

Protamine Reactions, Explosive Mediator Release, and Pulmonary Vasoconstriction

ONE OF THE LAST major problems to be addressed effectively prior to applying cardiopulmonary bypass (CPB) to human beings was neutralization of heparin to enable blood to clot after separation from CPB. The principle drug used throughout the history of cardiac surgery for counteracting the effect of the polyanion heparin is the polycation protamine, although several other compounds have been tried. Protamine has periodically been suspected of causing cardiovascular collapse by a number of mechanisms, but until recently, none was convincingly demonstrated.

In 1983, we identified severe acute ("catastrophic") pulmonary vasoconstriction as one cause of circulatory collapse associated with protamine reversal of heparin anticoagulation.¹ Further studies in patients demonstrated the concomitant release by the lung of large quantities of thromboxane A₂, a short half-life potent vasoconstrictor cyclooxygenase product of arachidonic acid.² This was reflected by a marked increase in the concentration of thromboxane B₂, its stable metabolite, in the peripheral circulation.

Inhibition of thromboxane synthesis in sheep inhibits pulmonary vasoconstriction and nearly complete occupation of thromboxane endoperoxide receptors by a specific receptor antagonist can prevent the pulmonary va-

soconstriction, demonstrating cause and effect.^{3,4} Depletion of platelets by a specific antiplatelet antibody did not inhibit either thromboxane generation or pulmonary vasoconstriction in sheep, suggesting that platelets are not the primary source of the thromboxane observed in this species.⁵ The search for a cellular source of thromboxane continues, and pulmonary intravascular macrophages appear as prime suspects in certain species, such as pig and sheep. These sessile macrophages reside in the lungs of these species and scavenge particles on a "first pass" basis.⁶ However, monkeys have few of these cells in their pulmonary circulation, and although reported in human lungs, their frequency is unknown in various diseases.⁷ Therefore, other cells should be suspected as the source of thromboxane in the human heparin-protamine pulmonary vasoconstriction response.

The possible role of the complement system is intriguing. Complexing large ionic molecules with large cationic molecules activates the complement cascade both *in vivo* and *in vitro*.⁸ Plasma C_{3a} and C_{4a} increase occurs uniformly with heparin neutralization in man.² However, plasma concentrations of C_{5a} were detected only in patients who also had increased concentrations of plasma thromboxane B₂.² Recent studies by Stahl *et al.* have demonstrated regional thromboxane generation, coronary vasoconstriction, ventricular wall motion abnormalities, and lactate production when C_{5a} is injected into the left anterior descending (LAD) coronary artery in pigs.⁹ This indicates that complement fragments may initiate thromboxane generation. However, administration of nafamstat mesylate, a protease and complement pathway inhibitor, attenuated but did not prevent pulmonary vasoconstriction

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in sheep.¹⁰ This may be due to incomplete prevention of complement activation since acute transient leukopenia, a marker of complement activation, was not prevented by nafamstat. An alternate hypothesis is that complement activation is not necessary for thromboxane generation when complexes are formed. The role of the complement system thus requires further investigation.

The reason the incidence of the reaction is so low in humans, whereas it is produced so reliably in sheep and pigs, has not been defined. One reason may be that the time interval between heparin and protamine administration is usually greater in patients than in the experimental animal. While true anaphylaxis to protamine (characterized by a specific anti-protamine IgE antibody) occurs almost exclusively in diabetic patients chronically receiving protamine-insulin injections, identification of the risk factors for pulmonary vasoconstriction has been elusive.¹¹ Valvular heart disease, pre-existing pulmonary hypertension, diabetes mellitus, and bolus injection have all been suspected but not confirmed.¹ Our group has reported a 1.5% incidence of pulmonary vasoconstriction in patients receiving a protamine infusion of 120 mg over approximately 12 min — an incidence far higher than that suspected by most clinicians.¹² This may be due in part to the evanescent nature of the pulmonary vasoconstriction in many patients or to other factors.

In this issue of ANESTHESIOLOGY, Morel and his associates report a careful investigation of the heparin-protamine reaction in an awake sheep.¹³ The blood vessels of sheep lungs appear to be ideal for study of this reaction as they sustain a reproducible response with each heparin-protamine challenge. The investigators documented the effect of a 600-fold difference in the protamine infusion rate: from 3 s to 30 min.¹³ All animals received 200 units/kg of heparin intravenously. After 5 min, an infusion of 2 mg/kg of protamine was administered intravenously at one of four rates. They observed that the fastest protamine infusion rate was invariably associated with pulmonary vasoconstriction and high concentrations of thromboxane B₂ in circulating blood, whereas the slowest rate of protamine administration was associated with neither. Intermediate rates of infusion were associated with intermediate concentrations of thromboxane and physiologic changes.

Clearly, this study establishes the rate of protamine administration as an important determinant of pulmonary vasoconstriction in sheep. The precise mechanism by which the speed of administration of protamine effects this response has not been determined in any species. Perhaps we should not be surprised at this rate dependence, however, as numerous examples have already been documented in the field of anesthesiology. Pharmacologic histamine liberation, which is associated with decreased systemic vascular resistance, is partially dependent upon the rate of infusion of *d*-tubocurarine or morphine. In-

deed, one episode of pharmacologic histamine liberation resulting in hypotension was observed by Morel and associates.² This documents nonimmunologic pharmacologic release of histamine without thromboxane generation as another cause of systemic hypotension associated with administration of this medication.

The implications of this study for clinical practice are uncertain. Many human protamine reactions have occurred at an infusion rate of 10 mg/min. Thus, rate dependence has not yet been demonstrated conclusively in humans. Even if pulmonary vasoconstriction was avoided by extremely slow administration of protamine in most patients destined to have an adverse response, a cost-benefit analysis would be required to determine whether the blood loss sustained during 30 min of persistent anticoagulation in a large number of patients would outweigh the benefits of avoiding the consequences of this adverse drug interaction in a small number. The minimum duration of infusion to avoid this response in humans would have to be defined to minimize blood loss as much as possible.

On the other hand, a strategy of inducing a temporary blockade of thromboxane receptors only for the duration of the potential burst of thromboxane liberation is more appealing.⁴ This would permit rapid protamine reversal of anticoagulation with restitution of clotting activity in a timeframe that should avoid unnecessary blood loss associated with persistent anticoagulation and permit prompt differentiation of surgical bleeding from inadequate heparin reversal or coagulopathy. Although blockade of thromboxane receptors is associated with platelet dysfunction, a sufficiently short-acting drug might avoid this problem.

This study by Morel and his associates constitutes an important building block in understanding the adverse cardiopulmonary responses to protamine neutralization of heparin. Complete understanding can be expected to add to the safety of reversal of anticoagulation in patients undergoing cardiac surgery, vascular surgery, and cardiac catheterization.

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