To the Editor:

Recently, Boisclair et al has given us an important clue to show the main trigger to coagulation activity during cardiopulmonary bypass (CPB). They observed the increase of factor IX activation peptide during CPB, which shows a strong correlation with the increase of prothrombin fragment F1 + 2. In contrast, they found no significant increase in factor XIIa levels during CPB. This activation pattern in the clotting cascade indicates that the clotting activity during CPB is not mainly triggered from the contact activation to the surface of the extracorporeal circuit, but from the tissue factor-factor VIIa mechanism, which Boisclair et al suggested to be generated from the subendothelial surfaces exposed as a result of surgical damage to blood vessels. However, their speculation seems rather unlikely. We cannot imagine that the major surgical insult of opening the thorax, which is completed before CPB, contributes to the clotting activation during CPB after an interval of more than 60 minutes. Moreover, if the surgical insult is the main procoagulant trigger, other major surgical procedures without CPB should manifest a much more profound procoagulant activity in the systemic blood that is not or to a lesser extent anticoagulated.

Alternatively, Boisclair’s result appears to us to imply other triggers to coagulation via the extrinsic pathway during CPB. Our recent study showed that the blood shed into the pericardial cavity and afterwards returning through cardiotomy suction during CPB is highly activated, quite contrasting with the activation of blood exposed to the low thrombogenic surfaces of modern extracorporeal circuits. Our supporting in vitro experiment using rabbit pericardium showed that the conventional dose of heparin could not prevent the clotting activity triggered by tissue factor of the pericardium. However, we miss the description in Boisclair’s report of whether they used cardiotomy suction during CPB as usual practice. If they avoided using cardiotomy suction in their study model, the observed clotting activity in their study seems to indicate another trigger.

Endothelial cells and monocytes have been shown to express tissue factor activity upon exposure to agonists such as tumor necrosis factor or endotoxin, which had increased activity observed during CPB. Because the clinical contribution of this procoagulant pathway has not been shown, Boisclair’s report would be a strong support for this hypothesis.

In conclusion, the nicely performed study of Boisclair et al would give us an important clue to speculate the major procoagulant trigger during CPB, if the information is provided whether they used cardiotomy suction in their study.

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REFERENCES

Response

Our paper on the nature of the thrombogenic stimulus in cardiopulmonary bypass (CPB) was primarily intended to direct attention toward tissue factor as a likely trigger factor of coagulation in this clinical setting. It had previously been widely believed that coagulation activation was initiated at the level of factor XII and other contact coagulation factors, although there was little direct evidence to support this. We found minimal change in factor XIIa and factor IX activation (increase in factor IX activation peptide) that was preceded by prothrombin activation (increase in F$_{1+2}$). Both these findings appeared incompatible with the idea of sequential cascade activation arising from initial factor XII activation. We were limited in our study by not being able to monitor each step of proteinase cascade. Subsequently, we have developed an enzyme-linked immunosorbent assay for factor X activation peptide and shown that this peptide also increases ahead of factor IX activation peptide. Compelling support for a limited role of factor XII in thrombogenesis has been obtained recently from a study of a severe factor XII deficient individual who underwent bypass; thrombin was generated in CPB in this patient, correlating with factor X activation. Therefore, all of these results suggest that the contact factor system is probably not primarily responsible for triggered coagulation in CPB. Tissue factor seemed the likely major trigger, and although we had no supporting data, it seemed reasonable to suggest that the accompanying surgery could provide a source of immediately available tissue factor. In their letter, Tabuchi and van Oeveren point to the possibility that blood shed into the pericardial cavity and subsequently returned to the patient by cardiotomy suction could be a source of coagulation activation. Although not stated in our paper, cardiotomy suction was used in all patients. An additional potential source of tissue factor activity may be monocytes activated on the foreign surfaces of the CBP equipment. Whereas Tabuchi and van Oeveren discount surgically induced activation as a trigger of coagulation in bypass, we prefer to keep open the options as to the nature of the trigger until more data is available. It is conceivable that this might constitute the sum of a number of distinct stimuli to the extrinsic pathway. Indeed, in our original paper we were careful to leave open the possibility that factor XII activation might even play a minor role in thrombogenesis.

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Procoagulant triggers during cardiopulmonary bypass [letter; comment]

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