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Aprotinin to Improve Cerebral Outcome after Hypothermic Circulatory Arrest: A Study in a Surviving Porcine Model

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ABSTRACT

Background. Aprotinin is a serine protease inhibitor, which is usually used during cardiac surgery to reduce blood loss. There is evidence that aprotinin has neuroprotective effects during ischemia. We planned this study to evaluate its potential neuroprotective efficacy during hypothermic circulatory arrest (HCA).

Methods. Twenty piglets with a median weight of 25.7 kg (interquartile range, 23.9-26.6) were randomly assigned to receive aprotinin or placebo prior to a 75-minute period of HCA at 18°C. Brain microdialysis parameters and neurological and histological scores were the primary outcome measures.

Results. Changes in brain metabolic parameters and histopathological findings were favorable in the aprotinin group. Brain lactate concentrations were significantly lower in the aprotinin group during the experiment (P = .02) along with blood lactate concentrations in the aprotinin group (P = .023). Brain glucose was significantly higher during the experiment (P = 0.02). Intracranial pressure tended to be higher in the control group. Two of 10 animals in the aprotinin group and 4 of 10 in the control group failed to reach full recovery on the seventh postoperative day. Four animals of 10 in the aprotinin group and 6 animals of 10 in the control group had brain infarction (P = .40).

Conclusions. The present data suggest that aprotinin mitigates cerebral damage and improves neurological outcome following a period of HCA.

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INTRODUCTION

Aprotinin is a nonspecific serine protease inhibitor that inhibits many proteases such as kallikrein, trypsin, and plasmin, which are involved in the inflammatory and hemostatic processes. It is regarded as an effective hemostatic agent because it inhibits fibrinolysis and preserves platelet function, thus markedly reducing blood losses during cardiac surgery [Royston 1987; Van Oeveren 1987; Van Oeveren 1990; Ivert 1998; Sedrakyan 2004]. Aprotinin has been previously shown to also reduce neutrophil activation during and after cardiopulmonary bypass (CPB) [Lord 1992; Hill 1995]. It inhibits the production of myeloperoxidase and neutrophil elastase; thus aprotinin has a protective effect by preventing neutrophil activation and production of histotoxic mediators within tissues [Van Oeveren 1990; Lord 1992; Hill 1995; Alonso 2000; Asimakopoulos 2000].

Recently, aprotinin has been shown to have relevant neuroprotective effects as it is associated with a lower risk of postoperative stroke after cardiac surgery [Frumento 2003; Sedrakyan 2004; Gillespie 2005]. We conducted this study to investigate whether aprotinin could improve cerebral outcome following a prolonged period of hypothermic circulatory arrest (HCA) in a surviving experimental model.

MATERIAL AND METHODS

Animals

Twenty female juvenile pigs (age range, 8-10 weeks) of a native stock, with a median weight of 25.7 kg (interquartile range [IQR], 23.9-26.6), were randomly assigned to receive either aprotinin or saline prior to a 75-minute period of HCA at a brain temperature of 18°C.

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, and 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.

Drug Administration

Piglets in the aprotinin group received the drug (Trasylol; Bayer, Leverkusen, Germany) according to the following protocol: loading dose with 30,000 KIU(Kallikrein Inhibitor Units)/kg intravenously; pump priming with 30,000 KIU/kg; and maintenance intravenous infusion with 10,000 KIU/kg per hour until weaning from CPB. Control animals received the same volume of saline infusion. The aprotinin dose was derived from dosages used in the clinical setting.

Anesthesia and Hemodynamic Monitoring

Anesthesia was induced with ketamine hydrochloride (350 mg intramuscularly) and midazolam (45 mg intramuscularly). A peripheral catheter was inserted into a vein of the right ear for administration of drugs and to maintain fluid balance with Ringer acetate. After induction with fentanyl (25 μg/kg), anesthesia was maintained 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) throughout the experiment, but not during HCA. Cefuroxime (1.5 g intravenously) was administered at anesthesia induction and before extubation.

After endotracheal intubation, the animals were maintained on positive pressure ventilation with 50% oxygen. An arterial catheter was positioned into the left femoral artery for arterial pressure monitoring and blood sampling. A thermodilution catheter (CritiCath, 7 F; Ohmeda, Erlangen, Germany) was placed through the left femoral vein to allow blood sampling, pressure monitoring in the pulmonary artery, and for recording the blood temperature and cardiac output. A 10 F catheter was placed in the urinary bladder for urine output monitoring. Temperatures were monitored from the central venous system, the rectum, and from the epidural and intracerebral spaces.

Brain Microdialysis and 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) 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 right side 1 cm anteriorly to the coronal suture. The intracerebral temperature was used as the primary measure of brain temperature. An intracerebral microdialysis catheter was inserted through a hole located at the right side 0.5 cm posterior to the coronal suture. A pressure-monitoring catheter (Codman Micro-Sensor ICP Transducer, Codman ICP Express Monitor; Codman & Shurtleff, Raynham, MA, USA) was placed through a hole located at the left side posterior to the coronal suture. The microdialysis catheter (CMA 70; CMA/Microdialysis, Stockholm, Sweden) was placed into the right brain cortex 0.5 cm posterior to the coronal suture to 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.

CPB and Experimental Protocol

Through a right thoracotomy in the fourth intercostal space, the right thoracic vessels were ligated, the pericardium was opened, and the heart and great vessels exposed. A membrane oxygenator (Midiflow D 705; 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 F arterial cannula, and the right atrial appendage was cannulated with a single 24 F atrial cannula. 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 F 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 heat exchanger was used for core cooling.

A cooling period of 60 minutes was carried out to attain a brain temperature of 18°C following a 75-minute period of HCA. Cardiac cooling with topical ice slush was begun and maintained throughout the HCA period. During HCA, the intracerebral temperatures were maintained at a level of 18°C with ice packs placed over the head. After 75-minutes of HCA, rewarming was started. During the cooling period, the temperature gradient between brain temperature and arterial perfusate was kept less than 10°C to allow gradual cooling and to prevent gaseous emboli. During rewarming, the heat exchanger temperature was not set above 38°C. Five minutes after the start of rewarming, furosemide (40 mg), mannitol (15 g), methylprednisolone (80 mg), lidocaine (40-150 mg), and calciumbioglyconate (2.25 mmol Ca^{2+}) were administered. The left ventricular sump cannula was removed after 45 minutes of rewarming, and weaning from CPB occurred about 60 minutes after HCA. After weaning from CPB, cardiac inotropy was provided with dopamine. pH-stat perfusion strategy was used.

After weaning from CPB, normothermia was maintained by a heat-exchanger mattress and heating lamps. The animals of both groups were extubated 8 hours after the start of rewarming when the rectal temperature approximated 37°C, and were moved to a recovery room.

During the experiment, hemodynamic and metabolic measurements for heart rate, systemic and pulmonary arterial pressures, central venous pressure, pulmonary capillary wedge pressure, cardiac output, intracranial pressure, intracerebral tissue oxygen partial pressure, temperatures, arterial and venous pH, oxygen and carbon dioxide partial pressure, oxygen saturation, oxygen concentration, hematocrit, hemoglobin, sodium, potassium, and glucose (Ciba-Corning 288 Blood Gas System; Ciba-Corning Diagnostic Corp, Medfield, MA, USA), lactate (YSI 1500 analyzer; Yellow

Springs Instrument Co, Yellow Springs, OH, USA), and leukocyte differential count (Cell-Dyn Analyzer; Abbot, Santa Clara, CA, USA) were recorded continuously or at baseline. These measurement were also recorded 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.

Postoperative Evaluation

Postoperative neurological and behavioral evaluations were performed at 24-hour intervals by an experienced observer masked to the experimental protocol using a species-specific quantitative behavioral score. The quantified assessment 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) was summed to obtain a final score, with a maximum score of 9 reflecting apparently normal neurological function and lower values indicating substantial brain damage.

Perfusion Fixation

All animals were sacrificed on the seventh postoperative day by intravenous injection of pentobarbital (60 mg/kg). Following a sternotomy, heparin (500 IU/kg) was administered, and the descending thoracic aorta was clamped. Ringer solution (1 L) was perfused through the ascending thoracic aorta through 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 min) was infused through the brain in the same manner to accomplish a perfusion fixation. Immediately thereafter, the entire brain was harvested, weighed, and immersed in 10% neutral formalin.

Histopathologic Analysis

The brain was allowed to fix en bloc for 1 week. Thereafter, 3-mm thick coronal samples were sliced from the left frontal lobe, thalamus (including the adjacent cortex) and hippocampus (including the adjacent brainstem and temporal cortex), and sagittal samples from the posterior brainstem (medulla oblongata and pons) and cerebellum were obtained. The specimens were fixed in fresh formalin for another week. After fixation, the samples were processed as follows: rinsing in water for 20 minutes and immersion in 70% ethanol for 2 hours, 94% ethanol for 4 hours, and absolute ethanol for 9 hours. Then the specimens were kept for 1 hour in absolute ethanol-xylene mixture and 4 hours in xylene and embedded in warm paraffin for 6 hours. The specimens were sectioned at 6 μm and stained with hematoxylin and eosin. The sections of the brain specimens of each animal were screened by an experienced senior pathologist (H.T.) unaware of the experimental design and the identity and fate of individual animals. Each section was carefully examined for the presence or absence of any ischemic or other kinds of tissue damage.

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); 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). In case of presence of more than one of these findings, the score from each region was calculated in a cumulative way. 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 a SPSS statistical program (SPSS version 10.0.7; SPSS, Chicago, IL, USA). Continuous and ordinal variables are expressed as the median with IQR (twenty-fifth and seventy-fifth percentiles). Analysis of variance for repeated measurements was performed. Differences between study groups were evaluated by Mann-Whitney *U* test. Significance levels are reported for comparisons with 2-tailed $P \leq .05$.

RESULTS

Comparability of the Study Groups

The median weight of pigs was 24.7 kg (IQR, 23.2-26.2 kg) in the aprotinin group and 26.4 kg (IQR, 24.4 to 28.5 kg) in the control group ($P = .04$). The median CPB cooling time was 60 minutes (IQR, 58-61 min) in the aprotinin group and 60 minutes (IQR, 60-60 min) in the control group ($P = .5$) The median CPB rewarming time was 62 minutes (IQR, 61-66 min) in the aprotinin group and 65 minutes (IQR, 62-70 min) in the control group ($P = .3$). The median total CPB time was 122 minutes (IQR, 118-130 min) in the aprotinin group and 125 minutes (IQR, 120-130 min) in the control group ($P = 0.4$). During HCA, the temperature did not significantly differ between the study groups (Figure 1). All animals were stable during the surgical procedures and survived until the seventh postoperative day.

Behavioral Score

No significant differences were observed among the groups in terms of behavioral recovery in any postoperative

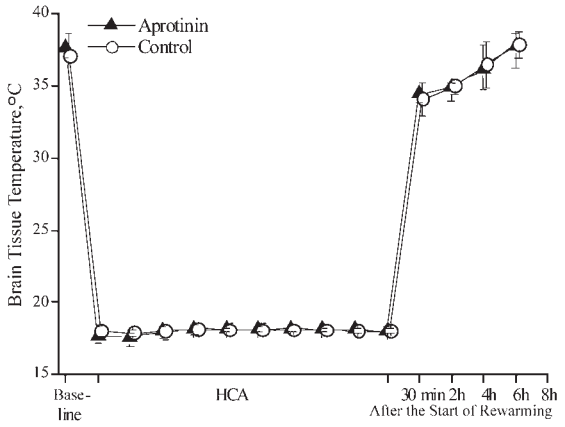

Figure 1. Brain tissue temperatures at each study interval in the study groups.

Table 1. Experimental Data*

	Baseline	End of Cooling	After the Start of Rewarming				*P* between Groups	*P*-Time × Group
			30 min	2 h	4 h	8 h		
Heart rate, beats/min							.25	.48
Aprotinin	102 (98-118)	—	144 (135-157)	125 (114-134)	137 (124-148)	160 (145-176)		
Control	109 (92-120)	—	160 (147-169)	122 (114-135)	157 (132-167)	158 (148-185)		
Cardiac index, L/min/m^2							.34	.76
Aprotinin	4.46 (4.21-4.65)	3.47 (3.24-3.62)	3.33 (2.94-3.63)	3.11 (2.82-3.20)	3.56 (3.10-3.74)	4.24 (3.45-4.98)		
Control	4.43 (3.81-4.00)	3.73 (3.57-4.00)	3.34 (3.10-3.59)	3.42 (3.17-3.77)	3.65 (3.49-3.94)	4.25 (4.00-4.89)		
Central venous pressure, mmHg							>.9	>.9
Aprotinin	4 (3-5)	3 (2-5)	2 (2-4)	4 (2-5)	5 (3-5)	4 (3-6)		
Control	4 (3-5)	3 (2-4)	3 (2-4)	4 (3-4)	4 (3-5)	4 (3-7)		
Hemoglobin, g/L							.16	.89
Aprotinin	77.5 (74-82.5)	55.5 (51.0-61.0)	53.7(50.0-65.75)	65.5 (55.5-82)	62.0 (60.2-70.5)	60.0 (54.7-72.2)		
Control	76.0 (71.0-82.0)	52.5 (47.5-59)	53.0 (47.5-59)	61.5 (56.7-67.7)	64.5 (59-66.2)	63.5 (57.2-66.5)		
Fluid balance, mL							.17	.49
Aprotinin	25 (−100-150)	1750 (1625-2100)	1725 (1600-2000)	975 (800-1300)	825 (600-1200)	675 (600-1000)		
Control	50 (0-300)	2050 (1800-2300)	2025 (1700-2450)	1200 (800-1550)	925 (700-1050)	950 (800-1150)		
Total leukocytes count, $\times 10^9$/L							.15	.24
Aprotinin	18.9 (17.9-20.7)	4.1 (2.5-5.3)	7.3 (5.4-10.3)	22.4 (18.4-28.1)	26.2 (22.3-32.4)	31.4 (28.1-34.0)		
Control	17.7 (15.9-19.3)	2.6 (2.2-3.2)	5.7 (4.6-7.7)	19.1 (16-24.2)	27.3 (22.6-34.9)	27 (25.9-34.0)		
Neutrophil count, 1×10^9/L							.15	.28
Aprotinin	10.4 (9.5-12.1)	2.4 (1.4-3.5)	3.6 (2.5-6.9)	17.1 (13.8-22.5)	21.6 (16.8-27.0)	27.4 (21.7-31.6)		
Control	8.7 (7.5-10.9)	1.5 (1.3-1.9)	2.8 (2.0-4.1)	14 (12.0-19.2)	21.9 (17.6-28.7)	22.7 (20.8-28.4)		
PaO_2, kPa							.49	.37
Aprotinin	36.4 (33.9-37.5)	106.6 (96.1-106.6)	57.8 (45.8-59.9)	36.15 (32.3-41.1)	34.5 (30.4-37.4)	30.7 (28.1-35.8)		
Control	34.6 (31.8-37.6)	106.6 (101.6-106.6)	55.5 (53.5-58.9)	32.8 (24.9-40.4)	29.6 (27.9-32.9)	29.8 (24.2-31.9)		
SvO_2, %							.012	.61
Aprotinin	81.0 (79.0-83.0)	—	61.4 (56.6-62.6)	72 (70.0-74.0)	74.5 (72.5-76.5)	69.5 (68.0-79.0)		
Control	79.5 (73.0-82.0)	—	57.7 (57.0-62.7)	67.5 (63.0-70.0)	70.5 (66.0-73.0)	69.5 (68.0-74.0)		
O_2 delivery, mL/min/m^2							.89	>.9
Aprotinin	53.5 (47.5-55.6)	34.8 (30.4-39.2)	29.4 (26.2-33.0)	30.0 (25.8-40.3)	34.1 (28.9-37.5)	36.9 (31.0-46.9)		
Control	50.7 (40.1-60.8)	37.2 (30.5-40.8)	29.3 (26.3-33.4)	31.3 (28.1-35.6)	33.8 (31.4-36.8)	38.8 (33.8-36.0.)		
O_2 extraction, mL/dL							.43	.83
Aprotinin	2.80 (2.48-3.02)	1.13 (1.12-1.27)	2.94 (2.49-3.29)	3.54 (2.70-3.92)	2.90 (2.72-3.30)	2.70 (2.46-3.32)		
Control	2.88 (2.70-3.54)	1.22 (1.08-1.41)	2.81 (2.58-3.16)	3.16 (3.04-3.58)	3.26 (2.89-3.50)	3.14 (2.56-3.24)		

*Values are shown as medians with interquartile ranges (twenty-fifth to seventy-fifth percentile). *P* between groups is according to the tests of between-subjects effects. Fluid balance = intravenous fluids given – cumulative diuresis.

day. However, 2 of 10 animals in the aprotinin group and 4 of 10 in the control group failed to reach full recovery on the seventh postoperative day.

Perfusion, Hemodynamic, and Metabolic Data

Tables 1 and 2 summarize the experimental and metabolic data. Blood lactate was significantly lower in the aprotinin group ($P = .023$) and blood glucose higher in the control group ($P = .025$).

Intracranial Measurements

Intracranial pressure tended to be higher in the control group up to 7 hours after the start of rewarming. No statistically significant differences were observed in terms of intracranial pressure and brain tissue oxygen partial pressure. Brain microdialysis measurements showed favorable changes in the aprotinin group. There was a significant difference in glucose level at 4 hours after the start of rewarming ($P = .02$). Lactate was significantly lower in the aprotinin group during 75 minutes of HCA ($P = .02$) and at 4 hours after the start of rewarming ($P = .03$). Overall, brain glucose concentrations tended to be higher and brain lactate concentrations lower in the aprotinin group (Figure 2). No significant differences were observed in terms of brain concentrations of pyruvate, glycerol, and glutamate, whose changes were somewhat favorable in the aprotinin group.

Table 2. Metabolic Data*

	Baseline	End of Cooling	After the Start of Rewarming				*P* between Groups	*P*-Time × Group
			30 min	2 h	4 h	8 h		
Venous glucose, mmol/L							.025	.27
Aprotinin	6.1 (5.6-6.7)	9.3 (6.8-9.8)	16.3 (13.9-17.3)	9.9 (9.1-12.0)	7.7 (6.6-9.0)	7.8 (7.4-8.5)		
Control	6.6 (6.0-7.1)	9.9 (8.0-11.0)	17.1 (16.3-17.8)	12.3 (11.3-12.7)	8.2 (7.9-9.1)	8.7 (7.9-9.0)		
Venous lactate, mmol/L							.023	.37
Aprotinin	0.9 (0.9-1.3)	1.6 (1.3-1.9)	3.9 (3.6-4.4)	2.4 (2.4-3.0)	1.3 (1.1-1.4)	1.1 (1.0-1.4)		
Control	1.4 (1.3-1.7)	1.8 (1.6-1.9)	4.2 (3.4-4.6)	3.3 (2.6-3.5)	1.5 (1.3-1.7)	1.3 (1.1-1.5)		
O_2 consumption							.11	.67
Aprotinin	12.1 (10.1-13.5)	4.1 (3.2-4.6)	9.0 (7.9-10.4)	10.1 (8.9-12.1)	9.4 (8.8-11.5)	11.9 (10.1-14.3)		
Control	13.0 (11.6-14.1)	4.4 (3.6-5.4)	9.8 (8.5-11.1)	11.0 (10.2-12.6)	11.4 (10.5-12.2)	12.7 (11.5-13.7)		
Blood osmolality, mmol/kg							.36	.59
Aprotinin	276 (275-280)	287 (283-289)	285 (281-287)	282 (278-287)	280 (278-284)	282 (280-284)		
Control	279 (276-283)	288 (286-290)	284 (282-287)	286 (278-285)	282 (278-285)	282 (277-287)		
Mean arterial pressure							.62	.57
Aprotinin	96.2 (88.7-99.3)	48.5 (47.0-51.0)	55.8 (50.3-59.7)	78.5 (69.0-87.3)	81.5 (78.7-92.7)	70.5 (65.7-76.7)		
Control	86.0 (81.3-99.0)	49.5 (46.0-51.0)	54.7 (53.3-56.0)	78.2 (64.3-86.0)	83.2 (75.7-98.7)	70.7 (67.3-77.7)		

*Values are shown as medians with interquartile ranges (twenty-fifth to seventy-fifth percentile). *P* between groups is according to the tests of between-subjects effects. PaO_2 indicates arterial oxygen partial pressure; SvO_2, mixed venous oxygen saturation.

Histological Assessment

Total histopathologic median score was 7 in the aprotinin group and 8 in the control group, without any statistically significant difference between the groups. There was no significant difference in any brain region between the study groups. Four animals of 10 in the aprotinin group and 6 animals of 10 in the control group had brain infarction (*P* = .40).

DISCUSSION

Since aprotinin was discovered in 1930, its clinical application has been sought for modulation of inflammatory response related to CPB and attenuation of ischemia-reperfusion injury. The latter condition initiates neutrophil activation, adhesion, and migration through the endothelium. Neutrophils produce free radicals, release proteolytic enzymes, and stimulate cytokine release leading to severe tissue injury [Weiss 1989; Jean 1998]. Depletion of neutrophils, inhibition of neutrophil adhesion, or inhibition of proteolytic enzymes such as elastase released from neutrophils reduces injury size and improves neurological deficient [Tsirka 1995; Nicole 2001].

In the present study, we investigated whether aprotinin could improve cerebral outcome following a prolonged period of HCA in a surviving experimental model. Analysis of the brain microdialysis parameters has produced some interesting findings. We have observed that the brain lactate level was significantly lower during 75 minutes of HCA and 4 hours after the start of rewarming following aprotinin treatment. Also the systemic levels of blood lactate were lower in the aprotinin group. Glucose tended to be higher during the experiment and this difference reached statistical significance 4 hours after the start of rewarming. We have previously shown that an increased concentration of brain glucose immediately after a period of HCA is beneficial to the brain [Pokela 2001]. This does not mean that hyperglycemia is beneficial to the brain during the reperfusion period, but rather that better preservation of brain glucose concentrations is associated with better outcome. This microdialysis finding is a constant in all our previous studies.

The histological damage noted in this study was in general milder than that seen in our previous studies on HCA. In the present study, aprotinin was associated with decreased histological brain damage and fewer infarcted areas. However, likely because of the limited number of animals, this difference did not reach statistical significance.

It has been demonstrated that ischemic brain edema is closely related to plasma and brain tissue bradykinin levels and pretreatment with aprotinin reduces cerebral water content after ischemia in a rat model [Kamiya 1993]. In this study, intracranial pressure tended to be lower but it failed to reach statistical significance. However, these findings along with favorable changes in brain glucose and lactate concentrations provide evidence of a certain neuroprotective efficacy of this drug. Indeed, our findings are in concert with previously reported evidence of improved cerebral metabolism after ischemia in aprotinin-treated animals [Kamiya 1993; Khan 2005].

The neuroprotective efficacy of aprotinin is not yet clear, but, besides its anti-inflammatory properties, it is possible that its inhibitory effects on platelet aggregation and throm-

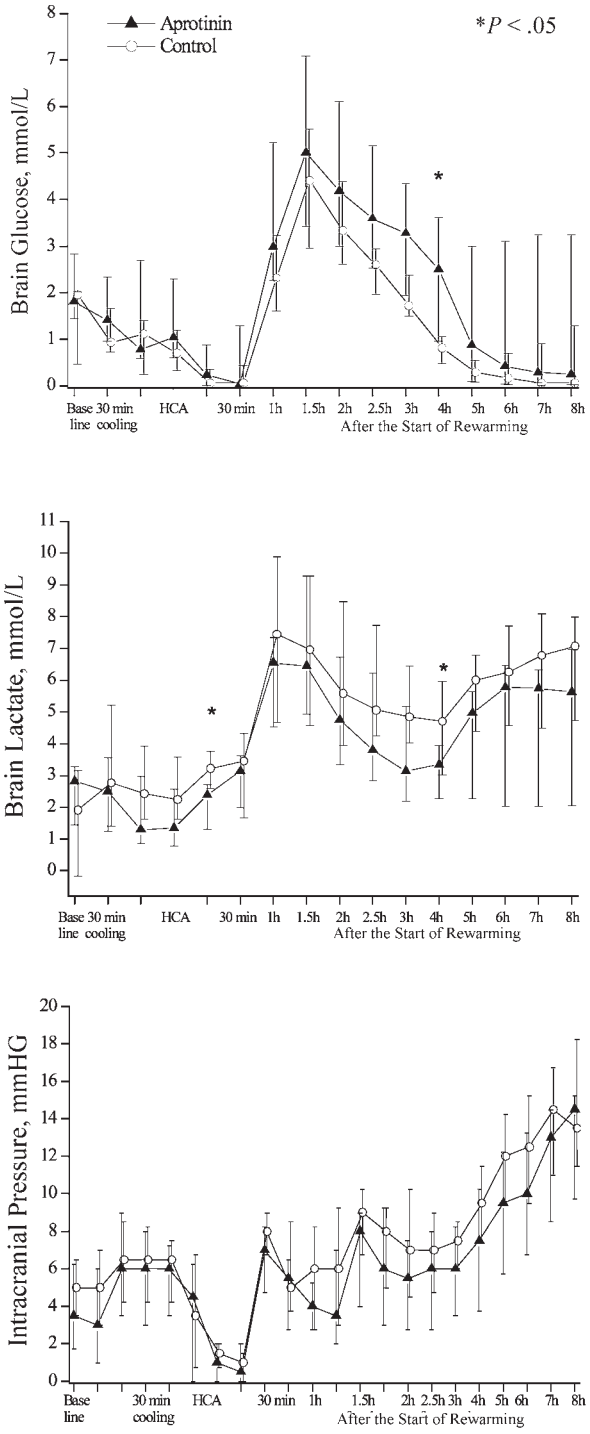

Figure 2. Changes in brain glucose and lactate concentrations as well as intracranial pressures during the study in the aprotinin and control group.

bosis [Van Oeveren 1990] may exert a further beneficial effect on the brain microvasculature after brain ischemia. In conclusion, the present data suggest that aprotinin mitigates cerebral damage and improves brain metabolism following a period of experimental HCA.

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