Maintenance of aerobic metabolism during global ischemia with perfluorocarbon cardioplegia improves myocardial preservation

JOHN T. FLAHERTY, M.D., JONATHAN H. JAFFIN, M.D., GEORGE J. MAGOVERN, JR., M.D., KIRK R. KANTER, M.D., TIMOTHY J. GARDNER, M.D., MICHAEL V. MICELI, PH.D., AND WILLIAM E. JACOBUS, PH.D.

ABSTRACT We used phosphorus-31 nuclear magnetic resonance to test the ability of a perfluorocarbon blood substitute that has been shown in previous studies to improve oxygen delivery to hypothermic myocardium to maintain aerobic high-energy phosphate metabolism during total global ischemia. Twenty-three isolated perfused rabbit hearts were subjected to 180 min of hypothermic (23°C) global ischemia followed by 45 min of normothermic reperfusion. Hearts received multiple doses of a cardioplegic solution that contained either oxygenated perfluorocarbon (Fluosol O₂), nonoxygenated perfluorocarbon (Fluosol N₂), or standard crystalloid hyperkalemic cardioplegic solution (STD-KCl) at 30 min intervals. Recovery of isovolumic left ventricular developed pressure (LVDP) was used to assess preservation of contractile function. Recovery of LVDP was 84 ± 19% of preischemic control values with Fluosol O₂, 68 ± 16% with Fluosol N₂, and 67 ± 17% with STD-KCl (p = .058 vs Fluosol N₂, and p = .056 vs STD-KCl). During 3 hr of ischemia intracellular pH (pHᵢ) fell to 6.68 ± 0.20 with STD-KCl and to 6.71 ± 0.14 with Fluosol N₂ but remained above 7.00 throughout the ischemic period with Fluosol O₂ (p < .0001 vs Fluosol N₂ or STD-KCl). Myocardial ATP content was better preserved at 107 ± 14% of control values with Fluosol O₂ compared to 60 ± 18% of control with Fluosol N₂ and 75 ± 21% of control with STD-KCl (p < .001 vs Fluosol N₂, p = .002 vs STD-KCl). Phosphocreatine (PCr) content rose an average of 77 ± 22% with Fluosol O₂ compared to 26 ± 15% with Fluosol N₂ and 44 ± 15% with STD-KCl (p < .001 vs Fluosol N₂ and STD-KCl). After reperfusion, pHᵢ and PCr rapidly returned to control values in all groups. Recovery of ATP content after reperfusion paralleled recovery of left ventricular function, while recovery of PCr did not. These results demonstrate the ability of an oxygenated perfluorocarbon blood substitute to (1) prevent the development of intracellular acidosis, (2) maintain ATP and phosphocreatine levels during prolonged periods of hypothermic global ischemia, and (3) reduce the accumulation of inorganic phosphate. Thus the addition of oxygenated perfluorocarbons to multidose hyperkalemic cardioplegia appears to permit sustained aerobic metabolism despite total global ischemia. Perfluorocarbons may provide additional myocardial protection for patients with compromised left ventricular function who require prolonged periods of elective ischemia while undergoing cardiac surgery.


OUR PREVIOUS WORK has demonstrated the effectiveness of multiple doses of a hyperkalemic cardioplegic solution for improving myocardial metabolism during global ischemia as well as for improving recovery of left ventricular function after reperfusion. Mass spectrometry allowed measurement of myocardial carbon dioxide and oxygen tensions during ischemia and reperfusion.¹ Phosphorus-31 nuclear magnetic resonance (³¹P NMR) allowed us to serially measure myocardial ATP, phosphocreatine (PCr), and inorganic phosphate (Pi) content as well as to monitor intracellular pH (pHᵢ).² Using these combined approaches we were able to demonstrate that multiple-dose cardioplegia resulted in lower intramural carbon dioxide tensions, less severe intracellular acidosis, and less depletion of high-energy phosphate stores compared with single-dose cardioplegia during an equivalent period
of global ischemia. Recovery of left ventricular function paralleled preservation of ATP content after reperfusion and/or prevention of intracellular acidosis during ischemia.

The present study was designed to test the hypotheses that pH and high-energy phosphate content would be even better maintained if aerobic metabolism could be sustained during ischemia by use of a cardioplegic solution containing oxygenated perfluorocarbon.

Materials and methods

Perfusion. Female New Zealand white rabbits (1.2 to 2.0 kg) were heparinized and anesthetized; their hearts were removed and quickly placed in cold (4°C) saline (150 mM sodium chloride). The ascending aorta was cannulated and the hearts were perfused with a modified Krebs-Ringer bicarbonate buffer solution containing 117 mM sodium chloride, 6 mM potassium chloride, 3.0 mM calcium chloride, 1.0 mM magnesium sulfate, 0.6 mM EDTA, and 16.7 mM glucose, with the final pH adjusted to 7.40 by the addition of approximately 24 mM sodium bicarbonate. The perfusate was bubbled continuously with 95% oxygen and 5% carbon dioxide. No phosphate was contained in the perfusate. Therefore all 31P NMR signals must be derived from tissue phosphorus metabolites. Perfusion pressure was 110 cm of water and the reservoir temperature was 40° to 41°C. Coronary flow was removed from the NMR sample tube by vacuum aspiration. Heart rate was held in the range between 150 to 170 beats/min by right ventricular pacing with a wick soaked in saturated potassium chloride, encased in polyethylene tubing, and connected to a Grass SD-9 stimulator. To measure left ventricular contractile function, a fluid-filled latex balloon was tied to the end of a 100 cm length of PE 190 polyethylene tubing, and connected to a Grass SD-9 stimulator. To measure left ventricular contractile function, a fluid-filled latex balloon was tied to the end of a 100 cm length of PE 190 tubing, carefully purged of air bubbles, and connected via a three-way stopcock to a Statham P 23 Db transducer. Isovolumic pressure was recorded during preschismic control and postschismic reperfusion periods with a Brush two-channel direct-writing recorder. The balloon was initially inflated via a syringe with a volume of H2O sufficient to produce a end-diastolic pressure of 10 mm Hg. All subsequent measurements of developed pressure were made at this end-diastolic volume. All hearts were subjected to 3 hr of global ischemia, during which the hearts were moderately hypothermic (23° ± 1°C). Total interruption of aortic inflow was accomplished by cross-clamping the perfusion line. A 10 ml dose of cold cardioplegic solution (10°C) was rapidly injected into the aortic root via a catheter attached to a side arm located just above the heart. Subsequent 20 ml doses at 23°C were administered at 30 min intervals throughout the 3 hr period of ischemia. Forty-five minutes of normothermic perfusion (37° ± 2°C) followed the period of ischemia. Recovery of left ventricular developed pressure (LVDP) was assessed after 15, 30, and 45 min of repuffusion. Postschismic recovery was calculated as a percentage of the preschismic control values. The balloon was deflated at the onset of ischemia and remained deflated throughout the ischemic period. The balloon was reinfated 15 min after initiating repuffusion with the same volume removed at the onset of ischemia, just before the first measurement of function. All hearts contracted spontaneously after repuffusion and did not require cardioversion.

NMR. 31P NMR spectra were obtained on a Bruker WH 180 spectrometer at 4.23 Tesla in a wide-bore superconducting magnet. At this field strength, phosphorus resonates at 72.89 MHz. The diameter of the phosphorus probe was 25 mm. This instrument was operated in the pulsed Fourier transform mode and interfaced to a Bruker 1080 computer, and the data were collect-

ed on low-density magnetic discs. Because of the field stability of the superconducting magnet, field/frequency lock was not required. Proton-decoupled spectra were collected from transients after 45 degree pulses delivered at 2 sec intervals, conditions previously documented to result in minimal spectral saturation. The data were accumulated with a 2K table at a 3000 Hz spectral width.

Estimation of tissue pH. Measurement of pH was determined from the chemical shift (δ) of the Pi peak by the following equation:

\[ \text{pH} = \text{pK} - \log \frac{\delta_b - \delta_A}{\delta_A - \delta_p} \]

To minimize effects of tissue inhomogeneity, chemical shift values were measured relative to the resonance of PCr, which is relatively pH independent over the range of pH encountered in these studies (pK_A = 4.6). The constants used in this equation are pK = 6.90, δ_A = 3.290 ppm, and δ_b = 5.805 ppm. The extensive validation of the method has been previously reported.

Quantitation of metabolites. Estimations of tissue PCr and ATP content, as well as Pi were obtained by planimetric measurement of the areas under the individual peaks allowing for the computer-determined normalization constant or scaling factor. A Hewlett-Packard digitizer was used to perform the area integrations. As a result of baseline irregularities and potential field inhomogeneity induced by tissue variability, quantitation of absolute metabolite content was not attempted. Thus the quantitative data derived for PCr, ATP, and Pi are expressed as percent of the preischmic control content. Data are presented as mean ± 1 SD, and statistical analyses were performed with the unpaired Student's t test or the repeated measures analysis of variance.

Experimental design. Twenty-three hearts were studied with three different hyperkalemic cardioplegic solutions. Nine hearts received cardioplegic solution containing 25 mM KCl and 44 mM glucose to which an oxygenated (95% O2, 5% CO2) perfluorocarbon (Fluosol DA, supplied courtesy of Alpha Therapeutics, Inc., and Green Cross Corp.) (20%) solution was added (Fluosol O2). Sodium bicarbonate was added in a quantity sufficient to titrate the cardioplegic solution to pH 7.40, yielding a final osmolality of 330 mOsm/l. Five additional hearts received cardioplegic solution similar in composition to the Fluosol O2 solution except that the perfluorocarbon was vigorously bubbled with 95% N2, 5% CO2 (Fluosol N2). A third group of nine hearts received standard hyperkalemic cardioplegic solution containing 25 mM KCl, 68 mM NaCl, 98 mM glucose, and 24 mM NaHCO3 (STD-KCl).

A control 31P NMR spectrum (300 pulses) was obtained during the preschismic period (10 min). After the onset of ischemia, three 150 pulse spectra (5 min) were sequentially obtained during 0 to 5, 5 to 10, and 10 to 15 min of ischemia. A 300 pulse spectrum was then collected between 20 and 30 min of ischemia. This sequence of four spectra was then repeated after each dose of cardioplegic solution administered at 30 min intervals. During the normothermic (37°C) reperfusion period, 150 pulse spectra were collected during 0 to 5, 5 to 10, and 10 to 15 min, and 300 pulse spectra during 20 to 30 and 35 to 45 min of reperfusion.

Results

Changes in pH. Before ischemia, control pH values were similar in all three groups: 7.16 ± 0.09 for Fluosol O2, 7.13 ± 0.12 for Fluosol N2, and 7.10 ± 0.07
for STD-KCl. In hearts receiving oxygenated perfluorocarbon the pH$_i$ remained above 7.00 throughout the 3 hr of ischemia (figure 1). The pH$_i$ at the end of the 180 min ischemic period was 7.10 ± 0.09 (p < .001 vs Fluosol N$_2$ and STD-KCl). In hearts receiving multiple doses of nonoxygenated perfluorocarbon, pH$_i$ fell more rapidly, reaching a final level of 6.71 ± 0.14 at the end of the ischemic period. In hearts receiving the standard crystalloid cardioplegic solution, pH$_i$ was 6.68 ± 0.20 at the end of the 180 min ischemic period. Thus the time course of change in pH$_i$ during the ischemic period in hearts receiving oxygenated perfluorocarbon was significantly different from that in the other two groups (p < .001). Hearts receiving the standard cardioplegic solution or the nonoxygenated perfluorocarbon solution demonstrated a rapid return of pH$_i$ to control levels after 10 min of reperfusion. In contrast, hearts receiving oxygenated perfluorocarbon showed an initial overshoot in pH$_i$, which reached 7.40 ± 0.13 during the first 10 min of reperfusion compared with 7.13 ± 0.24 for nonoxygenated perfluorocarbon and 7.15 ± 0.15 for standard cardioplegic solution (p = .057 vs Fluosol N$_2$, p = .002 vs STD-KCl).

With injections of cardioplegic solution, pH$_i$ rose 0.17 ± 0.09 pH units with oxygenated perfluorocarbon, 0.12 ± 0.09 pH units with nonoxygenated perfluorocarbon, and 0.07 ± 0.07 pH units with standard hyperkalemic cardioplegia (NS, p = .21 vs Fluosol N$_2$, p = .001 vs STD-KCl).

Changes in ATP content. In hearts receiving oxygenated perfluorocarbon cardioplegia, ATP levels remained above control values for the entire 3 hr period of ischemia (figure 2). ATP content at the end of the ischemic period was 107 ± 14% of control. In contrast, ATP content was 60 ± 18% in hearts receiving nonoxygenated perfluorocarbon cardioplegia and 75 ± 21% in hearts receiving standard crystalloid cardioplegia after 180 min of hypothermic global ischemia (p < .001 vs Fluosol N$_2$ and p = .002 vs STD-KCl).

The cyclic changes in ATP content in hearts receiving oxygenated perfluorocarbon were quite different from those in hearts receiving nonoxygenated perfluorocarbon (p = .002) or in hearts receiving standard crystalloid cardioplegia (p = .012). After each injection ATP content rose 19 ± 14% with oxygenated perfluorocarbon, compared with 11 ± 9% with non-oxygenated perfluorocarbon (p = .026 vs Fluosol O$_2$) and 14 ± 12% with standard crystalloid cardioplegia (NS, p = .13 vs Fluosol O$_2$). During the reperfusion period hearts in all three groups demonstrated a gradual decline in ATP content. However, the ATP content at the end of reperfusion remained proportional to the content at the end of the ischemic period. ATP content in the hearts that received oxygenated perfluorocarbon cardioplegia remained higher (76 ± 13% of control) compared with 57 ± 15% in hearts that received non-oxygenated perfluorocarbon (p = .047 vs Fluosol O$_2$) and 66 ± 15% in hearts that received standard crystalloid cardioplegic solution (NS, p = .16 vs Fluosol O$_2$).
Changes in PCr content. Myocardial PCr content showed the largest fluctuations after each injection of cardioplegic solution (figure 3). In hearts receiving oxygenated perfluorocarbon, PCr rose 77 ± 22% after each injection and then decreased over the ensuing 30 min. At the end of 3 hr of global ischemia, PCr content remained near control levels at 89 ± 25% of control. In contrast, in hearts receiving nonoxygenated perfluorocarbon, PCr increased by only 26 ± 15% (p = .08 vs Fluosol O₂) after each injection. At the end of the 3 hr ischemic period, PCr content in hearts receiving nonoxygenated perfluorocarbon had fallen to 14 ± 12% of control (p < .001 vs Fluosol O₂). In hearts receiving multiple doses of standard crystalloid KCl cardioplegic solution, PCr content rose 44 ± 15% after each injection (NS, p = .14 vs Fluosol O₂) and the PCr content at the end of the ischemic period was 32 ± 31% of control (p < .001 vs Fluosol O₂).

After reperfusion, hearts receiving oxygenated perfluorocarbon demonstrated an overshoot in PCr content, which peaked at 140 ± 24% of control within 5 min after reperfusion and then declined to normal levels (p < .001 vs Fluosol N₂ and p = .006 vs STD-KCl). Hearts receiving nonoxygenated perfluorocarbon did not show an overshoot, reaching only 76 ± 20% of control during the first 5 min of reperfusion. In hearts receiving STD-KCl the PCr content reached 96 ± 34% of control during the first 5 min of reperfusion. PCr content declined to approximately 87% of control by the end of the 45 min reperfusion period in all three groups.

Changes in Pi content. Pi levels also fluctuated widely...
after each injection of cardioplegic solution in all three experimental groups (figure 4). Hearts receiving Fluosol O₂ demonstrated the lowest mean Pi content (374 ± 80% of control) at the end of each 30 min period. After each injection Pi fell 255 ± 65% with Fluosol O₂, 195 ± 156% with Fluosol N₂, and 237 ± 112% with STD-KCl (NS). At the end of the 3 hr of global ischemia Pi reached only 374 ± 118% in the hearts receiving Fluosol O₂. In contrast, hearts receiving nonoxygenated Fluosol or STD-KCl reached 876 ± 312% and 813 ± 208%, respectively (p = .018, Fluosol O₂ vs Fluosol N₂; and p = .001, Fluosol O₂ vs STD-KCl).

After reperfusion, Pi content in all three groups of hearts fell rapidly toward control levels (136 ± 40%, 126 ± 23%, and 136 ± 83% of control, respectively, NS).

**Recovery of left ventricular function.** Before the onset of ischemia, control LVDP values were similar in all groups (105 ± 18 mm Hg for hearts receiving oxygenated perfluorocarbon, 112 ± 26 mm Hg for hearts receiving nonoxygenated perfluorocarbon, and 129 ± 24 mm Hg for hearts receiving standard crystalloid cardioplegia [NS]). After 60 min of ischemia and 45 min of reperfusion, LVDP returned to 84 ± 19% of control in hearts receiving the cardioplegic solution containing oxygenated perfluorocarbon (figure 5). LVDP in hearts receiving nonoxygenated perfluorocarbon returned to only 68 ± 16% and in hearts receiving the STD-KCl, LVDP returned to 67 ± 17% at the end of the 45 min of reperfusion (p = .058, Fluosol O₂ vs Fluosol N₂; p = .056, Fluosol O₂ vs STD-KCl).

Examination of mean left ventricular end-diastolic pressures revealed similar results, with hearts that received oxygenated perfluorocarbon demonstrating the lowest mean end-diastolic pressure (17 ± 4 mm Hg) at the end of the 45 min reperfusion period. In contrast, mean end-diastolic pressure was higher in hearts receiving nonoxygenated perfluorocarbon (25 ± 12 mm Hg) and in hearts receiving standard crystalloid cardioplegia (26 ± 17 mm Hg) (NS, Fluosol O₂ vs Fluosol N₂ or STD-KCl).

**Discussion**

The results of this study are consistent with our previous observations, in which we used mass spectrometry to demonstrate an increase in myocardial oxygen tension after each injection of an oxygenated perfluorocarbon containing cardioplegic solution during hypothermic global ischemia in isolated perfused rabbit hearts. In this work, myocardial oxygen tension rose 20 mm Hg after each injection of oxygenated perfluorocarbon, whereas no change was noted after

**FIGURE 4.** Time course of changes in Pi content (% control) during 3 hr of hypothermic global ischemia followed by 45 min of normothermic reperfusion.

**FIGURE 5.** Recovery of LVDP (% control) after 3 hr of hypothermic global ischemia and 15, 30, and 45 min of normothermic reperfusion.
injection of standard crystalloid cardioplegic solution. This finding suggested that the perfluorocarbon was capable of substantial oxygen delivery at low myocardial temperatures. Comparison of oxygen content in the aortic root and coronary sinus after each 10 ml injection of cardioplegic solution demonstrated uptake of 200 ml of dissolved oxygen per 100 g of left ventricular weight. In a blood-perfused, canine heart preparation in situ, increases in myocardial oxygen tension of 7 to 31 mm Hg were demonstrated after each injection of perfluorocarbon at injectate temperatures of 4° to 20° C, while the ability of blood to deliver oxygen at similar temperatures was limited. Myocardial oxygen uptake was 22 to 23 ml/100 g of left ventricular weight, confirming the ability of perfluorocarbon to deliver oxygen at mean myocardial temperatures of 16° to 21° C. It was thus predicted that perfluorocarbons might provide sufficient oxygen to allow sustained oxidative metabolism during global ischemia at low myocardial temperatures. This idea was substantiated by our current studies.

In the present work, multiple injections of the oxygenated perfluorocarbon containing cardioplegic solution maintained pH above 7.0 throughout 3 hr of total global ischemia. The minimum pH observed at the end of each 30 min interinjection period appeared, if anything, to be rising during the second and third hours of ischemia. Likewise, the minimum PCR content observed before each injection also appeared to be rising, especially during the last 90 min of the ischemic period. ATP content remained above control levels throughout the ischemic period. These results clearly demonstrate that oxygenated perfluorocarbon cardioplegia allows excellent preservation of high-energy metabolites, which most likely is due to the efficiency of ATP and creatine phosphate production linked to mitochondrial oxidative phosphorylation.

The results of this study also show that the preservation of ventricular function after reperfusion correlates well with the preservation of myocardial ATP content and the prevention of intracellular acidosis during ischemia. There are several reasons why this might be the case. Membrane function as well as membrane integrity have been proposed as mechanisms by which ATP may lead to improved functional recovery. Severe declines in myocardial ATP content during ischemia were shown to correlate with irreversible damage and poor recovery of ventricular function after reperfusion. Preservation of ATP content may also be important for minimizing loss of nucleotide bases after degradation of ATP to adenosine and other purine metabolites. With respect to changes in pH, the decline in tissue ATP content and the development of intracellular acidosis will proceed in parallel. This is a result of the known chemistry of any ATPase reaction: $\text{ATP} + H_2O \rightarrow \text{ADP} + P_i + H^+$. Therefore the hydrolysis of ATP results in the generation of both $P_i$ and excess hydrogen ions; the accumulation of either is capable of inducing cellular damage. Under anaerobic conditions the metabolic regeneration of ATP will not prevent intracellular acidosis, whereas aerobic ATP regeneration will minimize changes in pH. This relates to chemistry of the ATP synthetic pathways. Gevers convincingly argues that the net conversion of glucose to lactate is a stoichiometrically neutral pathway. Let us look at this step by step. A proton is produced by the phosphorylation of glucose to glucose 6-phosphate, and also at the phosphofructokinase reaction. Two additional molecules of $H^+$ are generated during the oxidation of the 2 moles of glyceraldehyde 3-phosphate to 3-phosphoglyceric acid. Therefore at this point in the glycolytic pathway there is the net production of four protons. These protons, however, are consumed during the last two steps of the Embden-Meyerhoff pathway. It is not well appreciated or widely noted that a proton is required for the enolization of phosphoenolpyruvate to pyruvate. Likewise, a proton is consumed during the reduction of pyruvate to lactate. Since two molecules of lactate are formed per molecule of glucose, four protons are utilized during these last two steps of anaerobic glycolysis. Thus, the net proton balance for glycolysis suggests that it is a neutral metabolic pathway. Therefore, under anaerobic conditions the protons generated by ATP hydrolysis are not compensated for by glycolysis, and the result is tissue acidosis. Such is not the case for aerobic metabolism. One of the principal tenets of the Mitchell hypothesis is the electron transport–linked generation of a transmembrane pH gradient, with $H^+$ on the outside and $OH^-$ in the matrix. However, during the conversion of ADP + $P_i$ to ATP by the $F_o$-$F_1$ ATPase, this gradient is not only collapsed but also reversed. It is easily shown with a simple glass pH electrode that mitochondrial oxidative phosphorylation is stoichiometrically linked to a net alkalinization of the extramitochondrial medium. Therefore, under these conditions, the $H^+$ produced during ATP hydrolysis is directly balanced by the net $OH^-$ production of mitochondrial aerobic metabolism. The result would be a minimal change in pH. These considerations are confirmed in part by our experimental observations and by the stability of pH during normal cardiac work as measured by the NMR method.
Therefore we suggest that the development of intracellular acidosis during global ischemia is more likely the result of excess ATP utilization in the face of inadequate rates of ATP synthesis by mitochondria. The similarities in the time course of changes in pH and myocardial ATP content among the three experimental groups support a tight coupling between rates of ATP hydrolysis and the genesis of excess protons. It is also noteworthy that the hydrolysis of PCr not only maintains ATP but also results in intracellular alkalinization. After each injection of cardioplegic solution, ATP content and pH rose, suggesting the generation of hydroxyl ions and/or intracellular buffering.

The marked rises in PCr content observed after injections of oxygenated perfluorocarbon cardioplegic solution provide evidence of rapid synthesis of PCr by mitochondrial oxidative phosphorylation. PCr content consistently rose to above 150% of control after each injection, having fallen to nearly 80% of control during the 30 min interval between injections. With nonoxygenated perfluorocarbon cardioplegic solution, PCr content fell to nearly 20% of control and increased to only 40% of control after each injection of cardioplegic solution. Thus it would appear that less PCr was being produced from the same quantity of substrate in the absence of oxygen. This might be expected, since metabolism of 1 mole of glucose under anaerobic conditions results in the generation of only 2 moles of ATP compared with the generation of 38 moles of ATP under aerobic conditions. If one than assumes efficient transfer of phosphate from ATP to creatine by myocardial creatine kinase, the observed time course of changes in PCr is predictable. Likewise the standard crystalloid hyperkalemic cardioplegic solution contained 98 mM glucose instead of the 44 mM glucose contained in the two perfluorocarbon solutions. Therefore the increased quantity of glycolytic substrate might be expected to result in increased generation of PCr even under anaerobic conditions.

Results of the present study demonstrate a correlation between preservation of PCr content during ischemia and subsequent recovery of left ventricular function but failed to demonstrate a correlation between the PCr content after reperfusion and recovery of function. In all three experimental groups PCr nearly returned to preischemic control values after reperfusion, despite the observation of significant differences in function. Recovery of function appeared to correlate better with postischemic recovery of ATP content. This correlation of functional recovery with ATP but not creatine phosphate content after reperfusion was also observed in a previous study, in which we compared single and multidose hyperkalemic cardioplegia using $^{31}$P NMR.

Oxygenated perfluorocarbon cardioplegia also reduced the accumulation of Pi during the period of global ischemia. High levels of Pi could interfere with recovery of myocardial function by irreversibly altering the localization and thereby the function of mitochondrial creatine kinase.

Multidose administration of any cold cardioplegic solution would improve myocardial preservation during prolonged periods of global ischemia by several mechanisms. The first and probably most important mechanism is maintenance of myocardial hypothermia, since rates of metabolism are directly dependent on myocardial temperature. Intermittent administration of boluses of cold solution would act to counteract the tendency for spontaneous rewarming, which occurs in the clinical setting, and thus to maintain myocardial temperature in the desired range. Furthermore, hyperkalemia induces rapid and complete electrical standstill, which would further reduce rates of utilization of substrate and compounds containing high-energy phosphate during the early minutes of ischemia. Multiple doses of cardioplegic solution also provide additional substrate and buffering capacity to ischemic myocardium. The results of the present study also suggest that the glucose contained in the cardioplegic solutions is utilized to generate ATP and PCr and that the enhanced efficiency of glucose utilization by the delivery of oxygen by perfluorocarbons results in increased generation of high-energy metabolites. Intermittent doses of cardioplegic solution may also wash out accumulating metabolic end products such as hydrogen ions, carbon dioxide, and/or lactate. As an added benefit, the aerobic conditions made possible by the perfluorocarbons result in the synthesis of ATP within mitochondria, associated with the generation of hydroxyl ions, which also acts to neutralize the excess hydrogen ions generated by ATP hydrolysis. Thus tissue acidosis is markedly reduced.

In conclusion, the opportunity to maintain aerobic metabolism during prolonged periods of ischemia with oxygenated perfluorocarbon cardioplegia could provide the potential for optimizing myocardial preservation in patients who require long periods of aortic cross-clamping for the performance of complex cardiac surgical procedures.

References


Maintenance of aerobic metabolism during global ischemia with perfluorocarbon cardioplegia improves myocardial preservation.

_Circulation_. 1984;69:585-592
doi: 10.1161/01.CIR.69.3.585

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/69/3/585

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/