**Review**

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# Molecular aspects of cardiopulmonary bypass

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Acute inflammotory response to CPB is the main couse of morbidity and mortality associated with cardiac surgery. Inflamatory response after CPB is closely linked to activation of coagulation and is a multi pathway process. Therefore, individualized therapies might be more usefull in improved clinical outcomes.

**Key words:** CAB, inflammation, clinic

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Cardiac surgery is different from other specialities because blood is exposed to nonendotheliezed surfaces and then continuosly recirculated through the body. This triggers a serious specific events that eventualy leads to undesired activation of blood elements during surgery.

During Cardiopulmonary bypass (CPB) blood is drained from right atrium into the heart-lung machine (Figure 1).

Blood is then pumped through a membrane oxygenator into the arterial system usually to the distal ascendan aorta (Figure 2).

This contact activation with artificial surfaces triggers the inflammatory response to cardiopulmonary bypass as a massive defence system. Endothelial cells, neutrophils and complement system are the principal blood elements involved in this defence system. The resultant release of vasoactive substances and cytokines express a number deleterious effects to body which include bleeding, thrombosis and respiratory distress (Figure 3).

## Leucocyte Activation / Adhesion

Thus acute inflammatory response to CPB is the main cause of morbidity and mortality associated with cardiac surgery. Since the early dates of open heart surgery much has been learned about the mechanisms of inflammatory response. However debate continues and these effects are not the same in all patients. The sources of this variability might be due to enviromental and genetic causes. The role of genetic make-up in cardiovascular diseases is a well known entity. However there has been little knowledge about genetic phenotype and outcomes after CPB. This might result in better outcomes in terms of identifying the target population and then use spesicific genetic thearpies to reduce the inflammatory response in this patient group.

In recent years, open heart surgery without the use of CPB so called off pump surgery has gained a popularity. It has been reported that off pump surgery results in less mortality and morbidity. This has been linked to elimination off cardiopulmonary

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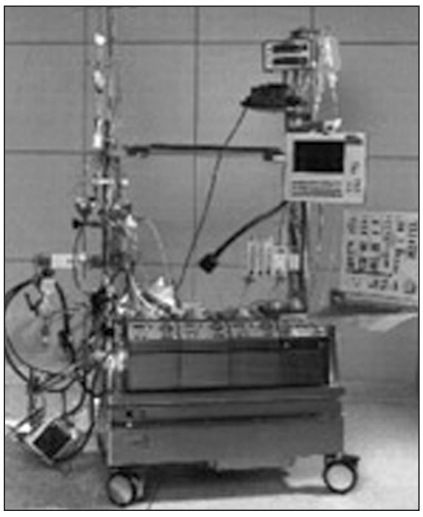

**Figure 1**
*Heart lung machine (http://members.rediff.com/isecthome.htm)*

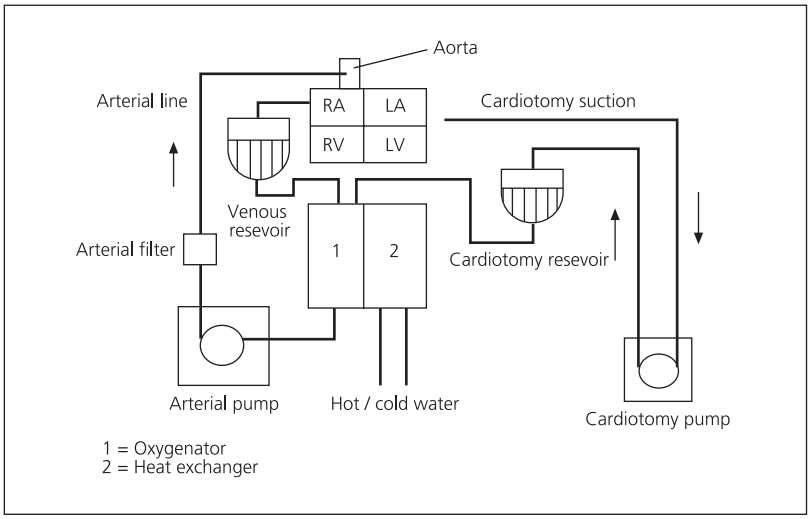


**Figure 2**
*Components of cardiopulmonary bypass*

bypass. Variations in genetic background may play a role in influencing pro-inflammatory cytokine levels. Determining the genotypes responsible from increased inflammatory response, might also beneficial to identify those patients to decide whether off-pump surgery should be used in specific patients.

Inflammatory response after CPB is closely linked to activation of coagulation. The major blood elements involved in inflammatory response are complement system, neutrophils, monocytes and endothelial cells. Thrombin and Factor Xa are known to have a proinflammatory effects besides their coagulative effects. Thrombin is a potent activator of mast cells which also has a chemoattractant activity for monocytes and leukocytes. Factor Xa acts as an receptor activator for monocytes and macrophages. Thus there is a considerable overlap between coagulation and inflammation. The acute inflammatory response and microembolization is the leading cause mortality and morbidity of CPB and cardiac surgery.

## Summaries of the Studies Related Inflammatory Markers and Clinical Outcomes

Rifon et al. demonstrated the relation of variation in tPA and PAI-1 levels in patients undergoing coronary artery bypass grafting (CABG). In 82 CABG patients receiving 216 grafts (136 Saphenous vein and 80 internal mammary artery) they examine the PAI-1 activity in 25 occluded grafts. They found a higher PAI-1 activity in those patients. When they

**Special Effects for Blood Contacting Surfaces**

Protein Absorption
Coagulation
Fibrinolysis
Platelet Adhesion / Activation Release → Embolization, Thrombus Material
Complement activation
Hemolysis

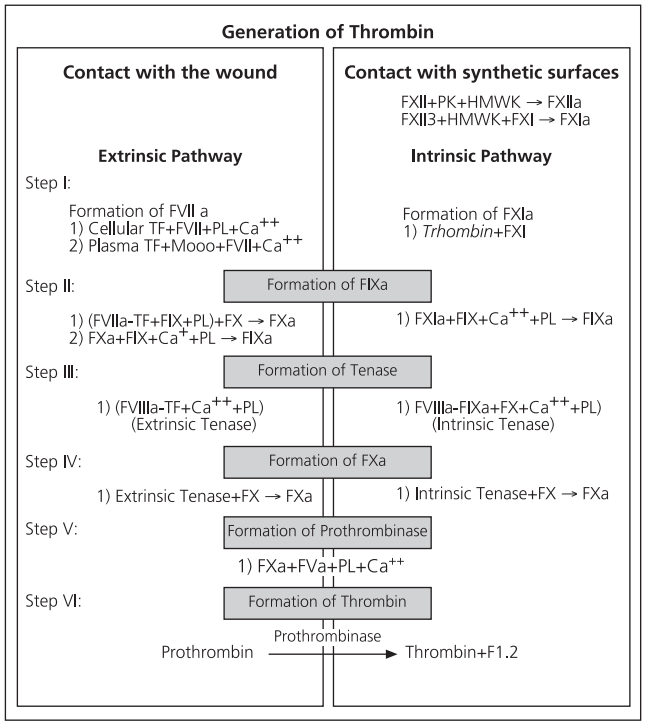


**Figure 3**
*Steps in contact activation.*
*(PK: prekallikrein, HMWK: high molecular weight kininogen, TF: tissue factor)*

looked at the tPA elution in those patients they found lower fibrinolytic response in those patients compared to those without an graft occlusion.

Galley et al. examine the relation between the IL-10 genotype and IL-10 concentrations after CPB. IL-10 is a well known anti inflammatory cytokine. They found lower IL-10 release in patients with homozygote G allele compared to A allele. They also correlated this with clinical outcome. They noticed a higher IL-10 levels and organ dysfunction in patients with A allele compared to G allele.

Shroeder et al. examine the genotype distribution and TNF-α levels in patients undergoing on-pump and off-pump cardiac operations. They found higher TNF-α levels in on-pump patients compared to off-pump patients in homozygous TNF-β2 allele.

Grunenfelder et al. studied the Apolipoprotein E and TNF-β polymorphisms in patients undergoing CABG. They found higher levels of IL-8 and TNF-α levels in patients with TNF-β*A329G polymorphism and APOE*E4 variant. Their results also correlated with the higher complication rates such as prolonged intubation and increased transfusion to patients without genetic variants. Another study by Tomasdottir et al. showed an increased rate of ventricular and pulmonary dysfunction in patients with TNF-β2 allele compared to TNF-β1 homo or heterozygotes. They conclude that this might be due to increased TNF-α and IL-6 release in these patients.

Lactic acidosis has known to associate with low cardiac output and poor outcome after cardiac surgery. Ryan et al. determined higher levels of lactic acid in TNFG -308A and IL-10G-1082 A alleles in patients after cardiac surgery.

Atrial Fibrillation is a well known patholgy after cardiac operations. Incidence is nearly 30%. Although etiology is multifactorial inflammation is suggested to play a role in development of this abnormal rhythm. A study by Gaudino et al. showed a increased atrial fibrillation rates in patients with GG genotype of IL-6 promoter gene. Same group also showed an increase rate of postopeartive renal and pulmonary complications with same genetic polymorphism.

Inflammatory response after CPB is a multipathway process. It involves positive and negative pathways for the surgery itself. In other words, treatment strategies towards inflammatory response might be deleterious in terms of wound healing, infection and myocardial dysfunction. Thus treatment for CPB induced inflammatory response should be performed without an another adverse effect. Therefore individualized therapies might be more usefull in improved clinical outcomes.

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