

Cardioplegia versus intermittent ischaemic arrest in coronary bypass surgery

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ABSTRACT No definitive method of myocardial preservation has been established and conclusions based on experimental data may not be applicable to patients with coronary artery disease. Fifty patients undergoing coronary bypass grafting were randomly assigned to one of two groups for myocardial preservation. In group A cold cardioplegia with external cardiac cooling was used and in group B ischaemic arrest with mild systemic cooling to 32°C. Myocardial preservation was assessed by analysis of enzymes specific to the heart, left ventricular biopsy, and electrocardiography. Equal protection of the myocardium was provided in both groups but the mean cross-clamp time in group A was significantly longer than in group B. This implies that cardioplegia confers greater protection than intermittent ischaemic arrest.

Most cardiac surgeons use some form of cold cardioplegia to protect the heart during coronary bypass grafting, but a minority prefer intermittent ischaemic arrest and obtain excellent clinical results. Recent prospective randomised studies comparing ischaemic arrest and cold cardioplegia have used topical hypothermia in the ischaemic group and report good myocardial preservation in both groups.¹⁻⁴ There has been only one investigation comparing intermittent ischaemic arrest as practised in our study with cold cardioplegia; this was a retrospective, non-randomised study,⁵ and it too showed a similar incidence of perioperative myocardial damage in the two groups.

In the present study we used quantitative cytochemical analysis of left ventricular biopsy specimens, measurement of plasma levels of myocardium-specific enzymes, and electrocardiographic analysis in a prospective randomised comparison of cold cardioplegia and intermittent ischaemic arrest.

Patients and methods

Fifty patients undergoing coronary bypass grafting were randomised to one of two methods of myocardial preservation: group A received cold cardioplegia and group B intermittent ischaemic arrest. Patients with ventricular aneurysms were

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excluded because interpretation of the perioperative ECG would not be standardised. All patients received the same anaesthetic regimen and were operated on by one surgeon. The characteristics of the two groups were similar (table 1), but cross-clamp time and perfusion time were longer in the group receiving cardioplegia.

SURGICAL MANAGEMENT

All patients had a similar perfusion regimen, which included individual caval cannulation, a BOS-10 oxygenator and priming with 1500 ml Hartman's solution. Systemic temperature was lowered to 25°C in group A and to 32°C in group B. The systemic flow rate was 24 l/min/m² in both groups, but it was reduced to 1.6 l/min/m² in group A when a systemic

Table 1 *Clinical data*

	Group A: Cold cardioplegia	Group B: Intermittent ischaemia
No of patients	25	25
Age (y)	55 (42-68)	56 (40-72)
Left ventricular end-diastolic pressure (mm Hg)	17	17
Ejection fraction (%)	51	49
Left ventricular wall movement		
Normal	5	8
Segmental abnormality	16	15
Diffuse abnormality	4	2
Average number of distal anastomoses	3.4	3.1
Number of endarterectomies	8	2
Aortic cross-clamp time (min)	61	31
Number requiring inotropic drugs	3	4
30-day mortality	0	1

temperature of 25°C was achieved. In both groups the left ventricle was decompressed by a vent.

The method of inducing cold cardioplegia was designed to produce profound cardiac hypothermia with myocardial septal temperatures in the range 10–20°C. A temperature probe (Edale Instruments Ltd, Cambridge) was placed 1 cm deep into the anterior portion of the ventricular septum and recordings were taken every 10 minutes. When the oesophageal temperature had reached 30°C the ascending aorta was cross-clamped and 1 litre of St Thomas' Hospital (STH) cardioplegic solution at 4°C was infused via a 12-FG needle into the aortic root. A pressure of 250 mm Hg was maintained in the litre bag and delivery of the solution was completed within three minutes. Electromechanical activity generally ceased after it had been infused for one minute. In addition, 4°C Ringer lactate solution was constantly run over the surface of the heart.

The posterior myocardium was kept insulated from the descending thoracic aorta. A further infusion of 500 ml of STH cardioplegic solution was given after 60 minutes of aortic cross-clamping or if the septal temperature rose above 19°C. All distal coronary anastomoses were performed during one period of aortic cross-clamping. After removal of the cross-clamp the proximal anastomoses were completed while the systemic temperature was returning to 37°C. During this period a mean aortic perfusion pressure of 50–60 mm Hg was maintained.

The method used for intermittent ischaemic arrest was as follows: a systemic perfusion temperature of 32°C was achieved and the heart electively fibrillated. Each distal coronary anastomosis was performed in less than 15 minutes of aortic cross-clamp time. Immediately on release of the cross-clamp the heart was defibrillated if spontaneous defibrillation had not already occurred. Distal and proximal anastomoses were then alternated to provide a period of at least 10 minutes in a beating decompressed heart while the proximal anastomosis was completed.

Measurement of myocardium-specific enzymes

The following enzymes were measured in plasma samples: aspartate transaminase, total creatinine phosphokinase, and the creatine kinase MB isoenzyme. The hydroxybutyric dehydrogenase isoenzyme of lactate dehydrogenase was not analysed owing to its late rise in plasma at 24 hours and its tendency to rise considerably with haemolysis. Serum albumin and total protein concentrations were measured to assess the possible effects of dilution.

Samples were taken at the time of induction of anaesthesia and three, six, 12, 24, and 48 hours after removal of the cross-clamp. Peak creatine kinase MB activities were measured and the percentage of

creatine kinase MB in relation to total creatinine phosphokinase was examined but these values did not add to the information gained from creatine kinase MB levels alone. The activity of the creatine kinase MB isoenzyme was determined photometrically on an immunological basis.⁶

Left ventricular biopsies

Full-thickness biopsy specimens of the apex of the left ventricle were taken, each measuring about 20 mm × 2 mm. Two biopsy samples were taken from each patient during cardiopulmonary bypass. The first was taken before the aorta was cross-clamped and the second at least 20 minutes after final release of the cross-clamp. This delay was included to avoid the period of perfusion washout. The biopsy samples were placed in hexane at –70°C within one minute. Specimens were processed on the day of sampling and cut on a cryostat at –30°C. Analysis of the specimens included quantitative birefringence and quantitative histochemical grading, the following enzymes being used: succinate dehydrogenase, acid haematin, myosin adenosine triphosphatases and monoamine oxidase.⁷

Electrocardiographic data

Standard 12-lead ECGs were recorded on all patients one day before and one and seven days after operation. Interpretation was by an independent observer who had no knowledge of which method of myocardial protection was used. The changes were categorised according to the modified Minnesota code.⁸ Postoperative ECG changes were recorded as "persistent" if they were present at one and seven days.

Statistical methods

In the analysis of myocardium-specific enzymes the value of each continuous variable is expressed as the mean plus or minus one standard error of the mean. Unpaired *t* tests, Wilcoxon, and median tests were used in the preliminary stages of the examination. Categorical variables were tested by the techniques of analysis of co-variance in certain instances. A *p* value of <0.05 was considered significant.

Results

Myocardial-specific enzyme analysis

The time-related creatine kinase MB levels are shown in fig 1. The mean values for the enzymes were similar up to 24 hours after release of the aortic cross-clamp. By 48 hours the mean values of creatine kinase MB were lower (*p* = 0.05) in the group having intermittent ischaemic arrest. This difference was unlikely to be a dilution effect as the

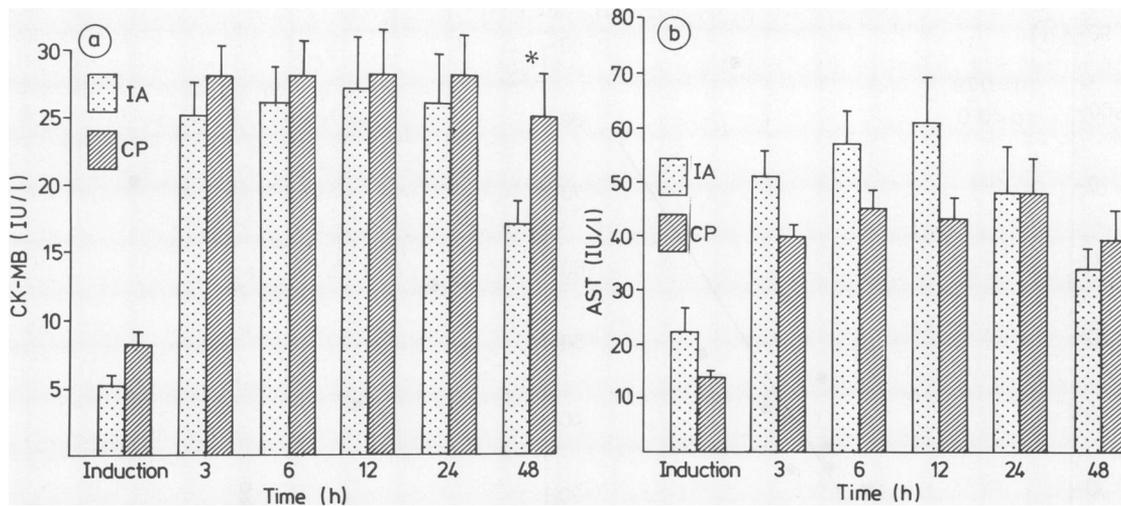


Fig 1 Peak creatine kinase MB (CK-MB) (a) and aspartate transaminase (AST) (b) activities at the time of induction of anaesthesia and three, six, 12, and 48 hours after removal of the aortic cross-clamp. IA—intermittent ischaemia; CP—cold cardioplegia. *— $p = 0.05$.

concentrations of albumin and total protein showed virtually no change in either group throughout the period of study.

When the 12-hour creatine kinase MB value was used as an indicator of myocardial necrosis a close correlation was found by regression analysis between myocardial necrosis and total ischaemic time in the intermittent ischaemic arrest group (fig 2). No such correlation was present in the cardioplegia group. Other factors, such as age, preoperative left ventricular ejection fraction, left ventricular end-diastolic pressure, number of grafts, and endarterectomy, showed no correlation with the 12-hour level of creatine kinase MB.

ECG analysis

The perioperative changes in the ECG according to the new Minnesota code are shown in table 2. One patient in each group had new Q waves, suggesting perioperative myocardial necrosis. Both of these patients had an abnormal rise of their serum creatine kinase MB isoenzyme levels. Four patients in the intermittent ischaemia group and seven patients in the cardioplegia group showed persistent ST changes. Most patients had unchanged ECGs after operation and a straightforward clinical course.

Quantitative birefringence of left ventricular biopsy specimens

Left ventricular biopsy specimens taken before and after the total ischaemic period were compared by the methods described above. Two of 25 patients in the cardioplegia group and one of 22 patients in the

intermittent ischaemia group showed evidence of deterioration in the second biopsy specimen (fig 3).

Clinical course

Clinical data are summarised in table 1. The two groups had similar preoperative left ventricular function. The number of distal anastomoses was also similar. Although more endarterectomies were performed in group A (8) than in group B (2) the difference did not achieve significance, nor was there any significant difference between the 12-hour creatine kinase MB levels in these two subgroups. In contrast, the aortic cross-clamp time was significantly longer ($p < 0.001$) in group A (61 ± 16 minutes) than in group B (31 ± 9 minutes).

The postoperative requirement for inotropic agents was similar in the two groups. In all instances isoprenaline was used, and it was given for less than 12 hours. One patient in group B died after three weeks owing to septicaemia secondary to a chest infection. No patient required intra-aortic balloon counter-pulsation. Two patients in group B developed atrial fibrillation within the first 48 hours, but all patients in group A remained in sinus rhythm.

Discussion

The efficacy of a cardioplegic solution depends greatly on the precise technique used, as a wide range of temperatures may be observed within the myocardium despite an apparently satisfactory technique.^{9,10} Possibly some regions of the heart do not receive adequate volumes of cardioplegic

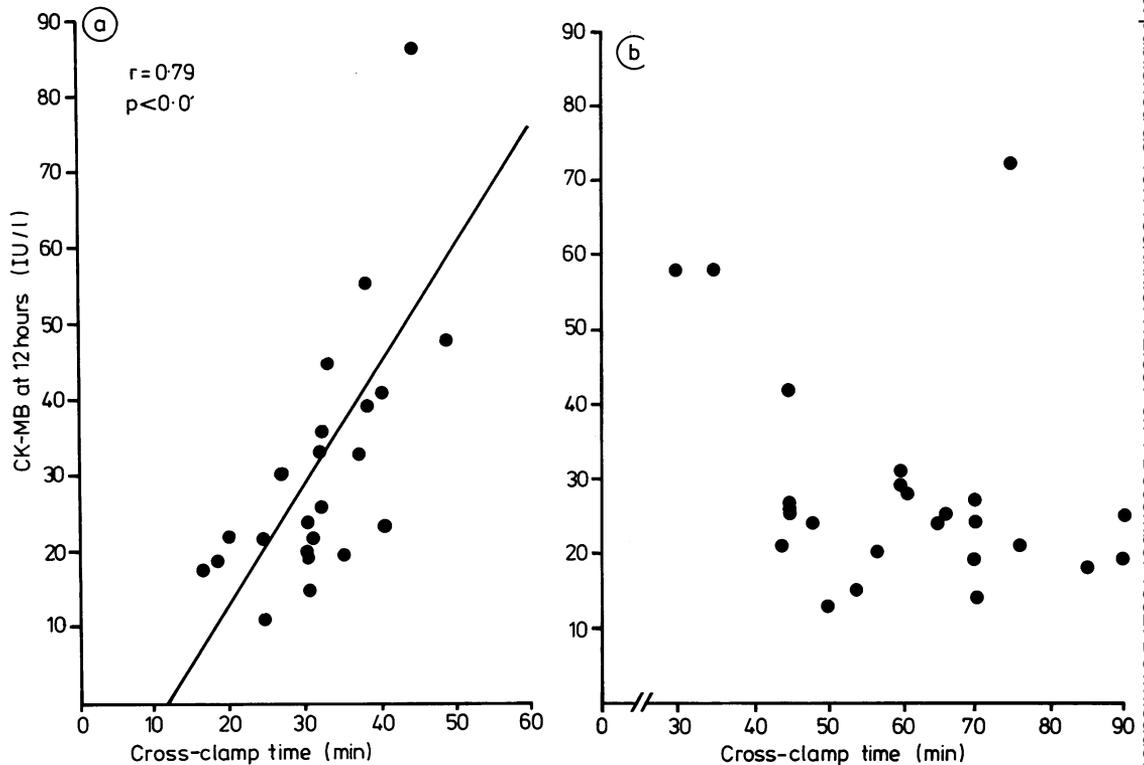


Fig 2 (a) Relationship between cross-clamp time and the 12-hour peak creatine kinase MB (CK-MB) activity in (a) the intermittent ischaemic arrest group and (b) the cardioplegia group. The line of identity is given. The regression equation is: $y = -18.52 + 1.57x$ $r = 0.79$, $p < 0.01$.

solution because of proximal coronary artery obstruction. Experimental reports have shown that such obstructions may interfere with the delivery of cardioplegic solutions to the distal ischaemic myocardial bed.¹¹⁻¹⁵ Perhaps therefore the regions of the heart at greatest risk from damage during the cross-clamp period are also those that receive the least benefit from cardioplegic arrest. Furthermore, flow from non-coronary collateral sources may wash out the cardioplegic solution. Despite these dis-

advantages, because it lowers systemic temperature and flow rate and delivers large volumes of cardioplegic solution cardioplegia has given excellent results in clinical practice.^{12,16}

Intermittent ischaemic arrest has been widely used in cardiac operations. The original basis for this method was that the oxygen debt is related to global myocardial ischaemia and can be repaid by a short period of coronary reperfusion.^{17,18} It was assumed that the heart would tolerate repeated short periods of aortic cross-clamping. There have, however, been many reports of myocardial damage arising from this technique.¹⁹ Several modifications, in particular mild systemic hypothermia (32°C), was used in this study to minimise intraoperative myocardial injury. A perfusion period of at least 10 minutes between ischaemic episodes may be more favourable than a five-minute period. Furthermore, reperfusion may be less damaging in a beating decompressed heart than in a fibrillating heart.¹⁹ Using such modifications, several groups have shown a low incidence of perioperative myocardial damage.^{20,21} The close correlation in the intermittent ischaemia group

Table 2 Electrocardiographic changes

ECG category*	Group A		Group B	
	Cold cardioplegia		Intermittent ischaemia	
	No	(%)	No	(%)
New Q waves	1	(4)	1	(4)
Persistent ST elevation	4	(16)	3	(12)
Persistent ST depression	3	(12)	1	(4)
No change	17	(68)	20	(80)

* As defined by modified Minnesota code.*

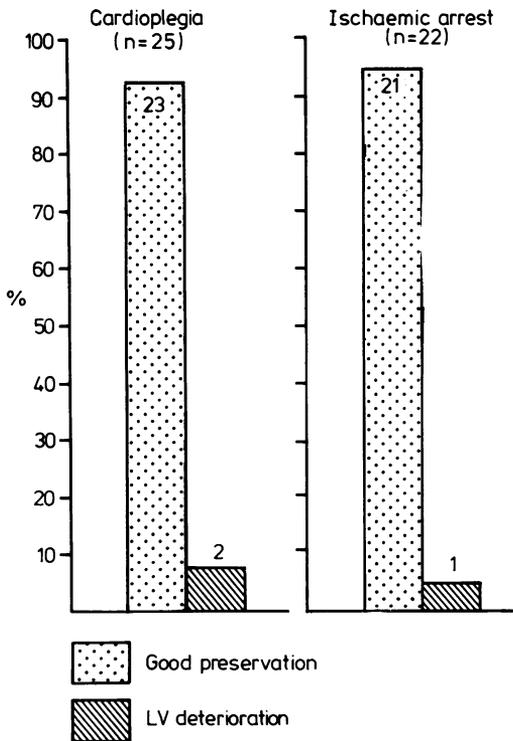


Fig 3 Assessment of myocardial preservation by quantitative birefringence of left ventricular biopsy specimens.

between aortic cross-clamp time and myocardial necrosis, as indicated by the 12-hour peak creatine kinase MB concentration, indicates a time limit for safety when this technique is used (fig 2). The aortic cross-clamp time in the cold cardioplegia group (61 minutes) was almost twice as long as in the intermittent ischaemia group (31 minutes). Within the time limits of this study therefore the aortic cross-clamp time during cold cardioplegia was irrelevant to the development of myocardial necrosis. This additional time is helpful for unexpected problems, such as a difficult disobliteration, and for the inexperienced operator. Furthermore, if there has to be extensive revascularisation requiring six or more grafts then cold cardioplegia is the safer technique.²²

The results of this prospective randomised study of patients with relatively normal preoperative global left ventricular function indicate that myocardial damage was similar in the two groups. The cross-clamp time, however, was twice as long in the cardioplegic group, which suggests that cold cardioplegia provides greater protection than intermittent ischaemic arrest.

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