Review

Reduction of infarct size *An attractive concept: useful—or possible—in humans?*

W KÜBLER, A DOOREY*

From the Abteilung Innere Medizin III (Kardiologie), University of Heidelberg, Germany

The extent of myocardial infarction—that is, the amount of necrotic myocardial tissue—is a main determinant of early and late prognosis in patients with acute myocardial infarction.¹

A vast number of animal experiments have been carried out in this field which have greatly contributed to our understanding of myocardial infarction, infarct extension, and the resulting haemodynamic, metabolic, and electrophysiological consequences. In addition, several careful clinical studies have been carried out. Despite these efforts spanning more than a decade, there is still no generally accepted method of reducing infarct size that is available for routine clinical use. Apart from the methodological problems of such research this dilemma seems to be predominantly due to biological, and especially metabolic, problems, which are discussed briefly in this paper.

Reduction in infarct size has been sought through many different approaches. In essence, they can be classified according to three main aims: (a) the reduction of myocardial energy demands; (b) the stimulation of glycolytic energy production; and (c) reperfusion in order to re-establish the blood supply and hence oxygen availability.

Reduction of myocardial energy demands

Although for varied reasons the results of many experimental infarct reduction studies are controversial, it is nowadays widely accepted that reduction in myocardial energy demands by the administration of beta blockers, nitrates, or calcium antagonists can lead to a delay in the development of irreversible ischaemic damage in the affected area.^{2,3}

It seems doubtful, however, that these positive results from animal experimentation can also be expected to apply to the clinical situation of a patient

with acute myocardial infarction. According to enzyme distribution patterns and metabolic profiles of high energy phosphates and glycolytic intermediates in early ischaemia, energy metabolism in the ischaemic human myocardium follows the same principles as, for example, in the canine heart.⁴ During the early phase of ischaemia mainly creatine phosphate (CP) breaks down, coincident with and probably closely related to the development of diastolic pump failure.⁵ This decline in CP can be ameliorated by a reduction in myocardial energy demands—for example, by cardioplegia.⁶ In the beating heart in situ, however, this period during which amelioration is possible lasts for only a few minutes. Thereafter the energy deficit in ischaemic myocardium—that is, net adenosine triphosphate (ATP) breakdown—can be influenced by a reduction in myocardial energy demands only to a very minor degree.⁶ As a patient with acute myocardial infarction will generally be under medical care at the earliest 30–60 minutes after the onset of symptoms—that is, after the onset of myocardial ischaemia—probably all interventions used to delay the infarcting process can be instituted only after CP breakdown has appreciably progressed. The effect of these interventions, therefore, has to be presumed to be greatly attenuated.

Although the experimental results have not always been convincingly positive, and the foregoing theoretical considerations even suggest an attenuated effect in patients, several well conducted studies in humans indicate a reduction in infarct size after the administration of beta blockers^{7–9} or nitrates.¹⁰ In evaluating these results reduced enzyme washout from the infarcting area (underestimation of infarct size), consequent to pharmacologically reduced energy demands and hence reduced perfusion in and around the ischaemic zone, has to be taken into account. At least one study included non-enzymatic (electrocardiographic) criteria of infarct size as well.⁹

Stimulation of anaerobic energy production

Insufficient myocardial oxygen supply leads via the

*Permanent address: Cardiology Division, Harvard Medical School, Brigham and Women's Hospital, Boston, Ma, USA.

Accepted for publication 7 August 1984

pasteur effect to an activation of anaerobic glycolytic energy production. Based on the activities of glycolytic enzymes in the human or canine heart—as assessed in vitro under nearly “optimal” conditions—glycolytic rates of flux could be expected to be sufficient to cover myocardial energy demands under ischaemic conditions. In vivo, however, such high rates of flux have never been measured, especially not during ischaemic conditions. This is due to the multistage regulation and control of the glycolytic chain. (This control of the metabolic chain is of great physiological importance, since it enables almost instantaneous adaptation of the rate of flux to the actual energy demands.) The main regulatory effectors, apart from some glycolytic intermediates and the ratio of nicotinamide adenine dinucleotide (NAD) to NADH (the reduced form), are the nucleotide phosphates, such as ATP, adenosine diphosphate (ADP), and adenosine monophosphate adenylic acid (AMP), inorganic phosphate, and the pH.⁶

The fall in the concentration of the high energy phosphates, such as CP and ATP, in the ischaemic myocardium can be slowed down by the reduction in myocardial energy demands. This, however, leads to a proportional reduction in the glycolytic flux due to the multistage control of this metabolic chain.⁶

In practice, stimulation of anaerobic glycolytic energy production has been achieved only by preventing or reducing intracellular acidosis by the application of buffer substances.¹¹ Such a buffer—for example, histidine—should be able rapidly to penetrate into the intracellular space, a prerequisite which cannot be adequately fulfilled under ischaemic conditions, as the buffer probably cannot be brought to the ischaemic area in sufficient concentration.

In order to stimulate glycolytic flux, the administration of substrates for glycolytic energy production—such as glucose—has been advocated, usually in combination with insulin and potassium.¹² Even if the problem of bringing sufficient amounts of glucose to the ischaemic area could be obviated, this therapeutic approach would still probably not be very rewarding. Because of the multistage control of the glycolytic pathway its overall rate of flux is not determined by the concentration of the main substrates, free glucose and glycogen. In the ischaemic canine heart, for example, free glucose is extensively metabolised only during the very early stages, and thereafter glycogen serves as a glycolytic substrate almost exclusively, as free glucose utilisation is blocked at the hexokinase reaction owing to accumulation of glucose-6-phosphate, as a consequence of the rate limiting step at the phosphofructokinase reaction. At this time glucose concentrations even increase owing to debranching of the glycogen tree. At least in the ischaemic canine myocardium, glycolytic flux stops despite

sufficient myocardial contents of glycogen and glucose. This halt of glycolytic flux occurs at the level of the phosphofructokinase reaction and is probably due to the lack of ATP for the phosphorylation of fructose-6-phosphate to fructose-1, 6-diphosphate.⁶

The main beneficial effect of glucose-insulin-potassium administration may be the subsequent reduction in plasma free fatty acid concentrations, substances which can increase myocardial oxygen consumption¹³ and which may also exert an arrhythmogenic effect.^{14 15}

Early reperfusion to re-establish blood supply and hence oxygen availability

The most critical substrate lacking in infarcting myocardium is oxygen, which becomes rate limiting for oxydative phosphorylation at very low values—that is, <1 mm Hg (critical oxygen tension). Hence, oxydative phosphorylation falls precipitously as oxygen tension declines to this range. As a consequence, for a given myocardial cell a situation of partly aerobic and partly anaerobic energy production seems to be rather unlikely. This view is supported by observations in monolayers of cultured heart cells, whose function and high energy phosphate concentrations decline sharply with decreasing oxygen tension below a critical value.^{16 17} Thus early reperfusion to re-establish blood supply and oxygen availability is probably the most promising approach to infarct reduction. Pertinent attempts began almost 20 years ago with intravenous administration of streptokinase. The generally negative results of these studies could probably be related in part to an excessive ischaemic period. A delay of 12–72 hours was usually allowed between the onset of symptoms and the start of treatment. This time lag is probably sufficient to induce irreversible ischaemic myocardial damage.

Thrombolytic treatment has again received great interest after Rentrop *et al* reported on its intracoronary use in patients with acute myocardial infarction.^{18 19} This form of treatment had been first tried by Chazov *et al*.²⁰ It is now well established that with the intracoronary administration of streptokinase an occluded “infarct” vessel can be reopened in 70–90% of patients. In fact almost every centre which uses this form of treatment has found that in some patients after thrombolytic reopening of the infarct vessel a dramatic improvement occurs in left ventricular function, the electrocardiogram reverts to normal, low creatine kinase values develop in plasma, and the perfusion defect in thallium-201 scintigrams disappears. Even though observations in individual patients have been so encouraging, however, the overall benefit of this form of treatment has not been firmly established despite a large number of clinical trials.²¹ Four con-

Reduction of infarct size

trolled randomised trials have yielded conflicting results, two being positive^{22,23} and the other two negative.²⁴⁻²⁶ The failure consistently to confirm the efficacy of such a theoretically promising technique may be attributed to any of three different causes: (a) the treatment may be harmful in some patients, (b) it may not be effective or of only marginal effectiveness in most patients, or (c) the protocols of the studies have been far from optimal—for example, the acceptance of an excessive ischaemic period.

HARMFUL EFFECTS

The possible hazards of thrombolytic treatment include mainly haemorrhagic complications and complications due to the invasive procedure. Haemorrhagic complications occur in as many as 10% of cases, but a fatal outcome that can be attributed to the intervention occurs in <1%.^{27,28}

The myocardial complications due to thrombolytic treatment are probably less serious. They include the occurrence of reperfusion arrhythmias (which are surprisingly benign in humans),^{29,30} myocardial haemorrhage (generally restricted to the necrotic zone),³¹ and myocardial damage due to calcium overload (occurring predominantly in already irreversibly damaged areas).³²⁻³⁵ Thus reperfusion may accelerate the necrobiotic process but does not induce additional irreversible myocardial damage.

BENEFICIAL EFFECTS

The beneficial effects of thrombolytic treatment in acute myocardial infarction depend mainly on two factors: (a) the duration of ischaemia in the affected area, and (b) the residual blood supply allowed by subtotal occlusion of the infarct vessel or the presence of collaterals or both.³⁶ As this residual flow cannot be assessed by non-invasive techniques, the limits of an ischaemic period that still allows successful reperfusion (that is, reduction in infarct size) cannot be given. As a rule of thumb the following criteria may favour reperfusion: (a) anginal pain for more than 10-15 min but not exceeding 3-4 hours; (b) ST elevation (>1 mm in leads I, II, and III) (>2 mm in leads V1-V6); (c) creatine kinase values still within normal limits; and (d) no contraindications (advanced age, haemorrhagic disorders, known malignancy, etc).

From the foregoing discussion it should be obvious that to improve the functional results of reperfusion, shortening of the ischaemic period should always be a primary aim. The ischaemic period can be shortened either by accelerating transport of the patient to hospital or by accelerating the process of reopening the infarct vessel or both. When the intracoronary route of thrombolysis administration is used a major delay often cannot be avoided while the cardiac catheterisation laboratory is being prepared. During this time

intravenous infusion of streptokinase could be started immediately after informed consent has been obtained from the patient. At coronary angiography 45% of the infarct vessels are open after this treatment, and a further 25-35% of infarct vessels may be subsequently reopened by the intracoronary administration of streptokinase. In this way the functional results of thrombolysis in acute myocardial infarction could be improved.³⁷

After reperfusion of the infarct vessel has been achieved, reocclusion occurs in about 10-25% of cases during the hospital stay.^{27,38} This high reocclusion rate would indicate the consideration of subsequent revascularisation procedures, such as angioplasty or bypass surgery or both. These procedures, however, entail added risks, and their use should at least be based on a potential beneficial effect—that is, the presence of salvaged myocardium in the perfusion area of the reopened vessel. The following criteria may favour subsequent revascularisation: (a) recurrence of anginal pain; (b) no new Q waves on the electrocardiogram; (c) a moderate increase in creatine kinase activity in plasma (<1000 IU/l); (d) a pronounced reduction in the thallium-201 perfusion defect after reperfusion; and (e) no contraindications. By applying such criteria revascularisation of irreversibly damaged myocardial tissue—a procedure of doubtful benefit at best—may be prevented.

Conclusions

The reduction of myocardial infarct size is a concept of great potential clinical importance. At present, the reopening of an occluded infarct vessel by thrombolysis seems to be the most promising approach. Although clearly effective in some patients, the general benefit of thrombolytic treatment in acute myocardial infarction has not yet been definitively established. Before this procedure can be finally evaluated the patients who may benefit may have to be more clearly identified, the procedure itself may have to be improved to reduce the ischaemic period of the infarcting myocardium and thus delay ischaemic damage, and criteria for subsequent revascularisation procedures have to be established. The final evaluation thus has to be based on randomised controlled clinical trials.

Our experiments were supported by a grant from the Deutsche Forschungsgemeinschaft Bonn, Germany (SFB 90—Cardiovascular System, University of Heidelberg). AD is an Alexander von Humboldt-Stiftung fellow.

We thank Wolfgang Kübler Jr for technical assistance.

References

- Braunwald E, Maroko PR. The reduction of infarct size—an idea whose time (for testing) has come. *Circulation* 1974; 50: 206–9.
- Jennings RB, Reimer KA. Biology of experimental acute myocardial ischemia and infarction. In: Hearse DJ, ed. *Enzymes in cardiology: diagnosis and research*. Chichester: Wiley, 1979: 21.
- Müller KD, Sass S, Gottwik MG, Schaper W. Effect of myocardial oxygen consumption on infarct size in experimental coronary artery occlusion. *Basic Res Cardiol* 1982; 77: 170–81.
- Kübler W. Glycolytic pathway in the myocardium. In: Muir JR, ed. *Prospects in the management of ischemic heart disease*. (Ciba Symposium). Amsterdam: Elsevier, 1974: 161–79.
- Katz AM, Hecht HH. The early “pump” failure of the ischemic heart. *Am J Med* 1969; 47: 497–502.
- Kübler W, Spieckermann PG. Regulation of glycolysis in the ischemic and the anoxic myocardium. *J Mol Cell Cardiol* 1970; 1: 351–77.
- Yusuf S, Ramsdale D, Peto R, et al. Early intravenous atenolol treatment in suspected acute myocardial infarction. *Lancet* 1980; ii: 273–6.
- Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomized trial. *Lancet* 1981; ii: 823–7.
- The International Collaborative Study Group. Reduction of infarct size with the early use of timolol in acute myocardial infarction. *N Engl J Med* 1984; 310: 9–15.
- Bussmann WD, Passek D, Seidel W, Kaltenbach M. Reduction of CK and CKMB indices of infarct size by intravenous nitroglycerin. *Circulation* 1981; 63: 615–22.
- Bretschneider HJ. Myocardial protection. *Thorac Cardiovasc Surg* 1980; 28: 295–302.
- Sodi-Pallares D, Testelli MR, Fishleder BL, et al. Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. *Am J Cardiol* 1962; 9: 166–82.
- Mjøs OD, Kjekshus JK, Levken J. Importance of free fatty acids as a determinant of myocardial oxygen consumption and myocardial ischemic injury during norepinephrine infusion in dogs. *J Clin Invest* 1974; 53: 1290–9.
- Oliver MF, Rowe MJ, Luxton MR, Miller NE, Neilson JM. Effect of reducing circulation free fatty acids on ventricular arrhythmias during myocardial infarction and on ST-segment depression during exercise-induced ischemia. *Circulation* 1976; 53 (suppl I): 210–2.
- Opie LH, Nathan D, Lubbe WF. Biochemical aspects of arrhythmogenesis and ventricular fibrillation. *Am J Cardiol* 1979; 43: 131–48.
- Barry WH, Pober J, Marsh JD, Frankel SR, Smith TW. Effects of graded hypoxia on contraction of cultured chick embryo ventricular cells. *Am J Physiol* 1980; 239: H651–7.
- Doorey AJ, Barry WH. The effects of inhibition of oxidative phosphorylation and glycolysis on contractility and high-energy phosphate content in cultured chick heart cells. *Circ Res* 1983; 53: 192–201.
- Rentrop KP, Blanke H, Karsch KR, et al. Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase. *Clin Cardiol* 1979; 2: 354–63.
- Rentrop P, Blanke H, Karsch KR, Kaiser H, Köstering H, Leitz K. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. *Circulation* 1981; 63: 307–17.
- Chazov EI, Matveeva LS, Mazaev KV, Sargin KE, Sadovskaya GV, Ruda MY. Intracoronary administration of fibrinolysis in acute myocardial infarction. (Russian) *Ter Arkh* 1976; 48: 8–9.
- Brooks N. Intracoronary thrombolysis in acute myocardial infarction. *Br Heart J* 1983; 50: 397–400.
- Anderson JL, Marshall HW, Bray BE, et al. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. *N Engl J Med* 1983; 308: 1312–8.
- Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. *N Engl J Med* 1983; 309: 1477–82.
- Khaja F, Walton JA Jr, Brymer JF, et al. Intracoronary fibrinolytic therapy in acute myocardial infarction. Report of a prospective randomized trial. *N Engl J Med* 1983; 308: 1305–11.
- Leiboff RH, Katz RJ, Wassermann AG, et al. A randomized angiographically controlled trial of intracoronary streptokinase in acute myocardial infarction. *Am J Cardiol* 1984; 53: 404–7.
- Swan HJC. Thrombolysis in acute evolving myocardial infarction. A new potential for myocardial salvage. *N Engl J Med* 1983; 308: 1354–5.
- Kübler W, Röhrig D, Schuler G, Schwarz F. Der akute Myokardinfarkt: Grundlagen der medikamentösen Therapie. *Verh Dtsch Ges Inn Med* 1982; 88: 41–56.
- Marder VJ. Pharmacology of thrombolytic agents. Implications for therapy of coronary artery thrombosis. *Circulation* 1983; 68 (suppl I): 2–5.
- Cox JL, Daniel TM, Boineau JP. The electrophysiological time-course of acute myocardial ischemia and the effects of early coronary artery reperfusion. *Circulation* 1973; 48: 971–83.
- Corr PB, Wittkowski FX. Potential electrophysiologic mechanisms responsible for dysrhythmias associated with reperfusion of ischemic myocardium. *Circulation* 1983; 68 (suppl I): 16–24.
- Fishbein MC, Y-Rit J, Lando U, Kanmatsuse K, Mercier JC, Ganz W. The relationship of vascular injury and myocardial hemorrhage to necrosis after reperfusion. *Circulation* 1982; 62: 1274–9.
- Reimer KA, Jennings RB. The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979; 40: 633–44.
- Shen AC, Jennings RB. Kinetics of calcium accumulation in acute myocardial ischemic injury. *Am J Pathol* 1972; 67: 441–52.
- Fleckenstein A, Janke J, Döring HJ, Leder O. Myocardial fiber necrosis due to intracellular Ca-overload. A new principle in cardiac pathophysiology. In: Dhalla NS, ed. *Myocardial metabolism: recent advances in studies in cardiac structure and metabolism*. vol. 4. Baltimore: University Park Press. 1974:563–80.
- Naylor WG. Calcium and cell death. *Eur Heart J* 1983; 4 (suppl C): 33–41.
- Schwarz F, Schuler G, Katus H, et al. Intracoronary thrombolysis in acute myocardial infarction: duration of ischemia as a major determinant of late results after recanalization. *Am J Cardiol* 1982; 50: 933–7.
- Schwarz F, Hofmann M, Schuler G, Kübler W. Combined intravenous and intracoronary versus intracoronary streptokinase therapy in acute myocardial infarction. *J Am Coll Cardiol* 1983; 1: R615.
- Gold HK, Leinbach RC, Palacios IF, et al. Coronary reocclusion after selective administration of streptokinase. *Circulation* 1983; 68 (suppl I): 50–4.