INVITED DISCUSSION

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APROTININ IN ISCHEMIA-REPERFUSION INJURY: FLAP SURVIVAL AND NEUTROPHIL RESPONSE IN A RAT SKIN FLAP MODEL

BRIAN C. COOLEY*

Finding a pharmacologic avenue for preventing ischemia/reperfusion injury remains a continuing quest. Both old and new agents have been investigated in this search. Dr. Stadelmann et al. have explored the use of a relatively old but important compound, aprotinin, for preventing ischemia-related flap necrosis. A broad-spectrum serine protease inhibitor, aprotinin has achieved clinical status for its hemostatic effects when given during cardiovascular surgery[1–3] and hip replacement surgery.[4] Despite its efficacy in reducing blood loss during these procedures, surgeons and scientists have not ascertained the mechanism of action for aprotinin.

Dr. Stadelmann's group has found that preischemic (but not postischemic) treatment with aprotinin leads to greater survival territory in ischemic rat flaps. The flap model, originally described by Finseth and Cutting,[5] is an axial-pattern island groin flap with a connecting random-pattern (contralateral groin) flap territory. The present authors modified this flap model by applying a 10-hour ischemic episode through clamping of the pedicle. Thus, the model has overlapping elements of both global and marginal ischemia. Along with this modification, these authors have reduced the flap dimensions of the original design from a 9 × 9 to a 6 × 6-cm flap in the same-sized rats. It would be helpful to know the area of flap survival without the ischemic interval in the smaller-dimensioned flaps. Finseth and Cutting describe this survival as (40.5 cm^2 + 10.4 cm^2) of an 81-cm^2 flap—62.8% total survival.[5] If a similar pattern/area of survival can be assumed in the present model, then the effect of preischemically administered aprotinin (with 52.3 ± 5.4% survival, close to 62.8%) simply may be negating the global ischemic episode. Further study is warranted to investigate separately these different sides of the ischemia question, using purer models for each type of ischemia (e.g., nonischemic Finseth and Cutting flap or unilateral 10-hour ischemic flap).

Dr. Stadelmann et al. have highlighted neutrophils as the potential targets for the beneficial effects of aprotinin. A rigorous control for the myeloperoxidase assay was not applied in their study, specifically, evaluation of the effect of aprotinin administration on neutrophil myeloperoxidase activity. Without this control, we can only assume that aprotinin did not interfere with the assay and that the assay accurately reflected the proportion of retained neutrophils in the biopsied flap tissue. The biopsy site was also located in an area where the effects of marginal and global ischemia may have been overlapping. This may account for the large scatter in the data among groups and time points, i.e., slight variations in the biopsy sites could lead to major differences in neutrophil levels.

Clinical use of aprotinin in coronary bypass surgery has emphasized its role in inhibiting enzymes of the coagulation cascade, fibrinolysis, and/or platelet adhesion/aggregation.[1–3] Neutrophil function after aprotinin administration is also protected and the degree of superoxide production is reduced,[6,7] although whether this is a direct effect or is mediated by coagulant/fibrinolytic/platelet-receptor pathways is unclear. A better understanding of the effect of aprotinin on neutrophils could help address this question.

Orthopaedic Microsurgery Research, Department of Orthopaedic Surgery, Medical College of Wisconsin, Milwaukee, WI

*Correspondence to: Brian C. Cooley, Orthopaedic Microsurgery Research, Department of Orthopaedic Surgery, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226.

Aprotinin may have a much broader, multiroad activity in tissue subjected to ischemia/reperfusion and marginal ischemia.

Perhaps the most revealing finding of this study is the lack of effect in the postischemic treatment group. Dr. Stadelmann et al. suggest that the preischemic treatment allows aprotinin to act on the neutrophils within the flap microcirculation or to have a direct and potentially multifaceted effect on the flap tissue. This could be differentiated with a free-flap transplantation model between syngeneic rats:[8,9] aprotinin could be given to one rat before raising and isolating a free flap, then the flap could be transplanted to an untreated rat, with reciprocal transplantation of an untreated flap to the treated rat. Another explanation is that the single bolus of aprotinin might have a delayed effect on the neutrophils, inhibiting their function after 10 hours, at the time of reperfusion. This effect of aprotinin on neutrophils would evidently not be immediate since the postischemic treatment group in the study showed no benefit. Aprotinin administration at various times before reperfusion could help address this issue. Because of the broad range of potential activity by aprotinin, much more work will need to be done to dissect its course(s) of action.

In summary, this study points to a new use—the prevention of reperfusion injury—for an established agent, aprotinin. With a beneficial effect only seen in the preischemic treatment group, the potential for clinical applications in reconstructive microsurgery may be quite limited since reperfusion injury is primarily a problem with extremity replantation and secondary ischemia after free-flap surgery, both of which would require a postischemia form of treatment for complications. Nevertheless, the data are important for offering further clues to the overall puzzle of ischemia/reperfusion injury.

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