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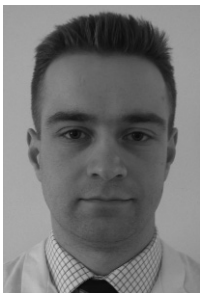
Propofol is Associated with Impaired Brain Metabolism during Hypothermic Circulatory Arrest: An Experimental Microdialysis Study



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ABSTRACT

Background. Propofol is a widely used anesthetic in cardiac surgery. It has been shown to increase cerebrovascular resistance resulting in decreased cerebral blood flow. Efficient brain perfusion and tissue oxygenation during cardiopulmonary bypass (CPB) is essential in surgery requiring hypothermic circulatory arrest (HCA). The effects of propofol on brain metabolism are reported in a surviving porcine model of HCA.

Methods. Twenty female juvenile pigs undergoing 75 minutes of HCA at a brain temperature of 18°C were assigned to either propofol- or isoflurane anesthesia combined with α-stat perfusion strategy during CPB cooling and rewarming. Brain microdialysis analysis was used for determination of brain metabolism, and tissue oxygen partial pressure and intracranial pressures were also followed-up until 8 hours postoperatively.

Results. Brain concentrations of glutamate and glycerol were significantly higher in the propofol group throughout the experiment ($P < .01$ and $P < .01$, respectively). The lactate/pyruvate ratio was significantly higher in the propofol group at 6-, 7-, and 8-hour intervals ($P < .05$, $P < .01$, and $P < .05$, respectively). The intracranial pressure was significantly higher at the 8-hour postoperative interval ($P < .05$) in the propofol group. A trend toward higher brain oxygen concentrations was observed in the isoflurane group.

Conclusions. Anesthesia with propofol as compared with isoflurane is associated with impaired brain metabolism during experimental HCA.

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INTRODUCTION

A period of hypothermic circulatory arrest (HCA) is often required during aortic arch surgery and repair of congenital heart defects. However, it is associated with evident detrimental effects on the brain. Because of this, alternative methods and drugs for better brain protection have been investigated. Isoflurane and propofol are anesthetic compounds with neuroprotective properties, and their effects have been studied in the settings of traumatic brain injury and stroke [Pinaud 1990; Kahveci 2001]. Propofol (2, 6-di-isopropylphenol) is a widely used anesthetic agent in cardiac surgery and in operations requiring HCA. It possesses favorable properties, such as rapid pharmacodynamics, cerebrovascular and metabolic effects similar to those of barbiturates, and the ability to reduce intracranial pressure (ICP) and cerebral metabolic rate of oxygen [Chong 1994; Ergun 2002]. However, several studies have shown that propofol increases cerebrovascular resistance resulting in decreased cerebral blood flow (CBF) [Vandesteene 1988; Lagerkranser 1997]. Interestingly, Kanbak and colleagues demonstrated no advantage of propofol over isoflurane in cerebral protection during coronary artery bypass surgery [Kanbak 2004]. These adverse effects of propofol are likely to be potentiated by the use of α-stat perfusion strategy, the latter having been shown to preserve the cerebral autoregulation but to have inferior neuroprotective efficacy compared with pH-stat perfusion strategy [Aoki 1993; Duebener 2002; Pokela 2003a].

Herein, we report the results of an experimental study on the effects on brain metabolism and postoperative outcome of propofol versus isoflurane during HCA employing α-stat perfusion strategy.

MATERIALS AND METHODS

Experimental Protocol

Twenty female juvenile pigs (age range, 8-10 weeks) from a native stock with a median weight of 28.9 kg in the propofol

group (interquartile range [IQR], 28.9-30.4 kg) and 27.7 kg (IQR, 26.5-28.6 kg) in the isoflurane group (P = .08), were assigned to undergo 75 minutes of HCA at a brain temperature of 18°C. Either propofol (n = 10) or isoflurane anesthesia (n = 10), combined with α-stat acid-base perfusion strategy, was used during cooling and rewarming cardiopulmonary bypass (CPB). All animals received humane care in accordance 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" prepared by the Institute of Laboratory Animal Resources, National Research Council (published by the National Academy Press, revised in 1996). The study was approved by the Research Animal Care and Use Committee of the University of Oulu.

The animals were sedated with ketamine hydrochloride (350 mg intramuscularly) and midazolam (45 mg intramuscularly). A peripheral IV catheter was inserted into the right ear for administration of drugs and to maintain fluid balance with Ringer acetate. Anesthesia was deepened with an intravenous bolus injection of fentanyl (25 μg/kg). In addition to propofol infusion (4 mg/kg per hour) in the propofol group and inhalated isoflurane (0.5 %) in the isoflurane group, the balanced anesthesia was maintained after endotracheal intubation by a continuous infusion of fentanyl (25 μg/kg per hour), midazolam (0.25 mg/kg per hour) and pancuronium (0.2 mg/kg per hour) in both study groups throughout the whole experiment, but not during HCA. The animals were maintained on positive pressure ventilation with 50% oxygen. Cefuroxime (1.5 g intravenously) was administered at anesthesia induction and before extubation. Electrocardiographic monitoring was performed throughout the experiment. An arterial catheter was positioned into the left femoral artery for arterial pressure monitoring and blood sampling. A thermodilution catheter (CritiCath, 7 French; Ohmeda, Erlangen, Germany) was placed through the left femoral vein to allow blood sampling, central venous pressure, pulmonary artery, and pulmonary capillary wedge pressure monitoring, and for recording the blood temperature and cardiac output. A 10 French catheter was placed in the urinary bladder for urine output monitoring. Temperatures were monitored from pulmonary artery blood, the rectum, and the epidural and intracerebral spaces. Through a right thoracotomy in the fourth intercostal space the pericardium was opened, and the heart and great vessels were exposed. After this, the baseline parameters were recorded.

A membrane oxygenator (D905 Eos; Dideco, Mirandola, Italy) was primed with 1 L of Ringer acetate and heparin (5000 IU). After systemic heparinization (500 IU/kg), the ascending aorta was cannulated with a 16 French arterial cannula, and the right atrial appendage was cannulated with a single 24 French atrial cannula. The animals in the propofol group required bolus injections of propofol before cannulation (mean 170 mg ± standard deviation [SD] 89 mg) to obtain lower arterial pressures at cannulation. Nonpulsatile CPB was initiated at a flow rate of 90 to 110 mL/kg per minute, and the flow was adjusted to maintain a perfusion pressure of 50 to 70 mmHg. A 12 French intracardiac sump cannula was positioned into the left ventricle through the apex of the heart for decompression of the left side of the heart during CPB. A cooling period of 60 minutes was carried out to attain a brain temperature of 18°C. A heat exchanger was used for core cooling. When the target temperature was reached, the ascending aorta was cross clamped just distal to the aortic cannula, and cardiac arrest was induced by injecting potassium chloride (40 mmol) through the aortic cannula. Cardiac cooling with topical ice slush was begun and maintained throughout the 75-minute HCA period. Similarly, the intracerebral temperatures were controlled and maintained at a level of 18°C with ice packs placed over the head. During the CPB phases, the heat exchanger-blood temperature gradient was set at 10°C. Five minutes after the start of rewarming, furosemide (40 mg), mannitol (150 g), methylprednisolone (80 mg), lidocaine (40 mg), and calcium glubionat (137.5 mg) were administered. The left ventricular sump cannula was removed after 45 minutes of rewarming, and weaning from CPB occurred about 60 minutes after HCA. Dopamin was postoperatively used as required. During rewarming and after weaning from CPB, heat-exchanger mattress, heating lamps, and ice packs regulated the temperatures. The animals of both groups were extubated 8 hours after the start of rewarming when the rectal temperature approximated 37°C, and the animals were moved to a recovery room.

Intracerebral Monitoring

A temperature probe was placed into the epidural space through a cranial hole made on the left side of the coronal suture. A catheter for measurement of intracerebral tissue oxygen partial pressure (Revodoxe Brain Oxygen Catheter-Micro-Probe, Ref CC1.SB; GMS, Mielkendorf, Germany) was placed through a hole located on the right side 1 cm anteriorly to the coronal suture. A pressure-monitoring catheter (Codman Micro-Sensor ICP Transducer, Codman ICP Express Monitor; Codman & Shurtleff, Raynham, MA, USA) together with a probe for monitoring intracerebral temperature (Thermocouple Temperature Catheter-Micro-Probe, Ref C8.B; GMS) were inserted through a hole located at the left side posteriorly to the coronal suture. The intracerebral temperature was used as the primary measure of temperature.

An intracerebral microdialysis catheter was inserted through a hole located at the right side 0.5 cm posteriorly to the coronal suture. The microdialysis catheter (CMA 70; CMA/Microdialysis, Stockholm, Sweden) was placed into the brain cortex at a depth of 15 mm below the dura mater. The catheter was connected to a 2.5-mL syringe placed into a microinfusion pump (CMA 106; CMA/Microdialysis) and perfused with Ringer solution at a rate of 0.3 μL/min (Perfusion Fluid CNS; CMA/Microdialysis). Samples were collected at different time intervals. The concentrations of cerebral tissue glucose, lactate, pyruvate, glutamate, and glycerol were measured immediately after collection with a microdialysis analyzer (CMA 600; CMA/Microdialysis) by using ordinary enzymatic methods.

Electroencephalography Monitoring

Cortical electrical activity was registered by 4 stainless-steel screw electrodes 5 mm in diameter implanted into the

skull over the parietal and frontal areas of the cortex using a digital electroencephalography (EEG) recorder (Nervus, Reykjavik, Iceland) and an amplifier (Magnus EEG 32/8, Reykjavik, Iceland). Sampling frequency was 256 Hz and bandwidth was 0.03 to 100 Hz. All EEG recordings were referenced to a frontal screw electrode, which, together with a ground screw electrode, was implanted over the frontal sinuses.

EEG was recorded for 10 minutes to get a baseline recording before the cooling period. After HCA, EEG recording was restarted and continued until extubation. Artifact periods were excluded from each 5-minute sample. The energy recovery of EEG was evaluated by an algorithm based on the nonlinear energy operator.

Biochemical Data

Blood gases, pH, electrolytes, serum ionized calcium, and glucose and hemoglobin levels (i-STAT Analyzer; i-STAT Corporation, East Windsor, NJ, USA) were measured at baseline, at the end of cooling (immediately before institution of HCA), and 30 minutes, 2 hours, 4 hours, and 8 hours after the start of rewarming. To control arterial carbon dioxide gas tension precisely, sampling was performed at least every 15 minutes during CPB.

Behavioral Evaluation

Postoperatively, all the animals were evaluated daily by an experienced observer who was blinded to the study group using a species-specific quantitative behavioral score. The quantified assessments of mental status (0 = comatose, 1 = stuporous, 2 = depressed, and 3 = normal), appetite (0 = refuses liquids, 1 = refuses solids, 2 = decreased, and 3 = normal), and motor function (0 = unable to stand, 1 = unable to walk, 2 = unsteady gait, and 3 = normal) were summed to obtain a final score, with a maximum score of 9 reflecting apparently normal neurological function and with lower values indicating substantial brain damage.

Histopathological Analysis

Each surviving animal was electively sacrificed on the seventh postoperative day. Immediately after intravenous injection of pentobarbital (60 mg/kg) and heparin (500 IU/kg), the thoracic cavity was opened, and the descending thoracic aorta was clamped. Ringer solution (1 L) was administered through the ascending thoracic aorta to the upper body, and blood was suctioned from the superior vena cava until the perfusate was clear of blood. Then 10% formalin solution (1 L/15 minutes) was infused through the brain in the same manner to accomplish perfusion fixation. Immediately thereafter, the entire brain was harvested, weighed, and immersed in 10% neutral formalin. The same method of fixation procedure was carried out in those animals that died before the seventh postoperative day. Details of fixation and sectioning of the brain have been previously described [Pokela 2003a]. The sections of the brain specimens of each animal were screened by a single neuropathologist unaware of the experimental design and fate of the individual animals. The signs of injury were scored as follows: 1 (slight edema, dark or eosinophilic neurons or cerebellar Purkinje cells), 2 (moderate edema, at least 2 hemorrhagic foci in the section), and 3 (severe edema, several hemorrhagic foci, infarct foci [local necrosis]). The total regional score was the sum of the scores in each specific brain area (cortex, thalamus, hippocampus, posterior brainstem, and cerebellum). A total histopathologic score was calculated by summing all the regional scores to allow semiquantitative comparison between the animals.

Statistical Analysis

Statistical analysis was performed using SPSS (SPSS version 11.0; SPSS, Chicago, IL, USA) and SAS (version 8.02; SAS Institute, Cary, NC, USA) statistical programs. Continuous and ordinal variables are expressed as the median with IQR (twenty-fifth and seventy-fifth percentiles). SAS procedure mixed was used for repeated measurements. Because the measurement intervals were uneven, spatial exponential covariance structure was defined in repeated statement. Complete independence was assumed across animals (by random statement). Reported *P* values are as follow: *P*-time indicates change over time; *P* between groups indicates a level of difference between groups; *P*-time × group indicates behaviour between groups over time. Mann-Whitney *U* test was used to assess the distribution of variables between study groups. The Fischer exact test was used to determine the significance of mortality rates between the groups. Significance levels are reported for comparisons with the 2-tailed test ($P \leq .05$).

RESULTS

Comparison of the Study Groups

Twenty-five pigs were operated on. One animal that underwent feasibility experiment suffered from mediastinitis, 1 died because of subdural hematoma, and 3 died of laryngeal spasm at extubation. These animals were excluded from the analysis. Ten pigs were included in both study groups. The groups did not differ significantly in any preoperative values. The most relevant experimental and metabolic data are shown in Tables 1 and 2.

Postoperative Outcome

The 7-day survival rates were 20% (2 of 10 animals) in the propofol group and 50% (5 of 10 animals) in the isoflurane group ($P = .35$). There were no statistically significant differences between the groups in terms of postoperative behavioral scores.

Intracranial Measurements

Changes in brain microdialysis parameters were more favorable in the isoflurane group (Figure 1). The extracellular concentrations of brain glutamate and glycerol were significantly lower in the isoflurane group compared to the propofol group ($P = .008$ and $P = .0046$, respectively). The glutamate levels rose more rapidly in the propofol group from 30 minutes of HCA and remained significantly higher until 30 minutes of rewarming. Furthermore, the brain glycerol concentrations were significantly higher already from the end of cooling until the end of the experiment. The lactate/pyruvate ratio was significantly lower in the isoflurane group at the 6-hour ($P =$

Table 1. Experimental Data*

	Baseline	End of Cooling	After the Start of Rewarming				*P* between Groups	*P*-Time × Group	*P*-Time
			40 min	2 h	4 h	8 h			
Mean arterial pressure, mmHg							.040	.054	<.001
Propofol	96 (89-106)	62 (60-64)	52 (51-54)	88 (83-93)	95 (93-102)	84 (72-92)			
Isoflurane	93 (86-110)	60 (57-66)	57 (56-58)	73 (60-83)	80 (71-94)	69 (67-75)			
Cardiac index							.81	.024	<.001
Propofol	4.2 (3.7-4.9)	2.1 (1.9-2.2)	3.0 (2.9-3.3)	3.1 (2.7-3.4)	3.2 (3.0-3.4)	3.5 (3.2-4.3)			
Isoflurane	4.3 (3.8-4.8)	2.6 (2.3-2.8)	2.9 (2.8-3.2)	2.8 (2.3-3.2)	3.0 (2.7-3.2)	3.6 (3.2-4.2)			
Intracranial pressure, mmHg							.51	.11	<.001
Propofol	5 (4-6)	3 (2-6)	6 (5-8)	10 (6-12)	11 (6-14)	18 (17-23)			
Isoflurane	6 (3-7)	2 (0-8)	8 (7-8)	8 (6-9)	7 (7-13)	13 (11-16)			
Cerebral perfusion pressure, mmHg							.061	.074	<.001
Propofol	91 (85-100)	60 (55-62)	46 (44-50)	77 (75-82)	84 (80-90)	66 (49-72)			
Isoflurane	88 (77-101)	55 (52-64)	48 (46-54)	63 (55-74)	73 (61-87)	56 (49-63)			
Intracerebral temperature, °C							.53	>.9	<.001
Propofol	37.3 (36.4-38.1)	17.7 (17.5-18.0)	34.7 (32.8-34.9)	35.4 (34.9-35.6)	36.4 (35.9-36.8)	38.0 (37.1-38.2)			
Isoflurane	37.4 (36.7-37.8)	17.4 (17.4-17.5)	34.8 (33.0-35.7)	34.8 (34.6-36.1)	36.2 (35.5-36.9)	38.0 (37.1-38.4)			
Fluid balance, mL							.28	.037	<.001
Propofol	350 (150-500)	2450 (2200-2600)	2750 (2500-2850)	2200 (1900-2500)	2000 (1650-2200)	2200 (1600-2400)			
Isoflurane	325 (200-400)	2625 (2550-2950)	2800 (2650-3550)	2000 (1800-2200)	2300 (1450-2450)	2400 (2000-2550)			
Hematocrit, %							.59	.15	<.001
Propofol	23.3 (23.0-24.5)	16.8 (16.0-18.0)	17.8 (17.0-19.0)	20.5 (19.0-22.0)	20.3 (18.0-22.0)	17.5 (16.5-20.0)			
Isoflurane	22.3 (22.0-26.0)	15.3 (15.0-17.0)	19.0 (18.0-19.0)	21.0 (20.0-22.5)	19.5 (17.0-21.5)	16.0 (14.5-19.0)			

*Values are shown as medians and interquartile ranges (twenty-fifth and seventy-fifth percentiles). Whole study period (from baseline to 8 hours after start of rewarming) was included in analysis. *P* between groups indicates the level of difference between groups; *P*-time × group, behaviour between groups over time; *P*-time, change over time.

.049), 7-hour ($P = .008$) and 8-hour ($P = .018$) postoperative intervals. No statistically significant differences were seen between the groups in the repeated measurements test in terms of concentrations of brain glucose ($P = .43$), lactate ($P = .10$) or pyruvate ($P = .41$). However, the lactate levels were higher in the propofol group already from beginning of cooling until 1 hour after HCA and tended to remain higher from 4 to 8 hours postoperatively. The concentration of brain glucose tended to be lower postoperatively in the propofol group compared to the isoflurane group.

ICP was lower during cooling and rewarming in the propofol group (Figure 2), but from 90 minutes after HCA the ICP was lower in the isoflurane group. At the 8-hour postoperative interval, a statistically significant difference was observed between the groups in terms of ICP ($P = .02$). The brain oxygen tension was somewhat higher in the isoflurane group from the beginning of cooling until 2 hours after HCA ($P = .095$).

EEG Recovery

Overall, the EEG recovered slowly and incompletely in both groups compared to previous studies of ours. EEG (Figure 2) recovered better in the isoflurane group, although no statistically significant difference between the groups was observed in the repeated measurements test ($P = 0.15$, *P*-time × group = .04). A statistically significant difference was observed at the 3-hour interval after HCA, median rates having been 11% in the isoflurane group versus 0% in the propofol group ($P = .028$). At the 7-hour interval after HCA, the median burst suppression rates were 46% versus 7% ($P = .265$). Eight hours after the end of HCA, the EEG contained too many artefacts for proper analysis.

Systemic Physiologic and Metabolic Data

Experimental and metabolic data are presented in Tables 1 and 2. The systemic oxygen consumption was higher in the propofol group ($P = .050$). Blood pH was lower in the propofol group ($P = .03$), accompanied by somewhat higher serum ionized calcium levels ($P = .092$). The carbon dioxide partial pressure tended to be higher in the propofol group ($P = .077$), although α-stat strategy with frequent blood-sample analysis was used during perfusion in both groups. The mean arterial pressure was higher in the propofol group ($P = .04$), although in this group there was a steep drop in vascular resistance from 5 minutes rewarming to 45 minutes of rewarming leading to lower mean arterial pressures during the rewarming phase. There was less alteration in vascular resistance throughout the experiment in the isoflurane group (*P*-time ×

Table 2. Metabolic Data*

	Baseline	End of Cooling	After the Start of Rewarming				*P* between Groups	*P*-Time × Group	*P*-Time
			40 min	2 h	4 h	8 h			
pH							.030	.56	<.001
Propofol	7.53 (7.50-7.59)	7.45 (7.44-7.51)	7.32 (7.29-7.34)	7.40 (7.38-7.43)	7.46 (7.41-7.49)	7.49 (7.48-7.52)			
Isoflurane	7.56 (7.55-7.58)	7.48 (7.46-7.51)	7.35 (7.32-7.38)	7.41 (7.40-7.44)	7.49 (7.46-7.51)	7.54 (7.51-7.57)			
$PaCO_2$, kPa							.077	.28	<.001
Propofol	36.0 (32.2-39.0)	39.0 (38.2-41.2)	41.2 (39.7-42.0)	42.7 (39.0-43.5)	41.2 (40.5-42.0)	39.7 (38.2-40.5)			
Isoflurane	34.5 (33.7-36.7)	36.7 (36.0-39.7)	38.2 (38.2-40.5)	43.5 (40.5-45.0)	39.7 (39.0-42.0)	38.2 (36.7-39.7)			
SvO_2, %							.74	>.9	<.001
Propofol	77 (73-81)	100 (99-100)	77 (72-77)	62 (54-63)	61 (55-65)	59 (54-63)			
Isoflurane	76 (74-81)	100	77 (75-80)	62 (54-67)	62 (59-64)	61 (55-63)			
O_2 delivery, $mL \times min^{-1} \times m^{-2}$							.52	.089	<.001
Propofol	48.8 (45.7-55.3)	21.3 (20.4-22.9)	30.7 (28.8-32.3)	31.3 (28.0-37.0)	33.0 (27.9-34.8)	36.6 (34.6-37.6)			
Isoflurane	48.3 (43.3-52.5)	25.0 (20.2-29.8)	31.2 (27.7-35.6)	27.8 (26.2-32.5)	31.4 (29.2-32.9)	29.8 (27.0-32.6)			
O_2 consumption, $mL \times min^{-1} \times m^{-2}$							.050	.030	<.001
Propofol	10.4 (9.4-13.0)	3.0 (2.9-3.1)	8.5 (8.0-9.4)	10.6 (9.9-12.3)	10.0 (9.6-12.0)	12.6 (10.5-13.8)			
Isoflurane	11.3 (10.1-11.8)	2.5 (2.2-2-8)	8.3 (7.5-8.6)	9.5 (9.1-10.6)	10.0 (9.4-10.2)	10.9 (10.1-11.3)			
O_2 extraction, mL/dL							.33	.44	<.01
Propofol	3.2 (2.9-3.7)	1.7 (1.6-2.0)	3.5 (3.3-3.6)	4.5 (3.9-5.2)	4.4 (3.4-5.3)	3.6 (3.5-5.0)			
Isoflurane	3.3 (2.7-3.9)	1.3 (1.2-1.5)	3.3 (3.1-3.7)	4.2 (4.1-5.0)	4.2 (3.8-4.4)	3.7 (3.3-4.1)			
Brain O_2 partial pressure, mmHg							.095	.68	<.001
Propofol	30.1 (23.5-46.0)	48.9 (10.4-78.5)	14.5 (10.9-20.4)	19.0 (10.0-24.0)	14.2 (6.6-25.4)	5.1 (2.7-12.5)			
Isoflurane	33.4 (26.7-47.6)	72.9 (37.0-92.7)	27.6 (21.1-34.1)	23.0 (20.9-25.4)	15.5 (9.9-25.6)	8.1 (4.0-13.7)			

*Values are shown as medians and interquartile ranges (twenty-fifth and seventy-fifth percentiles). Whole study period (from baseline to 8 hours after start of rewarming) was included in analysis. *P* between groups indicates the level of difference between groups; *P*-time × group, behaviour between groups over time; *P*-time, change over time; $PaCO_2$, arterial CO_2 partial pressure; SvO_2, mixed venous oxygen saturation.

group = .041). The higher arterial pressures in the propofol group led to higher ICPs and somewhat better cerebral perfusion pressures (*P* = .06). The rectal temperature was significantly lower in the isoflurane group (*P* = .037), but no accompanying difference was seen in terms of brain temperature.

Histopathologic Findings

The high mortality during the first postoperative day resulted in only minor histopathologic changes, because the number of survivors was low and histologically visible tissue damages, edema excluded, usually need more time to develop. Therefore, no significant differences were observed in the total histopathologic scores. The cortex score showed a trend to be higher in the propofol group, mainly because of edema changes (*P* = .12).

DISCUSSION

Brain microdialysis analysis provided the main outcome measures of this study. This tool allows direct, reliable biochemical neuromonitoring during multiple intervals during brain ischemia and after reperfusion. Although there still exists incomplete understanding of the pathophysiology of brain ischemic injury in in vivo settings, the glutamate excitotoxicity hypothesis suggests that excess glutamate in the extracellular space activates primarily *N*-methyl-*D*-aspartate glutamate receptors leading to overflow of calcium into the neurons and a calcium-dependent catabolic process [Paschen 1996]. In experimental models of HCA, brain glutamate levels increased after prolonged HCA, but without a clear association to postoperative outcome [Rimpiläinen 2001, 2002]. In this study, the brain glutamate concentrations were significantly higher in the propofol group already during cooling perfusion, suggesting that the neuronal damage starts as the result of the combined use of propofol and α-stat perfusion strategy.

The higher concentrations of brain glycerol in the propofol group throughout the experiment confirm a more severe neuronal damage as glycerol, when released from the cell membrane, is the ultimate indicator of brain damage. Indeed, glycerol concentrations have been shown to rise during and after cerebral ischemia, and glycerol has also been shown to be a sensitive and reliable marker of cell damage in experimental cerebral ischemia [Hillered 1998; Frykholm 2001].

Somewhat higher brain lactate concentrations were observed similarly in the propofol group already from the start of cooling until 1 hour after HCA, indicating anaerobic metabolism. However, some observations suggest that

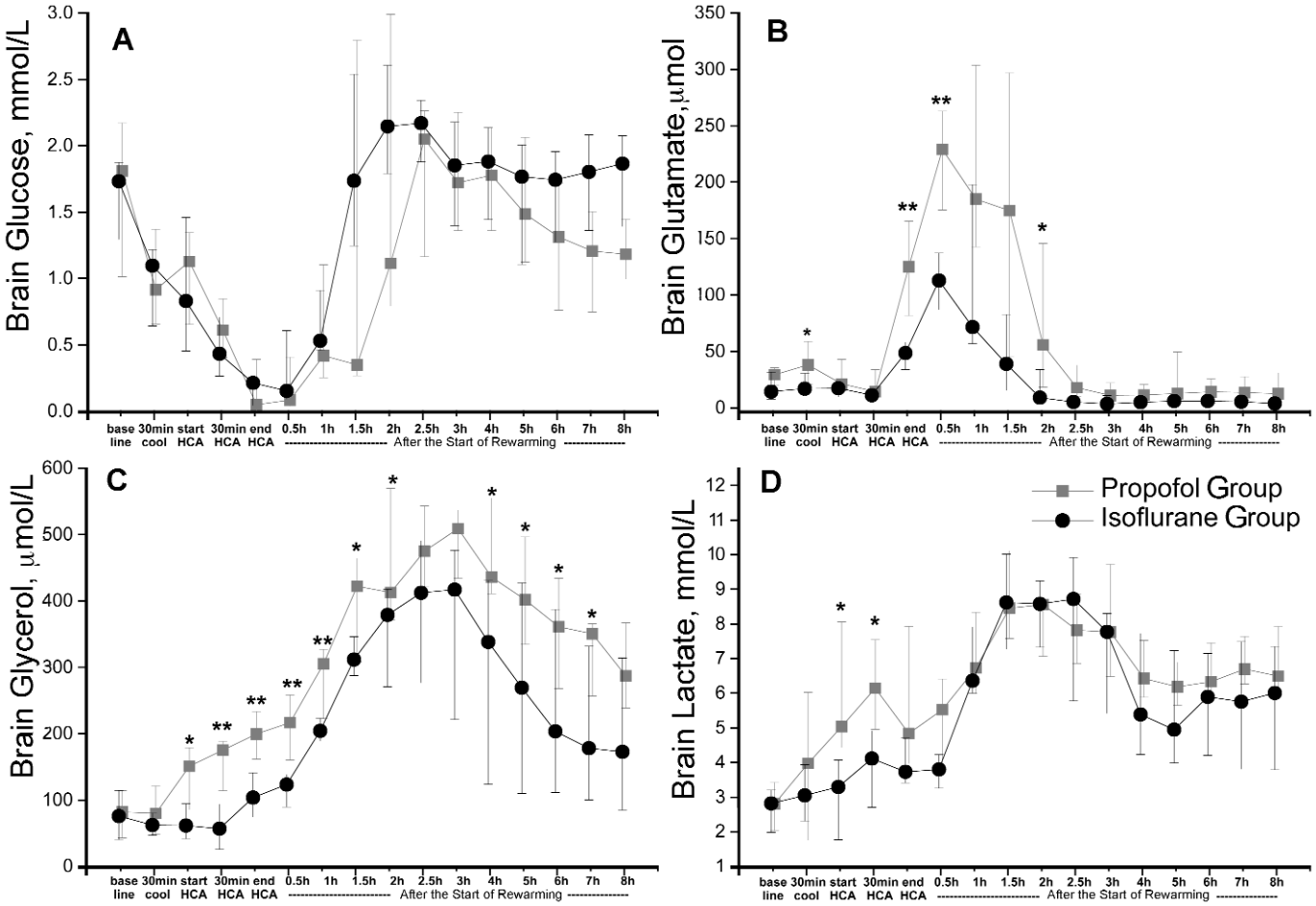

Figure 1. Peri- and postoperative changes of brain concentration of glucose (A), glutamate (B), glycerol (C), and lactate (D) after experimental hypothermic circulatory arrest in the study groups. *$P < .05$. **$P < .01$.

glial-derived lactate is preferred by neurons as energy substrate during the first phases of reperfusion [Schurr 1997; Bliss 2001].

In the present study, the isoflurane group was associated with more favorable changes of perioperative parameters as compared to the propofol group. This could be a consequence of more efficient brain perfusion and tissue oxygenation during CPB cooling and rewarming. Interestingly, the brain tissue partial pressure of oxygen was higher from cooling until 2 hours postoperatively in the isoflurane group, although not significantly, which is in line with the brain microdialysis findings.

ICP is one of the main determinants of outcome in neurosurgical patients. Propofol has been used to maintain neurosurgical anesthesia because it reduces cerebral metabolic rate, CBF, and ICP [Ergun 2002]. In the present study, ICP was lower in the propofol group during perfusion phases, but not from 90 minutes to 8 hours after HCA, during which higher mean arterial pressure was also observed, the result being a trend of higher cerebral perfusion pressures compared to the isoflurane group.

The EEG recovers from electrical silence through burst suppression to continuous EEG after HCA. A delay in such an EEG burst-suppression recovery is an indicator of brain damage [Binnie 1994; Stecker 2001]. We have previously reported a decreased EEG burst percentage recovery after HCA to be associated with an increased risk of developing histologically evident ischemic brain injury [Pokela 2003b]. In this study, EEG recovered more slowly in the propofol group, but no major conclusions can be drawn concerning the impact of brain injury on EEG and different anesthetics also suppress independently neuronal activity.

The significantly lower pH in the propofol group suggests that this anesthetic method is associated with impaired tissue perfusion, inadequate cooling, and metabolic acidosis. The significantly higher rectal temperature and systemic oxygen consumption also speaks in favour of this theory. Ozlu et al investigated the effect of propofol infusion anesthesia on acid-base status in children and found that the short-term use of propofol is associated with significantly lower postoperative pH levels compared with the thiopenthal group [Ozlu 2003]. Propofol infusion syndrome is a rare but often fatal syndrome, and the main features consist of cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure. Its development usually requires critical illness with triggering long-term infusion (>48 h) of high dose propofol

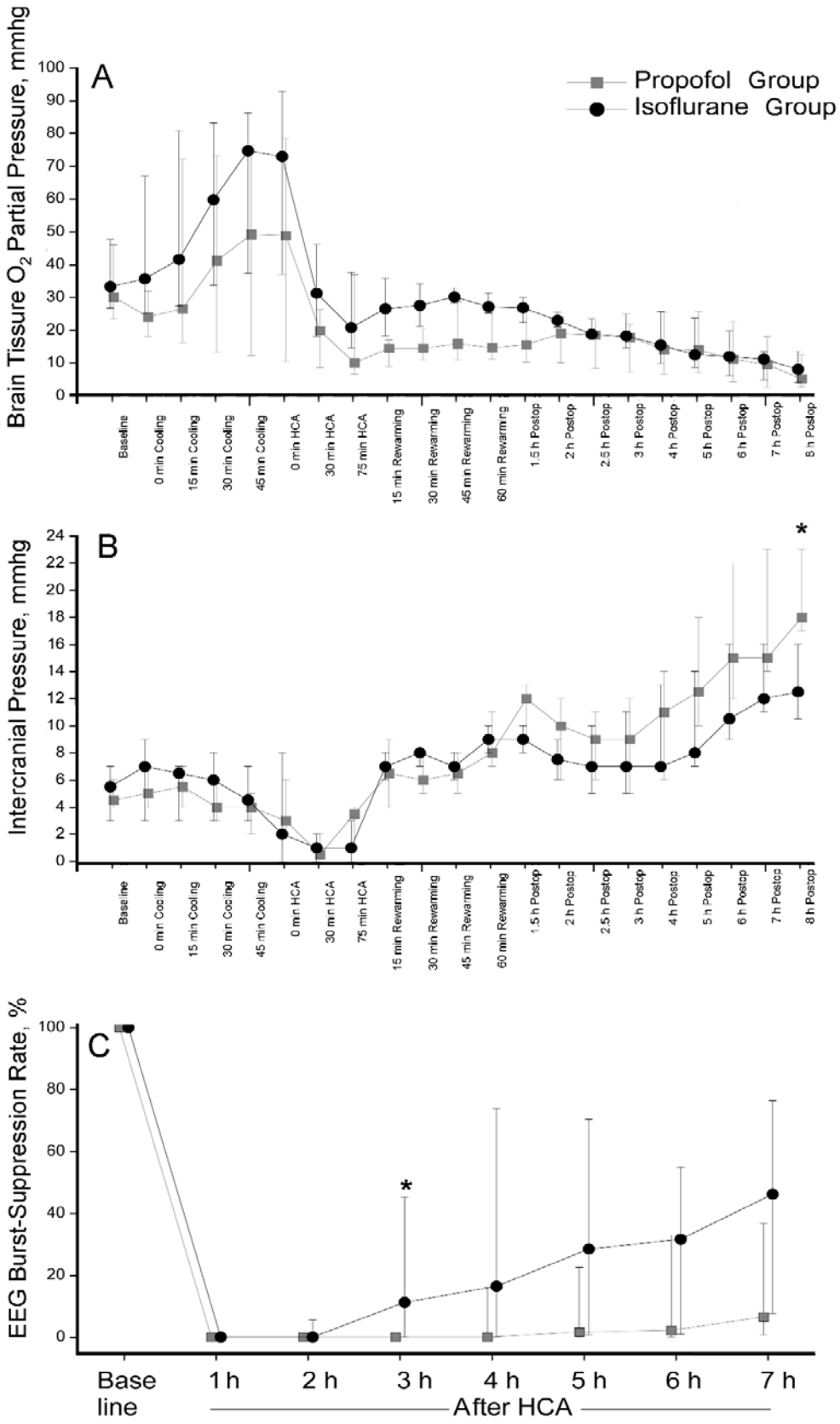

Figure 2. Brain tissue oxygen partial pressure (A), intracranial pressure (B), and electroencephalographic activity (C) recovery after experimental hypothermic circulatory arrest in the study groups. *$P < .05$. **$P < .01$.

(>4mg/kg per hour). Supportive treatments with catecholamines and corticosteroids also act as triggering factors [Vasile 2003]. We did not use high-dose propofol, and no cardiac failure was observed. Therefore, it is not likely that such acidosis can be ascribed to the above-mentioned syndrome. Propofol is recognized as a short-active anesthetic agent, but the pharmacokinetics of propofol are altered by mild hypothermia and the duration of action of muscle relaxants as atracurium is prolonged, as reported by Leslie and colleagues [Leslie 1995]. The status of deep hypothermia used in this study is likely to have decreased the liver metabolism of propofol even more. However, it is possible that the derangements in brain metabolism in the propofol group had already started during cooling.

Although we used a surviving porcine model for evaluation of postoperative recovery and brain histopathologic changes, we were not able to draw major conclusions about long-term end-points because most of the animals died on the first postoperative day, and therefore histopathologic changes had not yet developed, and, also, comparison of the animals from different time frames of death does not yield meaningful results. The early mortality in the propofol group similarly affected the behavioral scoring and no statistically significant differences were observed between the groups for the surviving animals.

However, the significantly differing changes in key brain microdialysis parameters reliably indicate a more severe acute brain injury in the propofol group. Meixensberger et al found a similar correlation between hypoxic oxygenation and metabolic disturbances after acute brain injury [Meixensberger 2001]. We conclude that propofol anesthesia combined with α-stat perfusion strategy, compared to the use of isoflurane, deteriorates the brain in surgery requiring HCA. This finding is important and clinically relevant because α-stat perfusion strategy is still the most commonly used acid-base perfusion strategy during hypothermic CPB in adults and propofol is one of the most used anesthetics in clinical practice.

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REVIEW AND COMMENTARY

Review Comments:

Was there any indication why cerebral resistance increased, whether due to contraction of the vessel, due to the endothelial dysfunction, etc?

Author's Response:

We did not comment further on the increased cerebrovascular resistance induced by propofol because the mechanisms underlying this phenomenon are unknown. It is possible that propofol, contrary to other vascular beds, has vasoconstrictive effects related or not to its metabolic effects on the brain. There is some evidence showing that propofol prevents endothelial dysfunction of the peripheral vessels, but to our knowledge, no evidence exists for the cerebrovascular district.

Furthermore, any discussion on the topic should take into account the fact that deep hypothermic circulatory arrest is a condition that can by itself induce changes in propofol concentrations and cerebrovascular and metabolic changes not occurring during normothermia and/or in absence of cardiopulmonary bypass.

We believe that further comments on this topic would be just speculation without any scientific value as we do not have data on possible changes that have occurred in the endothelium of the cerebral vessels. This is the reason why we have considered changes in the brain microdialysis parameters as the main outcome measures.