Effect of Different Types of Extracorporeal Circulation on Hemostasis Activation and Methods for its Monitoring

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ABSTRACT

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Extracorporeal circulation (ECC) is associated with complex activation of all components of hemostasis, the causes of which are multifactorial: surgical trauma, loss of vascular integrity, contact with non-endothelial surface, non-pulsatile flow, hypothermia, systemic inflammatory response, numerous drugs, and other. A key component of haemostasis activation is the excessive generation of tissue factor leading to the formation of thrombin to physiologically prevent bleeding. However, the imbalance of this reaction leads to both extremes - hypercoagulation and bleeding. Thrombin production (prothrombin fragments 1+2, thrombin-antithrombin complexes) and its activity (fibrinopeptide A) can be monitored by different methods. Hemostasis activation can be reduced by some methods: limitation of active suction, increase of biocompatibility of the coated circuits, reduction of priming volume, use of antifibrinolytics, and substitution of antithrombin (AT). Unfractionated heparin (UFH) is practically the only choice of systemic anticoagulation due to empirical experience and difficult real availability of direct thrombin inhibitors for i.v. administration (hirudin, lepirudin, argatroban).

However, even presence of high doses of heparin does not result in blockage of thrombin production. Thrombin is generated either by activation of the “internal system” in blood contact with an artificial non-endothelial surface of ECC, but much more by activation of the “external system” when the blood is drawn back from the field into ECC [1]. The first path can be reduced by the use of biocompatible surfaces of the ECC system and reduction of system surface, the second path only by alleviating or even completely eliminating blood back-suction previously activated after contact with air and surgically traumatized tissue. [1,2] The effort to minimize these effects has led to the development of the so-called minimally invasive extracorporeal circulation (MiECC) system which is characterized by a completely closed circuit (without contact of blood with air), absence of cardiotomy reservoir (for collection of drawn blood),
The test methodology maximally simulates an in vivo system where thrombin formation is induced by the addition of tissue factor with activation on the phospholipid surface replacing platelet glycoprotein IIb/IIIa formation of a stable clot. This situation is very complicated in terms of laboratory monitoring. The initial phase of the hemostatic process (initiation) begins with the release of TF from the injured endothelial surface. This produces an initial amount of thrombin, which in turn promotes platelet activation through protease-activated receptors (PAR) on the surface of platelets (amplification). This thrombin on the surface of platelets activates further generation (propagation) of thrombin which can promote the conversion of fibrinogen to fibrin, which (with the contribution of factor XIII) finally crosslinks platelets through its GPIb/IIIa formation of a stable clot.

From this the possibility of detection of the processes and the use of individual laboratory methods, which are designed to monitor the steady state, not to monitor dynamically changing conditions of coagulation in cardiac surgery, is very complicated by the interconnection of processes. The first option in this situation is to use global methods. Here it is possible to use viscoelastic methods that can after a certain modification - platelet mapping - provide a global view of hemostatic changes. The most widespread is the method of thromboelastography, which has recently been modified by an optical detection method that has contributed to reducing the robustness of the equipment and improving the reproducibility of results (rotational thromboelastography) [9,10]. Recently, the methodology has been modified to detect changes in platelet function (platelet mapping assay) [11]. Another option for global monitoring of coagulation activation is to monitor thrombin generation (thrombin generation test).
measurements in PRP, the potential of the entire blood coagulation system. This methodology provides us with very limited data on platelet function, since full blood provides very inconsistent results [12,13]. Finally, the impact of other factors that may make monitoring difficult, such as the effect of antiaggregation therapy or a systemic inflammatory response that may translate into a septic reaction, should be taken into account for monitoring of coagulation activation [14]. Platelet activation can be monitored by functional platelet assays. There are several methods from classical and most widely used aggregation methodologies, through flow cytometry to POCT tests using platelet binding capabilities.

Aggregometry methods are based on the possibility to detect platelet aggregation abilities after induction of platelet receptor agonists (optical aggregometry, impedance aggregometry) [15,16]. The use of these methodologies is, however, considerably limited by several effects that affect platelet function in cardiac surgical procedures, including the effects of individual types of extracorporeal circulation [9-11]. The monitoring of changes in the coagulation system by classical methods is of very limited significance, as many cardiac surgery factors significantly influence their outcome, especially the anticoagulant prophylaxis with heparin. In view of possible markers of coagulation activation, it is possible to monitor prothrombin fragments 1 and 2 [17,18] or F XII which is activated upon contact with foreign surfaces. However, the methodology, the limited availability and can’t be used in clinical practice [19]. Recently, new methodologies for flow cytometry have been developed to detect TF-bearing microparticles as basic inducers of coagulation reactions or experimental methodologies directly mimicking vascular activation.

However, these methodologies are only experimental and are not yet relevant for clinical use [20-23]. To monitor the effect of each type of extracorporeal circulation, monitoring of thrombin generation, as the initiator of all coagulation reactions, including platelet activation, remains a key point.

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