretic peptide, and cardiac troponin T [17–19]. Recent studies revealed evidence that trimetazidine treatment could have a positive influence on these prognostic factors (Table I). For all these reasons, expanded upon below and summarized in Figure 1, a therapeutic approach using trimetazidine could exert a positive influence on left ventricle remodeling, with potential prognostic relevance in patients with ischemic cardiomyopathy.

**Effects of trimetazidine in patients with ischemic cardiomyopathy**

On the basis of the hypothesis that free fatty acid inhibitors could act as metabolic modulators in the protection of ischemic myocardium, the effects of trimetazidine have been assessed in patients with ischemic cardiomyopathy. In these patients, mortality rate and quality of life are unsatisfactory and left ventricular dysfunction is the result of myocardial fibrosis, or hibernating or stunned myocardium. The therapeutic management of hibernating and stunned myocardium is fundamental in ischemic cardiomyopathy, because they are potentially reversible conditions.

Belardinelli et al [20] reported that trimetazidine exerted beneficial effects on chronically dysfunctional myocardium. Forty-four patients with ischemic cardiomyopathy and a previous acute myocardial infarction, multivessel coronary artery disease, and ventricular dysfunction (ejection fraction 33%) were treated with trimetazidine. After 2 months of treatment,
there was a significant improvement in the contractile response to low-dose dobutamine in chronically dysfunctional myocardium. Fragasso et al [21] demonstrated that trimetazidine restored the energetic status of myocardium in patients with heart failure. In these patients, the phosphocreatine (PCr)/ATP ratio, an important index of energetic status, was similar to that in healthy individuals, and significantly improved compared with that in a placebo group. These results appear particularly interesting, especially in view of previous evidence suggesting the PCr/ATP ratio to be a significant predictor of mortality [22].

The beneficial effects of trimetazidine in patients with ischemic cardiomyopathy are also evident in long-term follow-up. Brottier et al [23] assessed the value of trimetazidine treatment with in patients with severe ischemic cardiomyopathy. After 6 months of treatment, the patients reported a considerable improvement in symptoms and showed a greater LVEF compared with the placebo group. These effects are also evident in longer follow-up. We reported that 12 months of treatment with trimetazidine induced a significant improvement in ejection fraction and NYHA functional class in patients with ischemic cardiomyopathy and LVEF <40% [24].

The beneficial effects of trimetazidine are also present in elderly and diabetic patients. Vitale et al [25] reported 47 patients (aged 78 ± 3 years) with ischemic cardiomyopathy who were treated with trimetazidine and achieved significant improvement in ejection fraction and quality of life. Fragasso et al [26] reported an improvement in ejection fraction in diabetic patients with ischemic cardiomyopathy. These beneficial effects of trimetazidine were maintained in long-term follow-up, and contrast with the natural history of the disease, as shown by the progressive decrease in ejection fraction in the placebo group.

Effects of trimetazidine on proinflammatory status

A proinflammatory state is recognized in chronic heart failure, and the degree of immune activation corresponds to disease severity and prognosis. In patients with heart failure, greater concentrations of C-reactive protein have been related to higher rates of readmission to hospital and mortality [27]. Trimetazidine exerts positive effects on the inflammatory status that characterizes ischemic cardiomyopathy. After ischemia, a significant reduction in the infiltration of neutrophils to the ischemic area is reported [28]. Recently, in an experimental model of ischemia-reperfusion damage, we demonstrated that trimetazidine reduced cellular damage and preserved endothelial function. This effect was related to a preservation of expression of endothelial nitric oxide synthase.
The metabolic approach: effects on prognosis

Although the findings to date are highly suggestive, it remains to be ascertained whether the benefits discussed above would translate into improved survival rates. The question of whether there are prognostic benefits during trimetazidine treatment in patients with ischemic cardiomyopathy is still under investigation. Improvement in ejection fraction, NYHA class, and biochemical markers in these patients probably influences prognosis. In patients with ischemic left ventricular dysfunction and multivessel coronary artery disease, El-Kady et al. [32] reported positive effects of trimetazidine on prognosis: survival at 2 years was 92% among patients treated with trimetazidine and 62% among those treated with placebo. In a post-hoc analysis obtained from the 48 month extension of the Villa Pini d’Abruzzo trimetazidine trial [24], we observed that trimetazidine treatment reduced all-cause mortality (17% compared with 39% in controls) and admission to hospital because of heart failure (decreased by 47%) (unpublished observations).

Conclusions

A metabolic approach could have a relevant role in the therapeutic management of heart failure. Trimetazidine treatment has a positive influence on ventricular function, quality of life, various prognostic factors (inflammation and biochemical markers), and, probably, prognosis. Although its true relevance to prognosis needs to be ascertained by multicenter, randomized, placebo-controlled trials, the selective inhibition of 3-KAT with trimetazidine represents a new therapeutic opportunity in the management of patients with ischemic heart disease and heart failure.

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You are never too old

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Abstract

The case is reported of a 77-year-old man with a resuscitated cardiac arrest caused by an anterior acute myocardial infarction who underwent thrombolysis with streptokinase. Although coronary angiography revealed three-vessel disease with good distal vessels suitable for surgical revascularization, the patient refused to undergo the operation. He remained symptomatic on conventional medical therapy for about 14 months when, because of his poor compliance with his treatment and progression of the coronary artery disease, his cardiac symptoms became more frequent, reducing his quality of life. Cardiac rehabilitation and high-dose trimetazidine (120 mg/day) were used as additional means of optimizing his medical treatment, achieving a progressive relief of symptoms and an improvement in his quality of life, with good compliance.

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Keywords: Compliance, elderly, prognosis, trimetazidine

Case report

A 77-year-old man, asymptomatic and well until September 2003, suffered a resuscitated cardiac arrest while running to catch a train. Once resuscitated, he was transferred to the local General Hospital, where he was found to have an anterior acute myocardial infarction, and underwent thrombolysis with streptokinase.

Before this episode, the patient reported general good health. He had a normal body mass index. He had smoked about 15 cigarettes per day since he was 19 years old. He had a family history for coronary artery disease (CAD): one brother had undergone percutaneous coronary intervention, and two sisters had suffered an acute myocardial infarction. He had been taking antihypertensive drugs (amlodipine 10 mg) for the past 8 years, but had never reported cardiac symptoms or dyspnea in the past. On several occasions he was found to have high concentrations of cholesterol (total 286 mg/dL; low-density lipoprotein 203 mg/dL) and impaired fasting glucose (glycemia 120 mg/dL), but he had never taken the prescribed lipid-decreasing drug (pravastatin) or adopted a low-fat diet.

An echocardiogram before his discharge from hospital showed concentric left ventricular hypertrophy (septum 12 mm, posterior wall 11.5 mm), a dilated left ventricle (left ventricular end-diastolic diameter [LVEDD] 66 mm, left ventricular end-systolic diameter [LVESD] 46 mm) with a reduced left ventricular ejection fraction [LVEF] (41%), severe anterior wall hypokinesia, and apical akinesia (Figure 1).

Carotid vascular EchoDoppler showed the presence of bilateral hyperechogenic plaques without significant stenosis (<40%) at the carotid bulbs.

Submaximal exercise nuclear scintigraphy showed a fixed defect of the anterior wall and a reversible perfusion defect of the anterior wall and apex (Figure 2).

The patient refused to undergo cardiac catheterization. After 10 days he was discharged from hospital in a generally good condition. Medical therapy at discharge was aspirin, a β-blocker (bisoprolol 7.5 mg), an angiotensin converting enzyme (ACE) inhibitor (perindopril 8 mg), furosemide 25 mg, and a statin (pravastatin 20 mg).

One month after the acute myocardial infarction, the patient was seen in the outpatient clinic and clinical examination showed a good control of blood pressure and heart rate (56 beats/min). Biochemistry
confirmed an impaired fasting glucose (glycemia 118 mg/dL), but the patient refused to perform an oral glucose tolerance test. Total cholesterol and low-density lipoprotein cholesterol were respectively 235 mg/dL and 148 mg/dL. The dose of pravastatin was increased to 40 mg.

An electrocardiogram showed sinus rhythm and signs of a previous anterior myocardial infarction. The echocardiogram was substantially unchanged compared with that before discharge. In order to evaluate the presence of reversible myocardial ischemia, the patient was prescribed a maximal exercise electrocardiogram that he refused because he said he was feeling well. For the same reason, he refused to undergo outpatient cardiac rehabilitation.

About 1 year later, the patient had stopped taking his pravastatin and was not regularly taking his furosemide. When seen in the outpatient clinic, he was complaining of chest pain and dyspnea on low-to-mild effort (Canadian Class 2, New York Heart Association [NYHA] Class 2–3). He also reported occasional episodes of paroxysmal nocturnal dyspnea. Clinical examination, blood pressure, and heart rate were unremarkable. A new exercise test was performed, but was

Figure 1. Pre-discharge echocardiogram.

Figure 2. Pre-discharge submaximal exercise nuclear scintigraphy.
stopped because of worsening dyspnea and chest pain at medium-to-low workload, without electrocardiographic changes. On this occasion, the patient was offered coronary angiography, which he accepted. An echocardiogram showed a dilated left ventricle (LVEDD 71 mm, LVESD 50 mm), LVEF 34%, with anterior and lateral hypokinesia and apical akinesia.

Coronary angiography was performed in February 2005 and showed three-vessel disease, with good distal vessels (Figure 3). In view of the coronary angiography, surgical revascularization was proposed, which the patient declined.

Transdermal nitrates were prescribed, but were stopped after 2 weeks because of skin irritation. Medication with oral isosorbide dinitrate three times a day was therefore started.

In November 2005, the patient was again admitted to hospital for worsening symptoms: he reported an increase in the number of anginal episodes, which now occurred at low levels of exercise (one flight of stairs), and dyspnea. Physical examination showed signs of NYHA Class 3 heart failure. At the time of admission to hospital, the patient was taking an ACE inhibitor, a β-blocker for which he had halved the dose, a diuretic occasionally, a statin, and an antiplatelet agent, but in the summer he had stopped taking nitrates, because of poor compliance and lightheadedness. Biochemistry showed hypercholesterolemia (total cholesterol 265 mg/dL) and hyperglycemia (glycemia 121 mg/dL).

A chest X-ray revealed cardiomegaly and, initially, pulmonary edema, which reversed after intravenous furosemide. He was administered a vertical quality-of-life-visual analog scale and scored 4/10. The patient agreed to undergo a 3 week inpatient cardiac rehabilitation programme. This programme was followed by 3 months outpatient cardiac rehabilitation cycles involving 3 sessions of exercise per week.

The patient was discharged from hospital again, receiving bisoprolol 7.5 mg, trimetazidine 40 mg three times a day, perindopril 8 mg, atorvastatin 40 mg, furosemide 25 mg three times a day, aldactone 100 mg twice daily, and aspirin 100 mg. After 3 months, when he entered the outpatient cardiac rehabilitation cycle, he reported a significant improvement in symptoms and was asymptomatic for low-to-mild levels of exercise. Physical examination was unremarkable and there were no signs of heart failure.

About 7 months later, when the patient returned for his second cycle of outpatient cardiac rehabilitation, he did not report episodes of chest pain and he had slight dyspnea for moderate levels of exercise. An echocardiogram revealed that left ventricular dimensions had reduced (LVEDD 60 mm; LVESD 40 mm) and the ejection fraction had increased to 42%. A recovery of contractile function was observed in the anterior and lateral walls.

The vertical quality-of-life visual analog scale was again administered and the patient scored 7/10.

Comment

This case depicts the classical elderly patient with CAD who is reluctant to take drugs and does not want to undergo invasive procedures. This man was treated appropriately for his acute myocardial infarction and underwent an early conservative management in relation to his age. Despite receiving adequate β-blockade, as suggested by the low heart rate, and having adequate control of blood pressure, after an initial period of clinical stabilization the patient had episodes of angina in the morning hours that suggested the need for a better 24 h control of myocardial ischemia. Because of his general good

Figure 3. Coronary angiography (performed February 2005).
Case report
Cristiana Vitale

condition and the absence of serious comorbidities, in this patient there was a clear indication for myocardial revascularization; however, he refused to undergo surgical procedure. For this reason, the optimization of medical treatment was the main therapeutic target, aimed not only at reducing the frequency and severity of anginal attacks, but also at improving quality of life and life expectancy.

In elderly patients with ischemic heart disease, quality of life must be the one of most important objectives of medical practice. There are several tests available to investigate the subjective perception that the individual has about his own quality of life; these may be divided into generic and illness-specific tests. Among the first group, the vertical visual analog scale is the one of simplest tests to be administered to elderly people: on a 10 cm line marked every 1 cm, patients are asked to score their present quality of life, with 0 being the worst ever and 10 being the best ever [1,2].

In the clinical management of elderly patients with coronary artery disease, it is important to take into account their general clinical condition, and the presence of comorbidities, which may aggravate ischemic heart disease and interfere with pharmacological or interventional therapy, or both [3]. In spite of improvements in the techniques of percutaneous and surgical revascularization, these interventions are associated with increased peri-procedural mortality and morbidity. The incidence of periprocedural stroke is about 3.5%, and may represent a further cause of functional limitation, disability, and reduction in future quality of life. Similarly, percutaneous revascularization procedures in the elderly have a lesser percentage of success and a greater incidence of complications in comparison with those in younger patients [4]. Finally, the recent COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study has shown no benefit of interventional procedures in patients with chronic stable angina [5].

For all these reasons, revascularization (whether surgical or transcatheter) in elderly patients should be reserved for those with refractory angina in spite of maximal medical therapy, and those in whom angina compromises quality of life, the instrumental activities of daily living, or, even more so, the activities of daily living. Among other things, the anatomical characteristics of CAD, such as multivessel disease and distal coronary atherosclerosis, may limit the possibility of and opportunity for revascularization. The only study that has compared the effects of medical therapy and of revascularization on the quality of life in patients older than 75 years, the Trial of Invasive Versus Medical Therapy in Elderly Patients (TIME), has shown that optimized medical therapy is as effective as myocardial revascularization in improving 1-year quality of life, symptoms, and cardiovascular events [6].

In elderly patients, conventional antianginal therapy with nitrates, β-blockers, and calcium antagonists may be associated with a greater incidence of significant adverse effects. These are dependent, not only upon the hemodynamic actions of the drugs (effect on blood pressure and heart rate), but also on altered pharmacokinetics, linked to changes in body composition and renal and hepatic dysfunction and to a greater risk of interactions of the antianginal drugs with other medications used to treat comorbidities [7].

Addition of adjunctive treatment with metabolic agents, such as trimetazidine, to the standard care of elderly patients with ischemic heart disease may be particularly useful in the treatment of angina. In fact, in the elderly, the chronic reduction in blood flow caused by diffuse multivessel and distal coronary atherosclerosis may cause diffuse hibernation of the myocardium. Several studies have shown that the metabolic effect of trimetazidine may improve the efficiency of hibernated myocardium, through more efficient utilization of glucose in areas of myocardium with reduced oxygen availability, with a parallel improvement in left ventricular function [8,9].

The patient described here was an ideal candidate for a metabolic approach to treatment, because of the progressive reduction in his functional capacity and the progressive increase in incidence of chest pain. Furthermore, he was receiving adequate β-blockade, and therefore adjunctive hemodynamic therapy could have had limited results: several studies have shown that, in patients receiving adequate β-blockade, the adjunct of a hemodynamic agent does not increase ischemic threshold or improve symptoms [10–12].

The association of optimal medical therapy and cardiac rehabilitation may add an additional benefit in exercise tolerance and in terms of secondary prevention [13]. Cardiac rehabilitation and education in physical activity may also improve the control of several cardiovascular risk factors, such as diabetes, dyslipidemia, and arterial hypertension, reducing the amount of drugs used for the control of these risk factors and ischemia, and improving adherence to treatment, especially in elderly patients in whom the presence of comorbidities necessitates polytherapy. Nevertheless, although cardiac rehabilitation improves functional capacity in both young and elderly patients, the latter are often excluded from cardiac rehabilitation programs. Benetti et al [14] have shown that, in the elderly patients, cardiac rehabilitation increases functional performance and leads to a meaningful improvement of the quality of life.

The effect of metabolic treatment with trimetazidine on left ventricular function may also have prognostic
implications, because left ventricular function is one of the most important determinants of long-term outcome and development of heart failure in patients with CAD [15,16]. Recent studies have shown that trimetazidine improves left ventricular function and quality of life in elderly patients with ischemic cardiomyopathy, and improves survival in patients with coronary artery disease [9,17].

**Conclusion**

The clinical history of this patient represents a typical clinical example of ischemic CAD in an elderly patient with a poor compliance to medical treatment. This case also shows that the association of cardiac rehabilitation and optimal medical therapy represents a valid alternative to revascularization, not only in those patients for whom surgery is contraindicated, but for most patients with CAD. The adjunct of a metabolic drug, such as trimetazidine, to optimal medical therapy and exercise represents a supplementary tool to reduce the incidence and severity of symptoms, and to increase exercise tolerance and quality of life. The improvement in left ventricular function may have a beneficial effect, not only on global functional performance, but also on long-term prognosis.

**REFERENCES**

Abstract

Diabetes mellitus is an important risk factor for future cardiovascular events. To prevent cardiovascular disease, lifestyle modification is the first-line approach to the management of type 2 diabetes and metabolic syndrome, whereas strict glycemic control is the first objective in type 1 diabetes. However, aggressive treatment to control atherogenic dyslipidemia, increased blood pressure, and hyperglycemia is needed when non pharmacologic approaches alone are ineffective or insufficient.

Keywords: Cardiovascular events, diabetes mellitus, risk, cholesterol, hypertension, exercise

Introduction

Diabetes mellitus is a major health problem that affects more than 135 million people worldwide and is an important risk for future cardiovascular events in patients with or without ischemic heart disease [1]. Diabetic patients without overt coronary artery disease have a prognosis similar to that of non diabetic patients with coronary disease, whereas the cardiovascular death rate for diabetic patients with coronary disease is double that for those who are not diabetic [2]. Moreover, diabetes worsens outcomes in acute coronary syndromes, with a 5-year mortality of at least 50%. Thus patients with diabetes are prime candidates for primary or secondary prevention. The absolute risk of cardiovascular disease (CVD) in patients with type 1 (insulin-dependent) diabetes mellitus is lower than that in patients with type 2 (non insulin-independent) diabetes mellitus, in part because of their younger age and the lower prevalence of CVD risk factors, and in part because of the different pathophysiology of the two diseases. However, the relative risk of CVD in patients with type 1 diabetes compared with that of non diabetic individuals of similar age is dramatically increased in men and women. Furthermore, there are no data to suggest that the interventions documented to be of benefit in reducing CVD are less effective in patients with type 1 diabetes than in type 2 diabetes.

Risk factors

In patients without symptoms, intervention to prevent CVD is based on risk assessment. Cardiovascular risk factors have additive, or even multiplicative, effects on mortality, such that each should be addressed whenever it is possible.

Glycemic control

Although several clinical trials have shown a direct correlation between strict glycemic control and reduction of microvascular disease, the relationship between strict glycemic control and the reduction of macrovascular events has been less clear [3]. The UK Prospective Diabetes Study (UKPDS) found only borderline association between glucose control and the risk of myocardial infarction, with a marginal 16% reduction of risk after intensive hypoglycemic treatment compared with conventional treatment.

Drugs used for intensive treatment mainly influence fasting glucose concentrations, but not postprandial changes in glucose concentration [4]. The recent guidelines from the European Society of Cardiology and the European Association for the Study of Diabetes suggest that an improvement in control of postprandial glycemia may decrease cardiovascular risk and mortality [5]. The Diabetes Control and
Complications Trial (DCCT) has clearly shown that, in patients with type 1 diabetes, improved glycemic control translates into substantial reductions in macrovascular risk; in particular, improved glycemic control was particularly beneficial in younger patients with a shorter duration of diabetes [6]. A recent meta-analysis demonstrated that improved glycemic control led to substantial reductions in macrovascular risk in type 1 diabetes, but produced a smaller reduction in patients with type 2 diabetes [7]. The American Heart Association–American Diabetes Association recommendations for glycemic control are summarized in Table I [8]. It is important to underline that the only interventions that have been shown to be effective in reducing cardiovascular events in patients with diabetes mellitus are insulin in patients with acute coronary syndromes, and metformin and acarbose in primary and secondary prevention.

Dyslipidemia

Although total and high-density lipoprotein (HDL) cholesterol concentrations in patients with type 2 diabetes are similar to those in individuals without diabetes, diabetic patients tend to have greater concentrations of both triglycerides and small dense low-density lipoprotein (LDL). Several studies have clearly demonstrated that even a moderate reduction in LDL cholesterol in individuals with type 2 diabetes results in a substantial reduction of cardiovascular events, and that this risk reduction is independent of baseline lipid concentrations or co-medication. Observational data from the UKPDS demonstrated that an increase of 1 mmol/L (38.5 mg/dL) in LDL cholesterol was associated with a 57% increase in CVD, and that an increase of 1 mmol/L (4 mg/dL) in HDL cholesterol was associated with a decrease in CVD endpoint [9,10].

For primary prevention, the guidelines of the American Diabetes Association suggest that, in diabetic patients with a total cholesterol >3.5 mmol/L (>135 mg/dL), statin therapy is recommended to achieve a reduction in LDL of 30–40%, regardless of baseline LDL concentrations [8]. Evidence is lacking for a role of statin therapy for primary prevention in individuals with type 1 diabetes.

An independent relationship between increased plasma triglycerides and vascular risk remains controversial, and guidelines are less specific with regard to the goals for HDL cholesterol and triglycerides (Table I). Data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed that, in primary prevention, fenofibrate is effective in reducing cardiovascular events, and that this drug can be safely used in combination with statins for the treatment of diabetic dyslipidemia [11].

Hypertension

Arterial hypertension is a common comorbidity in diabetic patients. The Multiple Risk Factor Intervention Trial (MRFIT) and the PROspective Cardiovascular Munster (PROCAM) study have shown that arterial hypertension carries a greater cardiovascular risk in patients with diabetes than in non diabetic individuals [10,12]. Furthermore, the association of hypertension and diabetes is a much greater risk factor for cardiovascular events in women than in men (relative risk 4.6 compared with 2.4, respectively). The UKPDS and the Hypertension Optimal Treatment (HOT) trial have demonstrated that decreasing the blood pressure reduces the risk of cardiovascular events [13,14]. The European Society of Cardiology–European Association for the Study of Diabetes guidelines recommend lower blood pressure targets in patients with diabetes (<130/80 mm Hg) than in those without diabetes, and suggest, as the initial strategy, blockade of the renin–angiotensin–aldosterone system, especially in those patients at high cardiovascular risk [5].

Body weight and fat distribution

Most individuals with type 2 diabetes are overweight, and obesity worsens the metabolic and physiologic abnormalities associated with diabetes. Obesity, and in particular visceral obesity, per se, is a significant cardiovascular risk. Intra-abdominal or visceral adipose tissue has been proposed as the major site of fat deposition associated with the adverse metabolic consequences of obesity. It is believed that abdominal adiposity is the initial event that results in insulin resistance, by an increase in free fatty acid flux in the portal and systemic circulations. Intra-abdominal adipose tissue may also contribute to other mechanisms of increased atherosclerotic risk, including inflammatory, prothrombotic, and fibrinolytic factors.

Several studies have shown that weight loss is associated with a significant decrease in total and LDL cholesterol, triglycerides, and blood pressure, in addition to improved glycemic control, and is consequently associated with a significant reduction in morbidity and mortality for cardiovascular and other disease [15,16].

For type 1 diabetes, intensive insulin treatment results in weight gain. The Diabetes Control and Complications Trial showed that patients allocated randomly to intensive insulin therapy had greater weight gain than those receiving conventional insulin therapy. Despite this weight gain, improved glycemic control with intensive insulin therapy resulted in improvements in lipid concentrations and reduced the atherogenicity of the lipoprotein profile. In contrast to individuals without diabetes, in patients with
Refresher corner
Reducing the risks in diabetes

Table I. From American Heart Association (AHA)–American Diabetes Association (ADA) recommendations [8] for the primary prevention of cardiovascular disease in people with diabetes.

<table>
<thead>
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<th>Lifestyle management</th>
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<tr>
<td><strong>Weight</strong></td>
<td><strong>Lifestyle changes:</strong> increased regular physical activity can produce long-term weight loss of the order of 3–7% of starting weight, with improvement in blood pressure.</td>
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<td><strong>Medical nutrition therapy</strong></td>
<td><strong>Fats:</strong> Total dietary fat intake should be moderated (25–35% of total calories). Saturated fats: ≤7% of energy intake, cholesterol ≤200 mg/day. <strong>Trans-saturated fatty acids:</strong> &lt;1% of energy intake. <strong>Alcohol:</strong> 1 drink (a 354 mL [12-oz] beer, a 118 mL [4-oz] glass of wine) for adult women and 2 drinks for adult men. <strong>Sodium intake:</strong> 1200–2300 mg/day. <strong>Physical activity:</strong> 150 minutes of moderate-intensity aerobic physical activity or 90 minutes of vigorous aerobic exercise per week is recommended, and should be distributed over at least 3 days per week, with no more than two consecutive days without physical activity. <strong>Blood pressure:</strong> SBP &lt;130 mm Hg or DBP &lt;80 mm Hg. <strong>Lipids:</strong> LDL cholesterol ≤2.6 mmol/L (≤100 mg/dL), HDL cholesterol ≥1.3 mmol/L (≥50 mg/dL), triglycerides ≤1.7 mmol/L (≤150 mg/dL). <strong>Statin therapy</strong> should be initiated on the basis of risk factor assessment and clinical judgment. <strong>Lipids</strong></td>
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<td><strong>Lifestyle management continued</strong></td>
<td><strong>Glycemic control:</strong> The HbA1c goal for patients in general is ≤7%. The HbA1c goal for the individual patient is close to the normal (≤6%) as possible, without causing significant hypoglycemia. <strong>Aspirin therapy</strong> (75–162 mg/day) should be recommended as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are ≥40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). <strong>Physical activity</strong> has a positive effect on glycemic control in type 1 diabetes [18]. <strong>Metabolic syndrome</strong></td>
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mortality and increased incidence of CVD, even among populations initially free of diabetes and CVD. In particular, the relative risk for CVD associated with metabolic syndrome is greater in women than in men, and greater in studies in which the World Health Organization definition was used. Another recent meta-analysis confirmed these data and demonstrated that metabolic syndrome increases cardiovascular risk, and that cardiovascular risk conferred by metabolic syndrome is 3-fold greater in women than in men [20].

Several studies have demonstrated that lifestyle modification is the first-line treatment for obesity and its metabolic sequelae [21,22]. Treatment of individual components aims at controlling atherogenic dyslipidemia, increased blood pressure, and hyperglycemia when nonpharmacologic approaches alone are ineffective or insufficient [22–24].

Primary care physicians have a critical role in the early identification and treatment of patients who are at increased risk for the development of type 2 diabetes and CVD because of their obesity and associated complications.

**Antiplatelet agents**

Patients with diabetes have an increased risk of atherothrombosis, therefore antiplatelet therapy is indicated as first-line preventative strategy in type 2 diabetes [25]. Several studies have shown that aspirin reduces the risk of major cardiovascular events by about 25% in diabetic patients, and the American Diabetes Association recommends low-dose aspirin therapy for primary prevention in diabetic patients from age 40 years (Table 1).

**Conclusion**

Diabetes mellitus is an important risk for CVD. Lifestyle interventions are effective in the prevention of CVD events in patients with diabetes; however, pharmacologic treatment is often necessary. Cardiovascular preventative strategies should not be focused on glucose control therapy alone, but must include treatment of lipid profile and blood pressure. Therefore, in order to reduce cardiovascular risk, an aggressive management of lipids and blood pressure with pharmacologic treatment, together with lifestyle changes, must be implemented in all diabetic patients.

**REFERENCES**


Recruitment of compensatory pathways to sustain oxidative flux with reduced carnitine palmitoyltransferase I activity characterizes inefficiency in energy metabolism in hypertrophied hearts

Transport rates of long-chain free fatty acids into mitochondria via carnitine palmitoyltransferase I relative to overall oxidative rates in hypertrophied hearts remain poorly understood. Furthermore, the extent of glucose oxidation, despite increased glycolysis in hypertrophy, remains controversial. In the present study we explored potential compensatory mechanisms to sustain tricarboxylic acid cycle flux that resolve the apparent discrepancy of reduced fatty acid oxidation without increased glucose oxidation through the pyruvate dehydrogenase complex in the energy-poor, hypertrophied heart. We studied flux through the oxidative metabolism of intact adult rat hearts subjected to 10 weeks of pressure overload (hypertrophied; n = 9) or sham operation (n = 8), using dynamic carbon-13 nuclear magnetic resonance. Isolated hearts were perfused with 2,4,6,8,10,12,14,16-[13C]palmitate (0.4 mmol/L) plus glucose (5 mmol/L) in a 14.1 T nuclear magnetic resonance magnet. At similar tricarboxylic acid cycle rates, flux through carnitine palmitoyltransferase I was 23% lower in hypertrophied hearts (P < 0.04) than in sham-operated hearts, and corresponded to a shift toward increased expression of the L-carnitine palmitoyltransferase I isoform. Glucose oxidation via pyruvate dehydrogenase complex did not compensate for reduced palmitate oxidation rates. However, hypertrophied hearts displayed an 83% increase in anaplerotic flux into the tricarboxylic acid cycle (P < 0.03) that was supported by glycolytic pyruvate, coincident with increased levels of mRNA transcript for malic enzyme. We conclude that, in cardiac hypertrophy, fatty acid oxidation rates are reduced, whereas compensatory increases in anaplerosis maintain tricarboxylic acid cycle flux and account for a greater portion of glucose oxidation than previously recognized. The shift away from production of acetyl coenzyme A toward carbon influx via anaplerosis bypasses energy-yielding reactions, contributing to a less energy-efficient heart.

Commentary
Cardiac hypertrophy is associated with marked alterations in energy metabolism that may be important contributors to contractile dysfunction. Previous experimental and clinical studies have shown that fatty acid oxidation can decrease in the hypertrophic myocardium. However, there is confusion as to what happens to glucose metabolism in the hypertrophied heart. Although glucose uptake and glycolysis increase during cardiac hypertrophy, the subsequent oxidation of the pyruvate generated from glycolysis does not appear to increase. As a result, the pyruvate must either be converted to lactate or metabolized by some other pathway.

The study by Sorokina et al confirms that fatty acid oxidation is decreased in the hypertrophic heart, and that glucose oxidation rates do not increase to compensate for this decrease in fatty acid oxidation. Of importance is that this study also shows that pyruvate from glycolysis can be metabolized by an alternative metabolic pathway in the hypertrophied heart, in which carbons enter the tricarboxylic acid (TCA) cycle via a pathway called anaplerosis. The recruitment of this compensatory intermediary pathway, while less efficient in energy synthesis, may allow maintenance of TCA cycle activity in the hypertrophied heart. However, the most efficient pathway for pyruvate metabolism is entry into the TCA cycle via the pyruvate dehydrogenase complex (ie, glucose oxidation). There is now considerable evidence showing that shifting metabolism from fatty acid to glucose oxidation is a therapeutic strategy for treating the ischemic heart.
The 3-ketoacyl coenzyme A thiolase inhibitor, trimetazidine, affords a therapeutic approach that shifts cardiac energy metabolism from fatty acid to glucose oxidation in the heart. The findings of the study by Sorokina et al suggest that a similar approach may be useful in the hypertrophied heart. By stimulating glucose oxidation as a source of TCA cycle carbons, the potential exists to improve cardiac efficiency, as anaplerosis is an inherently inefficient process for energy synthesis compared with glucose oxidation. The authors concluded that “the potential salutary impact of therapeutic protocols for cardiomyopathy that augment glucose oxidation through pyruvate dehydrogenase complex may derive not only from a shift away from fatty acid oxidation but also from diverting glucose away from the less efficient oxidation via anaplerosis toward the more normal route of the pyruvate dehydrogenase complex”. The study by these authors provides a strong rationale for further examination of the potential benefits of using fatty acid oxidation inhibitors, such as trimetazidine, as an approach to improving cardiac function and cardiac efficiency in the hypertrophied heart.

**Featured research**

**Abstracts and commentaries**

**Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes**


Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined. Searches of the published literature, the web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline) were conducted. Criteria for inclusion in the meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. All occurrences of myocardial infarction and death from cardiovascular causes were tabulated. Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval (CI) 1.03–1.98; \( P = 0.03 \)), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI 0.98–2.74; \( P = 0.06 \)). Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. The study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

**Commentary**

This heterogenous meta-analysis of multiple data sources has already received a great deal of commentary in the medical, scientific, lay and financial press. Nonetheless, I thought it useful to emphasize points already expressed by others. There is no doubt the meta-analysis has ‘influenced’ patients’ preferences, doctors’ prescribing habits and consequently GlaxoSmithKline’s share price [1]. I would argue, however, that these ‘knee-jerk’ spinal reflexes need to be suppressed by higher centres!

The authors of the above article, and of the covering Editorial, go to some length to point out its failings. Among the most serious of these is the absolute number of events. The conclusions are based on 86 myocardial infarctions in the rosiglitazone group and 72 in the control group. There were 39 deaths from cardiovascular causes in the rosiglitazone group and 22 in the control group. These events were recorded among 27,843 patients, predominantly with overt diabetes, followed for 6–12 months. Based on simple arithmetic, and the worst case scenario, this corresponds to an annualized cardiovascular mortality of only 0.004%, suggesting that the diverse data sources may have resulted in incomplete follow-up and therefore ascertainment bias. The other concern, to me at least, is the underlying biological plausibility. The concerns raised by Nissen and Wolski regarding rosiglitazone have been likened to those raised by Garret FitzGerald over COX-2 inhibitors [2]. The concerns of FitzGerald, however, stemmed from a basic understanding of COX-2 biology underpinned by a long track record of focused and related clinical and basic research. With rosiglitazone the situation is more complex because the authors of the meta-analysis acknowledge in their discussion that the potential adverse cardiovascular effects do not seem to be shared by pioglitazone, another thiazolidinedione and peroxisome-proliferator-activated receptor gamma agonist. One is thus forced to hypothesize...
that the potential adverse effects of rosiglitazone are related to ‘off-target’ actions. Furthermore, these ‘off-target’ effects seem of too greater a magnitude to be explained by the seemingly modest apparent differences between pioglitazone and rosiglitazone on traditional cardiovascular risk factors such as lipid profiles.

In both the article above and its covering Editorial the US Food and Drug Administration are criticized for licensing glitazones on the basis of their efficacy in lowering blood glucose rather than mortality; the argument being that patients with type 2 diabetes do not die from hyperglycemia but from cardiovascular complications. This is clearly an area that needs to be watched carefully because it could easily become a slippery slope for rationally designed drugs that target a basic fundamental process in disease, in this case insulin sensitivity. Such rational design, based on the careful identification of a biological target and synthesis of a small molecule based on the target’s structure, maybe stilled in development by the crippling costs of mortality trials. To a simple clinician-scientist like myself the parachute isrationally designed to lower your terminal velocity, I do not need proof it also saves lives!

REFERENCES
CRP
CRP stands for C-reactive protein, a plasma protein produced by the liver. CRP is a member of the class of acute phase reactants, and levels rise when inflammatory processes occur in the body. CRP assists in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages, and therefore has an important role in immunity and defense against infections. Because CRP rises dramatically during inflammation, measurement of its level in the blood can be used as a marker of inflammation.

FFAs
FFAs stands for free fatty acids. Fatty acids present in the blood or cells are commonly found either as FFAs, or complexed to glycerol to form triacylglycerols or phospholipids. Since most long chain fatty acids are very insoluble, FFAs in the blood are primarily complexed to albumin as a carrier.

IL6
IL-6 stands for Interleukin-6. IL-6 is a pro-inflammatory cytokine involved in many immune responses, including physiological stress reactions. IL-6 is also involved in several diseases, including lymphoid malignancies. This cytokine binds to soluble IL-6 receptor circulating in blood, leading to signal transduction. A significant correlation between circulating IL-6 levels and insulin sensitivity has recently been found in humans.

Inflammatory markers
Measuring the blood levels of inflammatory markers can be useful in determining the progress of inflammatory disease processes, or the effectiveness of treatments used to treat inflammation. One such inflammatory marker is C-reactive protein (or CRP), the levels of which rise dramatically during inflammatory processes that occur in the body.

Krebs cycle
The Krebs cycle is also sometimes called the citric acid cycle or the tricarboxylic acid cycle. It is named after Hans Krebs, who first determined the chemical intermediates and reaction sequence of the cycle. The Krebs cycle is a series of mitochondrial enzyme-catalyzed chemical reactions involved in the conversion of carbohydrates, fats and proteins into carbon dioxide and water to generate a form of usable energy. It not only generates some energy in the form of ATP and GTP, it also produces reduced equivalents that are used by the mitochondrial electron transport chain for the production of ATP (in the presence of oxygen).

Metabolic syndrome
Metabolic syndrome is a combination of medical disorders that increase the risk of an individual developing cardiovascular disease and/or diabetes. These medical disorders include: fasting hyperglycemia or glucose intolerance, high blood pressure, central obesity, decreased HDL cholesterol, and elevated triglycerides. There is not an absolute consensus to the definition of metabolic syndrome, although the World Health Organization defines it as the presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following: hypertension, dyslipidaemia, central obesity, or microalbuminuria.

Mitochondria
Mitochondria are the ‘power house’ of eukaryote cells, and provide the energy necessary for cell function. Mitochondria have a double membrane, with the outer membrane being smooth and the inner membrane being highly convoluted, forming folds called cristae. The cristae greatly increase the inner membrane’s surface area. On the cristae are many of the enzymes responsible for producing ATP (the primary energy source of the cell). In burning fuels, such as fatty acids and carbohydrates, the mitochondria use oxygen to produce the ATP.

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

**Smooth muscle cells**

Smooth muscle cells are a type of non-striated muscle found within the blood vessels, as well as other hollow organs. Smooth muscle cells in the vasculature are primarily responsible for vessel tone. The control and structure of smooth muscle cells is fundamentally different from skeletal and cardiac muscle cells.

**3-ketoacyl-CoA-thiolase (3-KAT)**

3-ketoacyl-CoA-thiolase (3-KAT) is the last enzyme in the intramitochondrial pathway that is involved in the metabolism of fatty acids (fatty acid β-oxidation). Recent interest has focused on 3-KAT, since inhibition of this enzyme decreases fatty acid oxidation and protects the ischemic heart.