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Review article

The science and practice of cardiopulmonary bypass: From cross circulation to ECMO and SIRS

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"Perfusion": French verb 'perfuse' meaning to 'pour over'.

Heart disease is a major health problem in the World, and heart surgery is now common for revascularisation in coronary artery disease, heart valve repair and replacements, and heart and heart-lung transplantation. This includes surgery for adults with acquired heart disease and corrective and palliative surgery for both children (including neonates and infants) and adults with congenital heart conditions.

In England in the NHS, annually approximately 22–24,000 coronary artery bypass graft (CABG), operations and just over 11,000 valve procedures are performed. Whereas the number of CABGs performed has been approximately the same in recent years, valve surgery is increasing by about 5–10% every year. There is a general trend to more minimally invasive surgery and some surgeons are now using off pump surgery techniques. For congenital heart conditions, the number of procedures is increasing each year, especially for adults.[1]

Currently, it is estimated that more than one million cardiac operations are performed each year worldwide with use of the heart-lung machine. In most cases, the operative mortality is quite low, approaching 1% for some operations.

Cardiopulmonary bypass (CPB) is a key component of these highly invasive surgical procedures, many of which are complex. CPB takes over the functions of the heart and lungs and maintains blood oxygenation and circulation to the body whilst the heart and lungs are stopped during surgery.

HISTORY

Throughout the late 18th century and early 19th century, attempts were made to perfuse and aerate various organs. Jacobi in 1895 reported his experiment of blood flow through a artificially ventilated lung.[2] Subsequently a machine to preserve organs as well as complete animals was reported in 1926.[3] However, progressive degenerative changes compounded progress over the next few years. Although, Heparin's anticoagulant properties discovered during these years provided the necessary stimulus for perseverance over the next 30 years.

Lillehei and colleagues[4] reported their creative controlled cross-circulation technique successfully (Figure 1). They reported a series of 32 patients successfully operated upon by controlled cross-circulation.[5] Successful development of the oxygenator again led to the early demise of this important milestone in cardiac surgery.

The real breakthrough for cardiac surgery was the development of cardiopulmonary bypass. John Gibbon heralded the start of modern day open heart surgery by pioneering the use of heart lung machine. Although unsuccessful in his first patient, his second patient had her ASD closed successfully in 1953.[6] It was this successful operation that encouraged a number of researchers including Kirklin and colleagues to launch their open-heart program in 1955 using a modified Gibbon-IBM heart-lung machine.[7] The cardiopulmonary bypass circuit (Figure 2) consists the following components; oxygenator, blood pump, venous reservoir, arterial filter, and arterial and venous canulae.

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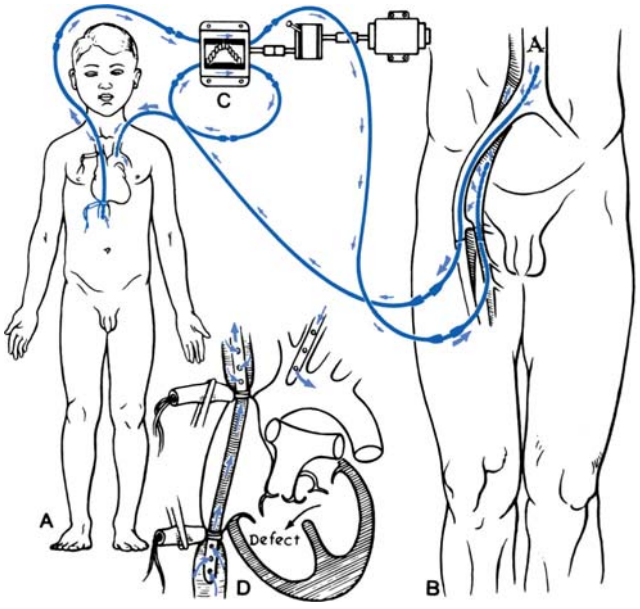

Figure 1. Controlled cross-circulation. (A) Patient with sites of arterial and venous cannulations. (B) Donor with sites of arterial and venous cannulations. (C) Motor pump to control exchange of blood between the patient and donor. (D) Close-up of the patient's heart, showing canula to draw venous blood from both the superior and inferior venae cavae. Arterial blood from donor entered patient's body through canula in the left subclavian artery.

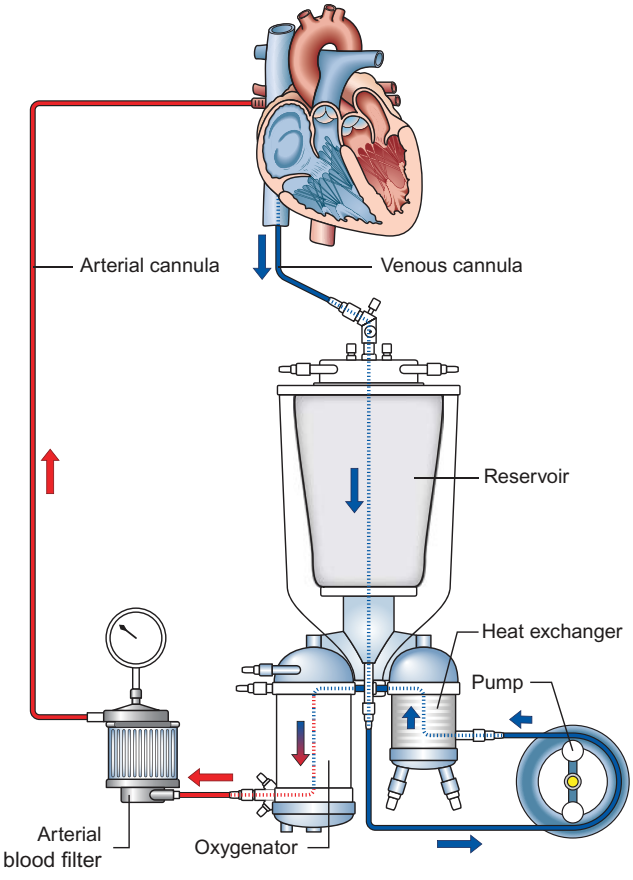

Figure 2. Overview of cardiopulmonary bypass circuit and its various components.

OXYGENATOR

In 1953 when Gibbon first successfully supported a patient with a vertical screen oxygenator,[8] this encouraged the development of oxygenators. Although direct contact bubble oxygenators were used initially, hollow fibre micro-porous oxygenators with blood flow outside the fibres have become the dominant type of oxygenator in use (Figure 3).

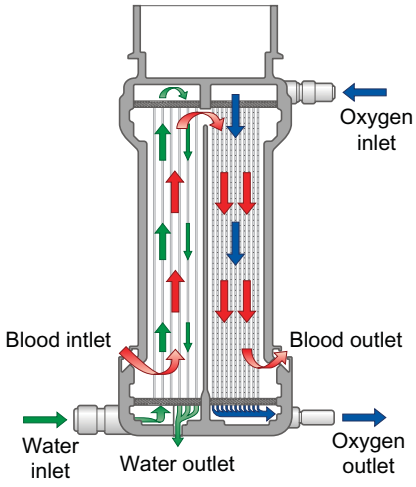

Figure 3. Schematic represenation of hollow fibre micro-porous oxygenator and oxygen, water, and blood flow.

A micro-filter bubble trap is also added to the arterial outflow. Depending on the operation, various suction systems are used to return blood from the surgical field, cardiac chambers, and/or the aorta. Aspirated blood passes through a cardiotomy reservoir and micro-filter before returning to the venous reservoir (Figure 4). Optionally, but increasingly being recommended, the field blood is washed in a cell saver system and returned to the perfusate as packed red cells. In addition to adjusting pump flow, partial and occluding clamps on venous and arterial lines are used to direct and regulate flow. Sites for

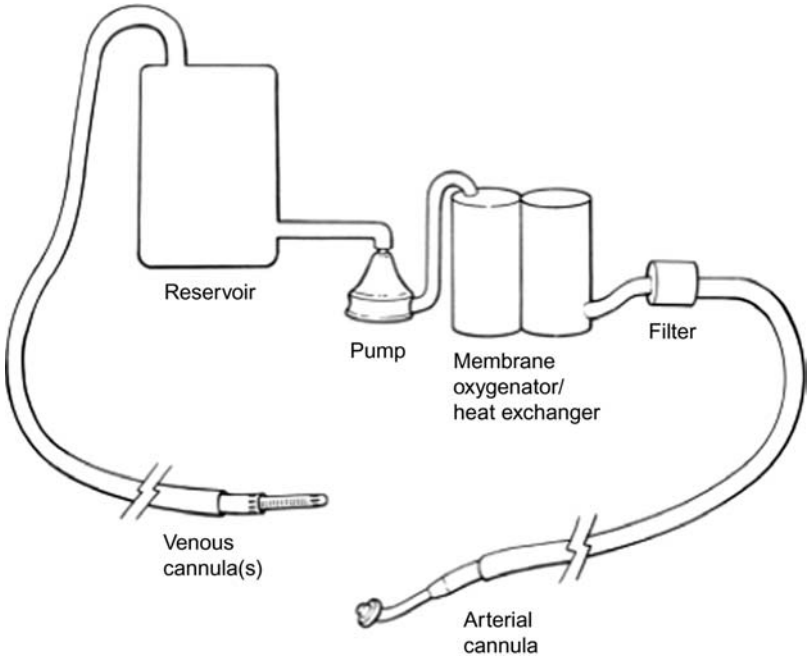

Figure 4. Aspirated blood passes through a cardiotomy reservoir and micro-filter before returning to the venous reservoir.

obtaining blood samples and sensors for monitoring pressures, temperatures, oxygen saturation, blood gases, and pH are included, as are various safety devices.

During CPB, an adequate volume should be maintained in the perfusion circuit if an interruption of systemic venous return should occur. This volume of fluid permits a reaction time of at least 10 s and is incorporated with the use of appropriate safety devices. The blood flow rate is maintained at 2 – 2.5 lts / m2 BSA to avoid inadequate tissue perfusion (e.g., increasing metabolic acidosis, venous oxygen desaturation, EEG changes). Perfusion pressure is also maintained at an adequate level so that organ preservation and function are not compromised.

Anticoagulation assessment is performed on a routine basis during CPB. Anticoagulation should be adequate to prevent clotting in the extracorporeal circuit and the consumption of clotting factors. During the time that the cardiopulmonary bypass machine is not being used actively to transfuse blood or support the patient, both the arterial and venous lines are securely clamped (Figure 5).

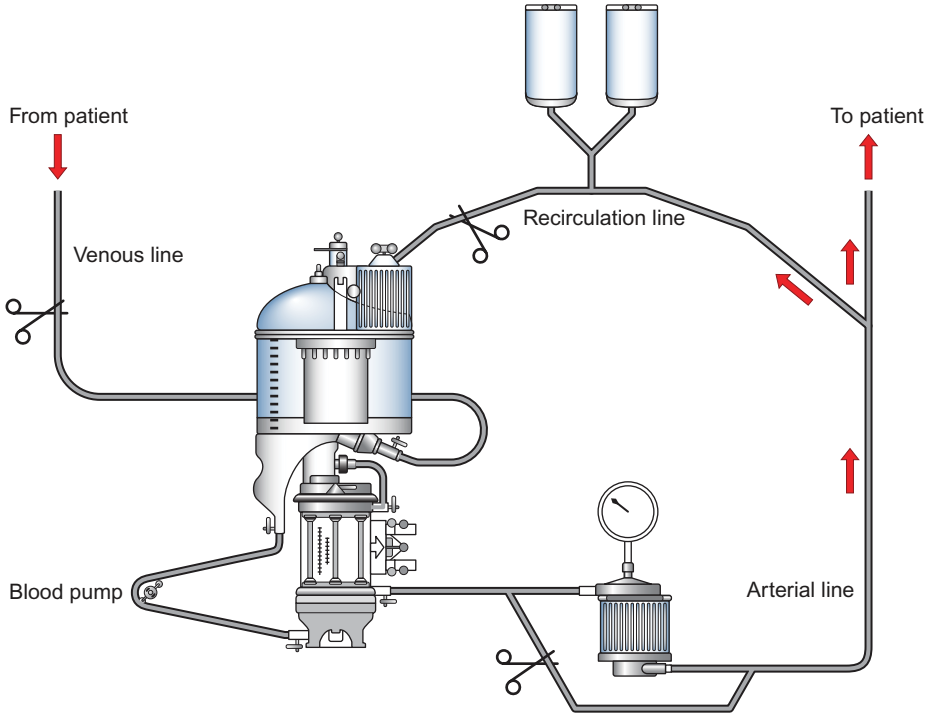

Figure 5. Arterial and venous lines are clamped when cardiopulmonary bypass machine is not in active use.

Optimal performance and safety of the cardiopulmonary bypass circuit is the prime concern of the clinical perfusionist. While operating the heart and lung machine, additional responsibilities include haemostasis management, blood gas analysis and myocardial protection. Although the weight of the patient, pre-existing conditions and the selected operative procedure will dictate certain characteristics of extracorporeal equipment selection, other aspects of equipment/component selection are not so affected. Cardiotomy suction and vent return lines should be tested prior to use for proper direction of flow. Permanent equipment should have periodic scheduled preventive maintenance, and records of such maintenance should be obligatory.

Artificial blood pumps are used to circulate blood through various organs and tissues, providing a bloodless field to operate on the heart. This is necessary to artificially support or temporarily replace a patient's circulatory or respiratory functions, such as in open heart surgery or other heart procedures. Aortic canulation for the return of oxygenated blood and right atrial canulation (single two stage canula or individual SVC [Superior Vena Cava] and IVC [Inferior Vena Cava] canulae) for gravity assisted drainage of deoxygenated blood in to the perfusion circuit are placed by the surgeon. Blood flow and oxygenation are regulated to optimise tissue oxygenation and protection.

VENOUS CANNULATION AND DRAINAGE

Principles of venous drainage

Venous blood usually enters the circuit by gravity into a venous reservoir placed 40 to 70 cm below the level of the heart. The amount of drainage is determined by central venous pressure; the height differential; resistance in cannulas, tubing, and connectors; and absence of air within the system. Central venous pressure is determined by intravascular volume and venous compliance, which is influenced by medications, sympathetic tone, and anaesthesia. Inadequate blood volume or excessive siphon pressure may cause venous or atrial walls to collapse against the canula producing "chattering" or "fluttering." This phenomenon is corrected by adding volume to the patient.

Venous cannulas and cannulation

Venous cannulas are usually made of flexible plastic, which may be stiffened against kinking by wire reinforcement. Tips are straight or angled and often are constructed of thin, rigid plastic or metal (Figure 6). Size is determined by patient size, anticipated flow rate, and an index of catheter flow characteristics and resistance (provided by the manufacturer).

Figure 6. Various venous cannulas tip orientations.

Three basic approaches for central venous cannulation are used: bicaval, single atrial, or cavoatrial ("two stage"). *Bicaval cannulation* and caval tourniquets are necessary to prevent bleeding and air entry into the system when the right heart is entered during CPB. Because of coronary sinus return, caval tourniquets should not be tightened without decompressing the right atrium. Bicaval cannulation without caval tapes is often preferred to facilitate venous return during exposure of the left atrium and mitral valve. For an average adult with 60-cm negative siphon pressure, a 30F cannula in the superior vena cava (SVC) and 34F in the inferior vena cava (IVC) or a single 42F cavo-atrial canula suffices. Canulae are typically inserted through purse-string guarded incisions in the right atrial appendage, lateral atrial wall, or directly in the SVC (Figure 7).

Extracorporeal membrane oxygenation (ECMO)

The term extracorporeal membrane oxygenation (ECMO) was initially used to describe long-term extracorporeal support that focussed on the function of oxygenation. Subsequently, in some patients, the emphasis shifted to carbon dioxide removal, and the term extracorporeal carbon dioxide removal was coined. Extracorporeal support was later used for postoperative support in patients following cardiac surgery. Other variations of its capabilities have been tested and used over the last few years, making it an important tool in the armamentarium of life and organ support measures for clinicians. With all of these uses for extracorporeal circuitry, a new term, extracorporeal life support (ECLS), has come into vogue to describe this technology.

Differences between ECMO and cardiopulmonary bypass:

(i) ECMO is frequently instituted using only cervical cannulation, which can be performed under local anesthesia whereas standard cardiopulmonary bypass is usually instituted by transthoracic cannulation under general anesthesia (Figure 8).
(ii) Unlike standard cardiopulmonary bypass, which is used for short-term support measured in hours, ECMO may be used for longer-term support ranging from 3-10 days and finally.
(iii) The purpose of ECMO is to allow time for intrinsic recovery of the lungs and heart; a standard cardiopulmonary bypass provides support during various types of cardiac surgical procedures.

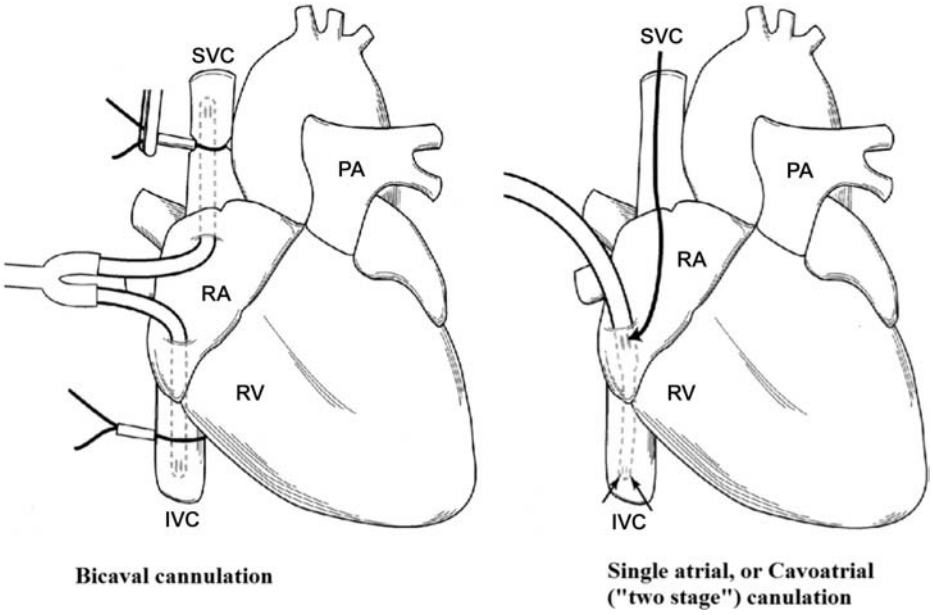

Figure 7. Insertion of canulae in bicaval cannulation and single atrial or Cavotrial cannulation.

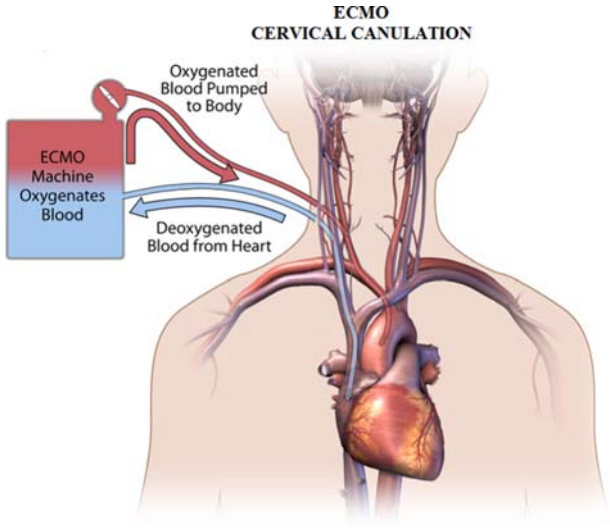

Figure 8. Depiction of oxygenated and deoxygenated blood flow in ECMO cervical canulation.

(iv) ECMO can be Veno – Arterial (VA-ECMO: usually deoxygenated blood is drained from Femoral vein and Oxygenated blood is delivered to Femoral artery) or Veno -Venous (VV-ECMO: usually deoxygenated blood is drained from Femoral vein and Oxygenated blood is delivered to Internal Jugular vein) (Figure 9).

Pumpless extracorporeal lung assist (Novalung)

An oxygenator with low flow resistance and high gas transfer efficiency is connected to cannulae placed in the femoral artery and vein. The circuit flow is driven by the femoral arterial pressure and is designed to operate without the help of a mechanical pump in an arterio-venous configuration (Figure 10). Based on this principle, adequate mean arterial blood pressure is mandatory. This device is attached to the systemic circulation (usually Femoral artery and vein) and receives only part of the cardiac output (1–2 L/min) for extracorporeal gas exchange.

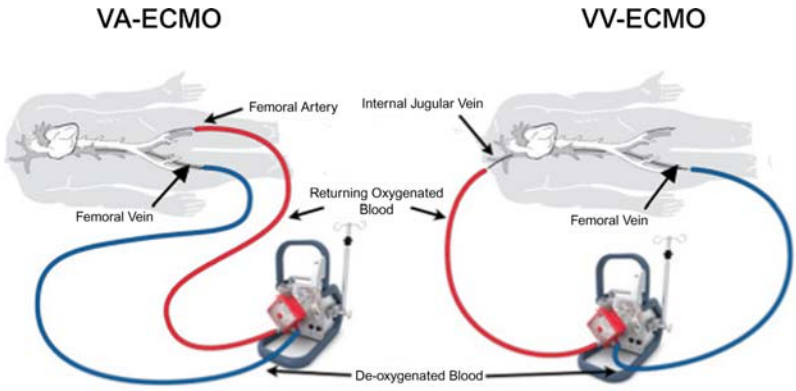

Figure 9. Veno-Arterial and Veno-Venous: Extracorporeal membrane oxygenation circuit.

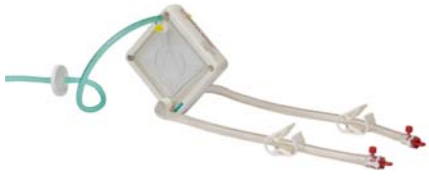

Figure 10. Pumpless extracorporeal lung assist with connected oxygen line.

Typical flows are up to 1 L/min, which allows excellent CO_2 removal. Oxygenation is limited, due to the inflow of relatively well-oxygenated arterial blood. The capability for efficient CO_2 removal allows for a reduction in ventilator settings. The simplicity of the circuit and its portability also make it suitable for emergency use and transfer. It has been used in patients with severe acute lung failure due to ARDS, inhalation injury, severe pneumonia, chest injury, foreign body aspiration, and after thoracic surgical interventions. Its use is relatively contraindicated in patients with haemodynamic instability, cardiac insufficiency or peripheral atherosclerosis.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN CARDIAC SURGERY

Introduction

The inflammatory response is arguably the most fundamental and potentially protective of all the bodily responses, Claude Bernard's thesis[9] in 1865 introduced his concept of the "Milieu Interieur." ("*The constancy of the internal environment is the condition for a free and independent life*"). The response is evoked by perceived attack by a wide range of stimuli – physical injury to body tissues, viral/bacterial infections, etc. The response involves the recognition, not only of the attack, but of its precise location and the consequent localisation of the body's defensive and reparatory processes at the precise site of the insult.

The inflammatory response is, therefore, essentially appropriate and protective. The peculiar significance of the inflammatory response in the context of cardiac surgery lies in the fact that this *localised* and protective response becomes *systemic and damaging* to patients' vital organs.

Systemic inflammatory response Syndrome (SIRS)

SIRS refers to the situation where the inflammatory response (Figure 11) process ceases to be focussed on a localised site of injury, and instead is disseminated throughout the circulation, affecting potentially all vital organs and contributing (if severe enough and of significant duration) to patient morbidity and mortality. The cardiac surgical literature contains extensive reports of disturbances in the function of lungs, brain, kidney, liver, gastrointestinal tract and the heart itself, induced by the initiation of systemic inflammation in cardiac surgical patients.

There appears to be a spectrum of severity in SIRS related to cardiac surgery, varying from the relatively mild to an acute life- threatening syndrome of acute multi-organ failure which carries a mortality rate of 50–90%. Although the clinical syndrome has been likened to a "sepsis-like" syndrome, characterised by severe vasodilatation, hypotension and massively increased vascular

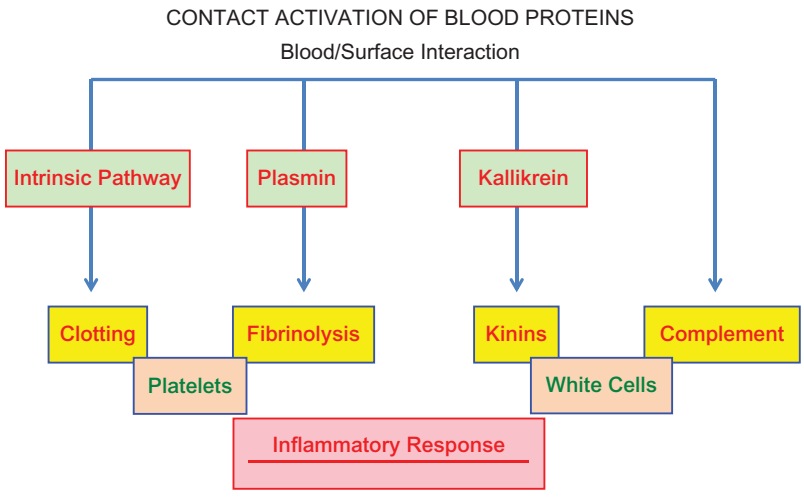

Figure 11. Overview of various pathways to inflammatory response intiated by contact actication of blood proteins.

permeability, at least in the initial phases, these features occur in the absence of overt bloodstream infection.[10]

Initiating mechanisms for SIRS in cardiac surgery

SIRS appears to be the outcome of a complex interaction leading to activation of cellular and humoral mediators of inflammation plus involvement of fibrinolytic and haemostatic systems.

The following specific contributing mechanisms have been reported.

- surgical trauma
- contact activation during CPB
- complement activation during CPB
- ischaemia – reperfusion injury e.g., Myocardium during aortic cross clamping.

Further discussion of the processes involved in contact activation are necessary. Contact activation (Figure 12) refers to the consequences of the exposure of the patients blood to the artificial surfaces/materials within the CPB circuit. Following the initial phase of protein deposition, coagulation

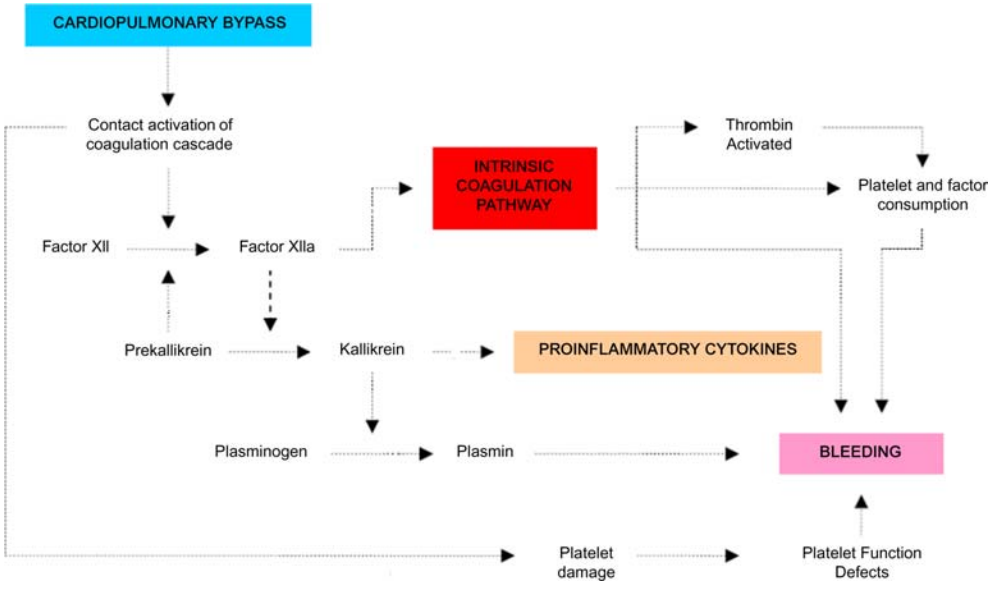

Figure 12. Contact activation of coagulation cascade via intrinstic coagulation pathway, proinflammatory cytokines and bleeding.

factor XII (Hageman factor) is activated. Activated factor XIIa induces a series of cascade systems involving coagulation,fibrinolysis, kallikrein and complement activation.The final common pathway of these cascade systems leads to activation of blood cells, platelets and most importantly, white cells (neutrophils and monocytes) leading to dissemination of an inflammatory response throughout the circulation.

Leucocyte – endothelial cell interaction

Central to the development of the inflammatory process is the interaction between activated neutrophils in circulating blood, and activated vascular endothelial cells, lining the luminal wall of blood vessels. Neutrophils become activated and respond by expressing adhesion molecular families (selectins and integrins) on their cell surface. They also produce and secrete soluble inflammatory mediators. The adhesion molecules render the neutrophils more adhesive.

Similarly, endothelial cells, activated by similar stimuli, express on the cell (luminal) surface the adhesion molecule ligands corresponding to those being expressed in the activated neutrophil. The increased adhesive capability of activated circulating neutrophils flowing over activated vascular endothelial cells results in a step-wise interaction comprising three distinctive steps: neutrophil rolling, neutrophil firm adhesion, and neutrophil transmigration (Figure 13).

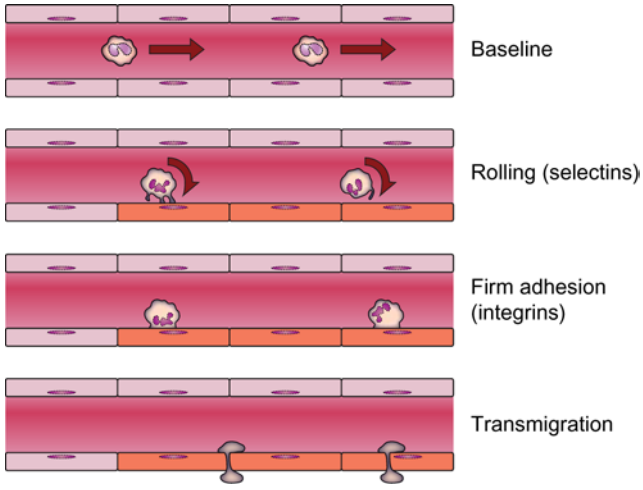

Figure 13. Edothelial cell-leukocyte adhesion cascade and its three distinctive steps.

Neutrophil rolling, the first phase of leukocyte-endothelial cell interaction, is a strange phenomenon, whereby neutrophils migrate out of the fast-flowing blood within blood vessels, and instead begin a slow "rolling" movement along the luminal surface of the vascular endothelial cells. This process is mediated by the Selectin family of adhesion molecules. Once rolling begins, many "rolling" neutrophils become firmly adherent to the luminal surface of the vascular endothelium. This firm adhesion, the second phase of the process, is mediated by the Integrin family of adhesion molecules. The third and final phase of neutrophil – endothelial cell interaction is transmigration, which refers to the movement of firmly adherent neutrophils through the blood vessel wall into the adjacent tissue. The potential significance of this final phase lies in the fact that the activated neutrophils, containing the "ammunition" to fight, perceive attack and move outside the vascular compartment into the tissues of vital organs (Figure 14), taking the inflammatory response with them.[11] These phases of neutrophil – endothelial cell interaction can be imaged and assessed qualitatively and quantitatively by the technique of intravital microscopy (Figure 15).

Protease activated receptors (PARs)

The discovery of a family of trans-membrane receptor proteins which are activated by proteolytic cleavage mediated by serine proteases, has prompted numerous studies which relate to the inter-relationship of inflammatory mechanisms with aspects of haemostasis and coagulation/thrombosis.

The receptors were initially identified in studies cloning the thrombin receptor,[12] now renamed as protease activated receptor (PAR1). PAR1 is the prototype member of four related thrombin receptors,

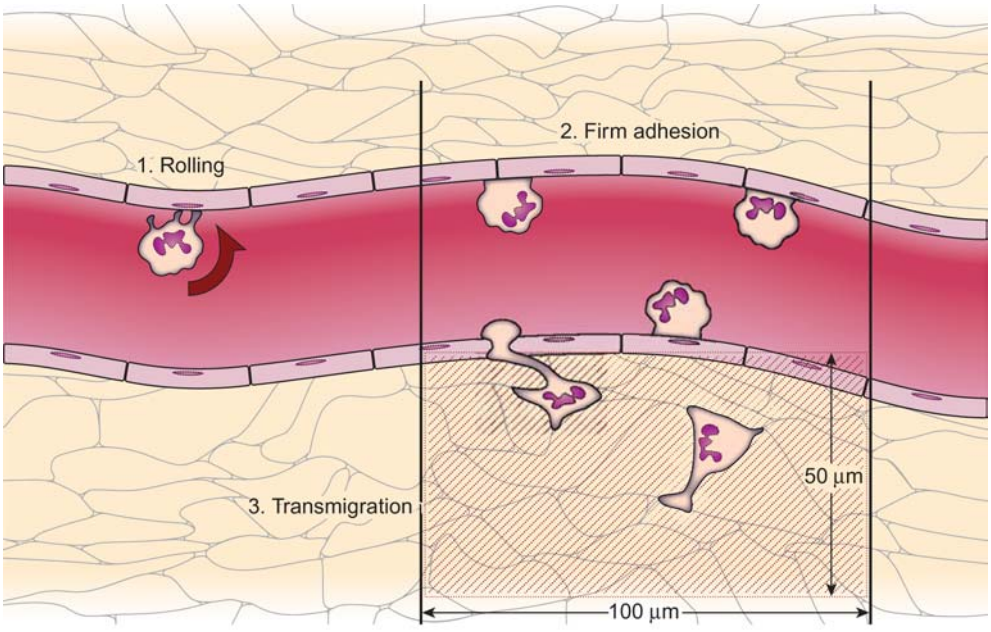

Figure 14. Neutrophil transmigration involves movement into vascular compartment into the tissues of vital organs.

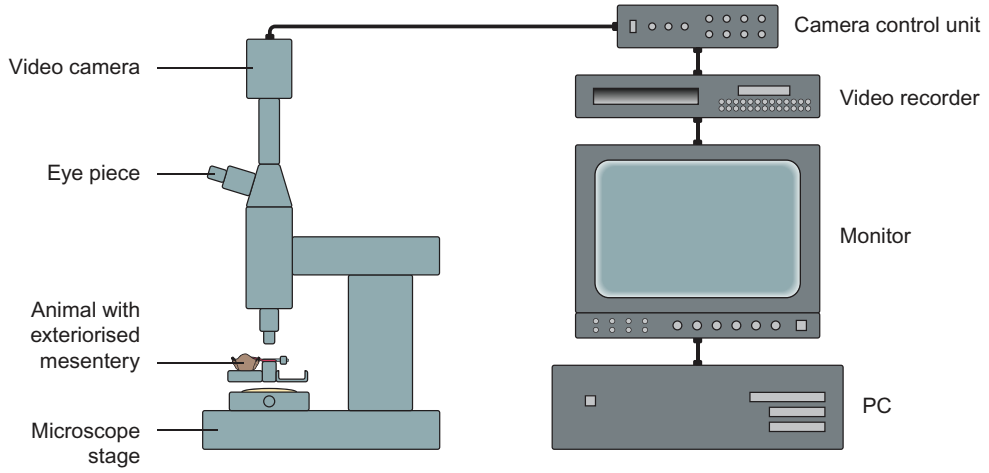

Figure 15. Use of intravital microscopy to image and assess endothelial cell interaction.

PARs 1 – 4. PAR-1 receptors on platelets are the principal route for thrombin-induced platelet activation requiring concentrations of thrombin (less than I U/ml). PAR receptors have now been identified on numerous cells, organs and tissues, including neutrophils and endothelial cells – of obvious interest in relation to inflammation, not least the potential role in leukocyte transmigration across vascular endothelium. Most recently, PAR -1 activation of platelets has been reported in patients acutely after ischaemic stroke. PAR has various locations: platelet; endothelium of gut, brain, lung, skin and skeletal muscle; neutrophil; mast cell; and other locations such as heart, fibroblasts, monocytes, T-Cells, osteoblasts, kidney, liver, pancreas, lymph nodes, etc.

Therapy and preventative strategies for inflammatory response in cardiac surgery

Ideally, any strategy to prevent or modify the harmful effects of SIRS should be preceded by an understanding of its pathophysiology. This is clearly a counsel of perfection, but such targeted therapies are more likely to be successful. Research performed in our department has focussed on two strategies:

(i) *Preoperative detection of patients at risk of developing severe and/or potentially life-threatening inflammatory response using the Cantharidin blister model:*
In our laboratory the Cantharidin blister model [13] has been investigated as a tool to analyse the inflammatory effect of cardiopulmonary bypass in vivo. The model can provide a detailed molecular insight into the extravascular leukocyte population during cardiopulmonary bypass. The Cantharidin blister model is non-invasive, has few side effects, is easily reproducible and can be maintained for several days to characterize both the induction and resolution of the innate inflammatory response. [14,15]

(ii) *The use of Aprotinin as an anti-inflammatory therapy:*
In the late 1980s, we pioneered the use of Aprotinin as a blood conservation agent.[16] However, it was the discovery of its anti-inflammatory properties in the year 2000, that Aprotinin was recognised as a anti-inflammatory agent, based on its ability to prevent leucocyte extravasation (Figure 16). Although Aprotinin was withdrawn in 2008 following preliminary results from a clinical trial as a blood conservation agent, a recent meta-analysis and a review demonstrated that there was no increase in mortality with Aprotinin as compared to other anti-fibrinolytic agents.[17,18] This may lead to a re-acceptance for the use of Aprotinin as an anti-inflammatory agent.

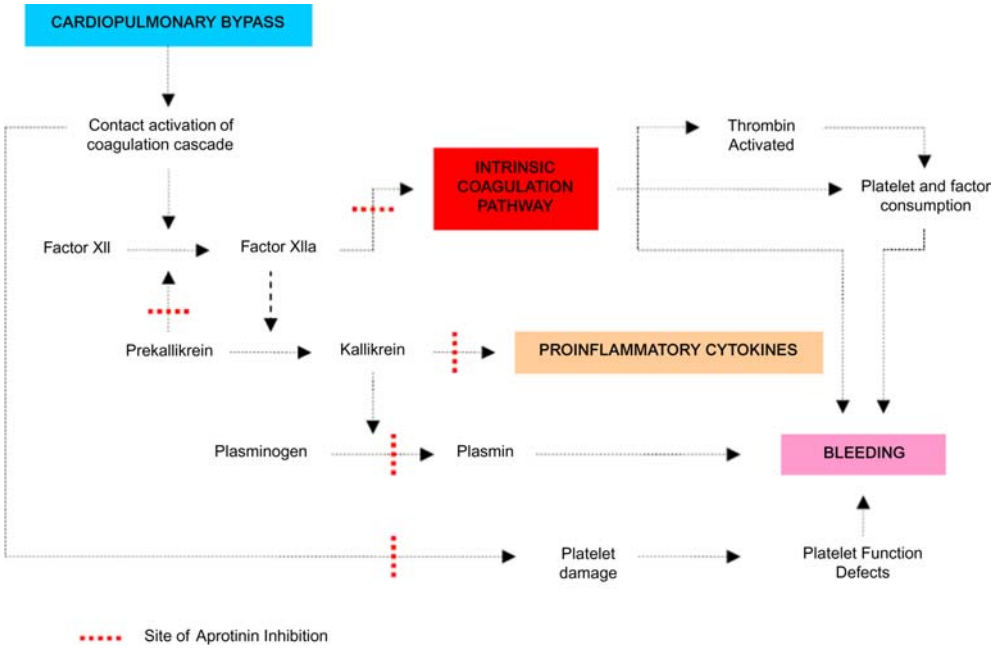

Figure 16. Sites of Aprotinin action as anti-inflammatory agent in coagulation cascade.

Other Strategies to modulate inflammatory response:

(i) *Biocompatibility:*
Heparin coating was probably the first to gain a sizeable acceptance by many cardiac surgeons, although the technique is by no means generally applied. Again, although many studies were carried out to demonstrate the anticipated reduction in the severity of the CPB -induced inflammatory response, the results were mixed and somewhat unconvincing. Mechanistically speaking, it could be argued that, although surface modification of the CPB circuit is a credible concept, heparin may not be the optimal substance for the coating.

Results with subsequent non-heparin based “bio-coatings” are available, but not yet obviously significantly superior. The laudable aim to reduce CPB related contact activation may also be achieved by reducing the surface area of the CPB circuit. The recent emergence of mini ~ CPB systems is a logical and potentially attractive option. The potential impacts on SIRS are at least twofold. Reduction of the surface area in extra-corporeal circuits has been shown

previously to reduce inflammatory response markers in a "dose dependent" relationship. In addition, the mini- CPB systems offer substantial reductions in priming volumes. Clinical use of the new mini-CPB systems has not, however, been free from new challenges, for example issues around the handling of air in the CPB circuit and vacuum assisted venous drainage, but the technology is stil1 evolving.

(ii) *The following may also be considered as alternative strategies:*
1. Reducing surgical tissue trauma: Minimal invasive approach.
2. Avoiding CPB: OPCAB procedures.
3. Inhibition of Neutrophil and Platelet activation.
4. Inhibition of Complement activation.
5. Leucocyte depletion.

CONCLUSION

Cardiac surgery has evolved greatly since Gibbon's first successful procedure using cardiopulmonary bypass and is now safe with minimal morbidity and mortality. The challenge remains – to further understand and develop cardiopulmonary bypass systems that minimize the deleterious effects on patients

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