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Aprotinin Concentration Varies Significantly According to Cardiopulmonary Bypass Conditions

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Abstract

Objectives—Although aprotinin is partially excreted unchanged in the urine, its primary site of metabolism is in the renal lysosomes following proximal tubule resorption. This study tested the hypothesis that plasma aprotinin concentration varies with cardiopulmonary bypass conditions.

Methods—Thirty-two piglets (weight 13.2 ± 1.9 kg) received aprotinin initial dose 30,000 KIU/kg, maintenance infusion 10,000 KIU/kg/h with CPB prime 30,000 KIU/kg. Aprotinin infusion was terminated at end of CPB and during hypothermic circulatory arrest (HCA). Piglets were randomized to four groups (n=8 per group): HCA, 60-minute period at 15°C LF; 10 mL/kg/min low-flow CPB at 25°C FF; full flow CPB at 37°C; control at 37°C without CPB. Blood samples were collected at 7 time points: after induction of anesthesia (baseline), after initial dose, 10, 50 and 115 min after start of CPB, just before end of CPB and 30 min after CPB. Plasma aprotinin levels were determined by modified functional assays.

Results—Aprotinin levels in the control group were significantly lower at each point after start of CPB than all groups with CPB ($P < .001$). In particular, during the reperfusion period aprotinin levels were higher in HCA and LF groups than FF group ($P < .05$). Throughout CPB, aprotinin levels in the HCA group remained unchanged ($P > .40$).

Conclusions—Bypass conditions affect plasma aprotinin concentration. Recently reported renal and neurological complications with aprotinin use during CPB may reflect excessive dosing and point to the need for real-time monitoring.

Aprotinin, a serine protease inhibitor, is a Kunitz-type protein consisting of 58 amino acids arranged in a single basic polypeptide with a molecular weight of 6512 Da. Aprotinin's ability to inhibit Kallikrein¹, trypsin², and plasmin³ in vitro has been known for decades. More recently aprotinin has been recognized to have a very broad spectrum of activity, including effects on both the contact and tissue factor pathways of coagulation, fibrinolysis, platelet and neutrophil function, and also on the endothelium.⁴

In both adults and children, aprotinin has been applied for its antifibrinolytic and platelet protective activity to reduce post-operative blood loss in patients at high risk of bleeding.^{5,6,7} In pediatric cardiac surgery it has also been applied to mitigate the inflammatory response to cardiopulmonary bypass and to improve neurologic outcome after prolonged hypothermic circulatory arrest (HCA).^{8,9} Although the risk of adverse events associated with aprotinin use in pediatric cardiac surgery appears to be low¹⁰, concerns regarding renal failure, stroke and death among high risk adult coronary bypass surgery patients has led to withdrawal of aprotinin from sale by its sole manufacturer at the recommendation of FDA.^{11,12}

Aprotinin levels have not been monitored routinely during CPB. Although it has been reported that the antifibrinolytic activity of aprotinin can occur at a concentration as low as 50 KIU/mL¹³, it is certain that the anti-inflammatory activity associated with kallikrein inhibition occurs at a much higher plasma aprotinin concentration than antifibrinolysis. In another study, in vitro plasma concentrations of aprotinin were associated with antifibrinolytic and anti-inflammatory activity at concentrations of 125 and 200 KIU/mL, respectively.¹⁴ No studies have attempted to correlate intraoperative blood levels of aprotinin with adverse events. In adults a standard loading dose is given irrespective of the patient's weight or body surface area according to the "Hammersmith" regimen. Furthermore, no consideration appears to have been given to the possibility that the half-life of aprotinin might vary according to bypass conditions as well as patient-related factors such as body surface area and renal function.

The primary site of metabolism for aprotinin is in the renal lysosomes following proximal tubule resorption. Aprotinin is also partially excreted unchanged in the urine. The half-life of aprotinin is usually short, approximately 0.7 hour under non-CPB conditions and at normothermia. However renal clearance is affected by renal blood flow and therefore CPB flow rate. We hypothesized that renal metabolic breakdown of aprotinin would be slowed by hypothermia. Thus, aprotinin concentration in plasma is expected to vary according to cardiopulmonary bypass conditions, particularly bypass temperature and flow rate. The current study was designed to test this hypothesis.

Methods

Surgical Procedure

Thirty-two experiments (each group: n=8) were performed on 5- to 6-week-old Yorkshire piglets (Archer Farms, Inc., Darlington, MD) with average body weight of 13.2 ± 1.9 kg. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication 85-23, revised 1985). Piglets were sedated with intramuscular ketamine (20 mg/kg) and xylazine (4 mg/kg). After endotracheal intubation (cuffed 5-mm tube) and a bolus of Fentanyl (25 µg/kg IV) the piglets were ventilated with a pressure-controlled respirator using an inspiratory oxygen fraction of 21% pre-CPB and 100% post-CPB at a rate between 10–18 breaths per minute to achieve an arterial pCO₂ between 38–42 mm Hg. Anesthesia was maintained with fentanyl (25 µg/kg/h), midazolam (0.2 mg/kg/h), and pancuronium (0.2 mg/kg/h) using an infusion pump. The animals were placed supine on a water-circulating heating mat to prevent hypothermia. Esophageal and rectal temperature probes were placed. The left femoral artery was cannulated and the catheter was advanced into the descending aorta for monitoring of blood pressure and blood gases. Blood pressure and body temperature were continuously monitored and recorded every 10 minutes. Blood gases were checked for pH, pO₂, pCO₂, sodium, potassium, calcium, glucose and lactate every 20 minutes during CPB in 0.5 mL samples using a blood-gas analyzer (Siemens, Rapidlab 1265, Erlangen, Germany). A catheter was placed through the femoral vein into vena cava for infusion of drugs. The right femoral artery was exposed for arterial CPB cannulation and an anterolateral thoracotomy was performed in the third intercostal space. After administration of heparin (300 IU/kg), an arterial cannula (8Fr, Biomedicus) was advanced through the femoral artery into the abdominal aorta. A 28F venous cannula (Harvey, MA) was inserted into the right atrium. The heart was not opened during the procedure.

Aprotinin Dosage Regimen

All animals received aprotinin initial dose 30,000 KIU/kg, maintenance infusion 10,000 KIU/kg/h, with CPB prime 30,000 KIU/kg. Aprotinin infusion was terminated at the end of CPB

and stopped during hypothermic circulatory arrest (HCA). Prime dose was not administrated to 37°C OFF (control group).

Blood Sample Collection for Aprotinin Concentration

Blood samples were collected from the arterial line at seven time points during the perioperative period: baseline (preloading), after loading dose, 10, 50 and 115 min after start of CPB, just before end of CPB and 30 min after CPB. Samples for standard curve were also collected from seven donor piglets. 9 mL blood was collected into plastic centrifuge tubes with 1 mL citrate. The plasma was prepared by centrifuging blood samples at $2000 \times g$ for 15 minutes at room temperature. Plasma was removed into polypropylene tubes and frozen at -20°C .

Aprotinin Functional Assay

Functional levels of aprotinin were determined by its inhibitory action against plasma kallikrein based on the method of Gallimore and colleagues.¹⁵ Briefly, test plasmas and standard solutions of aprotinin in normal piglet plasma (300 μL) were treated with acetone (200 μL) to remove possible interference of serine protease inhibitors present in piglet plasma. Acetone treated plasma (300 μL) was diluted with 1700 μL buffer [0.05 mol/l Tris, 0.15 mol/l NaCl (pH 8.0) containing 0.5 mg/L corn trypsin inhibitor]. Corn trypsin inhibitor (Haematologic Technologies Inc., Essex Junction, VT) inhibits activated factor XII present in piglet plasma from cleaving the chromogenic substrate. Diluted standard or test plasmas (50 μL) were added to the wells of a microtitre plate (F96; Costar Incorporated, Corning, NY) and incubated at 37°C for 2 min. Human plasma kallikrein (0.01 plasma equivalent units/ml, Diapharma Group Inc, West Chester, OH) was added (50 μL), mixed and incubated at 37°C for 5 min. Residual kallikrein activity was measured by the addition of an chromogenic peptide substrate (S-2302, Chromogenix, Lexington, MA) that is cleaved by kallikrein, liberating p-nitroaniline, which is then measured spectrophotometrically. Kallikrein substrate (1mmol/L) was added (50 μL) and incubated at 37°C for 20 min. The reaction was stopped by the addition of 50% acetic acid (50 μL) and the optical density at 405 nm measured using an automated plate reader. To allow for any nonspecific endogenous protease activity in plasma that could potentially cleave the substrate, blanks were prepared as already described, but substituting buffer for plasma kallikrein. The blank values were subtracted from the test values and a graph of A_{405} against aprotinin concentration of the standard solutions was plotted (Figure 1), and test plasmas were derived from the standard curve. Absorbance value of the blanks was primarily related to the degree of hemolysis of the samples rather than non-specific protease activity.

Bypass Management

A roller pump (Polystan, Vaerlose, Denmark) was used to generate nonpulsatile pump flow at 100 ml/kg body weight in all experiments. The oxygenator gas mixture consisted of 5% carbon dioxide and 95% oxygen in all CPB groups. pH-stat management was used in all CPB groups. The cardiopulmonary bypass circuit in all CPB groups consisted of 1000-mL filtered hard-shell venous reservoir (1361 Minimax, Medtronic, Minneapolis, MN), a membrane oxygenator (3381 Minimax Plus, Medtronic), a 40- μm arterial filter (Terumo, Tokyo, Japan) and 1/4-inch tubing. Venous drainage was by gravity. No cardiotomy suction was used. The venous line was left open during circulatory arrest. A sterile circuit was used in each experiment. The CPB circuit was primed with 800 mL blood. The blood used for priming of the CPB circuit to achieve a hematocrit of 30% on CPB was drawn on the morning of the experiment from an adult donor piglet. Before the start of CPB and just before reperfusion methylprednisolone (30 mg/kg), 10 mL sodium bicarbonate 7.4%, and furosemide (0.25 mg/kg) were added to the prime. After 10 minutes of normothermic bypass, piglets in 15°C HCA group and 25°C LF group underwent 40 minutes cooling to a nasopharyngeal temperature of 15°C and 25°C , respectively. After a 60-minute period of HCA at 15°C and 10 mL/kg/min low-flow CPB at 25°C , animals were

rewarmed on CPB to 37°C for 50 minutes. In 37°C FF group, esophageal temperature was kept at 37°C during CPB. Esophageal temperature in the control group was maintained at 37°C without CPB. Following weaning from CPB or time schedule, animals were observed for 120 minutes. Topical cooling was applied (Figure 2).

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD. Two-way repeated-measures mixed model analysis of variance (ANOVA) was used to compare aprotinin concentration, temperature, and MAP between experimental groups with a compound symmetry covariance structure to model repeated measures.¹⁶ Least-squares regression analysis was applied to predict absorbance from aprotinin concentration with R^2 used to assess the linear relationship and precision described by 95% confidence intervals.¹⁷ Two-tailed values of $P < .05$ with Bonferroni adjustment for multiple comparisons were considered significant. Data analysis was performed with SPSS statistical software (version 16.0; SPSS Inc, Chicago, IL). Power analysis indicated that a sample size of 8 piglets in each of the four experimental groups with measurements of aprotinin at each time point provided 80% power (2-tailed $\alpha=0.05$, $\beta=0.20$) to detect differences in plasma aprotinin levels of 75 KIU or larger assuming a standard deviation of 50 KIU (effect size = 1.5) using repeated-measures ANOVA (nQuery Advisor 7.0, Statistical Solutions, Boston, MA).

Results

Pre-operative variables were compared between the four experimental groups and no significant differences were detected in age, weight, temperature, pH, arterial oxygen tension, arterial carbon dioxide, hematocrit level, MAP, and plasma lactate levels between the groups (all $P > .10$).

The aprotinin standard curve based on linear regression revealed a tightly fitting inverse relationship with absorbance (Figure 1). The standard curve was derived from plasma of seven donor piglets. A standard assay curve was plotted as A_{405} versus aprotinin concentration in such that a least-squares regression line was obtained between 0 and 500 KIU/mL aprotinin. The slope data points around the fitted regression line indicate that aprotinin concentration has a strong inverse relationship with absorbance. ($R^2 = 0.904$)

Repeated-measures ANOVA indicated that esophageal temperature was significantly lower in 15°C HCA compared to 25°C LF groups and both were lower than groups at 37°C ($P < .001$, Figure 3). Esophageal temperature and MAP were successfully controlled during all experiments. Mean arterial pressure was significantly lower for HCA and LF groups on CPB compared to FF ($P < .001$, repeated-measures ANOVA, Figure 4).

Aprotinin levels at 10 min after the start of CPB were not significantly different between the groups undergoing CPB. All CPB groups had significantly higher aprotinin levels than control (37°C OFF) at each time point after the start of CPB ($P < .001$, Figure 5). Aprotinin levels in the 15°C HCA group were higher than the 37°C FF group at 50 ($P < .05$), 115 ($P = .003$), and 160 min ($P < .001$). Clearly, aprotinin levels in the HCA group remained consistently high with no significant changes over time during the CPB period (all $P > .40$). Piglets in the 25°C LF group had aprotinin levels significantly higher than 37°C FF at 115 min ($P < .05$). Compared to 10 min after the start of CPB, piglets in the 37°C FF group had aprotinin levels significantly lower at 50 ($P = .01$), 115 ($P < .001$) and 160 min ($P < .001$) on CPB. Mean plasma aprotinin concentration remained under 300 KIU/mL during CPB in all groups. Kaolin ACT was controlled at a level of over 480 sec in each group.

Discussion

Our data indicate that aprotinin concentration in plasma varies according to the conditions of CPB in the healthy young piglet with approximately equal body weight and normal renal function. Hypothermic CPB is associated with elevated levels of aprotinin in comparison with normothermic non-bypass conditions. Aprotinin concentration in 15°C HCA group was significantly higher than other groups at 160 min, presumably secondary to reduced metabolism of aprotinin. Furthermore, aprotinin concentration remained high in 15°C HCA group even after recovering to normothermia. This result emphasizes that aprotinin infusion should be stopped during HCA to avoid extremely high aprotinin concentrations.

The results of our study are consistent with a previous clinical report of Oliver and colleagues¹⁸ who reported that aprotinin concentration varied in pediatric patients despite use of a weight-based aprotinin dosing for CPB. Neonates and infants are at particular risk for subtherapeutic levels of aprotinin relative to older and heavier pediatric patients undergoing CPB primarily because of priming volumes in excess of blood volume and altered pharmacokinetics. Dosing regimens that achieve effective aprotinin concentrations for pediatric patients of all weight groups need to be developed and evaluated for their impact on perioperative transfusion requirements and blood loss as well as adverse events.

In contrast to pediatric patients, in adult patients it is common to use a standard dosing regimen that is not weight-based and does not take renal function into account. It is likely that the increased risk of renal failure in adults exposed to aprotinin is at least in part secondary to excessive blood levels leading to renal tubular overload of aprotinin. Dosing regimens that vary according to renal function and body surface area should be developed for adults as should a real-time method for monitoring aprotinin levels.¹²

CPB activates multiple humoral cascades including coagulation, complement and fibrinolysis. CPB also activates blood cells including platelets, neutrophils, monocytes, endothelial cells and lymphocytes.^{19,20} In a review by Mojcik and colleagues²¹ the effectiveness of aprotinin in controlling post bypass inflammation is emphasized. Greilich and colleagues²² showed that aprotinin significantly reduced IL-10 and peak IL-6 after extracorporeal circulation. In pediatric practice and particularly in neonates, generalized edema and pulmonary dysfunction are common clinical problems that may be a consequence of the inflammatory response to CPB. They may be ameliorated by use of intraoperative and postoperative infusion of aprotinin. In our experiment, aprotinin infusion was stopped just after the end of bypass. As a result, the aprotinin concentration dropped below effective concentration for anti-inflammatory activity. If aprotinin is to be used for its anti-inflammatory properties, then it is important that it be infused post-bypass.

One of the limitations in predicting plasma aprotinin concentration is that ultrafiltration is used during CPB for controlling blood volume and hematocrit. Also, modified ultra-filtration (MUF) is often applied for pediatric bypass. Therefore, changes in aprotinin concentration in the clinical setting will be more complicated than in the present study. Once again this emphasizes a need for real-time monitoring of aprotinin concentration.

In summary, aprotinin concentration in plasma varies according to CPB conditions. Aprotinin concentration at normothermia gradually decreases even with maintenance infusion during CPB. Hypothermia and reduced flow rate decrease aprotinin metabolism and excretion resulting in increased levels. In the future, bypass-specific dosing regimens should be developed. A real-time method for monitoring of aprotinin concentration could reduce the risk of adverse effects from aprotinin while optimizing its hemostatic and anti-inflammatory efficacy.

Acknowledgments

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Abbreviations

CPB	cardiopulmonary bypass
HCA	hypothermic circulatory arrest
FF	full flow
LF	low flow
MAP	mean arterial pressure

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Figure 1. Standard curve based on linear regression ($n = 7$ piglets). A standard assay curve was plotted as A_{405} versus aprotinin concentration in KIU/mL and whereby a least-squares regression line was fitted for aprotinin concentrations between 0 and 500 KIU/mL aprotinin using plasma from 7 donor piglets. Absorbance can be estimated by the linear equation: $y = -0.0014x + 1.094$, where x denotes concentration. Dotted lines represent 95% confidence intervals and R^2 indicates excellent linear fit to the data.

Figure 2.
Experimental protocol for each group.

Figure 3.

Changes in esophageal temperature for all groups; 15°C HCA group and 25°C LF group were significantly lower than 37°C groups; Temperature in 15°C HCA group was lower than 25°C LF group (* $P < .001$, mixed model repeated-measures ANOVA).

Figure 4. Changes in MAP for groups on CPB; HCA and LF were significantly lower than FF. (* $P < .001$, mixed model repeated-measures ANOVA).

Figure 5.

Aprotinin levels in plasma during cardiopulmonary bypass. As denoted by asterisks, all groups had significantly higher aprotinin levels compared to Control at each time point after the start of CPB ($P < .001$). †Plasma aprotinin levels at 115 min reperfusion in the LF group were significantly higher than FF group ($P < .05$). ‡Levels were higher in HCA group compared to FF group at 50 ($P < .05$), 115 ($P = .003$) and 160 min ($P < .001$). Levels in HCA group were significantly higher than LF group at 160 min ($P < .05$) and levels in FF group after reperfusion were significantly lower compared to FF at 10 min ($P < .001$).

TABLE 1

Baseline and preoperative characteristics for the experimental groups

Variable	37°C, OFF	37°C, FF	25°C, LF	15°C, HCA	P value*
Age (d)	24.8 ± 3.2	26.6 ± 3.1	28.5 ± 2.8	24.4 ± 5.4	.14
Weight (kg)	13.4 ± 1.6	12.7 ± 1.6	14.3 ± 2.5	12.2 ± 1.8	.18
Eso. temp. (°C)	36.9 ± 0.8	36.8 ± 0.5	37.3 ± 0.6	36.6 ± 0.3	.14
pH	7.48 ± 0.07	7.50 ± 0.04	7.50 ± 0.04	7.51 ± 0.08	.75
pO ₂ (mm Hg)	84.1 ± 10.7	83.2 ± 10.1	77.8 ± 9.1	81.9 ± 10.6	.63
pCO ₂ (mm Hg)	41.6 ± 3.5	38.6 ± 4.3	41.3 ± 4.8	42.6 ± 6.9	.44
Hematocrit (%)	29.0 ± 2.0	29.2 ± 1.9	27.7 ± 2.7	27.8 ± 2.6	.41
MAP (mm Hg)	87.5 ± 17.9	92.6 ± 17.8	84.9 ± 9.4	93.4 ± 15.2	.65
Lactate (mg/dL)	1.26 ± 0.43	1.32 ± 0.36	1.37 ± 0.68	1.06 ± 0.29	.57

HCA, hypothermic circulatory arrest; FF, full flow; LF, low flow.

* Based on F-test in ANOVA, indicating no significant group differences for any of the variables. The values are mean ± SD.