A ^{31}P–MAGNETIC RESONANCE STUDY OF ANTEGRADE AND RETROGRADE CEREBRAL PERFUSION DURING AORTIC ARCH SURGERY IN PIGS

To evaluate the effect of hypothermic circulatory arrest on brain metabolism, we used ^{31}P–magnetic resonance spectroscopy to monitor brain metabolites in pigs during 2 hours of ischemia and 1 hour of reperfusion. Twenty-eight pigs were divided into five groups. Anesthesia (n = 5) and hypothermic cardiopulmonary bypass groups (n = 5) served as controls. In the circulatory arrest (n = 6), antegrade perfusion (n = 6), and retrograde (n = 6) brain perfusion groups, the bypass flow rate was 60 to 100 ml · kg^{-1} · min^{-1}. In the antegrade group, the brain was perfused via the carotid arteries at a blood flow rate of 180 to 200 ml · min^{-1} during circulatory arrest at 15° C. In the retrograde group, the brain was perfused through the superior vena cava at a flow rate of 300 to 500 ml · min^{-1} during circulatory arrest at 15° C. The intracellular pH was 7.1 ± 0.1 and 7.3 ± 0.1 in the anesthesia and hypothermic cardiopulmonary bypass groups, respectively. In the circulatory arrest group, the intracellular pH decreased to 6.2 ± 0.1 and did not recover to its initial value (7.0 ± 0.1) during reperfusion (p < 0.05 compared with the value obtained from the control groups at the corresponding time). Inorganic phosphate did not return to its initial level during reperfusion. In three animals in this group, levels of high-energy phosphates, adenosine triphosphate and phosphocreatine, recovered partially but did not reach the levels observed before arrest. In the group receiving antegrade perfusion, cerebral metabolites and intracellular pH were unchanged throughout the protocol. During circulatory arrest in the retrograde perfusion group the intracellular pH decreased to 6.4 ± 0.1 and recovered fully during reperfusion (7.1 ± 0.1). High-energy phosphates also returned to their initial levels during reperfusion. These studies show that deep hypothermic circulatory arrest with antegrade brain perfusion provides the best brain protection of the options investigated. (J THORAC CARDIOVASC SURG 1995;110:55-62)

Carlos L. Filgueiras, MD, MSc,[a] BeAtrice Winsborrow, MSc, PhD,[a] Jian Ye, MD, MSc,[a] Jack Scott,[a] Alexander Aronov, MD, PhD,[b] Piotr Kozlowski, PhD,[a] Laleh Shabnavard,[a] Randy Summers, MSc,[a] John K. Saunders, PhD,[a] Roxanne Deslauriers, PhD,[a] and Tomas A. Salerno, MD, MSc,[b] *Winnipeg, Manitoba, and Toronto, Ontario, Canada*

Since the first experimental report by Gollan[1] and clinical introduction by Drew and Anderson,[2] deep hypothermic circulatory arrest has been a useful adjunct in complex cardiovascular surgery.[3-6] However, neurologic injury remains a serious consequence despite the protective effect of hypothermia.[7, 8] The mechanism of cerebral injury remains unclear. Some degree of cerebral cortical damage occurs regardless of the ischemic time, although the generally accepted safe duration of circulatory arrest ranges from 45 to 60 minutes.[9] The clinical consequences of this ischemic damage become evident when the ischemic interval is longer than 60 minutes.[10]

Various techniques have been used to overcome the disadvantages of total circulatory arrest, includ-

From the Institute for Biodiagnostics, National Research Council Canada,[a] Winnipeg, Manitoba, and the Division of Cardiothoracic Surgery, St. Michael's Hospital, University of Toronto,[b] Toronto, Ontario, Canada.

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Address for reprints: Roxanne Deslauriers, PhD, Institute for Biodiagnostics, National Research Council of Canada, 435 Ellice Ave., Winnipeg, Manitoba, Canada, R3B 1Y6.

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Table I. *Study groups*

Group	*No.*
I. Anesthesia	5
II. Hypothermic cardiopulmonary bypass	5
III. Circulatory arrest alone	6
IV. Circulatory arrest + antegrade cerebral perfusion	6
V. Circulatory arrest + retrograde cerebral perfusion	6

ing selective perfusion of the brachiocephalic artery[11] or internal maxillary vein,[12] intermittent hypothermic asanguineous cerebral perfusion,[13] hypothermic circulatory arrest with local surface cooling,[14] and deep hypothermia with continuous low-flow perfusion.[15,16] Although these modifications are used in many centers, few experimental data regarding their efficacy are available.

In this study antegrade and retrograde cerebral perfusion were performed in pigs during circulatory arrest under deep hypothermic conditions (15° C). ^{31}P–magnetic resonance spectroscopy was used to provide continuous, noninvasive measurements of the relative concentrations of adenosine triphosphate (ATP), phosphocreatine (PCr), inorganic phosphate (Pi), and intracellular pH (pH_i) of the brain.[17-23] The selective volume of interest was defined by ^{31}P–two-dimensional spectroscopic imaging.[24]

Material and methods

Animal preparation. All animals (juvenile pigs weighing 25 to 30 kg) received humane care in compliance with the guidelines of the Canadian Council on Animal Care.[25]

Preoperative anesthesia was induced with xylazine (2.2 mg/kg intramuscularly), ketamine (20 mg/kg intramuscularly), and atropine (0.03 mg/kg intramuscularly). Anesthesia was maintained after endotracheal intubation with pentobarbital (20 mg/kg per hour intravenously), halothane 0.75%, oxygen 60%, and nitrogen 39.25%. Pancuronium (0.05 mg/kg per hour) was given for muscle relaxation. A temperature probe was placed in the esophagus to monitor the core temperature. The right carotid artery and right external jugular vein were dissected and cannulated for arterial and venous pressure monitoring. A catheter was inserted into the bladder to measure urine output.

The animal was placed in the supine position in a custom-built polyvinylchloride cradle shaped to fit the bore of the magnetic resonance magnet. The head of the pig was fastened to a radiofrequency coil attached to the cradle, which was designed to hold the head in the active area of the magnet so that manipulations of the animal after the operation could be minimized.

The chest was opened via a median sternotomy. Heparin (500 IU/kg intravenously) was administered before cannulation. A 21F cannula was inserted into the ascending aorta to provide arterial return during cardiopulmonary bypass. Venous return to the bypass circuit was achieved with 24F and 28F cannulas inserted into the superior and inferior venae cavae. A 16F cannula was inserted into the innominate artery to provide antegrade perfusion of the brain. The left ventricle was vented via the left atrium. The lungs were not inflated during bypass or circulatory arrest.

The cardiopulmonary bypass circuit consisted of a Cobe roller pump (model C22.2, Cobe Laboratories Hospital Products Div., Lakewood, Colo.), cardiotomy reservoir (Cobe), arterial filter (Cobe Sentry), water bath (Lauda MGW type RMSG, VWR, London, Ontario, Canada), and a membrane oxygenator (Cobe CML) with integral heat exchanger. The circuit was primed with Krebs-Henseleit solution (1 L), homologous blood (1.5 L), and heparin (10,000 IU). Sodium bicarbonate was added to adjust the pH to 7.40, when necessary. Arterial blood gases were measured with a Cobe gas analyzer. Blood gases were measured at 37° C, and no correction was made for the temperature during hypothermia. The alpha-stat approach was used.[12] The bypass circuit was designed to allow elective changes to antegrade or retrograde brain perfusion and normal bypass. Hematocrit value was kept between 15% and 23%. Homologous blood transfusions were used to maintain the hematocrit value within these parameters.

Groups and protocol. Twenty-eight pigs were divided into five groups (Table I). Groups I ($n = 5$) and II ($n = 5$) served as controls. Group I received anesthesia alone. In group II the animals received hypothermic cardiopulmonary bypass. The arterial blood flow was maintained at 60 to 100 $ml \cdot kg^{-1} \cdot min^{-1}$ and the arterial pressure was kept between 60 and 100 mm Hg. The perfusate was cooled to achieve systemic hypothermia at 15° C. After 2 hours, the animals were rewarmed to 37° C and bypass was continued for 1 additional hour.

In group III (circulatory arrest with deep hypothermia, $n = 6$), when the esophageal temperature reached 15° C, bypass was discontinued, the pigs' blood was drained into the oxygenator reservoir, and circulatory arrest was maintained for 2 hours. External body cooling was not used, but the room temperature was maintained at 22° C. Bypass was then reestablished and the animals were rewarmed to 37° C for 1 hour of reperfusion. In group IV (deep hypothermic circulatory arrest with antegrade brain perfusion, $n = 6$), the brain was perfused with blood at 15° C via the innominate and carotid arteries for the 2 hours of circulatory arrest. The right carotid pressure was monitored continuously and was maintained at 65 to 85 mm Hg with a blood flow of 180 to 200 $ml \cdot min^{-1}$. After 2 hours, bypass was reestablished and the animals were warmed to 37° C for 1 hour of reperfusion. In group V (deep hypothermic circulatory arrest with retrograde brain perfusion, $n = 6$), the brain was perfused with blood at 37° C through the superior vena cava for the 2 hours of circulatory arrest. The right jugular venous pressure was monitored continuously and was maintained at 35 to 45 mm Hg with a concomitant blood flow of 300 to 500 $ml \cdot min^{-1}$. Once cardiopulmonary bypass was reestablished, the animals were gradually warmed to 37° C for 1

Table II. *pH_i measured from localized ^{31}P–magnetic resonance spectra of pig brains subjected to different methods of brain protection*

Time	Anesthesia ($n = 5$)	HCPB ($n = 5$)	Circulatory arrest		Antegrade ($n = 6$)	Retrograde ($n = 6$)
			$n = 3$	$n = 3$		
Bypass, 30 min	7.1 ± 0.1	7.3 ± 0.1	7.0 ± 0.0	7.2 ± 0.0	7.1 ± 0.1	7.2 ± 0.1
Circulatory arrest 10 min	7.1 ± 0.1	7.3 ± 0.1	6.3 ± 0.2*†	6.6 ± 0.2*†	7.2 ± 0.1	6.8 ± 0.3†
Circulatory arrest 50 min	7.1 ± 0.1	7.3 ± 0.1	6.2 ± 0.1*†	6.3 ± 0.1*†	7.2 ± 0.2	6.5 ± 0.1*†
Circulatory arrest 110 min	7.1 ± 0.1	7.3 ± 0.1	6.3 ± 0.1*†	6.2 ± 0.0*†	7.2 ± 0.1	6.4 ± 0.1*†
Reperfusion 10	7.1 ± 0.1	7.3 ± 0.1	6.2 ± 0.1*†	6.5 ± 0.1*†	7.2 ± 0.1	6.7 ± 0.4*†
Reperfusion 50	7.1 ± 0.0	7.3 ± 0.1	6.2 ± 0.1*†‡	6.9 ± 0.1†‡	7.1 ± 0.1	7.1 ± 0.2

HCPB, Hypothermic cardiopulmonary bypass.
*$p < 0.05$ compared with the anesthesia control group at the same stage of the experiment.
†$p < 0.05$ compared with the HCPB control group at the same stage of the experiment.
‡$p < 0.05$ compared with bypass before circulatory arrest within the same group.

hour of reperfusion. Minimal doses of inotropic support, homologous blood products, and crystalloid infusion were used to maintain the systemic pressure above 60 mm Hg during reperfusion.

Magnetic resonance study. Magnetic resonance experiments were performed at 4.7 T with a Bruker Biospec instrument (Bruker Medical Instruments, Inc., Billerica, Mass.) at ^1H and ^{31}P spectral frequencies of 200.4 and 81.1 MHz, respectively. Imaging was performed only to position the slice for spectroscopic imaging experiments. Within 10 minutes of the start of bypass, the animals were placed in the magnet, where positioning and shimming were performed, and one localized ^{31}P–magnetic resonance spectrum of the brain was obtained. Positioning the animals in the magnet and slice definition within the skull were performed with the standard multi-slice multi-echo imaging sequence (echo time = 30 msec). A 2 cm thick slice was positioned in the cortex. Magnetic field (B_o) homogeneity in the selected slice was optimized by shimming on its ^1H_2O time domain signal. The line width at half-height was typically 20 to 30 Hz. Two-dimensional spectroscopic imaging[24] was used to obtain localized ^{31}P–magnetic resonance spectra from the pig brains during bypass before arrest, circulatory arrest, and reperfusion. Spectra from 8 cm^3 localized volumes were acquired with 22-minute time resolution. Qualitative information about high-energy phosphates and Pi levels, as well as quantitative information on pH_i, was extracted from the magnetic resonance spectra. The pH_i values were calculated from the chemical shift difference between Pi and PCr. A detailed description at the magnetic resonance protocol used in these studies is given elsewhere.[26]

Statistical analyses. The data were expressed as the mean ± standard deviation of the mean. Statistics were performed with statistical software (Statistica/W, StatSoft, Tulsa, Okla.). Comparisons of brain pH_i between the groups throughout the protocol were carried out by means of the analysis of variance with further use of the Kruskal-Wallis test and the Tukey test. Comparisons of brain pH_i obtained before and after circulatory arrest within each group were performed by means of the Student's t and Wilcoxon matched pair tests. Statistically significant difference was said to exist at a probability value of less than 0.05 ($p < 0.05$).

Results

For all experiments, cooling from 37° C to 15° C required 40 ± 10 minutes during which magnetic resonance spectroscopic data were obtained. The period of circulatory arrest was 120 minutes. Rewarming required 42 ± 11 minutes during reperfusion. The pH_i values measured in brain tissue during bypass, circulatory arrest, and reperfusion are listed in Table II and in Fig. 1.

In the two control groups, that is, anesthesia and hypothermic cardiopulmonary bypass, the pH_i was 7.1 ± 0.1 and 7.3 ± 0.1, respectively. In group III, the pH_i decreased to 6.2 ± 0.1 during circulatory arrest ($p < 0.05$ compared with the control groups), and during reperfusion the pH_i increased to a maximum of only 6.9 ± 0.1 ($p < 0.05$ compared with control group II and to its values during bypass before arrest). Three animals in this group are reported separately because the pH_i at the end of reperfusion remained 6.2 ± 0.1 ($p < 0.05$ compared with the control groups), which was probably a consequence of low venous return during bypass before arrest, when the levels in the reservoir decreased gradually. In the animals subjected to circulatory arrest and antegrade perfusion of the brain, pH_i was 7.1 ± 0.1 before arrest and never decreased below 7.1 ± 0.1 during arrest and reperfusion. In the

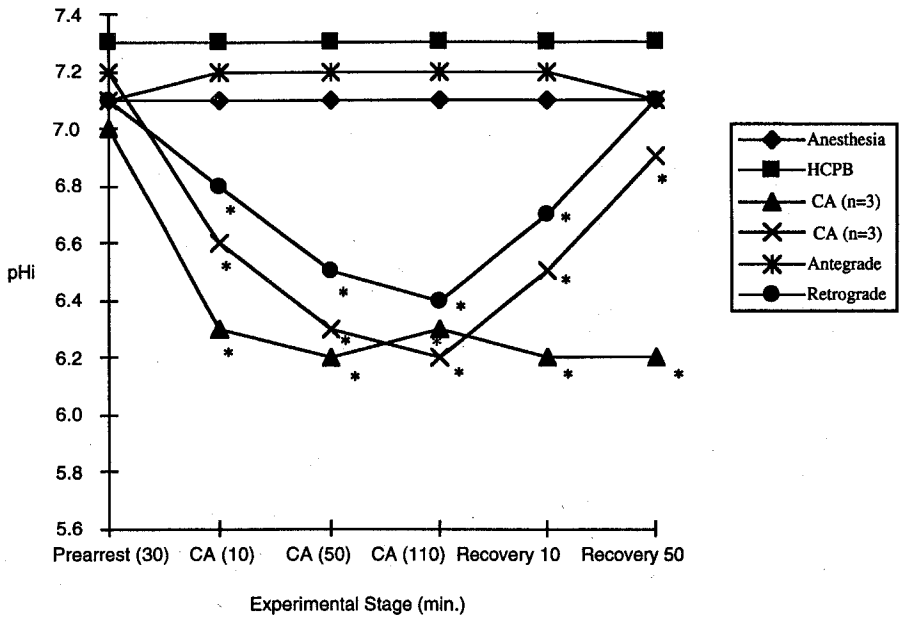

Fig. 1. Intracellular pH of the brain measured during cardiopulmonary bypass, circulatory arrest, and reperfusion. *HCBP,* Hypothermic cardiopulmonary bypass; *CA,* circulatory arrest; *pHi,* intracellular pH. *$p < 0.05$ compared with the control groups (*Anesthesia* and *HCPB*).

animals subjected to circulatory arrest and retrograde brain perfusion, pH_i was 7.1 ± 0.1 before circulatory arrest, 6.4 ± 0.1 ($p < 0.05$ compared with the control groups) during arrest, and 7.1 ± 0.2 during reperfusion.

Representative spectra from the five groups in this study are shown in Fig. 2. In group III, circulatory arrest alone, Pi increased during arrest and the high-energy phosphate levels decreased gradually; after 30 minutes of arrest, their levels were very low. During recovery, Pi remained higher than in the control groups. The ATP and PCr peaks recovered partially in the three experiments with normal venous return. ATP, PCr, and Pi did not recover in three experiments with low venous return. In group IV, subjected to circulatory arrest and antegrade brain perfusion, the ATP and PCr peaks were maintained at control values during the entire experiment and Pi remained low. In group V, circulatory arrest and retrograde brain perfusion, Pi increased and high-energy phosphate levels decreased during circulatory arrest. During recovery, the Pi level decreased and the ATP and PCr peaks returned to control values.

Discussion

The metabolic requirement of the brain for oxygen is high and its tolerance to ischemia is very low.[15] This poses a challenge during complex cardiac procedures in which circulatory arrest is required, such as during operations on the ascending aorta and arch. Pioneering work by Bigelow, Callaghan, and Hopps[27] in 1950 demonstrated that dogs undergoing deep hypothermia could survive. As a result, there was renewed interest in deep hypothermia in conjunction with circulatory arrest for cerebral protection.[28] The protective effect of deep hypothermia is attributed to reduced cerebral metabolism.[29] Although deep hypothermic circulatory arrest has played an important role in cardiac surgery over the past three decades,[30] the safe duration of circulatory arrest remains undefined. Ischemic times in excess of 45 minutes increase the risk of cerebral injury.[27, 29] Although Drew and Anderson first reported neurologic findings in patients who died after operations in which circulatory arrest was used, the mechanism of injury remained undefined. Muraoka and associates[31] reported subclinical abnormalities and neurologic alterations in computed tomographic scans of patients subjected to circulatory arrest of less than 45 minutes' duration. The development of cerebral infarction depends primarily on the duration of ischemia.[16]

Normal cerebral blood flow in the human being ranges from 45 to 60 ml/min per 100 gm brain tissue.[32] Reduction of flow to 20 ml/min per 100 gm

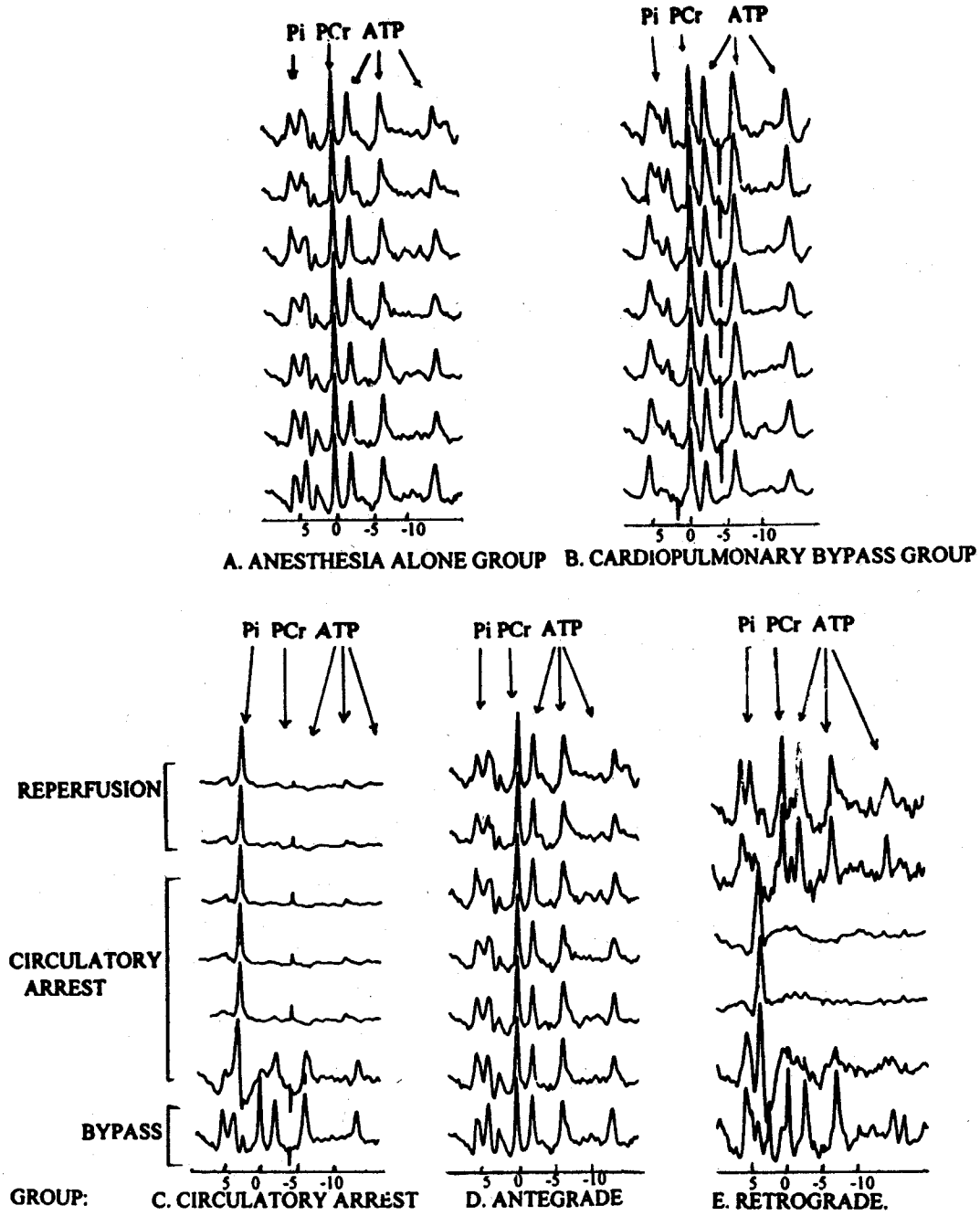

Fig. 2. Representative magnetic resonance spectra from the two control and three experimental groups.

under normothermic conditions is associated with reversible functional impairment and severe ischemia lasting 2 to 3 hours, and flow rates less than 8 to 12 ml/min per 100 gm brain tissue cause local infarction in conscious monkeys.[33] Low-flow hypothermic cardiopulmonary bypass has been used during operations for congenital heart disease.[34] The optimal perfusion flow rate in dogs during deep hypothermic cardiopulmonary bypass at 20° C was found to be 30 $ml \cdot kg^{-1} \cdot min^{-1}$ and a perfusion flow rate of 15 $ml \cdot kg^{-1} \cdot min^{-1}$ can lead to irreversible changes in the brain.[16] However, under deep hypothermic conditions, a *selective* perfusion flow rate of 10 $ml \cdot kg^{-1} \cdot min^{-1}$ at 15° C can maintain

brain high-energy phosphates and intracellular pH and has been demonstrated to be more beneficial to the brain than intermittent perfusion or a flow rate of 5 $ml \cdot kg^{-1} \cdot min^{-1}$ in the carotid artery.[35]

The temperature monitoring site is an important factor in all studies. O'Connor and colleagues[30] studied different sites and found no differences between cerebral and esophageal temperatures. The rectal temperatures were approximately 4° C lower. The esophageal temperature was monitored in all our experiments. In our studies, we used a heat exchanger to cool and warm the pig during the experiments. We avoided using a gradient higher than 10° C during cooling and warming. Superficial cooling around the pig head was not used because this procedure would create problems with the magnetic resonance coil and, consequently, with the magnetic resonance study. During all procedures the room temperature was kept at 22° C and the esophageal temperature varied from 14° to 17° C during circulatory arrest.

The valves in the venous system did not seem to be a major obstacle for retrograde brain perfusion, because recovery of the high-energy phosphate levels was observed at the end of reperfusion. The retrograde perfusion technique is easy to implement. Some blood flow is diverted to the upper limbs during retrograde perfusion, which is important in perfusing other parts of the body. With selective retrograde brain perfusion through the jugular or maxillary vein, blood flow to the brain would be more uniform. However, this is a more complex technique and provides no perfusion to the peripheral organs during circulatory arrest.

A line width of 20 to 30 Hz was measured for the proton magnetic resonance signal acquired from the whole slice. This number gives only an estimate of the B_o homogeneity within the selected slice (0.1 to 0.5 ppm). The final line width in the processed spectrum will depend on many factors, such as B_o homogeneity inside the voxel, the spin-spin relaxation time (T_2), and/or the width of the filter applied in postacquisition processing. In our case the B_o homogeneity measured from the proton signal (0.1 to 0.15 ppm) would suggest an 8 to 12 Hz line width in the phosphorus spectrum. A line broadening of 40 Hz was applied during data processing to improve the signal-to-noise ratio. This adds up to a line width of approximately 50 Hz. The spectral resolution was sufficient to calculate the pH_i from the acquired spectra.

The magnetic resonance spectra exhibited severe baseline distortion because of the rather long delay between excitation and data acquisition in the spectroscopic imaging technique. We did not find any of the baseline correction methods sufficiently reliable to allow a quantitative analysis of the spectra obtained by spectroscopic imaging. One important point is that nonlocalized spectra acquired with a surface radiofrequency coil are contaminated with signals from outside the brain (e.g., muscle). We made the choice to use localized spectroscopy and limit the analysis to quantitative measurements of pH_i and qualitative analysis of high-energy phosphate levels. The development in our laboratory of a highly prefocused selective pulse[36] will allow quantitative information on high-energy phosphate levels to be obtained from a spectroscopic imaging experiment.

The results of our experiments showed no intracellular acidosis after 2 hours of deep circulatory arrest and antegrade cerebral perfusion at a flow rate of 180 to 200 ml/min (group IV). Similarly, ATP and PCr levels were maintained and Pi was within normal limits. Hypothermic circulatory arrest alone (group III) caused persistent elevation in Pi levels. There was also lack of restoration of pH_i, ATP, and PCr, evident at 60 minutes of reperfusion. In the group subjected to circulatory arrest and retrograde brain perfusion (group V), the pH_i and high-energy phosphate levels decreased during circulatory arrest but returned to control values on reperfusion. This indicates better protection than with complete circulatory arrest. However, energy and pH preservation was not as good as in group IV (see Table II).

The discrepancy between the results obtained with the antegrade and retrograde techniques remains unexplained and requires further study. It is possible that retrograde flow may have been distributed between the brain and upper limbs. Cerebral perfusion with individual cannulation of the arch vessels was abandoned because of the simplicity of the deep hypothermic circulatory arrest method. Surgeons may be reluctant to return to this technique. Furthermore, our studies were carried out in pigs subjected to a 2-hour arrest period, which is seldom, if ever, used clinically.

We observed high levels of Pi and very low levels of pH_i, ATP, and PCr after only 30 minutes of hypothermic circulatory arrest (group III). Our studies suggest that when circulatory arrest is needed, even for short periods, antegrade brain perfusion provides the best cerebral protection. Retrograde brain perfusion would be a second

option when antegrade perfusion is not possible. Future magnetic resonance spectroscopic studies in experimental animals will focus on optimizing the conditions for retrograde perfusion and establishing the efficiency of brain perfusion with this technique.

Retroperfusion was recently introduced clinically, as a means of providing cerebral flow during deep hypothermic circulatory arrest.[37] Although superior to deep hypothermic circulatory arrest without cerebral perfusion, the retrograde brain perfusion method was not shown to be as metabolically safe as antegrade brain perfusion. Further technical modifications of retrograde perfusion of the brain may allow selective brain perfusion without upper limb perfusion.

In summary, ^{31}P–magnetic resonance studies in pig brain indicate that during deep hypothermic circulatory arrest some form of cerebral perfusion is beneficial. Given a choice, antegrade brain perfusion appears to be the superior technique from a metabolic point of view.

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