Immunological Response To CPB

CPB often related to some extent of pulmonary dysfunction

- Complement activation
- leucocytes
- endothelial cells with secretion of cytokines
- proteases, arachidonic acid metabolites & O_2 free radicals
- leucocyte adhesion to microvascular endothelium, leucocyte extravasation & tissue damage

“POSTPUMP SYNDROME”

“Systemic inflammatory response syndrome to CPB”

- Contact of blood components with the artificial surface of the CPB circuit
- Ischaemia - reperfusion injury
- endotoxemia
- operative trauma

Acute Lung Injury & Acute Respiratory Distress Syndrome (ARDS)

- ? Which inflammatory mechanisms may be related to lung injury after cardiac surgery
- ?? What is the incidence, & relation to systemic inflammation of ARDS after cardiac surgery.

Table 1. Criteria for ARDS

Timing	Oxygenation (Pao_2/Fio_2 in mm Hg)		PEEP (when ventilated) (cm H_2O)		Respiratory System Compliance (mL/cm H_2O)		Pulmonary Artery Wedge Pressure (mm Hg)	Chest Radiograph (extent of infiltrates)	
A Acute onset		Score		Score		Score			Score
	≥ 300	0	≤ 5	0	≥80	0	Not included	No infiltrates	0
	225–299	1	6–8	1	60–79	1		1 quadrant	1
	175–224	2	9–11	2	40–59	2		2 quadrants	2
	100–174	3	12–14	3	20–39	3		3 quadrants	3
	< 100	4	≥ 15	4	≤ 19	4		4 quadrants	4
B Acute onset	≤ 200 (acute lung injury is manifested when Pao_2/Fio_2 ≥ 300 mm Hg)		Not included		Not included		< 18 when measured or no clinical evidence of left atrial hypertension	Bilateral	

(A) Lung injury score as defined by Murray and associates [82]. The final score is obtained by the sum of individual scores divided by the number of criteria used. A final score > 2.5 is suggestive for ARDS. (B) As defined by the American–European Consensus Conference on ARDS [4]. ARDS (or acute lung injury) is present when all criteria are met.

ARDS = acute respiratory distress syndrome; PEEP = positive end-expiratory pressure.

Post CPB pulmonary dysfunction

- Alveolar-arterial oxygenation gradient
- intrapulmonary shunt
- degree of pulmonary oedema
- pulmonary compliance
- pulmonary vascular resistance

Cell activation during CPB

- Neutrophils
- Monocytes
- Macrophages
- Endothelial cells

Complement

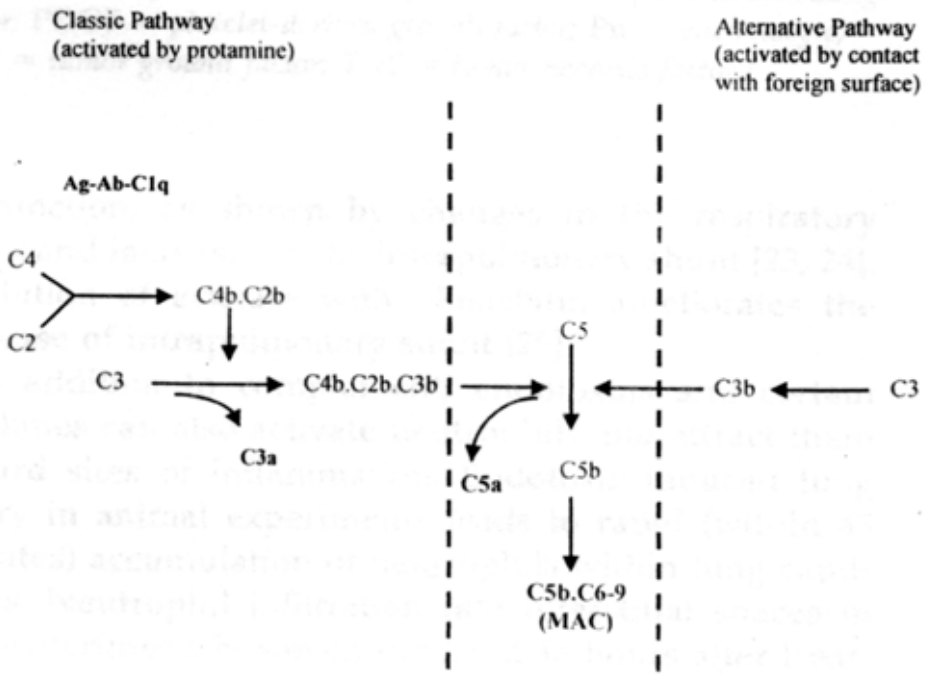

Fig 1. The complement cascade. Contact between complement components and the artificial surface of the bypass circuit activates the alternative pathway. Activation of the classic pathway also occurs, probably as a result of administration of protamine. Membrane attacking complex (MAC) is the final product of the reaction.

Neutrophils

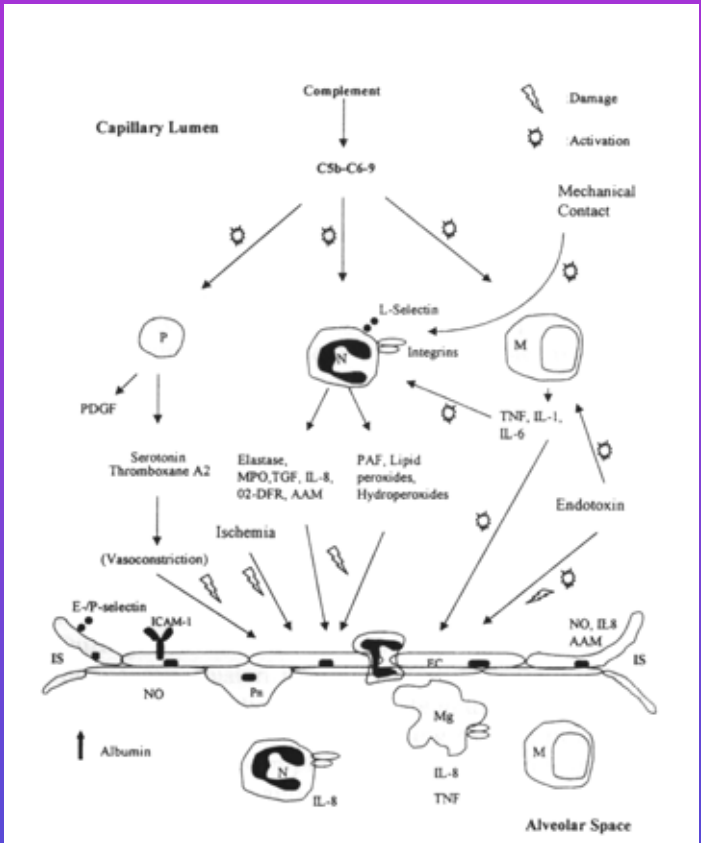

Fig 2. Leukocytes, endothelial cells (EC), *and humoral inflammatory mediators have been shown to play an important role in the cardiopulmonary bypass-induced lung injury. Complement activation and complement-independent mechanical injury activates leukocytes, which, in their turn, secrete several inflammatory mediators, such as proteases and cytokines. Complement, cytokines, and ischemia–reperfusion also activate endothelial cells. Endotoxin, probably released from intestinal bacteria, exerts similar effects on leukocytes and endothelium. This process leads to disruption of endothelial and epithelial integrity and allows albumin, plasma, and activated leukocytes to enter the interstitial and alveolar space, causing tissue edema and reducing pulmonary compliance and blood oxygenation.* (AAM = *arachidonic acid metabolites;* ICAM-1 = *intercellular adhesion molecule-1;* IL = *interleukin;* IS = *interstitial space;* LPS = *lipopolysaccharide;* M = *monocyte;* Mg = *macrophage;* MPO = *myeloperoxidase;* N = *neutrophil;* NO = *nitric oxide;* O_2-DFR = *oxygen-derived free radicals;* P = *platelet;* PAF = *platelet-activating factor;* PDGF = *platelet-derived growth factor;* Pn = *pneumocyte;* TGF = *tumor growth factor;* TNF = *tumor necrosis factor.*)

CPB associated lung injury

- After protamine administration, neutrophil counts in pulmonary artery exceeds the count in systemic arterial blood

Neutrophil dependent model for CPB related lung dysfunction

- Activation of neutrophils
- upregulation of adhesion molecules
- neutrophil adhesion to endothelium of lung vessels
- endothelial damage through proteases

Macrophages, Monocytes & Cytokines

- Pulmonary macrophages
- Activated monocytes
- Monocyte secreted proinflammatory cytokines

Macrophages

- Cytokine secretion
- Cytotoxic metabolites
- Chemoattractants for leukocytes

Monocyte

- CPB induces monocyte activation
- Activates endothelial cells, neutrophils & macrophages
- IL-8 increased in bronchial lavage fluid

Platelets

- Sequestration in pulmonary capillaries occurs during severe lung injury
- May contribute to endothelial injury & tissue oedema
- Collect in small vessels of lung during bypass

Endothelial cells

- ? Increased endothelial permeability
- endotheium activated by complement, cytokines, endotoxin & ischaemia-reperfusion
- von Willebrand factor elevated
- IL-8 increased
- NO exerts protective effect

Acute Respiratory Distress Syndrome

- Several characteristics of the CPB related lung injury bear resemblance to changes occurring during ARDS
- CPB appears on lists of risk factors for ARDS development
- Acute
- Noncardiogenic
- High permeability lung injury, characterised by interstitial & alveolar oedema
- Epithelial damage
- Rapid onset of pulmonary fibrosis

ARDS

- Free radical release, which put the endothelium under significant oxidative stress
- One part of multiorgan failure, with lung injury part of a more general state of systemic inflammation

Incidence & Mortality of ARDS after CPB

- 0.5% - 1.7% Incidence
- 91.6% Mortality
- Bacteremia
- At least 1 episode of hypotension
- Not CPB duration
- Poor preop LV cardiac function
- High dyspnoea class
- Emergency surgery
- CPB ALONE UNLIKELY RESPONSIBLE

Therapeutic Considerations

- Suppress secretion & function of various inflammatory mediators
- Leucocyte depletion
- Monoclonal antibodies
- Neutrophil adhesion inhibition

Conclusion 1

- Evidence suggests CPB is associated with deterioration of pulmonary function
- Alveolar-arterial oxygenation gradient
- Intrapulmonary shunt
- Degree of pulmonary oedema
- Pulmonary compliance
- Pulmonary vascular resistance

Conclusion 2

- Complement activation
- Neutrophils
- Monocytes
- Macrophages
- Platelets
- Endothelial cells