Strategies for optimisation of paediatric cardiopulmonary bypass
Somer, Filip Maria Jan Jozef De

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Chapter 5 Systemic inflammatory response

At the moment cardiac surgery starts; the baby is aggressed by many factors. This aggression by both surgery and cardiopulmonary bypass results in an inflammatory response. There is little doubt that this inflammatory response is responsible for a proportion of the mortality and morbidity associated with cardiac surgery. Certain organs and tissues are at higher risk of developing deranged function after the perfusion and in the postoperative period. At the greatest risk are the formed elements in the blood, the platelet and white cell, resulting in clotting problems and abnormal organ and tissue functions. In particular the pulmonary system, heart and myocardium, kidney and splanchnic bed, and the brain and cerebral circulation are specifically affected and thus contribute to early postoperative morbidity and mortality [1]. Small babies are even more at risk due to the larger volume and foreign surface area of the extracorporeal circuit in combination with the immaturity of many organs systems and the large amount of blood that after contact with tissue is returned into the systemic circulation.

The bio-incompatibility of cardiopulmonary bypass is multifactorial (Figure 1) and can be divided in two major groups: material independent and material dependent [2].
Pathophysiology and bioincompatibility of CPB

5.1. Material dependent

Under normal conditions, when blood is in a blood vessel with intact endothelium, no activation of blood proteins or elements will occur. However, the moment blood leaves this protected environment and comes into contact with damaged endothelium, other tissue or artificial surfaces several cascades of reactions will start. At the same time the shear stresses that work beneficial when applied on endothelium by releasing mediators such as nitric oxide, will now in absence of the endothelium activate blood elements. Aspects that contribute to this activation cascade are the surface characteristics [3], the sterilisation method and the chemical composition of the surface of the polymer. It is important to notice that there can be major chemical differences between the bulk material and the surface.
5.2. Blood interactions with polymers

5.2.1. Protein adsorption and complement activation

As soon as blood comes in contact with the hydrophobic polymer surfaces of the cardiopulmonary bypass the latter will be almost immediately covered with proteins. The formation of this protein layer is followed by the adherence of platelets. In addition to fibrinogen, γ-globulin preadsorbed to artificial surfaces enhances the platelet release reaction in vitro. In contrast, serum albumin passivates the surface towards platelet adhesion [4]. Glycosyl transferase reactions involving incomplete terminal oligosaccharide units were postulated as mediators for these platelet-protein interactions. These groups are present in fibrinogen, γ-globulin and many other glycoproteins in plasma, but are absent in albumin [5]. The highest concentration of fibrinogen on the material is realised after 15 minutes [5]. Fibrinogen adsorption has been used as a measure of thrombogenicity of materials. Aside from its role in the fibrin formation it will bind blood platelets via their surface glycoproteins IIb/IIIa and Gib [6]. However the platelets do not seem to interact with the material directly but through the adsorbed protein layer.

In high flow rate conditions it seems that the platelet response is a major determinant of blood incompatibility with artificial surfaces [2]. At this point it is important to put in perspective the effects of shear stresses near the wall of the hydrophobic polymers since this will contribute to leukocyte and platelet activation and in exceptional situations red blood cell lysis.

Although complement is activated to a large degree via the alternative pathway, it is only to a minimal extent, in adult surgery, linked to the foreign
materials. Other pathways must be playing a role in the complement activation such as factor XIIa, kallikrein and tissue factor [7]. Likewise, C3a and C5a anaphylatoxins may appear to be reduced in plasma where in reality they are adsorbed by the protein layers and thus are measured in lower amounts [8].

5.2.3. Contact activation

The intrinsic coagulation cascade as well as the fibrinolysis system are both initiated by the contact activation phase. Four proteins are activated during the contact phase: factor XII, high molecular weight kininogen (HMWK), prekallikrein and factor XI [9]. Adsorption of factor XII in presence of prekallikrein and HMWK produces active proteases, factors XIIa and XIIif [10]. In a feedback loop, factor XIIa cleaves prekallikrein to produce kallikrein and HMWK to produce bradykinin, a short acting vasodilator. Factor XIIa in the presence of kallikrein and HMWK also activates factor XI to factor XIa which activates the intrinsic coagulation cascade, which proceeds through factor IX to activate factor X and form thrombin [10]. Electrical charge (cationic or negatively charged surface) and the hydrophobicity of the artificial surface can also promote this initial contact activation with foreign material. The contact activation phase, as seen previously by factor XII and kallikrein, will also directly activate the complement system and initiate the plasminogen/plasmin formation. Contact activation may be more prominent at low flow than high flow conditions.

Interestingly, recent research [11-12] shows a much lower activation of the intrinsic pathway but on the other hand the activation pathway with KK and FXII on leukocytes may be more that what has been shown so, far.
5.3. Material independent

Other factors that influence the degree of inflammatory response do not depend on the material but are equally or more important for the initiation of an inflammatory response. A very aggressive activator is the cardiotomy suction. Especially in paediatric surgery the amount of blood recuperated by the cardiotomy reservoir can be quite large due to additional blood vessels (e.g. left vena cava superior), flow through collateral vessels etc. This aspirated blood is contaminated with tissue factor, tissue and fat fragments, free plasma haemoglobin, thrombin, tissue plasminogen activator and fibrin degradation products. All these elements in combination with the turbulent flow and the blood-air mixing in the aspiration lines will activate, through blood platelets and leukocytes, both coagulation and complement cascades. At the same time the aspirated fat emboli are an important source of cerebral embolisation [13] which, unfortunately cannot be prevented by the use of venous or arterial filters [14-15]. Important is also the presence of high amounts of S100BB in aspirated blood originating from fat, muscle and marrow in the mediastinal blood [16]. Since it had always been postulated that S100BB was a specific marker for brain damage and that the elevated plasma levels found after cardiopulmonary bypass were caused by damage of the brain.

A second factor is flow dynamics and fluid mechanical stresses (See also chapters 2 & 4). Especially stasis and eddy formation has an important impact on protein adsorption and thus on the formation of thrombi. Also shear stress is an important activator of primarily platelets and leukocytes. The magnitude and duration of shear stress will dependent from component to component.
and the blood flow characteristics in a given cardiopulmonary circuit, but will always be present to some extent. A high value with a short duration will be found in arterial cannulas while different magnitudes of shear but with longer duration are found in oxygenators and reservoirs [17,18]. Shear stress induced platelet activation is mediated by von Willebrand factor binding to platelet membrane receptors GPIb and GPIIb/IIIa [2]. Shear stress as small as 100 dynes/cm² will induce platelet and leukocyte activation [19].

A third factor is related to the use of homologous blood products and haemodilution. The risks of homologous blood transfusion such as immunobiological disorders [20] and transmission of infections are well documented [21]. Because of their young age infections caused to the use of homologous blood products should be avoided in every extent. Open-heart surgery without the use of homologous blood products is commonly performed in adults, but still difficult in small children because priming volume of the cardiopulmonary bypass circuit results in extreme haemodilution [22].

A fourth factor is related to the use of drugs. Best documented is the activation of the classical pathway of the complement system by the heparin-protamine complex. This will lead to monocyte and neutrophil activation [2, 23-24].

Finally also conduct of cardiopulmonary bypass as well as the genetic footprint of the child will play a role. The use of open or closed system [25], the oxygen tension used during cardiopulmonary bypass [2, 26-27], the cooling protocol [27, 28] and haemoglobin content when using deep hypothermic circulatory arrest [29] have all been put forward as variables that can influence inflammatory response. Of course every child is unique in his
genetic footprint and this can interact in the way they biologically will react on
the damage caused by the surgery and cardiopulmonary bypass. The
haptoglobin phenotype for example will determine the capacity for binding free
plasma haemoglobin [30] and might have an impact on the immune response
[31]. While the different platelet PL\(^A\) allelic frequency have been associated
with a predisposition for increased thrombogenicity [32], increased release of
IL8 and TNF after cardiopulmonary bypass [33] and more pronounced
neurocognitive decline after cardiopulmonary bypass [34]. Beside these
genetic factors also the pathology might influence the activation of the
different cascade. The higher incidence of fibrinolysis in cyanotic children is a
perfect example of the latter.

Inflammatory response to cardiopulmonary bypass is considerably more
complex than it seemed a decade ago. In children the analysis of
inflammatory response is even more complex due to different response of
neonates and children to cardiopulmonary bypass [35]. Nevertheless, it is
possible, based on our present knowledge to attenuate inflammatory
response. The large foreign surface area of the paediatric cardiopulmonary
bypass circuit, almost 4 times more than an adult circuit, remains an important
issue [5]. Changing this surface into a more blood compatible surface looks
promising. The aims of such a re-engineering should be elimination or
reduction of [2]:

1. Plasma protein adsorption in order to reduce cellular activation
2. Coagulation activation
3. Complement activation
4. Leukocyte activation
While at the same time the physical properties of the various bulk polymers are preserved.

Different approaches have been published in order to achieve these goals. Best known is heparin coating of polymers. In adults non-uniform results have been published over the years [36]. This might be related to the fact that in most clinical studies aspirated blood, recognised as one of the most injurious components [37], is still re-used. In paediatric open heart surgery this aspect will even gain in importance due to the larger amounts of aspirated blood. Nevertheless, lower inflammatory response is reported with heparin coated paediatric cardiopulmonary bypass [38-41], although not for all markers [42]. Also the use of phosphorylcholine coating was reported to be beneficial [43]. The attractive idea of combining surface amelioration with separation of aspirated blood for further reduction of the inflammatory cascade has not been realised yet due to technical limitations.

More controversial is the use of ultrafiltration for removal of inflammatory mediators [44-45] especially when compared to cardiopulmonary bypass circuits with a low priming volume and reduced foreign surface area.

A last method to control inflammatory response is by pharmacological interaction. Aprotinin has been reported to attenuate cellular and humoral response to cardiopulmonary bypass both in adult [46] and paediatric [47-49] populations. Also the use of some inhibitors [50] looks promising, but larger study cohorts are necessary to confirm these data.
5.4. Conclusion

The inflammatory response to cardiopulmonary bypass is considerably more complex than it seemed a decade ago. The acute phase response to trauma may be an integral part of this process. Our expanding knowledge of inflammatory mediators will allow a better understanding of cardiopulmonary related morbidity and may hopefully lead to improvement of biocompatibility of cardiopulmonary bypass resulting in less injurious systemic responses and diminished organ and tissue damage.

References


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