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In Reply:—Buffington suggests that the experimental model we used[1] and the model he used in a previous study[2] are similar. In fact, they are quite different. In the previous investigation by Buffington *et al.*, a baseline anesthetic (not "sedation") of morphine and chloralose was used.[2] The presence of any baseline anesthetic certainly has the potential of altering hemodynamic actions to superimposed isoflurane. This may be especially true for chloralose (an anesthetic we usually avoid because it produces metabolic acidosis). Our investigation was completed in chronically instrumented dogs with control observations made in the awake, unsedated state. Coronary blood flow was allowed to vary naturally in our experiments. Buffington *et al.*[2] controlled total flow through the left main coronary artery with a pump. In our investigation, collateral-dependent, stenotic, and normal regions were present. In the study by Buffington *et al.*, only stenotic and collateral-dependent zones were studied. No normal area was present: the "normal" zone had flow reduced by a pump and thus was similar to a region distal to a severe stenosis. Careful analysis of Dr. Buffington's work[2] (fig. 4) indicates that no significant increase in myocardial blood flow as measured by the radioactive microsphere technique occurred in the "normal" (actually stenotic) zone and that no significant decrease occurred in the collateral-dependent zone during isoflurane anesthesia. Because of small changes in collateral-dependent and "normal" zone flows, however, the ratio of perfusion between collateral-dependent and "normal" zones was slightly reduced in one of the several protocols. In our investigation, we calculated collateral-dependent to stenotic zone flow ratios as well as collateral-dependent to normal zone flow ratios and found no evidence of coronary steal with isoflurane. In contrast, adenosine produced a marked steal of collateral flow in our model.

Nevertheless, in our investigation, no increase in myocardial blood flow in a truly normal zone was observed during administration of isoflurane anesthesia. This was no surprise. The study conducted by Moffitt *et al.*[3] (referred to by Buffington in his letter) measuring coronary sinus blood flow in patients was unable to demonstrate an increase in coronary blood flow during isoflurane anesthesia. These investigators did find a small reduction in calculated coronary vascular resistance but only at one point during induction of anesthesia with isoflurane and *thiopental.* The decrease in coronary vascular resistance occurred concomitant with an increase in heart rate and a decrease in arterial pressure. Coronary steal, by definition, occurs independently of changes in systemic hemodynamics. Therefore, from Moffitt *et al.*'s clinical study, proof that "isoflurane does cause coronary dilation in humans" is debatable at best.

We are in total agreement with Buffington's comment that if coronary vasodilation does not exist to a significant degree, coronary steal will not occur. This appears to be the case for isoflurane. This agent certainly is not a potent coronary vasodilator compared to other drugs (adenosine, chromonar, and dipyridamole), which are known to cause steal.[4-7] *In vitro,* isoflurane does have direct actions to relax coronary vascular smooth muscle.[8] *In vivo,* however, isoflurane also possesses indirect actions (such as a decrease in inotropic state and reduction of afterload) that reduce myocardial oxygen consumption and increase coronary vascular resistance through metabolic autoregulation. The latter actions offset any weak direct coronary vasodilator effect. These mechanisms may explain the minimal change in coronary blood flow during isoflurane *in vivo,* and, in the absence of any significant coronary dilation, no coronary steal will be observed.

DAVID C. WARLTIER, M.D., PH.D.
Professor and Vice Chairman for Research
Department of Anesthesiology

MACC Fund Research Center
Medical College of Wisconsin
8701 West Watertown Plank Road
Milwaukee, Wisconsin 53226

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What Is the Mechanism of Action of Aprotinin?

To the Editor:—Although we compliment Dietrich *et al.*[1] on a much-needed clinical study describing the effect of high-dose aprotinin in patients undergoing myocardial revascularization, we believe that the data presented are insufficient to support the authors' conclusions regarding the mechanism(s) by which aprotinin reduces postoperative blood loss.

1. If the conclusion was that aprotinin could reduce formation of thrombin (as measured by thrombin–antithrombin III complexes (TAT)), then more detailed results of the TAT assays in the study groups should be provided in order to support these conclusions.
2. The authors propose a significant reduction in thrombin formation as a result of inhibition of the intrinsic system of coagulation. This should have resulted in the preservation of fibrinogen levels in the aprotinin-treated group. Unfortunately, fibrinogen levels were either not measured or not reported.
3. The authors conclude that the levels of fibrinogen–fibrin split products and the split products of cross-linked fibrin (D-dimers) were significantly reduced because of attenuated proteolytic activities of *thrombin and plasmin* in the treated group. We propose that the decreases in the treated group could have resulted solely from aprotinin's inhibition of plasmin. One should consider that during cardiopulmonary bypass, fibrin is still deposited on artificial surfaces but is subjected to decreased fibrinolysis during aprotinin treatment. Thus, the reduced levels of fibrin degradation products in the treated group may have resulted from decreased fibrinolytic activity, rather than from decrease in the activity of *both* thrombin and plasmin.
4. If the authors assume that inhibition of kallikrein activity can be achieved only by "high-dose" aprotinin during cardiopulmonary bypass (CPB), then they assume that other endogenous inhibitors of the kallikrein system (*e.g.*, α-2-macroglobulin) are rapidly consumed or rendered ineffective during CPB. It is necessary to document preservation of plasma prekallikrein levels with aprotinin therapy during CPB to better support this hypothesis.

Although several investigators have demonstrated a reduction of postoperative blood loss in patients undergoing cardiac surgery and treated with aprotinin,[2,3] we believe that the exact mechanism of aprotinin's effect is still not well understood, as demonstrated by the above issues. If the conclusions of Dietrich *et al.* (*i.e.*, the reduction by aprotinin of thrombin formation) are true, one might assume that inhibition of the intrinsic pathway of coagulation by aprotinin during CPB could predispose patients to hemorrhage in the intraoperative period. Paradoxically, the findings in this particular study showed that intraoperative blood loss during aprotinin treatment was decreased (636 ± 322 ml [control] *vs.* 363 ± 159 ml [aprotinin treated]).

PAUL M. ALLISON, M.D.
Director of Special Coagulation Laboratory
Parkland Memorial Hospital
Assistant Professor, Department of Pathology
University of Texas Southwestern Medical Center at Dallas

CHARLES W. WHITTEN, M.D.
Assistant Professor / Associate Director
Division of Cardiovascular / Thoracic Anesthesiology
University of Texas Southwestern Medical Center at Dallas

5323 Harry Hines Boulevard
Dallas, Texas 75235-9068

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In Reply:—Allison and Whitten raise some important questions concerning coagulation patterns during high-dose aprotinin treatment.

1. The course of the thrombin–antithrombin III complexes (TAT) during cardiopulmonary bypass (CPB) clearly demonstrated less thrombin formation during CPB under aprotinin treatment. We provided the TAT concentrations of all patients (fig. 3).[1] There was a significant correlation between the TAT concentration at the end of CPB and the intraoperative blood loss in the control group, whereas this correlation was not significant with aprotinin. Fibrinopeptid A, which is a very sensitive thrombin marker, was significantly increased at the end of CPB in the control group in comparison to the aprotinin group (22.0 ± 22 ng/ml in the aprotinin group *vs.* 11 ± 7 ng/ml in the control group; $P < 0.05$). Similar results were found by others.[2] Because of problems in the preanalytic phase we regard the TAT results to be more conclusive than the FPA concentrations. Therefore, only the TAT concentrations were provided.
2. Fibrinogen levels were measured but not reported since there were no significant differences between the groups. However, due to the acute phase reaction, fibrinogen is a very insensitive marker for the activity of thrombin and plasmin. After completing the study we determined the concentration of plasma fibrin by means of a fibrin-specific monoclonal antibody: at the end of CPB it was 15.0 ± 17 ng/ml in the control group, compared to 3.2 ± 2 in the aprotinin group ($P < 0.05$). These results are conclusive for the prevention of fibrin formation by aprotinin.
3. We measured prekallikrein levels and could not demonstrate significant differences at the end of CPB (42 ± 11 *vs.* 39 ± 6%, control *vs.* aprotinin). However, this is not surprising, because aprotinin does not inhibit the conversion from prekallikrein to kallikrein; it acts on the level of kallikrein and inhibits the action of kallikrein. Therefore, we could measure a significant difference in the concentrations of the α_2-macroglobulin complexes with kallikrein (2.3 ± 2.1 ng/ml vs. 1.3 ± 3.9 ng/ml at the end of extracorporeal circulation and 3.7 ± 2.7 *vs.* 0.9 ± 3.1 ng/ml at the end of operation, control group *vs.* aprotinin; $P < 0.05$).
4. These results taken together seem to justify the conclusion that the reduction of split products of the crosslinked fibrin (D-dimers) was due to attenuated proteolytic activity of thrombin and plasmin. It must be emphasized that activation of the intrinsic pathway of coagulation results not only in activation of coagulation but also in

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