

Heart and Metabolism

MANAGEMENT OF THE CARDIAC PATIENT

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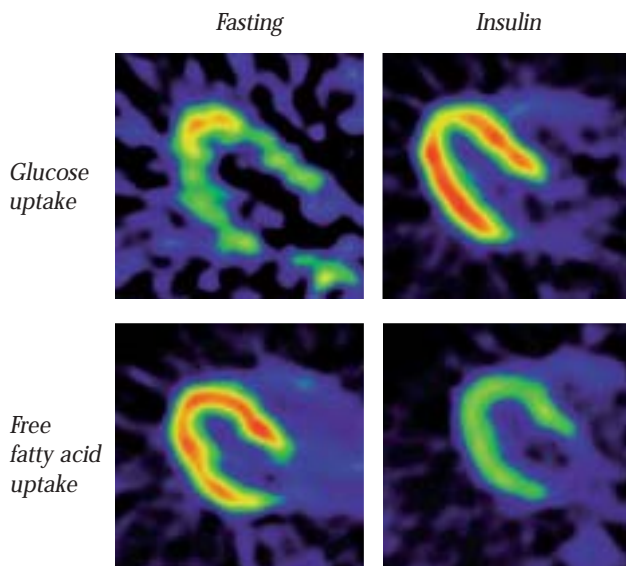
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Aims and Scope

Heart and Metabolism is a quarterly journal with a focus on the management of myocardial ischaemia. The purpose of the journal is to inform cardiologists and other specialists about new findings regarding the role of metabolism in cardiac patients and to create awareness of its potential clinical implications. The management of patients with angina, as well as heart failure, and hypertrophic and dilated cardiomyopathy will be discussed. Moreover, the effects of metabolic diseases like diabetes mellitus on the heart will be highlighted. Generally, each issue will include an editorial, a main article, and an interview with an eminent international specialist. These experts in the field will explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischaemic and non-ischaemic heart disease.

The cover photograph shows images of glucose and fatty acid uptake in the heart using positron emission tomography. Generally, glucose and fatty acids are alternative substrates for energy production. During fasting when there are high fatty acid levels in the blood, myocardial fatty acid uptake is preferred, unlike conditions in which glucose uptake is promoted (insulin). See article on p. 21.

Metabolic agents: a new approach in treating ischemic heart disease

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Myocardial ischemia results in a decrease in oxygen supply to the heart, thereby decreasing energy production in the heart. Therapeutic strategies for treating myocardial ischemia have concentrated on either increasing oxygen supply to the heart muscle or decreasing the oxygen demand of the muscle. While these approaches have dramatically improved the prognosis of patients with angina pectoris or those suffering an acute myocardial infarction, complications of myocardial ischemia remain a major cause of mortality and morbidity worldwide.

As the 20th century comes to an end, a new approach to treating myocardial ischemia is emerging, which involves improving the efficiency of oxygen utilization by cardiac tissue. It is now becoming clear that it is possible to increase cardiac efficiency by pharmacologically optimizing fuel use in the heart.^{1,2,3,4}

Fuel use by the heart

The production of energy (in the form of adenosine triphosphate [ATP]) is primarily derived in the heart from the catabolism of both fatty acids and carbohydrates (principally glucose). Normally a balance between these two pathways exists, with fatty acid oxidation providing 60–70% of overall cardiac ATP supply, and glucose and lactate providing the remainder. Glucose metabolism consists of two important components, glycolysis and glucose oxidation. Glycolysis is the initial sequence of reactions involved in the breakdown of glucose to pyruvate, while glucose oxidation involves the subsequent mitochondrial oxidation of pyruvate. Glycolysis is important in that it produces ATP without the need for oxygen. While glycolysis only contributes small yields of ATP (normally about 5% of total ATP produced by the aerobic heart), it is widely believed that this glycolytic supply of ATP is essential to maintain ionic

stability and cell integrity.^{2,4} During ischemia, glycolysis is accelerated, producing a greater proportion of the heart's ATP supply. However, if glycolysis is not coupled to glucose oxidation, protons and lactate are also a by-product of this pathway. As a result, acceleration of glycolysis during ischemia can have detrimental consequences if glucose oxidation does not increase in parallel.

Unlike glucose metabolism, all ATP production from the metabolism of fatty acids is oxygen-dependent and occurs in the mitochondria. As a result, fatty acid oxidation is not as efficient as glucose as a source of energy and requires more oxygen to produce an equivalent amount of ATP. However, another major problem with fatty acids is that, as oxidation of fatty acids increases, there is a concomitant decrease in glucose oxidation. This can lead to an uncoupling of glycolysis from glucose oxidation and an increase in proton and lactate production.⁴

Energy metabolism during and following ischemia

Increasing glycolysis and the contribution of glucose oxidation to residual oxidative metabolism during ischemia is one approach to benefiting the ischemic heart. However, fatty acid oxidation effectively competes with glucose oxidation for this 'residual oxygen', resulting in acidosis due to the accumulation of lactate and protons within the heart. During a severe ischemic insult this can lead to a substantial intracellular acidosis, which can lead to sodium and calcium accumulation within the myocyte. The requirement for energy to re-establish ionic homeostasis then leads to a decrease in cardiac efficiency.

Upon reperfusion of reversibly injured ischemic myocardium, contractile function recovers once energy production has been restored, and cytosolic calcium levels normalize.

However, due to both increases in circulating levels of fatty acids and changes in the cellular control of fatty acid metabolism, fatty acid oxidation dominates as a source of energy, which again leads to proton production, an uncoupling of glycolysis to glucose oxidation, and a decrease in cardiac function and efficiency.^{4,5}

Optimizing energy metabolism during and following ischemia

Two significant events have recently occurred that have resulted in a resurgence of interest in energy metabolism as a target for pharmacological therapy. The first is the observation that a number of existing pharmacological agents beneficial in treating angina exert their effects by optimizing energy metabolism. The second is the recent confirmation that glucose-insulin-potassium (GIK) infusions are beneficial in patients following acute myocardial infarction.

Pharmacological inhibition of fatty acid oxidation and stimulation of glucose oxidation have recently been shown to significantly improve cardiac efficiency in the heart (cardiac work/oxygen consumed). One agent used clinically to treat ischemic heart disease is trimetazidine, which acts by directly inhibiting fatty acid oxidation.⁶ This inhibition of fatty acid oxidation is accompanied by a significant increase in glucose oxidation and a decrease in myocardial acidosis.⁷ Several clinical trials have demonstrated the anti-anginal efficacy of trimetazidine, which is equivalent to that of propranolol and calcium channel blockers but without any hemodynamic or vasodilatory effects.⁸ Trimetazidine also has beneficial effects in the setting of acute myocardial infarction, coronary angioplasty and cardiac surgery.

Other inhibitors of fatty acid oxidation that may soon see clinical use are ranolazine,⁹ which is efficacious in chronic stable angina, or carnitine palmitoyl transferase-1 inhibitors. Direct stimulation of glucose oxidation both during and following ischemia may also benefit the ischemic heart. An example of this is dichloroacetate, which, while clinically beneficial,¹⁰ will probably not see widespread clinical use due to its poor pharmacokinetics. Two

other agents that also stimulate glucose oxidation and that may see clinical use are L-carnitine and propionyl L-carnitine. Both of these are natural compounds that stimulate glucose oxidation in the heart and are efficacious in angina pectoris. In a recent multicentre trial, L-carnitine was shown to reduce ventricular end-diastolic pressure and attenuate the progression of left ventricular dilatation in patients following a myocardial infarction.¹¹

Another approach to optimizing energy metabolism is to alter glucose and fatty acid availability to the heart. The concept that increasing glucose supply to the ischemic myocardium may protect the ischemic heart dates back to the 1960s, and was the rationale for the development of GIK therapy.¹² This therapeutic approach increases myocardial glucose uptake and promotes myocardial glycogen storage (depending on the degree of ischemia), which can serve as a source of glucose for glycolysis, thereby increasing ATP supply. However, this intervention also has the potential to increase hydrogen and lactate accumulation within the ischemic myocardium. The complex ramifications of this seemingly simple intervention require further study. New data from the ECLA (Estudios Cardiológicos Latinoamerica) Collaborative Group report a dramatic reduction in relative risk of in-hospital mortality from acute myocardial infarction with GIK.¹³ One possible benefit of GIK may actually be related to a decrease in circulating fatty acid levels, since insulin inhibits the mobilization of free fatty acids from adipocytes.

In conclusion, I believe the 21st century will see the start of an era in which optimizing energy metabolism in the heart will become an important clinical approach to treating ischemic syndromes. Inhibiting fatty acid oxidation or directly stimulating myocardial glucose oxidation may be one such approach to optimizing metabolism in the heart. ■

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Early detection of diabetic and non-diabetic subjects with increased cardiovascular risk: new risk indicators

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Cardiovascular disease continues to be the principal cause of death in the USA, Europe and a large part of Asia.^{1,2} However, over the last decade, mortality from cardiovascular disease has shown an annual decline which may be largely due to improvements in the treatment and secondary prevention of myocardial infarction.³ Nevertheless, congestive heart failure, a progressive disease, has emerged as one of the leading cardiovascular disorders in developed countries and is expected to become a major disease burden by the year 2020.⁴ This situation emphasizes the necessity of risk reduction among asymptomatic subjects in order to prevent clinical symptoms of cardiovascular disease, i.e. primary prevention.

Diabetes mellitus probably affects 5–7% of Western populations. It has been estimated that its prevalence will double to reach 200 million worldwide over the next 15 years, due to lifestyle changes, ageing and better treatment facilities giving a longer lifespan.^{5,6} Diabetes mellitus is associated with a three- to fourfold higher risk of cardiovascular mortality^{7–9} and an approximately 5- to 10-year reduced life-expectancy compared with non-diabetic subjects.¹⁰ The annual decline in cardiovascular mortality observed in the general population during the past 30 years has been almost absent in the diabetic population.¹¹ Consequently, the incidence and prevalence of cardiovascular disease among diabetic subjects will increase dramatically. Conventional cardiovascular risk factors are known to have a similar impact on diabetic as well as non-diabetic subjects,¹² and at all risk factor levels diabetic subjects have a two to three times higher absolute risk of a serious cardiovascular event than do non-diabetics.¹² Moreover, diabetic subjects have less favorable outcomes after myocardial infarction than do non-diabetic subjects.¹³ In view of these considerations, focus on primary prevention among diabetic subjects might be

even more important than among non-diabetic subjects.

The overall objective of cardiovascular disease prevention both in asymptomatic subjects and in subjects with clinically established cardiovascular disease is the same: to reduce the risk of subsequent cardiovascular events. There are, however, differences in treatment strategies used for primary and secondary prevention. In general, the use of intensive treatment strategies is more justified for secondary prevention than for primary prevention since benefits are easier to establish for secondary prevention. To decide whether drug therapy is also indicated for primary prevention, it is important to identify those asymptomatic subjects who have a relatively high absolute risk of cardiovascular disease (*Figure 1*).

Major risk factors for cardiovascular disease are hypertension, smoking, hypercholesterolemia, diabetes mellitus and a sedentary lifestyle. These risk factors, however, only explain about 50% of the prevalence and severity of coronary heart disease.^{14,15} Recently, much research has been undertaken to search for new risk factors or indicators for cardiovascular disease.^{16,17} *Risk factors* are defined as variables *causally* related to atherothrombosis, whereas *risk indicators* or *risk markers* are *indirectly* associated with atherothrombosis, for example because they reflect a pathophysiological mechanism causing atherothrombosis or because they are strongly associated with an unknown (and unmeasured) risk factor. Risk indicators, like risk factors, are useful because they allow so-called risk stratification. Risk stratification enables us to identify subjects especially prone to develop cardiovascular disease, in order to target preventive treatment on an individual level.

In this review, four promising new indicators of cardiovascular disease risk — slightly raised

urinary albumin excretion (microalbuminuria) and raised plasma levels of von Willebrand factor (vWF), C-reactive protein (CRP) and soluble vascular cell adhesion molecule-1 (sVCAM-1) — are described, with particular attention to the implications of these risk indicators for diabetic subjects. To provide some perspective on how these risk markers relate to cardiovascular disease, there is a brief introduction on the pathogenesis of atherothrombosis. Since 85% of all diabetic subjects have Type 2 diabetes mellitus, these subjects are the focus of this discussion.

Atherothrombosis

Atherothrombosis is a slowly progressive degenerative disease of large and middle-sized elastic and muscular arteries. The disease begins with formation of fatty streaks in adolescence and when progressed unabated develops into fibrous plaques and complicated lesions, culminating in thrombotic occlusions and cardiovascular events in later life. The most commonly held view of the pathogenesis of atherothrombosis is described in the so-called response-to-injury

hypothesis first postulated by Ross and Harker in 1976.¹⁸ In the latest update of this hypothesis, endothelial dysfunction is proposed to be the initiating factor leading to a series of specific cellular and molecular responses that can best be described as an inflammatory disease.¹⁹

Intact endothelium has important bioactive properties, i.e. it actively regulates vascular tone, permeability to macromolecules and leukocytes, the balance between coagulation and fibrinolysis, the composition of the sub-endothelial matrix, and the proliferation of vascular smooth muscle cells.²⁰⁻²² To carry out these functions, endothelium produces a variety of regulatory mediators (e.g. nitric oxide, prostanoids, endothelin, angiotensin II, tissue-type plasminogen activator, plasminogen activator inhibitor-1, vWF and several cytokines), components of the extra-cellular matrix (e.g. heparan sulfate proteoglycans, collagen and laminin) and adhesion molecules (e.g. vascular cell adhesion molecule-1 [VCAM-1] and E-selectin). When the properties of intact endothelium change, either in the basal state or after stimulation, in such a way that normal organ function is no longer

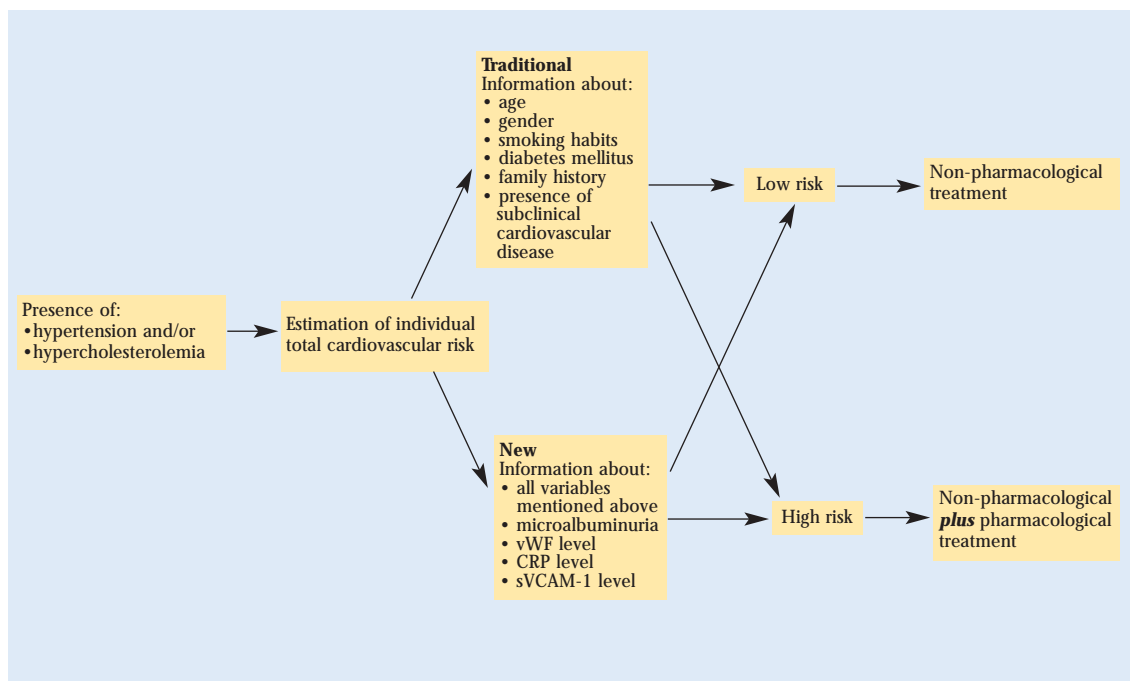


Figure 1. Possible strategies for risk stratification in primary prevention of cardiovascular disease. vWF, von Willebrand factor; CRP, C-reactive protein; sVCAM-1, soluble vascular cell adhesion molecule-1.

preserved, endothelial dysfunction is considered to be present.

Early manifestations of endothelial dysfunction include the appearance of specific adhesive molecules on the surface of the endothelial cells. Monocytes and T-lymphocytes attach to these molecules and transmigrate to the subendothelial space. Once in the arterial wall, monocytes become macrophages where they act as antigen-presenting cells to T-lymphocytes, as scavenger cells to remove noxious materials, and as a source of growth-regulatory molecules and cytokines. In all stages of atherothrombosis, macrophages and T-lymphocytes are present in the arterial wall, suggesting that atherothrombosis is an ongoing low-grade inflammatory disease.^{18,19}

Taken together, the initiating endothelial dysfunction and, subsequently, the ongoing low-grade inflammation of the arterial vessel wall are important (early) features of the atherothrombotic process. Therefore, markers reflecting endothelial dysfunction or low-grade inflammation might be useful for stratification of risk of cardiovascular disease.

Microalbuminuria

Albumin is a relatively large negatively charged protein (molecular weight 69 kDa, size 36 Å), which is usually excreted in small amounts in the urine (< 20 µg/min). Slightly raised urinary albumin excretion, known as microalbuminuria,²³ is defined as urinary albumin excretion 20–200 µg/min or 30–300 mg/24 h.²⁴

The filter through which albumin must pass before entering the urine, the glomerular capillary wall, is size- and charge-selective. Microalbuminuria is thought to be a consequence of increased albumin leakage through the glomerular capillary wall as a result of increased permeability of the wall, increased intraglomerular pressure, or both.^{25,26} Hyperglycemia and high blood pressure are generally accepted to be the main risk factors for developing microalbuminuria.^{27,28} Both can increase intraglomerular pressure.²⁹ Moreover, hyperglycemia can alter the charge selectivity of the glomerular capillary wall, thereby increasing its permeability.³⁰ In a healthy kid-

ney, over 99% of filtered albumin is reabsorbed by mechanisms that are probably close to saturation. A small increase in albumin filtered by the glomerulus will lead to an excessive supply of albumin to the renal tubulus. Although a compensatory increase of tubular reabsorption has been suggested, this might only be present in an early stage of increased albumin filtration.³¹ As a consequence, increased filtered albumin will lead to increased albumin excretion in the urine.³²

The prevalence of microalbuminuria is low in the general population and rises with age, resulting in a prevalence of about 8–10% in the general elderly population.^{28,33} The prevalence of microalbuminuria among diabetic and hypertensive subjects is much higher than that in the general population, i.e. approximately 30%^{28,34} and 20%,^{28,34} respectively.

Microalbuminuria as a cardiovascular risk indicator

Microalbuminuria is a well-recognized, strong and independent risk marker of cardiovascular disease among diabetic subjects.³⁵ In a systematic review, Dinneen and Gerstein³⁶ showed that microalbuminuria among Type 2 diabetic subjects was associated with a 2.4-fold (95% CI 1.8–3.1) increased risk of cardiovascular death compared with normoalbuminuria. In addition, elevated urinary albumin excretion has been found to be an independent risk marker for cardiovascular disease among non-diabetic subjects.^{37,38} Whether microalbuminuria is also a risk marker among hypertensive subjects is still the subject of debate.^{39,40} In a 10-year follow-up study, Samuelsson et al.⁴¹ showed that macroalbuminuria (i.e. albumin excretion above the microalbuminuria threshold) was associated with an approximately threefold increased cardiovascular risk among hypertensive males. Recently, we were the first to show that the presence of microalbuminuria was also associated with a threefold increased risk of cardiovascular mortality among hypertensive subjects.⁴²

In view of the strong and independent association between microalbuminuria and deterioration of renal function, the American

Diabetes Association recommends yearly routine urinalysis for the detection of microalbuminuria among diabetic subjects.²⁴ However, although microalbuminuria is strongly associated with a decline in renal function among Type 1 diabetic subjects,^{23,43} among Type 2 diabetic subjects microalbuminuria is much more strongly related to risk of cardiovascular disease.³⁶ Among 503 Type 2 diabetic subjects followed for 10 years, 2% died from uremia whereas 56% died from cardiovascular disease.³⁵ In other words, many Type 2 diabetic subjects will die of cardiovascular disease before renal failure develops. Thus, screening for microalbuminuria among Type 2 diabetic subjects should be used primarily as a means to stratify risk of cardiovascular disease.

Pathophysiological mechanisms

The underlying pathophysiological mechanism through which microalbuminuria is related to cardiovascular disease is unclear, although several mechanisms have been proposed which can be categorized into three main hypotheses (Figure 2). First, microalbuminuria could simply be a marker of an underlying pathophysiological process causing atherothrombosis (Figure 2). Several processes have been suggested. Microalbuminuria could reflect a systemic transvascular leakage of albumin^{44,45} caused by alterations in the extracellular matrix, which might predispose to greater penetration of atherogenic lipoprotein particles into the arterial wall.⁴⁶ Alternatively, microalbuminuria could reflect generalized endothelial dysfunction (without necessarily involving other layers of the vessel wall)⁴⁷. Accordingly, microalbuminuria is associated with increased plasma levels of proteins secreted by or shed from injured endothelium, such as vWF (see below)⁴⁸, thrombomodulin⁴⁹ and fibronectin.⁵⁰ Microalbuminuria could also reflect chronic low-grade inflammatory activity since it has been found to be associated with levels of proinflammatory cytokines.⁵¹ Furthermore, among Type 2 diabetic subjects, microalbuminuria has been found to be associated with impaired fibrinolytic activity⁵² and with a procoagulant state.⁵³ Finally, microalbuminuria has been proposed to be part of the insulin resistance syn-

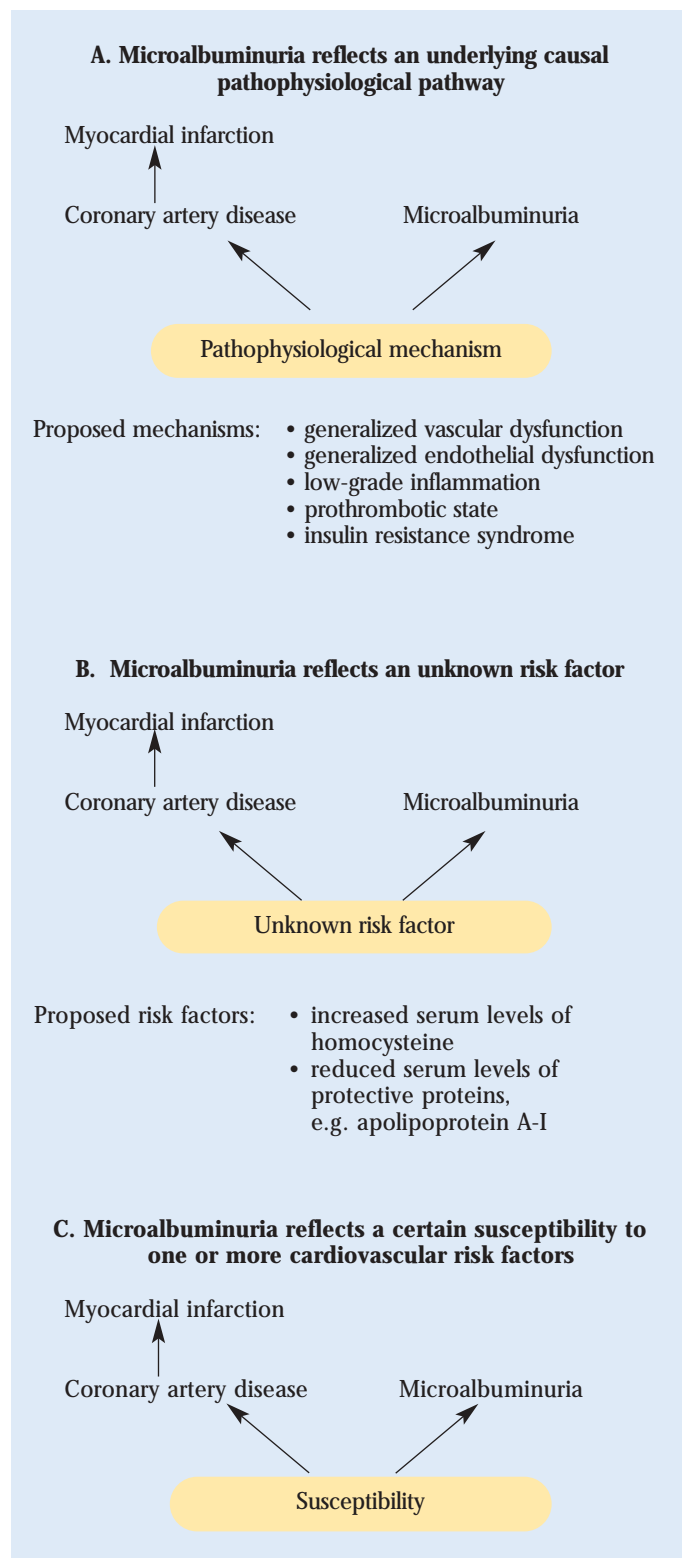


Figure 2. Proposed pathophysiological pathways through which microalbuminuria might be related to cardiovascular events.

drome,^{54,55} a cluster of cardiovascular risk factors (i.e. glucose intolerance, insulin resistance, hypertension, obesity and dyslipidemia), and might as such increase the risk of cardiovascular disease. Thus, microalbuminuria could reflect several pathophysiological pathways causing atherothrombosis.

The second hypothesis suggests that microalbuminuria might reflect a certain risk factor which has not yet been discovered (Figure 2). Hyperhomocysteinemia may be a candidate since an increased homocysteine level has been found to be associated with risk of atherothrombotic disease^{56,57} on the one hand and with the presence of microalbuminuria on the other.⁵⁸ A decreased level of cardioprotective proteins such as apolipoprotein A-I is another candidate.⁵⁹ These proteins could be lost in the urine along with albumin.

The third hypothesis proposes that microalbuminuria could reflect a certain susceptibility for developing atherothrombotic diseases (Figure 2). This hypothesis is based on the idea that some subjects may have a more pronounced inherent response to risk factors, thus predisposing them to increased cardiovascular risk.

In summary, microalbuminuria is a strong independent indicator of increased cardiovascular risk among non-diabetic and Type 2 diabetic subjects. Therefore, microalbuminuria can be used for stratification of risk of cardiovascular disease. Once microalbuminuria is present, cardiovascular risk factor reduction should be more 'aggressive'. Finally, it is of great importance to unravel the pathophysiological mechanism behind the association between microalbuminuria and cardiovascular risk in order to develop more specific treatments.

von Willebrand factor (vWF)

vWF, a multimeric glycoprotein, is secreted mainly by endothelial cells and megakaryocytes. vWF is continuously released into the bloodstream in small amounts. This results in plasma vWF concentrations of 50–150% (i.e. 0.5–1.5 U/ml)⁴⁸, as assessed by highly-specific electroimmunopheresis or ELISA. Once in the bloodstream, vWF mediates platelet adhesion to the subendothelium and serves as a carrier

protein for Factor VIII.

Levels of vWF can increase rapidly in response to acute endothelial injury, as a result of acute release of stored vWF from endothelial storage bodies, the so-called Weibel-Palade bodies. Plasma vWF concentration can also increase slowly due to an increase in vWF secretion in response to abnormal environments such as diabetes mellitus, hypertension, renal failure or malignancies.^{48,60,61}

To date, there is no consensus about which cut-off level should be used to define a high vWF concentration. The cut-off level which is used most often is a vWF level above 150%.

von Willebrand factor (vWF) as a cardiovascular risk indicator or risk factor

Increased levels of vWF have been found to be associated with the presence of peripheral,⁶² cerebral,⁶³ and coronary artery atherothrombotic disease.⁶⁴ Furthermore, vWF levels are higher among subjects with (compared to those without) cardiovascular risk factors, e.g. hypertension,⁶⁵ hypercholesterolemia,⁶⁶ smoking⁶⁷ and diabetes.^{68–71} Moreover, prospective studies have shown high levels of vWF to be associated with cardiovascular mortality among patients recently presenting with clinical manifestations of cardiovascular disease^{63,64,72} and among Type 2 diabetic subjects.⁶⁹

So far, similar prospective data among healthy subjects or subjects at high risk of developing atherothrombosis are lacking (except for one study among Type 2 diabetic subjects⁶⁹).

Pathophysiological mechanisms

The pathophysiological explanation for the association between increased cardiovascular risk and high vWF levels is not entirely clear (Table 1). The most commonly held view is that increased levels of vWF reflect generalized endothelial dysfunction.^{48,60,73} Accordingly, injury to endothelial cells has been shown to increase the secretion of vWF both in vitro and in vivo.^{48,60} Alternatively, it has been hypothesized that vWF, as an acute-phase reactant,⁷⁴ reflects endothelial activation and

Table 1. Proposed pathophysiological pathways through which high plasma levels von Willebrand factor (vWF), C-reactive protein (CRP) and soluble vascular cell adhesion molecule-1 (sVCAM-1) may be related to risk of cardiovascular events.

	vWF	CRP	sVCAM-1
Risk marker (indicator)			
• Generalized endothelial dysfunction	++++		+
• Acute-phase reactant	+	++++	+
• Generalized vascular dysfunction	++		++++
• Impaired renal function			+
Risk factor			
• Prothrombotic properties	++		
• Increased viscosity	+		
• Procoagulant properties		+	
• Increased transendothelial migration of leukocytes		+	+
• Proangiogenic properties			+

+ to ++++ indicates strength of evidence.

stimulation (without necessarily implying endothelial dysfunction) and as such reflects a low-grade inflammatory state. On the other hand, the bioactive properties of vWF might by themselves increase cardiovascular risk. (Note that if that were in fact the case, high vWF levels would be a risk factor rather than a risk indicator.) Plasma vWF has a key role in platelet adhesion, thrombus formation and coagulation. As a consequence, increased levels of vWF could induce a procoagulant and prothrombotic state,⁷⁵ thereby explaining the high risk of reinfarction among survivors of myocardial infarction with high vWF levels.⁷² Alternatively, increased vWF levels could increase plasma viscosity. vWF multimers are the largest known soluble human plasma protein molecules and by virtue of their size may increase plasma viscosity.⁷⁶ Moreover, high viscosity has been found to be related to increased risk of cardiovascular disease.⁷⁷⁻⁷⁹ Thus, increased vWF levels are strongly associated with risk of cardiovascular mortality among subjects with advanced atherosclerosis. Although similar associations are likely

to be present among other subgroups with high cardiovascular risk, prospective studies are necessary to confirm this.

C-reactive protein (CRP)

CRP, an acute-phase reactant, is a marker of inflammation which is often assessed in clinical practice to monitor inflammatory responses.⁸⁰ The synthesis of CRP in the liver is largely regulated by cytokines, in particular interleukin-6, which are secreted by activated leukocytes, fibroblasts and endothelial cells. The physiological role of CRP is not fully understood, although it has been suggested that CRP contributes to the inflammatory response.^{81,82} In healthy subjects, plasma CRP concentrations assessed by highly sensitive assays^{83,84} are generally low, i.e. 95% of the general population have a CRP level < 3 mg/l and 99% a level < 10 mg/l. In response to inflammatory stimuli, CRP levels can rise five- to more than 100-fold within 6 h. The plasma half-life and the fractional catabolic rate of CRP are constant in almost all conditions. Consequently, plasma CRP levels are thought to be determined only by the rate of synthesis, which basically reflects the presence, extent and activity of disease. Therefore, slightly increased, but conventionally normal, CRP levels may reflect a chronic, low-grade inflammatory state.

C-reactive protein (CRP) as a cardiovascular risk indicator or risk factor

Increased levels of CRP have been found to be associated with lipid levels, obesity, diabetes and pack-years of smoking.^{51,85,86} In addition, levels of CRP have been found to be higher among subjects with (compared with those without) (sub)clinical cardiovascular disease.⁸⁵ Moreover, several prospective studies have demonstrated a clear association between slightly increased CRP levels and risk of cardiovascular events among subjects at high risk of atherothrombotic events,⁸⁷ those with stable and unstable angina,⁸⁵ those with prior myocardial infarction,⁸⁸ and among apparently healthy men⁸⁹ and women.⁸⁶ For example, among subjects free of clinical cardiovascular

disease, risk of cardiovascular events was about three times higher among those with CRP levels in the upper quartile compared with those with CRP levels in the lower three quartiles.⁹⁰ Levels of CRP are higher among Type 2 diabetic subjects than among non-diabetic subjects.⁹¹ To date, no prospective data on CRP and cardiovascular disease in Type 2 diabetes have been published.

Pathophysiological mechanisms

It has been hypothesized that a chronic low-grade inflammation is the mechanism through which CRP is associated with increased risk of cardiovascular events (*Table 1*).⁸⁹ Alternatively, CRP might have bioactive properties which by themselves could counterregulate the inflammatory response. Both pro- and anti-inflammatory properties of CRP have been proposed.^{81,82} *In vitro* studies have shown that high levels of CRP could diminish the first step of neutrophil extravasation by downregulating the expression of L-selectin on the neutrophil surface⁸² and thus attenuate the normal inflammatory response. On the other hand, raised CRP levels can activate complement via the classic pathway⁸¹ and thus have proinflammatory properties. These data, however, should be interpreted with caution since the concentrations of CRP used in these experiments were often in a supraphysiological range.

Taken together, measurement of CRP levels may provide a novel method for assessing cardiovascular risk among healthy subjects as well as among subjects with clinical manifestations of atherothrombosis.

Soluble vascular cell adhesion molecule-1 (sVCAM-1)

Membrane-bound VCAM-1 is a member of the immunoglobulin superfamily, one of the main four classes of adhesion molecule receptors. Membrane-bound VCAM-1 is a ligand for leukocyte integrins and is thought to allow tethering and rolling of monocytes and lymphocytes as well as firm attachment and transendothelial migration of leukocytes,^{92,93}

both of which are important early in the atherothrombotic process. In the normal situation, there is a constitutively low expression of membrane-bound VCAM-1 on endothelial cells, smooth muscle cells, tissue macrophages,^{94,95} lymphoid dendritic cells and renal tubular cells.⁹⁶

Soluble forms (sVCAM-1) have been detected in plasma.⁹⁷ The release of sVCAM-1 in the bloodstream is reported to be in parallel with the expression of membrane-bound VCAM-1 on endothelial cells.⁹⁸ Plasma levels of sVCAM-1 can be assessed by highly-sensitive ELISA techniques. The concentration of sVCAM-1 normally present in plasma of healthy subjects has been found to be 400–600 ng/ml.⁹⁹ This concentration, however, is highly dependent on the ELISA technique used.

Membrane-bound VCAM-1 synthesis can be upregulated several-fold in response to stimuli such as cytokines,¹⁰⁰ modified lipoproteins¹⁰¹ and advanced glycation endproducts.¹⁰² Furthermore, plasma levels of sVCAM-1 can rise in response to increasing blood pressure induced by the cold pressor test, suggesting that increased pressure on endothelial cells can also upregulate VCAM-1 synthesis or increase its shedding from the cell membrane.¹⁰³ Finally, the presence of oxidants has been suggested to play a crucial role in the upregulation of VCAM-1 synthesis.¹⁰⁴ Interestingly, De Mattia et al.¹⁰⁵ showed that treatment with antioxidants decreased plasma sVCAM-1 levels among Type 2 diabetic subjects.

Soluble vascular cell adhesion molecule-1 (sVCAM-1) as a cardiovascular risk indicator or risk factor

In vitro experiments showed endothelial expression of VCAM-1 to be an early manifestation of experimental cholesterol-induced atherothrombosis.¹⁰⁶ Increased VCAM-1 expression has also been found to be present on human atherothrombotic plaques.¹⁰⁷ In addition, sVCAM-1 levels are associated with cardiovascular risk factors, i.e. hypertension,¹⁰⁴ impaired glucose tolerance¹⁰⁸ and hypertriglyceridemia.¹⁰⁹ Recent cross-sectional

studies have shown significant positive associations between sVCAM-1 levels and carotid artery intimal-medial thickness^{110,111} and the severity of peripheral arterial disease obtained by angiography.^{110,112} Two prospective studies, however, could not demonstrate high levels of sVCAM-1 to be associated with risk of cardiovascular events among apparently healthy subjects¹¹³ or among subjects with peripheral arterial disease.¹¹⁴

Levels of sVCAM-1 have been found to be higher among Type 2 diabetic subjects than among non-diabetic subjects.^{71,99,111} Recently, Otsuki et al.¹¹⁵ found sVCAM-1 levels to be positively associated with intimal plus medial complex thickness of the carotid arteries among diabetic but not among non-diabetic subjects. They reasoned that increased sVCAM-1 levels might be a specific indicator of atherothrombosis among diabetic subjects only. If so, levels of advanced glycation end-products, which are increased among Type 2 diabetic subjects compared with non-diabetic subjects, might play an important role, since they can strongly stimulate VCAM-1 synthesis. It would therefore be of particular interest to investigate the predictive value of sVCAM-1 for future cardiovascular disease among diabetic subjects.

Pathophysiological mechanisms

The most commonly held view is that increased plasma sVCAM-1 levels reflect increased membrane-bound VCAM-1 levels and thus reflect progressive formation of atherosclerotic lesions (*Table 1*).¹¹⁶ Alternatively, increased levels of sVCAM-1 could reflect generalized endothelial dysfunction, since plasma levels most likely originate mainly from endothelial cells and are closely correlated with vWF levels.^{110,113} Third, increased sVCAM-1 levels might simply be a marker of an acute-phase response, reflecting the progressive low-grade inflammation of the vessel wall. Accordingly, several cytokines which can induce an acute-phase reaction in response to proinflammatory antigens strongly increase the expression of VCAM-1 on cultured endothelial cells.¹¹⁷ Fourth, increased levels of sVCAM-1 might be explained not only by an increased

synthesis/shedding but also by impaired clearance of sVCAM-1 molecules. Although little is known about the route of elimination of these molecules, an important role of the kidney has been suggested.¹¹⁸ Finally, sVCAM-1 itself may have bioactive properties related to cardiovascular risk. For example, Koch et al.¹¹⁹ have recently shown that sVCAM-1 has proangiogenic properties.

Thus, there is growing evidence that increased levels of sVCAM-1 are associated with the degree of atherothrombosis, although prospective data are not conclusive. Future prospective studies should focus on the importance of increased plasma sVCAM-1 level for future risk of cardiovascular events, especially among diabetic subjects. ■

Conclusion

Current clinical practice follows the strategy of matching the intensity of treatment of individual patients to their risk of cardiovascular disease. Guidelines for primary prevention of coronary heart disease in clinical practice, however, are mostly based on the use of risk tables which include only conventional risk factors.^{120,121}

Although a rough risk estimate can be obtained from these tables, more precise risk stratification is needed. Therefore, we have described four promising new risk indicators which may provide increased precision in risk estimation, i.e. microalbuminuria and increased plasma levels of vWF, CRP and sVCAM-1

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Optimization of cardiac metabolism: a clinical reality

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The renaissance of clinical cardiac metabolism

There is a resurgence of interest in cardiac metabolism among practising cardiologists. This is largely due to the increasing evidence that metabolic manipulation can be efficaciously applied to numerous clinical situations, as was made clear at a symposium held during the last congress of the European Society of Cardiology (ESC) in Barcelona. One of the messages of this symposium was that cardiologists should have a solid understanding of cardiac metabolism in order to apply the lessons of recent studies to their therapeutic armamentarium. Based on a wholly rational approach, metabolic intervention is being used successfully in several settings of ischaemic heart disease, and its place in management is expanding.

Glucose-insulin-potassium (GIK) validates an experimental concept

The major energy-producing substrates in the heart are glucose and free fatty acids (FFA). For over 20 years, there has been increasing evidence that raising glucose metabolism and decreasing fatty acid oxidation can be beneficial in ischaemia. The major reason for this is that the adenosine triphosphate (ATP) yield (in moles per mole of oxygen) is greater with glucose metabolism than with fatty acid metabolism.¹ Although experimental arguments have been made for some time, it is only in recent years that hard clinical evidence has come to validate a metabolic approach to ischaemic heart disease.

The comeback of GIK

Professor C. Apstein, Director of the Cardiac Muscle Research Laboratory at Boston University, USA, participated at the ESC congress, offering convincing evidence that the provi-

sion of a high level of glucose and insulin is beneficial during acute myocardial infarction and postoperative cardiogenic shock. Beginning with the classic study by Sodi-Pallares et al.² in 1962 which first described benefit from a regimen of glucose, insulin and potassium (GIK), Professor Apstein retraced the subsequent disappointing trials with GIK, pointing out many of the limitations of these studies, including GIK being initiated as late as 48 h after the onset of chest pain and inadequate glucose and insulin administration. One of the best early randomized trials was done by Rackley et al.,³ showing that GIK improved cardiac function, decreased ventricular arrhythmias, and was associated with a trend towards decreased mortality.

The mechanism of action of GIK

GIK works by stimulating glucose uptake and glycogen synthesis while inhibiting fatty acid release from adipocytes. In the study by Rackley et al.,³ GIK induced an increase in the respiratory quotient, demonstrating a shift in energy substrate metabolism from lipids to carbohydrate. Related factors may also come into play, such as improved sodium and calcium homeostasis.

GIK today

The benefit of GIK persists even in the age of thrombolysis, as strongly shown by the DIGAMI (Diabetes Insulin-Glucose in Acute Myocardial Infarction) study⁴ in patients with diabetes or hyperglycaemia at admission. In that study, there was a 29% relative mortality reduction at 1 year in patients receiving GIK. The recent ECLA (Estudios Cardiologicos Latinoamerica) study,⁵ however, adds the most persuasive evidence of the value and applicability of GIK in myocardial infarction with a 66% relative risk reduction in in-hospital mortality in both diabetic and non-diabetic patients receiving thrombolytic therapy.

These studies with GIK have clearly validated the metabolic approach to myocardial ischaemia and have raised awareness about the value of a metabolic approach to treating ischaemic cardiac disease. However, as Professor Apstein noted, GIK can only be given intravenously and is only adapted to the acute coronary setting. Specific pharmacological agents that can shift energy metabolism from FFA to carbohydrate utilization can expand the role and clinical setting of the metabolic approach in cardiac disease.

Current and potential applications of metabolic intervention in ischaemic heart disease

Professor Apstein defined several different clinical situations in which a metabolic approach is now appropriate or may potentially be appropriate:

- situations with strong evidence for metabolic intervention:
 - acute myocardial infarction treated with thrombolysis,
 - before and after cardiac surgery, especially for postoperative hypotension and heart failure,
 - angina pectoris;
- situations with some evidence of benefit or with unproven but theoretical potential for benefit from metabolic intervention:
 - cardiogenic shock,
 - during percutaneous transluminal coronary angioplasty (PTCA),
 - in unstable angina with diffuse ischaemia due to severe coronary artery disease,
 - left ventricular hypertrophy with diffuse subendocardial ischaemia,
 - ischaemic cardiomyopathy with congestive heart failure.

Pharmacologic agents that can modify cardiac metabolism in ischaemia have been studied in several different clinical settings. The current evidence, however, is stronger for certain agents than for others.

Pharmacological agents can improve cardiac metabolism in ischaemia

Several metabolic agents, including etomoxir,

dichloroacetate, carnitine, ranolazine and trimetazidine, modify energy substrate utilization. Of these, trimetazidine is the best known and the most widely studied. Professor G. Lopaschuk has definitively shown that trimetazidine stimulates glucose oxidation through an inhibition of fatty acid metabolism in ischaemic hearts. In this way, trimetazidine improves ATP yield during ischaemia. Additionally, this shift in energy substrate preference has the effect of recoupling glycolysis to glucose oxidation, an effect which reduces intracellular acidosis. As a result, Professor Lopaschuk has shown that trimetazidine increases the recovery of cardiac work by 33% and improves cardiac efficiency by 24% in ischaemia and reperfusion.⁶ Trimetazidine also increases the turnover of membrane fatty acids, which avoids the accumulation of fatty acids in the cytoplasm.⁷ This activity gives trimetazidine a pronounced anti-ischaemic effect which has been shown to reduce infarct size in rabbits and to cause an increased recovery of ATP stores in dogs during ischaemia and reperfusion. This anti-ischaemic activity has been equally demonstrated in several well-controlled clinical studies in angina pectoris.

Metabolic intervention in clinical practice: experience in angina pectoris

As Dr G. Jackson (London, UK) observed, myocardial ischaemia is characterized by metabolic abnormalities; it therefore makes sense to tackle a metabolic problem using a metabolic agent. The absence of haemodynamic effects makes these agents even more attractive.

Efficacy and safety of a metabolic agent in monotherapy and combination therapy

Clinical studies with the fatty acid beta-oxidation inhibitor trimetazidine have shown it to be as effective as propranolol^{8,9} or nifedipine¹⁰ in treating angina in terms of clinical and ergometric parameters. Since trimetazidine has no haemodynamic effect, no serious side effects, and requires no dose adjustment in association with other drugs, its use in combination with haemodynamic agents has been tested. As expected because of the totally dif-

ferent modes of action, trimetazidine provides additive benefit — in terms of clinical and ergometric parameters — in combination with a beta-blocker,^{11–13} a calcium channel blocker^{12–15} or a long-acting nitrate.^{12,16} The combination of trimetazidine and propranolol was superior to propranolol and isosorbide dinitrate.¹¹

Role of a metabolic agent in diabetics and the elderly

Efficacious and safe due to its metabolic mode of action, trimetazidine can be prescribed in the elderly and in diabetic patients, populations which may be particularly sensitive to the side effects of haemodynamic drugs in ischaemic heart disease. Adverse drug reactions, including symptomatic bradycardia, heart failure and syncopal episodes, are more common in the elderly. In diabetic patients, beta-blockers can mask the awareness signs of hypoglycaemia while peripheral vasodilatation induced by calcium antagonists can be potentially hazardous due to diabetic autonomic neuropathy. Furthermore, diabetic patients derive most of their cardiac energy from the metabolism of fatty acids, and this is probably a contributing factor to the greater cardiac mortality found in diabetics.¹⁷ Indeed, as Dr Jackson pointed out, given the fact that impaired glucose oxidation may be a cardinal reason for the poor outcome of diabetic patients with coronary artery disease, there is reason to believe that metabolic agents which decrease fatty acid metabolism and increase glucose oxidation may be ideal for use in these patients.

In the TRIMPOL-I diabetic substudy,¹⁸ trimetazidine was shown to be effective and well tolerated in 50 diabetic patients, with no adverse effect on glycaemic control. Trimetazidine significantly improved both clinical and exercise test results. Ninety-eight per cent of patients rated the tolerability of trimetazidine 20 mg as excellent. Self-assessed quality of life never worsened but actually improved in over 75% of patients taking trimetazidine.

Metabolic agents are thus establishing themselves as an extremely valuable strategy in the treatment of angina pectoris. Two recent studies may lend weight to the expanding role of metabolic agents in different settings in the care of patients with coronary artery disease.

Recent studies with metabolic agents in different settings of ischaemic heart disease

Two recent studies demonstrate in extremely varied clinical settings the activity of trimetazidine.

Effects of metabolic manipulation on ischaemic left ventricular dysfunction

Improvement of ischaemia in patients with coronary artery disease is usually measured by the exercise test using chiefly the parameters of time to 1-mm ST-segment depression and total work and exercise duration.

Unfortunately, total work and exercise duration can be influenced by factors that are not purely ischaemic, such as patient motivation and muscular conditioning. It is obviously interesting to have an idea of the improvement in cardiac function itself, especially since ventricular dysfunction is known to precede ischaemic ECG changes. Stress echocardiography is particularly useful in this regard because it can provide an objective correlation between ischaemia and ventricular function. Improvement in wall motion and contractility can be directly visualized to define the true onset of ischaemia, and wall motion is not affected by patient motivation.

Dobutamine stress echocardiography (DSE) can further improve the usefulness of this technique by eliminating the artefactual problems posed by echocardiography during active exercise. Dobutamine is infused at a progressive rate, mimicking the progressive stress of an exercise protocol.

To objectively quantify ventricular function, the wall motion score index (WMSI) can be calculated by grading wall motion on a four-point scale in each of 16 ventricular segments. A grade of 1 is given if the wall motion

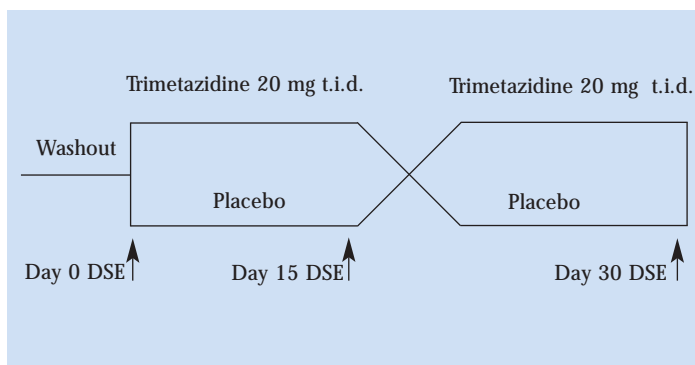


Figure 1. Study design for trimetazidine in coronary artery disease patients with ventricular dysfunction. DSE, dobutamine stress echocardiography.

is normal, 2 if there is hypokinesia, 3 if there is akinesia, and 4 if there is dyskinesia. The average of all segments is taken: a low score signifies a better ventricular function than a high score. During exercise or stress with dobutamine, the WMSI increases as ventricular function deteriorates in patients with ischaemia. The onset of ischaemia corresponds to the worsening of wall motion in a segment by at least one grade; for example, a segment that goes from hypokinetic to akinetic.

Using this technique, Professor S. Chierchia and colleagues studied the effects of the metabolic agent trimetazidine in a randomized, placebo-controlled, crossover study in 15 patients with documented coronary artery disease over two 15-day treatment periods (Figure 1).¹⁹ Ventricular function was assessed both at rest and during stress by DSE before and after the treatment periods with trimetazidine 20 mg and placebo. Compared with placebo, trimetazidine significantly decreased WMSI both at rest and at peak infusion. This is all the more impressive because peak dobutamine infusion dose and time were also significantly higher after the trimetazidine treatment period (Figure 2). Thus, trimetazidine improves resting ventricular function, prolongs time to ischaemic threshold, and preserves wall motion even at a higher cardiac stress.

This study further validates the benefit of a shift in energy substrate metabolism from fatty acids toward glucose and demonstrates the activity of a metabolic agent, trimetazidine, in improving not only the exercise test parameters but also cardiac function itself.

Value of metabolic manipulation during primary PTCA for acute myocardial infarction

Despite the great progress that has been made in recent years in reopening occluded coronary arteries by pharmacological thrombolysis or PTCA, there is clearly an excess early mortality in some patients, the so-called 'early hazard'.²⁰ Since catecholamines, induced by stress, increase circulating FFA levels, FFAs rapidly become the dominant energy substrate during reperfusion. Heparin, which is given in the setting of both PTCA and thrombolysis, also raises FFA levels. As a result, during reperfusion, fatty acid oxidation predominates in the cardiomyocyte while glucose oxidation is almost shut down. Although the cardiomyocyte is trying to rapidly re-establish its ATP

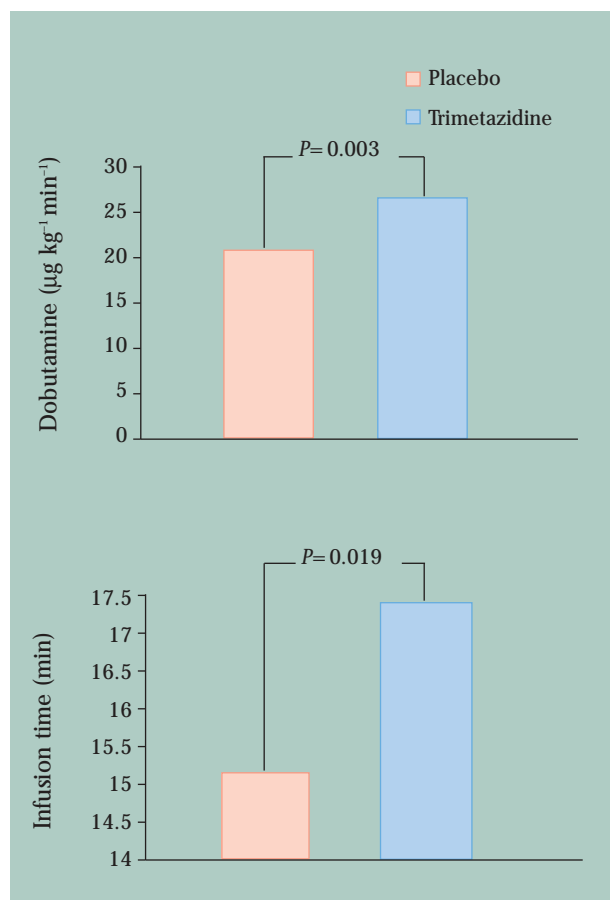


Figure 2. Effect of trimetazidine 20 mg on dobutamine infusion dose and time in coronary artery disease patients with ventricular dysfunction.

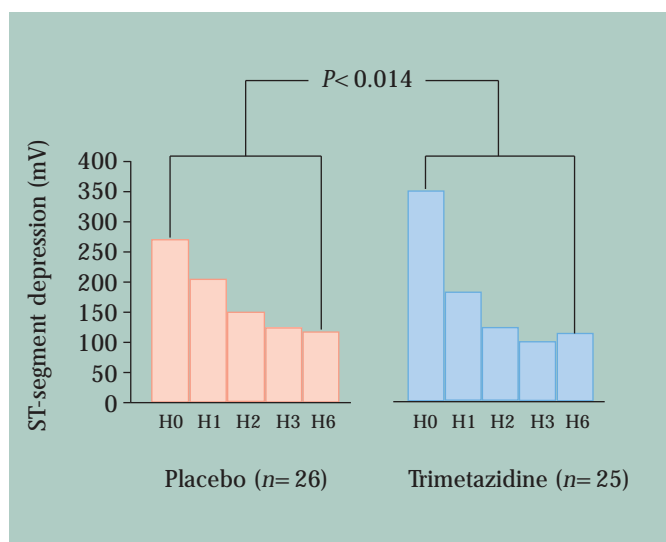


Figure 3. Earlier and more marked return to baseline of ST-segment elevation with trimetazidine ($P < 0.014$). H, hour.

stores, the excessive fatty acid oxidation leads to an uncoupling between glycolysis and glucose oxidation.

Thus, a likely role for metabolic intervention during primary PTCA for acute myocardial infarction would be to lessen the metabolic consequences of ischaemia and reperfusion by shifting energy substrate metabolism from fatty acids to glucose.

Although the exact nature and aetiology of reperfusion injury remain difficult to define, it is apparent that among patients with complete angiographic recanalization (TIMI grade 3 flow) of the coronary arteries, there is a wide spectrum of clinical outcomes. As shown by the group from Zwolle²¹ who evaluated a population having undergone successful primary PTCA, patients with a complete return of the ST-segment to baseline on the standard 12-lead ECG had the best outcome, while patients with incomplete resolution of ST-segment elevation had an increased relative risk of death, and those with no ST resolution had the worst outcome of all.

During the ESC symposium, Professor P.G. Steg (Paris, France) presented results from a multicentre, double-blind, randomized, placebo-controlled study to evaluate the effect of a shift in energy substrate metabolism from fatty acid to glucose on signs of reperfusion injury

in 94 patients undergoing PTCA for acute myocardial infarction. Patients received either a placebo IV bolus or an IV bolus of trimetazidine 40 mg followed by a continuous infusion of 60 mg over 48 h. Using a continuous vectorcardiographic system (MIDA), it was shown that trimetazidine significantly increased the rate of return to baseline of the ST-segment after primary PTCA (Figure 3). Furthermore, there was a lower frequency of ST exacerbation, although this did not attain statistical significance (23 vs 42%, $P = 0.11$).

It is probable that the improved electrocardiographic recovery seen with trimetazidine after primary PTCA is due to a more rapid reconstitution of ATP stores during reperfusion.

Conclusion

After decades of laboratory research and many false starts, metabolic therapies are enjoying a resurgence of interest. While GIK has paved the way and has shown its utility in acute myocardial infarction, pharmacological agents have a number of advantages, including oral administration and an excellent safety profile, both of which allow for broader clinical utilization. Trimetazidine, the most extensively studied metabolic agent in the clinical setting, is now available in most countries for the treatment of angina pectoris. Based on a wholly rational approach to treating heart disease, metabolic intervention is reshaping therapeutic strategies in ischaemic heart disease. ■

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Myocardial substrate metabolism imaged by PET

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Introduction

Recent methodological developments have provided us with the possibility for quantitative characterization of physiological and pathophysiological processes *in vivo* in humans. Positron emission tomography (PET), single photon emission tomography (SPET) and nuclear magnetic resonance (NMR) can be used to study myocardial energy metabolism non-invasively. The energy metabolism in the myocardium represents a link between oxygen delivery and functional performance. The quantitation of myocardial glucose utilization, fatty acid uptake and oxidation, perfusion, oxygen consumption, contractile function as well as characterization of cardiac presynaptic and postsynaptic neuronal activity are now possible. This allows study of the effects of nutritional interventions, medication, hormonal and neural activity as well as disease processes on the metabolism and function of the human heart.

Myocardial energy metabolism

Free fatty acids (FFA), glucose and lactate are the main fuels of the heart.^{1,2} Ketone bodies and amino acids are used to a lesser extent. Several factors affect the use of an individual substrate. These include the plasma concentration of the substrate and alternate substrates, myocardial blood flow and oxygen supply, hormone levels and regulatory effects of metabolites arising during degradation of substrates.¹

In the fed state, after a high-carbohydrate meal when insulin concentrations are increased, the use of glucose accounts for ~70% and lactate for ~30% of the oxygen uptake of the heart.¹ Conversely, in the fasted state the use of glucose accounts for ~30%, lactate for ~10% and FFA for ~60–70% of the oxygen uptake of the heart.¹ The uptake

of ketone bodies is concentration-dependent and their use is increased in uncontrolled diabetes and starvation.² Amino acid oxidation is enhanced after a protein-rich meal, but their use accounts for a small fraction of total oxygen consumption.²

Myocardial blood flow and oxygen consumption are tightly coupled, and changes in the coronary flow rate control the delivery of oxygen. Myocardial oxygen consumption reflects almost totally the overall energy demand of the heart and is determined by heart rate, systolic wall stress, contractility, myofibre shortening and the oxygen demand necessary to maintain basal myocardial metabolism.³ At rest, human myocardium is characterized usually by a blood flow of 80–100 ml 100 g⁻¹ min⁻¹ and oxygen consumption of ~10 ml 100 g⁻¹ min⁻¹.^{1,4}

Striking changes occur in substrate utilization during myocardial ischaemia. With the decline in oxygen delivery, oxidative metabolism decreases markedly but still remains the predominant (over 90%) source of residual adenosine triphosphate (ATP) production.¹ Since β -oxidation of FFA is very sensitive to ischaemia, the principal fuel-contributing substrate for the citric acid cycle during ischaemia is glucose. During mild ischaemia, lactate and other products are washed out from the cell and glycolysis can be maintained. However, during severe ischaemia, lactate and protons will accumulate in the myocardium and glycolysis is inhibited, which may contribute to lethal injury.¹

Imaging techniques to study myocardial energy metabolism *in vivo*

Imaging techniques are based on radioactive tracers or nuclear magnetic resonance. With the isotope techniques, the labelled compounds are administered to the subjects, and their kinetics can be studied using PET or SPET.

Positron emission tomography (PET)

PET enables us to study regional myocardial blood flow, glucose and fatty acid metabolism and oxygen consumption non-invasively in research as well as in clinical practice. In principle, an unlimited amount of compounds can be labelled with positron emitters. Based on the distribution and kinetics of the compounds studied by PET, quantitative metabolic parameters can be derived. The advantages of PET are non-invasive quantitation of regional metabolic rates in tissues with high resolution and sensitivity.^{5,6} At present, PET is the only technique that permits non-invasive measurement of regional myocardial energy substrate utilization in absolute terms.

Glucose metabolism

[¹⁸F]-2-fluoro-2-deoxy-D-glucose (¹⁸F]FDG) is a fluorine-18-labelled glucose analogue, which is transported to heart cell and phosphorylated. In contrast to glucose, it cannot be further metabolized and it remains trapped in the cytosol.^{7,8} Using [¹⁸F]FDG it is possible to study glucose transport and phosphorylation but not further metabolism.⁹ By using simple graphical analysis¹⁰ the glucose uptake rates in the myocardium can be calculated.

The method has been widely used to study myocardial glucose metabolism in various conditions such as coronary heart disease, diabetes, hypertension and cardiac failure. An

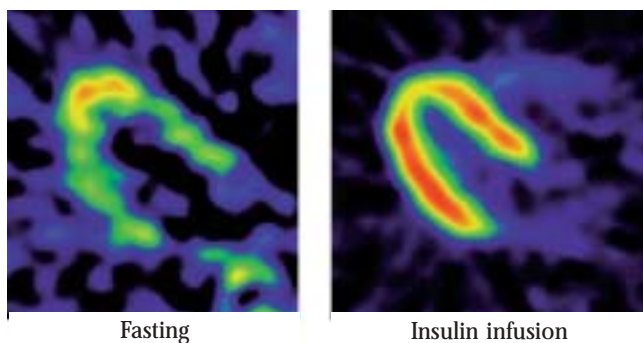


Figure 1. Transaxial 10 min PET images obtained 50 min after FDG injection during fasting (left) and during an insulin clamp (right). Increased FDG uptake is seen in the hibernating anterior wall during fasting but not during insulin stimulation. However, in a quantitative analysis, the hibernating anterior myocardium also responded strikingly to insulin (sixfold increase in glucose uptake). Reproduced from Mäki et al.¹¹

example of the potential of the method is given in a recent study about the regulation of glucose metabolism in the hibernating myocardium in humans (Figure 1).

Free fatty acid (FFA) metabolism

[1-¹¹C]-palmitic acid has been traditionally used as a natural tracer of FFA metabolism by PET. The rapid washout of the tracer is assumed to be associated with the oxidative metabolism of fatty acids and the slower washout with the incorporation to the myocardial triglyceride pool.^{2,12} However, [1-¹¹C]-palmitic acid is distributed between several tissue pools with variable turnover rates, which makes it mainly useful as a qualitative tracer in PET studies.¹² Recently, Bergmann et al.¹³ introduced a model to quantitate [1-¹¹C]-palmitic acid utilization with PET. This model is still complicated and requires simultaneous measurement of myocardial blood flow, which limits its use.

¹⁸F-labelled 6-thia-hepta-decanoic acid ([¹⁸F]FTHA) has recently been used to study fatty acid metabolism in the human heart.¹⁴⁻¹⁸ [¹⁸F]FTHA is a false long-chain fatty acid substrate and inhibitor of fatty acid metabolism.¹⁹ After transport into the mitochondria, it undergoes initial steps of β -oxidation and is thereafter trapped in the cell because further β -oxidation is blocked by sulphur heteroatom. Accumulation of [¹⁸F]FTHA has been suggested to be mainly tracing FFA oxidation in the heart.^{19,20} A similar graphical analysis such as is used with [¹⁸F]FDG has been successfully applied in quantitation of [¹⁸F]FTHA uptake in the heart^{14,17,18} (Figure 2).

Oxidative metabolism

The tracers [1-¹¹C]acetate and [¹⁵O]O₂ have been used for measuring myocardial oxygen consumption with PET in humans.^{4,21} [1-¹¹C]acetate has been widely used, but until recently this tracer has provided only an index of oxidative metabolism rather than absolute quantification. A new model for [1-¹¹C]acetate as a tracer of myocardial oxygen consumption has been introduced. This model allows quantification and has been applied in humans.²¹ The most substantial drawback of the method is the lack of information on pool sizes of metabolites.

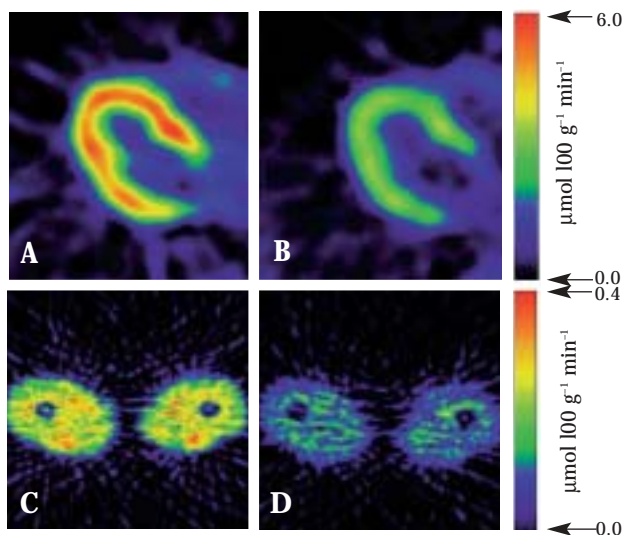


Figure 2. Examples of FFA uptake quantitative images measured using [^{18}F]FTHA. The myocardial mid-ventricular transaxial slice and cross-section of the femoral region measured in the fasting state (A, C) and during an insulin clamp (B, D) in the same subject. Reproduced from Mäki et al.¹⁸

The model employed using [^{15}O]O₂ also requires measurements of myocardial blood volume and flow, which are needed for corrections of spillover of the cardiac chamber, and corrections of wall motion and wall thickness.⁴ The model provides absolute values of myocardial regional oxygen consumption and extraction fraction. This model has been successfully applied in healthy humans⁴ and recently in patients with hypertension-induced left ventricular hypertrophy.²²

Single photon emission tomography (SPET)

SPET provides an alternative to PET at a lower cost. With SPET it is possible to detect radiation emitted by gamma-emitting isotopes, such as ^{99m}Tc, ²⁰¹Tl and ¹²³I, which have longer half-lives (6–72 h) than those used with PET. However, the sensitivity and resolution of SPET are not as high as those of PET. Moreover, attenuation and scatter corrections are difficult with SPET and thus absolute quantitation is not currently possible.²³

SPET has been successfully used to study myocardial FFA metabolism. Various FFA ligands have been applied and semi-quantitative analysis of FFA uptake and oxidation has been performed.²⁴

Nuclear magnetic resonance (NMR)

Use of ³¹P NMR to measure energy metabolism can provide information on ATP, creatine phosphate, inorganic phosphates, sugar phosphates and intracellular pH. As for its limitations, it provides information only about ATP levels and not about the rates of production or utilization of ATP. In addition, with ³¹P NMR measurement no data are obtained about which metabolic pathway produces the high-energy phosphates.⁶ NMR and ¹³C-labelled substrates can be used in measurements of tricarboxylic acid cycle activity (mainly glutamate pool), glucose uptake and glycogen turnover. NMR can be also used in *in vivo* studies but the high costs and complexity of quantitative analysis currently limit its use in this area.⁶

Clinical applications of metabolic imaging

The assessment of myocardial viability is a clinically important issue for the management of patients with post-ischaemic left ventricular dysfunction and particularly for those with severe impairment of left ventricular function.

Clinical investigations have demonstrated the utility of [^{18}F]FDG PET for detection of myocardial viability.^{25–29} In addition, [^{18}F]FDG imaging is able to identify patients at increased risk of having an adverse cardiac event or death.³⁰ The detection of viable myocardium by PET is based on the demonstration of preserved metabolic activity in regions of severely underperfused and dysfunctional myocardium. SPET imaging with FFA tracers has also been used as a clinical tool in the detection of myocardial viability.²⁴

At present, increased [^{18}F]FDG uptake relative to flow is regarded as the gold standard to predict viability and functional recovery and is superior to dobutamine echocardiography or SPET imaging in patients with severe left ventricular dysfunction.²⁹ ■

In Short

There are currently several imaging methods that can be successfully used to study myocardial energy metabolism. PET, SPET and NMR can all be used to study certain areas of this topic. The methods provide a powerful way to increase our understanding of cardiac physiology and the mechanisms of disease. Due to the unique features and large number of existing tracers, PET appears to provide the most complete insight into myocardial energy metabolism in vivo. In the detection of myocardial viability, PET is regarded as the gold standard. The future role of these methods in clinical cardiology remains unclear and further studies are needed. Novel applications also depend on improved instrumentation and development of new tracers.

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