

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

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## ABSTRACT

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## Mini Review

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. It is very difficult to monitor changes in coagulation activation in the laboratory. Massive release of tissue factor in cardiac surgery leads to both initiation of a coagulation reaction system and activation of primary hemostasis, i.e. platelets. In this situation, the effect of extracorporeal circulation with a few non-endothelial surfaces that also contribute to activation is added.

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 cardiomy reservoir (for collection of drawn blood),

biocompatible surface, reduced priming volume, use of a centrifugal blood pump, and the air bubble capture and removal system and the integrated blood cardioplegia delivery system at the latest generations of MiECC. [1-3] The conventional ECC system now also has a biocompatible surface, more often using a roller pump and a cardiotomy reservoir where the blood level is in contact with the air.

Due to surface shrinkage, MiECC systems can be operated with lower heparin dose and lower ACT target values (300 vs 400s) when this procedure is not generally accepted. Significant is also the reduction of priming volume, which substantially contributes to the activation of hemostasis (according to inconsistent literature data, purely crystalloid priming leads to hypercoagulation, use of colloids to hypocoagulation). There is a variety of papers in the literature documenting a lower level of systemic inflammatory response syndrome (SIRS) and hemostasis activation when using MiECC to conventional ECC, unfortunately without clear clinical benefit, except for reducing the volume of administered transfusion products [4,5]. Thrombocytes are one of the most affected key components of haemostasis in ECC. A common finding after ECC, partly due to simple dilution, partly to blood loss, is thrombocytopenia but there is also a significant platelet activation that, in addition to its role in primary hemostasis, play a key role in the promotion and amplification of hemocoagulation, where a small amount of thrombin released from the endothelium leads to activation of platelets through the PAR receptor family and through another more excessive thrombin burst.

[6] This hypercoagulation trend is evident even longer after the end of ECC. Most of the work investigating the effect of ECC on hemostasis has so far described only quantitative changes in platelet counts or their function using aggregometry methods. One of the more recent ways to protect at least part of the platelet population during conventional ECC is to use a commonly used cell-saver blood preservation method. This technique has been used for a long time in complex procedures for post-surgery recovery of washed red blood cells after prior gentle aspiration, centrifugation and whole blood washing. Newer generations of cell-savers allow even more gentle centrifugation and sequestration of platelet-rich plasma (PRP) remaining after separation of erythrocytes to obtain platelets that are thought to retain structure and function for returning to the patient after termination of ECC [7,8]. The study of morphological integrity and function of these platelets is the subject of an ongoing study.

The technologies used in the ongoing study for the conventional CPB group include 2.5m<sup>2</sup> capillary oxygenator, a standard calculated flow rate of 2.4 l/m<sup>2</sup>/min, a centrifugal pump, and a biocompatible surface (X-coating using bound heparin) is 1,700 ml (including 500 ml of synthetic colloid and 100 ml of 20% mannitol). The MiECC group uses a 1.5m<sup>2</sup> system, priming volume 800 ml (crystalloid + mannitol) calculated flow rate of 2.0-2.2 L/m<sup>2</sup>/min, the same centrifugal pump and coating of the circuit. The dose of

unfractionated heparin is standard 3 mg/kg i.v. bolus + 1 mg/kg to the priming volume, target ACT >400s. In the case of complex procedures with the assumption of longer ECC times and higher losses, with sufficient blood volume and Hkt >0.35, post-operative blood sequestration with 800 ml of whole blood into CPD-A solution is used before heparin administration and subsequent processing in the cell saver according to the algorithm recommended by the manufacturer: filling flow 100 ml/min with manual reduction to 70 ml/min after filling, PRP spill flow 20 ml/min.

Washed erythrocytes and recovered PRP are returned to the patient after termination of ECC and protamine/heparin binding. It is very difficult to monitor changes in coagulation activation in the laboratory based on the changes described above. Massive release of tissue factor in cardiac surgery leads to both initiation of a coagulation reaction system and activation of primary hemostasis, i.e. platelets. In this situation, the effect of extracorporeal circulation with several non-endothelial surfaces that also contribute to activation is added.

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 GPIIb/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).

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 function. These methodologies provide us with information about the potential of the plasma coagulation system and, in the case of

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 using 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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