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was that geopolitical areas (e.g., counties) correspond poorly to where patients actually receive their medical care. The areas mapped in figure 1 are the *hospital referral regions* that are defined by where Medicare patients were hospitalized for major cardiovascular and neurosurgical procedures. The Florida panhandle region overlaps with four such hospital referral regions, one of which has its greatest land coverage in neighboring Alabama: Pensacola (9.7 anesthesiologists/100,000 population), Panama City (7.2), Tallahassee (7.6), and Dothan (7.6). Hence, comparing the Aldretes' assessment and what is mapped in figure 1 is much like comparing apples and oranges.

The Aldretes also seem to impugn physician data obtained in the American Hospital Association's Annual Survey mailed to hospital administrators. In years in which AHA has inquired about physicians, the survey has specified medical staff membership at the time of the survey, leaving little subjectivity. The administrator has also been a most appropriate person to complete the form in relation to studies of anesthesiologists' availability, given that so many hospitals lack anesthesiologists (e.g., about one third nationally,³⁻⁶ 69% in rural Washington and Montana,⁷ and 71% in rural counties of the Florida panhandle according to the Aldretes). Thus, AHA Annual Survey data have enjoyed usage in ASA,^{3,4} personal,^{5,6} and other anesthesia-related studies⁸ in which the hospital is the unit of analysis.

Like the Aldretes, I would encourage anesthesiologists to consider rural sites, even though the challenges of developing a physician-directed anesthesia practice *de novo* may be substantial.

Frederick K. Orkin, M.D., M.B.A.
Department of Health Evaluation Sciences
The Milton S. Hershey Medical Center

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500 University Drive, H173
Hershey, Pennsylvania
forkin@hes.hmc.psghs.edu

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The Blood Sparing Effect of Aprotinin Should Be Revisited

To the Editor:—Capdevila *et al.*¹ noted that the mechanism underlying the beneficial effect of aprotinin was not fully elucidated. We wish to make some comments in this regard. The blood-sparing effect of aprotinin has long been attributed to an early protective effect of aprotinin on platelet membrane glycoproteins, mainly Gp1b, altered by the contact of blood components with the foreign, non-biological surface of the cardiopulmonary bypass circuit (CPB).^{2,3} Until recently the blood-sparing effect of aprotinin was only demonstrated in cardiac surgery conducted with CPB. During CPB, inhibition of fibrinolysis by aprotinin^{3,4} could explain the protective effect on platelet membrane glycoproteins. Plasmin and d-dimer may degrade Gp1b receptors and the von Willebrand factor, which is responsible for platelet adhesion.^{3,4} However, the inhibition of fibrinolysis is unlikely to be the mechanism by which aprotinin reduces intraoperative blood loss with CPB: the activation of fibrinolysis is apparent only at the end of CPB,³ whereas the Gp1b receptor consistently decreases within 5 min after start of CPB.³ Also, as noted by the authors, the reduction of intraoperative cytokine release by aprotinin has been assessed when a CPB is used.⁴ However, this effect has never been associated with any hemostatic changes.⁵

The intraoperative blood-sparing effect of aprotinin has been demonstrated in situations in which CPB is not used: elective liver resection⁶ and orthopedic surgery.^{7,8} Consequently, the blood-sparing effect of aprotinin cannot be attributed primarily to a protective effect on platelet function previously altered by the contact of blood cells with the non-biological surface of a CPB. However, available data are controversial. Inhibition of intraoperative hyperfibrinolysis has been demonstrated in elective liver resection.⁶ Conversely, in two prospective, randomized, placebo-controlled studies of hip surgery,^{7,8} a reduction in blood loss with high-dose aprotinin occurred but without any associated antifibrinolytic effect.^{7,8} In these two studies, fibrinolysis was assessed by two reliable tests: postoperative fibrinogen⁷ and d-dimer concentration.⁸ The effect of aprotinin on platelet function was investigated in two randomized, placebo-controlled studies of hip replacement surgery.^{7,9} In the former study,⁷ in the aprotinin and placebo groups: (1) the intraoperative platelet count and the bleeding time did not change significantly; (2) no evidence of *in vivo* intraoperative platelet activation was found (b thromboglobulin remained normal); and (3) no significant change in *in vitro* intraoperative ADP and collagen-induced platelet aggregability was observed. In the latter

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study,⁹ platelet function was altered intraoperatively in the control group, whereas (1) aprotinin preserved spontaneous platelet aggregation and ADP induced platelet aggregation and platelet adhesivity; and (2) postoperative platelet aggregates concentration decreased significantly with aprotinin when compared with placebo. We have not discussed liver transplantation because aprotinin has failed to significantly decrease blood loss in such cases.¹⁰

That aprotinin can achieve by different mechanisms an identical therapeutic goal in different surgical fields would be puzzling. Consequently, in regard to the mechanism of the blood-sparing effect of aprotinin, it is our opinion that this hypothesis should be revisited.

Claude Lentschener, M.D.

Staff Anesthesiologist

Dan Benhamou, M.D.

Professor Department of Anesthesiology

Hôpital Antoine-Béclère

Université Paris-Sud

157, rue de la Porte de Trivaux

92141 Clamart Cedex, Paris

France

dBenhamou.beclere@invivo.edu

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In Reply:—I would like to thank Dr. Lentschener and Dr. Benhamou for the attentive reading they have accorded to our article.¹

Although the mechanisms underlying the beneficial effects of aprotinin on blood loss during surgery were not fully elucidated, reconsidering the hypotheses evoked in the literature involving platelet receptor protection may not be fully justified.

The complex action of aprotinin, a natural serine protease inhibitor, is situated at the cross-section of several reactions triggered during surgery: contact phase activation, tissue factor and tissue plasminogen activator (tpa) release from subendothelial sites, plasmin activation by kallikrein and activated factor XII, as well as the release of kinins and activated C3b fragments.²⁻⁴ Furthermore, aprotinin activation depends on blood aprotinin levels, and as such the administered perioperative dose, whether or not cardiopulmonary bypass (CPB) is used.

Major surgery can activate the extrinsic coagulation pathway by the release of tissue factor from the endothelial cells.^{4,5} Aprotinin can limit the onset of disseminated intravascular coagulopathy (DIC) *via* its anti-VIIa activity.⁶

Aprotinin's role in the inhibition of fibrinolysis, reported primar-

ily in works concerning liver surgery,^{7,8} is based on the limitation of contact phase activation,⁹ direct anti-plasmin activity by inhibition of tpa release,^{7,10} and protein C activity.¹¹ Aprotinin also has been shown to have a local antifibrinolytic effect, limiting perioperative bleeding when injected directly into the pericardial cavity.^{12,13} During surgery performed without CPB, this antifibrinolytic effect probably implies aprotinin activity. Both the limited postoperative d-dimer values seen in our patients treated with aprotinin¹ and the greater number of patients in Janssens *et al.*'s¹⁴ control group presenting higher than normal d-dimer values seem to confirm the hypothesis.

It is not improbable that aprotinin's role in limiting bleeding is based on a multimodal mechanism. During surgery with CPB, aprotinin activity seems to primarily involve platelet receptor protection from plasmin activity and contact phase activation.¹⁵ In contrast, a more global action on fibrinolysis and DIC seems to predominate during major surgery without CPB.

In consequence, aprotinin would achieve one therapeutic goal by several different mechanisms of action.