Cardiopulmonary Bypass and Biocompatibility: A Review

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Abstract

Cardiopulmonary bypass (CPB) is a procedure that takes over the function of the heart and lungs in order to safely perform surgery on the heart and great vessels. The procedure oxygenates blood by pumping it through an extracorporeal perfusion circuit. Blood-material interaction in the perfusion circuit activates the blood and triggers clotting activity as well as an immune inflammatory response within the body. These events have synergistic effects and are not yet fully understood. The morbidity of CPB due to these biological responses has led to tremendous amounts of research into improved biocompatibility for cardiopulmonary bypass. Hemolysis, platelet rupture, and protein adhesion have been identified as the most important blood-material interactions for activating the blood. Surface area, surface roughness, and surface chemistry all can influence the blood-material interactions in the perfusion circuit and successful reduction in blood activation has been experienced in utilizing each of these as a material modification factor. A greater understanding of the biochemical events taking place during and after blood-material interaction must be gained before drastic improvement of biocompatibility can be made for CPB. Inhibition of the earliest activation events of the coagulation and complement pathways through material intervention is the best place to focus future efforts.

1. Introduction

Cardiopulmonary bypass (CPB) is a method of whole body perfusion in which the function of the heart and lungs is replaced with an extracorporeal circuit consisting of an artificial blood oxygenator, blood pumps, and other associated devices. The use of an extracorporeal circuit provides a controlled environment for surgery of the heart and great vessels [1]. The first cardiac operation utilizing mechanical takeover of the heart and lungs was performed in 1951 by Dr. Clarence Dennis at the University of Minnesota and resulted in death of the patient due to an unexpected complex congenital heart defect. This was followed by the first successful open heart surgery in 1953 by Dr. John Gibbon. Gibbon used his heart lung machine for cardiopulmonary bypass and repaired an arterial septal defect in an 18 year-old woman [2]. Since then, cardiac surgery with CPB has become extremely wide spread in medical practice with over 800,000 procedures performed every year world wide [1]. Extensive research has been done on this procedure since its onset in the 1950s to develop improvements in patient outcomes and this will continue into the future.

A CPB machine, or heart lung machine, is a complex system of cannulae, tubing, pumps, heat exchangers, an oxygenator, and reservoirs (Fig. 1). The first step in the process is delivery of oxygen depleted blood from the body to the extracorporeal circuit. A venous cannula sewn into the body provides the pathway for de-oxygenated blood to enter the machine. Centrifugal pumps then send the blood through a circuit of tubes to the oxygenator which removes carbon dioxide from the blood and infuses it with oxygen. This blood is then filtered, brought to a specified temperature in a heat exchanger, and then sent back into the body through an arterial

cannula sewn into the aorta. An aortic cross clamp is placed on the ascending aorta to prevent the blood that is returning from the extracorporeal circuit from entering the heart (Fig. 2). The CPB circuit also contains a separate circuit that infuses a solution into the heart to induce cardioplegia, which is the termination of heart beating, and provide myocardial protection which prevents the heart tissue from being damaged. All CPB procedures must be begin with heparinisation of the blood to prevent it from coagulating and forming clots in the machine which leads to an embolism [2].
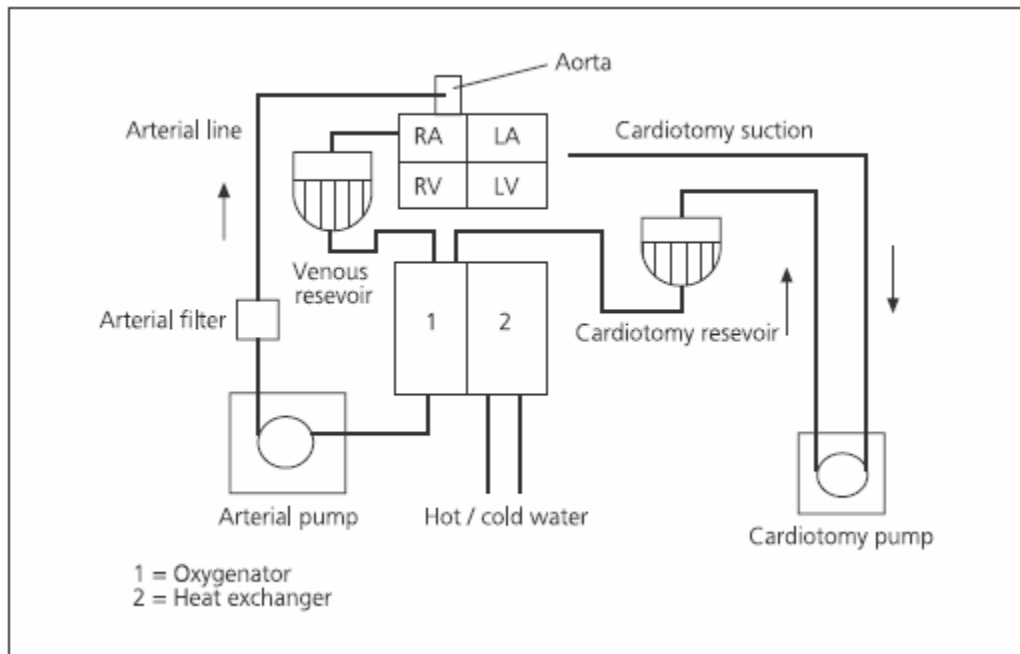

Figure 1. Schematic diagram of a typical cardiopulmonary bypasss perfusion circuit. RA, LA, RV, and LV represent the right atrium, left atrium, right ventricle, and left ventricle of the heart respectively [28].

While the safety of CPB has been established with low mortality rates, patients undergoing cardiac surgery with CPB have an inflammatory response that has deleterious effects on the body. These include, but are not limited to, impaired hemostasis, organ dysfunction, and cerebral injury resulting in the need for 30% to 70% of patients undergoing cardiac surgery with CPB to receive homologous blood transfusions [3]. The morbidity of CPB was once thought to be caused entirely by blood-material interaction within the extracorporeal circuit but is now also attributed to material-independent blood activation. Material-independent blood activation occurring during CPB can be caused by a variety of sources including blood exposure to air, reperfusion injury, hypothermia, and presence of endotoxemia [4]. This review will focus on the blood activation induced by contact with artificial surfaces in the extracorporeal circuit, the resulting systemic inflammatory response syndrome, the biomaterial surface characteristics that are involved with blood activation, and the recent improvements and future needs of CPB.
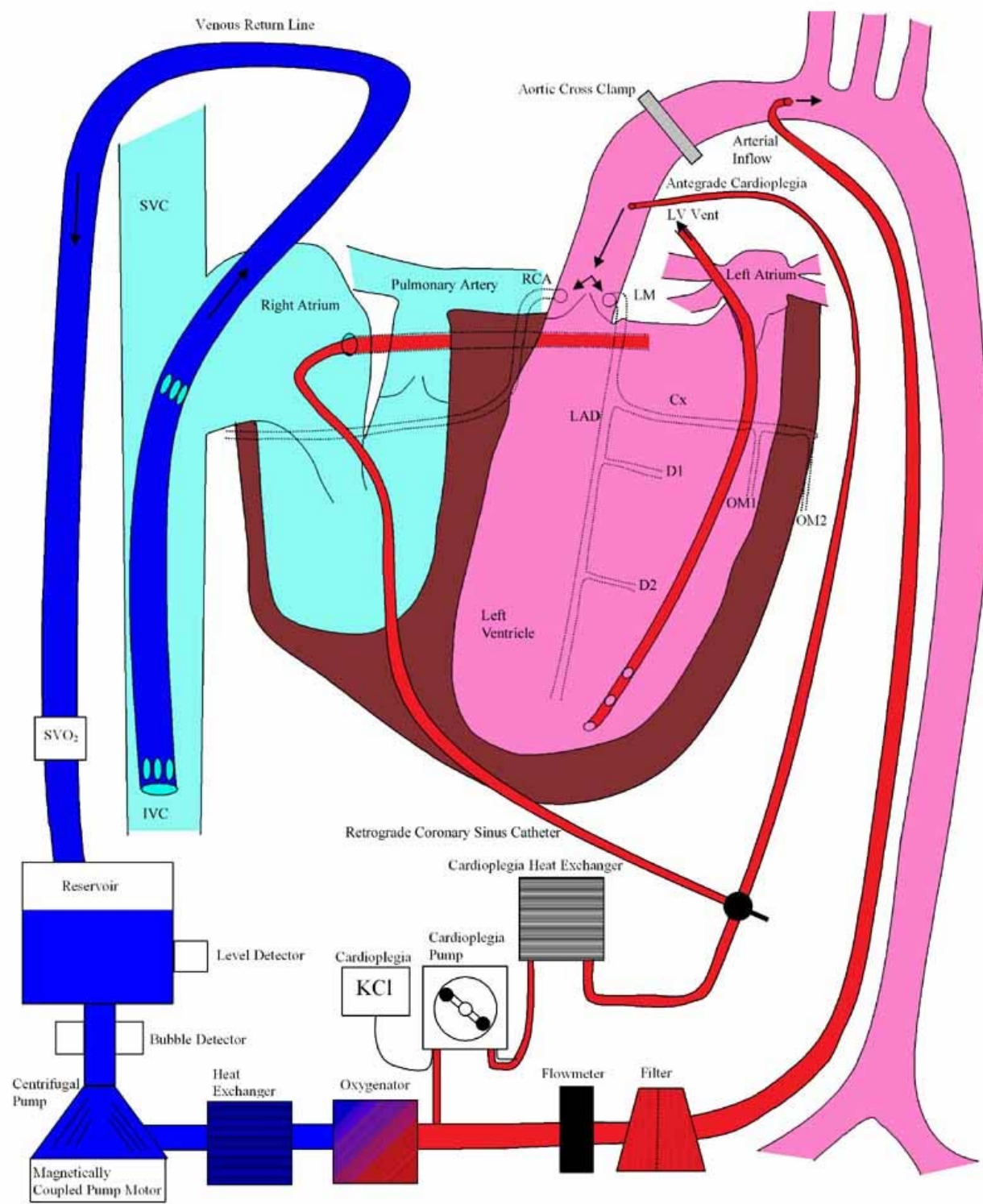
Figure 2. Diagram of cardiopulmonary bypass with heart and extracorporeal circuit interface. Blue = oxygen depleted blood. Red = oxygen replenished blood [28].

2. Biological Response to CPB

Blood circulating in the human body is in constant contact with a continuous luminal endothelial cell (EC) layer known as the endothelium which coats the interior of all blood vessels in the body. This EC layer is the barrier between the tissue cells of the blood vessel wall and the blood itself. The endothelium is capable of producing, secreting, and binding proteins or soluble factors to achieve hemostasis [5], and it plays a major role in regulating membrane permeability, lipid transport, vasomotor tone, coagulation, fibrinolysis, and inflammation [6]. This regulation is achieved by the expression of endothelial-derived surface proteins or secretion of biologically active soluble factors. During CPB, blood leaves the circulatory system and enters the extracorporeal circuit where it comes into contact with synthetic surfaces. This contact leads to activation of the blood which triggers coagulation effects and inflammatory response.

2.1 Hemostasis

In the human body the balance between thrombosis and bleeding is kept by the endothelium. The endothelial cells produce up to nine procoagulants and as many anticoagulants depending on the circumstances [7]. The process of stopping bleeding with clot formation and then restoring blood flow is known as hemostasis and it is a very complex process.

Upon injury to the blood vessel, the endothelium is disturbed and subendothelium proteins are released into the blood. These proteins, most notably von Willebrand factor, activate blood platelets which then aggregate at the site of the injury forming a plug to stop the bleeding. Activated platelets also release the contents of their stored granules which triggers a protein cascade to induce more coagulation and activate more platelets [8]. This process occurs almost immediately after disturbance of the endothelium and is known as primary hemostasis. The incisions made during cardiac surgery with CPB disrupt blood vessels and so initiate this chain of events.

Simultaneous to the platelet activation of primary hemostasis is the initiation of secondary hemostasis. Secondary hemostasis is concerned with converting the protein prothrombin to thrombin which cleaves fibrinogen to fibrin. Fibrin is a fibrillar protein that is polymerized in long cross-linked strands forming a sort of mesh. This mesh acts in conjunction with platelet aggregation over a wound site to form a blood clot. Thrombin, therefore, is the real key to controlling the bleeding and thrombotic complications of CPB [8]. Fibrin formed by secondary hemostasis occurs via two pathways: the contact activation pathway and the tissue factor pathway. The tissue factor pathway is the more important of the two; however both pathways lead to the production of thrombin. The contact activation pathway is triggered when the group of proteins known as the contact system comes into contact with the artificial surfaces of the extracorporeal circuit or the subendothelial surface. It begins with conversion of factor XII to its active form which initiates the coagulation cascade of signaling and conversion events that ultimately convert prothrombin to thrombin (Fig. 3). The tissue factor pathway is also initiated during cardiac surgery by the return of shed blood from cut vessels to the blood stream [9]. The shed blood contains tissue factor which starts a separate coagulation cascade also leading to thrombin production.

Hemostasis related events are extremely important to CPB because as platelet activation and coagulation cascades begin the clotting process, coagulation proteins and platelets are used up leading to disseminated intravascular coagulation (DIC). As the coagulation process uses

clotting agents it eventually induces fibrinolysis, the breaking down of clots to resume blood flow, through activation of plasminogen to plasmin. Plasmin is a protease that breaks down the fibrin mesh. DIC is characterized by hemorrhaging occurring all over the body and sets in when coagulation processes take place for extended periods of time leaving insufficient coagulants in the blood vessels for clotting. The thrombosis and subsequent abnormal bleeding associated with CPB typify DIC and are a serious concern for the procedure [4].
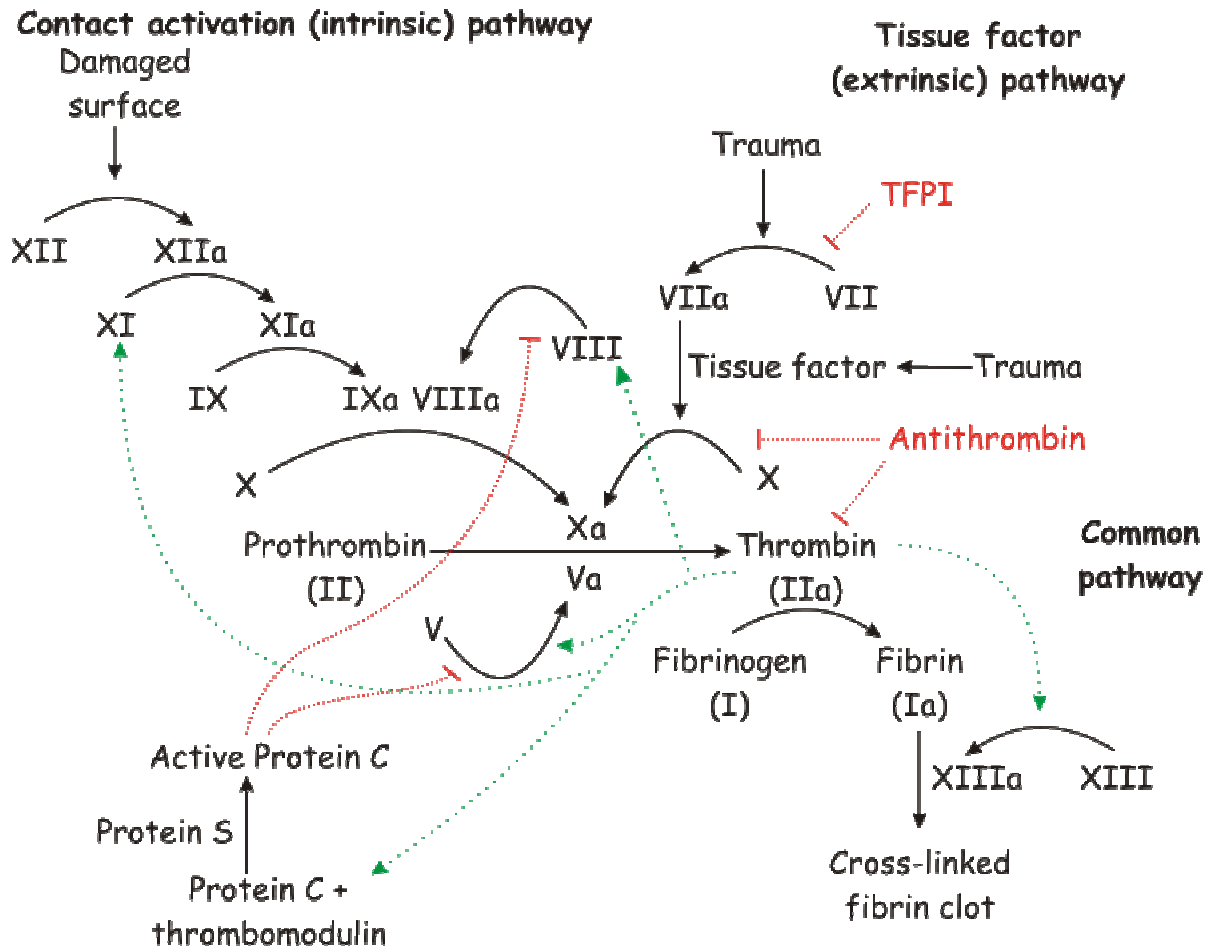

Figure 3. Schematic of the two separate coagulation cascades. Ultimate result is formation of cross-linked clot (bottom right). Roman numerals followed by "a" indicates an activated factor. Both pathways cause cleavage of prothrombin to thrombin which cleaves fibrinogen to fibrin (center) [29].

2.2 Systemic Inflammatory Response

Systemic inflammatory response syndrome (SIRS) resulting from CPB is an inflammatory state affecting the whole body and is thought to be caused by multiple events: blood component contact with the artificial surface of the bypass circuit, ischemia–reperfusion injury, endotoxemia and operative trauma. SIRS is both a common and serious side effect of CPB that can ultimately lead to organ dysfunction [4]. The inflammatory response is a very complex process and a synergistic one with the pivotal step being activation of nuclear

factor kB (Fig. 4).

CPB, especially the associated blood-material interaction, triggers the alternative complement pathway of the immune system. The EC layer of blood vessels contains surface inhibitors that limit the activation of cofactor C3 which begins the complement pathway. The lack of EC layer in the extracorporeal circuit, therefore, allows C3 to be activated thus starting the alternative complement pathway which leads to the formation of the membrane attack complex and ultimately targeted cell death. Pharmacological agents such as heparin and protamine are generally administered before CPB due to their ability to inhibit the classic complement pathway [10].

Activation of complement pathway factors and their byproducts have an immunostimulant effect that provokes synthesis of pro-inflammatory cytokines [11]. Cytokines are molecules secreted by immune cells that carry signals between cells and induce a certain response. Increased levels of pro-inflammatory cytokines have generally been associated with negative outcomes after cardiac surgery and induce the release of NO by EC and smooth muscle cells through the inducible form of the enzyme NOS (iNOS). Together, iNOS and pro-inflammatory cytokines play a major role in SIRS by activating nucleus factor kB (NF-kB).
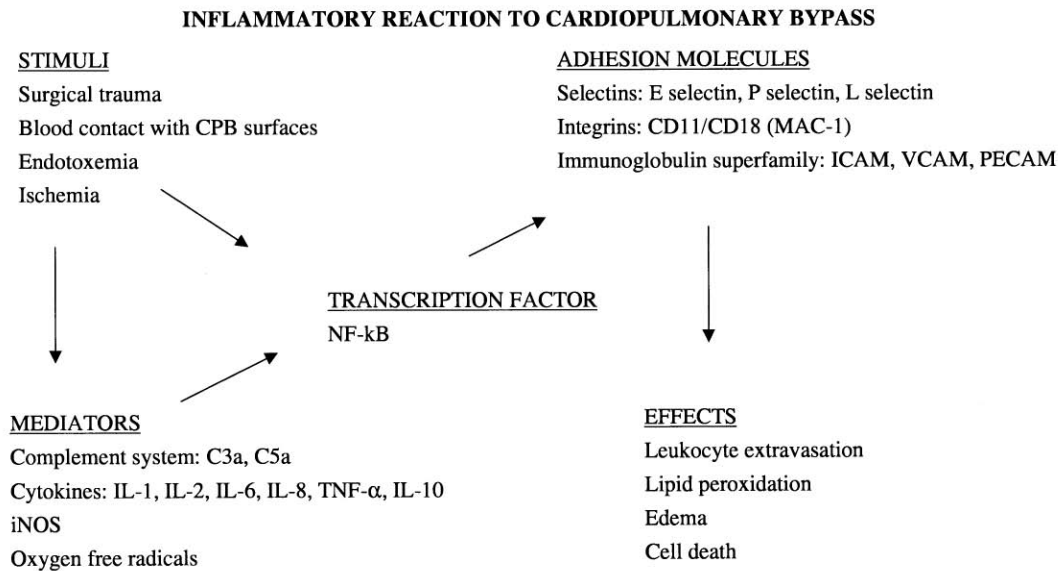
INFLAMMATORY REACTION TO CARDIOPULMONARY BYPASS

STIMULI

Surgical trauma

Blood contact with CPB surfaces

Endotoxemia

Ischemia

ADHESION MOLECULES

Selectins: E selectin, P selectin, L selectin

Integrins: CD11/CD18 (MAC-1)

Immunoglobulin superfamily: ICAM, VCAM, PECAM

TRANSCRIPTION FACTOR

NF-kB

MEDIATORS

Complement system: C3a, C5a

Cytokines: IL-1, IL-2, IL-6, IL-8, TNF-α, IL-10

iNOS

Oxygen free radicals

EFFECTS

Leukocyte extravasation

Lipid peroxidation

Edema

Cell death

Figure 4. Schematic of the inflammatory process induced by CPB. The key role of NF-kB leading to the EC and leukocytes activation is highlighted [30].

NF-kB is a protein complex that controls the transcription of DNA. The inactive form of NF-kB is found in the cytoplasm of EC and leukocytes under normal conditions. When these cells come into contact with iNOS and pro-inflammatory cytokines NF-kB is activated and then translocates to the nucleus where, binding to DNA, it is able to induce the expression of several inflammatory mediators including more pro-inflammatory cytokines and iNOS as well as adhesion molecules (Fig. 5). Adhesion molecules are proteins that cause the expression of selectins in the cell membranes of EC, platelets and leukocytes and are pivotal to the inflammatory response system.

Selectins are intramembranous proteins that provide an adhesion site for integrin proteins on other cells. The adhesion molecules resulting from NF-kB activation cause E-selectin, P-

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selectin, and L-selectin to be expressed on EC, platelets and leukocytes respectively. Platelets and leukocytes are able to form a bond through their selectins which causes platelets to become involved in the inflammatory response and not function properly as clotting agents. The expression of L-selectin on leukocytes induces a morphological change in the cells that causes them to roll or tumble along the EC layer. This brings about the binding of neutrophil leukocytes to EC through E-selectin and L-selectin (Fig. 6). This bond causes the neutrophil to express specific integrins and the EC to express new selectins including intercellular adhesion molecule 1, endothelial-leukocyte adhesion molecule 1, and vascular adhesion molecule. The binding of integrins with ICAM and VCAM initiates firm adhesion of neutrophils on EC, leading to their transendothelial migration into the interstitial fluid phase. Subsequent infiltration of the neutrophil into the perivascular tissue results in their release of oxygen-derived free radicals, proteases, and elastases, leading to nonspecific cellular damage [12]. On a local basis, this process, although destructive, is protective. On a systemic basis, as occurs in CPB, end-organ damage occurs because of neutrophil adhesion throughout entire vascular beds [5].

As mentioned earlier, the inflammatory response has a very synergistic effect and each phase influences both previous and subsequent phases. SIRS is directly associated with CPB, especially with the blood activation due to contact with artificial surfaces. With a basic understanding of hemostasis malfunction and SIRS that this blood activation causes it becomes pertinent to investigate a major source of this activation which is blood-material interaction.
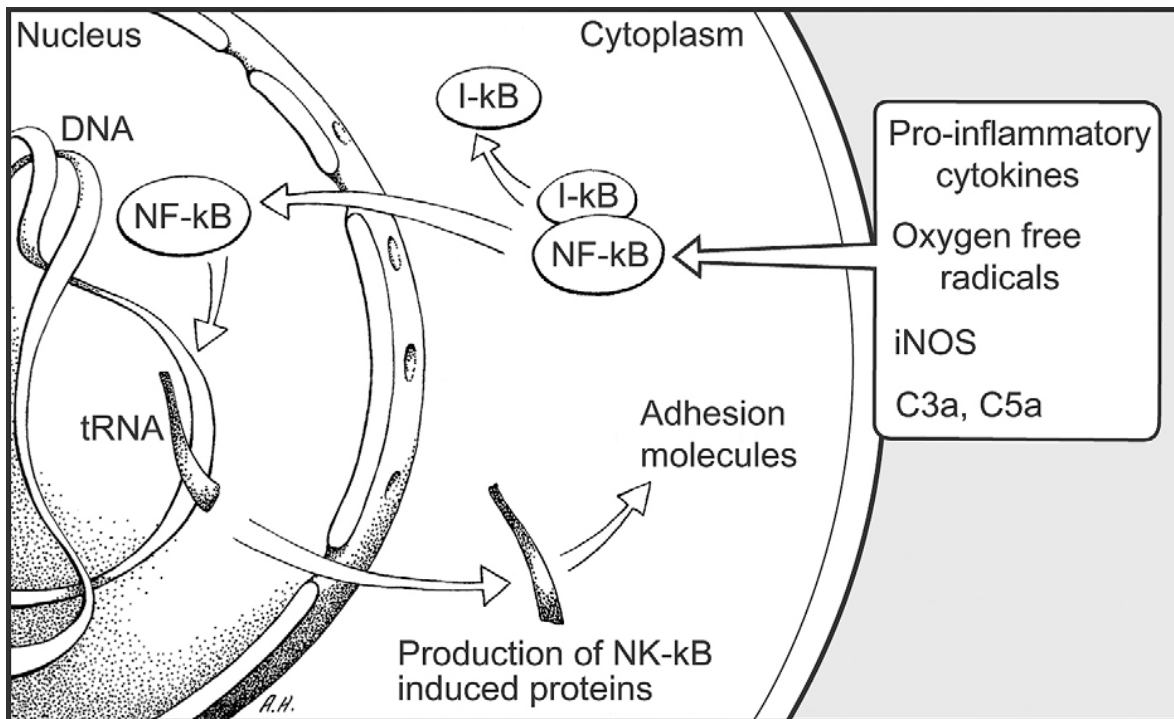

Figure 5. Pathways leading to the activation of NF-kB and the production of adhesion molecules [30].
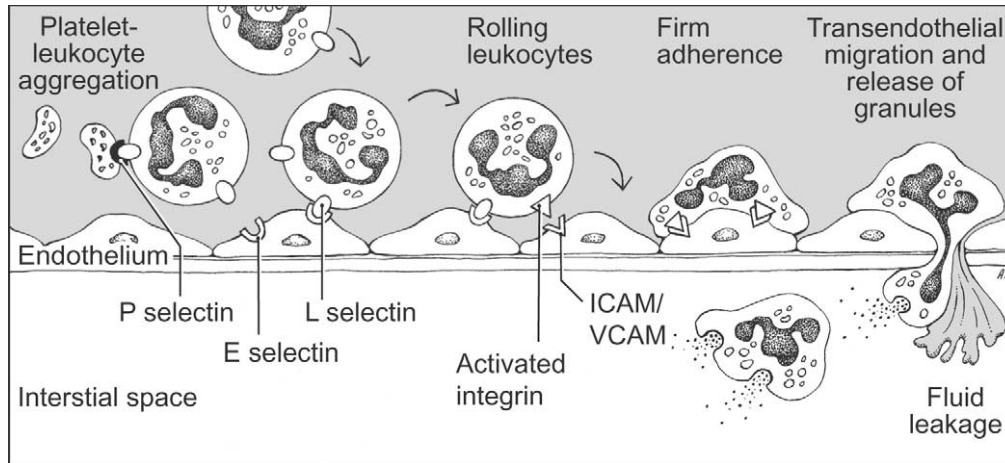
Figure 6. EC, platelets and leukocytes interaction leading to leukocytes extravasation, granule release and fluid leakage into the interstitial space [30].

3. Blood-material interaction

3.1 Protein Adhesion

The first event that takes place when blood comes into contact with the synthetic surfaces of the extracorporeal circuit is rapid protein adsorption onto these surfaces. This adhesion makes these proteins what blood components interact with when flowing through the circuit and so the changes in blood composition and activation of blood can be attributed to these adhered proteins [13]. For this reason protein adsorption to biomaterial surfaces is of much interest for mitigating the deleterious effects of CPB.

The two proteins of major importance regarding adhesion to the biomaterial surface are fibrinogen and albumin. Fibrinogen is the precursor to fibrin, which plays a critical role in thrombosis. Fibrinogen also interacts with platelets. In 1969 Zucker et al. showed that platelets attach to surface adsorbed fibrinogen [14]. This reaction partially explains the thrombocytopenia, or low platelet presence in blood, observed during and after clinical cardiac surgery. Activation of platelets in the circuit can also disrupt the hemostatic balance in the circulatory system and if platelets bind to fibrinogen in the circuit they are not available in the blood vessels for clotting. Albumin is a very water soluble protein whose adherence to the biomaterial surface is important because it inhibits adherence of leukocytes and platelets [15]. With the role that platelets play in hemostasis and leukocytes in the inflammatory response it is ideal in terms of biocompatibility if these cells have minimal interaction with the biomaterial. The effects of albumin on thrombus formation and inflammatory response have lead to its utilization in the preparation of biomaterials aimed at improving biocompatibility [13].

Biomaterial characteristics that influence protein adhesion are surface roughness, surface area and surface chemistry. The impact that these factors have on protein adhesion and biocompatibility of the material will be investigated in a later section.

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3.2 Hemolysis and Platelet Reaction

Hemolysis is the breaking open of erythrocytes, or red blood cells, and the release of hemoglobin. Erythrocytes are the blood cells responsible for carrying oxygen and delivering it to the body. Hemolysis is of major concern in CPB because if erythrocytes are damaged then the body does not receive adequate oxygen during cardiac surgery leading to hypoxia and major complications. Hemolysis during CPB is caused by erythrocytes impacting the biomaterial surface or by elevated shear stress in the shear flow caused by surface roughness [16].

Platelets adhere to and aggregate on the biomaterial surface via proteins adhered to the surface. Platelets that adhere to the surface also release constituents that can activate other platelets and increase aggregation [17]. Platelet rupture can also occur in the extracorporeal circuit due to the same factors as hemolysis: surface impact and shear stress. Platelet rupture is of major consequence to the hemostatic balance because platelet activation factors are released upon rupture and ruptured platelets cannot aggregate to form clots in blood vessels. Therefore, platelet reaction to the extracorporeal circuit can cause thrombocytopenia and aid in SIRS. The surface roughness is the critical biomaterial characteristic for hemolysis and platelet rupture during CPB and will be discussed below.

4. Biomaterial Considerations

Since protein adhesion, hemolysis, and platelet rupture have been identified as the main factors in alteration of blood components during CPB, it is logical to now investigate what aspects of the biomaterial affect these activities. Surface roughness has been directly correlated to an increase in shear stress within the blood flow. With shear stress being the primary cause of hemolysis and platelet rupture this surface characteristic is of critical importance to the biocompatibility of extracorporeal circuit surfaces. Surface area has a direct relationship with protein adhesion because increased surface area allows more space for proteins to interact with and adhere to as well as more opportunity for proteins to be in the proper orientation for surface adhesion. The chemical composition also has a major influence on protein adhesion as this dictates protein structure and presentation of bonding sites.

4.1 Surface Roughness and Shear Stress

Hemolysis occurring within the extracorporeal circuit during CPB has two main causes: erythrocytes bursting upon impact with the synthetic surfaces of the CPB tubes and pump and shear stresses large enough to cause rupture [18]. Studies conducted by Maruyama et al. have shown that the primary cause of hemolysis is rupture due to shear stress and identified the shear stress level required for hemolysis to be between 719 Pa and 903 Pa [16,18].

Surface roughness of the biomaterial surface in CPB circuitry is characterized by sharp peaks and valleys. These peaks increase the turbulence of the flow around them which results in elevated shear stress levels [16]. With the ultimate goal of producing more biocompatible materials for CPB circuitry Maryuma et al. conducted experiments to determine the threshold of surface roughness, R_a, which produces shear stress levels large enough to cause significant hemolysis. This level is between $R_a = 0.6$ μm and $R_a = 0.8$ μm. Measuring the level of hemoglobin in the blood allows for quantification of hemolytic activity. Hemoglobin concentrations indicating significant hemolytic activity were found between 0.6 μm and 0.8 μm

and with surface roughness values less than these producing normal amounts of hemoglobin in the blood (Fig. 7). The level of hemoglobin concentration is also proportional to the square of the shear rate indicating that hemolysis increases with shear stress (Fig. 8).

With the knowledge of this threshold range for the point at which surface roughness causes shear stress sufficient for hemolysis biomaterial producers can attempt to manufacture extracorporeal circuit tubing and other CPB apparatuses with R_a levels below it. This will reduce hemolysis and platelet rupture during cardiac surgery with CPB leading to a reduction in the deleterious effects of the procedure.

4.2 Surface Area

The surface area of the tubing in extracorporeal circuitry has a large influence on protein adsorption to the surface of the biomaterial. The increased surface area allows more space for the adherence of blood proteins like fibrinogen and albumin. As previously discussed, adherence of these proteins can disrupt or promote the hemostatic balance upheld by the blood vessel endothelium. For this reason, many studies have been conducted to measure the effect that varying material surface area has on inflammatory activity and found a direct link between reduction of platelet activation and leukocyte activity and reduced surface area. This biomaterial characteristic represents a relatively simple way of improving the biocompatibility of CPB circuitry.
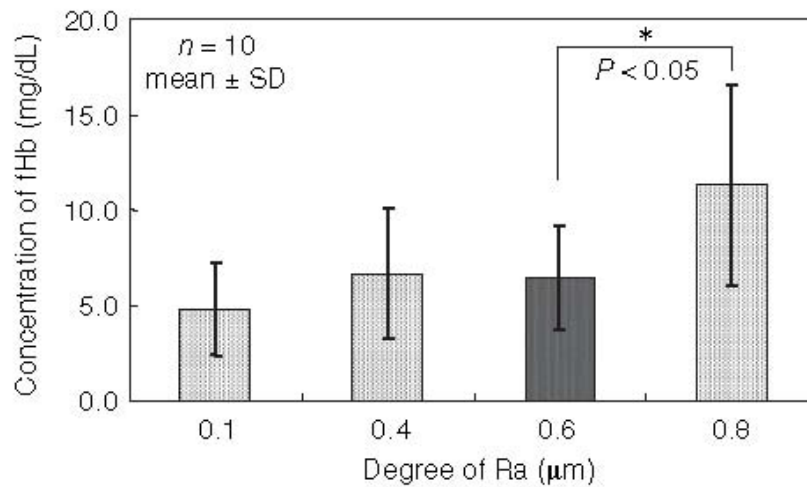

Figure 7. Hemolysis due to surface roughness ranging from R_a 0.1μm (without roughened surface) to 0.8 μm. fHb = free hemoglobin released upon rupture of red blood cells [16].
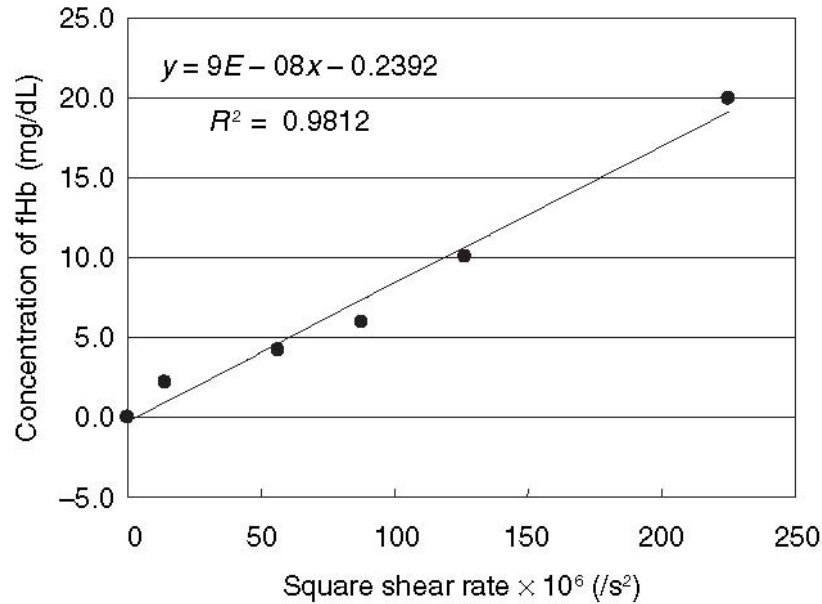
Figure 8. Relationship between square shear rate and hemolysis level. The hemolysis level increased approximately in proportion to the square shear rate [16].

4.3 Surface Chemistry

The surface chemistry of the biomaterial surface in cardiopulmonary bypass procedures can have a major influence on the proteins that adhere to the surface. Many studies have been devoted to developing chemical coatings for CPB circuitry that will provoke adherence of specific proteins intended to prevent blood activation or at least reduce it. There has been interest in low molecular weight heparin, platelet aggregation inhibitors, platelet-preserving agents, and inhibitors for complement, kallikrein and leukocyte sequestration [19]. The most popular method of surface chemistry alteration is heparin-coated circuits [20]. Heparin is a highly-sulfated glycosaminoglycan and it is widely used as an injectable anticoagulant. Coating CPB circuitry with this chemical has been shown to significantly reduce complement and leukocyte activation in patients undergoing cardiac surgery with full systemic anticoagulation [21]. Essentially, the presence of heparin on the biomaterial surface presents the activation of certain complement cofactors and also inhibits the signaling process for leukocyte activation.

Another surface chemistry modification procedure is performed with surface-modifying additive (SMA). The mechanism of antithrombogenicity of the SMA is mainly based on the effect of limiting platelet interaction with the surface and subsequently reducing platelet activation. This is in contrast to the heparin-coated material which still allows platelet binding. Complement activation assessed by the terminal complement complex is not influenced by SMA [22].

Other surface chemistry modification methods involve pre-coating of the material with albumin or an albumin attractant. This is because albumin does not allow attachment of leukocytes or platelets and inhibits their adherence to the material surface [23]. This method has been shown to reduce blood activation in some cases but results are variable due to the many other factors involved [24].

Modifying the surface chemistry of the extracorporeal circuit has profound effects on blood activation. Coating the material with antithrombogenics can reduce thrombosis in some cases and the inflammatory response in others but usually not both at once. Developing methods for selective protein adherence to the material surface or pre-coating with proteins that inhibit blood activation is another approach that has had some success [15]. It would seem that a greater understanding of the processes involved with blood activation, thrombosis, and the inflammatory response is needed before surface chemistry modification techniques can completely alleviate all of the deleterious effects of CPB.

5. Improvements in Biocompatibility

Over the past half-century a multitude of strategies have emerged for limiting the host response to biomaterials. In the field of CPB, these strategies broadly fit into three categories: pharmacology, therapeutic filtration and material interventions [25]. This paper is focused on biomaterial interaction with blood during CPB and the resulting morbidity. A truly biocompatible material is likely unachievable due to the multitude of blood components and the synergistic effects of blood activation, but certainly there are material intervention approaches that can reduce the level of hemostatic imbalance and inflammatory response seen in patients undergoing cardiac surgery with CPB.

A wide range of materials is employed in the construction of the CPB circuit (Table 1). These materials present a large surface area that a patient's blood is in contact with during the perfusion process of CPB. Certain surfaces are functional, meaning they are meant to interact with the blood, while others are passive such as tubes and reservoirs (Table 2). When attempting to modify a biomaterial surface the functionality must not be compromised. For this reason it is generally best to attempt to improve the biocompatibility of the tube and reservoir materials as these sections serve no purpose but to transport or store the blood and not to oxygenate, filter, or change its temperature.

Table 1. Materials used in the construction of the perfusion apparatus [25].

• Polycarbonate
• Polyurethane
• Polyester
• Polyamide
• Polyvinyl-chloride
• Stainless steel
• Aluminum

As was previously discussed, larger surface area generally means more blood-surface interaction in the circuit. A study by Gorlay has proven that reducing the surface area of the circuitry tubes by decreasing diameter can reduce the expression of a neutrophil integrin that is vital to systemic inflammatory response, thus reducing the response itself. Reducing surface area is therefore a viable approach to improving the biocompatibility of blood.

Table 2. The active and passive materials of the perfusion circuit. The materials used in the active areas of the circuit are more difficult to modify or replace due to their active role in the perfusion apparatus. The passive materials perform a mainly containing function and can, on the whole, be modified with relative impunity providing the mechanical requirements are maintained [25].

Active materials	Passive materials
Membrane surface	Tubing
Filter screens	Reservoir and filter casing

Polyvinyl-chloride (PVC) is a material commonly used in the production of CPB machine tubing. This material is rigid by itself and needs a liquid portion added so that it is flexible, an important requirement of circuit tubing. The PVC blend used typically contains 80% plasticizer to ensure that the desired mechanical properties of the polymer are obtained. The plasticizer is usually di-2-ethyl-hexyl-phthalate (DEHP) which has been shown to present health risks to those exposed to it in other branches of science and medicine. Additionally, because the DEHP is liquid it tends to migrate to the surface of the polymer, thus the surface of the PVC tubing is predominantly DEHP, and not PVC [26]. Gorlay's study removed the DEHP from the surface of the PVC tubing using a methanol washing method and compared the results of using both plasticized and unplasticized PVC tubing in the perfusion circuitry. The results are shown in Figure 9 and suggest that it is the presence of DEHP on the surface of the polymer that is largely responsible for the contact-mediated inflammatory process. Removal of this plasticizer from the surface of PVC perfusion tubes represents another effective technique for making the surface more biocompatible.

Another approach to improving the biocompatibility of the material is to use an alternative to plasticized PVC for the circuit tubing. Polyolephin is a polymer often used for blood bags that contains no plasticizer [27]. A study conducted by Gorlay tested the activation of neutrophils in blood passed over sheets polyolephin and contrasted it with traditional PVC of the same geometry. The test showed that use of polyolephin drastically reduces the expression of the neutrophil integrin described above (Fig. 10). These results indicate that, if the correct mechanical properties can be instilled into the polymer, and the material can be produced economically, then polyolephin may be a real alternative to PVC in the perfusion circuit [25].
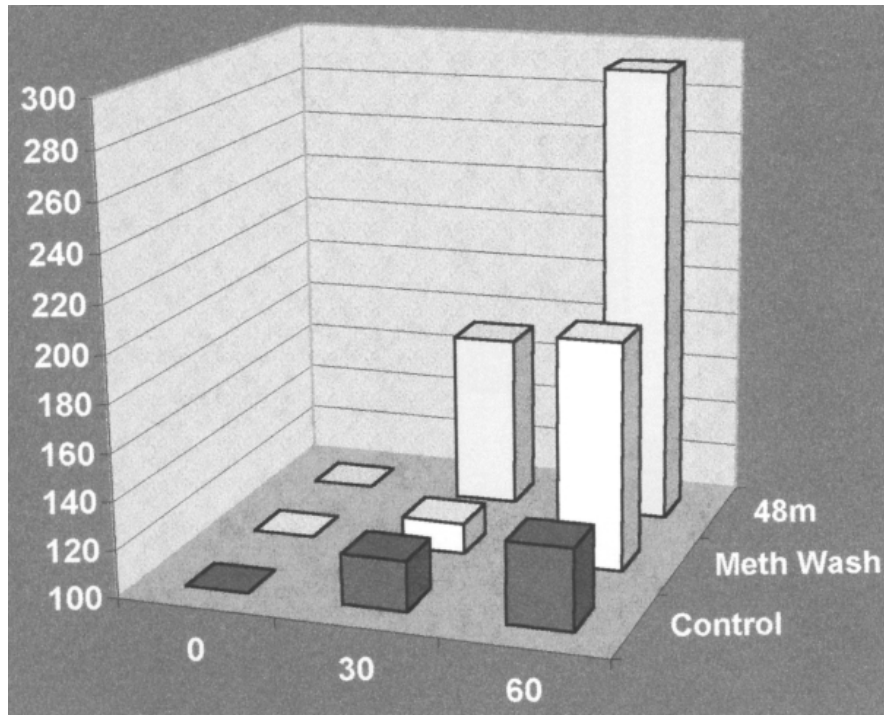
Figure 9. The effect of washing DEHP from the surface of plasticized PVC on neutrophil integrin expression in blood undergoing extracorporeal circuit perfusion. The methanol washing process resulted in a reduction in integrin expression when compared to untreated material in a tube of the same 48 cm^2 surface area. This treatment was extremely effective in enhancing biocompatibility and confirms the role of DEHP in the inflammatory process. Integrin expression is expressed as a percentage of the baseline value. Horizontal axis represents time in hours on CPB [25].

6. Conclusions

Cardiopulmonary bypass is an extremely useful procedure and without it open heart surgery would currently be impossible. That being said, the morbidity associated with CPB is certainly not ideal and much of it is known to arise as a result of blood-material interaction in the extracorporeal perfusion circuit. There are a variety of health defects resulting from hemostatic imbalance and systemic inflammatory response syndrome due to this interaction and a comprehensive understanding of the biochemical events involved with these processes has not yet been achieved. For this reason it has been very difficult to improve the biocompatibility of the circuit but progress is being made.

Surface roughness of the biomaterial surface has been established as the cause of a shear stress level that induces hemolysis. This shear stress level and the associated surface roughness threshold for producing it are now known.

Research on blood protein adhesion to the biomaterial surface has come along way and lead to discovery of the enormous influence that the adhered proteins in the circuit have on thrombogenesis and SIRS in the body. Surface chemistry modification technology has also made it possible to limit and reduce the coagulation and inflammatory effects of blood activation in the circuit.

Moving forward there is still a lot of work to be done in making CPB safer for patients. A broad distribution of material intervention techniques should be applied to increase the biocompatibility of the extracorporeal circuit including, but not limited to, reducing surface area of the circuit, applying alternative polymers containing no plasticizer, and coating the circuit in heparin or other chemicals that will inhibit the activation of inflammatory response and coagulation cascades.
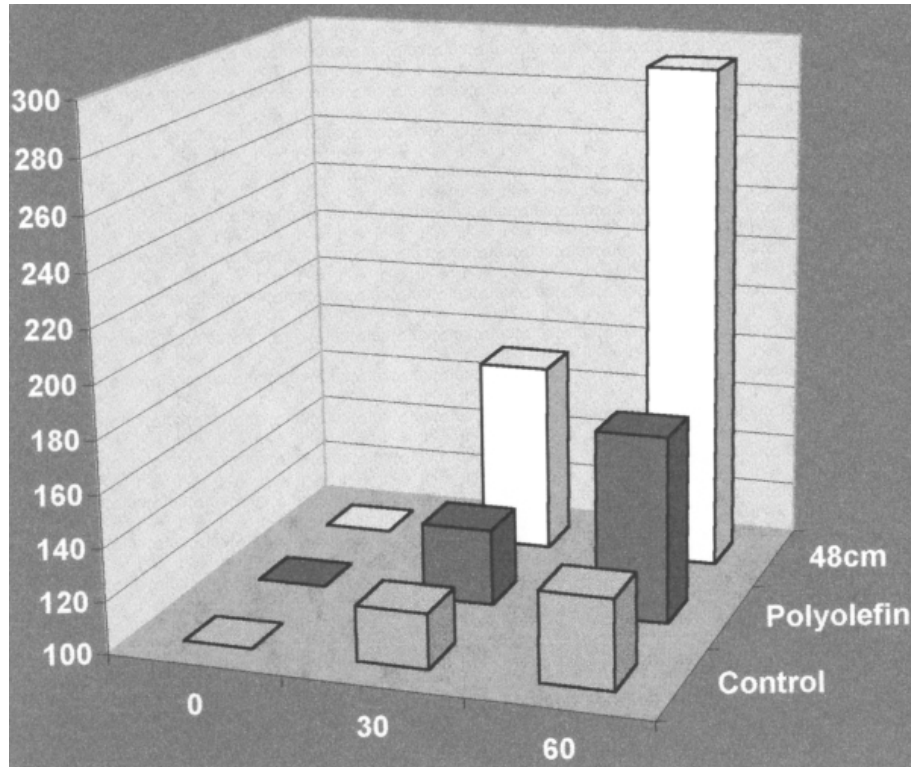

Figure 10. Polyolefin is an alternative to PVC for many applications, and in this series of studies proved to be very effective in terms of reducing neutrophil activation. These results show the effect of using polyolefin as an alternative under recirculation conditions. The difference in neutrophil integrin expression was statistically significant. 48 cm represents the 48 cm^2 surface area PVC tube test case. Polyolefin test used same tube dimensions and geometry. Horizontal axis represents time in hours on CPB. Neutrophil integrin expression is expressed as a percentage of the baseline value [25].

7. References

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