

activation of fibrinolysis. Therefore, the antifibrinolytic activity of aprotinin is due not only to its antiplasmin properties but also to the inhibition of kallikrein.

5. We believe that our results provide strong evidence that inhibition of the contact activation of coagulation is the main aspect of aprotinin's effect on blood loss. This is supported by the prolongation of the global coagulation tests of activated clotting time and activated partial thromboplastin time. The reduced intraoperative blood loss with aprotinin does not contradict this, because it is well known that the inhibition of the intrinsic pathway of coagulation does not lead to an increased bleeding tendency. The reduction in bleeding tendency with aprotinin is caused by better-preserved coagulation patterns, which lead to less stimulation of platelets and therefore better preserved platelet function.

It was beyond the scope of our article to provide all data that led to our conclusions. We agree with Allison and Whitten that more studies are needed to delineate the precise mode of action of aprotinin. We hope, however, that our study has contributed to this end.

W. DIETRICH, M.D.
J. A. RICHTER, M.D.
*Institute for Anesthesiology
German Heart Center Munich*

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Effects of Aprotinin on Postoperative Bleeding

To the Editor:—In a recent study,¹ Dietrich *et al.* studied the effects of high-dose aprotinin treatment in 20 patients undergoing cardiac surgery. They found an important decrease of postoperative bleeding and consumption of blood products during the perioperative and postoperative periods when compared to a control group.

We have performed a comparable study in two groups of 25 patients (aprotinin and control) with the same protocol. Our results concerning total postoperative bleeding and homologous blood requirement are identical to those of Dietrich *et al.*, as are results concerning clotting parameters. We agree with the authors about the interpretation of the important decrease of the complex of thrombin with antithrombin III (TAT) and of D-dimers in the aprotinin group. However, we think that the important reduction of D-dimers we have observed in our study also may be explained by a direct inhibiting effect of aprotinin on the produced plasmin.

In addition, we measured the fibrinolytic activity in the preoperative period by the euglobulin clot lysis time (ECLT). The responders were defined by a 30-min reduction of ECLT after 20-min venous stasis, compared with the same test before stasis. The results at the end of the first postoperative hour and total bleeding are shown in the table 1.

Although we have not observed any difference on tissue plasminogen activator (tPA) concentration (data not shown), it seems difficult to eliminate a vascular wall involvement in inhibition of fibrinolysis by aprotinin. Indeed, our results suggest an efficacy of aprotinin mainly during the early postoperative period. The small number of patients and the effects of other treatments on bleeding might explain the lack of significance on total bleeding. It is well recognized that the response to venous stasis (as a responder or a nonresponder) depends on a balance between tPA and plasminogen activator inhibitor (PAI).² Our preliminary results show a better PAI activity in the aprotinin group.

Lothstr. 11
8000 München 2
Germany

W. SCHRAMM, M.D.
M. SPANNAGL, M.D.
*Coagulation Laboratory
Clinic for Internal Medicine
University Munich
Ziemssenstr. 2
8000 Munich 2
Germany*

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TABLE 1. Bleeding after Aprotinin or Placebo

	Group	Placebo	Aprotinin	
H1	NR	193 ± 80	182 ± 56	
	R	375 ± 294	179 ± 82	<i>P</i> < 0.05
T	NR	883 ± 267	872 ± 354	
	R	1382 ± 1000	755 ± 340	NS
	NR + R	1157 ± 593	799 ± 59	<i>P</i> < 0.05

Postoperative bleeding (milliliters, means ± SD) from insertion of chest tubes to the end of the first postoperative hour (H1), and total bleeding (T) in responder patients (R), nonresponder patients (NR), and both groups. NS = not significant.

Additional studies are needed to determine whether aprotinin effects are caused by an anti-tPA effect³ or a decreased urokinase plasminogen activator secondary to an antikallikrein effect of aprotinin.

JEAN-PIERRE MERLE, M.D.
JEAN-PIERRE LANÇON, M.D.
Department of Anesthesiology

F. DUTRILLAUX, M.D.
Laboratory of Hemostasis

JEAN-FRANÇOIS OBADIA, M.D.
Department of Cardiovascular Surgery

B. CAILLARD, M.D.
Department of Anesthesiology

Hopital Universitaire du Bocage
F21034
Dijon
France

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Inotropic Effect of Amrinone

To the Editor:—The article by Rooney *et al.*¹ is a worthwhile contribution to our understanding and appreciation both of the character and of the limitation of amrinone as an inotropic agent in surgery and anesthesia. Over a decade since becoming clinically available, amrinone, unlike dobutamine, has gained little popularity in surgical as well as other anesthetized patients who need urgent hemodynamic support. Without the indirect effect from afterload reduction, amrinone can be considered only a mild or weak inotropic agent, as shown by the isovolumetric peak left ventricular pressure increase of 12.8% after 500 μ M. For patients without heart failure, the afterload reduction effect of amrinone may not be beneficial.

Recently, in a different preparation, we studied the direct effect of infusion of amrinone on isolated rabbit myocardial septum.² With concentrations ranging from 1 to 1,000 μ g/ml, the results showed that at concentrations greater than 10 μ g/ml, amrinone caused slight (5–11%) increases in peak developed tension and maximal acceleration (dT/dt). In contrast to Rooney *et al.*'s study, we did not observe a dose-dependent increase of contractility. Our conclusion is that amrinone is not a strong inotropic agent and cannot be treated the same as dobutamine or dopamine.

TAI-SHION LEE, M.D.
Associate Professor

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In Reply:—We appreciate the interest of Lee and Virtusio regarding our work describing the isolated cardiac effects of amrinone.¹ Their particular concern is whether amrinone is really much of a positive inotropic agent. We agree that it has only a mild positive inotropic effect *in vitro*. Perhaps it does not produce much of a tachycardia because it is also not a potent direct positive chronotropic agent. We also observed that amrinone did not produce coronary vasodilation above the metabolic demand in the isolated heart. Its major effect *in vivo* probably is peripheral venodilation and arteriolar vasodilatation.² With administration of amrinone, the increase in cardiac output without a change in myocardial oxygen consumption in patients with congestive heart failure likely reflects a reduction in afterload and enddiastolic ventricular volume more than it does a direct positive inotropic effect.³ A reduction in ventricular filling pressure by amrinone may decrease wall tension in patients with dilated ventricles and so counteract any increase in myocardial oxygen consumption due to a direct mild inotropic effect. Higher loading doses than originally recommended, however, may result in a greater inotropic effect.⁴

LOURDES VIRTUSIO, M.D.
Research Associate

Department of Anesthesiology
University of California—Los Angeles School of Medicine
Harbor/University of California—Los Angeles Medical Center
1000 West Carson Street
Torrance, California 90509

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Differences in inotropy *in vivo* and *in vitro* may be due to species differences or to adrenergic stimulation. Amrinone may be more effective in the presence of catecholamines, and afterload reduction may stimulate an adrenergic response. Whether amrinone or traditional drugs such as digitalis, epinephrine, isoproterenol, dopamine, or dobutamine are better choices for inotropic support, alone or with peripheral vasodilators, after cardiopulmonary bypass has been debated recently.^{4,*} The combined use of amrinone and other inotropic agents also has been discussed. It appears that milrinone and other newer phosphodiesterase III inhibitors† under development have greater positive inotropic effects that may approach the effects of the natural and synthetic catecholamines.

DAVID F. STOWE, M.D., PH.D.
Associate Professor of Anesthesiology and Physiology
The Medical College of Wisconsin
Staff Anesthesiologist