Review Article

Inflammation and coagulation following minimally invasive extracorporeal circulation technologies

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Abstract: Minimally invasive extracorporeal perfusion technologies are based on the use of a minimally invasive extracorporeal circulation (MiECC) system. This includes a closed CPB circuit; biologically inert blood contact surfaces; reduced priming volume; a centrifugal pump; a membrane oxygenator; a heat exchanger; a cardioplegia system; a venous bubble trap/venous air removing device; and a shed blood management system. Some of these items, alone or in combination, are able to modify the blood activation usually elicited by cardiopulmonary bypass (CPB). The hemostatic system activation is less activated and lower degrees of thrombin generation and platelet activation have been found in numerous studies. Additionally, the reduced level of hemodilution plays an important role in preserving clot firmness after CPB with MiECC. These biochemical changes are reflected by a blood loss containment, a reduced need for allogeneic blood transfusions, and, in some studies, by a lower thromboembolic complications rate. The activation of the inflammatory cascade is in turn limited by MiECC, both directly (through a blunting of the contact-phase activation) and indirectly (through a limited thrombin generation, platelet activation, and consequent lower release of pro-inflammatory cytokines). The clinical consequences of this are mainly demonstrated by a lower rate of postoperative atrial fibrillation; other inflammation-derived outcomes appear favorably affected by MiECC (lung function, acute kidney injury) but the multi-factorial nature of these complications makes difficult to clearly attribute this pattern to a lower degree of inflammation. Overall, the existing body of evidence is in favor of MiECC with respect to standard CPB.

Keywords: Inflammation; hemostatic system; cardiopulmonary bypass (CPB); minimally invasive extracorporeal circulation (MiECC)

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Introduction

Minimally invasive extracorporeal circulation technologies (MiECT) include a number of interventions aimed to reduce the clinical impact of cardiopulmonary bypass (CPB) and to consequently contain postoperative morbidity and mortality. In the past, different kind of CPB circuits were defined as "minimally invasive CPB", creating a confused scenario. Recently, the definition of a minimally invasive extracorporeal circulation (MiECC) system was standardized (1). A MiECC system must include: (I) a closed CPB circuit; (II) biologically inert blood contact surfaces; (III) reduced priming volume; (IV) a centrifugal pump; (V) a membrane oxygenator; (VI) a heat exchanger; (VII) a cardioplegia system; (VIII) a venous bubble trap/venous air removing device; and (IX) a shed blood management system.

Some of these items, and namely closed, biocompatible circuits with shed blood management have a recognized impact on the inflammatory reaction to CPB and on the

hemostatic system activation during cardiac operations. The present review analyzes the mechanisms underlying the effects of MiECT on inflammation, coagulation, and the related clinical outcomes.

Hemostatic system activation during standard CPB and MiECC

Thrombin generation

Despite heparin, thrombin is extensively formed during CPB (2). Thrombin is generated via the intrinsic (contact phase activation) and extrinsic [tissue factor (TF)] pathways; the first is triggered by contact with foreign materials of CPB (material-dependent blood activation) and the second by TF released by the surgical damage to tissues (material-independent blood activation). However, the material-dependent activation is responsible for minor degrees of thrombin generation (3), whereas the material-independent activation is a powerful source of thrombin generation (4).

Two of the main characteristics of a MiECC may impact on thrombin generation during CPB. The first is the presence of a biocompatible coating and reduced foreign surface: biocompatible circuits limit the material-dependent thrombin generation (5). The second (and probably most important) is the closed nature of the MiECC circuit with shed-blood management system, which impacts on the material-independent thrombin generation. TF is extensively released during surgery: both soluble and cell-bound TF concentrations increase during cardiac surgery, especially being expressed by the epicardium, endocardium, adventitia, and sternal bone (2,6).

TF accumulated in the pericardial space is suctioned and re-admitted to the systemic circulation in open CPB circuits. MiECC circuits do not allow re-infusion of shed blood without a previous washing process with cell-savers, and therefore limit thrombin generation via the extrinsic pathway. Previous studies have demonstrated that closed circuits with separation of surgical field suction or elimination of cardiotomy suction induce a significant reduction in thrombin generation markers (4,7,8).

Limiting thrombin generation during CPB is not only beneficial in terms of a reduced blood activation, but even in terms of coagulation factors preservation. A continuously activated thrombin generation creates an alteration in the hemostatic balance after heparin antagonization with protamine: on one side, there are large amounts of thrombin which may trigger clot formation and thrombotic complications; on the other, coagulation factors are reduced in concentration and may be responsible for postoperative bleeding (*Figure 1*).

Not surprisingly, different studies addressed the impact of MiECC on markers of the hemostatic system activation and point-of-care coagulation tests. Rahe-Meyer (9) compared a MiECC with a standard CPB circuit testing the whole blood coagulation with thromboelastometry, but he could not find any significant difference during and after CPB. Conversely, Zeitani and associates (10) found shorter coagulation times at thromboelastography in MiECC-treated patients, and reduced levels of prothrombin fragment 1.2 (a thrombin generation marker). This reduction in thrombin generation was recently confirmed by Paparella and associates (11), together with a limitation of fibrinolysis assessed by reduced levels of plasmin-antiplasmin complexes. Anastasiadis and associates (12) found shorter prothrombin time and activated partial thromboplastin time in MiECC-treated patients, which may be linked to a reduced factors consumption.

Overall, there is a concordant scientific information on the beneficial properties of MiECC in reducing thrombin generation, fibrin generation, fibrinolysis.

Platelet activation

The reaction of platelets to CPB is complex and multifactorial. Platelets represent a complex structure which is able to react to a number of stimuli, to interact with the endothelium and sub-endothelial space (adhesion); to interact each other through fibrin links (aggregation); to bind heparin and heparinoids; and finally to release a number of active mediators.

Within the context of the "dynamic" interpretation of the hemostatic process, platelets play a pivotal role not only as fundamental components of the final clot, but even in the process of thrombin generation (13). The early phase of the hemostatic process (initiation) starts with TF release from an injured endothelial surface. This produces a limited amount of thrombin, which in turn promotes platelet activation through the protease-activated receptors (PAR) on the platelet surface (amplification). This thrombin mediated platelet activation generates, on the platelet's surface, a burst of thrombin generation (propagation) that is able to promote the conversion of fibrinogen into fibrin, which (with the contribution of factor XIII) cross-links platelets through their receptor GPIIb/IIIa finally generating a stable clot.

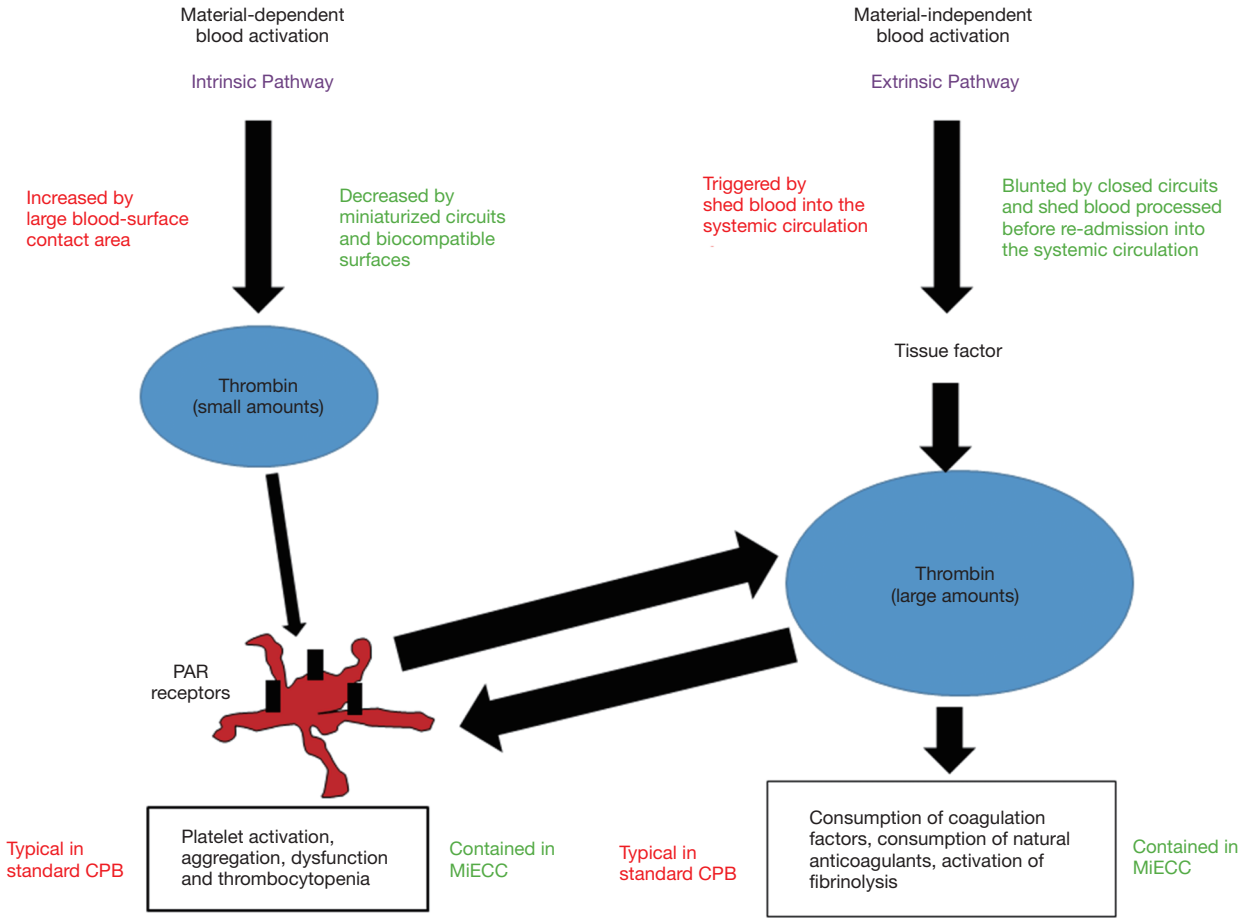

Figure 1 Activation of coagulation pathways during cardiopulmonary bypass. CPB, cardiopulmonary bypass; MiECC, minimally invasive extracorporeal circulation; PAR, protein activated receptors.

This dynamic context may be easily disrupted in presence of large amounts of TF. The model of standard CPB, with large amounts of shed blood re-admitted to the systemic circulation without washing out TF and other active mediators is a typical model of artificial alteration of the dynamic hemostatic balance; however, other models are present in nature. Activated monocytes produce TF (blood-borne TF) during sepsis and inflammation, leading again to thrombin generation and platelet activation.

As already pointed out, the model of MiECC is linked to a relatively low thrombin generation, and therefore platelet activation should be better contained. There is a limited amount of studies on platelet count and activation in MiECC. In 2002, Fromes and associates (14) demonstrated that patients treated with MiECC showed a better preservation of platelet count than patients treated with standard CPB. Platelet activation (assessed by beta-thromboglobulin levels) showed slightly lower platelet activation in the MiECC group at all times of CPB. von Willebrand factor activity was reduced in MiECC with respect to standard CPB in a study from Wippermann and associates (15). A study based on multiple electrode aggregometry (9) found a better preservation of platelet function during and after CPB in MiECC-treated patients., and better-preserved platelet counts were identified by Anastasiadis and associates (12).

The effects of standard and reduced heparin anti-coagulation

The evidence of a reduced thrombin generation during MiECC introduces the possibility to modify the standard anticoagulation protocol. Actually, heparin is used during CPB to neutralize the pro-coagulant effects of thrombin, by

enhancing the natural binding of antithrombin to thrombin. This effect is generally achieved with an unfractionated heparin (UFH) loading dose of 300–400 IU/kg, followed by additional bolus doses to reach and maintain an activated clotting time (ACT) >450–480 seconds. Theoretically, in presence of a low thrombin generation, lower doses of UFH and a shorter ACT may be sufficient to avoid thrombosis of the CPB circuit. This approach was followed by different authors many years before the MiECC concept was defined and applied in many institutions. In the 1990s, Ovrum and associates conducted studies on reduced heparinization (UFH loading dose 100 IU/kg and target ACT >250 seconds) using heparin-bonded circuits demonstrating the feasibility of this technique (16,17). However, tip-to-tip heparin bonding was the only change that they applied to a conventional CPB, and shed blood was freely re-admitted to the systemic circulation. Conversely, the group of Aldea (18) excluded the cardiotomy suction from the circuit, creating a model which could be considered the ancestor of modern MiECC. Within this model, systemic heparinization was again reduced, resulting in fewer complications and namely less thromboembolic events.

Lately, our group demonstrated that this approach results in a preservation of the circulating antithrombin levels (19), and subsequently proposed a closed system with separation of shed blood, a collapsible venous reservoir, a biocompatible treatment (phosphorylcholine coating), a centrifugal pump and reduced systemic heparinization (UFH loading dose 150 IU/kg and target ACT >300 seconds) (20).

Even in recent years, feasibility of reduced systemic heparinization with target ACT of 250–300 seconds was confirmed in the context of MiECC (21). However, the real effects of this strategy in improving the clinical outcome remain to be established.

Hemodilution and coagulation

One of the pillars of MiECC is the reduction of pump prime volume. This results in a reduced hemodilution during and after CPB. The hemostatic system is certainly affected by the quantity and quality of hemodiluting fluids. Many studies addressed the impact of hemodilution on viscoelastic tests. In an interesting study on cardiac surgery patients, Martin and associates (22) could demonstrate that hemodilution with Ringer's solution was leading to a hypercoagulable state represented by a shortening of the reaction times, whereas hemodilution with 6% hetastarch and normal saline was leading to a hypocoagulable conditions represented by a decreased clot firmness. Other authors confirmed that there is a hemodilution-related hypercoagulation related to a shortening of the reaction times in thromboelastometry and thromboelastography (23,24). Conversely, hemodilution seems to decrease the clot firmness in other studies.

In contrast with this concept, other authors found a general behaviour of hypocoagulation in patients undergoing hemodilution. A meta-analysis from Hartog and associates (25) focused on hydroxyethyl starch dilution could demonstrate a general decrease in clot firmness and variable effects on clotting times. Recently, we could demonstrate in a large series of about 800 cardiac surgery patients that severe hemodilution on CPB induces a significant prolongation of clotting times and reduction of clot firmness (26). Hemodilution decreases platelet marginalization at the endothelial wall surface, reducing the primary hemostatic effect of platelet adhesion.

Overall, it is likely that MiECC-related containment of hemodilution may result in a better control of the pro-hemorrhagic effects of CPB.

Inflammatory reaction during standard CPB and MiECC

The evidence that CPB is responsible for a whole-body inflammatory reaction dates back to the 1970s. In more recent years, a number of technical improvements have been applied to CPB circuits, aimed to blunt the inflammatory reaction. However, even if certainly reduced in terms of clinical outcomes, the pattern of a systemic inflammatory reaction syndrome (SIRS) still remains evident in cardiac surgery patients. CPB is not the sole responsible for SIRS, since patterns of SIRS have been demonstrated even in off-pump coronary surgery; however, much of the pathway leading to SIRS recognize a direct (blood-foreign surface contact activation) or indirect (link between hemostatic system activation and inflammation) link to CPB.

Contact of blood with the foreign surface of CPB circuit and oxygenator triggers activation of factor XII into factors XIIa (which initiates the intrinsic pathway of coagulation) and XIIf (27).

It is factor XIIf which triggers complement activation through the classical pathway, leading to terminal complement complex (TCC) formation, which in turn is responsible for cell membrane attack, lysis, and cellular death (27).

Table 1 Main studies addressing inflammatory markers in minimally invasive extracorporeal circulation *vs.* standard CPB

Author, journal, date	Study type	Main results
Fromes *et al.*, *Eur J Cardiothorac Surg*, 2002 (14)	RCT	MiECC limited the drop in mononuclear phagocytes, neutrophil elastase release, TNF-α, IL-6. No differences in IL-1 release
Abdel-Rahman *et al.*, *Ann Thorac Surg*, 2005 (33)	RCT	MiECC limited the release of neutrophil elastase and terminal complement complex
Remadi *et al.*, *Am Heart J*, 2006 (34)	RCT	Lower levels of C-reactive protein in MiECC group
Immer *et al.*, *Ann Thorac Surg*, 2007 (35)	Cohort study	MiECC limited the release of IL-6 and TCC
Ohata *et al.*, *J Artif Organs*, 2007 (36)	RCT	MiECC limited the release of neutrophil elastase and IL-8
Huybregts *et al.*, *Ann Thorac Surg*, 2007 (37)	RCT	MiECC associated with reduced leukocytosis and urinary IL-6
Gunaydin *et al.*, *Perfusion*, 2009 (38)	RCT	MiECC associated with lower levels of IL-6 and C3a
Mazzei *et al.*, *Circulation*, 2007 (39)	RCT	No differences in levels of IL-6 in MiECC *vs.* in OPCAB
Formica *et al.*, *ASAIO J*, 2013 (40)	RCT	No differences in inflammatory patterns of endothelial activation between MiECC and OPCAB
Strarinieri *et al.*, *Perfusion*, 2017 (41)	Retrospective	No differences in C-reactive protein between MiECC and CPB
Gygax *et al.*, *Artif Organs*, 2018 (42)	RCT	MiECC resulted in lower levels of TCC, no differences in TNF-α, Higher levels of IL-6
Kiessling *et al.*, *Heart Surg Forum*, 2018 (43)	RCT	No differences in pro-inflammatory cytokines between MiECC and open/closed CPB

C3a, complement fraction a; CPB, cardiopulmonary bypass; IL, interleukin; MiECC, minimally invasive extracorporeal circulation; OPCAB, off-pump coronary artery bypass; RCT, randomized controlled trial; TCC, terminal complement complex; TNF, tumor necrosis factor.

Factor XIIa cleaves prekallikrein to kallikrein, which in turns trigger bradykinin formation from high molecular weight kininogen, leading to vasodilation and increased cell membrane permeability (28). Kallikrein elicits plasmin generation, and plasmin in combination with factor XIIa activates the alternative complement activation pathway, generating the complement fraction C3a and C5a which induce a pro-inflammatory reaction of neutrophils, macrophages, and monocytes (29).

Aside of the contact-phase activation, there is another important source of SIRS during CPB. As already stressed, during standard CPB thrombin is extensively formed, and thrombin activates platelet through their thrombin receptors of the PAR family. Platelets react to this activation by inducing further thrombin generation, and by releasing the pro-inflammatory cytokines interleukin (IL)-6 and IL-8, powerful neutrophil activators.

Considering the above-mentioned mechanisms underlying the CPB-induced SIRS, it can be certainly be hypothesized that MiECC may theoretically at least partially blunt or limit the inflammatory reaction.

The reduced blood-foreign surfaces interface represented by miniaturized circuit could limit the contact-phase activation. To this respect, an even larger role is played by the standard biocompatible coating that is a pre-requisite of a MiECC system. Heparin-bonded surfaces are associated with a containment of the inflammatory reaction to CPB (30-32). Finally, the recognized thrombin generation limiting effect of shed blood separation could reduce the important role of thrombin in triggering the inflammatory reaction.

There are in fact numerous studies demonstrating that MiECC is accompanied by a reduced activation of the inflammatory cascade (*Table 1*). Fromes and associates (14), in 2002, found that by the end of CPB the levels of IL-6 were significantly lower in the MiECC group than in standard CPB, that the levels of tumor necrosis factor-alpha rised more in the standard CPB group, and that neutrophil elastase release was lower in the MiECC group. Immer and associates (35) showed that MiECC limits the release of IL-6 and TCC. Abdel-Rahman and associates (33) confirmed lower values of neutrophil elastase release and

TCC in MiECC patients *vs.* standard CPB, and Remadi and associates (34) found lower levels of C-reactive protein after 24 and 48 hours from surgery in MiECC patients *vs.* conventional CPB.

Other studies found similar results in favor of MiECC *vs.* standard CPB (36-38). An important randomized controlled study from Mazzei and associates (39) demonstrated that the release of IL-6 in MiECC patients was similar to what measured in off-pump coronary revascularization. The finding that MiECC is comparable to off-pump cardiac surgery in terms of inflammatory reaction was more recently confirmed by Formica and associates (40).

Overall, the majority of the clinical studies confirm the hypothesis that MiECC induces less inflammatory activation than standard CPB, even if different results were observed in other studies (41-43).

The impact of MiECC on coagulation and inflammation-related clinical outcomes

The existing body of scientific literature seems in agreement with the concept that MiECC is associated with a reduced hemostatic system and inflammatory cascade activation. However, from the clinical point of view, a containment in the release of various coagulation and inflammation markers is not "*per se*" a guarantee of a better outcome. For this reason, different studies investigated coagulation and inflammation-related outcomes, with or without concomitant measure of biochemical markers.

Outcomes associated with the hemostatic system activation may be summarized into four items: perioperative blood loss; need for surgical re-exploration; allogeneic blood products transfusions; and thromboembolic complications.

A lower degree of blood loss (intraoperatively or chest drain postoperatively) was found by Remadi and associates (34) and Gerritsen and associates (44), but this result was not confirmed by Abdel-Rahman and associates, who did not observe any difference in surgical re-exploration rate (33). Conversely, there is a general agreement on a lower rate of allogeneic blood products transfusions in MiECC *vs.* standard CPB (34,44-46). Thromboembolic complications, and namely stroke and neurologic damage, were found at a lower degree in MiECC patients in two meta-analyses (47,48).

More difficult is the definition of inflammation-related outcomes. Atrial fibrillation is certainly (even if partially) linked to the release of inflammatory markers, and different studies (12,45,49) and meta-analyses (47,48) showed a lower rate of atrial fibrillation in MiECC-treated patients.

Lung function after CPB is another potential inflammatory-related outcome. To this respect, results in the literature are more conflicting. Yilmaz and associates did not find any difference in pulmonary complications between MiECC and conventional CPB (50), whereas Kolat and associates found a lower rate of respiratory insufficiency in MiECC-treated patients (51), and a better postoperative oxygenation was detected by van Boven and associates (46). In general, mechanical ventilation time is shorter in MiECC patients, but this outcome measure reflects many other non-inflammatory related factors.

Other potential outcomes related to the release of inflammatory markers include acute kidney injury and visceral organs complications. However, the multi-factorial nature of these outcomes does not allow to clearly attribute the benefits reported by some authors to the containment of the inflammatory reaction exerted by MiECC.

Conclusions

The evidence that MiECC exerts a beneficial effect in terms of both the hemostatic system activation and the inflammatory cascade is sound. A lower thrombin generation is probably the main factor leading to this pattern, since thrombin is the main hinge between coagulation and inflammation. This is certainly reflected by a better outcome in terms of blood loss and transfusion needs. Less evident, given the multifactorial nature of many inflammation-related complications, is the translation of the limited activation of the inflammatory cascade into a better clinical outcome.

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Footnote

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