Expert Consensus

VV extracorporeal life support for the Third Millennium: will we need anticoagulation?

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Introduction

The circulation of blood outside of the body was first entertained as far back as 1693 when Jean Baptiste Denis performed experiments cross-transfusing the blood of a human with "the gentle humours of a lamb" in an attempt to cure an illness in a nobleman. By 1953, John Gibbon and his wife Mary through their development of the first cardiopulmonary bypass (CPB) machine the circulation and oxygenation of blood outside the body was realized when a young lady underwent the repair of an atrial septal defect (ASD) (1). The inadvertent discovery of heparin in 1916 by Jay McLean (2) along with the characterization of coagulation and the cascade [defined by mid 1960s by the International Committee on Thrombosis and Haemostasis (ICHT) (3)] led to the ability to anticoagulate during this surgery and became the starting point to where we have evolved today in the management of patients on extracorporeal life support (ECLS).

What remains the challenge in present day is the blood biomaterial interaction and this is a barrier, which requires the use of systemic anticoagulation with or without circuit surface modifications to prevent thrombus formation within the circuitry. Unfractionated heparin (UNFH) remains the gold standard for ECLS although newer agents such as direct thrombin inhibitors (DTI) are now being considered by some as a first line option (4) and definitely in certain circumstances when UNFH cannot be used for ECLS. Technology and surface modifications continue to evolve to miniaturize ECLS devices making them more portable and biocompatible. There is no doubt in the third millennium that VV ECLS will no longer require anticoagulation and can therefore be used to support all patients who require it regardless of their acuity and risk for hemorrhage.

Present antithrombogenic measures used during ECLS

The use of ECLS is not without its challenges and complications, of which the most common are those related to hemostasis and thrombosis. The scope of this paper will focus primarily upon a brief review of present day thromboprophylaxis with a more detailed overview of where the technology should evolve to obviate the need for systemic anticoagulation during ECLS.

There is need to constantly balance the risks of bleeding against the risks of thrombosis both in the circuit and the patient; the patient's anticoagulation must be customized for their specific pathophysiology (5). Immediately upon exposure of the patient's blood to artificial non endothelial surfaces an inflammatory response is initiated which involves a multitude of cellular and humoral protein-driven cascades (5,6). Protein adsorption drives activation of the coagulation cascade, platelet adherence and thrombus formation. Moreover, this exposure drives stimulation of the various arms of the inflammatory apparatus including complement activation, cytokine release and production, and the recruitment of a variety of leukocytes. The activities of these, with multiple feedback loops, create a hypercoagulable state and drive the need to use systemic anticoagulation.

Systemic anticoagulation in current use

Historically the anticoagulant of choice has been UNFH.

Discovered in 1916 and in clinical use since 1937, UNFH is by far the most widely used agent for systemic anticoagulation (7). In addition there is a vast and ever expanding amount of literature describing its use, its monitoring, and its effects during ECLS. For the scope and purpose of this review the details of UNFH action and monitoring will not be covered with any detail but suffice it to say that its effect is indirect, it is reliant upon the adequate presence of antithrombin, and only about 1/3 of the dose given can actually bind to antithrombin to increase antithrombin activity. The main advantages of UNFH are related to its short half-life and potential reversibility by protamine sulfate. However, it is not without complications and disadvantages ranging from unpredictable dose-response relationships, difficulty in reliable monitoring of therapeutic targets due to influence of pathophysiology, resistance to therapy (at times due to relative or absolute antithrombin deficiency) to heparin-induced thrombocytopenia (HIT) (8). Even though true HIT is probably a relatively rare event, it carries the potential for catastrophic complications.

In recent years there has been a growing volume of literature describing the use of DTIs in the context of ECLS. Recently, several excellent reviews detailing the cumulative experience in their use in this context with specific recommendation have been published (5,9,10). In general, DTI are not dependent on antithrombin for their effect but work by direct inhibition of both circulating and clot-bound thrombin—exposing the two major advantages over heparin. Moreover, their selective binding to thrombin makes their pharmacodynamics more predictable. On the downside they do not have a specific reversal agent, even though at least for bivalirudin the use of activated factor VII has been proposed as a possibility (11) and the cumulative experience with their use in this context is still sparse. Most of the literature on DTI use in ECLS relates to two commercially available products: Bivalirudin and Argatroban. Of note, in a recent survey of ECLS centers, while most responders did not use any anticoagulation other than UNFH in the months prior to answering the survey, over 50% of the responders answered that they do or can use DTI if indicated. Classic indications often reported included HIT, heparin resistance not responsive to antithrombin or FFP administration, and development of thrombosis while on heparin therapy.

Bivalirudin is a 20–amino acid synthetic polypeptide analog of hirudin, which binds to the active site of thrombin. It has a half-life of approximately 25 minutes and undergoes mostly proteolytic degradation, leaving metabolism almost independent of the liver and kidney [~20% renal elimination (12,13)], even though infusion doses should be adjusted according to renal function (4). Moreover, due to this proteolytic metabolism, in patients with cardiac standstill or in areas of stasis, anticoagulation eventually resolves and can result in thrombus formation which can lead to catastrophic results and therefore such patients might benefit from another form of anticoagulation (14,15). There have been no prospective studies examining the use of bivalirudin in patients undergoing ECLS but in the past several years two retrospective case series have been published. Ranucci *et al.* (4) reviewed 21 patients (9 children) on ECLS after cardiac operations and reported significantly more bleeding transfusion requirement in the heparin group while another retrospective study (16) reported no significant differences between bleeding or thrombosis. Both groups concluded that DTIs are a potential alternative to heparin in patients on ECLS, with one of the groups reporting a switch from heparin to bivalirudin as the first choice for anticoagulation in patients post cardiotomy. Specifically in children a retrospective case-series reporting on 12 patients was published by Nagle *et al.* (17) showing that bivalirudin can be safely used in neonates and children with maintenance dose ranges reflecting considerable inter-patient variability.

Argatroban the other common DTI, is an l-arginine derivative with a half-life similar to bivalirudin at 15 minutes; it undergoes hepatic metabolism which might represent a possible obstacle as many of the patients treated with ACLS have hepatic functional impairment. Monitoring and therapeutic targets are similar to bivalirudin as published in the ELSO anticoagulation guidelines. Its use for ECLS has been published in case reports and series for adult and pediatric patients with suspected or diagnosed HIT (18-24).

Surface modifications in current use

Current surface modifications available in clinical practice for intravascular and extracorporeal application can be divided into two major groups: biomimetic (heparin) and bio passive [phosphorylcholine (PPC), albumin and poly-2-methoxyethylacrylate (PMEA)]. Current commercially available circuitry is often a combination of both biometric capability and bio passive effect (see *Table 1*) (25-27).

Biomimetic surfaces

The vast majority of available data on surface-modified

Table 1 Some clinical surface modifications in present use

Surface modification category	Specific modification surface treatment
Passivation	Albumin/heparin multilayer
Biomimetic Functionalization	Polypeptide/heparin coating
	End-point immobilized heparin
	Covalently Coupled Heparin with Polyethylene Oxide and Sulfonate Groups

circuits and membranes comes from the CPB literature. In this context, the advent of heparin-bound circuits (HBC) has been first described by Gott *et al.* in 1963 (28). HBC have been studied extensively and have been shown to improve the biocompatibility (29-33) and perhaps the clinical outcomes (29,32,34) of extracorporeal circuits. A meta-analysis by Mangoush *et al.* further concluded that HBC reduce the incidence of post-operative blood transfusions, resternotomy rates, duration of ventilation, and ICU and hospital length of stay (35). A later meta-analysis, with different methodology, reconfirmed only the effect on ICU length of stay and demonstrated a reduction in atrial fibrillation events (36).

In line with the accruing evidence of HBC benefits, a recent survey has found that HBC use is on the rise (37) and in fact Bembea *et al.* demonstrated that over 50% of 117 ELSO (Extracorporeal Life Support Organization) centers used partial or complete HBCs. Additional studies further tested the possibility of reducing the heparinization during short CPB support using HBC with conflicting results (38,39). The main concerns regarding the use of HBC are related to the lack of effect on surface interaction and resultant worsening of thrombocytopenia (6,40). The effect of HBC on the induction of HIT is more controversial (41-43), although newer coating techniques using covalent bonding claim to obviate the leaching of heparin from the surface modification (42). Despite the binding of heparin to circuitry, the use of these circuits usually still requires some form of systemic anticoagulation so the concern of heparin leaching is only relevant when DTI is used in the presence of HIT.

Biopassive surfaces

PPC coating has been shown to be thromboresistant (44-48) and might even be noninferior to HBC in pediatric patients (49). It can also be utilized in cases of HIT where exclusion of all potential sources of heparin is needed. Furthermore, two studies by Ranucci *et al.* have shown that the use of PPC coating can allow a safe reduction in systemic heparinization during intraoperative ECLS (50,51). However, a prospective study on the combination of PPC and heparin coating has failed to demonstrate a significant clinical effect (52).

PMEA has also been shown to be biocompatible and might reduce the need for procedural platelet infusions in comparison to HBC (53). However, Itoh *et al.*have found increased incidence of post-procedural leukopenia and possibly systemic inflammatory response syndrome (SIRS) in a small prospective trial comparing HBCs to PMEA (54).

It is important to note that studies on the biocompatibility of coated circuits during ECLS are scarce. The current hypothesis on ECLS thrombogenicity states that thrombosis mechanisms during ECLS differ from those during CPB in several ways (36,42): ECLS is a closed circuit, thus activation of coagulation is related only to the blood/biomaterial interactions unlike CPB where other non-material interactions occur such as blood/air interface, hemolysis, cardiotomy suction; ECLS tends to cause more bleeding than thrombosis and its thrombogenicity can sometimes be related to the underlying condition of the patient and the support of ECLS is continued for many days/weeks with long-term exposure to the systems elements. As such, extrapolation of results from the current studies on CPB to ECLS might not be accurate. Moreover, the use of coated circuits might have an additional effect on drug adsorption during ECLS (55), although studies on the subject are scant. The final issue to consider is the extent of coating needed for circuits and whether coating the oxygenator and if present, the arterial filters are sufficient (56).

Future surface modifications to obviate systemic anticoagulation

In order to succeed with no systemic anticoagulation during ECLS the surface necessary to conquer/calm the blood/biomaterial interaction must be endothelial-

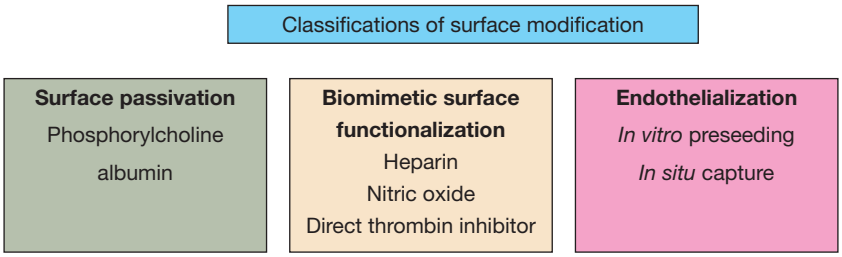

Figure 1 Surface Modifications can be classified into three groups of development: surface passivation, biomimetic surface functionalization, and endothelialization of the blood contacting surfaces.

like. During ECLS plasma proteins readily adsorb to the artificial surface influencing the cellular elements of the blood. More specifically it is known that fibrinogen adsorbs readily to ECLS circuits, changing its conformation thus creating a strong affinity for platelet adhesion. The end result is platelet adhesion/activation ultimately initiating coagulation. Fibrinogen is not the sole protein adsorbed obviously other epitopes which activate leucocytes also adsorb and the entire adsorption process results in the body's response to a "foreign" surface. The endothelium is the master controller of hemostatic balance within the body. It releases both pro and anticoagulants along with anti-inflammatory agents in response to feedback loops and chemotactics. It therefore makes sense to mimic surface modifications along this path. The most recent reviews of hemocompatibility strategies in the modification of artificial surfaces range from 1993 to 2011 (57-62). There is no doubt many groups continue to research in this arena and surface modifications essentially fall within three classifications of development: surface passivation, biomimetic surface functionalization, and endothelialization of the blood contacting surfaces (*Figure 1*). As described above biopassive surface modifications and biomimetic surface modifications are already in clinical practice. For the purposes of this section the focus will be on new biomimetic strategies for surface modification as well as the challenges of endothelialization of artificial surfaces

Future biomimetic surface modifications

Presently all focus on anticoagulation during ECLS is related to thrombin inhibition and manipulation of the coagulation cascade. Despite this platelet consumption continues and thrombotic events are not completely eradicated. If the focus was to be redirected to platelet inhibition however, then understanding the endothelium's role in active platelet inhibition by the local release of nitric oxide (NO) is imperative. NO has a near complete yet fully reversible and short-lived effect on platelets. This effect is fully reversible within milliseconds once the platelet is no longer exposed to the NO and the platelet's function is preserved in its entirety (63). Prevention of platelet activation during passage through the extracorporeal circuit is the basis upon which NO donors such as *N*-diazeniumdiolates have been developed. These materials are designed to be incorporated into the backbone of the polymer by either blending them into the matrix or by modifying their polymer structure to incorporate the NO within it (64-70). This prevents the leaching of the materials from the surface yet upon contact with water vapor there is local release of the NO. This local release only affects platelets directly in contact with the artificial surface while the rest remain unaffected. Thus normal hemostatic response is maintained with no systemic effects. These surface modified circuits are able to reduce platelet consumption, preserve platelet activity and reduce thrombus formation with the extracorporeal circuit in experimental models of extracorporeal circulation (71). With the ability to control NO release by chemical manipulation of the pH environment, they also have longevity despite a finite reservoir of NO within the circuit. With further study of NO releasing surfaces, it has become evident that these surfaces have an affinity for fibrinogen adsorption and thus although platelet function and number are well preserved, fibrinogen consumption occurs. Most recently Yu *et al.* have demonstrated the ability to incorporate argatroban within the circuit (72). In combination with NO releasing modification this surface is ideal for ECLS as it preserves normal hemostasis within the patient but provides local thromboprophylaxis within the circuit). Drawbacks are as with many new bioactive modifications, they cannot undergo regular tubing manufacturing as their bioactivity is

Table 2 Characteristics of ideal extracorporeal surface modification

Characteristics	Heparin bonded	PPC	No releasing	No generating	Combination NO and DTI	EDC
Cover entire circuit	✓	?	×	✓	±	✓
Longevity	✓	✓	✓	✓	✓	?
No systemic anticoagulation	×	×	✓	✓	✓	✓
Normal manufacture	✓	✓	×	×	×	×
Prevent thrombosis	×	×	✓	✓	✓	✓
Preserve platelet function	×	×	✓	✓	✓	✓
Reduce inflammation	±	±	✓	✓	✓	✓

?, unknown; ±, in some instances/partially; √, yes; ×, no. PPC, phosphorylcholine; EDC, endothelialization; DTI, direct thrombin inhibitor; NO, nitric oxide.

destroyed by heat thus different methods for extrusion and sterilization must be developed.

An alternative NO biomimetic surface that does not decompose with heat exposure but also can provide a local thromboprophylactic effect is one in which catalysts are impregnated into the surface to generate NO from endogenous sources, such as *S*-nitrosothiols (RSNOs) through reduction/oxidation reactions causing decomposition of the RSNO and NO surface release. RSNOs circulate within the blood in picomolar to nanomolar amounts (73,74). This modification eliminates the need for the finite source of NO. By incorporation of certain metal ions such as copper directly into the polymer systems, NO-releasing decomposition of the RSNOs occurs locally and continuously to prevent platelet adhesion and activation. Unfortunately there is risk for leaching of the copper with this approach and the local release is only effective as long as the endogenous source of RSNO is replete (75). More recently the approach to this has evolved to use metal-organic frameworks (MOFs). In short these are metal ions that combine with organic ligands to form multidimensional shapes. Their physical characteristics are enticing for drug-delivery systems (76-81) and specifically copper-based MOFs have demonstrated the capability to be incorporated into the polymer material without leaching and provide excellent NO generation for local antiplatelet effect. This surface modification with MOFs is safe, extrudable, sterilizable, and active even after exposure to blood making them a very desirable option for ECLS circuitry (82).

Future endothelialized surface modifications

As discussed above the most effective surface to obviate systemic anticoagulation and retain normal hemostatic function within the patient is endothelium. Work related to endothelialization of artificial surfaces has been ongoing for decades. First attempts to preseed surfaces were carried out in the early 1980s. This was initially considered for vascular grafts and cardiac assist devices but with improving techniques can now be considered for lung assist devices and therefore perhaps prolonged ECLS as well. The complexity of endothelialization is beyond the scope of this review however touching upon the basic benefits and challenges of creating such a surface modification are important to understand. The goal of endothelializing ECLS circuitry is to recreate the endothelium. This provides a quiescent durable monolayer of functional endothelial cells to carry out all the complex hemostatic and anti-inflammatory functions of the endothelium (83). The challenge is how to achieve this coating of the circuit. Presently there are two main approaches: (I) pre-endothelialization of the circuitry *in vitro* (83,84) or (II) *in situ* capture ("fallout seeding" or "self endothelialization") of circulating endothelial progenitor cells to surfaces modified to provide a favourable environment for cellular attachment (85-87). Although enticing there are several challenges with endothelialization of such a large surface, which include creation of a functional monolayer of quiescent endothelial cells that can hold in retention on the surface in the midst of variable often hostile flow conditions. If there is a local gap between cells then this can lead to sites for platelet adhesion/activation. But more importantly than this, it is not a surface modification that can be readily available for immediate use in any patient. It requires time to develop the endothelialization of the device. There is no doubt that as tissue engineering and surface modification techniques evolve, at some point a custom endothelialized

circuit will be attainable for each patient as needed, when needed.

Conclusions

Will we need systemic anticoagulation for VV ECLS in the third millenium? As this review has shown it is extremely unlikely that systemic anticoagulation will be required. We have yet to find the perfect surface modification however several are close (*Table 2*). The persistence of multidisciplinary teams in the areas of chemistry, bioengineering, medicine and industry has pushed the development of biocompatible devices to the forefront addressing both the successes and failures. The goal of a biomimetic, nonthrombogenic extracorporeal surface is close to being realized. Such success will change the landscape of critical care medicine allowing for more safety not just with ECLS but also for all forms of intravascular and extracorporeal devices.

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Footnote

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