

Understanding the Delicate Balance between Bleeding and Thrombosis: Can We Use It to Our Advantage?

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Abstract: Hemostasis remains an issue in cardiac surgery because many patients are preoperatively on platelet-inhibiting drugs, whereas other patients such as those with an evolving acute myocardial infarction present themselves in a more prothrombotic status. Classical laboratory tests such as activated partial thrombin time and plasma thromboplastin are poor in predicting blood loss

and bleeding problems postcardiac surgery. This is explained by the fact that these tests are performed on plasma instead of on whole blood. Whole blood coagulation tests are superior in detecting coagulation deficits and bleeding because they take the cellular interaction in the coagulation cascade into account. **Keywords:** cell-based hemostasis, cardiac surgery. *JECT. 2012;44:P13–P15*

Over the years, more patients with important comorbidities are scheduled for cardiac surgery. As a consequence, more patients present with a metabolic syndrome and a diseased endothelium. The latter will make patients more vulnerable for both thrombosis and bleeding peri- and postoperatively. Interventional cardiologists are also confronted with this type of patient, and extensive research has resulted in new drugs designed for inhibiting the coagulation cascade and platelet function. Although these drugs have improved patient outcome after percutaneous coronary intervention procedures (1), they pose surgical teams with new challenges during the operative (2) and immediate postoperative periods (3).

CELL-BASED COAGULATION

It is well known to surgical teams that classical tests for monitoring the extrinsic and intrinsic pathway such as plasma thromboplastin (PT) and activated partial thrombin time are poor predictors of blood loss postoperatively. This observation is explained by the concept of cell-based coagulation (4). In brief, this theory states that coagulation is more than a cascade of proteins but actually starts on

cells. Three separate phases exist: initiation, amplification, and propagation (5). Initiation starts on tissue factor-bearing cells such as monocytes and converts FX into FXa.

Amplification starts when the small amount of FXa produced by the combination of tissue factor and FVIIa leads to a limited amount of thrombin generation. This thrombin will then express FVa, FVIIIa, and FIXa at the platelet surface. In the propagation phase, the assembled enzyme complexes on the platelet surface lead to the production of sufficient thrombin to support additional platelet activation and finally lead to a thrombin burst.

The problem with PT and a partial thromboplastin time is that these tests are performed on plasma, thus excluding the impact of activated cells. Cardiopulmonary bypass (CPB) is well known to activate blood platelets and tissue factor-bearing cells. When these cells are activated, for example by cardiotomy suction, large amounts of additional thrombin can be produced (6–8).

Based on this, reliable information of the residual coagulation after cardiac surgery can only be obtained from whole blood tests. However, even with whole blood tests, several tests will be necessary. Viscoelastic tests such as thromboelastography are excellent for validation of the overall coagulation profile but are less performing in detecting the impact of platelet-inhibiting drugs. To evaluate the activity of such drugs (e.g., clopidogrel), whole blood platelet aggregation tests are now becoming common (9–12).

To preserve cellular and endothelial function, several measures can be taken. Immediately after contact with

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blood, the foreign material of the CPB will absorb platelet-activating proteins such as fibrinogen, von Willebrand factor, and fibronectin. Most of the activation will take place through the GPIIb/IIIa receptors of the platelet. Use of a hemocompatible surface coating will reduce the absorbance of these proteins and thus the number of activated platelets (13). For the same reason, patients, who are still on GPIIb/IIIa inhibitors at the time of the operation, show an attenuated inflammatory and prothrombotic reaction (14–16) at the expense of higher blood loss postoperatively. Avoiding retransfusion of blood that has been activated by contact with tissue in the mediastinal and pleural cavities is beneficial in controlling the circulating thrombin concentration (7,8).

Finally, one should try to define the optimal performance window for each component of the extracorporeal circuit. The latter is especially important for prolonged perfusion such as extracorporeal membrane oxygenation and a vascular access device. There is no doubt that the contact time between the blood and the foreign materials as well as the surface of that foreign material play an important role in bleeding and thrombosis (17–19). Development and change of material properties is a task for industry, but the choice of the appropriate components for a given patient can be addressed by the perfusionist.

CAN WE USE PARTS OF THE COAGULATION CASCADE TO OUR ADVANTAGE?

Platelets play an important role in the coagulation cascade and can be considered the first step in wound healing. Once activated, thrombin will be generated and growth factors are released, which creates an optimal environment for formation of a fibrin network and the start of the healing process. For this reason, platelet-rich plasma has been proposed for ameliorating wound healing in patients with disturbed healing such as diabetics. However, the technique has not been shown to be advantageous in the majority of cardiac operations (20,21).

Proteins form the matrix of a clot and are responsible for most of the tensile strength of the clot. Some commercial biological glues mimic this by crosslinking proteins with glutaraldehyde. This glue is very beneficial for vascular repair (22), but the glutaraldehyde is toxic (23) for the surrounding tissues (24,25). Another disadvantage of this type of glue is the fact that it only uses albumin as a protein source, and as a result, the crosslinked glue will be very rigid and this can cause serious problems (26). New research is developing the use of an autologous mixture of plasma proteins to obtain a biological glue with better mechanical characteristics and lower glutaraldehyde concentrations (27). Although autologous glutaraldehyde glue has been successfully used as a vascular adhesive and

is less toxic than heterologous glues in animal models (28), the quest for a nontoxic rapid crosslinker remains.

CONCLUSION

Thrombosis and especially bleeding remains an issue during and post cardiac surgery. The introduction of a new generation of platelet inhibiting drugs on one hand and the lack of antidotes for these drugs has made today's surgery even more complex. Attenuation of cellular activation during cardiac surgery will improve hemostasis postsurgery. More research is needed to understand coagulation issues during CPB, especially the interaction among blood flow, blood–material interaction, and inflammatory endothelium.

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