Recovery from Cardiac Bypass and Elective Cardiac Arrest

THE METABOLIC CONSEQUENCES OF VARIOUS CARDIOPLEGIC PROCEDURES IN THE ISOLATED RAT HEART

By David J. Hearse, David A. Stewart, and Ernst B. Chain

ABSTRACT

Isolated perfused working rat hearts were subjected to elective cardiac arrest for 20 or 30 minutes. Various methods of arrest, either singly or in combination and with or without coronary perfusion, were studied. The functional recovery of the heart following the termination of arrest was related to the concentration of adenosine triphosphate (ATP) and creatine phosphate in the myocardium at the end of the period of arrest. In turn, these concentrations depended on the method used to induce arrest. Normothermic ischemic arrest or electrical fibrillation led to a marked reduction in high-energy phosphates and poor functional recovery. In contrast, coronary perfusion with hypothermic solutions or solutions containing high concentrations of potassium induced arrest without depleting ATP or creatine phosphate. These procedures conferred considerable protection on the myocardium and thus permitted good recovery. The energy status and the recovery associated with ischemic arrest were improved by combining the ischemia with potassium-induced arrest, intermittent coronary perfusion, or hypothermia. In the latter instance, a time- and temperature-dependent relationship was demonstrated. The results stress the importance of maintaining ATP and creatine phosphate levels during arrest; such maintenance requires the provision of a continuous supply of oxygen and nutrient, which may perhaps be best achieved by ensuring continuous and adequate coronary perfusion.

KEY WORDS

creatine phosphate
hypothermic arrest
adenosine triphosphate
potassium-induced arrest
coronary perfusion
defibrillation
ischemic arrest

Elective cardiac arrest (cardioplegia) in combination with cardiopulmonary bypass is used extensively during open heart surgery. Since its introduction (1), this technique for providing a motionless surgical field has contributed greatly to the increasing sophistication and success of cardiac surgery. Under experimental conditions, cardiac arrest can be induced by a variety of procedures including ischemia following aortic cross-clamping, electrically triggered ventricular fibrillation, topical hypothermia or hypothermic perfusion, and the introduction of acetylcholine, tetrodotoxin, or high concentrations of potassium into the coronary tree. Ischemic arrest, hypothermic arrest, and electrical fibrillation, either singly or in combination, are in widespread clinical use. Until myocardial tissue-damaging effects were reported (2–5), potassium citrate-induced arrest was also widely used.

Each cardioplegic procedure has a different biochemical basis; therefore, each is likely to have different metabolic and functional consequences. Despite several detailed experimental (6–14) and clinical (15, 16) studies of the biochemical and functional consequences of various methods of elective cardiac arrest, considerable controversy (15–18) still exists over the merits and the hazards of different cardioplegic procedures. In addition, the importance of maintaining coronary perfusion during bypass and arrest is often questioned (17, 19, 20).

Studies to date point out the importance of ensuring maximum metabolic protection (particularly with respect to energy metabolism) during elective cardiac arrest and of using only those methods of arrest which cause minimum metabolic and morphologic damage. The recurrent controversy over the suitability of various cardioplegic procedures illustrates how difficult it is to relate and evaluate available information. These difficulties can be explained in part by the variety of experimental models and conditions that have been studied. A major complication arises over
coronary perfusion: hypothermic arrest, potassium-induced arrest, and electrical fibrillation can all be achieved with continuous, intermittent, or no coronary perfusion. The heart can be arrested with potassium by loading the coronary tree with a single volume of potassium citrate prior to the termination of coronary flow; under these conditions, tissue ischemia coexists with potassium-induced arrest and it is difficult to dissociate the metabolic effects of potassium from those of ischemia.

Additional difficulties arise from the use of experimental animal models, e.g., isolated perfused guinea pig hearts. Although a Langendorff (21) perfusion provides a good model for cardiac bypass with coronary perfusion, it has limited value in attempts to assess functional recovery, e.g., the ability to do external work, after arrest and bypass. The recent availability of the isolated working heart preparation (22) overcomes this problem.

We therefore decided to undertake a series of studies using the isolated perfused working rat heart; we assessed how various methods of elective cardiac arrest, with and without coronary perfusion, affected the functional recovery of the heart after arrest. In addition, we attempted to relate the cardioplegic method and the recovery of the heart to changes in cellular energy metabolism with particular reference to adenosine triphosphate (ATP) and creatine phosphate.

Methods

Male rats (280–320 g) of the Sprague-Dawley strain maintained on a standard diet were used in these experiments. All substrates and enzymes used in the analysis of tissue extracts were obtained from the Boehringer Corporation.

PERFUSION TECHNIQUES

Rats were lightly anesthetized with diethyl ether, the left femoral vein was exposed, and heparin (200 IU, iv) was administered. One minute after the administration of heparin, the heart was excised (22) and placed in ice-cold perfusion medium until contraction had ceased. The heart was then mounted on the perfusion apparatus. The mounting procedure and the apparatus were based on those described by Neely et al. (22) and Chain et al. (23), but two modifications were employed. First, an electronic flowmeter (Devices Instruments Ltd.) calibrated for flow at 37°C was introduced to measure aortic flow rates, a pressure transducer (S.E. 4-82, S.E. Laboratories Ltd.) was attached to the aortic cannula, and a direct-writing multichannel recording system (M19 recorder, Devices Instruments Ltd.) equipped with an instantaneous rate meter was used to record aortic flow rate, aortic pressure, and heart rate. Second, constant-head devices designed to accurately maintain a constant level of perfusate and hence a constant perfusion pressure were added to all perfusion fluid reservoirs. The perfusion apparatus was designed so that it could be used for two modes of perfusion which could be readily interconverted. (1) In the nonworking Langendorff preparation, hearts were perfused via the aorta as described by Langendorff (21) with a perfusion pressure of 65 cm H₂O. This mode of perfusion was used for an initial washout period and also for periods of elective cardiac arrest in which coronary perfusion was required. (2) In the working system, hearts were perfused via the left atrium as described by Neely et al. (22) at an atrial perfusion pressure of 20 cm H₂O. The left ventricle spontaneously ejected 40–50 ml perfusate/min against a hydrostatic pressure of 100 cm H₂O. The aortic output and the coronary flow could be pooled and recirculated. This preparation was used for the control working period prior to elective cardiac arrest and for the recovery period following arrest.

It was therefore possible to simulate cardiac bypass with coronary perfusion (with or without elective cardiac arrest) by converting the preparation from an atrially perfused working heart to a Langendorff preparation (with or without cardiac arrest).

In all perfusions, with the exception of the hypothermic studies, the perfusion fluid was maintained at 37°C. In all experiments, the heart was kept in a water-jacketed chamber at the same temperature as the perfusion fluid. In studies with no coronary perfusion, the heart chamber was maintained at 37°C or the desired degree of hypothermia. Nonperfusion of the coronary system was achieved by clamping the cannulas leading to the aorta and the left atrium. In fibrillation studies, electrical fibrillation was maintained with a constant source (50 cycles a-c, 2-4 ma). Defibrillation was achieved with 15-v d-c single or multiple pulses 2-5 msec in duration.

PERFUSION MEDIUM

Krebs-Henseleit bicarbonate buffer (24), pH 7.4, plus glucose (11.1 mm) was the standard perfusion fluid. In studies with potassium-induced arrest, the concentration of potassium in the buffer was increased to 16 mm and the concentration of sodium was correspondingly decreased. The perfusion fluid was equilibrated with 95% O₂-5% CO₂ (aortic O₂ partial pressure was over 600 mm Hg). Precautions (25) were taken to prevent the precipitation of calcium. Before use, the perfusion fluid was filtered through a cellulose-acetate filter with 5.0-μm pores (Millipore Ltd.).

PERFUSION-TIME SEQUENCE

To allow an estimate of recovery and to eliminate errors resulting from variation between individual hearts, a control working perfusion period preceded all periods of experimental cardioplegia. Immediately after mounting, the heart was perfused using a nonrecirculating Langendorff system for a 5-minute washout period. The preparation was then converted to a working heart system for a 15-minute period. During this time, the stability of the preparation was confirmed and control values for rate, aortic pressure, aortic flow rate, and coronary flow rate of the working heart were established. As an index of external work, aortic flow rate against a hydrostatic pressure of 100 cm H₂O was monitored. At
the end of the control period, each preparation was subjected to cardioplegia under one of a variety of conditions. (1) Continuous electrical fibrillation with normothermic coronary perfusion for a 30-minute period (Langendorff preparation, 65 cm H₂O perfusion pressure) with defibrillation at the end of the experimental period. (2) Potassium-induced arrest with normothermic coronary perfusion for a 30-minute period (Langendorff preparation, 65 cm H₂O perfusion pressure). (3) Hypothermic (4°C) coronary perfusion for a 30-minute period (Langendorff preparation, 65 cm H₂O perfusion pressure). (4) Normothermic ischemic arrest (no coronary perfusion) for 20- and 30-minute periods. (5) Normothermic potassium-induced arrest (30 minutes) without coronary perfusion. (6) Normothermic alternate nonperfusion (5 minutes) and perfusion (5 minutes), commencing with nonperfusion, for a total period of 30 minutes (Langendorff preparation, 65 cm H₂O perfusion pressure) and continuous electrical fibrillation with defibrillation at the end of the experimental period. (7) Condition 6 without fibrillation (as a control to condition 6, these hearts were subjected to a "defibrillation" pulse at the end of the experimental period). (8) Condition 6 except that the experimental period was commenced with a period (5 minutes) of perfusion as opposed to a period of nonperfusion. (9) Condition 7 except that the experimental period was commenced with a period (5 minutes) of perfusion as opposed to a period of nonperfusion. (10) Ischemic arrest for 20- and 30-minute periods with hypothermia (4°C, 15°C, 21°C, and 30°C). (11) Normothermic perfusion without arrest for 30 minutes (Langendorff preparation, 65 cm H₂O perfusion pressure) but with a defibrillation pulse at the end of the experimental period. Condition 11 constituted a control experiment.

At the end of the experimental period cardioplegia was terminated, and the hearts were converted to a working system. Recovery of aortic flow and the other parameters was monitored over a 15-minute period; recovery values were expressed as percents of the control values. At least six hearts were studied under each of the experimental conditions.

**TISSUE ANALYSIS**

In a parallel series of experiments, hearts were subjected to the experimental periods (at least eight hearts for each) described in the preceding section. However, at the end of the experimental period, instead of allowing the hearts to recover, the perfusions were terminated by freezing the hearts between stainless steel tongs (26) cooled to the temperature of liquid nitrogen. To remove frozen perfusate around the edges of the heart and also to remove the atrium, the heart was placed on a block of solid CO₂ and the unwanted parts were chipped away with a spatula that had been cooled in liquid nitrogen. The remaining frozen muscle was then powdered in a percussion mortar maintained at the temperature of liquid nitrogen. A small portion (about 100 mg) of the powder was transferred to a weighed container for the determination of dry weight. A second portion (about 200 mg) was used for the determination of ATP and creatine phosphate.

**Dry Weight Determination.**—The weighed tissue sample was dried for 12 hours at 105°C, cooled in vacuo, and reweighed for the determination of water loss. Because of the possibility of tissue edema and residual perfusion fluid in tissue preparations, all results were expressed per gram dry weight.

**ATP and Creatine Phosphate Determination.**—The frozen tissue powder was placed in a preweighed tube containing 4.0 ml of ice-cold 6% (v/v) perchloric acid, rapidly homogenized, and reweighed. The solution was centrifuged (10 minutes, 2,000 g), and the supernatant fluid was adjusted to pH 7.0 by the addition of 30% (w/v) KOH saturated with KCl. The solution was recentrifuged (10 minutes, 2,000 g), the supernatant fluid was retained, and its volume was recorded. The resulting solution was then used for the determination of ATP and creatine phosphate as described by Opie et al. (27).
<table>
<thead>
<tr>
<th>Conditions during experimental period</th>
<th>Duration (minutes)</th>
<th>Heart rate (beats/min)</th>
<th>Peak systolic pressure (cm H₂O)</th>
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<td>Normothermic coronary perfusion without cardioplegia</td>
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<td>Normothermic potassium-induced arrest with coronary perfusion</td>
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<td>209 187 185 188</td>
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<td>Hypothermic (4°C) coronary perfusion</td>
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<td>Normothermic ischemic arrest with intermittent coronary perfusion, fibrillating preparation, recovery period preceded by period of nonperfusion</td>
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Control values were obtained 2 minutes prior to the onset of arrest. Recovery values were obtained 5, 10, and 15 minutes after the termination of arrest. Each value represents the mean for six hearts.
Results

NORMOTHERMIC CORONARY PERFUSION WITHOUT CARDIOPLEgia

These hearts (N = 6) were perfused aerobically for 30 minutes without cardioplegia and served as a control for the other conditions studied. The results (Fig. 1 and Table 1) showed that, after conversion to an atrially perfused working preparation following 30 minutes of Langendorff perfusion, all hearts recovered to 100% of the control aortic output in less than 1 minute. The results of tissue analysis (Table 2) showed that, at the end of the 30-minute period of aerobic perfusion the concentrations of ATP and creatine phosphate in the hearts (N = 8) were 26.2 ± 1.7 μmoles/g dry weight and 20.5 ± 1.6 μmoles/g dry weight, respectively. These concentrations are in the ranges associated with normal healthy myocardial tissue.

ELECTRICAL FIBRILLATION WITH NORMOTHERMIC CORONARY PERFUSION

Hearts (N = 8) were perfused aerobically and subjected to continuous electrically induced ventricular fibrillation for 30 minutes. At the end of this period, concentrations of ATP and creatine phosphate (Table 2) were 9.2 ± 1.7 μmoles/g dry weight and 10.9 ± 3.1 μmoles/g dry weight, respectively. These levels were less than half of those observed in the control hearts, and this difference was clearly reflected in the recovery profiles (Fig. 1). On defibrillation and conversion to working preparations, the hearts (N = 6) recovered to only 80% in the first minute and even after 15 minutes had only recovered to 85% of the control value. These results illustrate the marked effect on recovery attributable to electrical fibrillation.

POTASSIUM-INDUCED ARREST WITH NORMOTHERMIC CORONARY PERFUSION

Hearts (N = 8) were arrested with potassium and perfused aerobically for 30 minutes. At the end of this period, the concentrations of ATP and creatine phosphate in the myocardium (Table 2) were 20.8 ± 1.2 μmoles/g dry weight and 35.5 ± 2.6 μmoles/g dry weight, respectively. As with the nonarrested control hearts, the recovery profile...
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(Fig. 1) for these hearts (N = 6) reflected the high concentrations of ATP and creatine phosphate; it reached 100% recovery in approximately 1 minute and was maintained at this or a higher level for the duration of the experiment.

HYPOTHERMIC CORONARY PERFUSION

Hearts (N = 8) were hypothermically arrested for 30 minutes by aerobic perfusion at 4°C. At the end of this period, the myocardial concentrations of ATP and creatine phosphate (Table 2) were 20.5 ± 1.0 μmoles/g dry weight and 25.8 ± 1.8 μmoles/g dry weight, respectively. Again, these levels were reflected in the recovery profiles (Fig. 1) of the hearts (N = 6).

NORMOTHERMIC ISCHEMIC ARREST

Coronary perfusion was halted for a period of either 20 minutes (8 hearts) or 30 minutes (8 hearts). After 20 minutes of normothermic ischemia, the concentrations of ATP and creatine phosphate had declined to 13.5 ± 0.8 μmoles/g dry weight and 4.3 ± 0.4 μmoles/g dry weight, respectively; after 30 minutes, they had declined further to 5.3 ± 0.9 μmoles/g dry weight and 2.8 ± 0.4 μmoles/g dry weight (Table 2). In comparison with the control hearts, the recovery profile after 20 minutes of ischemic arrest (Fig. 2 left) was greatly reduced. Recovery was variable, slow, and incomplete, a result which is in agreement with the observed low concentrations of myocardial high-energy phosphates. When ischemic arrest was extended to 30 minutes (Fig. 1), these concentrations were even lower, resulting in a further reduction in recovery.

NORMOTHERMIC POTASSIUM-INDUCED ARREST WITHOUT CORONARY PERFUSION

Hearts (N = 8) were arrested by perfusing the coronary arteries with high-potassium (16.0 mM) buffer for 1 minute, coronary perfusion was then terminated, and the arrested hearts were maintained at 37°C for 30 minutes. At the end of this period, the concentrations of ATP and creatine phosphate in the myocardium (Table 2) were 11.1 ± 4.2 μmoles/g dry weight and 9.4 ± 2.1 μmoles/g dry weight, respectively. The recovery (Fig. 1) of these hearts was poor, reaching only 40% after 15 minutes. The recovery and the high-energy phosphate levels were, however, considerably better than those observed with 30 minutes of ischemic arrest alone. This finding indicates a protective role for the potassium.

NORMOTHERMIC ISCHEMIC ARREST WITH INTERMITTENT CORONARY PERFUSION

In ischemic arrest, the severity of damage depends on the duration of ischemia. In an attempt to circumvent major ischemic damage, hearts (N =
were aerobically perfused (5 minutes) between periods (5 minutes) of ischemia. After a total of 30 minutes, the hearts were converted to continuously perfused working preparations. The results (Fig. 3), in contrast to those obtained after 30 minutes of uninterrupted ischemic arrest (Fig. 1), showed considerably improved recovery. Again, the extent of recovery reflected the concentration of high-energy phosphates in the myocardium (Table 2) at the end of the experimental period. Figure 3 shows the recovery for hearts \( N = 6 \) in which the arrangement of the intermittent perfusion was such that the recovery phase was preceded by a 5-minute period of nonperfusion and for hearts \( N = 6 \) in which the recovery phase was preceded by a 5-minute period of perfusion. Although the total duration of nonperfusion and perfusion was the same in both cases, the recoveries were significantly different. Hearts perfused immediately prior to recovery exhibited better recovery in both the short and the long term. This result agrees with the higher concentrations of ATP and creatine phosphate existing under these conditions (Table 2). These differences illustrate well the rapidity with which cellular concentrations of ATP and creatine phosphate can change.

**Normothermic Ischemic Arrest with Intermittent Coronary Perfusion and Continuous Electrical Fibrillation**

The intermittent perfusion described in the preceding section resulted in a rapid resumption of beating during the perfusion period. To maintain continuous arrest throughout the experimental period, the preceding study was repeated with continuous electrical fibrillation. The observed recoveries (Fig. 3) further reinforced the observations made in the preceding sections. First, electrical fibrillation reduces cellular concentrations of ATP and creatine phosphate and these reductions in turn lead to considerably reduced recoveries. Second, the concentrations of ATP and creatine phosphate (Table 2) can change so rapidly that the extent of the duration of ischemia prior to the resumption of perfusion and beating can drastically modify the final recovery profile.

**Ischemic Arrest with Hypothermia**

The recovery following ischemic arrest (Fig. 1 and Fig. 2 left) and the corresponding ATP and creatine phosphate values (Table 2) showed that damage progressed rapidly with increasing durations of ischemia. Clinically, ischemic arrest in combination with topical hypothermia is widely used. We therefore investigated how the recovery of the heart was affected by both the degree of hypothermia and the duration of ischemia. Hearts were subjected to 20 and 30 minutes of ischemic arrest at 4°C, 15°C, 21°C, 30°C, and 37°C. The recoveries (normothermic) and the high-energy phosphate values are illustrated in Figure 2 (right and left) and Table 2, respectively. The results illustrate a marked temperature-time dependence; very good recovery occurred with severe hypothermia (4°), but a rapidly deteriorating recovery occurred when the temperature was greater than 15-20°C. The high-energy phosphate values reflected the recovery; Figure 4 shows the correla-
Correlation ($r = 0.96, P < 0.001$) between the final recovery and the total concentration of ATP and creatine phosphate in the experiments involving hypothermic arrest.

**Discussion**

The results of the experiments described in this paper illustrate how the cardioplegic method affects the survival and the subsequent recovery of the heart. In each instance, the recovery was closely related to the levels of ATP and creatine phosphate in the myocardium at the end of the period of arrest. In general, the higher the total level of high-energy phosphates, the greater was the rate and the extent of recovery. Cardioplegic methods, e.g., ischemic arrest, which achieve their objective by bringing about the increased utilization or the depletion of cellular energy reserves are detrimental to the survival and the recovery of the tissue.

The observed poor recovery following ischemic arrest was not unexpected. From a theoretical viewpoint and from a knowledge of the rapid, deleterious metabolic changes which follow coronary artery occlusion (28–30), one would expect anoxic cardiac arrest, induced by the cessation of coronary perfusion, and the resulting tissue ischemia to produce tissue damage. In a previous study (31), we have proposed that the ability of the heart to survive during and to recover from anoxia is closely related to the availability of myocardial high-energy phosphates, particularly ATP. The depletion of ATP and creatine phosphate described in the present paper agrees with the findings of Isselhard et al. (9) who studied the changes in the concentrations of substrates and metabolites of the glycolytic pathway, ATP, adenosine diphosphate, adenosine monophosphate, and creatine phosphate in the guinea pig heart during normothermic ischemic arrest. Despite the stimulation of anaerobic glycolysis, energy liberation was insufficient to meet cellular energy demands, and ATP and creatine phosphate were severely depleted. In studies of human myocardium during bypass, depletion of ATP and creatine phosphate has been reported (32).

The reduction of high-energy phosphates and the poor cardiac recovery associated with normothermic ischemic arrest can be markedly altered by the use of topical hypothermia. Our results showed a time-dependent relationship between the degree of hypothermia and the recovery of the hearts. This finding paralleled a similar relationship between the level of high-energy phosphates and the recovery of the hearts. These results are consistent with the fact that, in addition to inducing cardiac arrest, hypothermia has the advantage of conferring considerable protection on the myocardium by greatly reducing the metabolic rate (2, 3, 16, 33, 34). Bretschneider (8) has reviewed the effect of normothermic and hypothermic arrest on the survival and the recovery time of the human heart and has also shown that protection increases with increasing degrees of hypothermia.

Cardiac recovery to control values and maintenance of ATP and creatine phosphate can only be obtained with hypothermic perfusion or severe (4°C) topical hypothermia. In contrast, recovery to levels above the control values can be obtained following normothermic arrest by continuous perfusion of the coronary arteries with 16 mm potassium. It is interesting to note that, in addition to the recovery exceeding 100%, the level of creatine phosphate in the myocardium at the end of arrest also exceeded the control value. This finding may reflect a much reduced cellular energy requirement during arrest; a similar elevation of creatine phosphate during aerobic potassium-induced arrest has been reported by Lochner et al. (7). These workers studied the myocardial concentrations of ATP and creatine phosphate and the recovery of the Langendorff-perfused guinea pig heart after periods of
potassium-induced arrest under aerobic and anaerobic conditions. They demonstrated that the heart could be resuscitated after 90 minutes of potassium chloride–induced arrest.

Due to observed tissue-damaging effects, potassium-induced arrest is no longer used clinically. However, it is important to appreciate that in the clinical studies there was no coronary perfusion and thus ischemia also existed, the concentrations of potassium employed were very high, and also potassium citrate was used instead of potassium chloride. The presence of high concentrations of citrate may exacerbate damage by preventing anaerobic ATP production by inhibition (35) of the glycolytic pathway. Our results demonstrated that the introduction of the element of ischemia into potassium-induced arrest reduced the high-energy phosphates and also recovery. However, in contrast to ischemic arrest alone, recovery was superior. This finding may possibly be explained by energy conservation through a more rapid arrest and by the reported (7) ability of potassium chloride to depress muscle metabolism.

Several studies of the metabolic consequences of electrically induced ventricular fibrillation have been reported. Although Lamprecht (32) has concluded that fibrillation combined with coronary perfusion has little influence on cardiac metabolism, other workers (36, 37) have reported deleterious effects on myocardial metabolism and function. Our results indicated that 30 minutes of electrically induced fibrillation reduced the cardiac recovery profiles. Myocardial ATP and creatine phosphate levels were also considerably reduced. The mechanism of this depletion is not known, but presumably there is either an increased rate of utilization due to the intense electromechanical activity or a reduced rate of energy production possibly due to a degree of subendocardial ischemia induced by the fibrillation.

In conclusion, the results described in this paper, in addition to underlining the importance of the concentration of high-energy phosphates in the survival and the recovery of the heart, illustrate (from the intermittent perfusion studies) how rapidly cellular concentrations of these intermediates can change. From the viewpoint of myocardial protection during cardioplegia, these studies stress the importance of maintaining levels of cellular high-energy phosphates. This latter condition requires the provision of a continuous supply of oxygen and substrate, which may possibly be best achieved by ensuring continuous and adequate coronary perfusion.

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