METABOLIC CORRELATES OF NEUROLOGIC AND BEHAVIORAL INJURY AFTER PROLONGED HYPOTHERMIC CIRCULATORY ARREST

Thirty-two inbred weanling puppies were divided into four groups to study the effect on cerebral blood flow and metabolism of different hypothermic strategies for cerebral protection similar to those used during cardiac operations in infancy. All animals were cooled to 18° C. The animals in the hypothermic control group were immediately rewarmed. One group underwent 30 minutes of hypothermic circulatory arrest at 18° C; another group had 90 minutes of hypothermic circulatory arrest at 18° C, and the final group had low-flow cardiopulmonary bypass (25 ml/kg per minute) at 18° C for 90 minutes. All animals had preoperative and postoperative neurologic and behavioral evaluation and extensive intraoperative monitoring of cerebral blood flow, cerebral vascular resistance, and oxygen and glucose uptake and metabolism: quantitative electroencephalography was also monitored before, during, and after operation, but those results are reported separately. Two animals in the 90-minute arrest group died, and all the survivors showed evidence of clinical, neurologic, and behavioral impairment on postoperative day 1, with residual abnormalities in all but one animal on day 6. In contrast, the survivors in all the other groups showed no significant clinical or behavioral sequelae. Cerebral metabolism was reduced only to 32% to 40% of baseline values at 18° C in all groups, although systemic metabolism was only 16% of normal. Cerebral metabolism returned promptly to baseline in all groups during rewarming and remained at baseline levels throughout the 8 hours of follow-up. Cerebral blood flow showed marked hyperemia in the hypothermic arrest groups during rewarming but then significant reductions below baseline values in all groups except the controls at 2 and 4 hours after the operation, lasting as late as 8 hours after the operation in the 90-minute arrest group. Cerebral vascular resistance showed increases in all groups at 2 and 4 hours after the operation, which persisted in the 90-minute arrest group at 8 hours. Cerebral metabolism was maintained at baseline levels despite postoperative decreases in cerebral blood flow and increases in cerebral vascular resistance by increases in oxygen and glucose extraction. The result was very low sagittal sinus oxygen saturations in all groups, most marked in the 90-minute arrest groups, which had a saturation of only 24% 8 hours after the operation. Our data show a severe, prolonged disturbance in cerebral blood flow and cerebral vascular resistance after 90 minutes of hypothermic circulatory arrest at 18° C, which correlates with clinical evidence of cerebral injury. The presence of similar but milder inappropriate hemodynamic responses in animals after 30 minutes of arrest at 18° C, and even after prolonged low-flow cardiopulmonary bypass at 18° C, suggest that strategies to improve cerebral protection during hypothermia—including use of colder temperatures—need to be explored. (*J THORAC CARDIOVASC SURG* 1995;109:959-75)

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Supported by grant HL-45636-02 from the National Heart, Lung, and Blood Institute and in part by the Cardiothoracic Research Fund, Mount Sinai Medical Center, New York, N.Y.

Received for publication May 18, 1994.

Accepted for publication Dec. 9, 1994.

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0022-5223/95 \$3.00 + 0 12/1/62743

Although hypothermic circulatory arrest (HCA) is widely used during operations for correction of congenital heart disease in infancy, the risk of brain injury is still of concern, especially when longer durations of HCA are required. The optimal conditions for maximizing cerebral protection during HCA are not well established: there is controversy about the rate and technique of cooling, the best temperature at which to arrest the circulation, how to assess adequacy of cooling, and whether there is a need for surface cooling at any stage of the procedure. Furthermore, the relative safety of HCA compared with low-flow cardiopulmonary bypass (LFCPB), an alternative technique for some procedures, is also uncertain.

An increasing awareness that at least subtle cerebral injury occurs in some patients after prolonged durations of HCA, combined with a definite trend toward the repair of complex congenital heart disease in neonates, has provided the impetus for renewed interest in improving cerebral protection during HCA. We have developed a model for the study of cerebral injury after HCA in the weanling puppy, in which we can correlate intraoperative and postoperative measurements of cerebral blood flow, vascular resistance, metabolism, and quantitative electroencephalography (EEG) with long-term outcome, determined by comparison of preoperative and postoperative assessment of neurologic and behavioral status, as well as QEEG.

Previous studies with this model have shown postoperative increases in slow-wave QEEG activity, suggestive of subtle cerebral injury, in animals subjected to either HCA or LFCPB for 60 minutes at 18° C, but not in animals after HCA for 60 minutes at either 13° or 8° C.¹ Despite the abnormalities in EEG after 60 minutes of HCA at 18° C, however, no obvious neurologic or behavioral deficits were noted.

In the current study, puppies were subjected to 90 minutes of HCA or LFCPB at 18° C to assess whether QEEG abnormalities during or after the operation correlate with clinical evidence of cerebral injury, which was anticipated with so prolonged a duration of HCA. The 90-minute HCA group was compared with a group of puppies subjected to cooling to 18° C and immediate rewarming; to a group that underwent 30 minutes of HCA at 18° C; and to a group that had 90 minutes of LFCPB at 18° C: in the comparison groups we did not expect to find clinical evidence of cerebral impairment.

The results of these experiments, in which neuro-

logic and behavioral abnormalities were found only in the 90-minute HCA group, confirm that QEEG is a sensitive indicator of cerebral injury occurring during and immediately after HCA. The studies also suggest that LFCPB offers greater cerebral protection than HCA for a long procedure at 18° C.

The details of the QEEG findings can be found in the accompanying report (see page 925). In this paper we examine the metabolic data from each of the four groups in an attempt to determine the possible mechanism of the cerebral injury that occurred in some animals in the 90-minute HCA group. The data from this study confirm our previous observations of derangements in cerebral blood flow and cerebrovascular resistance lasting up to 8 hours after HCA: these inappropriate cerebrovascular responses to hypothermia are more severe after longer durations of HCA and are less pronounced after LFCPB.² The correlation of significantly decreased cerebral blood flow and increased cerebrovascular resistance after 90 minutes of HCA with clinical and EEG evidence of cerebral injury suggest that these derangements after HCA may be involved in the genesis of cerebral damage after cardiac operations in infancy.

Materials and methods

Inbred weanling beagles (Marshall Farms, North Rose, N.Y.), 3 months of age, weighing 3.5 to 5 kg, were randomly assigned to one of four experimental groups:

1. Hypothermic control group: Puppies were cooled to 18° C and then immediately rewarmed.
2. Thirty-minute HCA group: Puppies were cooled to 18° C, subjected to 30 minutes of HCA, and then rewarmed.
3. Ninety-minute HCA group: Puppies were cooled to 18° C, subjected to 90 minutes of HCA, and then rewarmed.
4. Ninety-minute LFCPB group: Puppies were cooled to 18° C, underwent LFCPB at 25 ml/kg per minute for 90 minutes, and were then rewarmed.

Each animal underwent epidural electrode placement, preoperative and postoperative telemetric EEG monitoring, and neurologic/behavioral assessment, as well as intraoperative measurements and monitoring, including QEEG.

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research, and the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH Publication 85-23, revised 1985). The protocol for these experiments was approved by the Mount Sinai Institutional Animal Care and Use Committee and is described in detail in the accompanying manuscript.

Experimental protocol

Neurologic and behavioral evaluation. The presence of clinical cerebral injury in the puppies was assessed by a veterinarian unaware of the experimental group to which each animal was assigned. These evaluations were carried out before the operation, on the first postoperative day, and daily until the sixth postoperative day. Each assessment consisted of observation of behavioral characteristics and performance of a formal neurologic examination: the details can be found in the accompanying paper.

EEG studies. Telemetric QEEG studies were carried out, with the animals awake, both before the operation and 1 week after the operation. In addition, QEEG was monitored throughout the acute experimental protocol. The details of surgical epidural electrode placement have been described previously,¹ and the ways in which EEG recording and analysis were carried out are described in the accompanying report.

Acute experimental protocol. Animals were premedicated, anesthetized, and intubated as previously described. They were supported by positive-pressure ventilation and paralyzed with pancuronium. Temperature probes were placed in the esophagus and rectum. The sagittal sinus was cannulated as previously described,³ and an epidural temperature probe was placed in most of the animals. The femoral artery and vein were also cannulated, and a thermodilution catheter was threaded into the pulmonary artery.

The animals were then heparinized and begun on nonpulsatile CPB with a single cannula used in the right atrium and return to the ascending aorta. Membrane oxygenators (VPCML plus, Cobe Laboratories, Lakewood, Colo.) were primed with a solution containing homologous blood, albumin, furosemide, heparin, dextrose, saline, and potassium chloride as previously described. CPB was established at a rate of 100 ml/kg per minute. Hematocrit value was maintained between 22% and 28%. A cooling blanket was used as an adjunct to core cooling, but, in contrast to previous experiments,¹⁻⁴ no ice packs to the head were used. As cooling progressed, pH was maintained within the physiologic range (7.35 to 7.45), uncorrected for temperature, in accordance with alpha-stat principles. When the esophageal temperature reached 20° C, the bypass flow rate was reduced to 50 ml/kg per minute until an esophageal temperature of 18° C was reached.

In the animals in the LFCPB group, flow was reduced to 25 ml/kg per minute for 90 minutes once an esophageal temperature of 18° C was reached. In the HCA groups, the circulation was arrested at 18° C for the appropriate duration, and in the control group perfusion/surface rewarming was begun immediately after cooling was complete. Rewarming was carried out at a flow rate of 75 to 100 ml/kg per minute until an esophageal temperature of at least 36° C was reached. The animals were then weaned from CPB.

Metabolic and physiologic measurements. As in previous experiments with this model,¹⁻⁴ multiple samples were obtained and measurements made at each of several time points during the acute experimental protocol. The measurements enabled subsequent calculation of the following variables:

Table I. Behavioral and neurologic outcome

	<i>n</i>	<i>Day 1</i>	<i>Day 6</i>
Behavioral score			
Hypothermic control	8	0 ± 0	0.1 ± 0.1
30 min HCA	8	0 ± 0	0.3 ± 0.2
90 min HCA	8	7.4 ± 1.3	3.9 ± 2.0
90 min HCA	6	5.5 ± 0.6	0.8 ± 0.3
90 min HCA	2 (died)	13 ± 0	13 ± 0
90 min LFCPB	8	0.1 ± 0.1	0 ± 0
Neurologic score			
Hypothermic control	8	0 ± 0	0.1 ± 0.1
30 min HCA	8	0 ± 0	0.1 ± 0.1
90 min HCA	8	11.0 ± 0.7	6.5 ± 1.6
90 min HCA	6	10.3 ± 0.7	4.3 ± 1.1
90 min HCA	2 (died)	13 ± 0	13 ± 0
90 min LFCPB	8	0 ± 0	0 ± 0

Values are shown as mean ± standard error.

1. Cerebral blood flow, measured with injected radiolabeled microspheres as previously described³
2. Cardiac output measured by the thermodilution technique
3. Cerebral and systemic vascular resistance
4. Cerebral and systemic oxygen consumption
5. Cerebral and systemic oxygen extraction
6. Cerebral glucose consumption and extraction

Physiologic and hemodynamic variables, such as blood gases, arterial pressure, and hematocrit, were also monitored at the same times during the experiment, and QEEG data were collected throughout for later analysis.

The time points at which measurements were performed were as follows:

1. Baseline, at 37° C before CPB
2. After cooling, immediately before institution of HCA or LFCPB
3. During rewarming, at 30° C, usually 15 minutes after the start of rewarming
4. Two hours after the start of rewarming, off bypass, with the chest closed, at 37° C
5. Four hours after the start of rewarming
6. Eight hours after the start of rewarming

Statistical analysis. All results are expressed as the mean ± standard error. Results were compared by analysis of variance. A *p* value < 0.05 was accepted as statistically significant. Statistical treatment of the QEEG data is described in the accompanying report.

Results

Morbidity and mortality. There were no deaths in the hypothermic control, 30-minute HCA, and 90-minute LFCBP groups. Two puppies died after 90 minutes of HCA at 18° C, for an overall mortality of 6% (2/32). The mortality in the 90-minute HCA group was 25% (2/8).

Both of the puppies that died had low cardiac output after the experiment: one had a metabolic

Table II. Comparison of perfusion cooling and rewarming times

	<i>n</i>	Weight (kg)	CPB cooling (min)	CPB warming (min)
Hypothermic control	8	3.9 ± 0.2	39 ± 1	40 ± 2
30 min HCA	8	4.1 ± 0.1	39 ± 1	41 ± 1
90 min HCA	8	4.5 ± 0.3	40 ± 1	48 ± 2 ^{a,c}
90 min HCA	6	4.4 ± 0.4	39 ± 1	48 ± 3 ^{a,c}
90 min HCA	2 (died)	4.8 ± 0.3	43 ± 3	48 ± 3
90 min LFCPB	8	4.3 ± 0.2	39 ± 1	45 ± 2

Values are shown as mean ± standard error.

^a*p* < 0.05 versus control.

^c*p* < 0.05 versus 30 min HCA (18° C).

acidosis and an isoelectric EEG after the operation, and the second had multiorgan failure.

Neurologic outcome. All the animals in the control, 30-minute HCA, and 90-minute LFCPB groups appeared entirely normal neurologically and behaviorally on day 1, although one or two in each group had minor abnormalities when tested on day 6, as shown in Table I.

The excellent neurologic recovery in all the control groups is in marked contrast to the findings in the survivors in the 90-minute HCA group, which were all impaired neurologically and behaviorally when evaluated on day 1: they were unable to stand, had poor appetite, indifferent affect, and abnormal reflexes. At the time of subsequent evaluation on day 6, however, one animal appeared completely normal, and all the others had improved considerably, although some unsteadiness of gait and abnormality of reflexes remained. The two animals that died did so within the first 12 hours and were therefore unable formally to be evaluated neurologically even at the first postoperative time point: neither was judged likely to have made a significant neurologic recovery.

Because of the apparent disparity in the neurologic outcome of those animals that died and the remainder in the 90-minute HCA group, which made quite a good recovery eventually, the data from all the animals in this group (*n* = 8) and the data from the surviving animals only (*n* = 6) were statistically compared with the data from the survivors (*n* = 8) in all the other groups. The data from the two animals that died are also presented in all the tables to allow comparison, although no statistics for these two animals were calculated.

Some differences were noted in baseline values between the two animals that died in the 90-minute HCA group and the animals in all other groups: the cerebral blood flow is low; the baseline cerebrovascular resistance is high; the cerebral oxygen extraction is elevated, and the sagittal sinus oxygen content

is depressed. These observations suggest the presence of some deviation from normal cerebrovascular flow characteristics in these animals before the start of the experiment, which may have predisposed them to cerebral injury after 90 minutes of HCA.

Preoperative and intraoperative variables. There were no significant differences in the weights of the animals in the different experimental groups, as shown in Table II, or in the duration of cooling. The duration of rewarming was slightly greater in those animals with longer periods of HCA: they tended to be weaned from bypass slightly later because of greater general instability. In the two animals that subsequently died, the weights appear somewhat higher than average and the duration of cooling somewhat longer.

In all groups pH was comparable at baseline and remained within a physiologic range throughout the experiment, as seen in Table III. Within these physiologic limits, all groups had a significant increase in pH with hypothermia, as would be expected with alpha-stat pH management. After rewarming, there was a tendency toward slightly higher pH in the groups with longer durations of hypothermia.

Arterial oxygen tension was greater than 150 mm Hg at all time points in all groups. Arterial carbon dioxide tension was between 34 and 40 mm Hg in all groups throughout the experiment, with a tendency toward lower arterial carbon dioxide tensions during rewarming in the groups with longer durations of hypothermia.

Hematocrit values ranged between 25% and 32%. The hematocrit value in the 90-minute HCA group was slightly higher at baseline than in the other groups, and in all groups the hematocrit value fell during cooling and early rewarming.

Mean arterial pressure in all groups was comparable at baseline. At the end of cooling and during rewarming, mean arterial pressure in the LFCPB

Table III. Acid-base, blood gas, and hematocrit values

		Baseline (37° C)	End of CBP cooling (18° C)	30° C	After start of rewarming		
<i>n</i>					2 hr	4 hr	8 hr
Arterial pH							
Hypothermic control	8	7.38 ± 0.01	7.44 ± 0.02*	7.39 ± 0.01	7.44 ± 0.02*	7.40 ± 0.02	7.35 ± 0.01
30 min HCA	8	7.39 ± 0.01	7.45 ± 0.02*	7.35 ± 0.01 ^{*b}	7.44 ± 0.02 ^{*b}	7.42 ± 0.01	7.39 ± 0.01
90 min HCA	8	7.37 ± 0.01	7.43 ± 0.02*	7.37 ± 0.03	7.44 ± 0.03 ^{*b}	7.42 ± 0.01	7.41 ± 0.01 ^a
90 min HCA	6	7.36 ± 0.02	7.45 ± 0.02*	7.39 ± 0.01 ^c	7.48 ± 0.01*	7.44 ± 0.01*	7.41 ± 0.01 ^{*a}
90 min HCA	2 (died)	7.39 ± 0.03	7.38 ± 0.03	7.32 ± 0.12	7.33 ± 0.06	7.38 ± 0.02	7.42 ± 0.05
90 min LFCPB	8	7.38 ± 0.01	7.46 ± 0.01*	7.40 ± 0.02	7.49 ± 0.01 ^{*a}	7.44 ± 0.01*	7.39 ± 0.01
Pao ₂ (mm Hg)							
Hypothermic control	8	205 ± 13	278 ± 19*	215 ± 28	194 ± 7	190 ± 10	172 ± 10
30 min HCA	8	169 ± 9	273 ± 22*	298 ± 15 ^{*a}	182 ± 11	174 ± 13	177 ± 9
90 min HCA	8	159 ± 14 ^a	288 ± 14*	344 ± 14 ^{*a,b}	217 ± 25*	204 ± 11*	181 ± 15
90 min HCA	6	153 ± 16 ^a	295 ± 18*	334 ± 16 ^{*a}	230 ± 33*	204 ± 15*	178 ± 20
90 min HCA	2 (died)	178 ± 31	266 ± 11	372 ± 27	178 ± 5	201 ± 10	190 ± 10
90 min LFCPB	8	159 ± 8 ^a	278 ± 14*	282 ± 34 ^{*a}	186 ± 14	185 ± 9	163 ± 9
Paco ₂ (mm Hg)							
Hypothermic control	8	37 ± 1	35 ± 1	34 ± 1*	36 ± 1	39 ± 1	38 ± 1
30 min HCA	8	38 ± 1	35 ± 1*	39 ± 1 ^{a,b}	37 ± 2	41 ± 2	41 ± 1
90 min HCA	8	38 ± 2	35 ± 1	36 ± 2 ^c	34 ± 1 ^{*c}	40 ± 1	40 ± 1
90 min HCA	6	40 ± 2	34 ± 1*	36 ± 2	34 ± 2 ^{*c}	40 ± 1	40 ± 1
90 min HCA	2 (died)	34 ± 1	35 ± 5	34 ± 4	35 ± 1	42 ± 4	38 ± 3
90 min LFCPB	8	39 ± 1	35 ± 1*	33 ± 1*	35 ± 1*	38 ± 1	40 ± 1
Hematocrit							
Hypothermic control	8	0.29 ± 0.01	0.25 ± 0.01*	0.25 ± 0.01*	0.29 ± 0.01	0.30 ± 0.01	0.32 ± 0.01*
30 min HCA	8	0.28 ± 0.01	0.26 ± 0.01*	0.24 ± 0.04*	0.30 ± 0.01	0.32 ± 0.01*	0.32 ± 0.01*
90 min HCA	8	0.31 ± 0.01 ^{b,c}	0.28 ± 0.01	0.25 ± 0.01*	0.33 ± 0.02 ^a	0.33 ± 0.02	0.32 ± 0.01
90 min HCA	6	0.31 ± 0.01 ^{b,c}	0.28 ± 0.01 ^{*a}	0.26 ± 0.01*	0.32 ± 0.01	0.32 ± 0.01	0.33 ± 0.01
90 min HCA	2 (died)	0.30 ± 0.04	0.26 ± 0.01	0.23 ± 0.01	0.38 ± 0.10	0.35 ± 0.07	0.29 ± 0.02
90 min LFCPB	8	0.28 ± 0.01	0.27 ± 0.01	0.26 ± 0.01	0.30 ± 0.01	0.31 ± 0.02*	0.33 ± 0.01*

Values are shown as mean ± standard error. Pao₂, Partial pressure of oxygen; Paco₂, partial pressure of carbon dioxide.

**p* < 0.05 versus baseline (37° C).

^a*p* < 0.05 versus control (18° C).

^b*p* < 0.05 versus LFCPB (18° C).

^c*p* < 0.05 versus 30 min HCA (18° C).

group tended to be slightly higher than baseline and in the HCA groups slightly lower than baseline, resulting in a significant difference between HCA and LFCPB groups at these time points, as shown in Table IV.

At later time points, although the arterial pressures are no longer significantly different, there is a lower cardiac output in both HCA groups at 4 hours, which persists in the 90-minute HCA group until 8 hours after the operation. During cooling and rewarming, CPB flow was comparable in all groups.

Temperature measurements. We measured both esophageal and rectal temperature at all time points in all puppies, but we also measured epidural temperature in most of the animals in each group, as indicated in Table V. We based decisions such as when to terminate cooling on the esophageal temperature, which we had found, in earlier experimental work, to correlate well with intracerebral tem-

perature. As can be inferred from Table V, epidural temperature tended to lag behind esophageal temperature by 30 to 35 minutes of cooling. Rectal temperature remained significantly higher than either esophageal or epidural temperature at the end of cooling in all groups and was slower to respond to rewarming than either esophageal or epidural temperature.

Cerebral blood flow and vascular resistance (Table VI). Cerebral blood flow showed somewhat greater variability at baseline than some of the other physiologic measurements. However, with the exception of the two animals in the HCA group that ultimately died, in which cerebral blood flow was markedly lower at baseline, all groups were comparable. During rewarming, the cerebral blood flow in both HCA groups increased markedly, whereas the cerebral blood flow in the control hypothermia group and the LFCPB group did not exceed baseline

Table IV. Mean arterial pressure, cardiac output, and CPB flow

		Baseline (37° C)	End of CBP cooling (18° C)	30° C	After start of rewarming		
	<i>n</i>				2 hr	4 hr	8 hr
MAP (mm Hg)							
Hypothermic control	8	62 ± 4	55 ± 7	72 ± 8	70 ± 6	84 ± 3*	82 ± 4*
30 min HCA	8	68 ± 4	58 ± 5 ^b	63 ± 8 ^b	66 ± 3	77 ± 4	77 ± 4
90 min HCA	8	71 ± 4	61 ± 6	69 ± 10 ^b	62 ± 2	74 ± 3	71 ± 6
90 min HCA	6	72 ± 5	58 ± 8 ^b	69 ± 14 ^b	63 ± 2	76 ± 3	77 ± 6
90 min HCA	2 (died)	71 ± 6	70 ± 4	70 ± 14	61 ± 5	67 ± 2	52 ± 3
90 min LFCPB	8	68 ± 4	72 ± 6 ^a	87 ± 7*	68 ± 3	80 ± 7	80 ± 4*
Cardiac output (ml/kg/min)							
Hypothermic control	8	159 ± 9	—	—	193 ± 12*	175 ± 11	184 ± 18
30 min HCA	8	166 ± 7	—	—	188 ± 13	149 ± 8 ^b	169 ± 8
90 min HCA	8	166 ± 12	—	—	151 ± 14 ^{a,b,c}	126 ± 12 ^{*a,b,c}	151 ± 15 ^a
90 min HCA	6	168 ± 15	—	—	167 ± 13	142 ± 6 ^{*a,b}	170 ± 11
90 min HCA	2 (died)	158 ± 18	—	—	104 ± 14	77 ± 0.1	95 ± 2
90 min LFCPB	8	174 ± 11	—	—	190 ± 10	181 ± 17	171 ± 9
CPB flow (ml/kg/min)							
Hypothermic control	8		49 ± 1*	98 ± 2*			
30 min HCA	8		50 ± 0*	100 ± 0*			
90 min HCA	8		51 ± 1*	102 ± 2*			
90 min HCA	6		52 ± 1*	103 ± 2*			
90 min HCA	2 (died)		50 ± 0	100 ± 0			
90 min LFCPB	8		50 ± 0*	100 ± 0*			

Values are shown as mean ± standard error. MAP, Mean arterial pressure.

**p* < 0.05 versus baseline (37° C).

^a*p* < 0.05 versus control (18° C).

^b*p* < 0.05 versus LFCPB (18° C).

^c*p* < 0.05 versus 30 min HCA (18° C).

levels (Fig. 1). Cerebral blood flow was significantly below baseline values at 2 and 4 hours after HCA or LFCPB, but not in the control hypothermia group. At 8 hours after the operation, cerebral blood flow had returned to baseline levels in the 30-minute HCA and LFCPB groups, but was still diminished in the 90-minute HCA group when considered as a whole, principally because the two animals that subsequently died had extremely low cerebral blood flows.

As might be expected from the data on cerebral blood flow, cerebral vascular resistance (Fig. 2) was very low during rewarming in the HCA groups and then significantly higher than baseline at 2 and 4 hours after HCA. However, cerebral vascular resistance was also significantly higher than baseline in both the LFCPB and the hypothermic control groups at 2 and 4 hours after the operation. At 8 hours, the cerebral vascular resistance was still significantly elevated for the 90-minute HCA group, again principally because of the very great elevation of cerebral vascular resistance in both animals that died.

The data for cerebral vascular resistance differed from the data for systemic vascular resistance. Sys-

temic vascular resistance showed the expected elevation with hypothermia but then a gradual fall to normal levels by 2 hours after HCA or LFCPB. In the HCA groups, systemic vascular resistance did show a slight increase at 4 hours, most marked in the 90-minute HCA group, largely because of inclusion of the two animals that died.

Metabolic data. The metabolic changes during and after hypothermia show considerably less variability between groups than was seen with cerebral blood flow and cerebral vascular resistance, as seen in Table VII. All groups showed a marked fall in cerebral oxygen consumption with hypothermia, with a reduction to 32% of baseline metabolic rate at 18° C. There was a prompt return to baseline levels of oxygen consumption on rewarming. Baseline levels of oxygen consumption were then sustained throughout the 8 hours of follow-up (Fig. 3), except in the two animals in the 90-minute HCA group that subsequently died: these animals had a very low cerebral oxygen consumption by 8 hours after the operation.

Systemic oxygen consumption was comparable in all groups at the outset but fell more dramatically

Table V. *Temperature monitoring*

		<i>Baseline</i> (37° C)	<i>End of CBP cooling</i> (18° C)	30° C	<i>After start of rewarming</i>		
	<i>n</i>				2 hr	4 hr	8 hr
Esophageal temperature (° C)							
Hypothermic control	8	37.3 ± 0.1	17.9 ± 0.1*	30.3 ± 0.2*	37.3 ± 0.1	37.3 ± 0.1	37.4 ± 0.1
30 min HCA	8	37.4 ± 0.1	17.9 ± 0.1*	30.0 ± 0.1*	37.5 ± 0.2	37.2 ± 0.2	37.6 ± 0.1
90 min HCA	8	37.5 ± 0.2	17.9 ± 0.1*	30.4 ± 0.2*	37.2 ± 0.2	36.9 ± 0.2* ^b	37.6 ± 0.1
90 min HCA	6	37.5 ± 0.3	17.9 ± 0.1*	30.4 ± 0.2*	37.3 ± 0.3	36.9 ± 0.3 ^b	37.7 ± 0.1
90 min HCA	2 (died)	37.4 ± 0.4	18.1 ± 0.2	30.3 ± 0.3	36.9 ± 0.2	37.0 ± 0.6	37.3 ± 0.3
90 min LFCPB	8	37.3 ± 0.2	18.0 ± 0.1*	30.0 ± 0.1*	37.3 ± 0.2	37.5 ± 0.2	37.5 ± 0.1
Rectal temperature (° C)							
Hypothermic control	8	37.8 ± 0.2	21.1 ± 0.3*	27.2 ± 1.1*	37.8 ± 0.2	37.7 ± 0.2	37.9 ± 0.2
30 min HCA	8	37.8 ± 0.2	23.5 ± 0.5* ^a	28.2 ± 1.4* ^b	37.4 ± 0.4	37.6 ± 0.2	37.7 ± 0.4
90 min HCA	8	37.9 ± 0.2	22.7 ± 0.3* ^a	26.5 ± 0.4* ^c	37.8 ± 0.3	37.2 ± 0.2	38.0 ± 0.2
90 min HCA	6	37.8 ± 0.3	23.0 ± 0.2* ^a	26.7 ± 0.6*	37.8 ± 0.4	37.1 ± 0.3	37.9 ± 0.3
90 min HCA	2 (died)	38.2 ± 0.3	21.8 ± 1.1	26.1 ± 0.4	37.8 ± 0.4	37.6 ± 0.3	38.2 ± 0.4
90 min LFCPB	8	37.7 ± 0.3	23.2 ± 0.7* ^a	26.5 ± 0.7*	37.8 ± 0.2	37.8 ± 0.2	38.1 ± 0.1
Epidural temperature (° C)							
Hypothermic control	5	37.3 ± 0.2	19.5 ± 0.5*	28.9 ± 0.5*	37.3 ± 0.2	37.2 ± 0.3	37.4 ± 0.1
30 min HCA	5	37.6 ± 0.2	18.8 ± 0.2* ^a	29.3 ± 0.3*	37.3 ± 0.4	37.3 ± 0.4	37.5 ± 0.1
90 min HCA	5	37.6 ± 0.3	19.3 ± 0.5*	28.6 ± 0.6*	37.0 ± 0.5	36.9 ± 0.4	37.7 ± 0.3
90 min HCA	4	37.6 ± 0.5	18.8 ± 0.6*	29.5 ± 0.1*	37.0 ± 0.8	36.6 ± 0.6	38.2 ± 0.2
90 min HCA	2 (died)	37.7 ± 0.2	20.1 ± 0.5	27.3 ± 0.9	37.0 ± 0.4	37.2 ± 0.2	37.0 ± 0.4
90 min LFCPB	5	37.5 ± 0.3	19.1 ± 0.6*	28.4 ± 0.4*	37.4 ± 0.2	37.8 ± 0.4	37.7 ± 0.2

Values are shown as mean ± standard error.

**p* < 0.05 versus baseline (37° C).

^a*p* < 0.05 versus control (18° C).

^b*p* < 0.05 versus LFCPB (18° C).

^c*p* < 0.05 versus 30 min HCA (18° C).

than cerebral oxygen consumption; to 16% of control values with hypothermia to 18° C. Systemic oxygen consumption was slower to recover to baseline levels than cerebral metabolism, but then it rebounded and remained higher than baseline levels at 2 and 4 hours after HCA and LFCPB. The postoperative higher-than-baseline values of systemic metabolism were not seen in the hypothermic control group.

The data for cerebral oxygen extraction (Table VIII and Fig. 4) explain how cerebral oxygen metabolism was maintained at baseline values despite the presence of significant cerebral hypoperfusion after the operation. Oxygen extraction fell significantly during hypothermia and rewarming; it then increased markedly in all groups at 2 hours and in all but the hypothermic control group at 4 hours after the operation. In the 90-minute HCA group, extraction of oxygen was still higher than in the hypothermic control and 30-minute HCA groups as late as 8 hours after the operation.

As might be expected from the foregoing extraction data, sagittal sinus oxygen saturations rose with hypothermia and then fell significantly below base-

line in all groups at 2 and 4 hours after hypothermia (Table VIII and Fig. 5). The values for sagittal sinus oxygen saturation were most depressed after the operation in the 90-minute HCA group, falling as low as 30% in the survivors at 4 hours. In the two animals that subsequently died, the sagittal sinus oxygen extractions were extremely low after the operation (22% at 4 hours and 24% at 8 hours), but they were disturbingly depressed (to 37%) even before the onset of the experiment, at baseline.

Systemic oxygen extraction, unlike cerebral oxygen extraction, was not elevated after the operation in any but the 90-minute HCA group, and in contrast to samples from the sagittal sinus, only in the 90-minute HCA group were mixed venous oxygen saturations depressed after the operation.

Data for cerebral glucose metabolism (Table IX) echo the findings for oxygen metabolism. Cerebral glucose metabolism was reduced to 40% of baseline values by hypothermia to 18° C and then returned promptly to baseline values after rewarming (Fig. 6). In the 90-minute HCA group, there was a period of increased glucose use during rewarming; this was especially marked in the two animals that ultimately

Table VI. Cerebral blood flow and vascular resistance

	<i>n</i>	Baseline (37° C)	End of CBP cooling (18° C)	30° C	After start of rewarming		
					2 hr	4 hr	8 hr
CBF (ml/100 gm/min)							
Hypothermic control	8	58 ± 8	47 ± 9	59 ± 5	42 ± 2	45 ± 5	80 ± 6
30 min HCA	8	68 ± 3	62 ± 9 ^a	132 ± 17 ^{a,b}	37 ± 3*	37 ± 2*	80 ± 5
90 min HCA	8	65 ± 6	72 ± 31	144 ± 13 ^{a,b}	33 ± 3*	28 ± 2 ^a	54 ± 9 ^{a,b,c}
90 min HCA	6	72 ± 5	81 ± 41	137 ± 17 ^{a,b}	33 ± 2*	30 ± 2 ^a	65 ± 7
90 min HCA	2 (died)	44 ± 2	46 ± 20	163 ± 2	34 ± 13	24 ± 4	19 ± 9
90 min LFCPB	8	76 ± 6	64 ± 7 ^a	66 ± 7	43 ± 3*	38 ± 3*	80 ± 7
CVR (mm Hg/ml/100 gm/min)							
Hypothermic control	8	1.1 ± 0.1	1.6 ± 0.4	1.2 ± 0.1	1.7 ± 0.2*	1.9 ± 0.2*	1.0 ± 0.1
30 min HCA	8	1.0 ± 0.1	1.0 ± 0.2	0.5 ± 0.1 ^{a,b}	1.8 ± 0.2*	2.1 ± 0.2*	1.0 ± 0.1
90 min HCA	8	1.1 ± 0.1	1.4 ± 0.3	0.5 ± 0.1 ^{a,b}	1.9 ± 0.2*	2.6 ± 0.2*	1.7 ± 0.5 ^{b,c}
90 min HCA	6	1.0 ± 0.1	1.3 ± 0.3	0.5 ± 0.1 ^{a,b}	1.9 ± 0.1*	2.6 ± 0.3*	1.2 ± 0.1
90 min HCA	2 (died)	1.5 ± 0.2	1.8 ± 0.9	0.4 ± 0.1	2.0 ± 0.6	2.7 ± 0.4	3.3 ± 1.7
90 min LFCPB	8	0.8 ± 0.1	1.3 ± 0.2*	1.4 ± 0.2*	1.5 ± 0.1*	2.3 ± 0.3*	1.0 ± 0.1
SVR (mm Hg/ml/kg/min)							
Hypothermic control	8	0.39 ± 0.03	1.11 ± 0.14*	0.73 ± 0.08*	0.35 ± 0.03	0.47 ± 0.02	0.45 ± 0.04
30 min HCA	8	0.40 ± 0.02	1.13 ± 0.09 ^{ab}	0.62 ± 0.08 ^{ab}	0.36 ± 0.03	0.51 ± 0.03*	0.45 ± 0.03
90 min HCA	8	0.44 ± 0.04	1.18 ± 0.12*	0.67 ± 0.09 ^{ab}	0.42 ± 0.04	0.60 ± 0.05 ^{ab}	0.46 ± 0.03
90 min HCA	6	0.43 ± 0.04	1.11 ± 0.15 ^{ab}	0.66 ± 0.12 ^{ab}	0.38 ± 0.04	0.53 ± 0.04	0.45 ± 0.04
90 min HCA	2 (died)	0.44 ± 0.09	1.39 ± 0.07	0.70 ± 0.14	0.54 ± 0.01	0.81 ± 0.04	0.50 ± 0.06
90 min LFCPB	8	0.38 ± 0.04	1.4 ± 0.11 ^a	0.86 ± .07*	0.35 ± 0.02	0.45 ± 0.05	0.46 ± 0.03

Values are shown as mean ± standard error. CBF, Cerebral blood flow; CVR, cerebral vascular resistance; SVR, systemic vascular resistance; systemic blood flow = cardiac output.

**p* < 0.05 versus baseline (37° C).

^a*p* < 0.05 versus control (18° C).

^b*p* < 0.05 versus LFCPB (18° C).

^c*p* < 0.05 versus 30 min HCA (18° C).

died. Cerebral glucose extraction (Fig. 7) was significantly increased after the operation in the 90-minute HCA group at 2, 4, and 8 hours after the operation and in the LFCPB group at 4 hours, coinciding with low cerebral blood flow and high cerebral vascular resistance at these times.

Cerebral flow-metabolism coupling (Table X and Fig. 8). In previous work, we have used the ratio cerebral blood flow/cerebral oxygen metabolism to try to assess whether cerebral blood flow is varying appropriately with cerebral metabolism.¹⁻³ We have assumed that the ratio cerebral blood flow/cerebral oxygen metabolism that exists at baseline, when cerebral autoregulation is presumably intact, represents the ideal value: a significantly higher ratio suggests "luxury perfusion" and a low ratio suggests inadequate cerebral blood flow. By this standard, there is marked hyperemia during rewarming in both the 30-minute and 90-minute HCA groups but no such "luxury perfusion" in the hypothermic control or LFCPB groups. All groups show a lower-than-ideal ratio at 2 hours, which persists in all but the hypothermic control group at 4 hours. By 8

hours the ratio cerebral blood flow/cerebral oxygen metabolism has returned to values not significantly different from baseline in all groups, although the ratio is still significantly lower in the 90-minute HCA group than in all other groups.

Discussion

The data from this study demonstrate that some cerebral injury occurs if HCA is carried out for 90 minutes at 18° C in puppies without packing the head in ice. The cerebral insult is evident from the results of neurologic and behavioral evaluation on postoperative day 1 and from intraoperative and postoperative QEEG studies. Similar evidence of cerebral injury is not seen after 30 minutes of HCA under the same conditions or after 90 minutes of LFCPB at 18° C.

The failure to demonstrate significant behavioral changes in the survivors 1 week after the operation (and the presence of more marked changes in EEG power during the operation than are present on telemetric recordings on day 6, as discussed in the accompanying paper) both suggest that the cerebral

Fig. 1. Cerebral blood flow in all four experimental groups during recovery from hypothermia. Values for all time points after the start of rewarming (Table VI) are expressed as a percent of baseline cerebral blood flow. Both HCA groups showed significantly higher cerebral blood flows during rewarming when compared to baseline. Cerebral blood flow was significantly below baseline values at 2 and 4 hours after HCA and LFCPB, but not in the control group. * $p < 0.05$ versus baseline (37° C); ^a $p < 0.05$ versus control (18° C); ^b $p < 0.05$ versus LFCPB (18° C); ^c $p < 0.05$ versus 30 min HCA (18° C).

Fig. 2. Cerebral vascular resistance during recovery from hypothermia. Values for all time points after the start of rewarming (Table VI) are expressed as a percent of baseline cerebral vascular resistance. Groups are as previously described. Two and 4 hours after hypothermia, cerebral vascular resistance is significantly increased in all groups. * $p < 0.05$ versus baseline (37° C); ^a $p < 0.05$ versus control (18° C); ^b $p < 0.05$ versus LFCPB (18° C); ^c $p < 0.05$ versus 30 min HCA (18° C).

Fig. 3. Cerebral oxygen metabolism at all time points for all four groups (see Table VII). Cerebral metabolism is significantly lower in all groups at the end of cooling but returns to baseline rates by 2 hours after the start of rewarming and is sustained at baseline levels throughout the recovery period.

Table VII. Cerebral and systemic oxygen metabolism

		Baseline (37° C)	End of CBP cooling (18° C)	30° C	After start of rewarming		
		n			2 hr	4 hr	8 hr
CMRO ₂ (ml/100 gm/min)							
Hypothermic control	8	3.8 ± 0.3	1.0 ± 0.1*	3.2 ± 0.2	3.7 ± 0.1	3.7 ± 0.3	4.1 ± 0.3
30 min HCA	8	3.7 ± 0.2	1.3 ± 0.2*	3.4 ± 0.3	3.5 ± 0.3	3.6 ± 0.3	4.4 ± 0.4
90 min HCA	8	3.9 ± 0.3	1.5 ± 0.4*	3.8 ± 0.5	3.4 ± 0.1	3.2 ± 0.2	4.1 ± 0.5
90 min HCA	6	3.9 ± 0.4	1.7 ± 0.6*	3.7 ± 0.4	3.4 ± 0.1	3.2 ± 0.2	4.8 ± 0.3
90 min HCA	2 (died)	3.9 ± 0.3	0.9 ± 0.2	4.3 ± 2.2	3.4 ± 0.1	3.1 ± 0.1	2.1 ± 1.2
90 min LFCPB	8	4.1 ± 0.4	1.2 ± 0.1*	3.6 ± 0.7	3.9 ± 0.3	3.7 ± 0.4	4.7 ± 0.2
SMRO ₂ (ml/kg/min)							
Hypothermic control	8	7.7 ± 0.5	1.2 ± 0.2*	4.2 ± 0.3*	9.5 ± 0.9	8.2 ± 0.5	9.4 ± 0.5
30 min HCA	8	7.9 ± 0.3	1.5 ± 0.3*	3.3 ± 0.3 ^{a,b}	10.6 ± 0.6*	8.8 ± 0.2	9.0 ± 0.4
90 min HCA	8	7.4 ± 0.1	1.2 ± 0.04*	3.3 ± 0.1 ^{a,b}	11.0 ± 0.5*	8.9 ± 0.4*	9.0 ± 0.5*
90 min HCA	6	7.3 ± 0.2	1.2 ± 0.1*	3.5 ± 0.1 ^b	11.0 ± 0.5*	9.2 ± 0.5*	9.5 ± 0.4*
90 min HCA	2 (died)	7.7 ± 0.1	1.2 ± 0.1	2.9 ± 0	10.8 ± 1.8	8.2 ± 0.1	7.6 ± 0.8
90 min LFCPB	8	8.1 ± 0.4	1.2 ± 0.1*	4.5 ± 0.4*	10.5 ± 0.6*	9.7 ± 0.7*	9.3 ± 0.6

Values are shown as mean ± standard error. CMRO₂, Cerebral oxygen consumption; SMRO₂, systemic oxygen consumption.

**p* < 0.05 versus baseline (37° C).

^a*p* < 0.05 versus control (18° C).

^b*p* < 0.05 versus LFCPB (18° C).

^c*p* < 0.05 versus 30 min HCA (18° C).

injury in the survivors of 90 minutes of HCA is usually subtle and that considerable recovery after this kind of injury is possible.

These observations should come as no surprise to

clinicians who use HCA to deal with repair of congenital heart defects in infants. The ongoing collaborative study of children undergoing repair of transposition of the great arteries at Boston Chil-

Table VIII. Cerebral and systemic oxygen extraction

	<i>n</i>	<i>Baseline</i> (37° C)	<i>End of CBP cooling</i> (18° C)	30° C	<i>After start of rewarming</i>		
					2 hr	4 hr	8 hr
Cerebral O ₂ extraction (ml/dl)							
Hypothermic control	8	6.9 ± 0.4	2.6 ± 0.4*	5.5 ± 0.3	8.9 ± 0.2*	8.3 ± 0.4	5.3 ± 0.5*
30 min HCA	8	5.6 ± 0.4	2.3 ± 0.4*	2.8 ± 0.3 ^{a,b}	9.3 ± 0.4*	9.7 ± 0.6*	5.6 ± 0.6
90 min HCA	8	6.5 ± 0.7	2.6 ± 0.4*	2.8 ± 0.4 ^{a,b}	10.9 ± 1.1*	11.5 ± 0.6 ^a	8.4 ± 0.7 ^{a,b,c}
90 min HCA	6	5.7 ± 0.7	2.7 ± 0.6*	2.8 ± 0.4 ^{a,b}	10.5 ± 0.6*	10.9 ± 0.4*	7.6 ± 0.5 ^{a,c}
90 min HCA	2 (died)	8.9 ± 0.4	2.2 ± 0.5	2.7 ± 1.4	12.1 ± 5.1	13.4 ± 1.7	10.7 ± 1.3
90 min LFCPB	8	5.5 ± 0.3	2.1 ± 0.5*	5.2 ± 0.7	9.1 ± 0.6*	9.9 ± 0.6*	6.0 ± 0.3
Sagittal sinus O ₂ (%)							
Hypothermic control	8	52 ± 2	83 ± 4*	56 ± 2	39 ± 3*	45 ± 3*	67 ± 3*
30 min HCA	8	59 ± 4	85 ± 3*	82 ± 3 ^{a,b}	35 ± 4*	37 ± 4 ^a	64 ± 4
90 min HCA	8	56 ± 6	86 ± 4*	83 ± 4 ^{a,b}	34 ± 3*	28 ± 3 ^{a,b,c}	46 ± 5 ^{a,b,c}
90 min HCA	6	62 ± 5	85 ± 5*	83 ± 4 ^{a,b}	33 ± 2*	30 ± 4 ^{a,b,c}	54 ± 3 ^a
90 min HCA	2 (died)	37 ± 10	87 ± 4	83 ± 12	37 ± 4	22 ± 5	24 ± 4
90 min LFCPB	8	59 ± 3	88 ± 4*	63 ± 5	38 ± 3*	36 ± 1 ^a	62 ± 3
Systemic O ₂ extraction (ml/dl)							
Hypothermic control	8	4.9 ± 0.3	2.5 ± 0.3*	4.2 ± 0.3	5.0 ± 0.4	4.8 ± 0.3	5.4 ± 0.4
30 min HCA	8	4.8 ± 0.3	2.9 ± 0.6*	3.3 ± 0.3 ^{a,b}	5.8 ± 0.4	6.0 ± 0.4 ^a	5.4 ± 0.1
90 min HCA	8	4.6 ± 0.3	2.3 ± 0.1*	3.2 ± 0.1 ^{a,b}	7.7 ± 0.9 ^{a,b,c}	7.5 ± 0.7 ^{a,b}	6.3 ± 0.5*
90 min HCA	6	4.5 ± 0.4	2.3 ± 0.1*	3.4 ± 0.1 ^b	6.7 ± 0.2 ^a	6.4 ± 0.2 ^a	5.7 ± 0.2*
90 min HCA	2 (died)	5.0 ± 0.7	2.4 ± 0.1	2.9 ± 0	10.8 ± 3.2	10.7 ± 0.2	8.0 ± 1.0
90 min LFCPB	8	4.7 ± 0.2	2.5 ± 0.2*	4.5 ± 0.4	5.7 ± 0.5	5.5 ± 0.4	5.6 ± 0.5
Mixed venous O ₂ (%)							
Hypothermic control	8	66 ± 2	83 ± 3*	66 ± 3	66 ± 3	68 ± 2	66 ± 3
30 min HCA	8	65 ± 3	79 ± 4	76 ± 3	60 ± 3	55 ± 7 ^{a,b}	65 ± 1 ^{a,b}
90 min HCA	8	70 ± 2	86 ± 1*	78 ± 1 ^a	54 ± 3 ^a	54 ± 5 ^{a,b}	60 ± 4 ^{a,b}
90 min HCA	6	71 ± 3	87 ± 1*	78 ± 1 ^a	58 ± 1*	59 ± 3*	66 ± 1
90 min HCA	2 (died)	67 ± 1	84 ± 2	80 ± 0.5	42 ± 4	38 ± 13	42 ± 11
90 min LFCPB	8	65 ± 1	84 ± 1*	67 ± 3	62 ± 3	65 ± 1	66 ± 3

Values are shown as mean ± standard error.

**p* < 0.05 versus baseline (37° C).

^a*p* < 0.05 versus control (18° C).

^b*p* < 0.05 versus LFCPB (18° C).

^c*p* < 0.05 versus 30 min HCA (18° C).

dren's Hospital⁵ has also demonstrated subtle neurologic injury and the presence of subclinical seizures in many patients after long intervals of HCA. In addition, a number of earlier clinical studies have demonstrated that longer durations of HCA in infants may impair later cognitive ability even in children with no obvious neurologic or behavioral disability.

The current study is unique in allowing us to correlate the occurrence of demonstrable cerebral injury with the physiology of recovery after HCA: it permits us to theorize about the possible mechanisms of cerebral injury after prolonged HCA. Our data show that the animals in the 90-minute HCA group had an initial hyperemia after hypothermia, followed by a prolonged increase in cerebrovascular resistance and decrease in cerebral blood flow. So that cerebral metabolism can be maintained at baseline levels, a marked increase in oxygen extrac-

tion occurs after the operation, reflected by very low levels of sagittal sinus oxygen saturation for a period of at least 4 hours after the operation.

Among the animals that had the worst outcome and ultimately died, the perturbations in cerebral blood flow and resistance characteristic of the entire 90-minute HCA group were most extreme and may well have contributed to their ultimate death. However, although the derangements in cerebral blood flow and resistance (and the consequent increased oxygen and glucose extraction and depressed sagittal sinus oxygenation) were also seen to some extent in the 30-minute HCA and the LFCPB groups, these abnormalities were more pronounced and more prolonged in the 90-minute HCA group: this is true even when the two animals with the most severe injuries were excluded from the analysis.

In keeping with observations in children, in whom low jugular venous oxygen saturations have been

Fig. 4. Cerebral oxygen extraction for all groups during recovery from hypothermia. Values for all time points after the start of rewarming (Table VIII) are presented as a percent of baseline values. Oxygen extraction fell significantly at 30° C in the HCA groups but then increased markedly in all groups at 2 hours and in all but the hypothermic control group at 4 hours after the operation. In the 90 min HCA group, extraction of oxygen was still higher than in all other groups as late as 8 hours after the operation. * $p < 0.05$ versus baseline (37° C); ^a $p < 0.05$ versus control (18° C); ^b $p < 0.05$ versus LFCPB (18° C); ^c $p < 0.05$ versus 30 min HCA (18° C).

reported to be predictive of postoperative cerebral injury,⁶ the two puppies that died had ominously low sagittal sinus saturations. Review of their preoperative values, not only of oxygen saturation but also of cerebral blood flow and vascular resistance, suggests that they may have had baseline disturbances in cerebral blood flow and resistance that predisposed them to more serious injury after HCA. Similar predisposing problems may be detectable by monitoring jugular venous oxygen saturations in infants, and we recommend that this be a routine preoperative precaution for infants in whom long intervals of HCA are anticipated.

Although milder versions of the same cerebral hemodynamic disturbances present in the 90-minute HCA puppies were seen in the 30-minute HCA group, the outcome of the puppies who underwent 30 minutes of HCA confirms previous experience suggesting that shorter durations of HCA are safer than more prolonged intervals: only mild intraoperative decreases in EEG power during recovery without later EEG changes or clinical impairment were present after 30 minutes of HCA (as detailed in the accompanying report). Our earlier study in which we

used 60 minutes of HCA at 18° C also failed to demonstrate clinical impairment, although EEG evidence suggestive of cerebral injury was present.¹ In the current study, both clinical and EEG evidence of at least transient cerebral injury were present after 90 minutes of HCA. This suggests that cooling to 18° C may be adequate protection for short but not for long durations of HCA, as would be predicted from theoretic calculations based on the degree of metabolic suppression that occurs with this degree of cooling.

In this study, the clear difference in outcome after 90 minutes of LFCPB versus 90 minutes of HCA at 18° C demonstrates the greater safety of LFCPB for prolonged procedures at 18° C: this finding is also emerging from the clinical study comparing HCA and LFCPB in infants at Boston Children's Hospital.⁵ The improved outcome after LFCPB correlates with milder disturbances in cerebrovascular hemodynamics in the LFCPB group, although there is still a seemingly inappropriate rise in CVR and a fall in CBF lasting several hours after the operation, provoking increased oxygen extraction and resulting in low sagittal sinus oxygen saturations. The most

Fig. 5. Sagittal sinus oxygen saturation. Values for percent saturation are given for all groups, as previously described, for all time points, corresponding to the data in Table VIII. Significant increases in sagittal sinus saturation were seen in all groups at the end of cooling, but sagittal sinus saturations were significantly depressed at 2 and 4 hours after the start of rewarming. * $p < 0.05$ versus baseline (37° C); ^a $p < 0.05$ versus control (18° C); ^b $p < 0.05$ versus LFCPB (18° C); ^c $p < 0.05$ versus 30 min HCA (18° C).

striking difference between the HCA and LFCPB groups is the complete absence of hyperemia during rewarming in the LFCPB group, possibly implicating this "luxury perfusion" in the pathogenesis of cerebral injury after HCA.

A vulnerable interval⁴ occurs after the operation, even after relatively short durations of HCA and after LFCPB, during which compromised cerebral blood flow sets the stage for possible cerebral ischemia. Thus meticulous attention to assure adequate oxygenation is warranted for several hours after the operation, even when these less extreme techniques involving hypothermia are used. Jugular venous oxygen saturations may be helpful in detecting those patients in whom the ability to extract additional oxygen to offset the inappropriate decrease in cerebral blood flow that occurs during this vulnerable period postoperatively is nearing the limits for this compensatory mechanism.

Despite the precariousness of the cerebral circulation in the postoperative period, we do not see cerebral metabolism fail to return promptly to base-

line values after HCA, even in those animals who later are found to have had some cerebral injury. In our puppies, cerebral metabolism recovers quickly during rewarming and is sustained at baseline levels for many hours thereafter. Our observations encompass the times at which Greeley and his colleagues⁶ find cerebral metabolism to be depressed in children after undergoing HCA and then extend considerably longer. We also find, in contrast to Greeley, that increased oxygen extraction does occur after the operation, whereas cerebral blood flow is reduced. The absence of cerebral metabolic depression after HCA in most of the animals in our study may reflect less severe injury than is occurring in Greeley's experiments: mild or patchy cerebral hypoxemia may not be reflected by a depression in overall cerebral oxygen consumption. In the two animals that were more severely damaged and subsequently died, cerebral metabolism did fall in the late postoperative period, but only after an initial rebound to baseline values in the early recovery period. An alternate explanation for the discrepancy

Fig. 6. Cerebral glucose metabolism in all four groups at all time points. There was a significant reduction in the use of glucose by the brain at the end of cooling, but glucose metabolism returned promptly to baseline values after rewarming (see Table IX). * $p < 0.05$ versus baseline (37°C); ^a $p < 0.05$ versus control (18°C); ^b $p < 0.05$ versus LFCPB (18°C); ^c $p < 0.05$ versus 30 min HCA (18°C).

Table IX. Cerebral glucose metabolism

					After start of rewarming		
	<i>n</i>	Baseline (37° C)	End of CBP cooling (18° C)	30° C	2 hr	4 hr	8 hr
CMRGlu (mg/100 gm/min)							
Hypothermic control	8	6.7 ± 0.6	1.4 ± 0.2*	9.3 ± 1.1	6.7 ± 0.6	5.8 ± 0.6	6.9 ± 0.6
30 min HCA	8	7.7 ± 0.5	3.3 ± 0.6* ^a	13.6 ± 2.3	5.5 ± 0.6	6.2 ± 0.3	7.9 ± 0.6
90 min HCA	8	7.7 ± 0.7	4.1 ± 1.5* ^a	19.1 ± 3.2* ^{a,b,c}	6.0 ± 0.5	5.5 ± 0.4	8.3 ± 1.2
90 min HCA	6	8.3 ± 0.9	4.7 ± 2.0* ^a	14.6 ± 1.6* ^b	6.1 ± 0.2	5.8 ± 0.4	9.6 ± 1.0 ^a
90 min HCA	2 (died)	6.1 ± 0.2	2.3 ± 0.3	32.5 ± 2.0	5.7 ± 2.3	4.8 ± 0.4	4.4 ± 2.2
90 min LFCPB	8	7.5 ± 0.6	3.1 ± 0.6* ^a	9.1 ± 1.6	5.6 ± 0.6	5.9 ± 0.6	8.2 ± 0.5
Glucose extraction (mg/dl)							
Hypothermic control	8	12 ± 1	4 ± 1*	16 ± 2	16 ± 1	13 ± 1	9 ± 1
30 min HCA	8	12 ± 1	6 ± 1* ^a	10 ± 2 ^{a,c}	15 ± 1	17 ± 1	10 ± 1
90 min HCA	8	12 ± 1	7 ± 1* ^a	14 ± 2	18 ± 1*	20 ± 1*	17 ± 2* ^{a,b,c}
90 min HCA	6	12 ± 1	7 ± 1* ^a	11 ± 2	19 ± 1*	19 ± 1*	15 ± 1 ^a
90 min HCA	2 (died)	14 ± 1	6 ± 2	20 ± 1	17 ± 1	21 ± 5	23 ± 1
90 min LFCPB	8	10 ± 1	5 ± 1*	14 ± 2	13 ± 1	16 ± 1*	11 ± 1

Values are shown as mean $\pm$ standard error. CMRGlu, Cerebral glucose consumption.

* $p < 0.05$ versus baseline (37°C).

^a $p < 0.05$ versus control (18°C).

^b $p < 0.05$ versus LFCPB (18°C).

^c $p < 0.05$ versus 30 min HCA (18°C).

between our observations and those of Greeley and associates is to postulate that there are different mechanisms of cerebral injury after HCA, not all of which are associated with an early fall in cerebral oxygen consumption.

On the basis of our data, we strongly advocate the

use of temperatures lower than 18°C for those situations in which long intervals of HCA are absolutely essential. As in previous work,¹ we have again demonstrated in this study that cerebral metabolism is reduced only to 32% to 40% of baseline values by cooling to 18°C , even though systemic metabolism

Fig. 7. Cerebral glucose extraction in all four groups during recovery from hypothermia. Values were significantly increased in the 90-minute HCA group at 2, 4, and 8 hours after the operation and in the LFCPB group at 4 hours. * $p < 0.05$ versus baseline (37°C); ^a $p < 0.05$ versus control (18°C); ^b $p < 0.05$ versus LFCPB (18°C); ^c $p < 0.05$ versus 30 min HCA (18°C).

Table X. Relationship of cerebral blood flow to cerebral oxygen consumption

					After start of rewarming		
	<i>n</i>	Baseline (37° C)	End of CBP cooling (18° C)	30° C	2 hr	4 hr	8 hr
CBF/CMRO ₂							
Hypothermic control	8	14.9 ± 1.0	45.0 ± 6.5*	18.6 ± 1.1	11.4 ± 0.3*	12.3 ± 0.6	20.1 ± 1.9*
30 min HCA	8	18.4 ± 1.0	52.4 ± 8.0*	39.1 ± 4.4 ^{a,b}	10.9 ± 0.5*	10.6 ± 0.7*	19.1 ± 1.8
90 min HCA	8	17.3 ± 2.4	46.1 ± 6.3*	42.1 ± 6.6 ^{a,b}	9.8 ± 0.9*	8.8 ± 0.4 ^a	12.5 ± 1.0 ^{a,b,c}
90 min HCA	6	19.3 ± 2.8	45.2 ± 8.2*	39.1 ± 5.4 ^{a,b}	9.7 ± 0.5*	9.3 ± 0.4*	13.5 ± 1.0 ^{a,c}
90 min HCA	2 (died)	11.3 ± 0.5	48.6 ± 10.2	51.0 ± 26.0	10.0 ± 4.2	7.6 ± 1.0	9.5 ± 1.2
90 min LFCPB	8	18.5 ± 0.9	58.7 ± 7.5*	22.0 ± 3.6	11.4 ± 0.8*	10.5 ± 0.7*	17.0 ± 0.8

Values are shown as mean ± standard error. CBF, Cerebral blood flow; CMRO₂, cerebral oxygen consumption.

* $p < 0.05$ versus baseline (37°C).

^a $p < 0.05$ versus control (18°C).

^b $p < 0.05$ versus LFCPB (18°C).

^c $p < 0.05$ versus 30 min HCA (18°C).

is more dramatically suppressed. Our findings are in agreement with recent studies of cerebral metabolism during hypothermia in 1-week-old piglets by Mault and colleagues,⁷ but our estimates of residual cerebral metabolism after cooling to 18°C are much higher than those in the classic studies of Michenfelder and Milde,⁸ in which only 12% of baseline cerebral oxygen consumption remains, and are also higher than Greeley's measurements in children.⁶

If we accept the premise that cerebral ischemia is well tolerated for 5 minutes at 37°C , by our calculations this means that HCA is safe for only 12 to 15 minutes at 18°C . The more optimistic estimates of

Michenfelder and Milde⁸ suggest a safe duration of 42 minutes, and Greeley's data⁶ indicate a range of 39 to 65 minutes. Even with the most reassuring estimates, the safe interval for HCA at 18°C is still too short for many clinical interventions. Cooling to 13°C and even further before HCA achieves far greater reductions of metabolism—to 20% of baseline at 13°C and to 5% at 8°C ¹—resulting in better anticipated tolerance of cerebral ischemia at these colder temperatures. In an earlier study in our weanling puppy model, neurologic and behavioral evidence of cerebral injury was *not* seen after 90 minutes of HCA at 13°C .³

Fig. 8. Ratio of cerebral blood flow (CBF) to cerebral metabolic rate of oxygen (CMRO₂), giving an estimate of appropriateness of cerebral blood flow. Data are from Table X. A ratio similar to what is seen at baseline, when cerebral autoregulation is intact, seems likely to represent an ideal value. By this standard, all groups had significant "luxury perfusion" by the end of cooling and only the HCA groups showed a marked hyperemia at 30° C. All groups show a lower-than-ideal ratio at 2 hours, which persisted in all but the hypothermic control group at 4 hours. By 8 hours, the ratio CBF/CMRO₂ had returned to values not significantly different from baseline in all groups, although the ratio was still significantly lower in the 90 min HCA group than in the other groups. **p* < 0.05 versus baseline (37° C); ^a*p* < 0.05 versus control (18° C); ^b*p* < 0.05 versus LFCPB (18° C); ^c*p* < 0.05 versus 30 min HCA (18° C).

It should be borne in mind that we are using the esophageal temperature as a guide for the adequacy of hypothermia: if rectal temperature is used to monitor cooling, our data suggest that the concurrent cerebral temperature may well be several degrees lower than the measured rectal temperature, affording greater protection than at an equivalent esophageal temperature.

Several investigators have recently confirmed the value of packing the head in ice during procedures requiring longer durations of HCA.⁷ Although only a minority of clinicians use this very simple precaution regularly, it has been our long-standing clinical practice and has been used in all our previous studies in weanling puppies.¹⁻⁴ Core cooling alone was used during this protocol because we wished to enhance the probability of finding unequivocal clinical evidence of cerebral injury. It is possible that packing the head in ice might have improved the outcome in the animals in the 90-minute HCA group.

Our data show some decrease in cardiac output in the 90-minute HCA group at the later postoperative time points. Similar decreases in systemic output were not seen after 90 minutes of LFCPB or in the

other control groups. Cardiac output was not measured in our earlier study in which we used 90 minutes of HCA at 13° C, but it is likely that the heart as well as the brain are better protected during HCA if the temperature is colder. The fact that even healthy puppy hearts show impaired function after prolonged HCA at 18° C provides an additional argument for using lower temperatures for prolonged HCA in infants whose hearts are especially vulnerable to injury because of underlying congenital heart disease and concurrent surgical manipulation.

In summary, we have shown unequivocally that 90 minutes of HCA at 18° C results in cerebral injury in puppies. Our data suggest that for those infants whose operation requires prolonged HCA, temperatures colder than 18° C should be used. Because of the apparently inappropriate response of the cerebral vasculature to even short intervals of HCA, as well as to LFCPB in the presence of hypothermia, other strategies to protect the brain from injury during cardiac operations should continue to be explored.

We thank Richard Smith and Russell Jenkins for their technical assistance in the conduct of these experiments.

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