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The Effect of Controlled Aprotinin Administration Through Cardiotomy Suction during Cardiopulmonary Bypass

Jun-Li Liu, MD, PhD, MPS, CCP; Alfred H. Stammers, MSA, CCP; Hong Zheng, MD; Nancy J. Mills, MPS, CCP; Jeffery D. Nichols, MPS, CCP; Scott A. Kmiecik, MPS, CCP; Ryan J. Kohtz, MPS, CCP; Craig M. Petterson, MPS, CCP

Division of Clinical Perfusion Education, University of Nebraska Medical Center, School of Allied Health Professionals, Omaha, Nebraska

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Abstract: Cardiotomy suction enhances inflammation and fibrinolysis during cardiopulmonary bypass (CPB). Aprotinin has been shown to reduce the generalized inflammatory insults associated with CPB. The purpose of this study was to evaluate the effect of Aprotinin administration through cardiotomy suction on the inflammatory and fibrinolytic responses during CPB. A pig model of CPB was utilized including 8 animals divided into control and treatment groups. In the treatment group, Aprotinin was infused into the cardiotomy suction (3000 KIU/min), while the same volume of saline was infused in the control group. D-dimer, platelet count, and IL-8 level were analyzed from systemic and cardiotomy suction. It was found that Aprotinin significantly suppressed the increase in D-dimer levels in the systemic (476.3 ± 341.2 vs. 1218.8 ± 281.3 ng/ml, $p < 0.05$) and the cardiotomy suction (565.0 ± 192.5 vs. 1875.0 ± 125.0 ng/ml, $p < 0.05$). Platelet count fell in both groups during CPB, although the reduction was greater in the control (13.1 ± 5.1 vs. 37.9 ± 13.8 %, $p < 0.05$). In addition, IL-8 level in the suction solution was significantly lower in the Aprotinin group (56.5 ± 18.0 vs. 136.3 ± 14.8 pg/ml, $p < 0.05$). In conclusion, this study suggested that Aprotinin treatment of the cardiotomy solution might be an effective way of reducing fibrinolysis, platelet reduction, and inflammation associated with CPB. **Keywords:** inflammation, fibrinolysis, suction, Aprotinin. *JECT. 2002;34:203–208*

During the past few decades, cardiopulmonary bypass (CPB) has made significant contributions to the advances in cardiac surgery for congenital heart defects, coronary heart disease, valvular heart diseases, and end-stage heart failure of various etiologies. However, CPB has been shown to be associated with a generalized inflammatory reaction, hemolysis, and profound alterations of hemostasis (1–3).

Cardiotomy suction exposes blood components such as red blood cells, platelets and plasma proteins, to blood-air interface, blood-tissue interface, and subsequent mechanical stress where activation, injury, and destruction may occur (4). This can lead to an activation of leukocyte and platelets, as well as a release of biologically active substances. It has been shown that cardiotomy suction is a major resource of inflammation and hemostatic alteration during CPB (5).

Aprotinin (Trasylol) is a naturally occurring, nonspecific serine protease inhibitor obtained from bovine lung. It is a low-molecular weight (6512 Dalton) peptide containing 16 different amino acids in a chain of 58 members, forming a kringle domain shape with three disulfide bonds (6). Aprotinin has been shown to inhibit plasmin, kallikrein, complement, cathepsin G, chymotrypsin, and trypsin while preserving platelet function during CPB (7). The greatest effect of Aprotinin relative to cardiac surgery is the prevention of certain complications of CPB, namely hyperfribrinolysis, platelet activation as well as the generalized inflammation (7).

In the present study, we investigated the influence of locally administered Aprotinin through the cardiotomy suction on the detrimental effects of the cardiotomy suction on proinflammatory cytokines, activation of platelets, and hemolysis factors.

Address correspondence to: Jun-Li Liu, MD, PhD, Division of Clinical Perfusion Education, University of Nebraska Medical Center, 985155 Nebraska Medical Center, Omaha, NE 68198-5155.
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MATERIALS AND METHODS

Animal Preparation

All animals used in this study received humane care in compliance with the Guide for the Care and Use of Laboratory Animal as published by National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Anesthesia was induced by administration of a mixture of ketamine (20 mg/kg) and xylyzine (2mg/kg) intramuscularly. Maintenance of anesthesia was achieved by the administration of pentothal (100 ug/kg) and muscle relaxant pavulon (500 ug/kg). Subjects were placed in a supine position, intubated, and ventilated with a tidal volume of 20–30 ml/kg at a rate of 15–20 breath/min. Electrocardiogram leads were placed for continuous monitoring of cardiac conditioning. Femoral arterial and venous lines were placed for hemodynamic monitoring, medication infusion, and blood sampling.

The hair along the anterior aspect of the sternum was shaved, and a midline incision was made from the level of the sternal notch to the xyphoid process. The thorax was opened with an oscillating sternal saw. The great vessels were dissected free in preparation for cannulation. Prior to cannulation the subjects received a bolus dose of bovine lung heparin (300 IU/kg). A purse string suture was placed in the aorta and cannulation was achieved with a 7.0 soft flow arterial cannula. A second purse string suture was placed in the right atrium and cannulation was achieved utilizing a 36/46 Fr dual stage cannula. Adequate anticoagulation (kaolin ACT greater than 480 sec) was assured via the administration of additional heparin during CPB.

At the termination of each experiment, the animal was euthanized by administration of sodium thiopental (4 mg/kg) and potassium chloride (20 mEq) directly into the aorta root.

Cardiopulmonary Bypass Circuit

A standard CPB circuit was utilized that consisted of a hollow fiber membrane oxygenator (Optima, COBE Cardiovascular, Arada, CO, USA), a soft-shell venous reservoir (COBE Cardiovascular, Arada, CO, USA), a filtered cardiotomy reservoir (COBE cardiovascular, Arada, CO, USA), a 40 micron arterial line filter (Sentry, COBE Cardiovascular, Arada, CO, USA), a centrifugal pump (Medtronic, Brooklyn Park, MN, USA), and polyvinyl chloride tubing. The circuit was primed with 2000 ml of plasmalyte-A, 50 ml of 8.4% sodium bicarbonate, and 5000 IU of bovine lung heparin. An in-line blood gas monitor was used in both the arterial and the venous line during the CPB procedure.

The cardiotomy suction system consisted of a twin-roller pump and a polycarbonate filtered (40 μm) reservoir, which emptied into the venous reservoir. The roller pump was set at just non-occlusive occlusion. The circuit was primed and de-aired, the occlusion of the roller was set by clamping the outlet tubing and rotating the arterial pump-head to achieve a line pressure of 200 mmHg with pump head static, and adjusting the roller occlusion to produce a pressure drop of 100 mmHg/min.

During CPB, flow rate was maintained between 1.8 to 2.4 l/min/m^2. The following hemodynamic parameters were controlled by adjusting the flow rate and applying vasoactive agents (Phenylephrine or Sodium Nitroprusside): mean blood pressure was maintained at 50–80 mmHg, central venous pressure at 0–3 mmHg, and mixed venous saturation at 60–80%. In all pigs, pH was maintained between 7.35 and 7.45 by adjusting the flow rate, administration of $NaHCO_3$ (8.4%), and adjustment of the ventilation rate. Carbon dioxide tension was maintained at 40 to 45 mmHg and arterial oxygen tension between 150 and 200 mm Hg throughout the experiment.

Subjective Groups

Eight male swine weighing between 45 and 55 kg were prospectively randomized into two groups: Aprotinin group (n = 4) or control group (n = 4). Aprotinin (3000 KIU/ml) was administered through the cardiotomy suction assembly at a rate of 1 ml/min (33 drops/min) in the Aprotinin group during experiment. Plasmalyte was dripped into the cardiotomy suction assembly at the same rate in the control group. All other interventions were identical in these two groups.

The outlet of the cardiotomy reservoir was clamped, and released at 5-min intervals. The total volume of the suctioned blood was recorded.

Blood Collection, Processing, and Laboratory Assays

Prior to sternal incision, a blood sample was taken from the femoral arterial line for determination of baseline values. Additional samples were drawn at 10 min, 60 min, and 120 min after the initiation of CPB. Blood samples were taken simultaneously from the femoral arterial line and from the cardiotomy suction line proximal to the venous reservoir. The final sample was drawn 30 min after the termination of CPB and Protamins administration (1 mg Protamine sulfate to 100 U heparin) from the femoral artery.

The blood samples were measured for platelet count, plasma levels of IL-8, and D-dimer. The plasma level of IL-8 was determined by IL-8/NAP-1 ELISA (Cytoscreen, Biosource International, Camarillo, CA, USA). The plasma level of D-dimer was determined by a commercial latex agglutination assay (Sigma).

For ELISA and D-dimer tests, blood samples were collected in laboratory red top tubes and centrifuged at 4,000 RPM for 15 min at 4 °C. The plasma was stored in 2 ml aliquots at −80°C and processed within 30 days of the experiment.

Statistics

All values were expressed as mean ±SDEV. The differences among groups and within each group were tested by two-way analysis of variance. When significant difference was found, Fisher's protected least significant *post hoc* analysis was utilized for further multiple comparisons. The $p < 0.05$ was considered significant.

RESULTS

There were no significant differences in blood loss (blood volume aspirated into cardiotomy) between the Aprotinin group and the control group (1450.0 ± 443.5 vs. 1716.7 ± 535.7 ml, $p > 0.05$).

In the control group, CPB significantly increased the D-dimer levels in systemic circulation 120 min after the initiation (971.3 ± 330.1 vs. 135 ± 0 ng/ml, $p < 0.05$) and 30 min after the termination of CPB (1218.8 ± 281.3 vs. 135 ± 0 ng/ml, $p < 0.05$). Ten minutes after the initiation of CPB, the D-dimer level in cardiotomy suction solution was significantly increased (1250.0 ± 306.2 vs. 135 ± 0 ng/ml, $p < 0.05$) (Fig. 1).

The increase in D-dimer in the cardiotomy suction solution 10 min (1250 ± 612 vs. 348 ± 0 ng/ml, $p < 0.05$) and 120 min after the initiation of CPB (1875.0 ± 125.0 vs. 565.0 ± 192.5 ng/ml,, $p < 0.05$) and in systemic circulation 120 min after the initiation (971.3 ± 330.1 vs. 288.8 ± 153.8 ng/ml, $p < 0.05$) and 30 min after the termination of CPB (1218.8 ± 281.3 vs. 476.3 ± 341.3 ng/ml, $p<0.05$) were completely prevented by the administration of Aprotinin (Fig 1).

Platelet count fell significantly in both groups 60 min (control: 17.0% vs. 100%, $p < 0.05$; Aprotinin: 36.8% vs. 100%, $p < 0.05$) and 120 min (control: 13.1% vs. 100%, $p < 0.05$; Aprotinin: 37.9% vs. 100%, $p < 0.05$) after the initiation of CPB. However, the reductions were significantly higher in the control group (Fig. 2).

IL-8 levels were significantly elevated in systemic circulation (95.8 ± 10.3 vs. 33.5 ± 3.1 pg/ml, $p < 0.05$) and in suction solution (136.3 ± 14.8 vs. 33.5 ± 3.1 pg/ml, $p < 0.05$) at the end of and 30 min after the termination of CPB (120.3 ± 20.1 ±33.5 ± 3.1 pg/ml, $p < 0.05$) in the control group. IL-8 levels were reduced in the Aprotinin group, which was significant in the suction solution at the end of CPB (136.3 ± 14.8 vs. 56.5 ± 18.0 pg/ml, $p < 0.05$, Fig. 3).

DISCUSSION

CPB is associated with a so-called post-pump syndrome involved with a generalized inflammation and profound dysfunction of hemostasis (1, 2). The inflammatory response is indicated by the activation of the complement system, cytokine production, and neutrophil activation (8).

Cytokines comprise a group of small molecular weight proteins. They act as the physiological messengers of the inflammatory responses. They bind to specific receptors on the membrane of target cells eliciting changes by activating secondary intracellular messengers. TNF-α and IL-1 are secreted primarily by activated monocytes. They activate neutrophils, macrophages, and endothelial cells. IL-6 is produced by activated monocytes and endothelial cells. IL-8 is produced by injured endothelial cells, activated monocytes and neutrophils, and IL-8 acts as chemoattractant for leucocytes. (3).

An increasing number of studies demonstrate that elevated systemic plasma concentrations of the proinflammatory cytokines are associated with adverse outcomes and worsening of several physiologic measurements in various clinical settings (9, 10). Elevated TNF-α plasma levels have been shown to correlate with postoperative

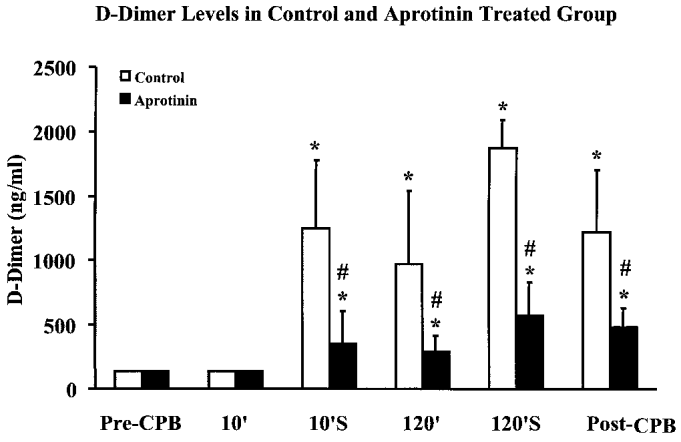

Figure 1. Pre-CPB: pre-bypass; 10′: 10 min after the initiation of CPB; 10′S: 10 min after the initiation of CPB in the suction solution; 120′: 120 min after the initiation of CPB, 120′S: 120 min after the initiation of CPB in the suction solution; Post-CPB: 30 min after the termination of CPB; *: significantly different than pre-bypass; #: significantly different than control group.

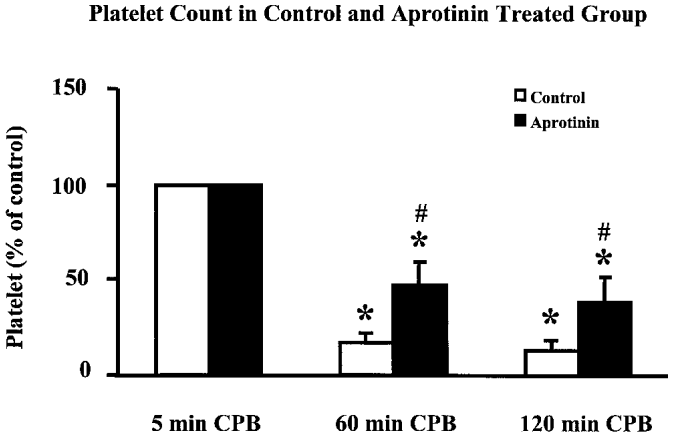

Figure 2. 5min CPB: 5 min after the initiation of CPB; 60min CPB: 60 min after the initiation of CPB; 120 min CPB: 120 min after the initiation of CPB; *: significantly different than 5 min after the initiation of CPB; #: significantly different than control.

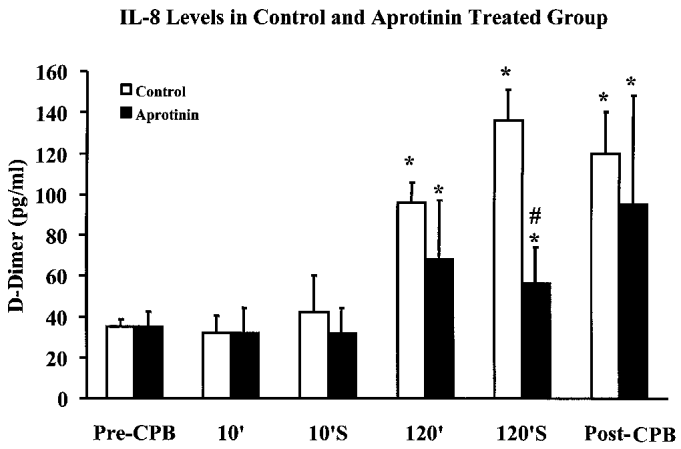

Figure 3. Pre-CPB: pre-bypass; 10′: 10 min after the initiation of CPB; 10′S: 10 min after the initiation of CPB in the suction solution; 120′: 120 min after the initiation of CPB, 120′S: 120 min after the initiation of CPB in the suction solution; Post-CPB: 30 min after the termination of CPB; *: significantly different than pre-bypass; #: significantly different than control group.

organ dysfunction after thoracoabdominal aneurysm repair (11), whereas elevated IL-6 plasma concentrations correlate with death rates during sepsis (12). Hennein et al demonstrated a correlation between postoperative serum levels of IL-8 and IL-6 and left ventricular wall motion abnormalities and myocardial ischemia (13). In the current study, we found that IL-8 was significantly increased at the end of CPB, suggesting the occurrence of inflammation induced by CPB.

CPB causes a 40% to 60% decline in platelet count and decreases platelet function (5). The lower count occurs immediately and is due to dilution of the patient's blood with priming solutions, interaction between platelets and foreign surfaces, formation of microaggregates, and possibly sequestration of some platelets by the reticuloendothelial system. The cardiotomy sucker system may further decrease platelet numbers by direct trauma, aggregation, and filtration. It has been documented that mechanical trauma is the major cause of platelet α-granule release and the volume of blood aspirated by cardiotomy suction correlate directly with platelet loss (14). In the current study, platelet count was significantly reduced in both groups, which is consistent with previous findings.

Cardiotomy suction has been shown to be a major cause of hemolysis, inflammation, and fibrinolysis associated with CPB (15, 16). It has also been documented that the addition of pericardial blood to the perfusate increases circulating thrombin (17). Hansbro et al showed that the return of the cardiotomy suction blood to the circulation is the principal source of plasma free hemoglobin (18). There is a direct relationship between hemolysis and blood contact with pericardial and pleural surfaces, physical stresses at the sucker tip, and the amount of negative pressure within the system (18).

In addition, cardiotomy suction has been implicated as a major source of neurological injurious effect associated with CPB. Moody and colleagues (19) first documented the presence of small capillary and arterial dilatations (SCADs), an indicator of neuropsychological deterioration, in autopsy specimens from patients who had undergone CPB. CPB with cardiotomy suction produces a greater density of small capillary and arterial dilatations than CPB without cardiotomy suction (19).

Theoretically, it is suggestive to eliminate cardiotomy suction from the CPB circuit. However, the amount of blood aspirated by the left ventricular vent and the cardiotomy suckers may be significant, and the idea of discarding such blood may not be practical. Such a policy requires additional transfusions of banked blood, which is associated with inflammatory response and the risk of transmission of blood-borne infectious disease. Moreover, blood bank blood has few functioning platelets. A better approach is to try to limit the detrimental effects induced by cardiotomy suction, which can be achieved by simultaneous administration of serine protease inhibitors into the suction surface.

Aprotinin is a low molecular serine protease inhibitor (7). It prevents hyperfribrinolysis by inhibiting kallikrein and plasmin at serum concentrations of 200 KIU/ml and 50 KIU/ml, respectively (7). It reduces platelet activation directly by stabilizing membrane receptors and indirectly via inhibiting complement, cathepsin G, and plasmin-induced a-granule secretion (20). It has been shown that Aprotinin reduces postoperative bleeding and transfusion requirements and hastens restoration of bleeding times to the normal range after CPB (7). For instance, Mohammad et al (21) showed that Aprotinin significantly reduced the progressive increase in prothrombin fragments and thrombin-antithrombin complex in a simulated CPB study. It also significantly reduced monocyte expression of tissue factor and Mac-1 (21). They concluded from this study that during simulated CPB, Aprotinin immediately inhibits kallikrein and thrombin formation via the intrinsic coagulation pathway. The ability of Aprotinin to inhibit monocyte tissue factor provides a means to reduce thrombin formation in blood aspirated from the wound during open-heart surgery.

In the current study, we found that local administration of Aprotinin through the cardiotomy suction significantly reduced the increment of D-dimer levels in both the suction solution and in the systemic circulation. The reduction in the suction solution reached a significant level 10 min after the onset of CPB, which suggested that the inhibiton of fibrinolysis in the suction circuit played an important role in the decreased fibrinolysis in the systemic circulation.

Shigeta et al evaluated the platelet function during human cardiac surgery, with or without Aprotinin. They

found that Aprotinin had indirect effects to inhibit platelet activation by inhibiting plasmin activity (6). A significant preservation of platelet GPIb receptors with Aprotinin was observed during CPB, which was obtained in the initial phase of bypass and maintained during CPB, resulting in a significant improvement in hemostasis during and after CPB. In the current study, we found that cardiotomy suction application of Aprotinin significantly alleviated the reduction in platelet count during CPB. This result is consistent with the previous study. In addition, this result suggested that cardiotomy suction is an important source of platelet reduction.

The potential role of Aprotinin in reducing the inflammatory effects of surgery is related to reducing neutrophil-induced tissue injury (7). Aprotinin has been shown to blunt the inflammatory cytokines, such as TNF-a, IL-6, IL-8 release in human and to prevent the upregulation of neutrophil CD11b integrin expression (7). Furthermore, in vitro studies have shown that Aprotinin in relatively low concentrations is as effective as platelet activating factor antagonists in preventing cytokine-induced cytotoxicity. In addition, Aprotinin directly inhibits the expression of certain molecules on the endothelium and leukocyte (7).

Studies in patients undergoing cardiac surgery show that the white cells become significantly stiffer after surgery (22). Humans given high-dose Aprotinin therapy do not experience this, and their white cells are able to pass through filters, and presumably the microvasculature, more normally (22). Administration of Aprotinin is associated with a significant reduction in injury to ischemic myocardium by the ability to suppress the formation of the toxic C5b-9 complex (22).

However, different results on the anti-inflammatory effects of Aprotinin have been documented. For example, Ashraf et al (23) reported in a prospective, randomized study performed on 38 patients undergoing elective coronary artery bypass grafting, that low dose Aprotinin failed to modify proinflammatory cytokines such as IL-6, IL-8, and plasma elastase release. The use of low-dose Arotinin does not suppress the inflammatory effect on kallidrein. Similarly, a low dose of systemic Aprotinin may not achieve effective anti-inflammatory concentrations at the major inflammatory producing sites such as the chest cavity where the cardiotomy suction occurs.

In our present study, we found that locally administered Aprotinin significantly reduced the increase of IL-8 in the suction solution. It trended towards lower IL-8 in the systemic circulation, although the difference did not reach a significant level. This result suggested that the generalized inflammation during CPB is caused by multi factors. Cardiotomy suction is an important contribution to the inflammatory responses associated with CPB.

There were several limitations in the current study. First, all results were obtained from swine models. To apply the occlusions clinically, further investigation is needed. Second, the sample size is relatively small. Results such as the difference of the systemic IL levels at the end and after CPB between the two groups might be able to reach significant level if a larger sample size was used.

In summary, in this study we found that administration of Aprotinin through the cardiotomy suction significantly decreased the D-dimer levels in the systemic circulation and in the suction solution during and after CPB. It also reduced the reduction of systemic platelet count associated with CPB. In addition, the IL-8 level in the cardiotomy suction was significantly lowered. These results suggest that Aprotinin treatment of the cardiotomy solution may reduce fibrinolysis, platelet loss, and generalized inflammation associated with CPB.

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