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Commentary

A central paradox of controlling coagulation in the patient undergoing thoracotomy and cardiopulmonary bypass (CPB) emerges as the cardiac surgeon strives to achieve blood fluidity within the CPB circuit and the patient's vasculature, as well as an effective procoagulant response to ensure protective hemostasis in the wound (Fig 1). Heparin, the gold standard for CPB, inhibits the coagulation mechanism at multiple levels, especially in the final common pathway, thereby blocking in parallel the intravascular and extravascular procoagulant responses. However, the properties of heparin allowing it to so effectively target the final common pathway of coagulation underlie its potential causation of excessive bleeding in hemostatically compromised patients.

The properties of thrombin emphasize the biologic complexity and dichotomous nature of the coagulation mechanism when it is integrated into the context of host

response effector mechanisms. Thrombin activates cellular elements through cleavage of protease-activated receptors; short-term consequences of this mechanism include activation of platelets, and longer-term implications of protease-activated receptor stimulation may include changes in vascular smooth muscle cell properties underlying restenotic and other vascular lesions.¹ As a procoagulant enzyme per se, thrombin magnifies and modulates its biologic effects in a dichotomous fashion; thrombin activation of factor XI provides a positive feedback mechanism reinforcing the generation of procoagulants through the intrinsic system.² Thrombin also stimulates the thrombin activatable fibrinolysis inhibitor, thus diminishing the efficacy of clot lysis.³

In contrast to the above procoagulant effects of thrombin, after binding to the endothelial cofactor thrombomodulin, this enzyme also cleaves the plasma zymogen protein C, resulting in formation of activated protein C (APC).⁴ APC is the key enzyme in the endogenous antithrombotic protein C–protein S (the latter a cofactor for APC) mechanism, which damps the final common pathway by proteolytically inactivating factors Va and VIIIa. APC also appears to have other vasculoprotective effects resulting from its interaction with plasminogen activator inhibitor-1 and by mechanisms yet to be fully characterized. In the latter context, APC affords protection against a lethal dose of intravenous *Escherichia coli*, and, in models of myocardial ischemia, APC appears to limit tissue injury by effects that may extend beyond its coagulant properties.⁴ The importance of the protein C–protein S pathway as a natural anticoagulant mechanism is emphasized by the prothrombotic diathesis observed in patients with significant functional deficiency of either plasma protein.⁴

On the basis of this discussion, formation of APC is expected when thrombin is generated. In the current issue of the Journal (see page 422), Petäjä and colleagues report that APC is generated during CPB and coronary reperfusion. Enhanced APC formation during the immediate reperfusion period is not unexpected. Restoration of blood flow delivers both key substrates for energetic metabolism and effector mechanisms capable of inflicting vascular damage, such as polymorphonuclear leukocytes, complement, and coagulation components to systemic cardiac vasculature. The net result is increased generation of thrombin, causing both cleavage of fibrinogen with release of fibrinopeptide A (Fig 2 in Petäjä and colleagues) and increased APC formation (Fig 1, C and D in Petäjä and colleagues). Furthermore, that patients who demonstrate more robust formation of APC (“good responders”) are those with enhanced hemodynamic performance (Fig 3 in

Fig 1. Schematic depiction of the procoagulant response to thoracotomy/cardiopulmonary bypass (CPB). TAFI, Thrombin-activatable fibrinolysis inhibitor; APC, activated protein C; TF, tissue factor.

Petäjä and colleagues) is also not unexpected because effective reperfusion will generate both a procoagulant (production of fibrinopeptide A) and anticoagulant (production of APC) response. However, there is the intriguing possibility that APC may be doing more than simply reflecting hemodynamic status, based on its vasculoprotective effect in animal models of ischemia. This is an area for future study that may reveal yet another example of the interdependence of the coagulation mechanism and cardiovascular function.

How can we integrate these findings into a broader understanding of the role of the coagulation mechanism in CPB procedures?

1. Local (wound) and CPB-induced activation of

coagulation during thoracotomy/CPB trigger is unavoidable (thus anticoagulant therapy is required) and is integral to the protective response mounted to invasion of the extravascular and intravascular spaces. An important component of this procoagulant response is the triggering of endogenous antithrombotic mechanisms, such as activation of formation of APC. Thus more selective antithrombotic therapy administered to patients during CPB/reperfusion, with the goal of sparing natural anticoagulant mechanisms, might be expected to buttress vascular protective pathways.

2. Nonspecific inhibition of the coagulation mechanism by an agent such as heparin is also more likely to damp natural antithrombotic mechanisms tied to the

procoagulant pathway, such as the protein C–protein S mechanism.

3. From a general perspective of prothrombotic mechanisms operative in thoracotomy/CPB (Fig 1), more selective control of coagulation might be achieved by damping effects of the intrinsic system without critically interfering with extravascular clotting. In this regard, targeting factor IX/IXa would inhibit both activation of the intrinsic system by the CPB tubing, as well as tissue factor–dependent, monocyte-mediated mechanisms in the CPB circuit (where low levels of tissue factor favor activation of factor IX over that of factor X)⁵ and has been shown to be effective in canine and baboon models.^{6,7} Such a selective anticoagulant approach would be expected to more minimally affect the generation of natural antithrombotics, such as the protein C pathway.

The coagulation pathway is an integral part of the host response to surgical procedures, and events that begin as an apparently simple response to stem local blood loss can actually have wide-ranging implications as locally formed thrombin modulates cellular properties (including direct effects on the vasculature), activates protein C, and exerts a range of other effects as well. Selective damping of the procoagulant mechanism to limit intravascular coagulation during surgery will undoubtedly be the future direction of anticoagulant therapy. The goal of such therapy will be to maintain extravascular hemostasis and allow natural

antithrombotic mechanisms, such as formation of APC, to occur with minimum inhibition while preventing thrombosis in the CPB circuit and vasculature.

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