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PROTECTION OF ISCHEMIC MYOCARDIUM BY WHOLE-BODY HYPOTHERMIA AFTER CORONARY ARTERY OCCLUSION IN DOGS

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Abstract

Anesthetized dogs were cooled to a core body temperature of 26°C or maintained at a body temperature of 37°C during periods of 5 and 10 hours of LAD coronary artery occlusion. Subsequent macroscopic dehydrogenase enzyme mapping showed that ischemic injury was 25 per cent less after 5 hours of coronary occlusion and 20 per cent less after 10 hours of occlusion in hypothermic dogs than in normothermic controls. The heart rate and left ventricular minute work in hypothermic dogs decreased to roughly half the levels measured in normothermic animals, while left ventricular contractility was 10 to 40 per cent lower in hypothermic dogs than in normothermic dogs. However, cardiac index and left ventricular end-diastolic pressure were unchanged by whole body cooling. Thus, hypothermia appeared to diminish the oxygen requirements of the ischemic myocardium without reducing the performance of the heart as a pump. Hypothermia may be useful as a therapeutic adjunct to myocardial revascularization or pharmacologrc interventions.

Key words: acute myocardial infarction, India ink, myocardial protection, nitrobluetetrazolium

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Introduction

The survival of myocardium distal to an occluded coronary artery depends on a delicate balance between oxygen supply and oxygen demand. Interventions that either reduce myocardial oxygen requirements or increase myocardial oxygen availability have been found to decrease ischemic injury [1-3]. Whole-body and local hypothermia have been used extensively in patients during cardiopulmonary bypass surgery to lower myocardial oxygen demand and thereby minimize the ischemic injury resulting from temporary anoxia [4, 5]. However, the value of lowering the body temperature to decrease ischemic injury after coronary occlusion is not clear. Several investigators have concluded that hypothermia is contraindicated in recent myocardial infarction because of a high incidence of ventricular fibrillation observed in dogs [6-10]. However, in all of these studies a coronary artery was ligated after the animal was hypothermic, when the heart is highly vulnerable to mechanical stimulation. Other studies, in which coronary occlusion preceded hypothermia, have shown that dogs not only tolerated moderate hypothermia (25 to 30 °C) without ventricular fibrillation, but also demonstrated better hemodynamic recovery following rewarming than controls [11-14]. Ginks and colleagues [15] reported a significant reduction in ischemic injury after coronary occlusion in dogs using a combination of hypothermia, intra-aortic balloon counterpulsation, intravenous propranolol, and coronary reperfusion; but the simultaneous use of several interventions did not permit the evaluation of hypothermia alone. The objective of the present study was to determine if moderate hypothermia, without rewarming, reduces ischemic injury after coronary artery occlusion in the anesthetized, open-chest dog.

Animal preparation

Twenty-eight mongrel dogs, of both sexes, weighing between 4 and 18 kilograms, served as subjects. Anesthesia was induced by intravenous pentobarbital sodium (35.5 ± 1.7 mg/Kg) and was maintained at stage III plane II according to the criteria of Lumb [16] by additional doses (3.5 ± 0.3 mg/Kg) given as needed. The chest was opened by median sternotomy and the heart was supported in a pericardial cradle formed by suturing the free edges of the incised pericardium to the chest wall. Ventilation was maintained through a cuffed endotracheal tube by an intermittent positive-pressure ventilator using room air. Blood pH, pCO_2, and pO_2, were monitored in several dogs to determine that ventilation was adequate. The exposed heart was frequently moistened with Ringer's solution containing sodium lactate to prevent desiccation. In 23 dogs, the left anterior descending coronary artery was isolated above the first major diagonal branch and was occluded with a silk suture. In five control dogs, a suture was passed under the artery but the vessel was not occluded. Coronary occlusion was verified by the appearance of ST segment elevation in the epicardial electrogram obtained from the ischemic region, and by cyanosis and systolic bulging of the ventricular wall distal to the ligature. The unipolar epicardial electrode consisted of a 1 cm diameter felt pad sutured to the epicardium and attached to a medicine dropper containing saline and the electrode lead by a strip of l/8 inch umbilical tape. The epicardial electrode was referenced to the combined standard limb lead (Wilson central terminal). Ventricular arrhythmias were treated with 0.5 to 2.0 mg/Kg doses of intravenous lidocaine.

Hemodynamic measurements

Aortic and left ventricular pressures were measured using Statham P23Db pressure transducers connected to saline-filled polyethylene (PE 260) catheters. Pressure signals and the first derivative of left ventricular pressure, dP/dt, were displayed on a Physiograph recorder (Narco Bio-Systems, Houston, Texas) together with either Lead II of the electrocardiogram or the epicardial electrogram. Heart rate, left ventricular end-diastolic pressure, left ventricular systolic pressure, and maximum dP/dt were measured directly from the Physiograph records. Cardiac output was measured using the saline indicator dilution technique and the continuous flow conductivity cell described by Geddes and associates [17].The change in blood resistivity with the addition of sodium chloride ($\Delta\rho/\Delta c$) is a function of blood temperature and packed cell volume. Thus, the values of $\Delta\rho/\Delta c$ at 37°C. and different packed cell volumes, reported previously by Geddes and co-workers [17], were corrected to blood temperature, t, using the expression

$$\left(\frac{A\rho}{\Delta c}\right)_{t\ ^{o}C} = (1 + 0.036(37 - t))\left(\frac{A\rho}{\Delta c}\right)_{37\ ^{o}C}.$$

Sodium heparin (1.0 mg/Kg) was given intravenously every 2 to 3 hours to prevent clot formation in the cell. Cardiac index, stroke index, peripheral vascular resistance, and left ventricular minute work were calculated by established methods.

Induction of hypothermia

Hypothermia was induced by covering the dogs with bags of flake ice and by circulating ice water through the coils of a rubber mat under the dogs. Esophageal or blood (subclavian artery) temperature was continuously monitored using a thermistor (Yellow Springs Instrument Co., Yellow Springs, Ohio). When the core body temperature reached 27 ^{o}C, the ice was removed and the body temperature was allowed to equilibrate. A body temperature near 26 °C was maintained by bags of ice or warm overhead lights as needed.

Identification and quantitation of ischemic myocardium

In dogs with coronary occlusions, the region of myocardial ischemia was identified by perfusing a dilute India ink suspension through the patent coronary vascular bed. Cardiac perfusion was accomplished by withdrawing the left ventricular pressure catheter to the aortic root (verified by pressure measurements). A ligature was placed around the right brachiocephalic artery containing the catheter. The left subclavian artery, the precava, the postcava, and the aorta were ligated in succession. Ringer's solution containing sodium lactate (37 ^{o}C) was first perfused through the coronary arteries via the aortic catheter at 120 to 150 mmHg pressure to clear the heart of blood. The atria1 appendages were incised to permit drainage of fluid. Perfusion with Ringer's solution was stopped when the effluent from the atria1 appendages cleared (about 200 ml of perfusate was required). Then, a 10 percent mixture by volume of India ink (Pelikan

drawing ink, black No. 17) in Ringer's solution (37 °C) was perfused at 120 to 150 mmHg pressure until the posterior wall of the left ventricle was uniformly blackened (about 50 ml of ink perfusate was required). The hearts of dogs that did not receive coronary occlusions were perfused only with Ringer's solution. The ventricles were sectioned into five, 0.5 to 1.0 cm thick transverse slices. The slices were weighed and photographs showing the "mirror image" surfaces were taken using Polaroid Continuous Tone (Type 46L) black-and-white transparency film. A red filter was used to intensify the contrast between inked and noninked myocardium. Enlarged (8 x 10 in^2) black-and-white prints (Kodak Velox F-2 photographic paper), similar to the one shown in Figure l(a), were cut and weighed to determine the ratio of unperfused to perfused area for each slice surface. The average ratio of areas for both surfaces of a slice was multiplied by the tissue weight to determine the weight of ischemic myocardium in each slice.

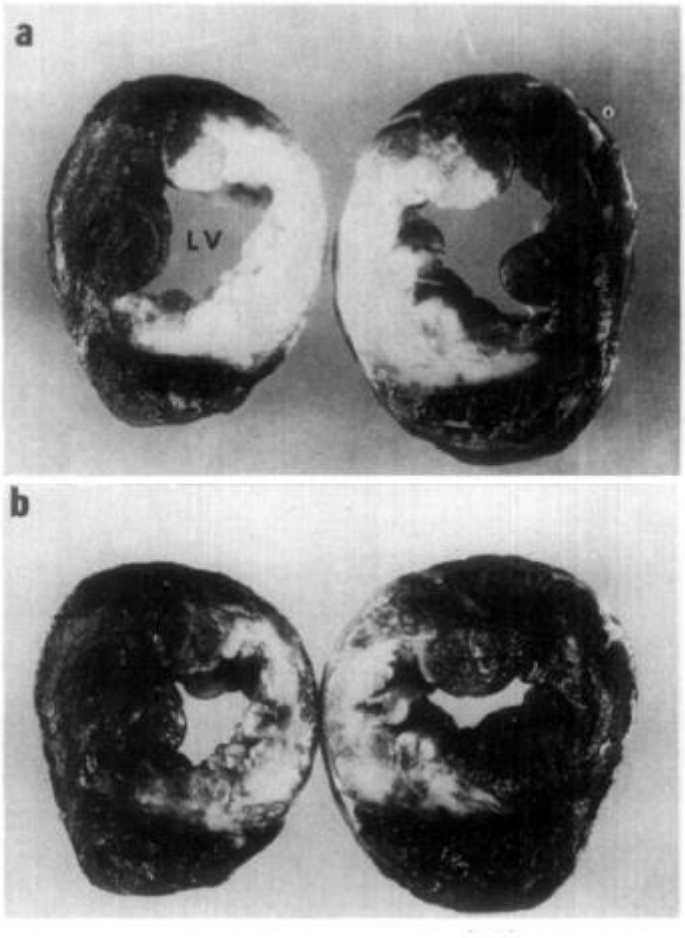

Figure 1. Representative photographs of "mirror image" ventricular slices taken from a dog heart after 5 hours of LAD coronary artery occlusion. The anterior wall of the left ventricle (LV) is directed towards the center of the photographs. (a) shows the opposing surfaces of the two slices after India ink perfusion. The light areas of the cut surfaces are uninked (ischemic). (b) shows the same surfaces of the slices after incubation in NBT stain.

Macroscopic enzyme mapping of ischemic myocardium

Nitrobluetetrazolium (NBT) staining was used to identify injured myocardium, since histologic indices of myocardial injury may not be reliably quantitated during the first 12 hours of coronary occlusion. Viable cells, containing active dehydrogenase enzymes, reduce NBT forming a deep purple diformazan deposit. In contrast, injured cells irreversibly lose dehydrogenase enzymes within 2 to 4 hours from the onset of ischernia and do not form the diformazan residue [18]. The ventricular slices were incubated for 30 minutes at 37 °C in a preheated solution consisting of 0.5 mg/ml of NBT (ICN Pharmaceuticals Inc., Cleveland, Ohio) in 0.1 M phosphoric acid buffer (pH 7.4) without substrate.

After incubation in NBT, the slices were re-photographed. Enlarged black-and-white prints, similar to the one shown in Figure l(b), were cut and weighed without knowledge of treatment group to determine the ratio of unstained to stained area for each slice surface. Any area with less than maximum staining was considered injured. The average ratio of both slice surfaces was used to calculate the weight of enzyme-deficient myocardium in each slice. In dogs with coronary occlusions, the percentage of ischemic myocardium having decreased NBT staining was determined for the whole heart. Expression of the amount of injured (unstained) myocardium as a percentage of the ischemic (uninked) myocardium reduced the effect of inevitable variations in size and homogeneity of infarcts produced in dogs.

Microscopic evaluation of injury

In several dogs with coronary occlusions, the ventricular slices were prepared for light microscopy to evaluate histopathology in areas of decreased NBT staining. The slices were fixed in 10 percent buffered neutral formalin immediately after the macroscopic analysis. Following at least one week in formalin fixative, blocks containing equal portions of NBT stained and unstained tissue were embedded in paraffin and cut at a thickness of 8 to 10 μ in a plane parallel to the NBT stained surface. The sections were stained with hematoxylin and eosin and were examined for signs of early myocardial necrosis.

Experimental design

The left anterior descending coronary artery was occluded in 23 dogs and sham-occluded in five dogs. Beginning 30 minutes later, the body temperature of 12 dogs with coronary occlusions and all five sham operated control dogs was reduced to 26°C. The body temperature of the remaining 11 dogs was maintained at 37°C. Hemodynamic data were collected immediately before occlusion and at one hour intervals thereafter. In sham-operated dogs, the intact hearts were perfused with Ringer's solution and the sliced ventricles were stained with NBT, 5 hours after sham-occlusion. These dogs served to determine the incidence of myocardial injury during hypothermia alone. In dogs with coronary artery occlusions, the intact hearts of surviving animals were perfused with Ringer's solution and India ink to define the region of ischemia after either 5 or 10 hours of coronary occlusion (five normothermic and five hypothermic dogs at each time period). The ischemic region was measured grossly in transverse slices of the ventricles,

and the slices were stained with NBT to identify injured myocardium within the ischemic region. The extent of myocardial injury was evaluated grossly and was expressed as a percentage of the ischemic region. In eight hypothermic dogs and six normothermic dogs, ventricular slices were prepared for histopathologic study. Histochemical and hemodynamic measurements were analyzed by unpaired Student's t-tests.

Results

The hearts of sham-operated dogs subjected to 4.5 hours of hypothermia contained no visible areas of decreased dehydrogenase enzyme. This indicated that hypothermia alone did not produce detectable myocardial injury. The incidence of arrhythmias and ventricular fibrillation was not significantly increased by hypothermia after coronary occlusion. Of the 23 dogs that received coronary occlusions, two hypothermic dogs and one normothermic dog developed ventricular fibrillation. The data from these dogs have not been included in the following analysis. The use of lidocaine to treat arrhythmias and delay of cooling until after the intense post-occlusion arrhythmic period (i.e., 30 minutes) probably contributed to the low incidence of ventricular fibrillation in these studies.

Size of the ischemic region

The ischemic region produced by ligation of the left anterior descending coronary artery was clearly visible in transverse ventricular slices after perfusing the heart with India ink solution (Figure l(a)). This region was located in the anterior wall of the left ventricle, including the anterior papillary muscle and reaching the adjacent lateral and septal walls. The average weight of ischemic myocardium was 13 g, ranging from 6 to 30 g; the average weight of the twenty dog hearts was 78 g, ranging from 52 to 132 g. The size of the ischemic region did not differ significantly between groups in this study ($p > 0.05$).

Myocardial injury in the ischemic region

Following NBT staining, portions of the ischemic region with decreased intracellular dehydrogenase enzyme were readily visible upon gross inspection of the tissue and were easily quantitated in black-and-white photographs of the ventricular slices (Figure l(b)).

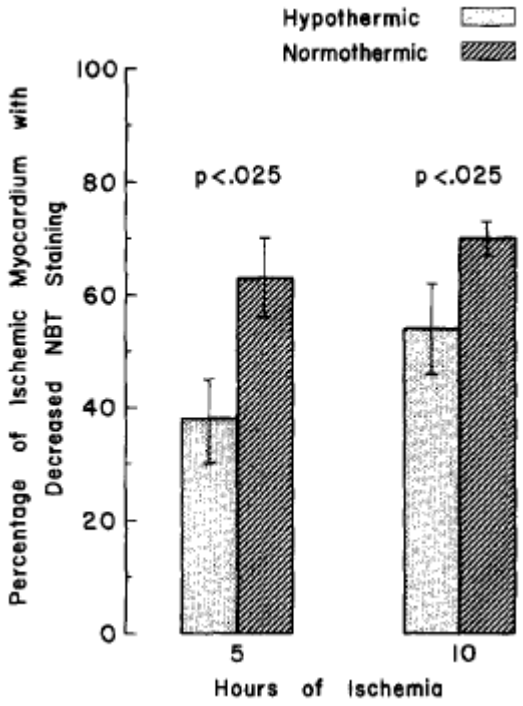

Figure 2. The effect of reducing body temperature to 26 °C on the percentage of the ischemic myocardium with decreased dehydrogenase enzyme after either 5 or 10 hours of coronary artery occlusion. Bars represent group means (n = 5). Vertical lines indicate one standard deviation.

Figure 2 shows the effect of moderate hypothermia on ischemic injury. The percentage of the ischemic region that did not react with NBT was significantly lower in hypothermic dogs than in normothermic dogs after either 5 or 10 hours of coronary occlusion. Five hours after coronary occlusion, the injured tissue appeared grossly as a patchy, pale area in the ischemic subendocardium of the hypothermic dog hearts. In contrast, in the ischemic region of normothermic dog hearts, the injured tissue appeared as a transmural area of greater pallor, containing fewer foci of stained myocardium. After 10 hours of coronary occlusion, the injured area extended transmurally in both groups and the pallor of the unstained tissue was increased, but, fewer foci of stained tissue were observed in the ischemic region of normothermic dog hearts. Microscopic study of the ventricular slices after 10 hours of coronary occlusion confirmed results obtained by gross histochemical staining. Few damaged cardiac muscle cells were present in NBT unstained areas of hypothermic dog hearts, whereas, in normothermic dog hearts, NBT unstained areas contained numerous damaged cardiac muscle cells. The histological features of damaged fibers after 10 hours of coronary occlusion consisted of hyalinized sarcoplasm with mild interstitial edema and neutrophilic infiltration. Qualitatively, there was no difference between hypothermic and normothermic dogs in the appearance of the damaged cells. Damaged fibers could not be evaluated by light microscopy after only 5 hours of coronary occlusion.

Effects of coronary occlusion and hypothermia on hemodynamics

Approximately 2 hours of surface cooling was required to reduce the core body temperature to 26 ^{o}C. Figure 3 shows that heart rate and mean blood pressure were significantly lower in hypothermic dogs than in normothermic dogs after 2 to 3 hours of coronary occlusion. Vascular resistance increased in both groups during the first 5 hours of coronary occlusion, but remained lower in hypothermic dogs than in normothermic dogs.

Figure 4 shows that stroke index was increased significantly in hypothermic dogs, but cardiac index in the two groups did not differ significantly. Left ventricular minute work was typically lower in hypothermic dogs than in normothermic dogs.

Figure 5 shows that both the maximum rate of rise of left ventricular pressure and the left ventricular systolic pressure were decreased by hypothermia. Table I compares the left ventricular end diastolic pressure (LVEDP) in hypothermic and normothermic dogs during 10 hours of coronary occlusion. LVEDP was not significantly different between the two groups.

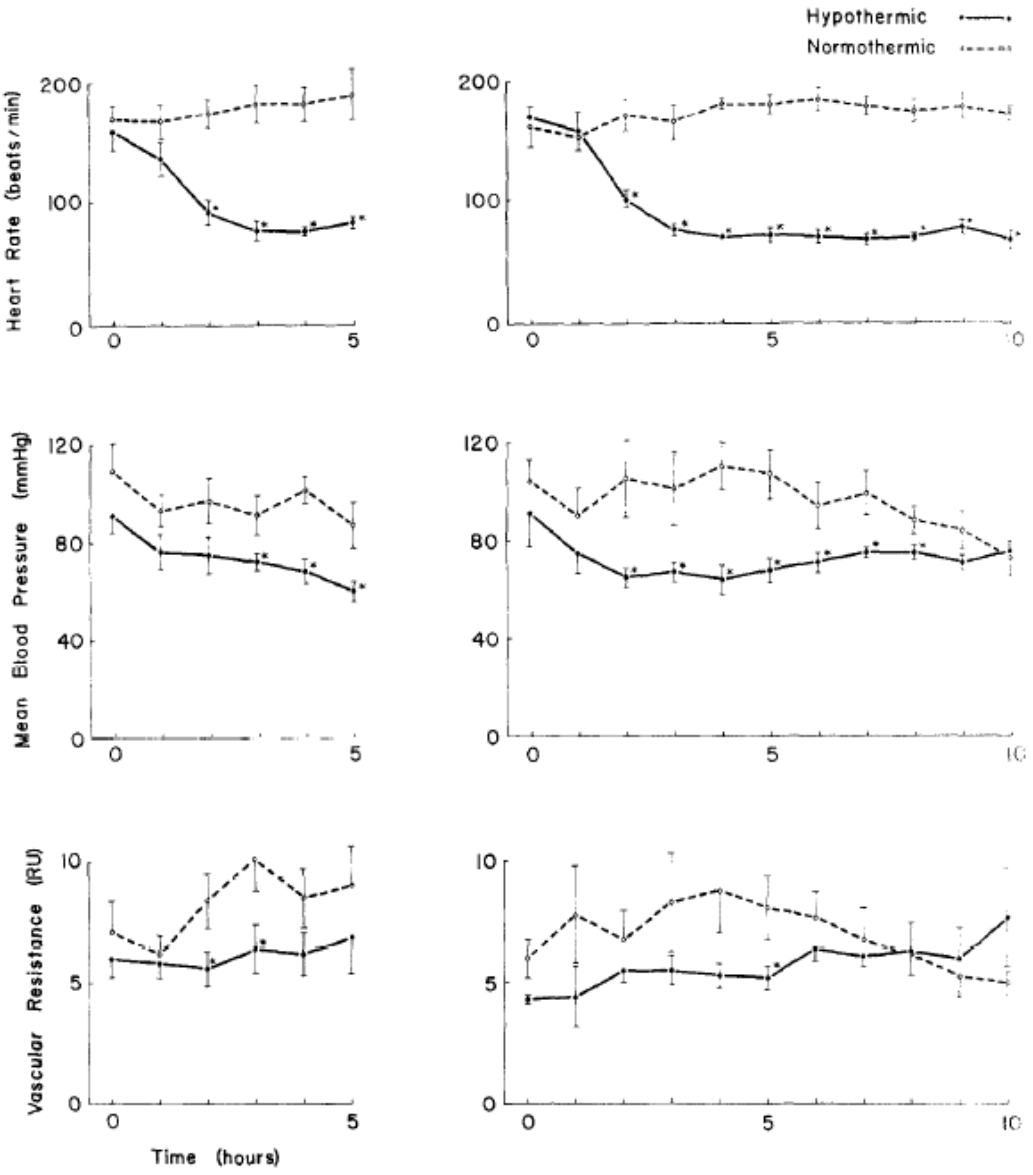

Figure 3. The effect of hypothermia on heart rate, mean blood pressure, and vascular resistance during periods of 5 and 10 hours of coronary artery occlusion. Time "0" indicates occlusion. Points represent the mean (n = 5) ± one standard deviation. * indicates that the mean values of the hypothermic and normothermic groups differ significantly (p< 0.05).

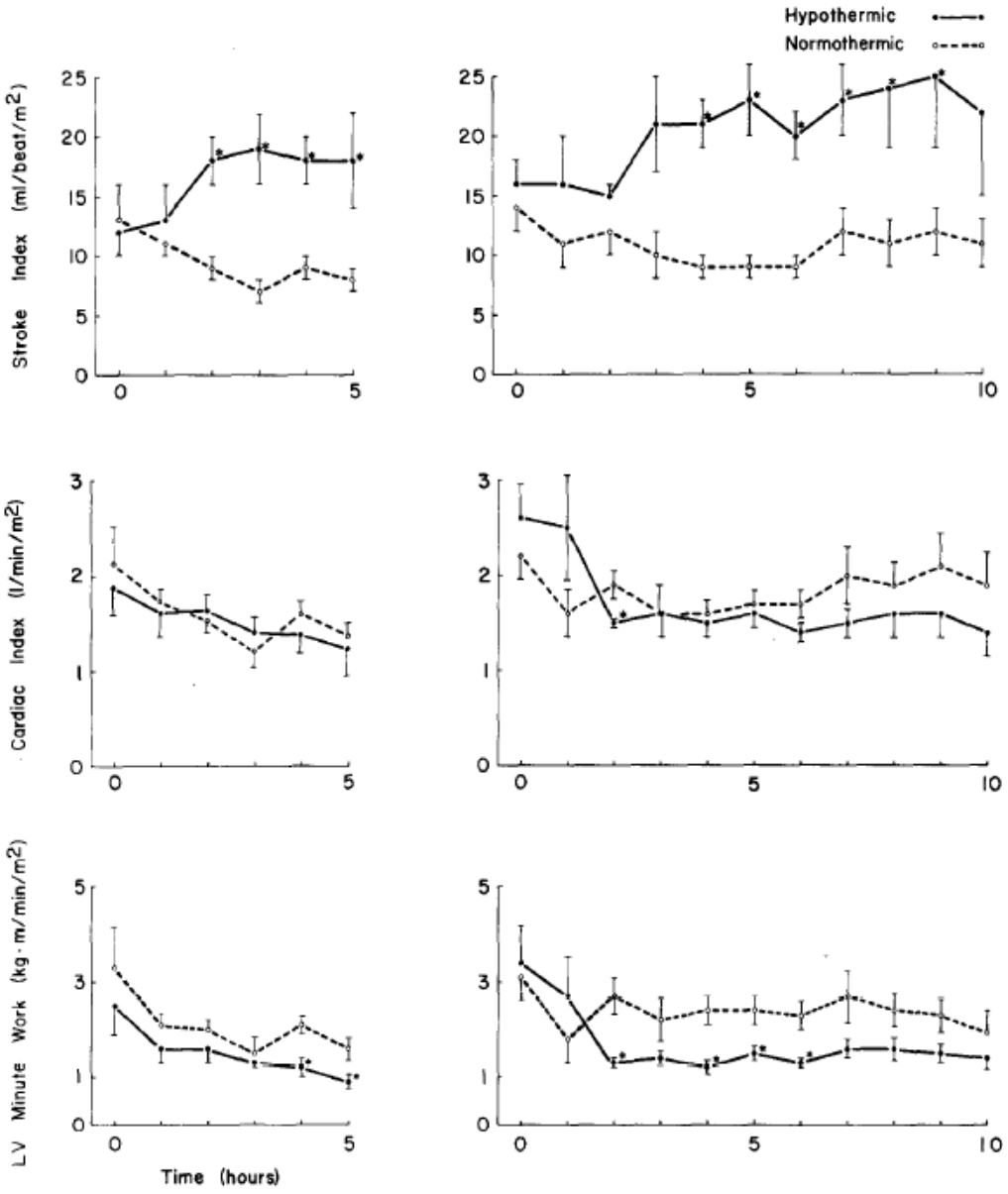

Figure 4. The effect of hypothermia on stroke index, cardiac index, and left ventricular (LV) minute work during periods of 5 and 10 hours of coronary artery occlusion. Time "0" indicates occlusion. Points represent the mean (n = 5) ± one standard deviation. * indicates that the mean values of the hypothermic and normothermic groups differ significantly (p < 0.05).

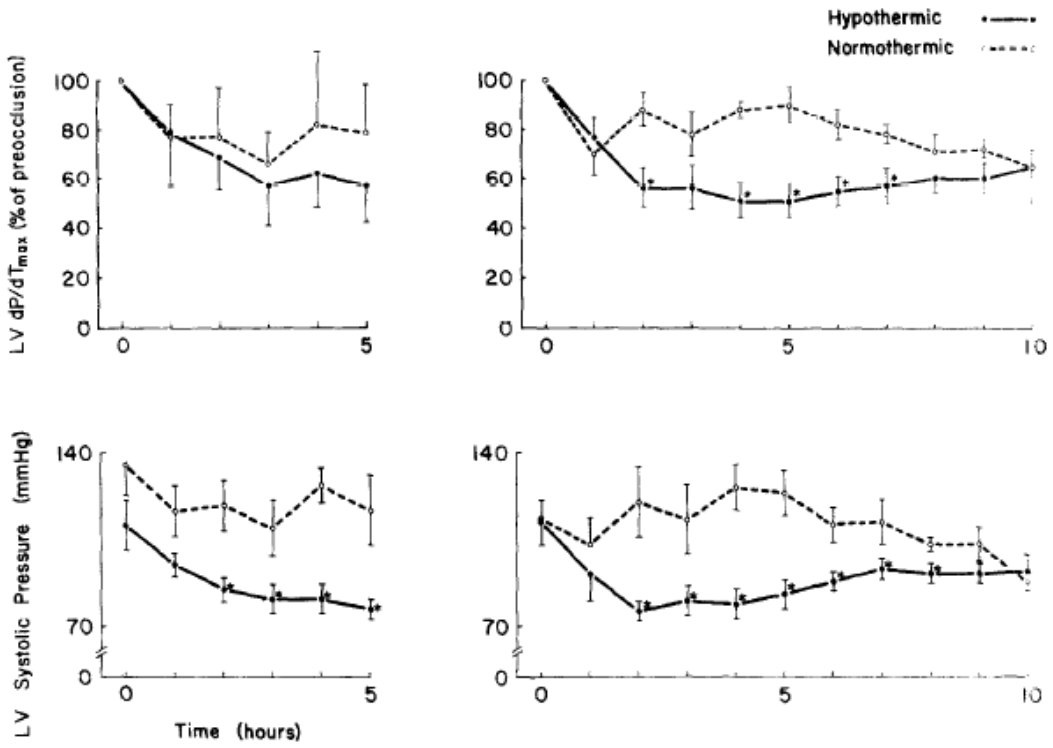

Figure 5. The effect of hypothermia on maximum left ventricular (LV) dP/dt and LV systolic pressure during periods of 5 and 10 hours of coronary artery occlusion. Time "0" indicates occlusion. Points represent the mean (n = 5) ± one standard deviation. The absolute values of dP/dt at time "0" were 2,640 mmHg/sec in the hypothermic group and 4,680 mmHg/sec in the normothermic group of the 5 hour study (p < 0.05) and 3,120 mmHg/sec in the hypothermic group and 3,160 mmHg/sec in the normothermic group of the 10 hour study (p = N.S.). * indicates that the mean values of the hypothermic and normothermic groups differ significantly (p < 0.05).

Table 1. Left ventricular end-diastolic pressures.

Time (hours)	*Number of dogs in each group*	*Hypothermic (mean LVEDP ± S.D.)*	*Normothermic (mean LVEDP ± S.D.)*	*Hypothermic–normothermic*	*t*	*p*
0	10	0.5 ± 0.8	0.5 ± 0.8	0	0	0.5
1	10	1.5 ± 1.2	1.5 ± 1.2	0	0	0.5
2	10	2.5 ± 1.3	0.8 ± 0.6	+1.7	1.7	> 0.1
3	10	3.0 ± 1.8	1.0 ± 1.1	+2.0	1.6	> 0.1
4	10	3.0 ± 1.3	2.5 ± 1.3	+0.5	0.9	> 0.1
5	10	2.5 ± 1.3	2.5 ± 1.8	0	0	0.5
6	5	0.0 ± 0.0	2.0 ± 2.2	−2.0	1.0	> 0.1
7	5	0.0 ± 0.0	1.0 ± 1.1	−1.0	1.0	> 0.1
8	5	0.0 ± 0.0	2.0 ± 1.3	−2.0	1.6	> 0.1
9	5	0.0 ± 0.0	1.0 ± 1.1	−1.0	1.0	> 0.1
10	5	0.0 ± 0.0	1.0 ± 1.1	−1.0	1.0	> 0.1

Discussion

Prevention of cardiogenic shock and death after acute myocardial infarction is largely dependent upon the containment of infarct size. Since an imbalance between oxygen supply and demand in the ischemic tissue results in myocardial necrosis, interventions that improve this balance could significantly reduce the size of an infarct. Thus, beta-adrenergic blockade with propranolol [1], intra-aortic balloon counterpulsation [19], and nitroglycerin [3] have been shown to decrease ischemic injury following coronary artery occlusion. In the present study, whole body hypothermia appeared to decrease the extent of ischemic injury produced by either 5 or 10 hours of coronary occlusion. Histochemical staining of the sliced ventricles showed less metabolic deterioration in the ischemic region of dog hearts cooled to 26 °C. Histologic findings after 10 hours of occlusion were consistent with the histochemical results, indicating that the morphologic tissue damage was also less in the ischemic region of hypothermic dog hearts.

A possible explanation of these findings is that hypothermia decreased oxygen demand in ischemic myocardium. This is inferred from the following observations. First, the decrease in heart rate during hypothermia implies that minute myocardial oxygen consumption was reduced because pressure was developed fewer times each minute. Blair [20] has reported that the direct effect of reduced temperature on the metabolic rate of the myocardium causes the decline in heart rate and a parallel decrease in oxygen consumption during cooling to 25°C. Second, depressed contractility in hypothermic dogs, indicated by decreases in both the maximum rate of rise of left ventricular pressure, $(dP/dt)_{max}$, and the peak systolic pressure, implies that the oxygen consumption during active contraction was decreased. Reduced contractility has also been reported by Holobut and Stazka [21] and by Delin and associates [22] in normal dogs cooled to comparable body temperatures. However, these findings conflict with reports showing a positive inotropic effect of hypothermia in normal dogs and in dogs with infarction, probably because of differences in experimental conditions such as method of measuring contractility, ventricular loading, and level of anesthesia [23, 24]. Third, lower left ventricular afterload (i.e., systemic vascular resistance) in hypothermic dogs may have contributed to a reduction in

myocardial oxygen demand by decreasing cardiac minute work (external power). Since oxygen utilization is known to be higher for pressure work than for volume work [25], hypothermic hearts probably consumed less oxygen to maintain the same cardiac index as normothermic hearts by increasing the stroke index against a reduced aortic pressure.

The finding that hypothermia increased stroke index while end-diastolic pressure remained unchanged suggests that the performance of the left ventricle was improved. Enhanced performance may have resulted from decreased afterload. Our results are consistent with other studies, which have shown that hypothermia improves cardiac function and does not promote heart failure in dogs with myocardial infarction [11] or cardiogenic shock [12, 13, 26, 27]. Although hypothermia may only inhibit the necrosis of ischemic myocardium, which, upon rewarming, will ultimately become infarcted, this study suggests the potential value of cooling *per se* as a means of protecting the heart until a definitive procedure, such as aortocoronary bypass, can be initiated. Maroko and colleagues [28] have shown that ischemic myocardium in dogs at normal body temperature may be salvaged if revascularization is accomplished within 2 to 4 hours after coronary occlusion. Since clinically the delay between the onset of acute ischemia and admission to surgery often exceeds four hours, the preoperative use of whole-body hypothermia might well extend the time frame within which revascularization could be successfully completed.

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