

DIABETES AND CARDIOVASCULAR DISEASE: THE ROAD TO CARDIOPROTECTION

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Heart 2005;91:1621–1625. doi: 10.1136/hrt.2005.063008

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Diabetes is a metabolic disease whose incidence and prevalence has significantly increased in recent decades, mainly because of an increase in type 2 diabetes, which represents almost 90% of all cases of diabetes. The World Health Organization estimates that, by 2025, there will be 300 million diabetic patients (5.4% of the world population). Older patients are most affected by diabetes, as the disease prevalence increases with age, at least up until 75 years. The progressive aging of the global population could explain about half of the predicted increase of diabetic patients in the near future.¹

Macrovascular disease (coronary artery disease, stroke, and peripheral vascular disease) is responsible for the majority of morbidity and mortality associated with type 2 diabetes. In the UK prospective diabetes study (UKPDS),² the 10 year risk of all macrovascular complications was four times that of microvascular complications. Coronary artery disease is the leading cause of death among diabetic patients, and women have a higher cardiovascular risk than men.

Diabetics have a worse prognosis after an acute coronary syndrome than non-diabetic patients. This was documented both for ST elevation and non-ST elevation acute myocardial infarction (AMI). The Framingham heart study has also shown a higher mortality rate, as well as reinfarction and heart failure rates, in diabetic patients, both during the acute phase and in the post-infarction period, even after data adjustment for other risk factors.¹ Diabetic patients may, therefore, derive a greater benefit from therapies shown to be effective in treating ischaemic heart disease.

The challenge is, therefore, to protect the heart of diabetic patients more effectively. Can we achieve this goal? To answer this question we must first understand why patients with diabetes have a higher cardiovascular risk.

MECHANISMS FOR CARDIOVASCULAR DAMAGE AND PROTECTION IN THE DIABETIC HEART

Preconditioning

Preconditioning is the mechanism by which brief periods of sublethal ischaemia can render a heart more resistant to subsequent periods of more prolonged ischaemia (table 1).

In animal studies, infarct size was linearly related to blood glucose concentration during acute hyperglycaemia and during diabetes, in the presence or absence of preconditioning stimuli. Increases in serum osmolality caused by administration of raffinose did not increase infarct size or interfere with the ability of preconditioning to protect against infarction. These results indicate that hyperglycaemia is a major determinant of the extent of myocardial infarction.

Other studies showed different findings. Using a rabbit infarct model, it was shown that there was a significant positive correlation between area at risk and infarct size in both diabetic and non-diabetic hearts and, for a given area at risk, diabetic rabbits developed smaller myocardial infarctions than controls. In additional experiments, hyperglycaemia induced by intravenous glucose infusion in non-diabetic rabbits did not protect the ischaemic myocardium. It was concluded that diabetes in the rabbit induces a chronic and metabolic form of preconditioning.

Animal studies have shown that ischaemic preconditioning does not protect hearts from obese or lean type 2 diabetic animals. However, the susceptibility of the type 2 diabetic myocardium to ischaemic damage is lower than in non-diabetic hearts. In a study performed in dogs, infarct size was directly related to blood glucose concentrations in diabetic animals, but this relationship was abolished by higher concentrations of isoflurane. The results indicate that blood glucose and end tidal isoflurane concentrations are important determinants of infarct size during anaesthetic induced preconditioning.

The activation of pro-survival kinases, such as Akt and Erk1/2 (which have been termed the reperfusion injury salvage kinase (RISK) pathway),³ at the time of reperfusion, has been demonstrated to confer powerful cardioprotection against myocardial ischaemia–reperfusion injury. Evidence exists suggesting that the cardioprotective phenomena of ischaemic preconditioning and the recently described ischaemic postconditioning exert their cardioprotective effects

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Table 1 Preconditioning: key points

- ▶ Preconditioning is the mechanism by which brief periods of sublethal ischaemia can render a heart more resistant to subsequent periods of more prolonged ischaemia
- ▶ The RISK pathway is important in preconditioning
- ▶ Mitochondria are also involved in ischaemic preconditioning
- ▶ Angiotensin II blockade mimics preconditioning
- ▶ Diabetes also affects late preconditioning

RISK, reperfusion injury salvage kinase.

through the recruitment of the RISK pathway,³ at the time of reperfusion, and that the protection in these settings is mediated through the inhibition of mitochondrial permeability transition pore opening at this time.⁴

Studies show that the differential pattern of protein kinase cascade activation in the diabetic heart might account for the modulation of their response to ischaemia. It is also known that the protective effect of ischaemic preconditioning against myocardial ischaemia may come from improved energy balance. Under ischaemic conditions, more glycolytic metabolites are produced in the diabetic rats, and preconditioning inhibited these metabolic changes similarly in both groups. This suggests that diabetic myocardium may benefit more from preconditioning than normal myocardium, possibly as a result of reduced production of glycolytic metabolites during ischaemia and concomitant attenuation of intracellular acidosis.

Protein kinase C (PKC) has also been implicated in ischaemic preconditioning. Several studies have shown that PKC activation may contribute to the increased resistance of the diabetic heart to ischaemia–reperfusion injury.

Angiotensin II alters specific modulators of ischaemic injury, such as PKC and calcium transport. Exposure of glucose treated cells to angiotensin II during the pre-hypoxic period blocks glucose mediated cardioprotection. The reversal of hyperglycaemic preconditioning was associated with enhanced accumulation of calcium during hypoxia, an effect prevented by inhibition of the Na⁺/H⁺ exchanger and the T type calcium channel.

Diabetes and the resulting hyperglycaemia may also interfere with the cardioprotective effect of ischaemic late preconditioning, a phenomenon similar to preconditioning, but which is induced by a brief period of myocardial ischaemia 24 hours before ischaemia–reperfusion. Hyperglycaemia before and during the ischaemic period tended to increase infarct size and blocked cardioprotection by late preconditioning. Short term insulin treatment does not restore the cardioprotective effects of late preconditioning. Therefore, acute hyperglycaemia and diabetes block the cardioprotection induced by late preconditioning and cardioprotection is not restored by short term insulin treatment.

In another study performed to determine the effects of preconditioning on injury and expression of heat shock protein 70 in diabetic rat hearts, it was shown that, in addition to a greater susceptibility to ischaemic insults, the delayed cardioprotection of preconditioning was lost, and that this could at least partially be due to impaired synthesis of stress inducible heat shock protein 70 in diabetic rats.

Other mechanisms

Ischaemic heart from the mildly diabetic animal resists the accumulation of calcium, a major cause of necrosis. However,

the severely diabetic heart is more susceptible to ischaemia because of enhanced oxidative stress and eicosanoid mediated injury, accumulation of undesirable metabolic products, vascular dysfunction, and impairment in glycolytic ATP generation.

On the other hand, a number of pathogenic mechanisms can worsen the ischaemic injury by the superimposition of hypertension on diabetes. First, the coexistence of the two diseases leads to cardiac hypertrophy, enhancing susceptibility to ischaemic damage. Second, hypertension is associated with activation of neurohumoral mechanisms capable of exacerbating myocardial injury after an ischaemia–reperfusion insult. Third, the severity of the diabetic cardiomyopathy worsens when hypertension coexists. Diabetes and glucose intolerance may interact with certain survival pathways, through the activation of PKC and the downregulation of the Na⁺/H⁺ exchanger. Hypertension may also interact with these pathways through β adrenergic induced activation of PKC and salt induced alterations in the Na⁺/H⁺ exchanger. Elevations in afterload interfere with the ability of glucose intolerant and hypertensive rats to activate these and other survival pathways, thus increasing cell death.⁵

In diabetes mellitus, locally produced angiotensin II may lead to oxidative damage. Thus, angiotensin II receptor blockade may work as a cardioprotective mechanism by blocking the cardiac renin–angiotensin system.⁶

It has also been shown that the function and density of ATP sensitive potassium (KATP) channels, essential in ischaemic preconditioning, is altered in diabetic rat ventricular myocytes. Blockade of these channels by some sulfonylureas may worsen myocardial ischaemia by preventing preconditioning and may be responsible for the high cardiovascular mortality associated with diabetes.

In diabetics, excessive ethanol ingestion can further increase the cardiovascular risk. Ethanol is metabolised to acetaldehyde, a two-carbon carbonyl compound that can react with nucleophiles to form covalent addition products (Amadori products). These products are the precursors to the so called advanced glycation end products (AGE), which accumulate over time on plasma lipoproteins and vascular wall components and play an important role in the development of diabetes related cardiovascular disease.

STRATEGIES FOR PROTECTING THE DIABETIC HEART

Lifestyle changes

Cardioprotection by regular exercise may be exerted synergistically through improvement in many risk factors, in addition to direct effects on the myocardium, resulting in cardioprotection against ischaemia–reperfusion injury (table 2). Cardioprotective effects may include the development of collateral coronary arteries, induction of myocardial heat shock proteins, and improved cardiac antioxidant capacity.

Diabetic rats fed with a low ethanol diet showed a decrease in Hb-AGE when compared with diabetic controls. Circulating concentrations of HbA1c were unaffected by ethanol, pointing to the specificity of this action. These data suggest a possible mechanism for the so called “French paradox”, the cardioprotection conferred by moderate ethanol ingestion.

Hypoglycaemic drugs

Large clinical trials data

In UKPDS,⁷ type 2 diabetes patients were randomised to conventional versus intensive treatment (sulfonylureas or

insulin, aiming at a fasting glycaemia below 108 mg/dl); in a subgroup of obese patients, metformin was used as the primary therapeutic agent. This study has shown a significant decrease of microvascular (but not macrovascular) complications with an intensive treatment regimen. Subgroup analysis showed that metformin decreased macrovascular risk in obese patients.

The DIGAMI (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) study enrolled patients with AMI who received insulin and glucose intravenously or conventional treatment. One year follow up results showed a 30% lower mortality rate in the intensive treatment group. Subsequent studies suggested that treatment with intravenous insulin can have positive effects upon several aspects of the disease (besides glucose values).⁷

In DIGAMI 2, three treatment strategies were compared: acute insulin–glucose infusion followed by insulin based long term glucose control; insulin–glucose infusion followed by standard glucose control; and routine metabolic management according to local practice. The primary end point was all cause mortality. DIGAMI 2 did not support the finding that an acutely introduced, long term insulin treatment improves survival in diabetic patients following myocardial infarction when compared with a conventional management at similar levels of glucose control, or that insulin based treatment lowers the number of non-fatal myocardial reinfarctions and strokes.⁸ However, the DIGAMI 2 investigators stress that an epidemiological analysis confirms that the glucose value is a strong, independent predictor of long term mortality in these patients, emphasising that glucose control seems to be important in their management.

Other data

Using an animal model of reperfusion after low flow ischaemia, it was shown that insulin perfusion increased pre-ischaemic myocardial glycogen content in both diabetic and control hearts. Recovery of cardiac performance and myocardial creatine phosphate concentrations in the absence of insulin was greater in the diabetic hearts during reperfusion. Insulin perfusion improved recovery of cardiac performance and elevated creatine phosphate concentrations in both diabetic and control hearts. Results demonstrate greater cardioprotection against ischaemia/reperfusion injury in diabetics and with insulin perfusion.

Insulin mediated cardioprotection is independent of the presence of glucose at reperfusion. Moreover, the cell survival benefit of insulin is temporally dependent, in that insulin administration from the onset of reperfusion and maintained for either 15 minutes or for the duration of reperfusion reduced infarct size. In contrast, protection was abrogated if insulin administration was delayed until 15 minutes into reperfusion.⁹

In patients with type 2 diabetes, the use of sulfonylurea drugs may be harmful by preventing endogenous cardioprotective mechanisms; sulfonylurea drugs increased early mortality in diabetic patients after direct angioplasty for AMI. However, not all sulfonylureas are equal. Glimepiride is pharmacologically distinct from glibenclamide because of differences in receptor binding properties, which could result in a reduced binding to cardiomyocyte KATP channels. Results show that either acute loading or long term use of sulfonylureas may abolish the preconditioning response in humans. In fact, like ischaemic animals, diabetics seem to be

Table 2 Cardioprotection provided by the different hypoglycaemic agents: key points

- ▶ Exercise is an important part of the treatment
- ▶ Tight glucose control is essential
- ▶ Metformin decreases macrovascular complications in obese patients
- ▶ Sulfonylureas may have different impacts in cardioprotection
- ▶ Glitazones are important in the cardioprotection of patients without left ventricular dysfunction

much more cardiovascularly sensitive to sulfonylureas. Selective blockade of myocardial KATP channels with glibenclamide at therapeutic doses is associated with significantly impaired cardioprotection and, thereby, contributes to this increase in mortality. Unlike glibenclamide, glimepiride does not block the mitochondrial KATP channels of the myocardium. This finding is especially important in older persons with diabetes, in whom preconditioning has been shown to be impaired by attenuated activation of KATP channels. Acute or chronic administration of glibenclamide, but not glimepiride, induces potentially harmful cardiovascular effects in both diabetic and non-diabetic patients with coronary artery disease.¹⁰ In clinical studies, glimepiride was generally associated with a lower risk of hypoglycaemia and less weight gain than other sulfonylureas.

Are these data clinically relevant? In a study involving 602 diabetic and non-diabetic patients admitted for AMI, in-hospital mortality in diabetic patients was higher than in non-diabetic patients suffering AMI, regardless of whether or not they had been treated with sulfonylureas.

Therefore, despite clear evidence for an impairment of ischaemic preconditioning by sulfonylureas from various animal studies and from indirect experimental studies in humans, there is still little evidence these agents lower cardiovascular mortality in patients with type 2 diabetes mellitus. Glibenclamide—a sulfonylurea with well documented negative effects on ischaemic preconditioning under experimental conditions—failed to alter cardiovascular mortality in the UKPDS.² Taking smaller follow up studies into consideration, sulfonylureas do not appear to worsen the prognosis of patients with type 2 diabetes after AMI. In contrast, sulfonylurea treatment may increase mortality in patients with type 2 diabetes when subjected to elective or emergency balloon angioplasty.¹⁰

This early risk is not explained by ventricular arrhythmias, but may reflect deleterious effects of sulfonylurea drugs on myocardial tolerance for ischaemia/reperfusion. However, for surviving patients, sulfonylureas were not associated with increased risk of serious late adverse events.¹¹

To clarify these effects, a double blind placebo controlled study was performed; the period of total coronary occlusion during balloon angioplasty of high grade coronary artery stenoses was used to compare the effects of glibenclamide and glimepiride. Mean ST segment shifts decreased in the glimepiride group, unlike the glibenclamide group. Accordingly, time to angina during balloon occlusion increased in the glimepiride group and remained unchanged in the glibenclamide group, showing that glimepiride maintains preconditioning, while glibenclamide might prevent it.

Another study assessed the effects of treatment with glibenclamide or insulin on the extension of left ventricular

dysfunction induced by acute ischaemia. Each patient was randomly assigned to either insulin or glibenclamide. Treatment was crossed over after 12 weeks and maintained for another 12 weeks. Results indicated that ischaemic myocardial dysfunction induced by dipyridamole infusion is less severe during treatment with insulin than with glibenclamide. Restitution of a preconditioning mechanism in insulin treated patients may be the potential beneficial mechanism.

Glitazones—peroxisome proliferator activated receptor γ agonists—act as insulin sensitisers. Data mainly from preclinical studies suggest that glitazones protect the heart from acute ischaemia/reperfusion injury and also might attenuate cardiac remodelling and heart failure. Mechanisms involved in this cardioprotection are multifactorial and not yet completely understood. Glitazones decrease triglycerides, fibrinogen, visceral fat, blood pressure, and microalbuminuria, and improve vascular function. However, fluid retention by glitazones may induce or worsen congestive heart failure in diabetics with left ventricular dysfunction.

Cardiovascular drugs

β Blockers have an established role in cardioprotection, both in primary and secondary preventive studies, and there is evidence that their cardioprotection is even greater in diabetics.¹² Common belief that β blockers increase the complication rate in diabetes and worsen glycaemic control has no scientific basis and should not limit their use in diabetics with coronary artery disease.

As both angiotensin II and renin–angiotensin system activation are important deleterious factors in diabetes, it is not surprising that angiotensin converting enzyme (ACE) inhibitors confer a notable survival benefit in diabetics with heart failure¹² and/or coronary artery disease,¹³ as emphasised by current guidelines.¹⁴

Candesartan, an angiotensin II receptor blocker, lowers blood pressure and preserves left ventricular diastolic function in diabetic rat hearts. It also reduces the thickening of the capillary basement membrane, decreasing cardiomyocyte diameter, increasing matrix metalloproteinase-2 activity, and decreasing inflammatory cytokines. These mechanisms may explain why, in diabetics with heart failure¹⁵ and coronary artery disease,¹⁶ angiotensin II receptor blockers are endorsed by current guidelines.

Diabetic dyslipidaemia is characterised by moderately high concentrations of serum cholesterol and triglycerides, small and dense low density lipoprotein (LDL) particles, and low high density lipoprotein (HDL) cholesterol concentrations. Recent clinical trials have demonstrated the benefits of statins in both diabetic and non-diabetic patients, thus supporting aggressive treatment of diabetic dyslipidaemia for coronary artery disease prevention. It is believed that an important part of the derived benefit in diabetics may be due to the pleiotropic effects of statins (improvement in endothelial function, and anti-inflammatory and anti-oxidant effects).

Other strategies

Studies suggest that the attenuation of the protection afforded by ischaemic preconditioning in diabetic rats may be related to the decrease in calcitonin gene related peptide release. Others have demonstrated that the myocardial protective effect induced by heat stress could not be extended

to the diabetic rat and that it seems to be unrelated to the heat shock protein 70 concentration.¹⁷ These data may be used in the future to improve cardioprotection in the diabetic population.

Can we achieve preconditioning in the human diabetic heart?

In a study to assess the impact of diabetes on ischaemic preconditioning, patients with a first anterior wall AMI who underwent emergency catheterisation less than 12 hours following onset of chest pain were studied: 490 patients without diabetes and 121 patients with non-insulin treated diabetes. Prodromal angina limited infarct size, enhanced recovery of left ventricular (LV) function, and improved survival in non-diabetics with AMI. Such beneficial effects were not observed in diabetics, suggesting that diabetes might prevent preconditioning.¹⁸

In an echocardiographic substudy of the HEART (early afterload reducing therapy) trial, the hypothesis that prior angina pectoris confers protection from remodelling after AMI was studied. LV dilation from days 1 to 90 was used as a measure of LV remodelling. In patients with angina during the three months preceding AMI, LV volume change and maximal creatine kinase were significantly lower. These protective effects may be secondary to recruitment of collaterals or ischaemic preconditioning of the myocardium and appear to be attenuated in diabetics.¹⁹

A prospective randomised study performed in diabetics undergoing coronary artery bypass graft surgery showed preoperative administration of isoflurane had a cardioprotective effect. Such an effect was prevented by glibenclamide, but could be restored in diabetics by preoperative shift from glibenclamide to insulin.

Studies performed in human tissue have investigated the effects of ischaemic preconditioning on diabetic and failing human myocardium and the role of mitochondrial KATP channels on the response in these diseased tissues. Ischaemia caused similar injury in both normal and diseased tissue. Preconditioning did not prevent the effects of ischaemia in diabetics. In the diazoxide treated groups, protection was mimicked in all groups except the diabetics. Interestingly, glibenclamide abolished protection in non-diabetic and diet controlled diabetic groups and did not affect diabetics receiving KATP channel blockers or insulin. These results show that failure to precondition the diabetic heart is caused by dysfunction of the mitochondrial KATP channels, and that the mechanism of failure in the diabetic heart lies in elements of the signal transduction pathway which are different from the mitochondrial KATP channels.²⁰

CONCLUSIONS

In recent years, the importance of diabetes as a cardiovascular risk factor has increased. The myocardial metabolism of diabetic patients is significantly impaired, due to several factors that determine a significant decrease in the mechanisms that protect the heart from insults, such as preconditioning, in regard to ischaemia/reperfusion injury. In order to change this reality, recent emphasis has been placed on optimising diabetes treatment (namely using insulin and cardioprotective oral hypoglycaemic drugs), as well as anti-ischaemic therapy. In the near future, knowledge from basic research—namely, improvement strategies for pro-survival pathways—may offer diabetic patients a

significant improvement in cardioprotection, thus decreasing the morbidity and mortality associated with diabetes.

Additional references appear on the *Heart* website—<http://www.heartjnl.com/supplemental>

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In compliance with EBAC/EACCME guidelines, all authors participating in Education in *Heart* have disclosed potential conflicts of interest that might cause a bias in the article

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